TITLE PAGE

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)

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Sponsor's Signatory: [redacted]

Personnel Responsible for Clinical and Statistical Analyses:

[redacted]

[redacted]

[redacted]

[redacted]

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

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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: N42896/700899, 704871/705811, 705811/702587, 705811/700899, 705811/705812, 702587/737946, 741027/705811, 741027/737952, 741027/765297, 705812/765297, 775629/781639, 741027/775629, 781639/805672 Avonex®: 070275AR, 080185A, P01112, 080440A, 080499A, P01105, 080185A
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.

CORE REPORT

GLOSSARY OF ABBREVIATIONS

AE	adverse event
AIDS	acquired immune deficiency syndrome
ALT (SGPT)	alanine aminotransferase
ARR	annualized relapse rate
AST (SGOT)	aspartate aminotransferase
ATA	Anti-therapeutic Antibodies
AUC	area under the concentration-time curve
β-hCG	β-human chorionic gonadotropin
BFR	brain fractional ratio
CES-D	Center for Epidemiologic Studies Depression Scale
CI	confidence interval
CL	clearance
C_{max}	maximum concentration
CNS	central nervous system
CRF	Case Report Form
CV	coefficient of variation
DIC	disseminated intravascular coagulopathy
DMC	data monitoring committee
ECG	electrocardiogram
EDSS	Expanded Disability Status Scale
EEA	European Economic Area
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
FACS	fluorescence-activated cell sorter
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
FSMC	Fatigue Scale for Motor and Cognitive Functions
FSS	Functional System Score
GGT	γ-glutamyl transferase
HAHA	human anti-humanized antibodies

GLOSSARY OF ABBREVIATIONS

HAM	human T-lymphotropic virus-1–associated myelopathy
HBsAg	hepatitis B surface antigen
HBcAb	hepatitis B core antibody
HepCAb	hepatitis C antibody
HIV	human immunodeficiency virus
HTLV	human T-lymphotropic virus
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN-β	interferon-β
Ig	immunoglobulin
im	intramuscular
IND	Investigational New Drug
INN	International Non-Proprietary Name
IRB	Institutional Review Board
IRR	Infusion-related reaction
ITT	intent to treat
iv	intravenous
IVRS	interactive voice response system
JCV	John Cunningham virus
LLN	lower limit of normal
LLOQ	lower limit of quantitation
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MELAS	mitochondrial myopathy, encephalopathy, lactacidosis, stroke
MFIS	Modified Fatigue Impact Scale
MMF	mycophenolate mofetil
MODS	multi-organ dysfunction syndrome
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSFC	MS Functional Composite

GLOSSARY OF ABBREVIATIONS

NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	not estimated
NK	natural killer
NOS	not otherwise specified
OCR	ocrelizumab
PML	progressive multifocal leukoencephalopathy
PP	per protocol
PRO	patient-reported outcome
Q	intercompartmental clearance
RRMS	relapsing-remitting multiple sclerosis
SAE	serious adverse event
SDP	sustained disability progression
SEM	standard error of the mean
SIRS	systemic inflammatory response syndrome
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
V1	central volume of distribution
V2	peripheral volume of distribution

1. INTRODUCTION

1.1 BACKGROUND

1.1.1 Disease

Multiple sclerosis (MS) is an inflammatory and demyelinating degenerative disease of the human central nervous system (CNS). It is a worldwide disease that affects approximately 300,000 people in Europe and 350,000 people in the United States. It is a disease of young adults, with 70% to 80% of patients having an age of onset (i.e., presentation to a physician) at between 20 and 40 years [1, 2]. MS is a heterogeneous disorder based on clinical course, magnetic resonance imaging (MRI) assessments, and pathologic analysis of biopsy and autopsy material [3]. The disease manifests itself in a large number of possible combinations of CNS deficits, including spinal cord, brainstem, optic nerve, cerebellar, cerebral, and cognitive syndromes.

Several clinical variants of MS have been defined on the basis of the frequency of relapses, amount of persistent disability following relapses, and/or rate of progression in neurologic disability. Of these, relapsing-remitting MS (RRMS) has been the most intensively studied.

Six drugs, in four classes, are currently approved in Europe, the United States, and many other countries worldwide for disease modification of relapsing forms and/or RRMS. These include interferon-β (IFN-β), which is approved in two forms: IFN-β-1a (Rebif® and Avonex®) and IFN-β-1b (Betaferon®/Betaseron®). Interferons are naturally occurring cytokines with multiple immunomodulatory effects. Other currently approved therapies include glatiramer acetate (Copaxone®), a random mixture of amino acids over-expressed in CNS myelin; mitoxantrone (Novantrone®), a chemotherapeutic; and natalizumab (Tysabri®). Natalizumab is a monoclonal antibody that binds to and inhibits α1 integrin, thereby inhibiting the migration of lymphocytes from the circulation into tissues. Fingolimod (Gilenya®) was recently approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with RRMS. Other non-approved drugs have been used with varying degrees of success; these include corticosteroids, methotrexate, cyclophosphamide, azathioprine, and intravenous (IV) immunoglobulin (Ig).

The benefits of currently approved first-line disease-modifying therapies for the reduction and prevention of disability in patients with RRMS are relatively modest. Two recent meta-analyses report an approximate 30% relative reduction in relapse rate and protocol-defined progression of disability compared with placebo [4]. Therefore, development of more effective therapies for the treatment of MS remains a high medical need.

1.1.2 Ocrelizumab

Ocrelizumab (OCR; rhuMAb 2H7, RO4964913, PRO70769) is a humanized, glycosylated monoclonal antibody. Ocrelizumab binds to the CD20 antigen present on normal and malignant B-cells, thereby depleting them. Ocrelizumab shares the same basic mechanism of action with rituximab (Rituxan® or MabThera®), a chimeric monoclonal antibody.

Clinical experience with rituximab has demonstrated B-cell depletion to be of major clinical benefit for the treatment of certain lymphoma types and rheumatoid arthritis. Robust positive proof-of-concept data exist for rituximab for the treatment of other autoimmune diseases, such as RRMS.

1.1.3 Rationale for Targeting B-Cells in MS

The traditional view of MS pathophysiology has held that the CNS inflammation seen in MS is principally mediated by $CD4^+$ pro-inflammatory (Th1, ThIL-17) T cells [5]; however, increasing evidence has shown that B-cells may also contribute to the MS disease process through both antibody-dependent and -independent mechanisms. B-cells may differentiate into plasma cells and produce CNS-directed auto-antibodies, triggering cellular and complement-dependent cytotoxicity [6]. B-cells may function as antigen-presenting cells and thereby activate effector T cells [7]. In this latter context, B-cells may be a predominant source of antigen presentation in the periphery. Alternatively, as a site of latent viral infections such as Epstein-Barr virus infection, B-cells may preferentially drive CNS autoimmune responses through molecular mimicry with myelin basic protein [8]. More recently, human B-cells have been shown to exhibit regulated secretion of both pro-inflammatory and anti-inflammatory cytokines, a function that appears to be abnormal in patients with MS [9, 10].

Production of cytokines and chemokines by B-cells may also contribute to the formation of ectopic lymphoid-like structures, resulting in localized sites for auto-antigen presentation and further immune activation [11, 12]. Accordingly, targeting B-cells in MS may beneficially disrupt pathologic inflammatory processes in both the periphery and CNS of patients.

Given the robust proof-of-concept evidence of efficacy with both OCR and rituximab in RRMS, anti-CD20 therapy appears to be a very promising approach to disease modification in patients with RRMS. Moreover, because OCR is a humanized antibody, rather than a chimeric antibody (such as rituximab), it may have improved dose tolerability, immunogenicity, and safety with repeated and/or long-term use.

1.1.4 Avonex

The active comparator chosen for this study was Avonex® (IFN-β-1a), which was introduced in the United States in 1996 and in Europe in 1997 and was included as an open-label comparator arm for the first 24-week cycle.

1.2 RATIONALE

This study (WA21493/ACT4422g) served as both a proof-of-concept study for OCR in RRMS and a dose-finding study for the planned Phase III program. It also provided preliminary information comparing OCR with Avonex.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective in this study was to investigate the effect of OCR given as two dose regimens, 600 (2×300) mg or 2000 (2×1000) mg IV (Table 1), on the total number of gadolinium-enhancing T1 lesions observed on MRI scans of the brain at weeks 12, 16, 20, and 24 compared with placebo.

2.2 SECONDARY OBJECTIVES

The secondary objectives of this study were to evaluate the efficacy and safety of OCR compared with placebo, as reflected by the following:

- 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 from baseline to week 24 in total volume of T2 lesions on MRI scans of the brain
- 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.

3. MATERIALS AND METHODS

3.1 OVERALL STUDY DESIGN

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:

- **OCR 1000 mg dose regimen:** Dual infusions of 1000 mg in Cycle 1 followed by single infusions of 1000 mg for the subsequent treatment cycles (patients who received this regimen are referred to as the "OCR 1000 mg group" throughout this report)

- **OCR 600 mg dose regimen:** Dual infusions of 300 mg in Cycle 1 followed by single infusions of 600 mg for the subsequent treatment cycles (patients who received this regimen are referred to as the "OCR 600 mg group" throughout this report).

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, as described in Table 1. 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. See Table 1 for an overview of dosing during the treatment period.

In Cycle 1, patients in Groups A and B received two intravenous (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.

To ensure that the patients' first cycle of OCR consisted of a dual infusion, those who missed their dosing during Cycle 2, (e.g., as the result of an ongoing infection, received this dosing during Cycle 3 (two infusions separated by 14 days) such that:

- Patients in Group A received the first infusion of OCR 1000 mg iv followed by a placebo IV infusion
- Patients in Group B received the first infusion of OCR 600 mg IV followed by a placebo IV infusion
- Patients in Groups C and D received two infusions of OCR 300 mg IV

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 (the extent of exposure to OCR is presented in Section 7.2).

Table 1 Overview of the Study Design and Dosing Regimen

Screening	Randomization	Treatment Period (96 Weeks; Four Treatment Cycles[1])						Treatment-Free Period		
		1st Cycle		2nd Cycle [2,8]		3rd Cycle [3,8]	4th Cycle [8]	Follow-up Period (24 Weeks)	B-Cell Monitoring Period[4] (Variable)	Observation Period[4] (24 Weeks)
28 Days	Group	Day 1	Day 15	Day 1	Day 15	Day 1	Day 1			
	A (1000 mg dose regimen)	**Ocrelizumab** 1000 mg IV	**Ocrelizumab** 1000 mg IV	**Ocrelizumab** 1000 mg IV	**Placebo** IV	**Ocrelizumab** 1000 mg IV[6]	**Ocrelizumab** 600 mg IV[6]			
	B (600 mg dose regimen)	**Ocrelizumab** 300 mg IV	**Ocrelizumab** 300 mg IV	**Ocrelizumab** 600 mg IV	**Placebo** IV	**Ocrelizumab** 600 mg IV[7]	**Ocrelizumab** 600 mg IV[7]			
	C (Placebo)	**Placebo** IV	**Placebo** IV	**Ocrelizumab** 300 mg IV	**Ocrelizumab** 300 mg IV	**Ocrelizumab** 600 mg IV[7]	**Ocrelizumab** 600 mg IV[7]			
	D[5] (Avonex)	**Avonex** 30 µg IM every week		**Ocrelizumab** 300 mg IV	**Ocrelizumab** 300 mg IV	**Ocrelizumab** 600 mg IV[7]	**Ocrelizumab** 600 mg IV[7]			

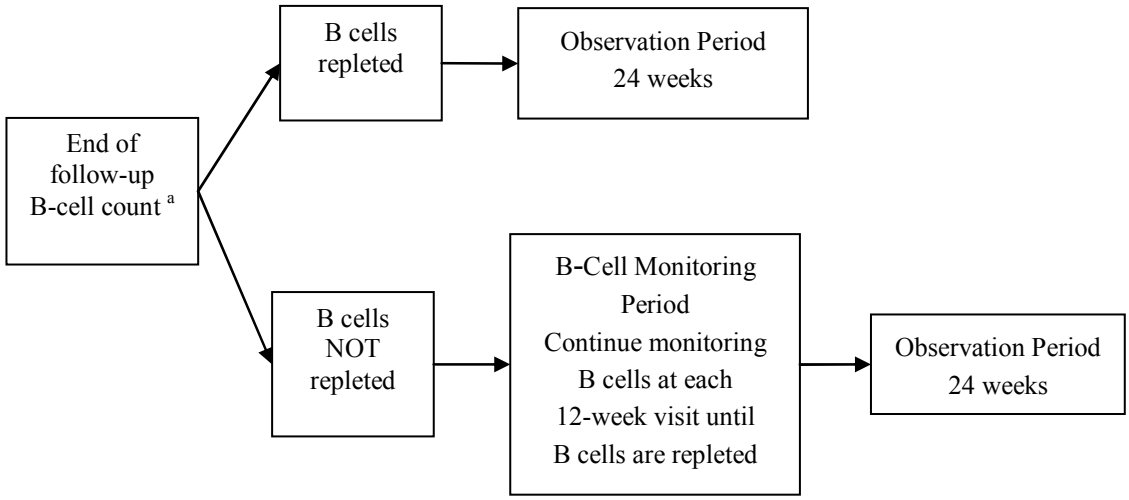
1. Each treatment cycle had a duration of 24 weeks.
2. All groups received a dual infusion, i.e., two iv infusions separated by 14 days. To maintain the blind in Groups A, B, and C until database closure for the primary analysis, the dual infusion was either OCR followed by placebo (Groups A and B) or OCR followed by OCR (Group C).
3. As of the third treatment cycle, single OCR infusion were administered in all groups. However, patients who missed their 2nd treatment cycle dosing, received the dosing of the 2nd treatment cycle (two infusions separated by 14 days) during the 3rd treatment cycle.
4. See also Figure 1.
5. Patients in Group D (Avonex) were offered OCR 600 mg on a voluntary basis. After the first treatment cycle, patients willing to continue in the study were started on OCR within 4 weeks of completing their last dose of Avonex. Patients who completed their first treatment cycle on Avonex and did not wish to receive OCR completed the 24-week visit (visit 9) and were contacted 15 to 30 days after this visit to capture any additional safety information (Avonex Follow-up Contact).
6. Patients were treated with the 1000 mg dose until a preferred dose was chosen on the basis of the primary analysis, at which time investigators and ethics committees were informed of the preferred dose. After the preferred dose was chosen, patients received the preferred dose (600 mg) for their next treatment cycle(s).

Table 1 Overview of the Study Design and Dosing Regimen (cont.)

7. Patients were treated with the 600 mg dose until a preferred dose was chosen on the basis of the primary analysis, at which time investigators and ethics committees were informed of the preferred dose. After the preferred dose was chosen, patients received the preferred dose (600 mg) for their next treatment cycle(s).
8. Prior to the 2nd, 3rd, and 4th dosing cycles, a clinical evaluation was performed to ensure that the patient remained eligible for re-treatment. Methylprednisolone 100 mg iv was administered prior to OCR or placebo infusions. Avonex-treated patients had methylprednisolone administered according to the OCR/placebo schedule.

Treatment-free period consisted of a 24-week follow-up Period, a B-cell monitoring period of variable duration, and a 24-week observation period. Upon completion of the treatment period or after withdrawal from OCR (or placebo for patients in Group C withdrawing during the Cycle 1), all patients who had received OCR entered the treatment-free period, starting with the 24-week follow-up period. At the end of the follow-up period, patients whose B-cell counts had repleted entered the 24-week observation period (see Figure 1). Patients whose B-cells had not repleted entered the B-cell monitoring period, during which time B-cell counts and additional assessments were performed every 12 weeks until B-cells were repleted. Once the B-cells were repleted, these patients entered the observation period, which included an assessment at the end of 24 weeks.

Figure 1 B-Cell Monitoring and Observation Periods in OCR-Treated Patients



[a] As defined in Section 5.3.1.4 of the protocol, page 1600.

The total study duration is approximately 172 weeks (approximately 3.3 years), including screening period, treatment period, and treatment-free period, and assumed a 24 week B-cell monitoring period.

This report presents data collected up to Week 144 (starting from the day of the first infusion) with a cut-off date of 9 March 2012.

3.1.1 Protocol Amendments

This report is written using the version of the study protocol in place at the time of the clinical cut-off (Version C dated 15 October 2011, page 1530). Two protocol amendments were implemented. A list of major protocol changes is given below; full amendment histories, including administrative and typographic changes, are provided from page 1714.

Protocol Version B (first amendment), dated 11 June 2008, introduced the following changes:

- Collection of persisting gadolinium-enhancing T1 lesions was added.
- The transition to Cycle 2 for patients enrolled into Group D was clarified.
- An exclusion criterion relating to potential hypersensitivity as a result of human serum albumin contained in the Avonex vials was added.
- A risk-benefit reassessment/stopping rule was added.
- Consistency was provided in the EDSS increase for assessment of disability progression within the protocol.
- The difference between treatment withdrawal and study withdrawal was clarified.
- The window for study MRI scans was clarified; it was also clarified that the sites would not receive reports from the central MRI reading center.
- A requirement of blood samples in order to have baseline values for patients in Group D prior to first OCR dose was added.
- The assessment of protocol-defined relapses was clarified.
- A standardized questionnaire for the telephone interview was provided.
- The frequency of JC virus plasma sampling was increased.
- Procedures for sample analysis for suspected progressive multifocal leukoencephalopathy (PML) were provided.
- An exploratory investigation of patient-reported outcome (PRO) scales for potential implementation in Phase III was added.
- Retreatment criteria were provided.
- The requirement for clinical evaluations prior to re-dosing with OCR was clarified.
- Reporting of clinical relapses and secondary progressive MS as AEs was included.
- Consistent terminology for the grading of infusion reaction intensity was provided.

Protocol Version C (second amendment), dated 15 October 2011, introduced one change: the addition of an open-label extension period of the study following the treatment-free period. Results from the open-label extension period will be reported separately.

A local amendment in Canada (amendment to Protocol A) added the following stopping rule: “The risk/benefit of study treatment should be reassessed with the patient when sustained disability progression occurs, prior to any further dosing. Disability progression is defined as an increase of ≥ 1.0 point from the baseline EDSS when the baseline score is 5.0 or less, and ≥ 0.5 when the baseline score is 5.5 or more, that is not attributable to another etiology (e.g. fever, concurrent illness, or concomitant medication). Sustained

means that the increase is confirmed at a regularly scheduled visit at least 24 weeks after the initial documentation of the progression."

3.2 ADMINISTRATIVE STRUCTURE AND STUDY CONDUCT

3.2.1 Ethics

3.2.1.1 Local Regulations/Declaration of Helsinki

The investigator ensured that this study was conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. The study fully adhered to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline or with local law if it afforded greater protection to the patient. For studies conducted in the European Union/European Economic Area (EEA) countries, the Sponsor and the investigator ensured compliance with the European Union Clinical Trial Directive [2001/20/EC]. For studies conducted in the United States or under a U.S. Investigational New Drug (IND), the investigator also ensured adherence to the basic principles of "Good Clinical Practice" as outlined in the current version of 21 CFR, subchapter D, part 312, "Responsibilities of Sponsors and Investigators," part 50, "Protection of Human Patients," and part 56, "Institutional Review Boards."

In other countries where a "Guideline for Good Clinical Practice" exists, the Sponsor and the investigators strictly ensured adherence to the stated provisions.

3.2.1.2 Informed Consent

It was the responsibility of the investigator, or a person designated by the investigator (if acceptable by local regulations), to obtain signed informed consent from each patient prior to participating in this study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. For the patient not qualified or incapable of giving legal consent, written consent was obtained from the legally acceptable representative. In the case where both the patient and his/her legally acceptable representative were unable to read, an impartial witness was present during the entire informed consent discussion. After the patient and representative had orally consented to participation in the trial, the witness' signature on the form attested that the information in the consent form was accurately explained and understood. The investigator or designee also explained that the patients were completely free to refuse to enter the study or to withdraw from it at any time, for any reason. The case report forms (CRFs) for this study contained a section for documenting patient informed consent. It was obligatory to complete this document appropriately. If new safety information resulted in significant changes in the risk-benefit assessment, the consent form was reviewed and updated. All patients (including those already being treated) were informed of the new information, given a copy of the revised form and gave their consent to continue in the study. Models for informed consent forms (one for the United

States and one for the rest of the world) are provided from page 1921. A copy of a blank CRF is provided on page 1957.

3.2.1.3 Independent Ethics Committees/Institutional Review Boards

Independent Ethics Committees (IECs): For EEA member states, the Sponsor or its deputy/representative submitted to the Competent Authority and Ethics Committees the protocol and any accompanying material provided to the patient (such as patient information sheets or descriptions of the study used to obtain informed consent as well as any advertising or compensation given to the patient).

Approval from the committee was obtained before starting the study and was documented in a letter to the investigator specifying the date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of the IEC's approval were re-submitted by the investigator in the United States and by the Sponsor in the EEA member states in accordance with local procedures and regulatory requirements.

When no local review board existed, the investigator was expected to submit the protocol to a regional committee. If no regional committee existed, Roche assisted the investigator in submitting the protocol to the European Ethics Review Committee.

Institutional Review Boards (IRBs): It was the understanding of the Sponsor that this protocol (and any modifications) as well as appropriate consent procedures and advertisements, were reviewed and approved by an Institutional Review Board. This board must operate in accordance with the current Federal Regulations. The sponsor received a letter or certificate of approval prior to initiation of the study, and also whenever subsequent amendments/modifications were made to the protocol.

IEC and IRB details are provided on page 2870, the list of investigators is provided on page 2847, and the list of sites with complete addresses is provided on page 2860.

3.2.2 Audits

The Roche Clinical Quality Assurance group or designee conducted audits at three investigator sites. In addition, alliance partner Quintiles performed an internal process audit at Quintiles, Milan, Italy. Furthermore, co-development partner Genentech performed two investigator site audits.

No critical audit findings were observed. Appropriate corrective and preventive actions were undertaken for all audit findings. The audit certificate is provided on page 2998.

3.2.3 Data Quality Assurance

The overall procedures for quality assurance of clinical study data were described in the Sponsor's (or designee) Standard Operational Procedures.

Accurate and reliable data collection was ensured by verification and cross-check of the CRFs against the investigator's records by the study monitor (source document verification), and the maintenance of a drug-dispensing log by the investigator.

The data collected were entered into the study database from the working copy of the CRF faxed from the site. Laboratory values for tests conducted at the central laboratory were transferred from the central laboratory to the Sponsor.

A comprehensive validation check program verified the data and discrepancy reports were generated accordingly for resolution by the investigator. As patients completed the study (or prematurely withdrew) and their CRFs signed by the investigator became available, final checks were performed on these original CRFs. A comparison check was run to identify and resolve any discrepancies between the first and second data entry.

Throughout the study the Study Management Team reviewed data according to the SMT Data Review Plan as described in the Data Quality Plan.

3.3 SELECTION OF STUDY POPULATION

3.3.1 Overview

Men and women 18 to 55 years of age, inclusive, who were diagnosed with RRMS in accordance with the revised McDonald criteria [13] and met the eligibility criteria provided below were eligible for enrollment in the study. No patients who enrolled in this study were re-randomized to this study.

3.3.2 Inclusion Criteria

Patients must have met the following criteria to be eligible for study entry:

- ability to provide written informed consent and to be compliant with the schedule of protocol assessments
- diagnosis of RRMS in accordance with the revised McDonald criteria (2005)
- ages 18 to 55 years inclusive
- 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
- EDSS at baseline from 1.0 to 6.0 points
- evidence of MS disease burden as defined below:
    - At least six T2 lesions on an MRI scan done in the year prior to screening, based on local reading. Should an MRI scan be unavailable within the last year or showing less than six T2 lesions, a screening MRI scan with at least six T2 lesions is required for the patient to be eligible, OR
    - Patient had 2 documented relapses within the year prior to screening

- For sexually active female and male patients of reproductive potential, use of reliable means of contraception as described below as a minimum (adherence to local requirements, if more stringent, was required):
  - Two methods of contraception throughout the trial, including the active treatment phase AND for 48 weeks after the last dose of OCR, or until their B-cells have repleted, whichever was longer
  - Acceptable methods of contraception include one primary (e.g., systemic hormonal contraception or tubal ligation of the female partner, vasectomy of the male partner) AND one secondary barrier method (e.g., latex condoms, spermicide) OR a double barrier method (e.g., latex condom, intrauterine device, vaginal ring or pessary plus spermicide, e.g., foam, vaginal suppository, gel, cream)
- For patients of non-reproductive potential (adherence to local requirements, if more stringent, was required):
  - Women may have been enrolled if postmenopausal (i.e., spontaneous amenorrhea for the past year confirmed by a follicle-stimulating hormone (FSH) level $>$ 40 mIU/mL) unless the patient was receiving hormonal therapy for their menopause or surgically sterile.
  - Men may have been enrolled if they were surgically sterile (castration).

3.3.3 Exclusion Criteria

Patients who met the following criteria were excluded from study entry:

- secondary or primary progressive MS at screening (Visit 1)
- disease duration of $>$ 15 years in patients with an EDSS $\leq$ 2.0
- incompatibility with MRI (contraindications for MRI included but were not restrictive to known allergy to gadolinium contrast dyes, renal impairment that would contraindicate gadolinium injection, claustrophobia, weight $\geq$ 140 kg, pacemaker, cochlear implants, intracranial vascular clips, surgery within 6 weeks of entry into the study, coronary stent implanted within 8 weeks prior to the time of the intended MRI, etc.)
- contraindications to or intolerance of oral or iv corticosteroids, including methylprednisolone administered iv, according to the country label, including: psychosis not yet controlled by a treatment
- hypersensitivity to any of the constituents
- Known presence of other neurologic disorders, including but not limited to, the following:
  - history of ischemic cerebrovascular disorders (e.g., stroke, transient ischemic attack) or ischemia of the spinal cord
  - history or known presence of CNS or spinal cord tumor (e.g., meningioma, glioma)

- history or known presence of potential metabolic causes of myelopathy (e.g., untreated vitamin B12 deficiency)
- history or known presence of infectious causes of myelopathy (e.g., syphilis, Lyme disease, human T-lymphotropic virus (HTLV-1), herpes zoster myelopathy)
- history of genetically inherited progressive CNS degenerative disorder (e.g., hereditary paraparesis; mitochondrial myopathy, encephalopathy, lactacidosis, stroke [MELAS] syndrome)
- neuromyelitis optica
- history or known presence of systemic autoimmune disorders potentially causing progressive neurologic disease (e.g., lupus, anti-phospholipid antibody syndrome, Sjogren's syndrome, Behcet's disease)
- history or known presence of sarcoidosis
- history of severe, clinically significant brain or spinal cord trauma (e.g., cerebral contusion, spinal cord compression)
- history of PML

- Exclusions Related to General Health:
  - pregnancy or lactation
  - lack of peripheral venous access
  - history of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies
  - significant, uncontrolled disease, such as cardiovascular (including cardiac arrhythmia), pulmonary (including obstructive pulmonary disease), renal, hepatic, endocrine, or gastrointestinal
  - congestive heart failure (New York Heart Association III or IV functional severity)
  - known active bacterial, viral, fungal, mycobacterial infection or other infection (including tuberculosis or atypical mycobacterial disease [but excluding fungal infection of nail beds]) or any major episode of infection requiring hospitalization or treatment with iv antibiotics within 4 weeks prior to screening (visit 1) or oral antibiotics within 2 weeks prior to screening (visit 1)
  - history or known presence of recurrent or chronic infection (e.g., hepatitis B or C, human immunodeficiency virus [HIV], syphilis, tuberculosis)
  - history of cancer, including solid tumors and hematologic malignancies (except basal cell, in situ squamous cell carcinomas of the skin, and in situ carcinoma of the cervix or the uterus that had been excised and resolved)
  - history of alcohol or drug abuse within 24 weeks prior to randomization
  - history of or currently active primary or secondary immunodeficiency
  - history or laboratory evidence of coagulation disorders

- Exclusions Related to Medications:
  - treatment with any investigational agent within 4 weeks of screening (visit 1) or five half-lives of the investigational drug (whichever was longer)
  - receipt of a live vaccine within 6 weeks prior to randomization
- Exclusions Related to Medications Potentially Used for the Treatment of MS:
  - Incompatibility with Avonex use, including:
  - prior history of severe depression and/or suicidal behavior in the 12 months prior to screening
  - prior cessation of Avonex therapy due to poor tolerability or inadequate efficacy
  - prior cessation of Avonex due to toxicity, which was likely to recur
  - hypersensitivity to Avonex
  - previous history of inadequate response to IFN-β as judged by the investigator
  - history of hypersensitivity to human serum albumin
  - previous treatment with rituximab
  - previous treatment with lymphocyte-depleting therapies (e.g., Campath, anti-CD4, cladribine, cyclophosphamide, total body irradiation, bone marrow transplantation), except mitoxantrone, which should not be used within 48 weeks prior to randomization
  - treatment with lymphocyte trafficking blockers (e.g., natalizumab, FTY720) within 24 weeks prior to randomization
  - treatment with IFN-β, glatiramer acetate, iv Ig, plasmapheresis, or immunosuppressive therapies (e.g., mycophenolate mofetil [MMF], cyclosporine, or azathioprine) within 12 weeks prior to randomization
  - systemic corticosteroid therapy within 4 weeks prior to randomization
- Exclusions Related to Laboratory Findings:
  - positive serum β-human chorionic gonadotropin (β-hCG) measured at screening
  - vitamin B12 below the lower limit of normal
  - positive screening tests for hepatitis B (hepatitis B surface antigen [HBsAg] positive, or positive hepatitis B core antibody [total HBcAb]) confirmed by a positive viral DNA polymerase chain reaction) or hepatitis C (HepCAb)
  - positive rapid plasma reagin
  - findings consistent with conditions other than MS noted on screening MRI scan obtained as required
  - CD4 cell count < 300/μL
  - serum creatinine > 1.4 mg/dL (> 124 μmol/L) for women or > 1.6 mg/dL (> 141 μmol/L) for men
  - aspartate aminotransferase (AST/SGOT) or alanine aminotransferase (ALT/SGPT) ≥ 2.0 upper limit of normal (ULN)

- platelet count < 100,000/μL (< 100 × 109/L)
- hemoglobin < 8.5 g/dL (< 5.15 mmol/L)
- total neutrophil count < 1.5 × 103/μL
- serum IgG < 5.65 g/L or IgM < 0.55 g/L

In addition, for selected patients, or selected centers based on local Ethics Committees or country Health Authority requirements, additional diagnostic testing may have been required to exclude tuberculosis (e.g., chest X-ray, tuberculin skin or blood test), Lyme disease, HTLV-1–associated myelopathy (HAM), acquired immune deficiency syndrome (AIDS), hereditary disorders, connective tissue disorders, or sarcoidosis. Additional tests were requested when the investigator judged that these specific diagnostic tests were required.

