TITLE PAGE

RESEARCH REPORT NO. 1062910

Update Clinical Study Report – WA21493 – 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. 1062910, March 2016.

Study Sponsor(s)	F. Hoffmann-La Roche Ltd. / Genentech Inc.
Study Dates:	First Patient Entered: 13 January 2008 Data cut-off: 22 January 2015
Trial Phase:	II
Indication:	Relapsing Remitting Multiple Sclerosis (RRMS)
Name of Principal Investigator:	**Affiliation:**
Prof. [redacted]	[redacted] Switzerland
Sponsor's Signatory:	[redacted]

Personnel Responsible for Clinical and Statistical Analyses:

Study Statistician	[redacted]
Clinical Scientist	[redacted]

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

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SYNOPSIS OF RESEARCH REPORT 1062910 (PROTOCOL WA21493)

COMPANY: NAME OF FINISHED PRODUCT: NAME OF ACTIVE SUBSTANCE(S):	(FOR NATIONAL AUTHORITY USE ONLY)
TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	Update Clinical Study Report – WA21493 – 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. 1062910, March 2016.
INVESTIGATORS / CENTERS AND COUNTRIES	78 centers from Europe and North America
PUBLICATION (REFERENCE)	Provided in the Primary CSR: 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	First Patient Entered: 13 January 2008 Data cut-off: 22 January 2015
CLINICAL PHASE	II
OBJECTIVES	This Update Clinical Study Report (CSR) provides safety data collected during the treatment-free period (TFP) and the open-label extension period (OLE) of this study (cut-off: 22 January 2015), and allows qualitative assessment on persistence of treatment effects. An addendum to the Primary CSR is also included in the present CSR. This addendum provides a listing of adverse events (AEs) that occurred during the main treatment period with onset up to Week 96 that were missing from the clinical database at the time of the preparation of the Primary CSR. Post-hoc analyses using the data from the main (96-weeks) study period are also presented in this addendum. The objectives of the main study period are provided in the Primary CSR. The objective of the OLE was to evaluate the safety and tolerability of one dose of ocrelizumab during the OLE period.
STUDY DESIGN	Study WA21493 was a Phase II, multicenter, randomized, parallel-group, placebo- and Avonex-controlled, dose-finding study designed to evaluate the efficacy, as measured by brain magnetic resonance imaging (MRI) lesions, and safety of two dose regimens of ocrelizumab in patients with relapsing-remitting multiple sclerosis (RRMS).
NUMBER OF SUBJECTS	Main study: 220 patients, OLE: 103 patients.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Main study: Men and women ranging from 18-55 years of age inclusive, with RRMS in accordance with the McDonald criteria (2005). Patients must have experienced at least 2 documented relapses within the last 3 years prior to screening, at least one of which occurred within the last year prior to screening. OLE: Prior to retreatment with ocrelizumab, patients were evaluated for the following conditions and laboratory abnormalities: • Severe (Grade 3) infusion-related reaction (IRR) to a previous ocrelizumab infusion • Any significant or uncontrolled medical condition or treatment-emergent, clinically significant laboratory abnormality • Active infection • Absolute neutrophil count <1.5 x 10^3 μl • CD4 cell count < 250/μl • Hypogammaglobulinemia: IgG < 4.0 g/l.
TRIAL DRUG / STROKE (BATCH) No.	Main study: batch numbers provided in the Primary CSR. OLE: OCR 200 mg/867856, 925173, 461740, 499115, 634132.
DOSE / ROUTE / REGIMEN / DURATION	Group A: Dose 1: 2 intravenous (IV) infusions of ocrelizumab 1000 mg separated by 14 days. Dose 2 (Week 24): one infusion of ocrelizumab 1000 mg and one infusion of placebo separated by 14 days. Dose 3 (Week 48): single infusion of ocrelizumab 1000 mg. Dose 4 (Week 72): single infusion of ocrelizumab 600 mg. Group B: Dose 1: 2 IV infusions of ocrelizumab 300 mg separated by 14 days. Dose 2: one infusion of ocrelizumab 600 mg and one infusion of placebo separated by 14 days. Doses 3 and 4: single infusion of ocrelizumab 600 mg. Group C: Dose 1: 2 IV infusions of placebo separated by 14 days. Dose 2: 2 infusions of ocrelizumab 300 mg separated by 14 days. Doses 3 and 4: single infusion of ocrelizumab 600 mg. Group D: Dose 1: weekly intramuscular (IM) injections of Avonex® 30 μg. Dose 2: 2 infusions of ocrelizumab 300 mg separated by 14 days. Doses 3 and 4: single infusion of ocrelizumab 600 mg. The dose of ocrelizumab in the OLE consisted of 600 mg ocrelizumab administered as infusions of ocrelizumab 300 mg on Days 1 and 15 followed by a single infusion of 600 mg every 24 weeks.
REFERENCE DRUG / STROKE (BATCH) No.	Main study: placebo and Avonex batch numbers are provided in the Primary CSR. OLE: not applicable as all patients received ocrelizumab.
CRITERIA FOR EVALUATION	
Clinical and Imaging Outcomes:	Brain MRI including the acquisition of the following scans: T2-weighted MRI scan, T1-weighted MRI scan (without gadolinium enhancement), T1-weighted MRI scan (with gadolinium enhancement), relapses (protocol-defined and clinical), Expanded Disability Status Scale (EDSS) scores,

	Karnofsky Performance Scale score (OLE only).
PHARMACODYNAMICS:	Pharmacodynamic (PD) assessments included: • 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 (natural killer) cells (CD16, CD56). • Quantitative immunoglobulin (Ig) levels including total Ig, IgG, IgM, and IgA isotypes.
PHARMACOKINETICS:	Pharmacokinetic assessments are presented in the Primary CSR.
SAFETY:	For both TFP and OLE, the safety evaluations consisted of the following: AEs, deaths, serious AEs (SAEs), withdrawals due to AEs, vital signs/physical examinations, concomitant treatments/surgical procedures, 12 lead electrocardiograms (ECGs), pregnancy testing, neurological examinations, and safety MRI. In addition, the following laboratory data were examined: complete routine hematology, chemistry, urinalysis, thyroid function tests, and anti-drug antibodies (ADAs, referred to in the protocol as human anti-humanized antibodies, HAHA). Antibodies against mumps, rubella, varicella, S. pneumoniae, and Epstein Barr virus are collected during the main part of the study. The results were listed for the TFP only.
STATISTICAL METHODS	Clinical and imaging parameters were handled like safety outcomes; that is, they were listed and summarized by treatment, but no formal statistical analyses were performed.

METHODOLOGY

After 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 study consisted of a 96-week treatment period followed by a TFP of variable duration (minimum 48 weeks). This period included at least 3 visits at Week 108, Week 120, and Week 144, and consisted of

- 24-week safety follow-up period;
- B-cell monitoring period of variable duration;
- 24-week observation period.

Patients who had completed both the main (96-week) treatment period and the TFP (at least through Week 120) were invited to participate in the OLE. During the OLE patients received ocrelizumab 600 mg every 24 weeks. Patients who withdrew from the OLE entered into B-cell monitoring until their B cells were repleted. B-cell repletion was defined as the number of B cells above the lower limit of normal (LLN) of 80 cells/μL or a return to baseline values, whichever was lower. Patients who were not eligible, or chose not to enter the OLE, were monitored until their B cells were repleted, then entered a 24-week observation period.

CLINICAL AND IMAGING OUTCOMES

Treatment-free Period

During the TFP, the annualized protocol-defined relapse rate adjusted by geographical region (Eastern Central Europe/Asia, North America and Western Europe) was 0.220, 95% CI [0.146, 0.333] in Group A, 0.058, 95% CI [0.028, 0.120] in Group B, 0.073, 95% CI [0.037, 0.144] in Group C, and 0.065, 95% CI [0.031, 0.136] in Group D. Annualized clinical relapse rate (including protocol-defined relapses, Poisson Model, adjusted by geographical region) was 0.342, 95% CI [0.233, 0.504] in Group A, 0.147, 95% CI [0.084, 0.257] in Group B, 0.095, 95%

CI [0.046, 0.194] in Group C, and 0.111, 95% CI [0.057, 0.218] in Group D. Annualized relapse rates were higher in Group A compared with the other treatment groups.

Mean and median EDSS were similar in all treatment groups. There was little change in EDSS over time in any of the treatment groups.

Open-label Extension

Brain volume after 2 years in OLE was similar to OLE baseline. During this period, mean new/enlarging T2 lesion count decreased from 0.80 (standard deviation [SD]=3.48) to 0.08 (SD=0.28), and the mean total number of Gadolinium-enhancing T1 lesions decreased from 0.13 (SD=1.12) to 0.00 (SD=0.00).

The annualized protocol-defined relapse rate adjusted for geographical region for the all exposed population was 0.056, 95% CI [0.032, 0.097]. This rate was higher in Group A: 0.245, 95% CI [0.142, 0.424]. Adjusted annualized clinical relapse rate in the all exposed population was 0.086, 95% CI [0.050, 0.147]. This rate was higher in Group A: 0.236, 95% CI [0.125, 0.449].

At OLE baseline, the mean EDSS was 3.14 (SD=1.68) and the median was 3.50. No clinically relevant worsening in EDSS over time was observed during the OLE.

PHARMACODYNAMIC RESULTS

Treatment-free Period

Median times to B-cell repletion were numerically higher in Groups A and B (74.0 weeks and 71.9 weeks, respectively) compared with Groups C and D (62.0 weeks and 59.0 weeks, respectively); however the CIs were wide and overlapping.

Total serum Ig, IgG or IgA levels remained stable throughout the TFP. Serum IgM levels were lower compared with baseline values by approximately 35% in all treatment groups and remained stable during the TFP.

Open-label Extension

A total of 86 patients (90.5%) enrolled in the OLE had repleted B cells at baseline. The proportion of patients with repleted B cells was similar between treatment groups. Treatment with ocrelizumab in the OLE led to B-cell depletion in all patients within 24 weeks after the first dose. Memory B-cells ($CD19^{+}$, $CD38^{lo}$, $CD27^{+}$) were depleted efficiently after administration of ocrelizumab. No 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 naïve B-cells ($CD19^{+}$, $CD21^{+}$, IgM^{+}, IgD^{+}).

Small decreases from baseline in total Ig, IgA and IgG and larger decrease in IgM were observed following ocrelizumab treatment. Serum IgM levels decreased from baseline after ocrelizumab treatment by approximately 25% and remained stable during the OLE.

PHARMACOKINETIC RESULTS

Pharmacokinetic assessments are presented in the Primary CSR.

SAFETY RESULTS

Treatment-free Period

An overview of AEs is presented in Table 1. During the TFP, the proportion of patients with AEs was higher in Group A compared with the other treatment groups: 70.0% versus 50.0% in Group B, 36.7% in Group C, and 38.8% in Group D. This difference was mainly driven by MS relapses that were reported as AEs and occurred with a higher incidence in Group A compared with the other treatment groups. Sixteen patients (32.0%) in Group A had MS relapse AEs versus 9 (18.8%), 5 (10.2%), and 6 (12.2%) in Groups B, C, and D, respectively. The percentage of patients with at least one infection was also higher in Group A compared with the other treatment groups. Sixteen patients (32.0%) in Group A had an AE from the System Organ Class (SOC) Infections and Infestations versus 11 (22.9%), 11 (22.4%), and 9 (18.4%) in Groups B, C, and D, respectively. However, infection AE rate per 100 patient years was similar among the treatment groups: 34.77, 95% CI [23.49, 51.45] in Group A, 23.49, 95% CI [14.61, 37.79] in Group B, 33.84, 95% CI [22.28, 51.39] in Group C, and 22.25, 95% CI 13.18, 37.57 in Group D.

Most AEs were Grade 1 or Grade 2 in intensity. There were 2 Grade 3 AEs in each of the Groups B, C, and D, and 4 Grade 3 AEs in Group A. There were 2 Grade 4 AEs, both occurring

in Group A: suicidal ideation and immune thrombocytopenic purpura. Two patients died during the TFP: 1 in Group B due to unknown cause, and 1 in Group C due to injury from accident.

A total of 12 patients had SAEs during the TFP. SAE rate per 100 patient years was 6.95, 95% CI [2.89, 16.71] in Group A, 5.53, 95% CI [2.07, 14.73] in Group B, 1.54, 95% CI [0.22, 10.92] in Group C, and 3.18, 95% CI [0.80, 12.71] in Group D. Two SAEs were considered related to the study drug by the investigator: breast cancer that resolved with sequelae and a life-threatening immune thrombocytopenic purpura that was unresolved at the time of the database lock. Both SAEs occurred in patients randomized to Group A. The patient who experienced immune thrombocytopenic purpura withdrew from the TFP due to this event. There were no other withdrawals due to AEs.

One pregnancy was reported in a patient randomized to Group B. No delivery complications were reported, and no congenital defects or infant AEs were reported.

There were no safety findings related to laboratory parameters, ECGs, vital signs or physical examination.

Table 1 Overview of Adverse Events

	Group C N=49	Group B N=48	Group A N=50	Group D N=49
Number and proportion of patients with at least one AE	18 (36.7%)	24 (50.0%)	35 (70.0%)	19 (38.8%)
Number and proportion of patients with Grade 3 or 4 AEs	2 (4.1%)	2 (4.2%)	5 (10.0%)	2 (4.1%)
Deaths	1	1	0	0
Number and proportion of patients with at least one SAE	1 (2.0%)	4 (8.3%)	5 (10.0%)	2 (4.1%)
Withdrawals due to AE	0	0	1[a]	0
Number and proportion of patients with selected AEs				
Infections	11 (22.4%)	12 (25.0%)	16 (32.0%)	9 (18.4%)
Pregnancy	0	1	0	0

[a] according to the withdrawal page of the CRF

Group A: Dose 1 = OCR 1000 mg (Day 1 and 15); Dose 2 = OCR 1000 mg Day 1, placebo Day 15; Dose 3 = OCR 1000 mg; Dose 4 = OCR 600 mg.

Group B: Dose 1 = OCR 300 mg (Day 1 and 15); Dose 2 = OCR 600 mg Day 1, placebo Day 15; Dose 3 and Dose 4 = OCR 600 mg.

Group C: Dose 1 = Placebo (Day 1 and 15); Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg.

Group D: Dose 1 = Avonex 30 μg/week; Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg.

OCR = ocrelizumab

Open-label Extension

An overview of AEs reported during the OLE is provided in Table 2. A total of 66 patients (64.1%) had at least one AE. Most AEs were Grade 1 or Grade 2 in intensity. Five patients had a total of 8 treatment-emergent Grade 3 AEs: bronchopneumonia, asthenia, sinusitis, headache, IRR, osteoarthritis, MS relapse, and non-alcoholic steatohepatitis. No Grade 4 or Grade 5 treatment-emergent AEs were reported. Three patients had SAEs: one patient had bronchopneumonia, one patient had hepatitis A, and one patient had uterine prolapse. Among those, only the SAE of bronchopneumonia was considered related to the study drug by the investigator. There were no AEs leading to permanent discontinuation of study drug.

The most common AEs were from the SOCs Infections and Infestations (42 patients, 40.8%), Nervous System Disorders, mainly MS relapse (15 patients, 14.6%), and IRRs (22 patients, 21.4%). Most IRRs occurred after first infusion and no IRRs were reported after the fourth and the subsequent doses. Most IRRs were Grade 1 or Grade 2 in intensity. Only one Grade 3 IRR was reported; it occurred after the first infusion. No serious, life-threatening or fatal IRRs were reported.

There were no safety findings related to laboratory parameters, ECGs, vital signs or physical examination.

Table 2 Overview of Adverse Events

	Group C N=29	Group B N=31	Group A N=19	Group D N=24	All exposure for OLE N=103
Number and proportion of patients with at least one AE	17 (58.6%)	19 (61.3%)	12 (63.2%)	18 (75.0%)	66 (64.1%)
Number and proportion of patients with Grade 3 AEs	1 (3.4%)	2 (6.5%)	1 (5.3%)	1 (4.2%)	5 (4.9%)
Deaths	0	0	0	0	0
Number and proportion of patients with at least one SAE	2 (6.9%)	0	0	1 (4.2%)	3 (2.9%)
Withdrawals due to AE	0	0	0	0	0
Number and proportion of patients with selected AEs					
Infections	10 (34.5%)	13 (41.9%)	8 (42.1%)	11 (45.8%)	42 (40.8%)
IRRs	4 (13.8%)	8 (25.8%)	3 (15.8%)	7 (29.2%)	22 (21.4%)
Pregnancy	0	0	0	0	0

Group A: Dose 1 = OCR 1000 mg on Day 1 and 15; Dose 2 = OCR 1000 mg Day 1, placebo Day 15; Dose 3 = OCR 1000 mg; Dose 4 = OCR 600 mg; OLE first dose = 300 mg on Day 1 and 15; subsequent OLE doses = 600 mg.