These additional tests may have been locally required to decide if a patient was suitable for the study and were done upon agreement with the Medical Monitor. Results were collected locally and kept in the patient's file, but not recorded on the CRF.

In certain circumstances, and upon agreement with the Medical Monitor, patients were allowed to be screened a second time (e.g., if a patient experienced an infection during the 4-week screening period).

3.3.4 Criteria for Withdrawal from Treatment or Study and Replacement Policy

Patients had the right to withdraw from the study at any time for any reason.

Patients who decided to prematurely discontinue study treatment ("refuses treatment") were asked if they could still be contacted for further information. The outcome of that discussion was documented both in the medical records and on the CRF. If lost to follow-up, the investigator contacted the patient or a responsible relative by telephone followed by registered mail or through a personal visit to establish as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient's withdrawal was made with an explanation of why the patient was withdrawing from the study.

Patients were informed of circumstances under which their participation may have been terminated by the investigator without the patient's consent. The investigator may have withdrawn patients from the study in the event of intercurrent illness, AEs, or treatment failure, after a prescribed procedure, for lack of compliance with the study and/or study procedures (e.g., dosing instructions, study visits), cure, or if it was felt by the investigator that it was in the best interest of the patient to be withdrawn from the study. Any reasons for withdrawal, administrative or other, were documented and explained to the patient. If the reason for removal of a patient from the study was an AE, the principal specific event was recorded on the CRF. The patient was followed until the AE had resolved, if possible.

An excessive rate of withdrawals can render a study non-interpretable; therefore, unnecessary withdrawal of patients was avoided. If a patient decided to withdraw, all efforts were made to complete and report the observations as thoroughly as possible prior to withdrawal.

It was important to distinguish between "withdrawal from treatment" and "withdrawal from study." Patients who withdrew from treatment were encouraged to remain in the study for the full duration of the Treatment-Free Period (minimum of 48 weeks).

Patients were required to be withdrawn from treatment under the following circumstances:

- Grade 4 infusion reaction
- pregnancy during the study
- active hepatitis B or C infection, either new onset or reactivation in the case of hepatitis B
- evidence of PML

3.3.5 Concomitant Medication, Treatments, and Procedures

3.3.5.1 Definitions

A concomitant medication was any drug or substance (including over-the-counter medications) taken during the study (including the screening period). This included any preventative vaccines (e.g., tetanus or flu vaccines) received during the course of this study. A concomitant procedure was any therapeutic or elective intervention (e.g., surgery, biopsy) or diagnostic evaluation (e.g., blood gas measurements, bacterial cultures) performed during the study (including the Screening Period).

Concomitant medications and procedures were reported at each visit on the relevant CRFs, starting with the baseline visit (for medications and procedures taken between screening and baseline), with the exception of medications taken for the treatment of MS, which were provided for the 2-year period prior to the baseline visit.

3.3.5.2 Treatment of MS and its Symptoms

The investigator attempted to maintain therapies or treatments for symptoms related to MS (e.g., spasticity, incontinence, pain, fatigue) reasonably constant throughout the study. However, changes may have been made if appropriate for a patient's well-being according to the clinical judgment of the treating investigator.

Therapies for MS noted in the exclusion criteria "Exclusions Related to Medications Potentially Used for the Treatment of MS" were NOT permitted during the study treatment period with the exception of systemic corticosteroids for the treatment of a relapse.

Patients who experienced a relapse may have received treatment with IV methylprednisolone or oral corticosteroids, if judged to be clinically appropriate by the investigator. The following standardized treatment regimen was used as warranted: methylprednisolone 1 g/day iv for a maximum of 5 consecutive days. In addition, at the discretion of the investigator, corticosteroids could be stopped abruptly or tapered over a maximum of 10 days.

Patients who completed the Treatment Period or withdrew may have received alternative treatment for MS as judged clinically appropriate by the treating investigator.

3.3.5.3 Immunization

Physicians reviewed the immunization status of patients being considered for treatment with OCR and were recommended to follow local/national guidance for adult vaccination against infectious disease. Immunization should have been completed ≥ 6 weeks prior to the first administration of OCR.

Patients who required de novo hepatitis B vaccination (which involves three separate doses of vaccine) should have completed the course ≥ 6 weeks prior to the first infusion of study drug.

Immunization with any live or live-attenuated vaccine (i.e., measles, mumps, rubella, oral polio vaccine, Bacille Calmette-Guerin, typhoid, yellow fever, vaccinia, cold adapted live influenza strain vaccine, or any other vaccines not yet licensed but belonging to this category) was not permitted within 6 weeks of first dosing, during OCR treatment, and for as long as the patient's B-cells were depleted.

Patients who were eligible for a yearly influenza vaccine or who required immunizations or boosters for other diseases could have received immunization with killed/toxoid vaccines consistent with normal clinical practice. The effect of OCR on the response to immunization is not known; patients receiving OCR may not mount a humoral response to recall antigens during B-cell depletion.

The investigator reviewed the patients' immunization history and vaccination status. Known dates of immunizations were recorded on specific CRF pages.

3.4 STUDY TREATMENTS

3.4.1 Dosage and Administration

Patients were randomly assigned to OCR at one of two dose levels, placebo, or Avonex:

- **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).

The dosing regimen for each treatment group is further detailed in Table 1. The first IV infusion of OCR or placebo, or the first IM injection of Avonex, was administered on Day 1.

To reduce potential infusion reactions, all patients received prophylactic treatment with methylprednisolone 100 mg, administered by slow IV infusion on Day 1 and with each subsequent OCR or placebo infusion. The infusion was to be completed approximately 30 minutes before the start of each OCR or placebo infusion.

To avoid any bias in the efficacy assessment, patients in Group D (Avonex) received the same regimen of methylprednisolone during the first treatment cycle as patients receiving OCR or placebo: two slow IV infusions of 100 mg on Day 1 and Day 15.

3.4.1.1 Administration of the OCR and Placebo Infusions

Patients in Group D received open-label study drug material (Avonex and OCR). OCR vials for Groups A, B, and C were provided as double-blind study material such that all study team members (study physicians including the treating and the examining investigators, pharmacist, nursing, and technical staff) remained blinded to the dose of OCR. The study drug infusions were always administered in a hospital or clinic environment under close supervision of the investigator or a medically qualified staff member with immediate availability of full resuscitation facilities. OCR infusions were given as a slow IV infusion. It was not to be administered as an IV push or bolus. Infusion pumps were used to control the infusion rate, and the study drug was infused through a dedicated line. It was important not to use evacuated glass containers (to prepare the infusion), which required vented administration sets because this causes foaming as air bubbles pass through the solution. The drug supplied was sterile.

After completion of the infusion, the IV cannula remained in situ for ≥ 1 hour in order to be able to administer drugs intravenously, if necessary in the event of a delayed reaction. If no AEs occurred during this period of time, the IV cannula was removed and the patient was discharged.

3.4.1.2 Administration of Avonex

The first IM injection of Avonex was administered on Day 1. Patients were instructed in the use of aseptic techniques and how to self-administer the injections by a nurse or physician. The first dose of Avonex was self-administered under the supervision of a nurse or physician. Thereafter, patients self-administered their Avonex treatment weekly without supervision of a nurse or physician. Patient understanding and use of aseptic self-injection techniques and procedures was periodically re-evaluated.

Note that patients randomized to Group D (Avonex) received a slow infusion of methylprednisolone at the time points corresponding to the OCR (or matching placebo) infusions during the Cycle 1.

3.4.2 Formulation and Packaging

The hospital units/pharmacy received a study medication package for each patient containing one box of Avonex lyophilized powder vials (4-week supply) or six single-use liquid vials with OCR and/or placebo. Re-supply of study medication packages was requested via the IVRS.

OCR is manufactured by Genentech Inc. as a sterile, clear, colorless, preservative-free liquid intended for dilution for iv administration.

OCR was supplied as a liquid formulation containing 30 mg/mL OCR in 20 mM sodium acetate at pH 5.3, with 4% trehalose and 0.02% polysorbate 20. The drug product was provided as a single-use liquid formulation in a 15-cc Type I USP glass vial, fitted with a 20-mm fluoro-resin laminated stopper and an aluminum seal with a flip-off plastic cap. Each vial contained a nominal 200 mg of OCR. No preservative was used, as each vial was designed for single use.

OCR drug product was diluted before administration. Solutions of OCR for IV administration were prepared by dilution of the drug product into an infusion bag containing 0.9% sodium chloride, to a final drug concentration of 0.7 to 2 mg/mL.

OCR-matching placebo was also supplied in 15-cc single-use vials. Placebo had the same composition and configuration as the drug product, but did not contain OCR. OCR placebo solutions for IV administration were prepared by dilution of the OCR placebo into infusion bags containing 0.9% sodium chloride, using an identical procedure as for the drug product.

Avonex was supplied as a sterile, white to off-white lyophilized powder for IM injection after reconstitution with the supplied diluent (Sterile Water for Injection, USP). Each vial of reconstituted Avonex contained 30 µg of IFN-β-1a.

The batch numbers and formulation numbers used in this study are provided below:

Product	Formulation Number	Batch Numbers
Ocrelizumab and placebo	496-4913/F03 and 496-4913/F04	N42896/700899, 704871/705811, 705811/702587, 705811/700899, 705811/705812, 702587/737946, 741027/705811, 741027/737952, 741027/765297, 705812/765297, 775629/781639, 741027/775629, 781639/805672
Avonex	529-0221	070275AR, 080185A, P01112, 080440A, 080499A, P01105, 080185A

3.4.3 Rationale for Dosage Selection

To ensure initial B-cell depletion and avoid early production of human anti-humanized antibodies (HAHA), a dual infusion of OCR was administered for the first treatment cycle. Thereafter, a single infusion of OCR was administered.

The selection of the 1000 mg × 2 OCR dose regimen was based on the two RRMS studies (U2787g and U3426g) conducted with rituximab in which two doses of rituximab 1000 mg, administered on Days 1 and 15 (i.e., as a dual infusion), were shown to be effective in reducing gadolinium-enhancing T1 lesions and the proportion of patients with relapses. Retreatment with OCR 1000 mg was administered as a single infusion, as this was anticipated to adequately deplete any newly formed B-cells (6 months after initial dosing with a dual infusion in Study U2787g, B-cell recovery [≥ 20 $CD19^+$ cells/µL] was evident in approximately 20% of RRMS patients, of which half had repleted to levels ≥ 40 $CD19^+$ cells/µL). A greater interval between dosing may result in loss of efficacy. In Study U2787g, it appeared that relapses recurred in rituximab-treated patients 9 to 12 months after a single treatment cycle with a dual infusion.

The 300 mg × 2 OCR dose regimen consisted of two individual infusions of 300 mg on days 1 and 15 (i.e., 600 mg) followed by 600 mg administered as a single infusion for subsequent 24-week treatment cycles. The selection of a dual infusion of OCR 300 mg was based on Study ACT2847, in which patients with rheumatoid arthritis treated with OCR doses of 200 mg IV given as a dual infusion demonstrated peripheral B-cell depletion and clinical efficacy with little or no evidence of HAHA response [14]. The 300 mg × 2 (or 600 mg) dose regimen was selected for this study because of concerns that a lower dose may not adequately deplete B-cells in the CNS of MS patients, which may be important for generating therapeutic efficacy. Safety advantages were also anticipated with this lower dose, as infusion reactions have been shown to be dose related. In addition, the risk of infections may be lower with this dose. Thus, the selected 300 mg × 2 dose regimen was anticipated to be the lowest dose in this study that would still show clinical efficacy.

3.4.4 Method of Treatment Assignment

Approximately 200 patients were to be randomized across the four treatment groups (approximately 50 patients per group). The treatment allocation was pre-assigned using the IVRS. Randomization code is provided on page 2840.

To ensure enrollment in a reasonable timeframe, it was anticipated that approximately 100 sites would be initiated. As the number of patients at each site may have been smaller than the number of treatment groups, stratified randomization by site was not advisable since it may have led to a substantial imbalance between the treatment groups. Instead, stratified randomization by geographic region was employed in order to balance treatment allocation across regions.

No replacement was planned for patients who withdrew from the study after randomization.

3.4.5 Blinding

In this partially blinded study, the randomization list was not available to the study centers, monitors, project statisticians, or Sponsor's project team. All individuals directly involved in this study remained blinded to the dose of OCR until the analysis of the primary parameter at week 24. Unblinding of the OCR doses should not have occurred except in emergency situations in which the identity of the study medication was necessary for patient management in the case of an SAE. Avonex was rater-blinded only.

Emergency codes were to be broken only when knowledge of the treatment was essential for the further emergency management of the patient. The Principal Investigator should have made every attempt to contact the Sponsor before unblinding any patient's treatment assignment, but must have contacted the Sponsor within 1 working day after the event.

Any request from the investigator for information regarding the OCR dose administered to a patient for another purpose was to be discussed with the Sponsor.

Unblinding of the OCR doses for ongoing safety monitoring by an independent Data Monitoring Committee (DMC) was performed according to procedures in place to ensure integrity of the data. Further details are described on page 1844.

Furthermore, to avoid unblinding of the OCR doses, investigators did not receive reports on MRI readings from the central MRI reading center or reports on laboratory parameters that could have unblinded the treatment regimens.

To facilitate analysis of the biologic samples collected in this study, the treatment code was released to the responsible analytical person when the samples were received at the analytical site and were ready for assay. The results of the analysis were not released with individual identification of the patient until the database was closed.

The password-protected and/or encrypted electronic Master Randomization List was kept by Clinical Supply in their secure system and was accessible only to the Randomization List Managers.

Beginning with Cycle 2, patients and investigators knew that all patients were receiving active drug (OCR).

3.4.6 Criteria for Dose Modification or Withdrawal from Treatment

No dose modifications of OCR were foreseen.

3.4.7 Treatment Accountability and Compliance

Accountability and patient compliance were assessed by maintaining adequate drug dispensing and return records. The pharmacists kept all drug vials to measure compliance.

Patients in Group D (Avonex) were asked to return all used and unused drug supply containers at each visit during the Cycle 1 as a measure of compliance.

3.5 CONCOMITANT MEDICATIONS

3.5.1 Definitions

A concomitant medication was any drug or substance (including over-the-counter medications) taken during the study (including the screening period). This included any preventative vaccines (e.g., tetanus or flu vaccines) received during the course of this study. A concomitant procedure was any therapeutic or elective intervention (e.g., surgery, biopsy) or diagnostic evaluation (e.g., blood gas measurements, bacterial cultures) performed during the study (including the Screening Period).

Concomitant medications and procedures were reported at each visit on the relevant CRFs, starting with the baseline visit (for medications and procedures taken between screening and baseline), with the exception of medications taken for the treatment of MS, which were provided for the 2-year period prior to the baseline visit.

3.5.2 Treatment of MS and its Symptoms

The investigator attempted to maintain therapies or treatments for symptoms related to MS (e.g., spasticity, incontinence, pain, fatigue) reasonably constant throughout the study. However, changes may have been made if appropriate for a patient's well-being according to the clinical judgment of the treating investigator.

Therapies for MS noted in the exclusion criteria "Exclusions Related to Medications Potentially Used for the Treatment of MS" were NOT permitted during the study treatment period with the exception of systemic corticosteroids for the treatment of a relapse.

Patients who experienced a relapse may have received treatment with iv (methylprednisolone) or oral corticosteroids, if judged to be clinically appropriate by the investigator. The following standardized treatment regimen was used as warranted: methylprednisolone 1 g/day iv for a maximum of 5 consecutive days. In addition, at the discretion of the investigator, corticosteroids could be stopped abruptly or tapered over a maximum of 10 days.

Patients who completed the Treatment Period or withdrew may have received alternative treatment for MS as judged clinically appropriate by the treating investigator.

3.5.3 Immunization

Physicians reviewed the immunization status of patients being considered for treatment with OCR and were recommended to follow local/national guidance for adult vaccination against infectious disease. Immunization should have been completed ≥ 6 weeks prior to the first administration of OCR.

Patients who required de novo hepatitis B vaccination (which involves three separate doses of vaccine) should have completed the course ≥ 6 weeks prior to the first infusion of study drug.

Immunization with any live or live-attenuated vaccine (i.e., measles, mumps, rubella, oral polio vaccine, Bacille Calmette-Guerin, typhoid, yellow fever, vaccinia, cold adapted live influenza strain vaccine, or any other vaccines not yet licensed but belonging to this category) was not permitted within 6 weeks of first dosing, during OCR treatment, and for as long as the patient's B-cells were depleted.

Patients who were eligible for a yearly influenza vaccine or who required immunizations or boosters for other diseases could have received immunization with killed/toxoid vaccines consistent with normal clinical practice. The effect of OCR on the response to immunization is not known; patients receiving OCR may not mount a humoral response to recall antigens during B-cell depletion.

The investigator reviewed the patients' immunization history and vaccination status. Known dates of immunizations were recorded on specific CRF pages.

3.6 ASSESSMENTS

3.6.1 Clinical Assessments

This study included the three study periods described below and assumed 24-weeks' duration for the B-Cell Monitoring Period. The following three study periods were applicable to all patients:

- Screening Period: up to 4 weeks

- Treatment Period: all patients underwent 96 weeks of study treatment, representing four 24-week treatment cycles. In the case of Avonex-treated and placebo patients, this included time on the originally randomized treatment and time on OCR.
- Treatment-free Period: a 24-week follow-up period, a B-cell monitoring period of variable duration, and a 24-week observation period. All patients entered the 24-week follow-up period after the last OCR treatment cycle, and the 24-week observation period, once B-cells were repleted, either at the end of the follow-up period or at the end of the B-cell monitoring period.

The schedule of assessments for the first 24-week study period is shown in Table 2.

Table 2 Schedule of Assessments and Procedures: Screening Through the end of the Follow-up Period

	Screen	*Baseline*		First Treatment Cycle (24 weeks)					Avonex F/U Contact[15]
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	
Week	***-4 to -1***		***2***	***4***	***8***	***12***	***16***	***20***	*24*	
Study day (visit window in days)	-28 to -1	1	15 (± 1)	29 (±4)	57 (± 4)	85 (±4)	113 (±4)	141 (±4)	169 (±4)	
Informed consent	x									
Medical history	x									
Review inc/excl criteria	x	x								
Physical examination	x	x	x						x	
Vital signs[1]	x	x	x	x	x				x	
12 lead ECG	x								x	
Height	x									
Weight	x								x	
Pregnancy test[2]	x	x	x			x			x	
Thyroid function tests[3]	x									
FSH[4]	x									
Serum Vit B12	x									
Hepatitis screening[5]	x									
Hepatitis B virus DNA[5]	x					x			x	
RPR, CD4 count	x									
Total Ig, IgA, IgG, IgM	x								x	
FACS[6]		x	x	x	x	x			x	
Routine safety lab[7]	x	x				x			x	
Patient-reported outcomes[21]		x							x	
Potential relapses recorded	x	x	x	x	x	x	x	x	x	

Table 2 Schedule of Assessments and Procedures: Screening Through the end of the Follow-up Period (cont.)

	Screening	*Baseline*	First Treatment Cycle (24 weeks)							Avonex F/U Contact[15]
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	
Week	***-4 to -1***		***2***	***4***	***8***	***12***	***16***	***20***	***24***	
Study day (window in days)	-28 to -1	1	15 (± 1)	29 (±4)	57 (± 4)	85 (±4)	113 (±4)	141 (±4)	169 (±4)	
EDSS and neurological examination	x	x				x			x	
MRI[8]	x	x		x	x	x	x	x	x	
Adverse events		x	x	x	x	x	x	x	x	x
Concomitant Treatment		x	x	x	x	x	x	x	x	x
Clinical genotyping[9]		x								
BSR/BRS (optional)[10]		x		x					x	
Pre-treatment with i.v. methyl-pred.[11]		x	x						x	
Drug (ocrelizumab /placebo) administration		x	x						x	
Group D										
Avonex compliance			x	x	x	x	x	x	x	
Antibodies[12]									x[20]	
HAHA[13]									x[20]	
Sample for JCV[19]									x[20]	
Groups A, B and C										
Antibodies[12]		x				x			x	
HAHA[13]		x				x			x	
Pharmacokinetic samples		x[14]	x[14]	x	x	x	x	x	x[14]	
Sample for JCV[19]		x							x	

Table 2 Schedule of Assessments and Procedures: Screening Through the end of the Follow-up Period (cont.)

	2nd to 4th Treatment Cycles							Follow Up Period		With-drawal WD	Del. Dosing Visit[17]	Unsched.Visit (Non-Dosing) [18]
Visit	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**			
Week	*26*	*36*	*48*	*60*	*72*	*84*	*96*	*108*	*120*			
Study Day (window in days)	183 (±1)	253 (± 14)	337 (± 14)	421 (± 14)	505 (± 14)	589 (± 14)	673 (± 14)	756 (± 14)	840 (± 14)			
Physical examination	x		x		x		x		x	x	x	
Vital signs[1]	x		x		x		x		x	x	x	
12 lead ECG			x				x		x	x		
Weight			x				x		x	x		
Pregnancy test[2]	x	x	x	x	x	x	x	x	x	x	x	
Hepatitis B virus DNA[5]		x	x	x	x	x	x					
Thyroid function tests[3]			x				x		x	x		
Total Ig, IgA, IgG, IgM			x		x		x		x	x		
FACS[6]			x		x		x	x	x	x		
Routine safety lab[7]		x	x	x	x	x	x	x	x	x		
Patient reported outcome[21]			x									
Potential relapses recorded	x	x	x	x	x	x	x	x	x	x		
EDSS and neurologic examination		x	x	x	x	x	x	x	x	x		
Telephone interview recorded[16]		x	x	x	x	x	x	x	x	x		
MRI[8]							x[8]			x[8]		
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant treatment	x	x	x	x	x	x	x	x	x	x	x	x
Pre-treatment with iv methylprednisolone[11]	x		x		x						x	
Drug (OCR/placebo) administration	x		x		x						x	
Antibodies[12]			x		x		x		x	x		
HAHA[13]		x	x	x	x	x	x	x	x	x		
Sample for JCV[19]		x	x	x	x	x	x	x	x	x		

Table 2 Schedule of Assessments and Procedures: Screening Through the end of the Follow-up Period (cont.)

1. Vital signs were obtained while the patient was in the semi-supine position (after 5 minutes), i.e., pulse rate, systolic and diastolic blood pressure, respiration rate, and temperature. On infusion visits, vital signs were taken within 45 minutes prior to the methylprednisolone infusion in all patients. In addition, for patients receiving OCR or placebo, vital signs were obtained prior to study drug infusion, then every 15 minutes (± 5 minutes) for the first hour, and then every 30 minutes (± 10 minutes) until 1 hour after the end of the infusion. On non-infusion days, vital signs could be taken at any time during the visit.
2. Serum β-hCG had to be measured at screening in women of childbearing potential. Subsequently, a urine β-hCG (sensitivity of ≥ 25 mIU/mL) was obtained. On infusion visits, the urine pregnancy test was performed prior to methylprednisolone infusion in all women of child-bearing potential. If positive, the dose was held and results were confirm with a serum pregnancy test.
3. sTSH was tested at screening, yearly during the treatment period, and at the end of the follow-up period. Anti-thyroid antibodies were assayed only at screening.
4. FSH: FSH only applicable to women to confirm the post-menopausal status.
5. Hepatitis screening and monitoring: all patients must have had negative HBsAg result and negative HepCAb screening tests prior to enrollment. If total HBcAB was positive at screening, HB virus DNA measured by polymerase chain reaction must have been negative to be eligible. For those patients enrolled with negative HBsAg and positive total HBcAb, HB virus DNA (polymerase chain reaction) had to be repeated every 12 weeks during the treatment period (up to 24 weeks after the last OCR infusion).
6. FACS: including CD19 and other circulating B-cell subsets, T cells, natural killer cells, and other leukocytes. On the infusion days (days 1 and 15) of Cycle 1, two blood samples should be collected, one prior to the methylprednisolone infusion, and the second 30 minutes (± 10 minutes) following the completion of the OCR/placebo infusion. For all other infusion visits, a blood sample was taken before the methylprednisolone infusion. At other times (non-infusion visits), samples may have been taken at any time during the visit.
7. Routine safety labs. Hematology, chemistry, and urinalysis: On infusion visits, all urine and blood samples were collected prior to the infusion of methylprednisolone. At other times, samples may have been taken at any time during the visit.

Table 2 Schedule of Assessments and Procedures: Screening Through the end of the Follow-up Period (cont.)