Group B: Dose 1 = OCR 300 mg on Day 1 and 15; Dose 2 = OCR 600 mg Day 1, placebo Day 15; Dose 3 and Dose 4 = OCR 600 mg; OLE first dose = 300 mg on Day 1 and 15; subsequent OLE doses = 600 mg.

Group C: Dose 1 = Placebo (Day 1 and 15); Dose 2 = OCR 300 mg on Day 1 and 15; Dose 3 and Dose 4 = OCR 600 mg; OLE first dose = 300 mg on Day 1 and 15; subsequent OLE doses = 600 mg.

Group D: Dose 1 = Avonex 30 μg/week; Dose 2 = OCR 300 mg on Day 1 and 15; Dose 3 and Dose 4 = OCR 600 mg; OLE first dose = 300 mg on Day 1 and 15; subsequent OLE doses = 600 mg.

OCR = ocrelizumab

CONCLUSIONS

No new safety findings were identified during the TFP or the OLE. No increase in the rate or incidence of infections or serious infections was observed during the TFP or the OLE period compared with the main 96-week treatment period. The IRR profile observed during the OLE was consistent with the main 96-week treatment period in terms of severity and nature of AEs.

CORE REPORT

GLOSSARY OF ABBREVIATIONS

ADA	anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BRS	Biomarker Research Samples
BSR	Biomarker Sample Repository
CDI	confirmed disability improvement
CI	confidence interval
CNS	central nervous system
CRF	Case Report Form
CSR	Clinical Study Report
DMC	data monitoring committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
EDSS	Expanded Disability Status Scale
ELISA	enzyme-linked immunosorbent assay
FACS	fluorescence-activated cell sorter
FSS	Functional System Score
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
HAHA	human anti-humanized antibodies
HBsAg	hepatitis B surface antigen
HBcAb	hepatitis B core antibody
HBV	hepatitis B virus
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN beta-1a	interferon beta-1a
Ig	immunoglobulin
IM	intramuscular
INN	International Non-Proprietary Name
IRB	Institutional Review Board
IRR	infusion-related reaction
ITT	intent-to-treat
IV	intravenous

JCV	John Cunningham virus
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MS	multiple sclerosis
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	natural killer
OLE	open-label extension (period)
PCR	polymerase chain reaction
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PRO	patient-reported outcome
RBC	red blood cells
RNA	ribonucleic acid
RRMS	relapsing-remitting multiple sclerosis
t.u.	titer units
SAE	serious adverse event
SOC	System Organ Class
SOP	Standard Operating Procedures
TFP	treatment-free period
TSH	thyroid-stimulating hormone
WBC	white blood cells

1. INTRODUCTION

Multiple sclerosis (MS) is an inflammatory and demyelinating disease of the human central nervous system (CNS). MS is a heterogeneous disorder based on clinical course, magnetic resonance imaging (MRI) assessments, and pathologic analysis of biopsy and autopsy material. 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.

The benefits of currently approved first-line disease-modifying therapies for the reduction and prevention of disability in patients with RRMS are relatively modest. Therefore, development of more effective therapies for the treatment of MS remains a high medical need.

Ocrelizumab (also known as RO4964913, rhuMAb 2H7, or PRO70769) is a recombinant humanized monoclonal antibody that selectively depletes CD20-expressing B cells, while preserving the capacity of B-cell reconstitution and preexisting humoral immunity. Innate immunity and total T-cell numbers are not affected. The precise mechanisms through which ocrelizumab exerts its therapeutic clinical effects in MS are not fully elucidated but involve immunomodulation through the reduction in the number and function of $CD20^{+}$ B cells.

This study (WA21493/ACT4422g) served as both a proof-of-concept study for ocrelizumab in RRMS and a dose-finding study for the Phase III MS development program. It also provided preliminary information comparing ocrelizumab with interferon beta-1a (IFN beta-1a) (Avonex®) indicated for the treatment of RRMS. The Primary Clinical Study Report (CSR) for this study presented the efficacy and safety data collected up to Week 144 (cut-off: 09 March 2012) [CSR 1034917].

This Update CSR provides all safety data collected during the treatment-free period (TFP) and the open-label extension period (OLE) of this study (cut-off: 22 January 2015), and allows qualitative assessment on persistence of treatment effects. The reporting period of the present Update CSR partially overlaps with the Primary CSR. The data presented for the TFP in this Update CSR replaces the data presented in the Primary CSR as they cover the entire duration of this period.

An addendum to the Primary CSR is also included in the present CSR (Section 8). This addendum provides a listing of adverse events (AEs) with onset up to Week 96 that were missing from the clinical database at the time of the preparation of the Primary CSR. Post-hoc analyses using the data from the main (96-weeks) study period

described in Section 3.8.8, including the placebo-controlled period, are also presented in this report in Section 8.

2. OBJECTIVES

The objective of the OLE was to evaluate the safety and tolerability of 600 mg of ocrelizumab administered every 24 weeks during the OLE period.

The objectives of the main study period are provided in Section 2 of the study protocol.

3. MATERIALS AND METHODS

3.1 OVERALL STUDY DESIGN

Study WA21493 was a Phase II, multicenter, randomized, parallel-group, placebo- and Avonex-controlled, dose-finding study designed to evaluate the efficacy, as measured by brain MRI lesions, and safety of two dose regimens of ocrelizumab in patients with RRMS. The overviews of the study design and dose regimens under investigation are shown in Figure 1 and Table 1, respectively.

After a 4-week screening period, eligible patients were randomized (1:1:1:1) to one of four treatment groups, A, B, C, or D (note: in the statistical outputs those groups are labelled ocrelizumab 1000 mg, ocrelizumab 600 mg, placebo and Avonex, respectively). The study consisted of a 96-week treatment period followed by a TFP of variable duration (minimum 48 weeks). This period included at least three visits at Week 108, Week 120, and Week 144, and consisted of

- 24-week safety follow-up period;
- B-cell monitoring period of variable duration;
- 24-week observation period.

Patients who had completed both the main (96-week) treatment period and the TFP (at least through Week 120) were invited to participate in the OLE. Patients were re-consented for participation and entered the OLE screening period where they underwent an evaluation for eligibility (see Section 3.4). During the OLE patients received ocrelizumab 600 mg every 24 weeks. Patients who withdrew from the OLE entered into B-cell monitoring until their B cells were repleted. B-cell repletion was defined as a number of B cells above the lower limit of normal (LLN) of 80 cells/μL or a return to baseline values, whichever was lower. Patients who were not eligible, or chose not to enter the OLE, were monitored until their B cells were repleted, then entered a 24-week observation period (see Figure 2).

Figure 1 Study Flow Chart

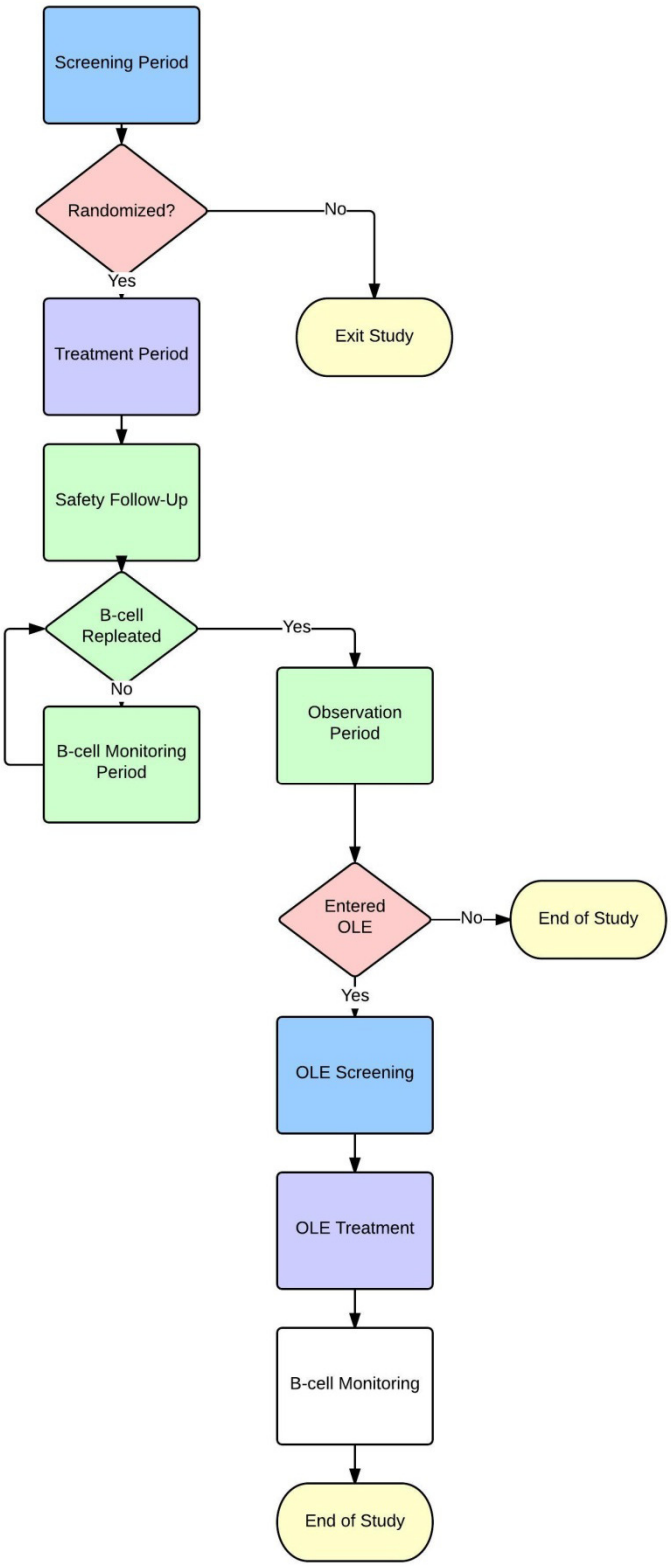


Table 1 Overview of Dose Regimens

Screening	Randomization	Treatment Period (96 Weeks)						Treatment-free Period [a]			Open-label Extension [b]
		Placebo-controlled Period (24 weeks)		OCR Treatment Period (doses separated by 24 weeks)				Safety Follow-up	B-cell Monitoring Period	Obs. Period Week 144 visit	screening+ treatment period
		Dose 1 [c]		Dose 2		Dose 3	Dose 4				
4 weeks	Group	Day 1	Day 15	Day 1	Day 15	Day 1	Day 1	24 Weeks	Variable Duration	24 Weeks	Every 24 weeks [d]
	A	OCR 1000	OCR 1000	OCR 1000	Placebo	OCR 1000	OCR 600				OCR 600
	B	OCR 300	OCR 300	OCR 600	Placebo	OCR 600	OCR 600				OCR 600
	C	Placebo	Placebo	OCR 300	OCR 300	OCR 600	OCR 600				OCR 600
	D	Avonex 30 μg IM qwk		OCR 300	OCR 300	OCR 600	OCR 600				OCR 600

Avonex = interferon beta-1a; IM = intramuscular; IV = intravenous; Obs = observation; OCR = ocrelizumab; qwk = weekly

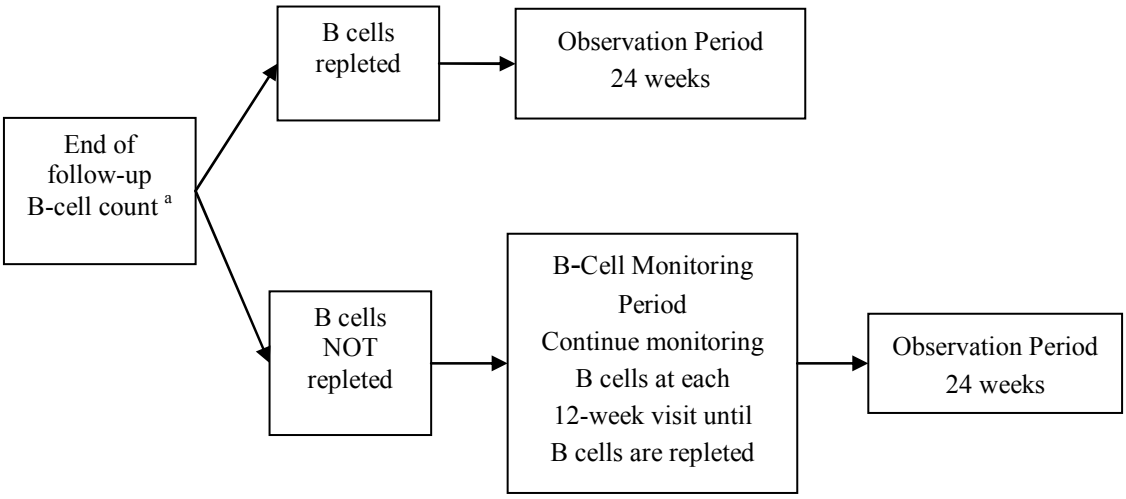
[a] There was a gap of variable duration between the TFP and the OLE.

[b] Patients who discontinued the OLE entered B-cell monitoring and were followed every 24 weeks until B cells have repleted.

[c] OCR dose in mg. Placebo and OCR were administered by IV infusion. Methylprednisolone 100 mg IV was administered prior to placebo or OCR infusions.

[d] The dose of ocrelizumab in the OLE consisted of 600 mg ocrelizumab administered as infusions of ocrelizumab 300 mg on Days 1 and 15 followed by a single infusion of 600 mg every 24 weeks.

Figure 2 B-Cell Monitoring and Observation Periods in Ocrelizumab-Treated Patients



[a] As defined in Section 5.3.1.4 of the protocol. At the end of the follow-up period, patients whose B-cell counts had repleted entered the 24-week observation period. 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.

Further details on study design are provided in the protocol and the Primary CSR.

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: 22 January 2015 (Protocol WA21493 Version D dated 03 April 2012). To date, three global protocol amendments have been implemented (Versions B, C, and D) and one local protocol amendment in Canada. A list of major protocol changes is provided below; full amendment histories, including administrative and typographic changes, are also provided.

Protocol Version B, dated 11 June 2008, introduced the following changes:

- Collection of persisting gadolinium-enhancing T1 lesions was added.
- The transition to Dose 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 Expanded Disability Status Scale (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 ocrelizumab dose was added.
- The assessment of protocol-defined relapses was clarified.
- A standardized questionnaire for the telephone interview was provided.
- The frequency of John Cunningham virus (JCV) 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 ocrelizumab 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, dated 15 October 2011, introduced one change: the addition of an OLE period of the study following the TFP.

Protocol Version D, dated 03 April 2012: the window for the Week 144 visit to allow patients the opportunity to enter the OLE following the TFP was increased from 24 weeks to 96 weeks.

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 $\geq$1.0 point from the baseline EDSS when the baseline score is 5.0 or less, and $\geq$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.”

A local amendment to protocol D in Denmark in December 2013 prolonged the OLE up to 4 years.

3.2 ADMINISTRATIVE STRUCTURE

The study was sponsored by F. Hoffmann-La Roche Ltd. who were responsible for the administration and conduct of the study. In addition, a number of external organizations were given roles and responsibilities for the administration or conduct of the study procedures (see Administrative Structure).

An external, independent Data Monitoring Committee (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.

3.3 ETHICS AND STUDY CONDUCT

The study was conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice (GCP), and the regulations and procedures described in the following sections of the protocol:

Compliance with laws and regulations	Protocol Section 12.1
Informed Consent procedures	Protocol Section 12.2. A sample ICF is provided.
Institutional Review Boards (IRBs) and/or Independent Ethics Committees (IECs) approval	Protocol Section 12.3. A list of IRBs and IECs is provided.
Data Quality Assurance and Data Collection and Management	Protocol Section 9. The blank Case Report Form (CRF) is provided.
Audits and GCP compliance	See statement of GCP compliance below and audit certificate.

The Roche Clinical Quality Assurance group conducted no audits at investigator site. Genentech conducted two investigator audits. In addition alliance partner/co-development partner Quintiles conducted three investigator audits and performed one study specific audit.

No critical audit findings were observed. For all audit findings appropriate corrective and preventive actions were undertaken.

Investigators were trained according to applicable sponsor Standard Operating Procedures (SOPs). Roche and the investigators strictly adhered to the stated provisions in these guidelines. This was documented by the investigator's signature on the protocol agreeing to carry out all of its terms in accordance with the applicable regulations and law and to follow International Conference on Harmonisation (ICH) GCP guidelines.

Approval from the IEC/IRB was obtained before study start and was documented in a letter to the investigator specifying the date on which the committee met and granted the approval. Roche also obtained approval from the relevant competent authority prior to starting the study. No modifications were made to the protocol after receipt of the IEC approval.

Protocol amendments were prepared by the sponsor and were submitted to the IRB/IEC and to regulatory authorities in accordance with local regulatory requirements. Approval was obtained from the IRB/IEC and regulatory authorities (as locally required) before implementation of any changes.