8. MRI scans included a T2 and T1 scan (with and without gadolinium enhancement) and were performed at screening in some patients and in all patients at baseline (with a window of up to 3 days prior to visit 2) and every 4 weeks for the first 24 weeks, except if patients were receiving corticosteroids for a relapse. In the latter case, every effort was made to obtain the scan prior to the first corticosteroid dose, if within 1 week of the next scheduled MRI. A regularly scheduled MRI was NOT to be done if the interval between the last dose of corticosteroid treatment and the scan was < 3 weeks. For patients withdrawing from treatment during Cycle 1, the MRI was performed at the withdrawal visit unless available in the prior 3 weeks. If the Week 24 (visit 9) MRI scan needed to be repeated, the scan was to be repeated within 4 weeks of visit 9. In addition, in a subgroup of patients (Groups A and B), a brain MRI scan was performed at weeks 96 (visit 16) and 48 weeks later, i.e., week 144 (± 4 weeks).
9. Clinical genotyping: If not done at baseline (visit 2), could be re-scheduled at next visit (visit 3).
10. BSR (Biomarker Sample Repository)/BRS (Biomarker Research Samples): plasma and whole blood samples to be taken from consenting patients for protein and RNA biomarker analyses. On infusion visits, samples were taken prior to methylprednisolone infusion.
11. All patients received prophylactic treatment with 100 mg of methylprednisolone administered by slow iv infusion to be completed approximately 30 minutes prior to the infusion of OCR or matching placebo (or at similar time points for patients in Group D). It was also recommended that the OCR or placebo infusion be accompanied by prophylactic treatment with acetaminophen/paracetamol (1 g) and antihistamine (iv diphenhydramine 50 mg; or equivalent dose of alternative) 30 to 60 minutes prior to the start of an infusion.
12. Antibodies: Included antibodies against mumps, rubella, varicella, S. pneumoniae, and Epstein-Barr virus.
13. HAHA: On infusion visits, samples were collected prior to the methylprednisolone infusion. During Cycle 1, one sample was needed. Thereafter, two samples were collected.
14. Pharmacokinetic samples were taken only during Cycle 1, at each visit, from visit 2 to visit 9. On dosing visits (visits 2, 3, and 9), pharmacokinetic samples were taken 5 to 30 minutes prior to methylprednisolone infusion. On dosing visits 2 and 3, pharmacokinetic samples were also taken 30 minutes (± 10 minutes) after the end of the OCR/placebo infusion.
15. Avonex follow-up contact: a telephone follow-up contact was scheduled 15 to 30 days after the last visit for patients in Group D who either completed the study at week 24 and who did not wish to start OCR treatment, or who withdrew from Avonex treatment during Cycle 1. A site visit could have also been scheduled if further investigations was needed (for example, additional examinations or laboratory tests).

Table 2 Schedule of Assessments and Procedures: Screening Through the end of the Follow-up Period (cont.)

16. A telephone interview was done on a 4-week basis between visit 9 (24 weeks) through visit 18 (120 weeks) to identify any new or worsening neurologic symptoms that warranted an unscheduled visit.
17. A delayed dosing visit was performed and recorded on the Delayed Dosing Visit CRF when the dose could not be administered at the scheduled dosing visit. Other tests/assessments may have been done as appropriate.
18. Unscheduled visit (non-dosing): Assessments performed at unscheduled (non-dosing) visits depended on the clinical needs of the patient. Other tests/assessments may have been done as appropriate. Unscheduled visits may have also taken place during the Treatment-Free Period (Follow-Up, B-Cell Monitoring, or Observation Periods)
19. Plasma samples for JC virus, were collected at visits 2, 9, 11 to 18, and withdrawal visit and also if PML was suspected.
20. Prior to first OCR dosing in those patients who wished to remain in the study.
21. Patient-reported outcome scales included the CES-D, MFIS, and MSFC (in countries where translations were available).

3.6.2 Pharmacokinetic Assessments

Blood samples were collected in patients randomized to OCR or placebo (Group A, B, or C) to evaluate the pharmacokinetics of OCR.

One of the secondary outcome measures for this study was the assessment of the pharmacokinetics of OCR based on serial samples taken before and after dosing. Serum samples were collected in the first treatment cycle for determination of OCR concentrations 5 to 30 minutes prior to the methylprednisolone infusion and 30 minutes ($\pm$10 minutes) following infusion of OCR, as well as at the time points detailed in Table 2. During the first 24 weeks of the Treatment Period (first cycle), patients had 10 samples collected for pharmacokinetic assessment. The total blood volume collected for pharmacokinetic assessments was approximately 35 mL. These samples were assayed for OCR concentration using an enzyme-linked immunosorbent assay (ELISA) at Genentech.

3.7 STUDY PARAMETERS

3.7.1 Efficacy Parameters

Brain MRI scans were obtained at baseline and at 4-week intervals between baseline and week 24. In addition, in a subgroup of patients (Groups A and B), a brain MRI scan was obtained at weeks 96 and 144.

The MRI included the acquisition of the following scans at each time point:

- T2-weighted MRI scan
- T1-weighted MRI scan (without gadolinium enhancement)
- T1-weighted MRI scan (with gadolinium enhancement)

MRI scans were read by a centralized reading center (MS/MRI Research Group, University of British Columbia, 2386 East Mall, Suite 211, Gerald McGavin Building, Vancouver, BC, V6T 1Z3, Canada). The MRI protocol is provided on page 1530. The centralized reading center was blinded to the treatment assignment, and the reading was performed in the absence of clinical information. All MRI scans were also reviewed locally by a radiologist for safety.

Relapse was defined as the occurrence of new or worsening neurologic symptoms attributable to MS and immediately preceded by a relatively stable or improving neurologic state of $\geq$ 30 days. Symptoms must have persisted for $>$24 hours and should not have been attributable to confounding clinical factors (e.g., fever, infection, injury, adverse reactions to concomitant medications). The new or worsening neurologic symptoms must have been accompanied by objective neurologic worsening consistent with an increase of at least half a step on the EDSS, or 2 points on one of the appropriate Functional System Scores (FSS), or 1 point on two or more of the appropriate FSS (see Appendix 3 of the protocol, page 1687). The change must have affected the selected FSS (i.e., pyramidal, gait, cerebellar, brainstem, sensory, or visual).

Sensory changes, episodic spasms, fatigue, mood change, or bladder or bowel urgency or incontinence were not sufficient to establish a relapse.

3.7.1.1 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.

3.7.1.2 Secondary Efficacy Parameters

Secondary endpoints were as follows:

- Annualized 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 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.

3.7.2 Pharmacodynamic and Pharmacokinetic Parameters

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.

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 ($CD19^+$ $CD38^{lo}$ $CD27^+$), plasma cells ($CD19^{lo}$ $CD38^{hi}IgD^-$ $CD27^+$), mature naive B cells ($CD19^+$ $CD21^+$ IgM^+, IgD^+), regulatory T cells ($CD3^+$ $CD4^+$ $CD127^{lo}$ $CD25^{hi}$), and memory cytotoxic T cells ($CD3^+$ $CD8^+$ $CD45RO^+$). Serum immunoglobulin (Ig, IgG, IgA and IgM) levels were also measured.

CD19 rather than CD20 was used as a surface B-cell marker in flow-cytometry to avoid false negatives due to interference by OCR bound to CD20 with CD20-specific detection reagents.

3.7.3 Safety Parameters

Safety was assessed through the occurrence of 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.

The study complied with all local regulatory requirements and adhered to the full requirements of the *ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2*.

3.7.3.1 Clinical Adverse Events

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, including an abnormal laboratory finding, symptom, or disease temporally associated with the use of a (investigational) medicinal product, whether or not considered related to the medicinal (investigational) product. Preexisting conditions that worsen during a study were reported as AEs.

Clinical relapses were evaluated both in the efficacy and safety analyses. Each clinical relapse was recorded as an AE. Although defined retrospectively, evolution of RRMS to secondary progressive MS was also recorded as an AE in the CRF.

B-cell depletion was the expected outcome of OCR treatment and was not an AE.

Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 3.

Adverse events not listed by the NCI CTCAE were graded using the following criteria[1]:

- Grade 1:Discomfort noticed but no disruption of normal daily activity
- Grade 2:Discomfort sufficient to reduce or affect normal daily activity
- Grade 3:Inability to work or perform normal daily activity
- Grade 4:Represents an immediate threat to life. Such events should also be reported as serious events.

[1] The scale used according to the protocol consisted of four grades; however, statistical outputs also include Grade 5, which corresponds to fatal events.

3.7.3.2 Serious Adverse Events

An SAE is any experience that suggests a significant hazard, contraindication, side effect, or precaution. It is any AE that, at any dose, fulfilled at least one of the following criteria:

- was fatal
- was life-threatening (note: the term “life-threatening” refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe)
- required in-patient hospitalization or prolongation of existing hospitalization
- resulted in persistent or significant disability/incapacity
- was a congenital anomaly/birth defect
- was medically significant or required intervention to prevent one or other of the outcomes listed above.

The exception to this definition of an SAE was when a patient was hospitalized following an MS relapse as long as the reason for hospitalization was to receive standard treatment with iv methylprednisolone. The rationale for this exception was that some countries and/or clinical sites routinely hospitalize patients who require administration of methylprednisolone in the event of an MS relapses. Thus, the SAE criteria for “hospitalization” would be met on the basis of local practice and would not reflect the seriousness of the event.

When the MS relapse resulted in hospitalization for any reason other than for routine treatment of the relapse (such as for a treatment course beyond the standard treatment) or when hospitalization was prolonged, the MS relapse was considered an SAE.

3.7.3.3 Neurologic Examination

A neurologic examination was performed at each scheduled and unscheduled visit. In the presence of newly identified or worsening neurologic symptoms, a neurologic evaluation was to be scheduled promptly. The treating investigator assessed whether the patient was experiencing:

- a relapse of MS at which time the patient was scheduled to see the examining physician, or
- another neurologic (non-MS) disorder

Study investigators screened patients for signs and symptoms of PML by evaluating neurologic deficits localized to the cerebral cortex, such as cortical symptoms/signs, behavioral and neuropsychologic alteration, retrochiasmal visual defects, hemiparesis, and cerebellar symptoms/signs (e.g., gait abnormalities, limb incoordination).

Telephone interviews to identify new or worsening neurologic symptoms that warranted an unscheduled visit were conducted by site personnel familiar with the patient.

3.7.3.4 Standard Laboratory Assessments

The following laboratory tests were performed. A central laboratory was used for all assessments (Quintiles Laboratories, The Alba Campus, Rosebank, Livingstone, West Lothian, Scotland, UK, EH54 7EG), with the following exceptions:

- urinalysis and urine microscopic examination were performed at the site (local laboratory)
- in women of childbearing potential, the urine pregnancy test was performed on site
- HAHA analysis was performed at Genentech (Genentech Inc., 1 DNA Way, MS 452b, south San Francisco, CA 94080, USA).

Quintiles Laboratories standard ranges are provided on page 1874.

Hematology: Hemoglobin, hematocrit, red blood cells, white blood cells (absolute and differential), and quantitative platelet count

Blood chemistry: AST/SGOT, ALT/SGPT, γ-glutamyl transferase (GGT), alkaline phosphatase, amylase, lipase, total protein, albumin, cholesterol, total bilirubin, urea, uric acid, creatinine, random glucose, potassium, sodium, calcium, phosphorus, lactic dehydrogenase, creatine phosphokinase, and triglycerides

Thyroid function test: Sensitive thyroid-stimulating hormone (TSH) and thyroid auto-antibodies

Fluorescence-activated cell sorter (FACS) including (but was not limited to) the following cells:

- maturation pathway of B-cells (including but not limited to CD19, CD21, IgD, and IgM)
- T-cells (CD3, CD4, CD8, CD25, CD45RO)
- NK cells (CD16, CD56)

Quantitative immunoglobulin: Ig levels (including total Ig, IgG, IgM, and IgA isotypes)

Antibody titers: measurement of antibody titers to common antigens (mumps, rubella, varicella, S. pneumoniae, and Epstein-Barr virus)

HAHA: serum samples for determination of antibodies against OCR

Urinalysis: a urine dipstick for blood, protein, nitrite and glucose and a microscopic examination if abnormal and applicable

Pregnancy Test: All women of childbearing potential had regular pregnancy tests.

3.7.4 Exploratory Analyses

3.7.4.1 Exploratory Efficacy Analyses

The results of the following exploratory analyses are presented in this report:

MRI outcomes

- Change in brain volume from baseline to Week 12 and Week 12 to Week 96
- Total number of new and/or enlarging T2 lesions observed on serial MRI scans of the brain at Weeks 4, 8, 12, 16, 20, 24 (average imputation method)
- Proportion of patients who remain free of new gadolinium-enhancing T1 lesions
- Time to first new gadolinium-enhancing T1 lesions developing over 24 weeks

Clinical efficacy outcomes

- Proportion of patients who remained free from relapse (clinical and/or protocol-defined relapses
- Proportion of patients requiring systemic methylprednisolone treatment or equivalent for an MS relapse during each treatment cycle and at Weeks 48 and 96
- Annualized clinical and/or protocol-defined relapse rate
- Sustained disability progression (SDP) during the treatment phase (up to 96 weeks)

3.7.4.2 Genotyping Analysis

An analysis of mandatory polymorphisms and biomarkers was performed but did not show any correlation between these markers and study endpoints. Results are available upon request.

3.7.4.3 Patient-reported outcomes

Analysis of PRO data did not yield any significant results and, therefore, is not described in this report.

3.8 ASSIGNMENT OF PREFERRED TERMS TO ORIGINAL TERMINOLOGY

For classification purposes, preferred terms were assigned by the Sponsor to the original terms entered on the CRF, using version 15.0 of the Medical Dictionary for Regulatory Activities (MedDRA) terminology for AEs and diseases and the International Non-Proprietary Name (INN) Drug Terms and Procedures Dictionary for treatments and surgical and medical procedures.

3.9 DATA REPORTING AND ANALYSIS PLAN

Statistical analyses were conducted according to the statistical analysis plan dated 5 July 2012 (page 1757).

3.9.1 Statistical Hypothesis and Planned Sample Size

The hypotheses to be tested were as follows:

- H_0 (null hypothesis): There is no statistically significant difference in the total number of gadolinium-enhancing T1 lesions at weeks 12, 16, 20, and 24 between the OCR groups and the placebo group.
- H_1 (alternative hypothesis): There is a statistically significant difference in the total number of gadolinium-enhancing T1 lesions at weeks 12, 16, 20, and 24 between the OCR groups and the placebo group.

On the basis of the rituximab proof-of-concept study, U2787g, the proportion of patients with gadolinium-enhancing T1 lesion counts at weeks 12, 16, 20, and 24 was estimated for the placebo and OCR groups (Table 3).

Table 3 Estimation of Proportion of Patients with Gadolinium-enhancing T1 Lesion Counts for the Placebo and OCR Groups

Total Gadolinium-Enhancing T1 Lesion Count at Week 12, 16, 20, and 24 (%)	Placebo	OCR
0	51.4%	80.3%
> 0–1	11.4%	9.1%
> 1–2	14.3%	7.6%
> 2–3	2.9%	0%
> 3	20.0%	3.0%

A sample size of 35 patients per group would be required to provide 80% power with a two-sided significance level of 0.05 to detect a difference in the total number of gadolinium-enhancing T1 lesions between each OCR group and the placebo group using the Wilcoxon rank-sum test. To allow for dropouts, 50 patients were expected to be randomized to each treatment group.

3.9.2 Analysis Populations

All analysis populations were defined and agreed upon prior to unblinding of the study. One patient population was defined for the purpose of the safety analysis and two patients populations were identified for the efficacy analysis. Efficacy analyses were performed using the intent-to-treat (ITT) population. The per-protocol (PP) population was used for all primary and secondary efficacy analyses in order to evaluate the influence of major protocol violators and as a sensitivity check for the ITT analysis. A summary of the analysis populations and a listing of reasons for exclusion from the populations were produced.

3.9.2.1 Intent-to-treat Population

All randomized patients who had received any study drug were included in the ITT population. Patients who prematurely withdrew from the study for any reason and for whom an assessment was not performed for whatever reason were included in the ITT analysis. Patients who received a therapy other than the intended therapy were summarized according to their randomized treatment.

3.9.2.2 Per-protocol Population

The PP population included all patients in the ITT population adhering to the protocol. Patients may have been excluded if they significantly violated the inclusion/exclusion criteria or deviated from the study plan. Only those patients with major violations (i.e., violations with the potential to affect the efficacy of study treatment) were excluded from the PP population. Examples of major protocol violations include, but are not limited to, the following: receipt of incorrect therapy, failure to receive $\geq$ 80% of the first infusion within 4 weeks of baseline, receipt of excluded MS medication, incorrect MS diagnosis, diagnosis of another neurologic disease (e.g., cerebrovascular accident) at baseline or during treatment period that may have had an effect on the endpoints, failure to provide informed consent, age $<$ 18 years, and corticosteroid use within 4 weeks of baseline. The reasons for exclusion were listed and summarized. Other violations considered to be minor were listed but did not lead to exclusion from the PP population. All decisions were made prior to unblinding and database lock.

3.9.2.3 Safety Population

This population was used for all summaries of safety data. The safety population included all patients who received any study drug and underwent at least one assessment of safety. Randomized patients who received incorrect therapy were summarized according to the therapy actually received. Patients who were not randomized but who received study drug were included in the safety population and summarized according to the therapy actually received. Patients who received more than one study therapy were summarized according to the treatment they actually received in the first infusion of the first treatment cycle.

3.9.2.4 All Patients

All patients randomized in this study.

3.9.2.5 Pharmacokinetic Population

The pharmacokinetic population included all patients who received any study drug and provided at least one measurable concentration value.

3.9.3 Reporting Convention and Derivation Rules

Unless otherwise specified, the analysis population for efficacy endpoints consisted of all randomized and treated patients (the ITT population). Patients were summarized according to the treatment to which they were randomized, using imputation by average or the last observation carried forward (LOCF) method for missing data.

All statistical tests were two sided. For secondary and exploratory endpoints the p-values reported should be considered as descriptive and not confirmatory. The key statistical comparisons were made using the data obtained during the placebo-controlled 24-week period, but the summary statistics went beyond this time point.

3.9.3.1 Primary Efficacy Analysis

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. The median total number of gadolinium-enhancing T1 lesions for each treatment group and the corresponding 95% confidence interval (CI) for the median are presented.

A missing value for the number of gadolinium-enhancing T1 lesions at a particular week was imputed with the average number of lesions on available scans obtained during the first 24 weeks of treatment. The total number of gadolinium-enhancing T1 lesions was then calculated as the sum of the individual number of lesions at weeks 12, 16, 20, and 24. It should be noted that as the result of the method of imputation for missing values, the total number of lesions for the primary efficacy endpoint may not be an integer. Patients who did not have any post-baseline gadolinium-enhanced scans/assessments were not included in the analysis.

3.9.3.2 Secondary Efficacy Analyses

ARR for each OCR group and the placebo group at week 24 was calculated using Poisson regression, offsetting for exposure time in years. Two Poisson models were fitted, one adjusting for geographic region only and the other adjusting for the number of relapses occurring within the 1 year prior to study entry, baseline EDSS (≤ 2.5, > 2.5), baseline presence of gadolinium-enhancing lesions (present or absent), prior treatment with IFN-β or glatiramer acetate, age (<40, ≥ 40 years), and geographic region. The adjusted ARR and the 95% confidence intervals for the relapse rates are presented. Diagnostic tests were conducted to ensure that the assumptions concerning Poisson regression were satisfied. If Poisson regression was not appropriate, alternative non-parametric methodology was investigated.

Patient relapse rate (calculated as the number of relapses for each patient divided by the number of years followed in the study for that patient) was also summarized by treatment group.

The proportion of patients who remained relapse free between week 0 and week 24 was analyzed using a Cochran–Mantel–Haenszel χ^2 test stratified by geographic region to compare each OCR group with the placebo group. The difference in the proportions along with the 95% confidence interval for the difference is presented. Relative risks were also produced for the comparison of each OCR group with the placebo group, along with corresponding confidence intervals. Patients who withdrew prematurely from the study were considered to have had a relapse in this analysis.

The same methods as specified for the primary efficacy endpoint were employed for the total number of gadolinium-enhancing T1 lesions at weeks 4, 8, 12, 16, 20, and 24 and for the total number of new gadolinium-enhancing T1 lesions at weeks 4, 8, 12, 16, 20, and 24.

The change in total volume of T2 lesions from baseline to week 24 was compared between each OCR group and the placebo group using the van Elteren test stratified by geographic region. The median change in the total volume of T2 lesions for each treatment group and the corresponding 95% confidence interval for the median are presented. Missing values were imputed using LOCF methodology.

3.9.3.3 Pharmacokinetic Analysis

OCR concentrations were determined using an ELISA with a lower limit of quantitation (LLOQ) of 50 ng/mL. Nonlinear mixed-effects modeling (software NONMEM) was used to analyze the sparse sampling dose-concentration-time data for OCR. Patients who had measurable OCR concentrations were included in the pharmacokinetic analysis unless they had a major protocol deviation that could have interfered with the pharmacokinetic evaluation or necessary information (e.g., blood sampling date) was missing. Individual population pharmacokinetic parameters (clearances and volumes) were estimated.

Details of the mixed-effects modeling analyses are described in the Modeling and Simulation Analysis Plan, and results are reported in the 'Population PK Report, RO4964913, Development of a Population Pharmacokinetic Model for OCR in Patients with RRMS (Protocol Number WA21493)'.

3.9.3.4 Pharmacodynamic Analysis

An exploratory graphical analysis was conducted to examine a number of potential pharmacokinetic-pharmacodynamic relationships. Individual model-predicted maximum concentration (C_{max}) and area under the concentration-time curve (AUC) for Cycle 1 (day 1 to week 24) were plotted against the number of gadolinium-enhancing T1 lesions at week 24, ARR at week 24, and change in total volume of T2 lesions from baseline to week 24. The number of gadolinium-enhancing T1 lesions over time was also explored by examining the time course by different quartiles of exposure. The proportion of patients who experienced an AE (super class terms) with $>5\%$ of the total number of AEs was compared with placebo and selected quartiles of individual predicted AUC and C_{max} values. Laboratory safety parameters at week 12 and week 24 were compared with OCR exposure values. The concentration of $CD19^{+}$ B-cells at week 24 was plotted against the number of gadolinium-enhancing T1 lesions at week 24, ARR at week 24, the change in total volume of T2 lesions from baseline to week 24, the concentration of monocytes at week 24, and the total concentration of IgG and IgM at week 24. The concentration of $CD19^{+}$ B-cells over time was also explored by examining the time course by different quartiles of exposure.

3.9.3.5 Safety Reporting and Analysis

All patients who received any study treatment and underwent at least one assessment of safety were included in the safety analysis. Verbatim descriptions of AEs reported during the study were mapped to MedDRA thesaurus terms.

All AEs were coded and tabulated by system organ class and preferred term for individual events within each body system, and are presented in descending frequency. Adverse events were also tabulated by severity and relationship to the study treatment. SAEs were summarized separately.

Associated laboratory parameters, such as hepatic function, renal function, and hematologic values, were grouped and are presented together. For each laboratory test, individual patient values were listed, and values outside the standard reference range were flagged. Marked abnormalities were also flagged and were tabulated for each laboratory test by treatment group.

Results for HAHA response to OCR were summarized descriptively (Anti-Therapeutic Antibody [ATA] assay).

The change from baseline for each of vital sign variable was computed and included in individual patient listings and summarized using descriptive statistics. Physical examination and ECG data were summarized descriptively and presented in individual patient listings.

An external, independent DMC reviewed safety data throughout the study on a quarterly basis. Analyses required for the DMC data review were performed as described in the DMC Charter (page 1844).

Glossaries of preferred terms are provided from page 2912.

3.9.4 Changes in Conduct of Study or Planned Analyses

Subgroup analyses for the primary and key secondary endpoints were performed for a number of demographic and baseline disease characteristics, including age (< 40, ≥ 40 years), sex, region (North America, other), baseline EDSS (≤ 3, > 3), number of gadolinium-enhancing T1 legions at baseline (0, > 0), number of relapses in the 3 years prior to randomization (< 2, 2, > 2), number of relapses in the 1 year prior to randomization (0, 1, > 1), prior treatment with disease-modifying drugs within 6 months prior to randomization (yes, no) and prior treatment with corticosteroid within 6 months prior to randomization (yes, no).

4. RESULTS: STUDY POPULATION

4.1 DISPOSITION OF PATIENTS

Of the 220 patients randomized, 218 received study treatment and 205 (93%) completed the 24-week placebo-controlled study period (Table 4). There were 54 screen failures; the main reasons were administrative, informed consent, serum IgG values and intolerability to Avonex. All patients randomized to the placebo group completed the first 24 weeks of treatment. The completion rates at week 24 for the other three treatment groups ranged from 89% (OCR 1000 mg group) to 93% (Avonex group). The number of patients completing all four treatment cycles until week 96 ranged from 78% in the OCR 1000 mg group to 89% in placebo group.

Approximately 90% of patients entered the safety follow-up period (including patients who discontinued study treatment early). Around 85% of all patients completed safety follow-up. Reasons for withdrawal from study treatment or safety follow-up are given in Section 4.2.

Approximately 60% of all patients entered B-cell monitoring after safety follow-up at week 120. Half of them completed B-cell monitoring indicating that B-cells repleted before week 144 of the study (see Section 6.2.1). The remaining 78 patients (25% of all randomized patients) remained B-cell depleted at the week 144 visit.

Approximately 50% of all patients entered the observation period. Sixteen to 22% of patients in all four arms completed the observation period at week 144.

Table 4 Patient Disposition

stdispos_w144_all Patient Disposition up to Week 144 (48 weeks after end of treatment) (All Patients Population)

Overall Disposition	Placebo N=54	Ocr 600 mg N=56	Ocr 1000 mg N=55	Avonex N=55
Number of Patients				
Randomized	54 (100%)	56 (100%)	55 (100%)	55 (100%)
Treated	54 (100%)	55 (98.2%)	55 (100%)	54 (98.2%)
Completed to Week 24	54 (100%)	51 (91.1%)	49 (89.1%)	51 (92.7%)
Completed to Week 48	51 (94.4%)	50 (89.3%)	46 (83.6%)	49 (89.1%)
Completed to Week 72	50 (92.6%)	49 (87.5%)	45 (81.8%)	49 (89.1%)
Completed to Week 96	48 (88.9%)	46 (82.1%)	43 (78.2%)	46 (83.6%)
Completed to Week 120	44 (81.5%)	44 (78.6%)	40 (72.7%)	45 (81.8%)
Completed to Week 144	42 (77.8%)	41 (73.2%)	37 (67.3%)	43 (78.2%)
Withdrawn from treatment phase of the study before Week 96	6 (11.1%)	9 (16.1%)	12 (21.8%)	8 (14.5%)
Withdrawn from treatment phase of the study and completed 48 weeks in follow-up	2 (3.7%)	2 (3.6%)	5 (9.1%)	3 (5.5%)
Entered Safety Follow-up	49 (90.7%)	48 (85.7%)	50 (90.9%)	49 (89.1%)
Withdrawn from Safety Follow-up	3 (5.6%)	2 (3.6%)	5 (9.1%)	1 (1.8%)
Completed Safety Follow-up	46 (85.2%)	46 (82.1%)	45 (81.8%)	48 (87.3%)
Entered B Cell Monitoring Period	33 (61.1%)	34 (60.7%)	36 (65.5%)	32 (58.2%)
Withdrawn from B Cell Monitoring Period	3 (5.6%)	0	2 (3.6%)	2 (3.6%)
Completed B Cell Monitoring Period	17 (31.5%)	13 (23.2%)	11 (20.0%)	15 (27.3%)
Completed B-Cell Monitoring without repleting	1 (1.9%)	0	0	1 (1.8%)
Entered Observation Period	31 (57.4%)	25 (44.6%)	20 (36.4%)	32 (58.2%)
Withdrawn from Observation Period	0	2 (3.6%)	0	0
Completed Observation Period	12 (22.2%)	9 (16.1%)	9 (16.4%)	12 (21.8%)

Patients are summarized according to their randomized treatment group. All percentages are based on N. Withdrawals are included from withdrawal visits, completion pages and deaths
Program : $PROD/cdpt3422/i21493g/stdispos.sas
Output : $PROD/cdpt3422/i21493g/reports/stdispos_w144_all.rl8
10AUG2012 12:24

4.2 PATIENTS WITHDRAWN PREMATURELY FROM TREATMENT

In total, 35 patients (16%) withdrew from the study prior to week 96: 6 patients in the placebo group, 9 patients in the OCR 600 mg group, 12 patients in the OCR 1000 mg group, and 8 patients in the Avonex group (Table 5). Eight patients withdrew for safety reasons (see Section 7.7), including 1 patient ([redacted]) in the OCR 1000 mg group who died in the course of systemic inflammatory response syndrome (SIRS, see Section 7.5). Twenty patients discontinued from the study during the treatment-free period (page 460). Ten patients withdrew from safety follow-up due to non-safety reasons. Patient [redacted] was reported as withdrawn from safety follow-up and treatment period due to death. Another 7 patients withdrew from study during B-cell monitoring (6 patients due to non-safety reason, 1 patient died). Two patients withdrew later from observation period due to administrative reasons.