3.4 SELECTION OF STUDY POPULATION

3.4.1 Overview

Men and women 18 to 55 years of age, inclusive, who were diagnosed with RRMS in accordance with the revised McDonald criteria (2005) and met the eligibility criteria provided below, were eligible for enrollment in the study. Inclusion and exclusion criteria for the main (96-week) treatment period are provided in Section 4 of the protocol.

3.4.2 Inclusion and Exclusion Criteria for Open-Label Extension Period

Patients who had completed both the treatment period and the TFP (at least through Week 120 regardless of their B-cell repletion status) were invited to participate in the OLE period of the study. Additional written informed consent to participate in the OLE period was obtained. Patients were allowed to enter the OLE regardless of whether they had repleted B cells.

Prior to retreatment with ocrelizumab, patients were evaluated for the following conditions and laboratory abnormalities. If any of these were present prior to re-dosing, further administration of ocrelizumab was suspended until resolved or held indefinitely:

- Severe (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Grade 3) infusion-related reaction (IRR) to a previous ocrelizumab infusion
- Any significant or uncontrolled medical condition or treatment-emergent, clinically significant laboratory abnormality
- Active infection
- Absolute neutrophil count <1.5 x 10^3 /μl
- CD4 cell count < 250/μl
- Hypogammaglobulinemia: immunoglobulin (Ig) G < 4.0 g/l.

In addition, consented patients who entered the OLE also needed to satisfy the exclusion criteria regarding use of concomitant MS therapy. Exclusions related to medications potentially used for MS were the following:

- Previous treatment with B-cell targeted therapies
- Any previous treatment with alemtuzumab (Campath®), anti-CD4, cladribine, cyclophosphamide, mitoxantrone, azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, total body irradiation, or bone marrow transplantation
- Any previous treatment with lymphocyte trafficking blockers
- Treatment with β interferons, glatiramer acetate, intravenous (IV) immunoglobulin, plasmapheresis, or other immunomodulatory therapies within 2 weeks prior to randomization
- Systemic corticosteroid therapy within 4 weeks prior to randomization

- Treatment with Ampyra®/Fampyra® unless on stable dose for ≥ 30 days prior to screening for the OLE. Patients were required to remain on stable doses throughout the treatment period.

3.4.3 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 could be terminated by the investigator without the patient's consent. The investigator could withdraw 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, when possible.

It was important to distinguish between "withdrawal from treatment" and "withdrawal from study." Patients who withdrew from treatment during the main treatment period were encouraged to remain in the study for the full duration of the TFP (minimum of 48 weeks). Patients who withdrew from OLE entered B-cell monitoring and were followed every 24 weeks until B cells repleted (there was no minimal duration for the follow-up period).

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

- Life threatening (Grade 4) IRR
- pregnancy during the study
- active hepatitis B or C infection, either new onset or reactivation in the case of hepatitis B
- evidence of PML.

Data collected during the TFP in patients who completed the main treatment period (96 weeks) as well as in patients who withdrew from treatment (main treatment period or OLE) and entered the TFP are presented in this report.

3.5 STUDY TREATMENTS

3.5.1 Dosage and Administration

Dosage and administration of ocrelizumab, placebo, and Avonex during the main treatment period are described in the Primary CSR and the study protocol.

The dose of ocrelizumab in the OLE consisted of 600 mg ocrelizumab administered as infusions of ocrelizumab 300 mg on Days 1 and 15 followed by a single infusion of 600 mg every 24 weeks.

Patients received methylprednisolone 100 mg, as a slow IV infusion, approximately 30 minutes before each ocrelizumab infusion. Further information on prevention and treatment of IRRs is provided in Section 6.4 of the protocol.

3.5.2 Formulation and Packaging

Ocrelizumab is manufactured by Genentech Inc. as a sterile, clear, colorless, preservative-free liquid intended for dilution for IV administration. Further details are provided in Section 6.3 of the protocol.

The batch numbers and formulation numbers used in the OLE are provided below:

Product	Material number	Batch Numbers
Ocrelizumab	39006298	867856, 925173, 461740, 499115, 634132

3.5.3 Rationale for Dose Selection and Dosing Intervals

The rationale for dose selection and dosing intervals is provided in Section 3.1.2 of the protocol.

3.5.4 Method of Treatment Assignment and Blinding

During the OLE, all patients received open-label ocrelizumab. Methods of treatment assignment, blinding and unblinding for the main treatment period are described in the Primary CSR and the protocol.

3.5.5 Criteria for Dose Modification or Withdrawal from Treatment

No dose modifications of ocrelizumab were foreseen. Criteria for withdrawal from treatment are provided in Section 3.4.3.

3.5.6 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.

3.6 CONCOMITANT MEDICATIONS

3.6.1 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 CRF, 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.

3.6.2 Treatment of Multiple Sclerosis 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 could receive 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 could receive alternative treatment for MS as judged clinically appropriate by the treating investigator.

3.6.3 Immunization

Physicians reviewed the immunization status of patients being considered for treatment with ocrelizumab 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 ocrelizumab.

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 ocrelizumab 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 receive immunization with killed/toxoid vaccines consistent with normal clinical practice.

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

3.7 ASSESSMENTS

3.7.1 Schedule of Assessments

The schedule of assessments from screening through the end of the follow-up period is provided in the protocol (Table 2). The schedule of assessments for the TFP is presented in Table 2. The schedule of assessments for the OLE period is presented in Table 3.

Table 2 Schedule of Assessments for Patients in the Treatment-Free Period

	Safety Follow-up		B-cell Monitoring Period[1] visits occur every 12 weeks		Observation Period[2] or Withdrawal[13]	Additional Assessments for Week 144 Visit[3]
Assessment	Week 108	Week 120	Every 12 weeks	Every 24 weeks	End of Observation	
Physical examination		x				
Vital signs		x				
12 lead ECG		x				
Weight		x				
Thyroid function tests		x				
Urine pregnancy test	x	x		x	x	
Routine safety lab[4]	x	x				
CBC and differential[5]			x	x	x	
Liver Function Tests[6]			x	x	x	
Total Ig, IgA, IgG, IgM		x		x	x	
Antibody titers[7]		x		x		
FACS[8]	x	x	x	x	x	
ADA[9]	x	x		x	x	
Potential relapses recorded	x	x	x	x	x	
EDSS and neurological examination	x	x	x	x	x	
Adverse events	x	x	x	x	x	
Concomitant Treatment	x	x	x	x	x	

Table 2 Schedule of Assessments for Patients in the Treatment-Free Period (cont.)

	Safety Follow-up		B-cell Monitoring Period[1] visits occur every 12 weeks		Observation Period[2] or Withdrawal[13]	Additional Assessments for Week 144 Visit[3]
Assessment	Week 108	Week 120	Every 12 weeks	Every 24 weeks	End of Observation	
Telephone interview recorded[10]	x	x	x	x	x	
BSR/BRS (optional)						x
MRI[11]						x
JCV[12]	x	x	x	x		x

1. Patients whose B cells had not repleted (returned to baseline or to the LLN, whichever was lower) at the last follow-up visit entered the B-cell monitoring period. Assessments were performed every 12 weeks (± 14 days) until B-cell repletion. Patients who entered the B-Cell monitoring period after withdrawing from the OLE (visits every 24 weeks) did not need to enter the observation period, but could end the study once their B-cells had repleted.
2. Patients whose B cells had repleted entered the 24-week observation period. The visit was performed at the end of the 24 weeks (± 14 days) period.
3. The Week 144 visit could either take place during the B-cell monitoring or the observation period.
4. Includes hematology, chemistry, and urinalysis.
5. Complete Blood Count and differential: hematology (hemoglobin, hematocrit, red blood cells (RBC), white blood cells (WBC) (absolute and differential), and quantitative platelet count.
6. Liver function: alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transferase (GGT), alkaline phosphatase, total bilirubin
7. Including antibodies against mumps, rubella, varicella, *S. pneumoniae* and Epstein-Barr virus.
8. Fluorescence-activated cell sorter (FACS) including CD19 and other circulating B-cell subsets, T cells, natural killer cells and other leukocytes.
9. ADA=anti-drug antibodies. Two samples were required.
10. A telephone interview was conducted every 6 weeks between visits during the B-cell monitoring period. During the observation period and for patients withdrawing from the OLE period, telephone interviews were conducted every 8 weeks until the last study visit to identify any new or worsening neurological symptoms that warranted an unscheduled visit (Protocol Appendix 7).
11. In a subgroup of patients (Groups A and B), a brain MRI scan was performed at Week 96 and Week 144 (± 4 weeks).
12. Plasma samples for JCV were collected every 12 weeks during the B-cell monitoring period, Week 144, and also in case PML was suspected.
13. Withdrawal visit for patients withdrawing during the B-cell monitoring or observation period.