Table 5 Reasons for Premature Withdrawals Before Week 96

stwithd_trex_saf_144 Patients Withdrawn from Trial Treatment by Cycle and Trial Treatment (Safety Population)

Reason for Withdrawal	Placebo N = 54 No. (%)	Ocr 600 mg N = 55 No. (%)	Ocr 1000 mg N = 55 No. (%)	Avonex N = 54 No. (%)
Cycle 1				
Safety	0 (0)	2 (4)	3 (5)	1 (2)
Adverse Event(a)	0	2	2	1
Death	0	0	1	0
Non Safety	1 (2)	3 (5)	5 (9)	3 (6)
Failure to return	1	0	0	0
Violation of selection criteria at entry	0	0	1	0
Refused treatment/did not cooperate	0	1	2	0
Withdrew consent	0	2	2	3
Cycle 2				
Safety	0 (0)	0 (0)	0 (0)	1 (2)
Adverse Event(a)	0	0	0	1
Non Safety	3 (6)	1 (2)	1 (2)	0 (0)
Insufficient therapeutic response	1	0	1	0
Refused treatment/did not cooperate	1	0	0	0
Withdrew consent	1	1	0	0
Cycle 3				
Safety	0 (0)	1 (2)	0 (0)	0 (0)
Adverse Event(a)	0	1	0	0
Non Safety	1 (2)	2 (4)	1 (2)	3 (6)
Insufficient therapeutic response	0	1	0	1
Refused treatment/did not cooperate	0	1	1	1
Withdrew consent	1	0	0	0
Administrative/other	0	0	0	1
Cycle 4				
Non Safety	1 (2)	0 (0)	2 (4)	0 (0)
Insufficient therapeutic response	0	0	1	0
Withdrew consent	1	0	1	0

Patient [redacted] withdrew from the treatment period on [redacted] with reason for withdrawal as 'DEATH' on the CRF, then withdrew fr m the safety follow-up period on the [redacted] wit reason for withdrawal also as 'DEATH'.
a) = Including intercurrent illness
Percentages are based on n.
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Output : $PROD/cdpt3422/i21493g/reports/stwithd_trex_saf_144.rl8
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[Modified by PDRD]

4.3 OVERVIEW OF ANALYSIS POPULATIONS

The ITT and safety populations comprised 218 patients who were randomized and received at least one dose of study treatment (Table 6). Two patients, one randomized to the OCR 600 mg group ([redacted]) and one randomized to the Avonex group ([redacted]), did not receive any study treatment and were excluded from analyses. The PP population comprised 197 patients. The pharmacokinetic population comprised 107 patients who received any amount of OCR and provided at least one measurable concentration value.

Table 6 Analysis Populations

stec11 Analysis Populations (All Patients Population)
Protocol(s): WA21493
Analysis: ALL PATIENTS Center: ALL CENTERS

	Placebo	Ocr 600 mg	Ocr 1000 mg	Avonex
No. of Patients Randomized	54	56	55	55
No. Included in ITT	54	55	55	54
No. Excluded from ITT	-	1	-	1
Received no dose of ocrelizumab/ocrelizumab placebo/Avonex	-	1	-	1
No. Included in PER PROTOCOL	53	47	48	49
No. Excluded from PER PROTOCOL	1	9	7	6
Patients in the ocrelizumab/placebo groups who receive < 80% of their first treatment cycle within 4 weeks of baseline and patients in the Avonex group who receive < 80% of their 1st treatment cycle	-	5	4	3
Levels of serum IgG <5.65 g/L or IgM < 0.55 g/L	-	2	2	-
Patients who receive study medication that has been mishandled (e.g. incorrect storage temperature) and therefore, drug potency may be effected	1	-	-	2
Positive screening tests for hepatitis B or hepatitis C	-	1	1	-
Received no dose of ocrelizumab/ocrelizumab placebo/Avonex	-	1	-	1
CD4 count < 300/microL	-	-	1	-
Does not have 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	-	1	-	-
Platelet count <100,000/microL (<100 x 10^9/L)	-	-	-	1

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Table 6 Analysis Populations (cont.)

stec11 Analysis Populations (All Patients Population)
Protocol(s): WA21493
Analysis: ALL PATIENTS Center: ALL CENTERS

	Placebo	Ocr 600 mg	Ocr 1000 mg	Avonex
No. Included in SAFETY	54	55	55	54
No. Excluded from SAFETY	-	1	-	1
No safety data reported on or after study day 1 (day of first infusion/injection with study drug)	-	1	-	1
Received no dose of ocrelizumab/ocrelizumab placebo/Avonex	-	1	-	1

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4.4 PROTOCOL VIOLATIONS

A summary of pre-specified protocol violations for exclusion from the analysis population is presented in Table 6. The most frequent reason for exclusion from the PP population was receipt of < 80% of their designated study drug dose. A listing of patients excluded from the analysis populations is provided on page 1447 and a listing of all protocol violations not leading to exclusion from PP population is provided on page 1451.

4.5 DEMOGRAPHIC DATA AND BASELINE CHARACTERISTICS

Baseline demographic data for all randomized and treated patients are summarized in Table 7. Demographic characteristics were well balanced across the four treatment groups. Most of the patients were female (59%–69%), and the majority were Caucasian (93%–98%). The mean age of patients across the four treatment groups ranged from 35.6 to 38.5 years (the absolute range was 19–56 years).

Table 7 Demographic Data (ITT Population)

stdm11_itt Demographic data (ITT Population)
Protocol(s): WA21493
Analysis: ITT Center: ALL CENTERS

	Placebo N = 54	Ocr 600 mg N = 55	Ocr 1000 mg N = 55	Avonex N = 54
Sex				
MALE	18 (33%)	20 (36%)	17 (31%)	22 (41%)
FEMALE	36 (67%)	35 (64%)	38 (69%)	32 (59%)
n	54	55	55	54
Age in years				
Mean	38.0	35.6	38.5	38.1
SD	8.80	8.49	8.70	9.25
Median	38.5	35.0	39.0	38.0
Min-Max	22 - 54	19 - 53	21 - 56	22 - 55
n	54	55	55	54
Weight in kg				
Mean	75.27	74.24	73.69	74.98
SD	18.289	19.940	19.147	17.493
Median	74.35	70.00	70.40	73.00
Min-Max	45.0 - 139.0	43.2 - 133.6	40.0 - 116.0	43.0 - 127.5
n	54	55	55	54
Height in cm				
Mean	170.33	170.22	169.33	171.01
SD	9.021	10.704	9.155	10.951
Median	169.00	170.00	167.00	170.00
Min-Max	155.0 - 193.0	150.0 - 197.0	153.0 - 205.0	150.0 - 202.0
n	54	55	55	54
Female reproductive status				
POSTMENOPAUSAL	3 (8%)	-	2 (5%)	1 (3%)
SURGICALLY STERIL.	5 (14%)	4 (11%)	4 (11%)	4 (13%)
WITH CONT. PROT.	28 (78%)	31 (89%)	32 (84%)	27 (84%)
n	36	35	38	32

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
With Cont. Prot. = With Contraceptive Protection
DM11 01AUG2012:18:46:38 (1 of 2)

Table 7 Demographic Data (ITT Population) (cont.)

stdm11_itt Demographic data (ITT Population)
Protocol(s): WA21493
Analysis: ITT Center: ALL CENTERS

	Placebo N = 54	Ocr 600 mg N = 55	Ocr 1000 mg N = 55	Avonex N = 54
Race				
AMERICAN INDIAN OR ALASKA NATIVE	-	1 (2%)	-	-
ASIAN (INDIAN SUBCONTINENT)	1 (2%)	-	-	-
BLACK	-	3 (5%)	2 (4%)	1 (2%)
MESTIZO	1 (2%)	-	-	-
WHITE	52 (96%)	51 (93%)	53 (96%)	53 (98%)
n	54	55	55	54
Ethnicity				
HISPANIC	6 (11%)	6 (11%)	7 (13%)	7 (13%)
NON-HISPANIC	48 (89%)	49 (89%)	48 (87%)	47 (87%)
n	54	55	55	54

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
With Cont. Prot. = With Contraceptive Protection
DM11 01AUG2012:18:46:38 (2 of 2)

Baseline disease characteristics for MS symptoms and relapses are summarized in Table 8 and Table 9. MS disease history was similar across the four treatment groups. On average, patients had shown symptoms of MS for 6.9 to 8.7 years prior to randomization and had a diagnosis of MS for 3.9 to 5.1 years. The median number of relapses within 1 year prior to randomization was 2.0 for all treatment groups. The median number of relapses within 3 years prior to randomization ranged from 2.0 to 2.5. The median time since the last onset of MS relapse was also similar in the four treatment groups (135–144 days).

Baseline characteristics from MRI brain scan are summarized in Table 10. A higher number of gadolinium-enhancing T1 lesions was observed in the OCR 600 mg group (mean of 3.9 and median of 1.0) at baseline, compared with the other three treatment groups (placebo group: mean of 1.6 and median of 0.0; OCR 1000 mg group: mean of 2.2 and median of 0.0; Avonex group: mean of 2.3 and median of 0.0). Of the patients in the OCR 600 mg group, 51% had one or more total gadolinium-enhancing lesions at baseline. In contrast, 45% of patients in both the placebo and OCR 1000 mg groups, and 34% of patients in Avonex group had one or more total gadolinium-enhancing lesions at baseline.

Mean T2 lesion volume at baseline was similar across the four treatment groups. Other baseline MRI results were generally similar across the four treatment groups.

There were no imbalances across the four treatment groups in Kurtzke FS scores (for pyramidal, cerebellar, brainstem, sensory, bowel/bladder, visual, and mental see page 461; for Modified Fatigue Impact Scale (MFIS) total scores, Fatigue Scale for Motor and Cognitive Functions (FSMC) total scores and Center for Epidemiologic Studies Depression Scale (CES-D) scores see page 464.

Table 8 Baseline MS Symptoms Characteristics (ITT Population)

stdm11_bas_ms Baseline Disease Characteristics (MS) (ITT Population)
Protocol(s): WA21493
Analysis: ITT Center: ALL CENTERS

	Placebo N = 54	Ocr 600 mg N = 55	Ocr 1000 mg N = 55	Avonex N = 54
Duration Since MS Symptom Onset (yrs)				
Mean	7.173	6.937	8.724	8.385
SD	6.1092	5.0005	6.6222	7.2007
Median	4.815	6.489	7.715	5.348
Min-Max	0.57 - 26.18	0.50 - 20.48	0.25 - 27.96	0.82 - 35.21
n	54	55	55	54
Duration Since MS Diagnosis (yrs)				
Mean	3.943	4.739	4.901	5.122
SD	4.5679	4.1143	4.3695	5.2360
Median	2.728	3.578	4.364	3.296
Min-Max	0.11 - 19.23	0.05 - 16.48	0.09 - 19.22	0.10 - 20.24
n	54	55	55	54
Disease Mod. Therapies 6 mths Prior to Rnd?				
N	48 (89%)	42 (76%)	41 (75%)	42 (78%)
Y	6 (11%)	13 (24%)	14 (25%)	12 (22%)
n	54	55	55	54

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
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Table 9 Baseline Relapse Characteristics (ITT Population)

stdm11_bas_rel Baseline Disease Characteristics (Relapses) (ITT Population)
Protocol(s): WA21493
Analysis: ITT Center: ALL CENTERS

	Placebo N = 54	Ocr 600 mg N = 55	Ocr 1000 mg N = 55	Avonex N = 54
Region (North America incl. USA, CDN)				
EASTERN CENTRAL EUROPE/ASIA	30 (56%)	30 (55%)	30 (55%)	30 (56%)
LATIN-AMERICA	2 (4%)	2 (4%)	2 (4%)	2 (4%)
NORTH AMERICA	14 (26%)	14 (25%)	15 (27%)	14 (26%)
WESTERN EUROPE	8 (15%)	9 (16%)	8 (15%)	8 (15%)
n	54	55	55	54
No. Relapses in the Past Year Category				
0	2 (4%)	-	1 (2%)	1 (2%)
1	24 (44%)	23 (42%)	20 (36%)	25 (46%)
2	20 (37%)	27 (49%)	25 (45%)	23 (43%)
3	7 (13%)	4 (7%)	8 (15%)	4 (7%)
>=4	1 (2%)	1 (2%)	1 (2%)	1 (2%)
n	54	55	55	54
No. Relapses in the Past Year				
Mean	1.6	1.7	1.8	1.6
SD	0.83	0.69	0.79	0.74
Median	2.0	2.0	2.0	2.0
Min-Max	0 - 4	1 - 4	0 - 4	0 - 4
n	54	55	55	54
No. Relapses in the Past 3 Years Category				
1	2 (4%)	1 (2%)	1 (2%)	-
2	27 (50%)	27 (49%)	29 (53%)	27 (50%)
3	16 (30%)	14 (25%)	15 (27%)	24 (44%)
>=4	9 (17%)	13 (24%)	10 (18%)	3 (6%)
n	54	55	55	54
No. Relapses in the Past 3 Years				
Mean	2.7	3.0	2.9	2.6
SD	1.17	1.39	1.40	0.71
Median	2.0	2.0	2.0	2.5
Min-Max	1 - 7	1 - 7	1 - 8	2 - 5
n	54	55	55	54

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
DM11 01AUG2012:18:39:58 (1 of 2)

Table 9 Baseline Relapse Characteristics (ITT Population) (cont.)

stdm11_bas_rel Baseline Disease Characteristics (Relapses) (ITT Population)
Protocol(s): WA21493
Analysis: ITT Center: ALL CENTERS

	Placebo N = 54	Ocr 600 mg N = 55	Ocr 1000 mg N = 55	Avonex N = 54
Time Since Last Onset of MS Relapse Cat.				
<=6 MONTHS	36 (67%)	38 (69%)	36 (65%)	37 (69%)
>6 MONTHS	18 (33%)	17 (31%)	19 (35%)	17 (31%)
n	54	55	55	54
Time Since Last Onset of MS Relapse (days)				
Mean	163.1	155.2	171.8	154.9
SD	103.20	92.73	98.62	96.17
Median	138.0	142.0	144.0	135.0
Min-Max	1 - 422	22 - 395	40 - 442	16 - 418
n	54	55	55	54

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
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Note: The number of patients experiencing relapse in the past 1 year and the number of patients experiencing relapse in the past 3 years were calculated as up to the date of randomization, whereas in Table 6 (protocol violations) the timeframe was up to the screening visit.

Table 10 Baseline MRI Brain Scan Characteristics (Safety Population)

stdm11_bas_les Baseline Disease Characteristics (Lesions) (ITT Population)
Protocol(s): WA21493
Analysis: ITT Center: ALL CENTERS

	Placebo N = 54	Ocr 600 mg N = 55	Ocr 1000 mg N = 55	Avonex N = 54
No. of Gd+ enhancing T1 lesions at baseline				
Mean	1.6	3.9	2.2	2.3
SD	4.05	9.88	6.33	5.31
Median	0.0	1.0	0.0	0.0
Min-Max	0 - 25	0 - 46	0 - 37	0 - 24
n	47	51	53	49
Baseline Gd+ T1 Lesions (0,>0)				
0	26 (55%)	25 (49%)	29 (55%)	33 (66%)
>0	21 (45%)	26 (51%)	24 (45%)	17 (34%)
n	47	51	53	50
Baseline Gd+ enhancing T1 lesions (Category)				
0	26 (55%)	25 (49%)	29 (55%)	32 (65%)
1-2	13 (28%)	12 (24%)	16 (30%)	9 (18%)
3-4	4 (9%)	7 (14%)	2 (4%)	1 (2%)
>4	4 (9%)	7 (14%)	6 (11%)	7 (14%)
n	47	51	53	49
Volume of T2 lesions at baseline				
Mean	8950.84	13972.61	13178.30	13209.11
SD	9776.261	19930.16	14271.38	17206.51
Median	4764.70	6687.50	7124.70	8246.80
Min-Max	47.4 - 39919.5	10.5 - 93777.6	202.8 - 59431.5	23.7 - 102912.0
n	47	51	53	49
No. Prev T1 Lesions in the Past 12 Months				
0	20 (54%)	16 (44%)	14 (47%)	21 (55%)
1	4 (11%)	5 (14%)	5 (17%)	1 (3%)
> 1	13 (35%)	15 (42%)	11 (37%)	16 (42%)
n	37	36	30	38
No. Prev T2 Lesions in the Past 12 Months				
0 - 5	3 (6%)	1 (2%)	3 (7%)	3 (7%)
6 - 9	7 (14%)	12 (27%)	11 (26%)	8 (19%)
> 9	41 (80%)	31 (70%)	28 (67%)	32 (74%)
n	51	44	42	43

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
The number of previous T1 and T2 lesions in the past 12 months recorded at Screening has not been completed for all patients.
DM11 01AUG2012:18:45:18 (1 of 1)

4.6 PREVIOUS AND CONCURRENT DISEASES AND TREATMENTS

There were no clear differences across treatment groups in previous and concomitant medicines or in previous or concurrent diseases that would impact the outcomes.

4.6.1 Previous Treatments for MS

Previous MS treatments were comparable across the four treatment groups (page 465). The most frequently used class of MS treatments was corticosteroids (received by 55%–71% of patients). Methylprednisolone was the most commonly received corticosteroid (44%–62%). Among patients who previously received corticosteroids, approximately 37% to 51% received the treatment within 6 months prior to randomization (page 476).

There was an imbalance in the percentage of patients who had received prior MS therapies. A higher percentage of patients had received prior MS therapies in both OCR groups (95% and 84%, respectively) than in the placebo (70%) or Avonex group (81%). This imbalance was driven by the low number of patients treated with cytokines in the placebo and Avonex arm (17% and 26%, respectively) compared to both OCR arms (33% and 38%, respectively). A similar number of patients were treated with corticosteroids across all four treatment arms (page 465).

4.6.2 Concomitant Treatment for MS

Concomitant treatments for MS are summarized on page 477. Approximately three quarter of the patients (56%–74% across the four treatment groups) received concomitant treatments for MS during the study. The most frequently used treatment classes were corticosteroids (36%), vitamins and minerals (22%) and anticonvulsants (15%).

Corticosteroids were given to a higher percentage of placebo (39%) and Avonex (43%) patients than to OCR patients (33% in the OCR 600 mg group and 29% in the OCR 1000 mg group). All patients received methylprednisolone for the prevention of infusion-related reactions (IRRs) (page 491). Approximately one third of patients received treatment for IRRs during the treatment period in all treatment arms (page 493).

4.6.3 Other Disease and Treatment not for MS

Treatment groups were well balanced with respect to previous and concurrent diseases recorded at baseline (page 496 and page 501, respectively). The most frequently reported previous conditions or diseases were infections (the most frequent being herpes zoster) and injuries. The most frequently reported concurrent diseases were psychiatric disorders (depression, anxiety, and insomnia), nervous system disorder (headache and migraine), and immune system disorders (drug hypersensitivity and seasonal allergy).

The most frequently reported previous treatments or interventions not for MS were ranitidine and hysterectomy (page 511). The most frequently reported concomitant treatments not for MS were paracetamol, chloropyramine, ibuprofen, multivitamin NOS, methylprednisolone, and alprazolam (page 511). Overall, there were no major differences between treatment groups in concurrent diseases or use of medications for conditions other than MS.

5. RESULTS: EFFICACY

5.1 OVERVIEW OF EFFICACY

The 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 11). 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 11 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) <0.0001	0.8 (2.16) <0.0001	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.

5.2 PRIMARY EFFICACY ENDPOINT

As shown in Table 12, there was a statistically significant reduction in the total number of gadolinium-enhancing T1 lesions at weeks 12, 16, 20, and 24 in patients receiving both doses of OCR compared with those receiving placebo ($p< 0.0001$). The mean (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.

Table 12 Total Number of Gadolinium-enhancing T1 Lesions on Serial MRI Scans of the Brain at Weeks 12, 16, 20, 24 (Average Imputation Method) (ITT Population)

Total Number of Gadolinium-enhancing T1 Lesions on MRI Scans of the Brain	Placebo (N=54)	Ocr 600 mg (N=55)	Ocr 1000 mg (N=55)	Avonex (N=54)
WEEK 12, 16, 20 and 24				
n	54	51	52	52
Mean (SD)	5.6 (12.53)	0.6 (1.52)	0.2 (0.65)	6.9 (16.01)
SE	1.71	0.21	0.09	2.22
Median	1.7	0.0	0.0	1.0
95% CI of Median	(0.4,3.0)	(0.0,0.0)	(0.0,0.0)	(0.0,2.0)
Range	0-79	0-7	0-3	0-78
Van Elteren Test (stratified)				
p-value		<0.0001	<0.0001	0.7496
Van Elteren Test (stratified*)				
p-value		<0.0001	<0.0001	0.3457
Wilcoxon-Mann-Whitney Rank Sum Test				
p-value		<0.0001	<0.0001	0.3721

Van Elteren test is stratified by region and presence of baseline gadolinium-enhancing lesions (absent or present).
* Van Elteren test is stratified by region only.
Average Method Imputation only occurs from Weeks 0-24; No Imputation at Weeks 96 and 144
For the calculation of Total Number of Gadolinium-enhancing T1 Lesions on MRI Scans of the Brain at a specific week before week 24, the missing value at a time point is imputed using the average of available observations at the other time points before week 24.
MRI data collected post week 24 for OCR 600 and 1000 mg groups only.
Source: page 552

A comparison of the numbers of the gadolinium-enhancing T1 lesions at single visits at week 12, 16, 20 and 24 shows a similar pattern between the two OCR arms and the two comparator arms (Table 12).

No clear separation in the primary endpoint was observed between the OCR 600 mg group and the OCR 1000 mg groups ($p = 0.15$). In additional comparisons, the difference between the Avonex and placebo groups in the total number of gadolinium-enhancing T1 lesions at weeks 12, 16, 20, and 24 was not statistically significant ($p = 0.35$, page 557).

The analysis of the categorized number of the gadolinium-enhancing T1 lesions supports the primary analysis and shows as well a statistical significance difference between the two OCR arms and placebo ($p < 0.0001$ respectively, Fisher's exact test, Table 13). The difference between the two OCR arms and the two comparator arms can primarily be seen in the categories of no T1 lesion count (39 and 43 patients in OCR 600 mg and OCR 1000 mg arms, respectively, versus 19 and 25 patients in placebo and Avonex arms, respectively) and more than 3 T1 lesions (4 and 0 patients in OCR 600 mg and OCR 1000 mg arms, respectively, versus 19 and 17 patients in placebo and Avonex arms, respectively).

The robustness of the results of the primary analysis was also demonstrated by consistent results from the analyses using the per-protocol population (page 564) In the latter, OCR patients showed significant reductions in the total number of gadolinium-enhancing T1 lesions at weeks 12, 16, 20, and 24 compared to placebo patients ($p<0.0001$). Another imputation method favoring the placebo and Avonex arms by replacing missing values with Zero and missing values in the OCR arms by the average also confirmed the result of the primary analysis of each OCR arms versus placebo ($p<0.0001$, respectively) (SDP, MRI page 568).

Table 13 Total Number of Gadolinium-enhancing T1 Lesions on Serial MRI Scans of the Brain at Weeks 12, 16, 20, 24 by Category (Average Imputation Method) (ITT Population)

Total Number of Gadolinium-enhancing T1 Lesions on MRI Scans of the Brain	Placebo (N=54)	Ocr 600 mg (N=55)	Ocr 1000 mg (N=55)	Avonex (N=54)
WEEK 12, 16, 20 and 24				
n	54	51	52	52
0	19	39	43	25
>0 - 1	7	2	6	5
>1 - 2	6	6	1	5
>2 - 3	3	0	2	0
>3	19	4	0	17
Fishers Exact Test				
p-value		<0.0001	<0.0001	0.4182

For the calculation of Total Number of Gadolinium-enhancing T1 Lesions on MRI Scans of the Brain at a specific week before week 24, the missing value at a time point is imputed using the average of available observations at the other time points before week 24.
No imputation for Weeks 96 and 144
MRI data collected post week 24 for OCR 600 and 1000 mg groups only.
Source: page 572

5.3 SUBGROUP ANALYSES OF PRIMARY ENDPOINT

The effect of OCR (600 mg and 1000 mg) was consistently positive across all subgroups compared with placebo and Avonex (Table 14). There appeared to be a larger treatment effect of OCR in younger patients (age < 40 years) and in patients with at least one gadolinium-enhancing T1 lesion at baseline.

Table 14 Subgroup Analyses: Mean Number of Gadolinium-Enhancing T1 Lesions at Weeks 12, 16, 20, and 24 (ITT Population)

	Placebo (N=54)		Ocr 600 mg (N=55)			Ocr 1000 mg (N=55)			Avonex (N=54)		
	N	Mean(SD)	N	Mean(SD)	Relative Reduction (%)	N	Mean(SD)	Relative Reduction (%)	N	Mean(SD)	Relative Reduction (%)
Overall	54	5.6(12.53)	51	0.6(1.52)	88.5%	52	0.2(0.65)	96.2%	52	6.9(16.01)	-24.2%
Age											
<40	28	8.3(16.62)	32	0.2(0.52)	97.7%	27	0.1(0.35)	99.0%	31	9.6(19.54)	-16.3%
>=40	26	2.7(4.20)	19	1.4(2.22)	47.2%	25	0.4(0.85)	86.8%	21	3.0(7.27)	-10.6%
<38 median)	23	9.8(17.99)	29	0.2(0.49)	98.4%	24	0.0(0.00)	100.0%	26	10.9(21.11)	-10.8%
>=38 (median)	31	2.4(3.99)	22	1.3(2.10)	47.1%	28	0.4(0.85)	83.7%	26	3.0(6.67)	-22.7%
Sex											
Male	18	3.7(5.61)	20	0.7(1.59)	80.4%	17	0.4(1.00)	90.4%	20	2.9(5.19)	22.7%
Female	36	6.5(14.82)	31	0.6(1.49)	90.9%	35	0.1(0.38)	97.8%	32	9.5(19.69)	-45.3%
Region											
North American	14	2.8(4.87)	14	0.9(1.92)	68.8%	14	0.0(0.00)	100.0%	13	13.0(21.61)	-358.8%
Other	40	6.5(14.21)	37	0.6(1.35)	91.6%	38	0.3(0.74)	95.5%	39	4.9(13.39)	25.1%
Baseline EDSS											
<=2.5	24	2.6(4.12)	18	0.1(0.47)	95.7%	18	0.4(0.98)	85.0%	26	8.3(19.95)	-219.3%
>2.5	30	8.0(16.13)	33	0.9(1.80)	88.3%	34	0.1(0.36)	98.5%	26	5.6(11.00)	29.7%
<=3 (median)	32	3.3(4.90)	22	0.2(0.64)	92.5%	24	0.3(0.86)	91.1%	29	9.2(20.23)	-182.3%
>3 (median)	22	8.9(18.46)	29	0.9(1.89)	89.4%	28	0.1(0.39)	98.4%	23	4.1(7.60)	54.7%
Number of baseline gadolinium-enhancing T1 lesions*											
missing	7	4.7(5.37)	4	0.7(0.85)	84.5%	2	0.3(0.16)	94.0%	3	0.0(0.00)	100.0%
0	26	1.2(2.24)	23	0.0(0.00)	100.0%	26	0.1(0.59)	90.7%	32	2.3(6.21)	-81.8%
>0	21	11.2(18.52)	24	1.2(2.03)	88.9%	24	0.3(0.73)	97.2%	17	16.9(24.15)	-50.9%

* missing baseline GD T1 lesions are imputed using screening values. If no baseline or no screening value, then baseline equals missing
MRI data collected post week 24 for OCR 600 and 1000 mg groups only.

Table 14 (ITT Population) (cont.)

	Placebo (N=54)		Ocr 600 mg (N=55)			Ocr 1000 mg (N=55)			Avonex (N=54)		
	N	Mean(SD)	N	Mean(SD)	Relative Reduction (%)	N	Mean(SD)	Relative Reduction (%)	N	Mean(SD)	Relative Reduction (%)
Number of relapses in the 3 years prior to enrollment											
<2	2	1.5(2.12)	1	0.0(NA)	100.0%	1	0.0(NA)	100.0%	0		
2	27	3.9(9.02)	25	0.2(0.60)	94.3%	27	0.2(0.60)	96.1%	26	4.1(10.92)	-3.4%
>2	25	7.7(15.79)	25	1.1(2.01)	85.8%	24	0.3(0.71)	96.3%	26	9.8(19.66)	-27.6%
Number of relapses in the 1 year prior to enrollment											
0	2	2.8(3.96)	0			1	0.4(NA)	85.7%	1	8.0(NA)	-185.7%
1	24	5.5(9.59)	22	0.7(1.44)	87.9%	20	0.1(0.31)	97.9%	23	2.7(7.13)	51.4%
>1	28	5.8(15.12)	29	0.6(1.60)	89.3%	31	0.3(0.80)	95.4%	28	10.4(20.37)	-78.3%
Prior treatment with disease modifying drugs within 6 month prior to enrolment											
Yes	6	6.5(5.84)	12	0.8(1.50)	87.9%	12	0.0(0.00)	100.0%	12	10.4(21.90)	-59.5%
No	48	5.5(13.16)	39	0.6(1.54)	89.0%	40	0.3(0.73)	94.9%	40	5.9(13.97)	-8.0%
Prior treatment with steroid within 6 month prior to enrolment											
Yes	20	8.1(17.49)	25	0.3(0.61)	96.2%	22	0.3(0.74)	96.7%	24	8.9(20.01)	-9.4%
No	34	4.1(8.36)	26	1.0(2.00)	76.3%	30	0.2(0.57)	95.8%	28	5.3(11.69)	-28.8%

* missing baseline GD T1 lesions are imputed using screening values. If no baseline or no screening value, then baseline equals missing
MRI data collected post week 24 for OCR 600 and 1000 mg groups only.
Source: page 577

5.4 SECONDARY EFFICACY ENDPOINTS

5.4.1 The Annualized Protocol-defined Relapse Rate

ARR at week 24 was significantly reduced in both OCR groups (0.127 in the OCR 600 mg group [p = 0.0019] and 0.213 in the OCR 1000 mg group [p = 0.0136]) compared with the placebo group (0.557), representing a reduction of 78% and 62%, respectively (Table 15).

Little difference in ARR was seen between the two OCR treatment groups. ARR was lower among Avonex patients (0.364) than placebo patients, but was higher than ARR among OCR patients.

Summaries of unadjusted relapse rate (the total number of relapses for each patient divided by the total number of patient-years) and patient relapse rate (the number of relapses for each patient divided by the number of years followed in the study up to week 24 for that patient) also suggest marked reductions in both OCR groups compared with the placebo group.

Table 15 Annualized Protocol-Defined Relapse Rate (ITT Population)

Efficacy Variable	Placebo (N=54)	Ocr 600 mg (N=55)	Ocr 1000 mg (N=55)	Avonex (N=54)
Cycle 1				
n	54	55	55	54
Total number of relapses	14	3	5	9
Total subject-years followed	26.0	24.2	24.1	25.4
Unadjusted annualized relapse rate *	0.539	0.124	0.207	0.354
Adjusted annualized relapse rate**	0.557	0.127	0.213	0.364
95% CI of adjusted annualized relapse rate	(0.370,0.839)	(0.054,0.299)	(0.110,0.414)	(0.220,0.602)
Overdispersion scale (Poisson model)		0.7474	0.7474	0.7474
p-value Poisson model		0.0019	0.0136	0.1814
Adjusted annualized relapse rate 2***	0.450	0.133	0.198	0.468
95% CI of adjusted annualized relapse rate	(0.252,0.802)	(0.055,0.324)	(0.094,0.418)	(0.278,0.787)
Overdispersion scale (Poisson model)		0.7135	0.7135	0.7135
p-value Poisson model		0.0110	0.0439	0.9100
Subject relapse rate****				
Mean(SD)	0.555(1.124)	0.118(0.497)	0.193(0.730)	0.344(0.777)
Median	0.000	0.000	0.000	0.000
95% CI subject relapse rate	(0.255 ,0.855)	(-0.013,0.250)	(-0.000,0.386)	(0.136 ,0.551)
p-value: t-test		0.0108	0.0494	0.2589
p-value: ANOVA***		0.0364	0.1884	0.9178

*: The total number of relapses that occurred during cycle divided by the total number of subject-years followed in this period.
**: adjusted for geographical region only
***: adjusting for number of relapses occurring within the 3 year prior to study entry, baseline EDSS (<=2.5, >2,5), baseline presence of gadolinium lesions (present or absent), prior treatment with IFN-b or glatiramer acetate, age (<40, >=40) and geographical region.
****: The number of relapses for each subject divided by the number of years followed from week 0 to week 24 for that subject. Mean and median across all subjects are present.
Source: page 592

The ARR remained stable in Cycles 2, 3 and 4 with some variation. No remarkable increase in the ARR could be observed during the treatment-free period (ie safety follow-up, B-cell monitoring and observation period). It should be noted that all patients received OCR potentially explaining the decrease in ARR after Cycle 1 for patients randomized to placebo or Avonex after treatment Cycle 1.

Table 16 Annualized Protocol-defined Relapse Rate over Time (ITT Population)

	Placebo	OCR 600 mg	OCR 1000 mg	Avonex
Cycle 1	0.557	0.127	0.213	0.364
Cycle 2	0.200	0.081	0.267	0.131
Cycle 3	0.307	0.317	0.145	0.266
Cycle 4	0.043	0.174	0.234	0.045
Safety follow-up (Week 120)	0.189	0.080	0.394	0.076
B-cell mon./obs. (Week 144)	0.035	0.075	0.275	0.068

Note: All patients received OCR after Cycle 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.

Source: page 592

5.4.2 Proportion of Patients Who Remained Relapse Free at Week 24 (Protocol-defined Relapses)

The proportion of patients who remained relapse free, as defined in the protocol, at week 24 is presented in Table 17. A higher proportion of patients remained relapse free in the two OCR groups than in the placebo group (75.9% in the placebo group, 85.5% in the OCR 600 mg group, and 87.3% in the OCR 1000 mg group); however, the differences were not statistically significant. The proportion of Avonex patients who remained relapse free was 77.8%. In this analysis, patients who discontinued early and reported no relapse were assumed to have relapsed. This analysis was a conservative approach, as more patients discontinued in the three active treatment groups than in the placebo group.

Table 17 Proportion of Patients Who Remained Relapse Free (Protocol-Defined Relapses) between Week 0 and Week 24 (ITT Population)

Proportion of Patients who Remain Relapse-free	Placebo (N=54)	Ocr 600 mg (N=55)	Ocr 1000 mg (N=55)	Avonex (N=54)
Cycle 1				
n****	41	47	48	42
Proportion	75.9%	85.5%	87.3%	77.8%
95% CI of proportion	(64.5%,87.3%)	(76.1%,94.8%)	(78.5%,96.1%)	(66.7%,88.9%)
Difference in proportion (vs. Placebo)		9.5%	11.3%	1.9%
95% CI of Difference		(-0.05,0.24)	(-0.03,0.26)	(-0.14,0.18)
Relative risk (RR)		0.60	0.53	0.92
95% CI of RR		(0.27,1.34)	(0.23,1.22)	(0.46,1.84)
P-value:CMH Chi-Squared test (stratified*)		0.1978	0.1310	0.8206
P-value:CMH Chi-Squared test (stratified**)		0.5907	0.4026	0.6595
P-value: Logistic model (stratified***)		0.4490	0.3599	0.7201
Number of patients in this Cycle by # of relapses (observed) (%)				
0	42(77.8%)	52(94.5%)	51(92.7%)	45(83.3%)
1	10(18.5%)	3(5.5%)	3(5.5%)	9(16.7%)
2	2(3.7%)	(0.0%)	1(1.8%)	(0.0%)
>=3	(0.0%)	(0.0%)	(0.0%)	(0.0%)

CMH = Cochran-Mantel-Haenszel.
**** patients who discontinued early are assumed to have relapse
* Cochran-Mantel-Haenszel chi-square test stratified by geographical region only.
** Cochran-Mantel-Haenszel chi-square test stratified by geographical region and baseline presence of gadolinium enhancing T1 lesions (present or absent)
*** adjusting for geographical region, number of relapses occurring within the 3 year prior to study entry, baseline EDSS (<=2.5, >2,5), baseline presence of gadolinium lesions (present or absent), prior treatment with IFN-b or glatiramer acetate, age (<40, >=40)
Source: page 598

An analysis of the proportion of patients being protocol-defined relapse-free over time showed a stable pattern with some minor variations (Table 19). The relapse-rates after Cycle 1 and during the treatment-free period were consistently around 90% across all four randomized treatment arms.

Table 18 Proportion of Patients Who Remain Relapse-Free over Time (ITT Population)

	Placebo	OCR 600 mg	OCR 1000 mg	Avonex
Cycle 1	75.9%	85.5%	87.3%	77.8%
Cycle 2	88.7%	94.0%	89.4%	92.0%
Cycle 3	86.0%	87.8%	93.5%	89.8%
Cycle 4	95.9%	91.3%	84.1%	97.8%
Safety follow-up (Week 120)	83.7%	91.7%	74.0%	93.9%
B-cell mon./obs. (Week 144)	95.7%	95.7%	82.2%	95.8%

Note: All patients received OCR after Cycle 1
Source: page 598

Table 19 presents a pre-specified alternative analysis in which patients who discontinued early without relapsing were assumed not to have relapsed. In this less conservative approach, the difference in the proportions of relapse-free patients between the active treatment groups and the placebo group increased: 16.8% (CI: 0.04, 0.29) in the OCR 600 mg group, 14.9% (CI: 0.02, 0.28) in the OCR 1000 mg group, and 5.6% (CI: – 0.09, 0.20) in the Avonex group.

Table 19 Proportion of Patients Who Remain Protocol Defined Relapse-free by Week 24 (Early Discontinuations are Considered as Relapse Free) (ITT Population)

etrelap_w24_prop_itt_49 Proportion of Patients Who Remain Protocol Defined Relapse-free by Week 24 (Early Discontinuations are Considered as Relapse Free) (ITT Population)

Proportion of Patients who Remain Relapse-free	Placebo (N=54)	Ocr 600 mg (N=55)	Ocr 1000 mg (N=55)	Avonex (N=54)
Cycle 1				
n	42	52	51	45
Proportion	77.8%	94.5%	92.7%	83.3%
95% CI of proportion	(66.7%,88.9%)	(88.5%,100%)	(85.9%,99.6%)	(73.4%,93.3%)
Difference in proportion (vs. Placebo)		16.8%	14.9%	5.6%
95% CI of Difference		(0.04,0.29)	(0.02,0.28)	(-0.09,0.20)
Relative risk (RR)		0.25	0.33	0.75
95% CI of RR		(0.07,0.82)	(0.11,0.95)	(0.34,1.63)
P-value:CMH Chi-Squared test (stratified*)		0.0110	0.0295	0.4686
P-value:CMH Chi-Squared test (stratified**)		0.0544	0.1518	0.6451
P-value: Logistic model (stratified***)		0.0569	0.1307	0.7067
Number of patients in this Cycle by # of relapses (observed) (%)				
0	42(77.8%)	52(94.5%)	51(92.7%)	45(83.3%)
1	10(18.5%)	3(5.5%)	3(5.5%)	9(16.7%)
2	2(3.7%)	(0.0%)	1(1.8%)	(0.0%)
>=3	(0.0%)	(0.0%)	(0.0%)	(0.0%)

CMH = Cochran-Mantel-Haenszel.
* Cochran-Mantel-Haenszel chi-square test stratified by geographical region only.
** Cochran-Mantel-Haenszel chi-square test stratified by geographical region and baseline presence of gadolinium enhancing T1 lesions (present or absent)
*** adjusting for geographical region, number of relapses occurring within the 3 year prior to study entry, baseline EDSS (<=2.5, >2,5), baseline presence of gadolinium lesions (present or absent), prior treatment with IFN-b or glatiramer acetate, age (<40, >=40)
Program : $PROD/cdpt3422/i21493g/etrelap_w24_prop.sas
Output : $PROD/cdpt3422/i21493g/reports/etrelap_w24_prop_itt_49.rl8
29AUG2012 19:02

5.4.3 Total Number of Gadolinium-enhancing T1 Lesions Observed on MRI Scans of the Brain at Weeks 4, 8, 12, 16, 20, and 24

Consistent with results of the primary analysis (excluding weeks 4 and 8), there was a statistically significant reduction in the total number of gadolinium-enhancing T1 lesions at weeks 4, 8, 12, 16, 20, and 24 in patients who received either dose of OCR compared with those who received placebo ($p < 0.0001$) (Table 20).

The difference between Avonex and placebo patients in the total number of gadolinium-enhancing T1 lesions at weeks 4, 8, 12, 16, 20, and 24 was not statistically significant ($p = 0.99$). The two OCR groups were similar in the total number of gadolinium-enhancing T1 lesions at weeks 4, 8, 12, 16, 20, and 24.

As shown in Figure 2 the reduction in the total number of gadolinium-enhancing T1 lesions occurred as early as week 8 in both OCR groups and was maintained or further reduced through week 24. In contrast, little reduction in the total number of gadolinium-enhancing T1 lesions was seen in the placebo and Avonex groups over time.

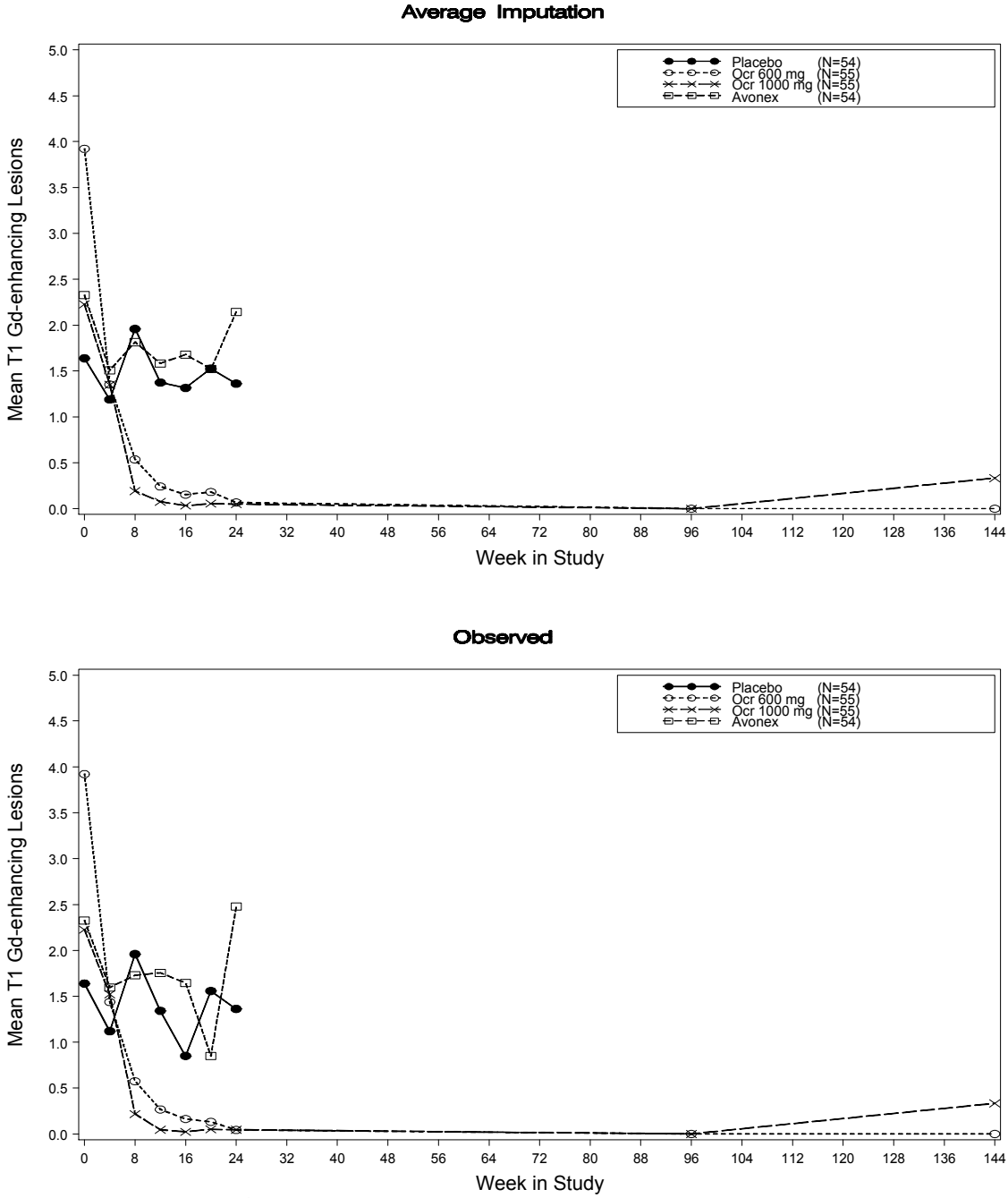
Table 20 Total Number of Gadolinium-Enhancing T1 Lesions at Weeks 4, 8, 12, 16, 20, and 24 (ITT Population)

Total Number of Gadolinium-enhancing T1 Lesions on MRI Scans of the Brain	Placebo (N=54)	Ocr 600 mg (N=55)	Ocr 1000 mg (N=55)	Avonex (N=54)
WEEK 4, 8, 12, 16, 20 and 24				
n	54	51	52	52
Mean (SD)	8.7 (17.54)	2.5 (5.10)	1.8 (5.26)	10.3 (22.15)
SE	2.39	0.71	0.73	3.07
Median	3.0	0.0	0.0	1.1
95% CI of Median	(1.4,5.0)	(0.0,0.0)	(0.0,0.7)	(0.0,3.0)
Range	0-102	0-23	0-35	0-109
Van Elteren Test (stratified)				
p-value		<0.0001	<0.0001	0.9994
Van Elteren Test (stratified*)				
p-value		0.0004	<0.0001	0.2725
Wilcoxon-Mann-Whitney Rank Sum Test				
p-value		0.0005	<0.0001	0.2821

Van Elteren test is stratified by region and presence of baseline gadolinium-enhancing lesions (absent or present).
* Van Elteren test is stratified by region only.
For the calculation of Total Number of Gadolinium-enhancing T1 Lesions on MRI Scans of the Brain at a specific week before week 24, the missing value at a time point is imputed using the average of available observations at the other time points before week 24.
No imputation for Weeks 96 and 144
MRI data collected post week 24 for OCR 600 and 1000 mg groups only.
Source: page 604

Figure 2 Mean Gd-enhancing T1 Lesions on MRI by Week

egmri_t1_mean_1 Mean Gd-enhancing T1 Lesions on MRI by Week (ITT Population)



Average Method Imputation only occurs from Weeks 0-24; No Imputation at Weeks 96 and 144

Program : $PROD/cdpt3422/i21493g/egmri_t1_mean.sas
Output : $PROD/cdpt3422/i21493g/reports/egmri_t1_mean_1.cgm
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At week 24, < 6% of OCR patients had any lesions and none had more than two lesions. In contrast, approximately 35% of Avonex and placebo patients had at least one T1 lesion and > 10% had three or more lesions.

Little difference was seen between the OCR 600 mg group and the OCR 1000 mg group in the total number of gadolinium-enhancing T1 lesions over time, particularly at the later visits. This result was consistent with findings from the primary analysis.

5.4.4 Total Number of New Gadolinium-Enhancing T1 Lesions Observed on MRI Scans of the Brain at Weeks 4, 8, 12, 16, 20, and 24

As shown in Table 21 there was also a statistically significant reduction in the total number of new gadolinium-enhancing T1 lesions at weeks 4, 8, 12, 16, 20, and 24 in patients who received either dose of OCR compared with those receiving placebo ($p < 0.0001$).

The difference between the Avonex and placebo groups in the total number of new gadolinium-enhancing T1 lesions at weeks 4, 8, 12, 16, 20, and 24 was not statistically significant ($p = 0.82$). The total number of new gadolinium-enhancing T1 lesions at weeks 4, 8, 12, 16, 20, and 24 was also similar in the two OCR groups.

There were no patients with new gadolinium-enhancing T1 lesions at week 96 and week 144 in the OCR 600 mg arm (page 609). In the OCR 1000 mg arm no patient after 96 week and one patient after week 144 had new gadolinium-enhancing T1 lesions.

Table 21 Total Number of New Gadolinium-Enhancing T1 Lesions at Weeks 4, 8, 12, 16, 20, and 24 (ITT Population)

Total Number of New Gadolinium-enhancing T1 Lesions on MRI Scans of the Brain	Placebo (N=54)	Ocr 600 mg (N=55)	Ocr 1000 mg (N=55)	Avonex (N=54)
WEEK 4, 8, 12, 16, 20 and 24				
n	54	51	52	52
Mean (SD)	5.1 (11.99)	0.8 (1.95)	0.8 (2.16)	6.2 (13.79)
SE	1.63	0.27	0.30	1.91
Median	2.0	0.0	0.0	1.0
95% CI of Median	(1.0,3.0)	(0.0,0.0)	(0.0,0.0)	(0.0,2.0)
Range	0-78	0-11	0-14	0-71
0	20	39	36	23
>0 - 1	5	1	8	8
>1 - 2	7	4	5	6
>2 - 3	2	1	1	0
>3	20	6	2	15
Van Elteren Test (stratified)				
p-value		<0.0001	<0.0001	0.8203
Van Elteren Test (stratified*)				
p-value		<0.0001	<0.0001	0.4985
Wilcoxon-Mann-Whitney Rank Sum Test				
p-value		<0.0001	<0.0001	0.4449
Fishers Exact Test				
p-value		0.0006	<0.0001	0.5197

Van Elteren test is stratified by region and presence of baseline gadolinium-enhancing lesions (absent or present).
* Van Elteren test is stratified by region only.
For the calculation of Total Number of Gadolinium-enhancing T1 Lesions on MRI Scans of the Brain at a specific week before week 24, the missing value at a time point is imputed using the average of available observations at the other time points before week 24.
No imputation for Weeks 96 and 144
MRI data collected post week 24 for OCR 600 and 1000 mg groups only.
Source: page 609

5.4.5 Change in Total Volume of T2 Lesions on MRI Scans of the Brain from Baseline to Week 24

The change from baseline in the volume of T2 lesions at week 24 is summarized in Table 22. At week 24, the median change from baseline was – 76.3 mm^3 in the OCR 600 mg group, – 163.4 mm^3 in the OCR 1000 mg group, and 2.6 mm^3 in the Avonex group, compared with 23.7 mm^3 in the placebo group (a negative change indicates improvement). The differences between the three active groups and the placebo group, however, were not statistically significant. Large variability in total T2 volume was present at baseline.

Table 22 Change in Total Volume of T2 Lesions on MRI Scans of the Brain from Baseline to Week 24 (ITT Population)

etmri_t2vol_chg_wk24_1 Change in Total Volume of T2 Lesions on Serial MRI Scans of the Brain from Baseline to Week 24 (ITT Population)

Efficacy Variable	Placebo (N=54)	Ocr 600 mg (N=55)	Ocr 1000 mg (N=55)	Avonex (N=54)
Total Volume of T2 Lesions (mm3)				
Baseline				
n	47	51	53	49
Mean (SD)	8950.84 (9776.261)	13972.61 (19930.158)	13178.30 (14271.383)	13209.11 (17206.511)
SE	1426.014	2790.780	1960.325	2458.073
Median	4764.7	6687.5	7124.7	8246.8
95% CI of Median	(2926.3,9200.2)	(5341.6,9779.7)	(5165.1,11354.8)	(5323.1,9932.3)
Range	47.4 - 39919.5	10.5 - 93777.6	202.8 - 59431.5	23.7 - 102912.0
Week 24				
n	43	45	46	46
Mean (SD)	8161.81 (8682.656)	11708.15 (15251.973)	13386.26 (14506.761)	14781.05 (20860.300)
SE	1324.093	2273.630	2138.905	3075.684
Median	4467.1	6648.0	7609.4	9182.7
95% CI of Median	(2749.8,8886.8)	(4986.0,9800.9)	(4796.3,13930.7)	(5112.4,13296.0)
Range	65.8 - 35070.5	13.2 - 65128.6	218.6 - 63493.0	23.7 - 128371.4
Change from Baseline to Week 24				
n	43	45	46	46
Mean (SD)	-112.31 (1464.206)	-878.84 (2756.839)	-600.89 (2105.964)	1040.06 (4510.140)
SE	223.289	410.965	310.508	664.984
Median	23.7	-76.3	-163.4	2.6
95% CI of Median	(-121.2,192.3)	(-297.6,-34.2)	(-679.5,60.5)	(-121.2,555.8)
Range	-5689.2 - 2504.9	-16298.6 - 1520.3	-7301.2 - 5212.5	-6713.8 - 25459.4
Wilcoxon-Mann-Whitney Rank Sum Test				
p-value		0.0886	0.1168	0.3686
Van Elteren Test (stratified*)				
p-value		0.1391	0.1596	0.4740
Ranked ANCOVA				
p-value		0.1558	0.2982	0.3553

* Van Elteren test is stratified by region only.
Ranked ANCOVA adjust geographical region, baseline Gd lesions (yes,no) and baseline T2 lesion volume. Missing values are imputed by Last Observation Carried Forward.
Program : $PROD/cdpt3422/i21493g/etmri_t2vol_chg.sas
Output : $PROD/cdpt3422/i21493g/reports/etmri_t2vol_chg_wk24_1.rl8
01AUG2012 18:39

5.4.6 Subgroup Analyses of Secondary Endpoints

For ARR, effect of OCR (600 mg and 1000 mg) was consistently positive across all subgroups compared with placebo and Avonex (Table 23).

Table 23 Subgroup Analyses of Unadjusted Annualized Protocol Defined Relapse Rate at Week 24 (ITT Population)

	Placebo (N=54)		Ocr 600 mg (N=55)			Ocr 1000 mg (N=55)			Avonex (N=54)		
	N	Relapse Rate	N	Relapse Rate	Relative Reduction(%)	N	Relapse Rate	Relative Reduction(%)	N	Relapse Rate	Relative Reduction(%)
Cycle 1											
Overall	54	0.539	55	0.124	77.1%	55	0.207	61.6%	54	0.354	34.3%
Age											
<40	28	0.538	33	0.066	87.7%	28	0.237	55.9%	31	0.201	62.6%
>=40	26	0.541	22	0.219	59.6%	27	0.174	67.8%	23	0.572	-5.7%
<38(median)	23	0.654	30	0.073	88.8%	24	0.180	72.5%	26	0.241	63.2%
>=38(median)	31	0.459	25	0.189	58.8%	31	0.230	49.8%	28	0.464	-1.1%
Sex											
Male	18	0.869	20	0.108	87.6%	17	0.378	56.5%	22	0.200	76.9%
Female	36	0.358	35	0.133	62.8%	38	0.123	65.5%	32	0.454	-26.7%
Region											
North American	14	0.137	14	0.154	-12.5%	15	0.308	-125.4%	14	0.474	-246.3%
Other	40	0.697	41	0.113	83.8%	40	0.170	75.6%	40	0.315	54.9%
Baseline EDSS											
<=2.5	24	0.533	19	0.000	100.0%	19	0.000	100.0%	26	0.325	39.1%
>2.5	30	0.544	36	0.188	65.4%	36	0.317	41.8%	28	0.382	29.8%
<=3(median)	32	0.468	24	0.000	100.0%	26	0.000	100.0%	30	0.291	37.8%
>3(median)	22	0.636	31	0.219	65.5%	29	0.386	39.3%	24	0.428	32.7%
Number of baseline gadolinium-enhancing T1 lesions											
missing	7	1.564	4	0.000	100.0%	2	0.000	100.0%	4	0.000	100.0%
0	26	0.077	25	0.089	-15.4%	29	0.325	-320.6%	33	0.384	-395.8%
>0	21	0.814	26	0.178	78.1%	24	0.091	88.8%	17	0.370	54.5%

Table 23 Subgroup Analyses of Unadjusted Annualized Protocol Defined Relapse Rate at Week 24 (ITT Population) (cont.)