BSR=Biomarker Sample Repository, BRS=Biomarker Research Samples

Table 3 Schedule of Assessments for Open-Label Extension Period

	Screen-ing for OLE[2]	Fifth to ninth doses										Withdrawal (WD)[15]
Dose[1]		5		6		7		8		9		
Visit	20[3]	21	22	23	24	25	26	27	28	29	30	
Week[4] (window days)	144 (+96 weeks)	146 (± 14)	148 (± 2)	168 (± 14)	170 (± 14)	192 (± 14)	194 (± 14)	216 (± 14)	218 (± 14)	240 (± 14)	242 (± 14)	
Informed consent for OLE	x											
Eligibility for re-treatment[5]	x	x	x		x		x		x		x	
Physical examination	x	x			x		x		x		x	x
Vital signs, ECG, and weight[6]	x	x	x		x		x		x		x	x
Pregnancy test	x	x	x	x	x	x	x	x	x	x	x	x
Total Ig, IgA, IgG, IgM	x	x		x		x		x		x		
FACS[7]	x	x		x		x		x		x		x
Routine safety lab[8]	x	x	x	x		x		x		x		x
HBV DNA[9]	x	x		x		x		x		x		x
Potential relapses recorded	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
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x
EDSS and neurological examination		x		x		x		x		x		x

Table 3 Schedule of Assessments for Open-Label Extension Period (cont.)

	Screen-ing for OLE[2]	Fifth to ninth doses										Withdrawal (WD)[15]
Karnofsky Performance Scale		x		x		x		x		x		x
MRI[10]	x										x	
Pre-treatment with methylprednisolone IV		x	x		x		x		x		x	
Administration of ocrelizumab IV		x	x		x		x		x		x	
Biomarker samples[11]		x		x		x		x		x		
ADA and PK samples[12]		x	x		x		x		x		x	
Sample for JCV[13]		x		x		x		x		x		x
Telephone interview[14]												

Table 3 Schedule of Assessments for Open-Label Extension Period (cont.)

	Tenth to seventeenth doses															
Dose	10		11		12		13		14		15		16		17	
Visit	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46
Week[4] (window days)	264 (± 14)	266 (± 2)	288 (± 14)	290 (± 14)	312 (± 14)	314 (± 14)	336 (± 14)	338 (± 14)	360 (± 14)	362 (± 14)	384 (± 14)	386 (± 14)	408 (± 14)	410 (± 14)	432 (± 14)	434 (± 14)
Eligibility for re-treatment[5]		x		x		x		x		x		x		x		x
Physical examination		x		x		x		x		x		x		x		x
Vital signs, ECG, and weight[6]		x		x		x		x		x		x		x		x
Pregnancy test	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Total Ig, IgA, IgG, IgM	x		x		x		x		x		x		x		x	
FACS[7]	x		x		x		x		x		x		x		x	
Routine safety lab[8]	x		x		x		x		x		x		x		x	
HBV DNA[9]	x		x		x		x		x		x		x		x	
Potential relapses recorded	x	x	x	x	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	x	x	x	x
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
EDSS and neurological examination	x		x		x		x		x		x		x		x	

Table 3 Schedule of Assessments for Open-Label Extension Period (cont.)

	Tenth to seventeenth doses															
Karnofsky Performance Scale	x		x		x		x		x		x		x		x	
MRI[10]																
Pre-treatment with methylprednisolone IV		x		x		x		x		x		x		x		x
Administration of ocrelizumab IV		x		x		x		x		x		x		x		x
Biomarker samples[11]	x		x		x		x		x		x		x		x	
ADA and PK samples[12]		x		x		x		x		x		x		x		x
Sample for JCV[13]	x		x		x		x		x		x		x		x	

1. OLE dosing began with Dose 5, a dual infusion, followed by subsequent doses which were single infusions every 24 weeks.
2. Screening for eligibility for OLE: this screening visit could occur as early as Week 120 or as late as 96 weeks following the Week 144 visit, which ended participation in the TFP of the study, provided patients met the re-treatment eligibility criteria for the OLE.
3. Visit 20 represented the screening visit for the OLE and could occur on the same day as the Week 144 visit of the TFP.
4. Designated week number for that visit. Given the variability of the time that patients entered the OLE, the actual week could differ.
5. Eligibility for re-treatment with ocrelizumab: assessed prior to each infusion (see Protocol Section 6.2.4).
6. Vital signs (e.g., pulse rate, systolic and diastolic blood pressure, respiration rate and temperature) were obtained while the patient was in the semi-supine position (after 5 minutes). On infusion visits, the vital signs and electrocardiogram (ECG) were obtained within 45 minutes prior to the methylprednisolone infusion in all patients. In addition, vital signs were obtained prior to ocrelizumab infusion, then every 15 minutes (± 5 min) for the first hour, then every 30 minutes (± 10 minutes), until 1 hour after the end of the infusion. On non-infusion days, vital signs were taken at any time during the visit.
7. Including CD19 and other circulating B-cell subsets, T cells, natural killer cells and other leukocytes. On infusion visits, blood samples were collected prior to the infusion of methylprednisolone.
8. Routine safety laboratory assessments: hematology, blood chemistry, urinary analysis and urine microscopic examination.
9. Hepatitis monitoring: for those patients enrolled with negative hepatitis B surface antigen (HBsAg) and positive total hepatitis B core antibody (HBcAb), hepatitis B virus (HBV) DNA polymerase chain reaction (PCR) was repeated every 24 weeks during the OLE period (up to 24 weeks post last ocrelizumab infusion).

Table 3 Schedule of Assessments for Open-Label Extension Period (cont.)

10. Brain MRI: performed with and without gadolinium at the beginning of the OLE if not already collected at the Week 144 visit from the TFP. This scan was done at the screening visit for the OLE or any time up to the dosing for the OLE (Dose 5). A follow-up MRI was obtained after the completion of Dose 8 (Year 2) or at early withdrawal if not performed during the last 24 weeks.
11. Biomarker samples: plasma and whole blood samples were taken from consenting patients for protein and ribonucleic acid (RNA) biomarker analyses. On infusion visits, samples were taken prior to methylprednisolone infusion.
12. Pharmacokinetic (PK) and ADA samples: on infusion visits, samples were collected prior to the methylprednisolone infusion.
13. Plasma and urine samples for JCV: collected every 24 weeks during the OLE period and also in case PML was suspected.
14. Telephone interviews continued every 8 weeks during the OLE period of the study.
15. Any patient who withdrew from the OLE period entered B-cell monitoring until their B cells have repleted.

3.7.2 Clinical and Imaging Assessments

3.7.2.1 Brain MRI Scans

Brain MRI included the acquisition of the following scans:

- 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. All MRI scans were also reviewed locally by a radiologist for safety.

For OLE, baseline MRI was performed only if not already collected at the Week 144 visit. A follow-up MRI was obtained after the completion of Dose 8 (2 years of treatment in OLE, referred to as Week 242 in the schedule of assessments, Table 3) or at early withdrawal if not performed during the last 24 weeks.

3.7.2.2 Assessment of Relapse

Patients were evaluated for relapses by the investigator at each visit throughout the study and, if necessary, at unscheduled visits to confirm relapses occurring between the visits.

New or worsening neurological events compatible with MS representing a clinical relapse were reported in the CRF. Patients with clinical relapses were referred to the EDSS rater who assessed the Functional System Scores (FSS)/EDSS independently to allow confirmation as to whether or not the clinical relapse(s) met the criteria for protocol defined relapse(s).

Protocol-defined 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 FSS, or 1 point on two or more of the appropriate FSS (see Appendix 3 of the protocol). 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.

Clinical relapses (i.e., regardless of whether they meet criteria for a protocol-defined relapse) were also recorded as AEs.

3.7.2.3 Assessment of Disability

Disability progression as measured by EDSS was assessed in all patients by the independent EDSS rater. The EDSS is a disability scale that ranges in 0.5-point steps from 0 (normal) to 10 (death). The EDSS is based on a standard neurological examination; the seven categories of the EDSS representing functional systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, and cerebral [or mental], plus "other") are rated and scored (collectively, functional system scores or FSS). Each score of the FSS is an ordinal clinical rating scale ranging from 0 to 5 or 6. These ratings are then used in conjunction with observations and information concerning ambulation and use of assistive devices to determine the EDSS score. The EDSS and the FSS are provided in Appendix 3 of the protocol. Neurostatus definitions used for EDSS assessment are provided.