	Placebo (N=54)		Ocr 600 mg (N=55)			Ocr 1000 mg (N=55)			Avonex (N=54)		
	N	Relapse Rate	N	Relapse Rate	Relative Reduction(%)	N	Relapse Rate	Relative Reduction(%)	N	Relapse Rate	Relative Reduction(%)
Number of relapses in the 3 years prior to enrollment											
<2	2	0.000	1	0.000		1	0.000		0	0.000	
2	27	0.370	27	0.000	100.0%	29	0.081	78.2%	27	0.237	36.0%
>2	25	0.782	27	0.256	67.2%	25	0.355	54.5%	27	0.471	39.8%
Number of relapses in the 1 year prior to enrollment											
0	2	0.000	0	0.000		1	0.000		1	2.173	
1	24	0.445	23	0.000	100.0%	20	0.110	75.2%	25	0.085	80.8%
>1	28	0.653	32	0.215	67.0%	34	0.274	58.1%	28	0.528	19.1%
Prior treatment with drugs within 6 month prior to enrolment											
Yes	6	0.365	13	0.349	4.3%	14	0.175	52.1%	12	0.681	-86.7%
No	48	0.560	42	0.054	90.4%	41	0.217	61.2%	42	0.256	54.3%
Prior treatment with steroid within 6 month prior to enrolment											
Yes	20	0.758	28	0.165	78.2%	22	0.000	100.0%	24	0.523	31.0%
No	34	0.419	27	0.082	80.3%	33	0.353	15.8%	30	0.215	48.6%

* missing baseline GD T1 lesions are imputed using screening values. If no baseline or no screening value, then baseline equals missing

Source: page 618

Also for the proportion of patients remaining relapse-free the effect of OCR (600 mg and 1000 mg) was consistently positive across all subgroups compared with placebo and Avonex, see Table 24. The subgroup analyses of patients with or without baseline disease activity showed a dose response relationship in favor of the 1000 mg regimen versus the 600 mg regimen. For those patients with positive count of gadolinium enhanced T1 lesions the ARR in patients treated with the higher dose was 0.091 compared to 0.178 in patients treated with the lower dose (Table 23). The same can be seen for the proportion of relapse-free patients where 11.2% more patients with disease activity were relapse-free in the high dose group compared to the low dose group (95.8% versus 84.6%, Table 24).

Table 24 Subgroup Analysis for the Proportion of Patients who Remain Relapse-free by Cycle (Protocol-defined Relapse) (ITT Population)

	Placebo (N= 54)		Ocr 600 mg (N= 55)			Ocr 1000 mg (N= 55)			Avonex (N= 54)		
	N	% Relapse Free	N	% Relapse Free	Relative Reduction(%)	N	% Relapse Free	Relative Reduction(%)	N	% Relapse Free	Relative Reduction(%)
Cycle 1											
Overall	54	75.9	55	85.5	39.6%	55	87.3	47.1%	54	77.8	7.7%
Age											
<40	28	78.6	33	90.9	57.6%	28	85.7	33.3%	31	87.1	39.8%
>=40	26	73.1	22	77.3	15.6%	27	88.9	58.7%	23	65.2	-29.2%
<38(median)	23	73.9	30	90.0	61.7%	24	91.7	68.1%	26	84.6	41.0%
>=38(median)	31	77.4	25	80.0	11.4%	31	83.9	28.6%	28	71.4	-26.5%
Sex											
Male	18	55.6	20	95.0	88.8%	17	88.2	73.5%	22	81.8	59.1%
Female	36	86.1	35	80.0	-44.0%	38	86.8	5.3%	32	75.0	-80.0%
Region											
North American	14	85.7	14	92.9	50.0%	15	80.0	-40.0%	14	71.4	-100.0%
Other	40	72.5	41	82.9	37.9%	40	90.0	63.6%	40	80.0	27.3%
Baseline EDSS											
<=2.5	24	75.0	19	94.7	78.9%	19	94.7	78.9%	26	80.8	23.1%
>2.5	30	76.7	36	80.6	16.7%	36	83.3	28.6%	28	75.0	-7.1%
<=3(median)	32	78.1	24	91.7	61.9%	26	96.2	82.4%	30	76.7	-6.7%
>3(median)	22	72.7	31	80.6	29.0%	29	79.3	24.1%	24	79.2	23.6%

Patients who discontinued early are assumed to have relapsed.
* missing baseline GD T1 lesions are imputed using screening values. If no baseline or no screening value, then baseline equals missing

Table 24 Subgroup Analysis for the Proportion of Patients who Remain Relapse-free by Cycle (Protocol-defined Relapse) (ITT Population) (cont.)

	Placebo (N= 54)		Ocr 600 mg (N= 55)			Ocr 1000 mg (N= 55)			Avonex (N= 54)		
	N	% Relapse Free	N	% Relapse Free	Relative Reduction(%)	N	% Relapse Free	Relative Reduction(%)	N	% Relapse Free	Relative Reduction(%)
Number of baseline gadolinium-enhancing T1 lesions*											
missing	7	42.9	4	100.0	100.0%	2	100.0	100.0%	4	50.0	12.5%
0	26	92.3	25	84.0	-108.0%	29	79.3	-169.0%	33	78.8	-175.8%
>0	21	66.7	26	84.6	53.8%	24	95.8	87.5%	17	82.4	47.1%
Number of relapses in the 3 years prior to enrollment											
<2	2	100.0	1	100.0		1	100.0		0		
2	27	77.8	27	92.6	66.7%	29	89.7	53.4%	27	81.5	16.7%
>2	25	72.0	27	77.8	20.6%	25	84.0	42.9%	27	74.1	7.4%
Number of relapses in the 1 year prior to enrollment											
0	2	100.0	0			1	100.0		1	0.0	
1	24	79.2	23	95.7	79.1%	20	90.0	52.0%	25	88.0	42.4%
>1	28	71.4	32	78.1	23.4%	34	85.3	48.5%	28	71.4	0.0%
Prior treatment with disease modifying drugs within 6 month prior to enrolment											
Yes	6	83.3	13	69.2	-84.6%	14	78.6	-28.6%	12	66.7	-100.0%
No	48	75.0	42	90.5	61.9%	41	90.2	61.0%	42	81.0	23.8%
Prior treatment with steroid within 6 month prior to enrolment											
Yes	20	70.0	28	82.1	40.5%	22	95.5	84.8%	24	70.8	2.8%
No	34	79.4	27	88.9	46.0%	33	81.8	11.7%	30	83.3	19.0%

Patients who discontinued early are assumed to have relapsed.
* missing baseline GD T1 lesions are imputed using screening values. If no baseline or no screening value, then baseline equals missing
Source: page 632

5.5 EXPLORATORY ANALYSES

5.5.1 MRI Outcomes

5.5.1.1 Change in Brain Volume as measured by BFR from Baseline to Week 12 and Week 12 to Week 96

A descriptive analysis of the change in brain volume from baseline to week 12 and from week 12 to week 96 was performed in the two OCR arms (Table 25). The mean values of the brain volume at baseline measured as brain fractional ratio (BFR) were similar in the two OCR arms. Brain volumes at week 12 remained the same (600mg) or were decreased (1.4%; 0.761 to 0.750) for the 1000mg arm. At week 96 volumes decreased versus the mean baseline 1.6% (OCR 600 mg arm) and 2.9% (1000 mg arm).

Table 25 Change in Brain Volume as Measured by Brain Fractional Ratio from Baseline to Week 12 and Week 12 to Week 96

etmri_brainvol_chg_1 Change in Brain Volume from Baseline to Week 12 and Week 12 to Week 96 (Observed Data) (ITT Population)

Efficacy Variable	Ocr 600 mg (N=55)	Ocr 1000 mg (N=55)
Brain Volume		
Baseline		
n	38	36
Mean (SD)	0.756 (0.0625)	0.761 (0.0566)
SE	0.0101	0.0094
25%,Median,75%	0.722,0.755,0.799	0.726,0.761,0.796
Range	0.630-0.883	0.593-0.878
Week 12		
n	39	34
Mean (SD)	0.756 (0.0600)	0.750 (0.0604)
SE	0.0096	0.0104
25%,Median,75%	0.713,0.758,0.806	0.711,0.756,0.783
Range	0.620-0.859	0.587-0.875
Week 96		
n	42	41
Mean (SD)	0.744 (0.0620)	0.739 (0.0589)
SE	0.0096	0.0092
25%,Median,75%	0.702,0.744,0.791	0.709,0.738,0.768
Range	0.618-0.864	0.600-0.868
Change from Baseline to Week 12		
n	35	29
Mean (SD)	-0.001 (0.0086)	-0.001 (0.0077)
SE	0.0015	0.0014
25%,Median,75%	-0.005,-0.001,0.005	-0.004,-0.002,0.003
Range	-0.029-0.015	-0.015-0.026
p-value*		0.4759
Change from Week 12 to Week 96		
n	39	33
Mean (SD)	-0.010 (0.0092)	-0.011 (0.0129)
SE	0.0015	0.0023
25%,Median,75%	-0.016,-0.011,-0.002	-0.016,-0.011,-0.003
Range	-0.028-0.009	-0.052-0.013
p-value*		0.9498

*Van Elteren test stratified by geographical region.
Program : $PROD/cdpt3422/i21493g/etmri_brainvol_chg.sas
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Page 1 of 1

5.5.1.2 Total Number of New and/or Enlarging T2 lesions Observed on Serial MRI scans of the Brain at Weeks 4, 8, 12, 16, 20, 24, 96 and 144 (Average Imputation Method)

The total number of new and/or enlarging T2 lesions at weeks 4, 8, 12, 16, 20, and 24 was reduced in patients who received either dose of OCR compared with those who received placebo ($p < 0.0001$) (Table 26). No clear difference in the total number of new and/or enlarging T2 lesions was observed between the two OCR groups. The total number of new and/or enlarging T2 lesions at weeks 4, 8, 12, 16, 20, and 24 was similar among Avonex and placebo patients ($p = 0.80$).

Table 26 Total Number of New and/or Enlarging T2 lesions Observed on Serial MRI scans of the Brain at Weeks 4, 8, 12, 16, 20, 24 (Average Imputation Method)

Total Number of New and/or Enlarging Gadolinium-enhancing T2 Lesions on MRI Scans of the Brain	Placebo (N=54)	Ocr 600 mg (N=55)	Ocr 1000 mg (N=55)	Avonex (N=54)
WEEK 4, 8, 12, 16, 20 and 24				
n	54	51	52	52
Mean (SD)	7.5 (13.76)	0.9 (2.05)	1.0 (3.17)	7.5 (16.69)
SE	1.87	0.29	0.44	2.31
Median	3.3	0.0	0.0	1.1
95% CI of Median	(1.4,4.8)	(0.0,0.0)	(0.0,0.0)	(0.0,2.0)
Range	0-84	0-12	0-21	0-82
0	16	37	39	23
>0 - 1	2	2	4	3
>1 - 2	5	4	5	7
>2 - 3	4	4	0	3
>3	27	4	4	16
Van Elteren Test (stratified)				
p-value		<0.0001	<0.0001	0.7987
Van Elteren Test (stratified*)				
p-value		<0.0001	<0.0001	0.1523
Wilcoxon-Mann-Whitney Rank Sum Test				
p-value		<0.0001	<0.0001	0.1341
Fishers Exact Test				
p-value		<0.0001	<0.0001	0.3071

Van Elteren test is stratified by region and presence of baseline gadolinium-enhancing lesions (absent or present).
* Van Elteren test is stratified by region only.
For the calculation of Total Number of new and/or enlarging T2 lesions on MRI Scans of the Brain at a specific week before week 24, the missing value at a time point is imputed using the average of available observations at the other time points before week 24.
Source: page 564

There were no patients with new and/or enlarging T2 lesions at week 96 and week 144 in the OCR 600 mg arm. In the OCR 1000 mg arm two patients after 96 weeks and one patient after week 144 had new and/or enlarging T2 lesions.

5.5.1.3 Proportion of Patients who Remain Free of New Gadolinium-enhancing T1 lesions

The proportion of patients with no new gadolinium-enhancing T1 lesions at week 24 is presented in Table 27. More patients remained free of new gadolinium-enhancing T1 lesions over the 24-week study period in the two OCR groups than in the placebo group: 35.2% in the placebo group, 76.5% in the OCR 600 mg group ($p < 0.0001$), and 69.2% in the OCR 1000 mg group ($p = 0.0002$). In the Avonex group, 45.3% of patients had no new gadolinium-enhancing T1 lesions at week 24 ($p = 0.83$ vs. placebo). The proportion of patients with no new gadolinium-enhancing T1 lesions at weeks 96 and 144 is presented on page 656 .

Table 27 Proportion of Patients who Remain Free of New Gadolinium-enhancing T1 lesions by Week 24 (ITT Population)

Proportion Having No New Gadolinium-enhancing T1 Lesions*	Placebo (N=54)	Ocr 600 mg (N=55)	Ocr 1000 mg (N=55)	Avonex (N=54)
Week 24				
n	19	39	36	24
Proportion	35.2%	76.5%	69.2%	45.3%
95% CI of Proportion	(22.4%,47.9%)	(64.8%,88.1%)	(56.7%,81.8%)	(31.9%,58.7%)
Difference in Proportion (vs. Placebo)		41.3%	34.0%	10.1%
95% CI of Difference		(0.24,0.59)	(0.16,0.52)	(-0.08,0.29)
Relative risk (RR)		0.36	0.47	0.84
95% CI of RR		(0.21,0.62)	(0.30,0.75)	(0.62,1.16)
P-value: CMH Chi-Squared test (stratified**)		<0.0001	0.0002	0.8348
P-value: CMH Chi-Squared test (stratified***)		<0.0001	0.0005	0.2917

* Only patients with post baseline scans are included in the analysis. Patients with a missing MRI scan are considered as not having any new gadolinium-enhancing T1 lesions.
** Cochran-Mantel-Haenszel chi-square test stratified by geographical region and baseline presence of gadolinium enhancing T1 lesions (present or absent)
*** Cochran-Mantel-Haenszel chi-square test stratified by geographical region only.
No imput[redacted]n for Weeks 96 and 144
Patient [redacted], randomized to Avonex, withdrew from the treatment period before any MRI assessments had been performed (pre week 4). Follow-up scans were performed, however, and hence, this patient is counted at week 144 only.
Source: page 656

5.5.1.4 Time to First New Gadolinium-enhancing T1 Lesions Developing over 24 Weeks

Kaplan–Meier estimates of the distribution of time to first new gadolinium-enhancing T1 lesions occurring over 24 weeks are presented in Table 28. The associated Kaplan–Meier curves for the four treatment groups are displayed in Figure 3. The stratified hazard ratio estimates (relative to placebo) were 0.29 (95% CI: 0.14, 0.60) for the OCR 600-mg group and 0.41 (95% CI: 0.21, 0.78) for the OCR 1000-mg group, indicating a reduction in the risk of experiencing a new gadolinium-enhancing event in the OCR group versus the placebo group. The stratified hazard ratio estimate (relative to the placebo group) was 1.09 (95% CI: 0.64, 1.88) for the Avonex group.

Over the 24-week study period, fewer patients developed new gadolinium-enhancing T1 lesions in the OCR groups than in the placebo and Avonex groups: 23.5% in the OCR 600-mg group and 30.8% in the OCR 1000-mg group, versus 64.8% in the placebo group and 55.8% in the Avonex group. In particular, very few OCR patients developed new gadolinium-enhancing T1 lesions after week 8.

Table 28 Time to First New Gadolinium-enhancing T1 Lesions Developing over 24 Weeks

etmri_t1new_tte_1 Time to First New Gadolinium-enhancing T1 lesions Developing over 24 Weeks (ITT Population)

	Placebo (N=54)	Ocr 600 mg (N=55)	Ocr 1000 mg (N=55)	Avonex (N=54)
No. of Subjects With New Gd+ T1 Lesions (%)	35/54 (64.8%)	12/51 (23.5%)	16/52 (30.8%)	29/52 (55.8%)
No. of Subjects Censored (%)	19/54 (35.2%)	39/51 (76.5%)	36/52 (69.2%)	23/52 (44.2%)
Time to first new Gd+ lesions (Days)				
Mean (SD)	83.0(7.35)	50.2(1.99)	107.6(7.32)	112.5(8.96)
Median	76.00	.	.	140.00
95% CI for Median	(34.00 - 140.00)			(58.00 -)
25th - 75th Percentile	30.0 - .	. - .	32.5 - .	33.5 - .
Min - Max	4.0 - 174.0+	5.0 - 175.0+	3.0 - 175.0+	25.0 - 174.0+
Stratified p-value				
Log-rank test		0.0004	0.0048	0.7467
Wilcoxon test		0.0010	0.0150	0.9041
Stratified Hazard Ratio (rel to Placebo)		0.288	0.407	1.094
(95% CI)		(0.138 - 0.599)	(0.214 - 0.775)	(0.635 - 1.883)
Unstratified p-value				
Log-rank test		0.0001	0.0019	0.2303
Wilcoxon test		0.0005	0.0076	0.1765
Unstratified Hazard Ratio (rel to Placebo)		0.296	0.403	0.740
(95% CI)		(0.153 - 0.572)	(0.223 - 0.730)	(0.452 - 1.212)
Proportion of subjects with new Gd+ T1 lesions				
at week 8	50.0%	23.5%	28.8%	38.5%
at week 16	59.3%	23.5%	28.8%	48.1%
at week 24	64.8%	23.5%	30.8%	55.8%

A + indicates a censored observation. Only patients with post baseline scans are included in the analysis. Mean, median, percentiles, 95% CI for median, and cumulative percentages are based on Kaplan-Meier estimates of the distribution time to first new Gd+ T1 lesion. Patients with missing Gd+ T1 lesion scans are considered as not having Gd+ T1 lesions. Stratified log-rank test is based on a model with two stratification variables, the geographical region and presence of baseline gadolinium-enhancing lesions (absent or present).
Program : $PROD/cdpt3422/i21493g/etmri_t1new_tte.sas
Output : $PROD/cdpt3422/i21493g/reports/etmri_t1new_tte_1.rl8
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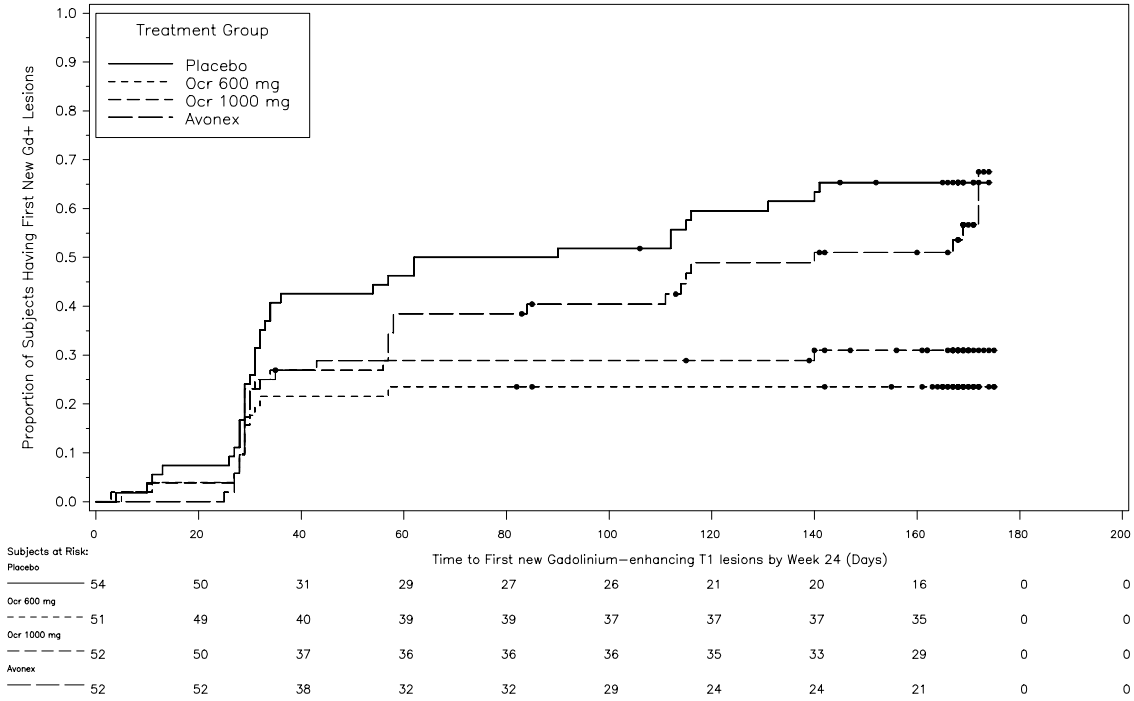
Figure 3 Time to First New Gadolinium-Enhancing T1 Lesions Developing over 24 Weeks

egtte_mri_wk24_1 Time to First New Gadolinium-enhancing T1 lesions Developing over 24 Weeks (ITT Population)



Program : $PROD/cdpt3422/i21493g/egtte_mri.sas / Output : $PROD/cdpt3422/i21493g/reports/egtte_mri_wk24_1.cgm
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5.5.2 Clinical Efficacy Outcomes

5.5.2.1 Proportion of Patients Who Remained Free from Relapse (Clinical and/or Protocol-defined Relapses)

The proportion of patients who remained free from relapse (clinical and/or protocol-defined relapse) at week 24 is summarized in Table 29. Similar to the results reported for protocol-defined relapse (see Section 5.4.2), a higher proportion of patients remained relapse free over the 24 week study period in the two OCR groups than in the placebo group. The analysis presented in Table 29 was based on a conservative approach in which patients who discontinued early and reported no relapse were assumed to have relapsed.

Table 29 Proportion of Patients who Remained Free from Relapses (Clinical and Protocol-defined) at Week 24 (ITT Population)

Proportion of Patients who Remain Relapse-free	Placebo (N=54)	Ocr 600 mg (N=55)	Ocr 1000 mg (N=55)	Avonex (N=54)
Cycle 1				
n****	39	45	48	37
Proportion	72.2%	81.8%	87.3%	68.5%
95% CI of proportion	(60.3%,84.2%)	(71.6%,92.0%)	(78.5%,96.1%)	(56.1%,80.9%)
Difference in proportion (vs. Placebo)		9.6%	15.1%	-3.7%
95% CI of Difference		(-0.06,0.25)	(0.00,0.30)	(-0.21,0.14)
Relative risk (RR)		0.65	0.46	1.13
95% CI of RR		(0.32,1.33)	(0.20,1.03)	(0.63,2.03)
P-value:CMH Chi-Squared test (stratified*)		0.2334	0.0523	0.6733
P-value:CMH Chi-Squared test (stratified**)		0.6172	0.1858	0.2585
P-value: Logistic model (stratified***)		0.3552	0.1218	0.2966
Number of patients in this Cycle by # of relapses (observed) (%)				
0	40(74.1%)	50(90.9%)	51(92.7%)	40(74.1%)
1	10(18.5%)	5(9.1%)	3(5.5%)	13(24.1%)
2	4(7.4%)	(0.0%)	1(1.8%)	(0.0%)
>=3	(0.0%)	(0.0%)	(0.0%)	1(1.9%)

**** patients who discontinued early are assumed to have relapse
CMH = Cochran-Mantel-Haenszel.
** Cochran-Mantel-Haenszel chi-square test stratified by geographical region and baseline presence of gadolinium enhancing T1 lesions (present or absent)
*** adjusting for geographical region, number of relapses occurring within the 3 year prior to study entry, baseline EDSS (<=2.5, >2,5), baseline presence of gadolinium lesions (present or absent), prior treatment with IFN-b or glatiramer acetate, age (<40, >=40)
Patients who discontinued early are assumed to have relapsed.
Source: page 659

Similar rates of patients remained relapse-free in each randomized treatment arm through Cycles 2 to 4, safety follow-up and B-cell monitoring/observation period. After 48 weeks of treatment approximately 65% of patients were free from relapse in the randomized Placebo and Avonex arms whereas 85-90% of patients were relapse-free in the two OCR arms. After 96 weeks the proportion of patients remaining relapse-free varied from 48.1% in the group of patients randomized to Avonex to 70.9% in OCR 1000 mg arm.

5.5.2.2 Proportion of Patients Requiring Systemic Methylprednisolone Treatment or Equivalent for an MS Relapse during each Treatment Cycle and at Weeks 48 and 96

The proportion of patients requiring systemic methylprednisolone or equivalent treatment for an MS relapse during the first cycle was reduced in both OCR groups compared with the placebo group: 7.3% in the OCR 600 mg group ($p = 0.09$) and 3.6% in the OCR 1000 mg group ($p = 0.015$) versus 24.1% in the placebo group (Table 30). The proportion in the Avonex group (22.2%) was similar compared to the placebo group.

Table 30 Proportion of Patients Requiring Systemic Methylprednisolone Treatment or Equivalent for an MS Relapse at Week 24

Proportion of Patients Requiring systemic methylprednisolone treatment or equivalent for an MS relapse	Placebo (N=54)	600mg (N=55)	1000mg (N=55)	Avonex (N=54)
Cycle 1				
n	13	4	2	12
Proportion	24.1%	7.3%	3.6%	22.2%
95% CI of proportion	(12.7%,35.5%)	(0.4%,14.1%)	(0.0%,8.6%)	(11.1%,33.3%)
Difference in proportion (vs. Placebo)		-16.8%	-20.4%	-1.9%
95% CI of Difference		(-0.30,-0.03)	(-0.33,-0.08)	(-0.18,0.14)
Relative risk (RR)		1.22	1.27	1.02
95% CI of RR		(1.03,1.44)	(1.08,1.49)	(0.83,1.26)
P-value:CMH Chi-Squared test (stratified*)		0.0174	0.0021	0.8218
P-value:CMH Chi-Squared test (stratified**)		0.0914	0.0146	0.3480
P-value: Logistic model (stratified***)		0.0889	0.0194	0.4125
Number of patients in this Cycle by # of relapses (observed) (%)				
0	41(75.9%)	51(92.7%)	53(96.4%)	42(77.8%)
1	10(18.5%)	4(7.3%)	1(1.8%)	9(16.7%)
2	3(5.6%)	(0.0%)	(0.0%)	2(3.7%)
>=3	(0.0%)	(0.0%)	1(1.8%)	1(1.9%)

* Cochran-Mantel-Haenszel chi-square test stratified by geographical region only.
** Cochran-Mantel-Haenszel chi-square test stratified by geographical region and baseline presence of gadolinium enhancing T1 lesions (present or absent)
*** adjusting for geographical region, number of relapses occurring within the 3 year prior to study entry, baseline EDSS (<=2.5, >2,5), baseline presence of gadolinium lesions (present or absent), prior treatment with IFN-b or glatiramer acetate, age (<40, >=40)
Source: page 667

A similar proportion of patients required systemic methylprednisolone or equivalent treatment for an MS relapse in each randomized treatment arm through Cycles 2 to 4, safety follow-up and B-cell monitoring/observation period (page 667). After 48 weeks of treatment approximately 30% of patients required systemic methylprednisolone or equivalent treatment for an MS relapse in the randomized placebo and Avonex arms whereas only 8-10% of patients required systemic methylprednisolone or equivalent treatment for an MS relapse in the two OCR arms. After 96 weeks the proportion of patients varied from 14.5% in the OCR 1000 mg arm to 40.7% to the group of patients randomized to Avonex.

5.5.2.3 Annualized Clinical and/or Protocol-defined Relapse Rate

As shown in Table 31, results for annualized clinical and/or protocol-defined relapse rate were similar to results for annualized protocol-defined relapse (see Section 5.4.1).

The annualized clinical and/or protocol-defined relapse rate at week 24 was reduced in both OCR groups compared with the placebo group: 0.223 in the OCR 600-mg group ($p = 0.003$) and 0.225 in the OCR 1000-mg group ($p = 0.004$), versus 0.753 in the placebo group. The annualized clinical and/or protocol-defined relapse rate in the Avonex group (0.691) was lower than that in the placebo group but higher than that in either OCR group.

Table 31 Annualized Clinical and Protocol-Defined Relapse Rate by Week 24 (ITT Population)

Efficacy Variable	Placebo (N=54)	Ocr 600 mg (N=55)	Ocr 1000 mg (N=55)	Avonex (N=54)
Cycle 1				
n	54	55	55	54
Total number of relapses	18	5	5	16
Total subject-years followed	26.0	24.2	24.1	25.4
Unadjusted annualized relapse rate *	0.693	0.206	0.207	0.630
Adjusted annualized relapse rate**	0.753	0.223	0.225	0.691
95% CI of adjusted annualized relapse rate	(0.511,1.109)	(0.108,0.460)	(0.109,0.463)	(0.459,1.041)
Overdispersion scale (Poisson model)		0.8210	0.8210	0.8210
p-value Poisson model		0.0034	0.0036	0.7627
Adjusted annualized relapse rate 2***	0.536	0.184	0.173	0.749
95% CI of adjusted annualized relapse rate	(0.314,0.915)	(0.087,0.390)	(0.080,0.372)	(0.485,1.157)
Overdispersion scale (Poisson model)		0.7594	0.7594	0.7594
p-value Poisson model		0.0085	0.0063	0.2660
Subject relapse rate****				
Mean(SD)	0.720(1.342)	0.197(0.627)	0.193(0.730)	0.614(1.171)
Median	0.000	0.000	0.000	0.000
95% CI subject relapse rate	(0.362 ,1.078)	(0.031 ,0.362)	(-0.000,0.386)	(0.302 ,0.927)
p-value: t-test		0.0113	0.0130	0.6653
p-value: ANOVA***		0.0289	0.0407	0.4912

*: The total number of relapses that occurred during cycle divided by the total number of subject-years followed in this period.
**: adjusted for geographical region only
***: adjusting for number of relapses occurring within the 3 year prior to study entry, baseline EDSS (<=2.5, >2,5), baseline presence of gadolinium lesions (present or absent), prior treatment with IFN-b or glatiramer acetate, age (<40, >=40) and
****: The number of relapses for each subject divided by the number of years followed from week 0 to week x for that subject. Mean and median across all subjects are present.
Source: page 675

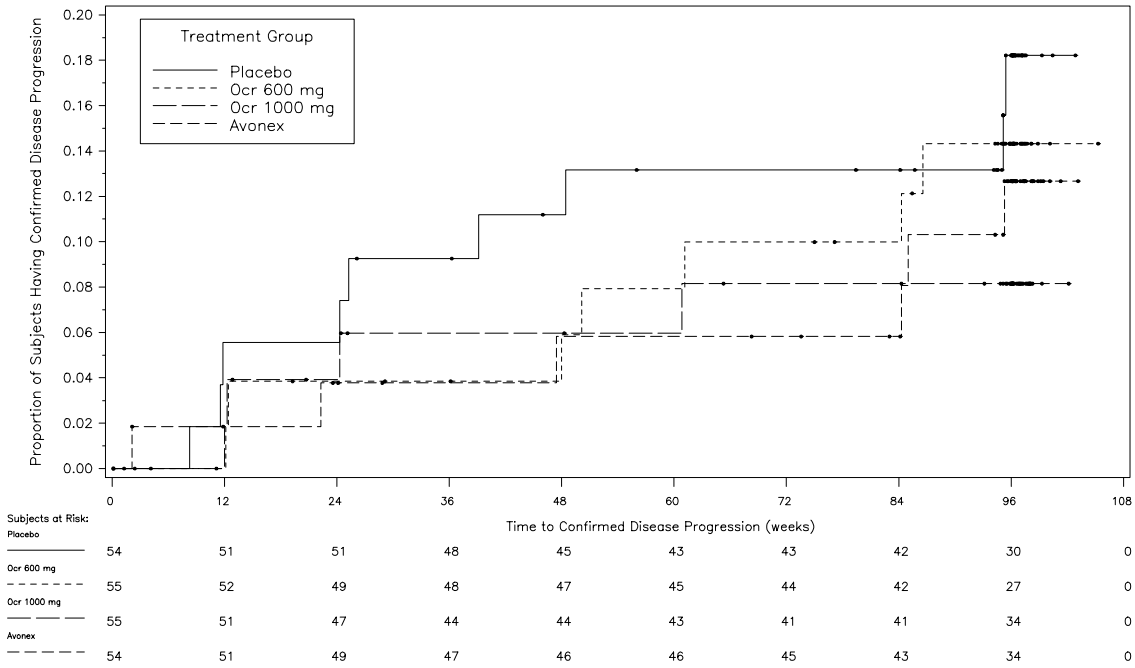
Similar relapse rates in each randomized treatment arm through Cycles 2 to 4, safety follow-up and B-cell monitoring/observation period were observed. After 48 weeks of treatment the relapse rate was 0.588 and 0.465 in the randomized placebo and Avonex arms respectively whereas the relapse rates were 0.156 and 0.2 in the OCR 600 mg and OCR 1000 mg arms, respectively. After 96 weeks the relapse rates varied from 0.24 in the OCR 1000 mg arm to 0.45 in the group of patients randomized to the placebo arm.

5.5.2.4 Sustained Disability Progression

Time to onset of SDP confirmed for 12 or 24 weeks was defined by a worsening in EDSS of 1.0 point (0.5 point if baseline EDSS was 5.5 or 6) confirmed for 12 weeks, as determined at regular monthly visits. The number of patients who experienced 12 weeks SDP and the Kaplan–Meier estimates of the distribution of time to SDP are summarized on page 683. In total 9, 7, 4 and 6 patients in placebo, OCR 600 mg, OCR 1000 mg and Avonex respectively had a confirmed 12 weeks progression event up to 96 weeks. A clear difference between the four arms could not be shown due to low event number. The corresponding Kaplan-Meier curve is presented in Figure 4.

Figure 4 Time to Onset of Sustained Disability Progression as Defined by the Sustained Worsening in EDSS of 1.0 Point (0.5 point if baseline EDSS is 6) for 12 Weeks in Duration Through to Week 96 (ITT Population)

egt2cdp12_w96_itt Time to Onset of Sustained Disability Progression as Defined by the Sustained Worsening in EDSS of 1.0 Point (0.5 point if baseline EDSS is 6 or 5.5) for 12 Weeks Through Week 96 (ITT Population)



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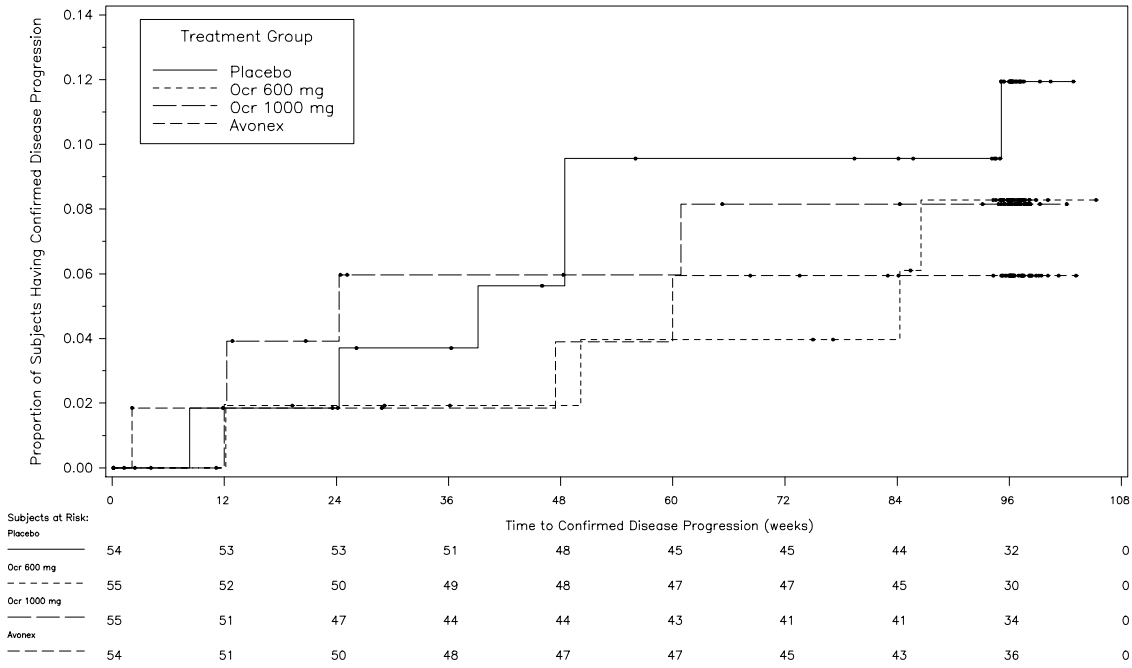
Fewer patients experienced a disease progression event confirmed for 24 weeks up to 96 weeks. The number of patients and the Kaplan–Meier estimates of the distribution of time to SDP are summarized on page 684 . In total 6, 4, 4 and 3 patients in placebo, OCR 600 mg, OCR 1000 mg and Avonex respectively had a confirmed 24 weeks progression event. A clear difference between the four arms could not be shown due to low event number. The corresponding Kaplan-Meier curve is presented in Figure 5.

Figure 5 Time to Onset of Sustained Disability Progression as Defined by the Sustained Worsening in EDSS of 1.0 Point (0.5 point if Baseline EDSS is 6) for 24 Weeks in Duration Through to Week 96 (ITT Population)

egt2cdp24_w96_itt Time to Onset of Sustained Disability Progression as Defined by the Sustained Worsening in EDSS of 1.0 Point (0.5 point if baseline EDSS is 6 or 5.5) for 24 Weeks Through Week 96 (ITT Population)



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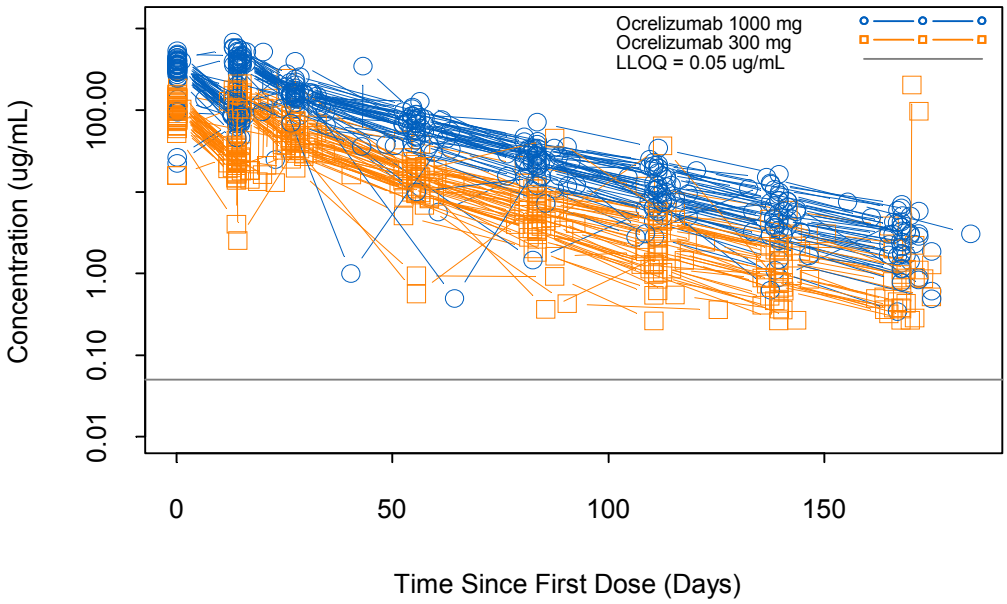
6. RESULTS: PHARMACODYNAMICS AND PHARMACOKINETICS

6.1 PHARMACOKINETICS

Plots of individual concentration-time profiles obtained in Cycle 1 indicate that OCR generally demonstrates a biphasic disposition, with a rapid initial decline in serum concentration followed by a more prolonged terminal disposition phase (Figure 6). Both the 600 mg and 1000 mg groups (i.e., a dose of 300 mg × 2 and 1000 mg × 2, resulting in a total dose of 600 mg and 2000 mg, respectively) showed a narrow spread of individual concentration-time profiles, indicating modest between-patient variability. Dose-normalized plots of individual concentration-time profiles showed a substantial overlap between the 1000 mg and 600 mg groups, indicating dose proportionality in this dose range.

Figure 6 OCR Concentration-Time Profiles by Dose



A two-compartment model with first-order elimination and a protocol-assumed variable rate zero-order infusion adequately characterized the pharmacokinetic data. A total of 812 serum concentrations from 107 patients with RRMS were used in this analysis. Results are summarized in Table 32.

Clearance (CL), central volume of distribution (V1), intercompartmental clearance (Q), and peripheral volume of distribution (V2) were 217 mL/day, 3240 mL, 196 mL/day, and 2420 mL, respectively. The terminal elimination half-life for OCR was 22.7 days. The individual predicted geometric mean AUC was 2548 μg × day/mL and 9235 μg × day/mL for the 600 mg (300 mg × 2) and 1000 mg (i.e., 1000 mg × 2) groups over the 24 weeks, respectively. The geometric mean C_{max} was 113 μg/mL and 382 μg/mL for the 600 mg and 1000 mg groups, respectively. OCR AUC and C_{max} were approximately dose proportional between 600 mg and 2000 mg.

Table 32 Population Pharmacokinetic Parameter Estimates

Parameter	Estimate (%SEM)	IIV % CV (%SEM)
CL (mL/day)	217 (3.27)	27.3 (18.7)
V1 (mL)	3240 (4.57)	31.2 (34.8)
Q (mL/day)	196 (18.1)	67.7 (38.3)
V2 (mL)	2420 (7.73)	NE
Correlation between IIV-CL and IIV-V1	0.585 (35.3)	NE
Correlation between IIV-CL and IIV-Q	−0.418 (37.6)	NE
Residual variability (% CV)	44.5 (11.3)	NE

CL = clearance; CV = coefficient of variation; NE = not estimated; Q = intercompartmental clearance; SEM = standard error of the mean; V1 = central volume of distribution; V2 = peripheral volume of distribution.

The magnitude of the effect of baseline body weight on CL and V1 was modest. Compared with the typical 70 kg patient, a smaller patient (40 kg) would have a 21% reduction in CL and a 17% reduction in V1, whereas a larger patient (130 kg) would have a 30% increase in CL and a 23% increase in V1. This effect of body weight is unlikely to be clinically meaningful; however, a more definitive assessment of this relationship should be made using a larger dataset.

Exploratory plots were generated to examine the relationship between OCR exposure in the first cycle and various efficacy and safety endpoints. Overall, no clear correlation was identified for any parameter. Patients showed similar pharmacodynamic, safety, and efficacy findings across the range of exposures within the two tested dose levels of 600 mg and 2000 mg. There appeared to be a trend for more IRRs with increasing C_{max}. It needs to be kept in mind, however, that the high 2000 mg dose was given over the same infusion duration (i.e. with a greater infusion rate versus the 600 mg dose), and generally infusion rate is indeed linked to IRR rates. Details on the pharmacokinetic analysis and results are provided on page 241.

6.2 PHARMACODYNAMICS

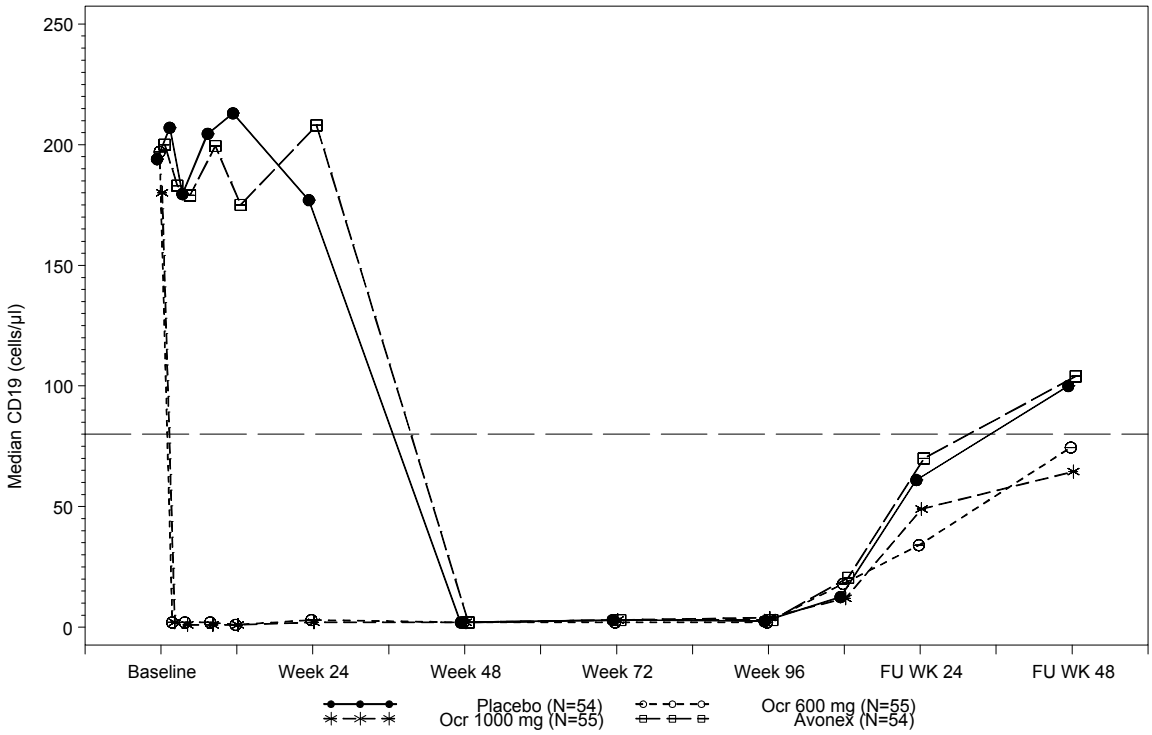
6.2.1 CD19+ B-Cells and Other FACS Results

Treatment with both doses of OCR led to rapid and complete depletion of $CD19^+$ peripheral B-cells (Figure 7). All patients had completely depleted peripheral $CD19^+$ cells (99% mean and median change from baseline) by Day 15[1] (page 685). At week 24, no patients demonstrated a return of peripheral $CD19^+$ cell counts to baseline values or to the lower limit of normal (LLN) of 80 cells/µL, which was used as protocol-defined measures of recovery.

[1] No FACS were taken between Day 1 and Day15

Figure 7 Median CD19^{+} Cells (Cells/μL) by Visit (Safety Population)

sgbcell_saf_144_facs2 Median CD19 (cells/μl) by Visit (Safety Population)



Line represents LLN = 80 cells/ul

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Change in the percentage of patients with absolute B-cell count (CD19^{+}) ≥80 cells / μL is shown on page 699 and change in mean number of B-cells by visit is shown on page 700. Mean values of CD19^{+} B-cells at week 4 and week 12 should be interpreted with caution, as they are sensitive to potential mix up of four samples at week 4 and one sample at week 12.

Mean plots of CD4 T cells, CD8 T cells, total CD3 T cells, NK cells (CD3^{-} CD56^{+}/CD16^{+}), memory B-cells (CD19^{+} CD38^{lo} CD27^{+}), plasma cells (CD19^{lo} CD38^{hi}IgD^{-} CD27^{+}), mature naive B-cells (CD19^{+} CD21^{+} IgM^{+}, IgD^{+}), regulatory T cells (CD3^{+} CD4^{+} CD127^{lo} CD25^{hi}), and memory cytotoxic T cells (CD3^{+} CD8^{+} CD45RO^{+}) measured over time are provided from page 701. Corresponding summary tables are provided from page 710.

Memory B-cells (CD19^{+}, CD38^{lo}, CD27^{+}) were depleted efficiently after administration of OCR and did not show a return to baseline at week 24. No clinically meaningful changes were observed in peripheral CD4 and CD8 T-cell counts and subsets, as well as in NK cells, plasma cells (CD19^{lo}, CD38^{hi}, IgD^{-}, CD27^{+}), and mature naive B-cells (CD19^{+}, CD21^{+}, IgM^{+}, IgD^{+}). The mean value of regulatory T cells at week 24 should be

interpreted with caution, as it was impacted by one outlier due to erroneous laboratory value.

Time to B-cell repletion analysis showed that repletion was faster in placebo and Avonex groups compared with the treatment groups that received OCR in first cycle (median time to repletion was 62.0 weeks in the placebo group, 71.0 weeks in OCR 600 mg group, 70.4 weeks in OCR 1000 mg group and 59.0 weeks in the Avonex group; page 784). However, these results should be interpreted with caution as repletion data were still immature at the time of the cut-off. B-cells repleted for more than 50% of the patients in all treatment groups by Week 144, except in the OCR 1000 mg group (where 56.4% of the patients were still depleted at Week 144). The cumulative probability of B-cells repletion is represented graphically on page 785).

6.2.2 Serum Immunoglobulin Levels

No clinically meaningful changes in total serum Ig, IgG or IgA levels were observed in any of the treatment groups (page 791 , and page 798, respectively). Serum IgM levels decreased by approximately 25% to 30% from baseline in both OCR groups over the placebo-controlled 24-week period (page 805). At screening, one patient (1.9%) in each treatment group had IgM levels below LLN and this number increased to 8 (16.7%) in both OCR groups by Week 24. A similar effect was observed in the open-label period when patients in the placebo and Avonex groups received OCR 600 mg. The proportion of patients with IgM levels below LLN increased to 30.2% in the OCR 1000 mg in Cycle 2 and remained stable throughout the study up to week 144. Mean IgM levels did not return to baseline values in any treatment group at Week 144.

7. RESULTS: SAFETY

7.1 OVERVIEW OF SAFETY

The overall proportion of patients with AEs was similar between treatment groups (Table 33). 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 33 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 (52.0%)	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.

Source: page 812 and page 840

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 600 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.page 931, page 934.

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.

7.2 EXTENT OF EXPOSURE TO STUDY TREATMENT

Extent of exposure to OCR is presented for the safety population in Table 34. For the first infusion on day 1, the mean dose of OCR received in the 600 mg group was 288.8 mg; all patients in the 1000 mg group received 1000.0 mg. For the second infusion on day 15, the mean dose of OCR received in the 600 mg group was 300.0 mg; the mean dose received in the 1000 mg group was 977.7 mg. The overall mean exposure to OCR in the placebo-controlled 24-week period was 572.4 mg (median of 600 mg) in the 600 mg group and 1942.2 mg (median of 2000 mg) in the 1000 mg group. The median total exposure to OCR in the study was 1800.0 mg in placebo and Avonex arms, 2400.0 mg in the OCR 600 mg arm and 4600.0 mg in OCR 1000 mg arm.

Table 34 Exposure to OCR Overall and by Infusion (Safety Population)

stocrmg_w144_saf Exposure to Ocrelizumab (mg) Overall and by Infusion (Safety Population)

	Placebo (N=54)	Ocr 600 mg (N=55)	Ocr 1000 mg (N=55)	Avonex (N=54)
Cycle				
Cycle 1 Day 1				
n	54	55	55	0
Mean	0.0	288.8	1000.0	
Std Dev	0.00	47.73	0.00	
Median	0.0	300.0	1000.0	
Min-Max	0.0-0.0	40.5-300.0	1000-1000	
Cycle 1 Day 15				
n	54	52	53	0
Mean	0.0	300.0	977.7	
Std Dev	0.00	0.21	130.33	
Median	0.0	300.0	1000.0	
Min-Max	0.0-0.0	298.5-300.0	82.4-1000	
Cycle 2 Day 1				
n	53	50	47	50
Mean	295.3	600.0	1000.0	300.0
Std Dev	34.00	0.25	0.00	0.00
Median	300.0	600.0	1000.0	300.0
Min-Max	52.5-300.0	598.3-600.0	1000-1000	300.0-300.0
Cycle 2 Day 15				
n	53	50	47	48
Mean	300.0	0.0	0.0	300.0
Std Dev	0.00	0.00	0.00	0.00
Median	300.0	0.0	0.0	300.0
Min-Max	300.0-300.0	0.0-0.0	0.0-0.0	300.0-300.0
Cycle 3 Day 1				
n	50	49	46	49
Mean	607.8	600.0	984.8	581.6
Std Dev	56.69	0.00	103.17	95.03
Median	600.0	600.0	1000.0	600.0
Min-Max	587.6-1000	600.0-600.0	300.3-1000	0.0-600.0
Cycle 4 Day 1				
n	49	46	44	46
Mean	600.0	600.6	636.4	600.0
Std Dev	0.03	3.83	116.32	0.00
Median	600.0	600.0	600.0	600.0
Min-Max	600.0-600.2	600.0-626.0	600.0-1000	600.0-600.0
Total Exposure				
n	54	55	55	50
Mean	1691.5	2154.7	4129.4	1710.0
Std Dev	376.33	620.78	1103.44	272.74
Median	1800.0	2400.0	4600.0	1800.0
Min-Max	0.0-2201	40.5-2426	1000-5000	300.0-1800

Patients are summarized according to first treatment actually received (if patients switch treatment they are summarized in the original treatment group).
n for each infusion includes only those patients that received that infusion (zero dose is not assumed for missed infusions)
Cycle 1 = 2 x 300mg infusions; 2 x 1000mg infusions and 2 x Placebo infusions; Cycle 2 = 2 x 300mg infusions and 1 x 1000mg infusion plus 1 x placebo infusion; Cycle 3 is 1 x 600mg infusion and 1 x 1000mg infusion

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An estimate of exposure to Avonex is summarized on page 846. Two patients (3.8%) received only partial injections for the week 2 injections; 96.2% received full injections at week 2. For all other weekly injections, 100% of patients continuing in the treatment period reported receiving full doses of Avonex. These exposure estimates should be interpreted with caution because the administration of Avonex was not under the supervision of a healthcare professional (with the exception of the first dose). Additionally, compliance rates were based only on returned vial counts and not witnessed first-hand.

Exposure to methylprednisolone was similar in all treatment arms and treatment cycles with a median of 100.0 mg. (page 848).

7.3 COMMON ADVERSE EVENTS

Table 35 shows AEs that occurred in ≥5% of patients in any treatment group during the placebo-controlled 24-week period. The most frequently occurring AEs were IRRs in both OCR groups and MS relapse in both the placebo and Avonex groups. In addition, 20.4% of Avonex-treated patients experienced flu-like symptoms. Most other AEs were reported at similar frequencies across the treatment groups.

Table 35 Adverse Events with an Incidence of ≥5% – 24-week Placebo-controlled Study Period (Safety Population)

Adverse Event	Placebo N = 54 No. (%)	Ocr 600 mg N = 55 No. (%)	Ocr 1000 mg N = 55 No. (%)	Avonex N = 54 No. (%)
Cycle 1 (n)	54	55	55	54
INFUSION RELATED REACTION	6 (11.1)	19 (34.5)	26 (47.3)	-
MULTIPLE SCLEROSIS RELAPSE	14 (25.9)	5 (9.1)	4 (7.3)	14 (25.9)
HEADACHE	4 (7.4)	4 (7.3)	8 (14.5)	8 (14.8)
URINARY TRACT INFECTION	5 (9.3)	4 (7.3)	4 (7.3)	4 (7.4)
UPPER RESPIRATORY TRACT INFECTION	2 (3.7)	5 (9.1)	7 (12.7)	2 (3.7)
FATIGUE	1 (1.9)	2 (3.6)	6 (10.9)	3 (5.6)
NASOPHARYNGITIS	4 (7.4)	2 (3.6)	3 (5.5)	3 (5.6)
INFLUENZA LIKE ILLNESS	-	-	-	11 (20.4)
BACK PAIN	1 (1.9)	2 (3.6)	3 (5.5)	2 (3.7)
ANXIETY	1 (1.9)	3 (5.5)	2 (3.6)	1 (1.9)
DIZZINESS	3 (5.6)	3 (5.5)	1 (1.8)	-
ASTHENIA	3 (5.6)	-	2 (3.6)	1 (1.9)
INSOMNIA	1 (1.9)	-	4 (7.3)	1 (1.9)
ARTHRALGIA	1 (1.9)	-	-	4 (7.4)
CHILLS	-	1 (1.8)	1 (1.8)	3 (5.6)
ORAL HERPES	3 (5.6)	2 (3.6)	-	-
INFLUENZA	-	1 (1.8)	3 (5.5)	-
RASH	-	3 (5.5)	-	1 (1.9)
MIGRAINE	-	3 (5.5)	-	-
MYALGIA	-	-	-	3 (5.6)

Percentages are based on n.
Multiple occurrences of the same adverse event in one individual counted only once for each infusion.
Investigator text for Adverse Events encoded using MedDRA version 15.0.
Source: page 849

The proportion of patients with AEs considered related to the study drug by the investigator (excluding IRRs) was lower in the OCR arms (30.9% in both arms up to Week 24) compared with placebo (44.4% up to Week 24, page 855). The most common AEs reported as related to the study drug were infections (all treatment arms) and influenza-like illness (all in the Avonex group, 18.5% of patients). Overall, from Cycles 2 to 4 and during the treatment-free period the most common AE reported as related were infections (all treatment arms).

Summaries of AEs with an incidence rate of at least 5% by cycle and number of AEs per 100 patient years by cycle are presented on page 849 and page 870, respectively.