3.7.3 Clinician-Reported Outcomes

The Karnofsky Performance Scale score allows patients to be classified according to their functional impairment. This scale is usually used to compare the effectiveness of different therapies and to assess the prognosis in individual patients. The lower the Karnofsky score, the worse the survival for most serious illnesses.

The treating physician assessed their patients at the beginning of the OLE and every 24 weeks thereafter.

3.7.4 Pharmacokinetic and Pharmacodynamic Assessments

Pharmacokinetic (PK) assessments are presented in the Primary CSR. Bioanalytical reports are provided.

Pharmacodynamic (PD) assessments included:

- 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[a], CD21, IgD, and IgM)
  - T-cells (CD3, CD4, CD8, CD25, CD45RO)
  - Natural killer (NK) cells (CD16, CD56).

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

- Quantitative Ig levels including total Ig, IgG, IgM, and IgA isotypes.

Further details on PD assessments are provided in Section 8.2.12 of the protocol and in Section 4.7 of the SAP.

3.7.5 Safety Assessments

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
- anti-drug antibodies (ADA, referred to in the protocol as human anti-humanized antibodies, HAHA)
- antibody titers for mumps, rubella, varicella, *S. pneumoniae*, and Epstein-Barr virus
- serial pregnancy tests (serum/urine β-human chorionic gonadotropin) 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*.

3.7.5.1 Clinical Adverse Events

The definition of AEs is provided in Section 7 of the protocol. Clinical relapses were also 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 ocrelizumab treatment and was not an AE.

Adverse events were graded according to 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.

For AEs leading to death, the most extreme intensity was overwritten by CTCAE for Grade 5 adverse events (death).

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

3.7.5.2 Serious Adverse Events

A serious adverse event (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.

3.7.5.3 Infusion-Related Reactions

An IRR CRF page was designed to record IRRs and the corresponding symptoms of the reactions. The AE was hard-coded as an IRR on the CRF page. IRRs were described as occurring "during infusion," "after completion of infusion while patient is in clinic," and "within 24 hours of completion of the infusion and patient is not in clinic." Symptoms of an IRR were collected. For each symptom reported, the most extreme intensity was collected.

3.7.5.4 Neurological Examination

A neurological 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.

3.7.5.5 Safety Laboratory Assessments

The following laboratory tests were performed:

- Hematology: hemoglobin, hematocrit, red blood cells, white blood cells (absolute and differential), and quantitative platelet count.
- Blood chemistry: aspartate aminotransferase (AST), alanine aminotransferase (ALT), 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.
- Antibody titers: measurement of antibody titers to common antigens (mumps, rubella, varicella, *S. pneumoniae*, and Epstein-Barr virus).
- ADA: serum samples for determination of antibodies against ocrelizumab.
- 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.

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
- ADA analysis was performed at Genentech (Genentech Inc., 1 DNA Way, MS 452b, south San Francisco, CA 94080, USA).

Quintiles Laboratories standard ranges are provided for Canada, Europe, Mexico, and USA.

3.8 DATA REPORTING AND ANALYSIS PLAN

Statistical analyses were conducted according to the statistical analysis plan dated 5 July 2012 and amended on 7 October 2014.

3.8.1 Analysis Populations

3.8.1.1 Intent-to-Treat Population

All randomized patients who had received any study drug were included in the intent-to-treat (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.

For the OLE, the ITT population included all patients who had received any dose of ocrelizumab in OLE.

3.8.1.2 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 received more than one study therapy were summarized according to the treatment they actually received in the first infusion of the first dose.

For the OLE, the safety population included all patients who received any dose of ocrelizumab in the OLE and had at least one assessment of safety in OLE.

3.8.2 Clinical and Imaging Outcome Measures

MRI scans, relapses, and EDSS scores were listed and summarized by treatment, but no formal statistical analyses were performed.

3.8.2.1 Treatment-Free Period

Clinical and imaging outcomes analyzed for the TFP included MRI scans, relapses, and EDSS scores. They were listed and summarized by treatment arm; no formal statistical analyses were performed.

MRI: All scheduled MRIs (up to and including 144 weeks) have been reported in the Primary CSR. Additional, unscheduled MRIs collected and not included in the previous CSR were listed.

Relapses: The following parameters were summarized:

- number of clinical and protocol-defined relapses
- annualized clinical and protocol-defined relapse rate
- proportion of patients that remained clinical relapse free.

EDSS scores were listed and summarized.

3.8.2.2 Open-Label Extension

MRI: Scheduled and unscheduled MRIs collected during OLE up to the database cut for this CSR were listed and summarized.

Relapses: The following parameters were summarized:

- number of clinical and protocol-defined relapses
- annualized clinical and protocol-defined relapse rate
- proportion of patients that remained relapse free at 48 weeks after the start of OLE dosing (protocol-defined relapses).

EDSS scores were listed and summarized.

Karnofsky Performance Scale assessments were listed and summarized by treatment group.

3.8.2.3 Calculation of Annualized Protocol-Defined and Clinical Relapse Rate (Treatment-Free and Open-Label Extension Periods)

Annualized relapse rates were calculated twice: first, for protocol-defined relapses only; second, for clinical relapses (including protocol-defined relapses). This approach is the same as was used in the Primary CSR.

TFP: The unadjusted annualized relapse rate was calculated as the total number of relapses that occurred during the safety follow-up, B-cell monitoring, and observation period, divided by the total number of patient-years followed in this period.

OLE: The unadjusted annualized relapse rate was calculated as the total number of relapses that occurred during the OLE period of the study divided by the total number of patient-years followed in this period.

The adjusted annualized relapse rate was calculated using Poisson regression, offsetting for exposure time in years and accounting for over-dispersion and adjusting for

geographical region. The exposure time was calculated as (early discontinued date/date for Week X − date of Day 1 + 1)/365. For the TFP, "Day 1" was Day 1 of this period; for OLE, "Day 1" was the date of the first dosing during OLE.

The unadjusted/adjusted annualized relapse rates from the models and the 95% confidence interval (CI) for the relapse rates were presented.

3.8.2.4 Calculation of Proportion of Patients who Remain Relapse Free (Protocol-Defined Relapse, Clinical and Protocol-Defined Relapses; TFP and OLE)

The proportion of patients who remained relapse free was calculated in two ways: first, for protocol-defined relapses only; second, for all clinical relapses (including protocol-defined relapses).

The proportion of patients who remained relapse free was presented. Along with the 95% CI of proportion, the number of patients (%) by the number of observed relapses in the categories 0, 1, 2, ≥3 relapses was presented.

Two proportions were presented for each of the two parameters: 1) Patients who withdrew prematurely from the OLE were considered as having had a relapse in this analysis; 2) patients who withdrew prematurely from the OLE were not considered as having had a relapse in this analysis.

3.8.3 Pharmacodynamic Analysis

For both TFP and OLE, the following laboratory data were examined:

- Circulating B-cell subsets, T cells, natural killer cells, and other leukocytes (FACS)
- Plasma immunoglobulins (total Ig, IgA, IgG, IgM).

The absolute values and changes from baseline at each visit were summarized for circulating B-cell subsets, T cells, natural killer cells, other leukocytes, and plasma immunoglobulins.

3.8.4 Safety Analyses

For both TFP and OLE, the safety evaluations consisted of the following: AEs, SAEs, withdrawals due to AEs, deaths, vital signs/physical examinations, concomitant treatments/surgical procedures, 12-lead ECGs, pregnancy testing, neurological examinations, and safety MRI. In addition, the following laboratory data were examined: complete routine hematology, chemistry, and urinalyses. This approach is the same as was used in the Primary CSR.

Antibodies against mumps, rubella, varicella, *S. pneumoniae*, and Epstein-Barr virus are collected during the main part of the study. The results were listed for the TFP only.

3.8.4.1 Exposure to Study Medication (Open-Label Extension Period only)

The amount (in milligrams) of ocrelizumab infused on Day 1 and Day 15 of the first dose in OLE and on Day 1 of the subsequent doses was listed and summarized using descriptive statistics.

3.8.4.2 Adverse Events and Deaths (Treatment-Free and Open-Label Extension Periods)

AEs were reported as described in Section 4.11.4 to Section 4.14 of the SAP for the TFP and OLE.

3.8.4.3 Laboratory Data (Treatment-Free and Open-Label Extension Periods)

Abnormal laboratory outcomes were reported. A summary of the number and percentage of patients with abnormal laboratory outcomes, along with each National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grade by laboratory parameter, was produced by treatment group.