Because MS relapse is considered both an AE and an expected event within the natural course of RRMS, some subsequent safety descriptions were pre-specified to exclude MS relapses from the analysis. A summary of AEs of clinical MS relapse by cycle is provided on page 872.

7.4 ADVERSE EVENTS BY INTENSITY

The majority of AEs in all treatment groups were NCI CTCAE Grades 1 (mild) or 2 (moderate), with $<2\%$ of patients experiencing a Grade ≥ 3 (severe) event (Table 36). Three patients experienced Grade 4 events: two in the Avonex group during Cycles 2 (IRR) and 3 (suicide attempt) and one in the OCR 1000 mg group during the monitoring/observation period (suicidal ideation) (page 878). Three fatal events occurred during this study (described in Section 7.5).

Table 36 Adverse Events by Intensity, Excluding MS Relapse – 24-week Placebo-controlled Study Period (Safety Population)

Category of Adverse Events	Placebo (N=54)	OCR 600 mg (N=55)	OCR 1000 mg (N=55)	Avonex (N=54)
Grade 5 adverse events	0	0	1	0
Grade 4 adverse events	0	0	0	0
Grade 3 adverse events	3	3	4	3
Grade 2 adverse events	15	22	21	16
Grade 1 adverse events	15	10	10	8

Note: patients with more than one AE are counted only once.
Source: page 878

7.5 DEATHS

One patient in the OCR 1000 mg group ([redacted] died during the placebo-controlled 24-week period (Day 92) due to SIRS. This patient was hospitalized with acute onset of encephalopathy and status epilepticus following [redacted] scheduled, Week 12 MRI scan. The patient began to feel un-well following infusion of gadolinium, for [redacted] MRI scan. At home, [redacted] became delirious and presented to the emergency room in status epilepticus. [redacted] developed hemolytic anemia and severe thrombocytopenia, with rapidly progressive multi-organ dysfunction. While hospitalized, the patient developed 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. The presumptive diagnosis was disseminated intravascular coagulation and systemic inflammatory response syndrome of unknown cause. A postmortem, clinico-pathological review board was convened. Following review, no definite etiology could be determined, however, PCR analyses were negative for viral DNA in both brain and liver pathological specimens. 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 [redacted]) died on Day 968 due to an injury. A patient randomized to OCR 600 mg arm ([redacted]1) died on Day 1,074 due to an unknown cause (this event was not included in the outputs presented in this report as it occurred after the Week 144 visit). 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.

Details of patient's cases are provided in patient narratives (page 161). A listing of deaths is provided on page 1523.

7.6 SERIOUS ADVERSE EVENTS

The proportion of patients who experienced SAEs during the placebo-controlled 24-week period was similar between study arms (Table 37). No SAEs of any system class or preferred term occurred in more than one patient in any treatment group. Of the seven SAEs reported in the placebo-controlled 24-week period, two were reported by the investigator as being related to study treatment (oral herpes infection in the placebo group and hypersensitivity reaction in the OCR 600 mg group; page 881 ; the patient was withdrawn from the study).

Table 37 Serious Adverse Events – 24-week Placebo-controlled Study Period (Safety Population)

Body System/ Adverse Event	Placebo N=54 No. (%)	Ocr 600 mg N=55 No. (%)	Ocr 1000 mg N=55 No. (%)	Avonex N=54 No. (%)
Cycle 1 (n)	54	55	55	54
ALL BODY SYSTEMS				
Total Pts with at Least one AE	2 (3.7)	1 (1.8)	2 (3.6)	2 (3.7)
Total Number of AEs	2	1	2	2
GASTROINTESTINAL DISORDERS				
Total Pts with at Least one AE	1 (1.9)	-	-	1 (1.9)
ABDOMINAL PAIN UPPER	1 (1.9)	-	-	-
INGUINAL HERNIA STRANGULATED	-	-	-	1 (1.9)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Total Pts with at Least one AE	-	-	1 (1.8)	-
SYSTEMIC INFLAMMATORY RESPONSE SYNDROME	-	-	1 (1.8)	-
IMMUNE SYSTEM DISORDERS				
Total Pts with at Least one AE	-	1 (1.8)	-	-
HYPERSENSITIVITY	-	1 (1.8)	-	-
INFECTIONS AND INFESTATIONS				
Total Pts with at Least one AE	1 (1.9)	-	-	-
ORAL HERPES	1 (1.9)	-	-	-
NERVOUS SYSTEM DISORDERS				
Total Pts with at Least one AE	-	-	-	1 (1.9)
MULTIPLE SCLEROSIS RELAPSE	-	-	-	1 (1.9)
PSYCHIATRIC DISORDERS				
Total Pts with at Least one AE	-	-	1 (1.8)	-
ANXIETY	-	-	1 (1.8)	-

Percentages are based on n.
Multiple occurrences of the same adverse event in one individual counted only once for each infusion.
Investigator text for Adverse Events encoded using MedDRA version 15.0.
Source: page 887

The summary of SAEs up to Week 144 is presented on page 915. The number of SAEs per 100 patient years by cycle is presented on page 893). Patient narratives are provided on s .

Throughout the four treatment cycles, 27 SAEs were reported in 23 patients (page 915).The most common SAEs were serious infections with a total of 9 serious infections reported in 9 patients (Cycle 1: 1, Cycle 2: 3, Cycle 3: 4, Cycle 4: 1, page 895). No serious infection was reported during follow-up or monitoring/observation periods. The number of serious infections per 100 patient years by cycle is presented on page 901.

Five SAEs that occurred in Cycle 3 (anal abscess, gingival infection, colitis, suicide attempt and back pain) and one SAE that occurred during follow-up (breast cancer) were reported as related to the study drug by the investigator (page 881).

7.7 ADVERSE EVENTS THAT LED TO WITHDRAWAL OF STUDY TREATMENT

Four patients experienced an AE leading to withdrawal from treatment during the placebo-controlled 24-week period (Table 38):

two patients in the OCR 600 mg group:

- SAE of hypersensitivity occurring within 24 hours of infusion but not identified by investigator as an IRR;
- non-serious AE of IRR;

one patient in the OCR 1000 mg group who experienced a SAE of anxiety;

one patient in the Avonex group who experienced a non-serious AE of vomiting.

Table 38 Adverse Events Leading to Withdrawal – 24-week Placebo-controllessd Study Period (Safety Population)

Body System/ Adverse Event	Placebo N=54 No. (%)	Ocr 600 mg N=55 No. (%)	Ocr 1000 mg N=55 No. (%)	Avonex N=54 No. (%)
Cycle 1 (n)	54	55	55	54
ALL BODY SYSTEMS				
Total Pts with at Least one AE	-	2 (3.6)	1 (1.8)	1 (1.9)
Total Number of AEs	-	2	1	1
GASTROINTESTINAL DISORDERS				
Total Pts with at Least one AE	-	-	-	1 (1.9)
VOMITING	-	-	-	1 (1.9)
IMMUNE SYSTEM DISORDERS				
Total Pts with at Least one AE	-	1 (1.8)	-	-
HYPERSENSITIVITY	-	1 (1.8)	-	-
INJURY, POISONING AND PROCEDURAL COMPLICATIONS				
Total Pts with at Least one AE	-	1 (1.8)	-	-
INFUSION RELATED REACTION	-	1 (1.8)	-	-
PSYCHIATRIC DISORDERS				
Total Pts with at Least one AE	-	-	1 (1.8)	-
ANXIETY	-	-	1 (1.8)	-

Percentages are based on n.
Multiple occurrences of the same adverse event in one individual counted only once for each infusion.
Investigator text for Adverse Events encoded using MedDRA version 15.0.
Source: page 903

Two patients withdrew from treatment due to AEs during the open-label phase (both received OCR 600 mg): one experienced an IRR in Cycle 2 (Avonex group) and another had colitis in Cycle 3 (OCR 600 mg group; page 903). Both events were serious (page 909). The listing of patients with AEs leading to withdrawal is provided on page 1524 and patient narratives for all cases mentioned above are provided on page 161 .

7.8 ADVERSE EVENTS THAT LED TO DOSE MODIFICATION

During the placebo-controlled 24-week period, three patients required a dose modification: two as the result of an IRR (one patient in the OCR 600 mg group and another in the OCR 1000 mg group) and one as the result of inguinal hernia strangulated (Avonex group) (Table 39). In addition, two patients required a dose modification during the open-label period (both randomized to the placebo group): one due to an IRR in Cycle 2 and one due to influenza in Cycle 3 (page 918).

Table 39 Adverse Events Leading to Modification of the Infusion (Excluding Clinical MS Progression) – 24-week Placebo-controlled Study Period (Safety Population)

Body System/ Adverse Event	Placebo N=54 No. (%)	Ocr 600 mg N=55 No. (%)	Ocr 1000 mg N=55 No. (%)	Avonex N=54 No. (%)
Cycle 1 (n)	54	55	55	54
ALL BODY SYSTEMS				
Total Pts with at Least one AE	-	1 (1.8)	1 (1.8)	1 (1.9)
Total Number of AEs	-	1	1	1
INJURY, POISONING AND PROCEDURAL COMPLICATIONS				
Total Pts with at Least one AE	-	1 (1.8)	1 (1.8)	-
INFUSION RELATED REACTION	-	1 (1.8)	1 (1.8)	-
GASTROINTESTINAL DISORDERS				
Total Pts with at Least one AE	-	-	-	1 (1.9)
INGUINAL HERNIA STRANGULATED	-	-	-	1 (1.9)

Percentages are based on n.
Multiple occurrences of the same adverse event in one individual counted only once for each infusion.
Investigator text for Adverse Events encoded using MedDRA version 15.0.
Source: page 918

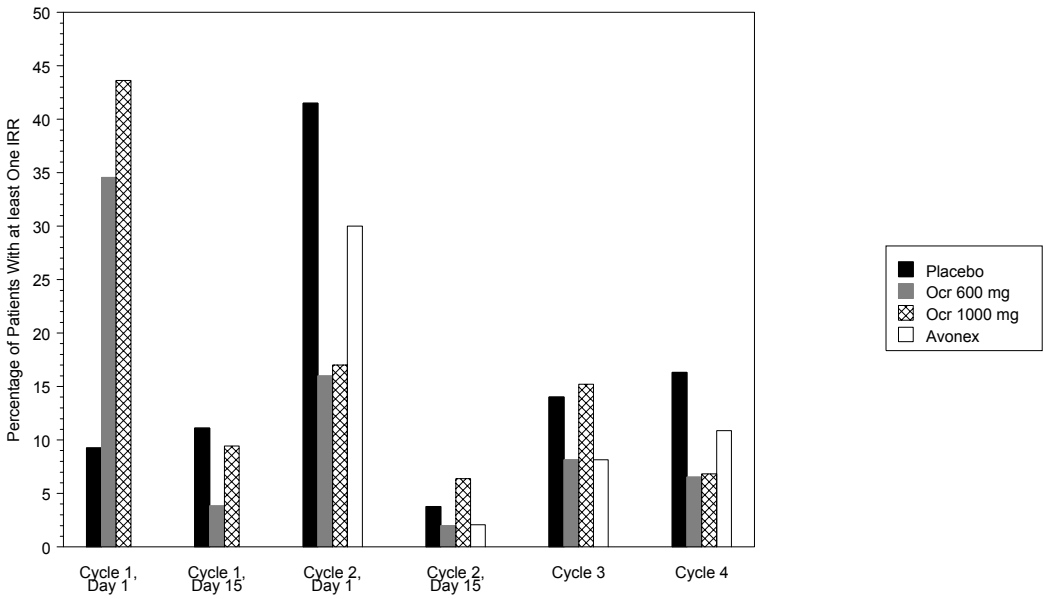
7.9 ADVERSE EVENTS OF SPECIAL INTEREST

7.9.1 Infusion-Related Reactions

Infusion-related reactions were reported more frequently in OCR patients during or after the first infusion (day 1), occurring in 34.5% of patients in the OCR 600 mg group and 43.6% of patients in the OCR 1000 mg group, compared with 9.3% of placebo patients (Figure 8 and page 924). The percentage of patients experiencing an IRR was lower after the second infusion (day 15): 9.3% in the placebo group, 3.8% in the OCR 600 mg group, and 9.4% in the OCR 1000 mg group.

Figure 8 Percentage of Patients with at Least One Infusion-related Reaction by Infusion and Treatment over Time (Safety Population)

sgirrbarchart_w144 Bar Chart Displaying the Percentage of Patients With At Least One IRR by Infusion and Treatment Over Time (Safety Population)



Placebo arm receives: Placebo (C1), Ocr 600 mg (C2-C4)
Avonex arm receives: Avonex (C1), Ocr 600 mg (C2-C4)

Percentages are based on n, number of patients that received the infusion
Program : $PROD/cdpt3422/i21493g/sgirrbarchart.sas
Output : $PROD/cdpt3422/i21493g/reports/sgirrbarchart_w144.cgm
29AUG2012 17:01

The most common symptoms were rash, throat irritation, pruritus, flushing, headache, tachycardia, and pyrexia (page 926). Most IRRs in both the OCR and placebo groups were Grades 1 or 2 (page 931). Four Grade 3 IRRs occurred during the study, one of them occurring in the OCR 1000 mg group in Cycle 1 Day 1. One patient experienced an IRR of Grade 4 on Day 1 in Cycle 2 (Avonex arm) and withdrew from the study due to this SAE. No fatal IRRs occurred during the study.

Overall, 3 patients on OCR withdrew due to IRRs: 2 reported as IRRs (page 934) and the other one as serious hypersensitivity. The investigator did not report this event as an IRR; however, the sponsor considered it to be infusion related. Three patients required a dose modification as the result of an IRR (page 937).

7.9.2 Infections

During the placebo-controlled 24-week period, there was no increase in the incidence of infections in the OCR groups compared with the placebo group (Table 40). Across the blinded treatment arms, the proportion of patients experiencing an infection was 37.0% in the placebo group, 43.6% in the OCR 600 mg group, and 30.9% in the OCR 1000 mg group. The proportion of patients with an infection was lower in the open-label Avonex group than in the blinded OCR and placebo groups. Infection rates did not increase over subsequent cycles and during follow-up and monitoring/observation periods.

Table 40 Infections by Cycle (Safety Population)

Preferred Terms/ Adverse Event	Placebo N=54 No. (%)	Ocr 600 mg N=55 No. (%)	Ocr 1000 mg N=55 No. (%)	Avonex N=54 No. (%)
Cycle 1 (n)	54	55	55	54
ALL PREFERRED TERMS				
Total Pts with at Least one AE	20 (37.0)	24 (43.6)	17 (30.9)	11 (20.4)
Total Number of AEs	28	33	28	13
Cycle 2 (n)	53	50	47	50
ALL PREFERRED TERMS				
Total Pts with at Least one AE	18 (34.0)	18 (36.0)	9 (19.1)	14 (28.0)
Total Number of AEs	29	23	13	15
Cycle 3 (n)	50	49	46	49
ALL PREFERRED TERMS				
Total Pts with at Least one AE	6 (12.0)	10 (20.4)	8 (17.4)	9 (18.4)
Total Number of AEs	7	11	12	14
Cycle 4 (n)	49	46	44	46
ALL PREFERRED TERMS				
Total Pts with at Least one AE	10 (20.4)	6 (13.0)	7 (15.9)	5 (10.9)
Total Number of AEs	11	6	8	5
Safety Follow-up (n)	49	48	50	49
ALL PREFERRED TERMS				
Total Pts with at Least one AE	8 (16.3)	9 (18.8)	8 (16.0)	6 (12.2)
Total Number of AEs	9	10	11	7
Monitoring/Observation (n)	46	46	45	48
ALL PREFERRED TERMS				
Total Pts with at Least one AE	5 (10.9)	3 (6.5)	5 (11.1)	3 (6.3)
Total Number of AEs	8	3	6	3

Source: page 940

The most frequently reported infections were urinary tract infections, upper respiratory infections, and nasopharyngitis (page 940). Most of the infections were of Grade 1 and 2 (page 948). One patient in the placebo group experienced a serious infection (oral herpes) during the placebo-controlled 24-week period (page 955). In addition, three patients had serious infections in Cycle 2, four in Cycle 3 and one in Cycle 4. No AEs reported as infection led to withdrawal of treatment. No opportunistic or fatal infections were reported in this study.

Summaries of infections and serious infections per 100 patient years are presented on page 961 and page 963 , respectively.

7.10 PREGNANCIES

Up to the cutoff date of the present report, two pregnancies were reported. One female patient reported a pregnancy while on treatment [redacted] One male patient reported a pregnancy in his female partner while on treatment. [redacted] Narratives for both cases are provided (page 161).

7.11 LABORATORY PARAMETERS

7.11.1 Shifts

Laboratory shift tables are presented on page 965. No between-group differences in shifts in any of the laboratory parameters were observed and shifts were not considered clinically significant. Two patients experienced isolated Grade 4 laboratory abnormalities during the placebo-controlled 24-week study period; neither abnormality led to an AE or to withdrawal from treatment.

7.11.2 Marked Laboratory Test Value Abnormalities

Isolated laboratory abnormalities were observed; however, no between-group differences in any of the laboratory parameters were found (page 1209). In the 600 mg OCR group, an isolated laboratory value for elevated potassium (7.0 mmol/L) occurred in a patient who was taking potassium supplements as a listed medication prior to screening and during the study. Another patient had an isolated laboratory value of low glucose (<2.20 mmol/L). All previous and subsequent values of potassium in the first patient and glucose in the second patient were within the reference range. One patient in the placebo group had a CPK level of 6033 IU/L on day 1, which normalized to 96 IU/L on day 85. No AEs were reported in association with these laboratory abnormalities.

In addition, one patient in the 1000 mg OCR group had an elevated GGT >5 times ULN at screening (505 U/L) and baseline (651 U/L), which was accompanied by transaminase elevations at baseline (AST 108 U/L, ALT 68 U/L) but no increase in bilirubin or alkaline phosphatase. GGT remained elevated in this patient reaching a maximum of 1441 U/L at week 12; AST and ALT remained elevated at levels comparable to baseline; alkaline phosphatase was mildly elevated at week 24 (121 U/L);

total bilirubin remained within normal limits throughout the 24-week treatment period. This event was reported as a laboratory AE by the investigator in association with duodenal irritation.

One placebo patient had an elevated GGT >5 times ULN at screening (558 U/L) in addition to ALT and alkaline phosphatase elevations. GGT (maximum value of 785 U/L at week 12), ALT and alkaline phosphatase elevations persisted while total bilirubin remained normal throughout the 24-week placebo-controlled treatment period.

The listing of all laboratory data with a laboratory grade of 3 or 4 is provided on page 1222 and the listing of marked laboratory abnormalities is provided on page 1248 .

7.11.3 Immunogenicity

Throughout the study five patients had positive HAHA titers at one or more time points (Table 41). All patients had a positive HAHA titer already prior to exposure to Ocrelizumab. Patients in the Avonex group were not tested for HAHA status at baseline or week 12, but 2 patients (4.4%) were HAHA positive at week 24 prior to first exposure to OCR in Cycle 2.

Table 41 HAHA Status by Visit – 24-week Placebo-controlled Study Period (Safety Population)

	Placebo (N=54)	Ocr 600 mg (N=55)	Ocr 1000 mg (N=55)	Avonex (N=54)
Baseline				
n	49	51	49	0
Negative	48 (98.0%)	50 (98.0%)	49 (100.0%)	0 (0.0%)
Positive	1 (2.0%)	1 (2.0%)	0 (0.0%)	0 (0.0%)
Week 12				
n	51	51	48	1
Negative	50 (98.0%)	50 (98.0%)	48 (100.0%)	1 (100.0%)
Positive	1 (2.0%)	1 (2.0%)	0 (0.0%)	0 (0.0%)
Week 24				
n	51	49	49	45
Negative	50 (98.0%)	48 (98.0%)	49 (100.0%)	43 (95.6%)
Positive	1 (2.0%)	1 (2.0%)	0 (0.0%)	2 (4.4%)

Source: page 1267

A summary of baseline HAHA status and change from baseline categories by visit is provided on page 1267 .

7.12 OTHER SAFETY TESTS

7.12.1 ECGs

Review of ECG data did not reveal any clinically significant between-group differences (page 1270). The majority of ECGs at every time point showed no abnormalities. ECG findings during the placebo-controlled 24-week period are described below. No AEs were associated with any of the described findings.

One placebo patient had sinus tachycardia noted on ECG at week 24 that was not present at screening.

A [redacted] in the 1000 mg group with screening ECG evidence of left ventricular hypertrophy and QRS widening had a week 24 ECG indicating incomplete right bundle branch block. A [redacted] in the 1000 mg group had sinus bradycardia on [redacted] screening ECG while under treatment with sotalol; [redacted] ECG at week 24 was normal.

A [redacted] in the Avonex group had ECG evidence of past anterior myocardial infarction and left bundle branch block at screening, with no abnormalities reported at week 24.

Left ventricular hypertrophy in slim patient at Week 96 not noted as abnormal on subsequent ECGs.

Abnormal ECG with myocardiodystrophy in one patient at Week 26 not noted as abnormal thereafter.

7.12.2 Vital Signs

Review of systolic blood pressure, diastolic blood pressure, pulse, and respiration data did not reveal any clinically significant between-group differences. A trend for increasing mean and median heart rate (approximately 5 to 10 beats per minute) was noted in all three infusion groups (in the placebo group and both OCR groups) toward the end of longer infusions, between approximately hours 3 and 6.5. In all three infusion groups, mean and median heart rate at subsequent non-infusion and pre-infusiol visits were similar to baseline values. Summaries of vital signs relative to infusion and non-infusion vital signs are presented on page 1350 and page 1350 respectively.

8. DISCUSSION

The primary objective of this study was to evaluate the efficacy of two doses of OCR (2 × 300 mg and 2 × 1000 mg) compared with placebo in reducing brain inflammation, as measured by the total number of gadolinium-enhancing T1 lesions observed on serial MRI scans of the brain at weeks 12, 16, 20, and 24. Key secondary objectives were to evaluate the efficacy of both OCR doses compared with placebo in reducing ARR at 24 weeks, and to evaluate the safety and tolerability of both doses of OCR after four cycles of treatment. This report presents the data obtained during the placebo-controlled 24-week period, the open-label treatment period where all patients received OCR (until Week 96), the 24-week follow-up period and the 24-week observation / monitoring period (total duration of 144 weeks).

8.1 STUDY POPULATION

Of the 220 patients randomized, 218 received study treatment and 204 (93%) completed the 24-week placebo-controlled study period. The number of patients completing all four treatment cycles until week 96 ranged from 89% in the placebo group to 78% in OCR 1000 mg group. Overall, the proportion of patients who prematurely withdrew from treatment was low, taking into account the duration of this study. Even though the rate of withdrawal tended to be higher in the OCR 1000 mg arm, most of the withdrawals occurred for non-safety reasons.

The ITT and safety populations comprised 218 patients who were randomized and received at least one dose of study treatment. The PP population comprised 197 patients. The most frequent reason for exclusion from the PP population was receipt of $<$ 80% of the designated study drug dose. Only a few protocol violations were reported and they did not impact the interpretation of the results of the primary analysis as demonstrated by the per protocol analysis.

Baseline demographic data as well as baseline MRI results, were generally well balanced across the four treatment groups. Patients enrolled in this study were representative of the general population of patients with RRMS. A higher mean number of gadolinium-enhancing T1 lesions was observed in the OCR 600 mg group at baseline compared with the other three treatment groups. However, category analysis showed that this apparent difference was driven by outliers.

A higher percentage of patients had received prior MS therapies (excluding corticosteroids) in both OCR groups than in the placebo or Avonex group. This imbalance was driven by the low number of patients treated with cytokines in the placebo and Avonex arm (17% and 26%, respectively) compared to both OCR arms (33% and 38%, respectively). Corticosteroids were given to a higher percentage of patients randomized to placebo and Avonex arms than to those randomized to OCR arms. This imbalance was numerically small and did not impact the interpretation of the study results.

8.2 EFFICACY

This study met its primary endpoint and key secondary endpoints. A statistically significant and clinically meaningful treatment effect on total gadolinium-enhancing 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. The robustness of the primary and key secondary analyses was demonstrated by the consistent results of sensitivity analyses. The change in the volume of T2 lesions at week 24, however, was not significantly reduced in OCR patients compared with placebo and Avonex patients. Exploratory endpoints presented in this report consistently favored both OCR doses over Avonex and placebo.

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 subgroups based on a wide range of patient characteristics. No notable differences between the OCR groups were detected in any of the endpoints for the overall population. The subgroup analyses of patients with or without baseline disease activity showed a dose response relationship in favor of the 1000 mg regimen versus the 600 mg regimen. However, these descriptive subset analysis results should be interpreted with caution, as sample sizes were small, many factors were examined simultaneously and no formal statistical analysis or adjustment for multiple comparisons was performed.

In exploratory analyses, OCR showed a superior treatment effect over Avonex in reducing the total number of gadolinium-enhancing T1 lesions and the formation of new gadolinium-enhancing lesions. OCR was also superior to Avonex in reducing ARR.

The treatment benefit of OCR was maintained throughout the study up to Week 144. No significant differences in efficacy endpoints between the study arms were observed during the open-label period or the treatment-free period.

As expected based on the current knowledge of the biology of MS, a reduction in the number of gadolinium-enhancing lesions detected by MRI translated into a significant reduction in relapses and an improvement in other clinical endpoints assessed in this study. It is hypothesized that changes in brain volume can reflect brain atrophy as a result of MS-related tissue loss and can thereby correlate with long-term clinical outcome in these patients. The results of this study suggest that the number of T1 weighted gadolinium-enhancing lesions detected by MRI is a reliable surrogate endpoint for clinical efficacy of OCR in patients with relapsing MS.

8.3 PHARMACOKINETICS AND PHARMACODYNAMICS

At the dose range tested in this study, OCR AUC 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. Exploratory analyses did not show any clear correlation between OCR exposure and various efficacy and safety endpoints.

Both doses of OCR led to a rapid and complete depletion of peripheral $CD19^+$ B-cells, which was sustained through the 96-week treatment period. A reduction in serum IgM levels, but not IgG or IgA levels, was observed in patients treated with both OCR doses, which is consistent with the known pharmacodynamic effects of OCR in other autoimmune disorders.

Time to B-cell repletion analysis showed that repletion was faster in placebo and Avonex groups compared with the treatment groups that received OCR in first cycle. This result suggest a possible correlation between duration on treatment (number of cycles) with OCR and the speed of B-cell repletion; however, this hypothesis was not formally tested and no conclusion can be reached at the time of writing of this report. Experience in patients with rheumatoid arthritis treated with rituximab for up to 9.5 years does not support this finding.

8.4 SAFETY

Both doses of OCR were generally well tolerated. Overall, with the exception of IRRs, safety profile of both OCR doses was similar to placebo. Although the total number of AEs was higher in the OCR 1000 mg arm compared with the three other arms, the percentages of patients with AEs were similar across all four treatment arms. This observation also holds true for SAEs, severe AEs and AEs resulting in premature withdrawal from study treatment. The only fatal AE reported during the placebo-controlled period of the study occurred in the OCR 1000 mg arm; however, despite of an extensive investigation of this case, its causal relationship with OCR remains unclear. The two other deaths that occurred in this study after the end of the treatment period in patient with repleted B-cells were considered unrelated to the study drug by the investigator.

IRRs occurring after the first infusion were the most commonly reported AEs in patients who received OCR. After the second infusion, however, the incidence of IRRs was similar to placebo. Most IRRs were mild or moderate in intensity and resulted in premature discontinuation of the study drug in less than 2% of patients. No clinically significant differences in frequency or intensity of IRRs were observed between the two OCR arms. The numerically lower rate of IRRs during first infusion following OCR 300mg infusion compared to OCR 1000mg infusion may be associated with differences in infusion rates (mg/h) rather than nominal dose administered. In clinical studies in patient with RA, when administered at same infusion rate, IRRs were similar across both dose groups (2 x 200mg and 2 x 500 mg).

There was no increase in the incidence of infections or serious infections in the OCR groups compared with the placebo group during the placebo-controlled 24-week period. Infection rates did not increase 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 were reported in this study.

The results obtained in this study suggest that both doses of OCR were effective in depleting B-cells. Both dose had similar safety profiles without clinically evident decrease in patient's immunocompetence.

9. CONCLUSIONS

Both 2 × 300 mg and 2 × 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.

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