3.8.4.4 Vital Signs (Treatment-Free and Open-Label Extension Periods)

Vital sign data, physical examination results, and ECG data were included in individual patient listings. Changes from baseline in vital signs were summarized by treatment group.

3.8.4.5 Immunogenicity

Samples for the determination of ADAs were analyzed using a validated bridging enzyme-linked immunosorbent assay (ELISA). Details of the methods of ADA analyses are provided in the bioanalytical reports.

A positive ADA sample was defined as one in which the presence of detectable ADAs could be confirmed by competitive binding with ocrelizumab. Only patients with at least one available sample for ADA assessment were included in the analysis of baseline prevalence and post-baseline incidence. The prevalence of ADAs at baseline was calculated from the total number of patients who tested positive for ADAs at baseline divided by total number of baseline evaluable patients. For the post-baseline incidence, patients were grouped into the following categories:

- Patients with treatment-emergent ADAs: post-baseline evaluable patients determined to have treatment-induced ADAs or treatment-enhanced ADAs during the study period.
    - Patients with treatment-induced ADAs: patients with a negative (or missing) baseline ADA result and at least one positive post-baseline ADA result.
    - Patients with treatment-enhanced ADAs: patients with a positive ADA result at baseline who had one or more post-baseline titer results that

were at least 0.60 titer units (t.u.) greater than the baseline titer result [Shankar 2014].

- Patients with no treatment-emergent ADAs: post-baseline evaluable patients with negative or missing baseline ADA result and all negative post-baseline results, or patients with treatment-unaffected ADAs.
    - Patients with treatment-unaffected ADAs: patients with a positive ADA result at baseline and no post-baseline titer results that were 0.60 t.u. greater than the baseline titer result. Patients with ADA positive at baseline and negative post-baseline are also included in this category.

3.8.5 Missing Data

Baseline values were not carried forward: that is, all change from baseline analyses were performed only for subjects with both a baseline and a post-baseline assessment available.

Details of how to handle missing values differ depending on the endpoint and are described in the relevant section of the SAP.

3.8.6 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 18.0 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. Glossaries of preferred terms are provided: AEs for TFP, AEs for OLE medications and procedures for TFP, medications and procedures for OLE, diseases for TFP, diseases for OLE, and medication and procedures baskets.

3.8.7 Changes in Conduct of Study or Planned Analyses

No changes in the conduct of the study were made.

In addition to the planned analyses described in the SAP Version 2, the following analyses were performed:

- Time between the last infusion of ocrelizumab in the main treatment period and the first infusion in the OLE
- Summary of MRI assessments at 2 years of OLE: brain volume, new/enlarging T2 lesion count, and total number of Gadolinium-enhancing T1 lesions
- Proportion of patients who remain clinical relapse-free (including protocol-defined relapses) in the OLE at 48 weeks and up to the cut-off
- Proportion of B-cell repleted patients at OLE baseline
- Time to B-cell repletion for the main treatment period and the TFP, including Kaplan-Meier curves of cumulative probability of B-cell repletion and corresponding summary statistics

- ADA analyses (see Section 3.8.4.5).

3.8.8 Analyses Included in the Addendum to the Primary CSR (Main Study)

The following analyses are presented in Section 8 for the main study (96-week treatment period):

- Previous treatments for MS
- confirmed disability improvement (CDI) for at least 12 weeks and 24 weeks (see Section 3.8.8.1)
- Listing of AEs that have been added to the clinical database since the database lock for the Primary CSR
- Proportion of patients with IRR by infusion and severity
- Infusions adjusted due to IRRs
- Listings of IRR symptoms by the first infusion of ocrelizumab and placebo
- Listings of malignancies and premalignant disorders
- Baseline prevalence and post-baseline incidence of ADAs (see Section 3.8.8.2).

3.8.8.1 Confirmed Disability Improvement

The CDI endpoint was analyzed only for the subgroup of patients with a baseline EDSS score $\geq$2.0. For patients with a baseline EDSS score $\geq$2 and $\leq$5.5, disability improvement was defined as a reduction in EDSS score $\geq$1.0 compared to baseline. For patients with a baseline EDSS score > 5.5, disability improvement was defined as a reduction in EDSS score of $\geq$0.5. All patients without disability improvement were counted as not improved, independent of follow-up time.

Disability improvements were considered only when they occurred after the date of randomization up to and including Week 96 (end of main treatment period), or up to withdrawal from treatment. Confirmation of sustained disability improvement could occur during the treatment period, in the TFP or the OLE.

Confirmation of disability improvement occurred at the regularly scheduled visit that was at least 12 weeks (84 days) after initial progression. If a patient had a missing EDSS at the scheduled visit occurring at least 84 days after an initial improvement or the scheduled visit occurred several days before the 84−day window after an initial improvement (e.g., the visit window was $\pm$4 days), confirmation of the disability improvement was assessed at the next scheduled visit. Disability improvement was confirmed if the EDSS values met the minimum change required for improvement.

The duration of CDI for at least 12 weeks was calculated as the time from the onset of CDI until the first visit where the EDSS score no longer fulfilled the criteria for CDI, and is summarized using Kaplan-Meier methods. For patients who had a sustained improvement until their last EDSS score, the duration of CDI was censored at the time of

the last assessment. In addition, the proportion of patients achieving CDI for at least 12 weeks is also presented.

CDI for at least 24 weeks (duration and proportion) was calculated in a similar way to that described above for CDI for at least 12 weeks.

3.8.8.2 Immunogenicity

Analyses were conducted as described in Section 3.8.4.5. If a patient had more than one ADA assessment prior to the first administration of ocrelizumab (i.e. patients who received placebo or Avonex during the first 24 weeks of the treatment period) the highest titer was used as baseline.

4. RESULTS: TREATMENT-FREE PERIOD

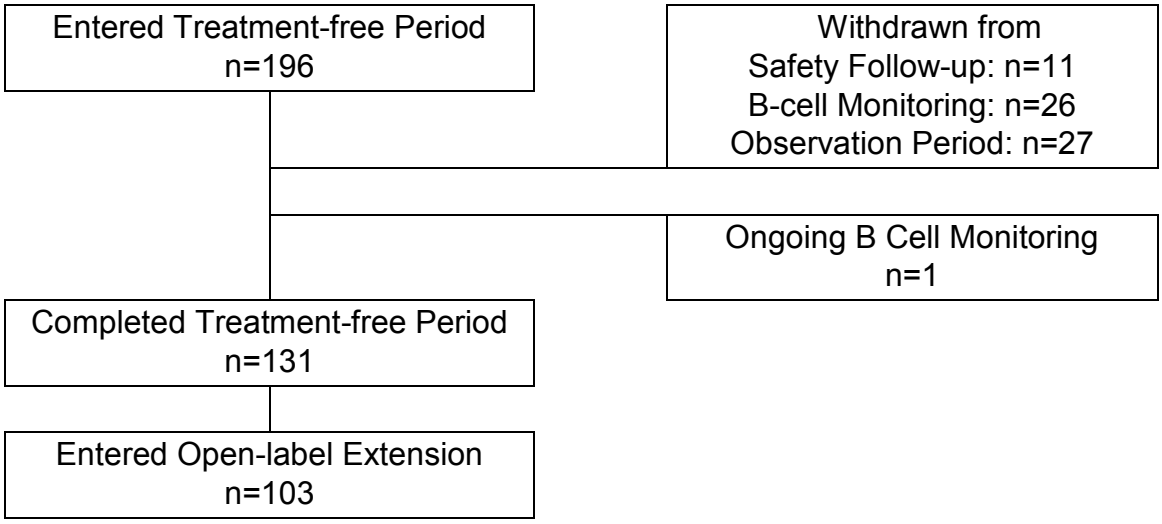
The reporting period of the present Update CSR partially overlaps with the Primary CSR. The data presented for the TFP in this Update CSR replaces the data presented in the Primary CSR.

4.1 STUDY POPULATION: TREATMENT-FREE PERIOD

4.1.1 Disposition of Patients

Patient disposition for the TFP is presented in Figure 3 and Table 4. Patient disposition for the treatment period is presented in the Primary CSR. A total of 196 patients entered the TFP and over 90% of them completed safety follow-up. A total of 133 patients entered the B-cell monitoring period. For one patient B-cell monitoring was still ongoing at the time of database lock. A total of 106 patients completed the B-cell monitoring period and entered the observation period. Patients who repleted B-cells during safety follow-up entered the observation period directly. A total of 158 patients entered the observation period and 131 patients completed this period. Among those, 103 patients entered the OLE (see Section 5 for details). Proportions of patients who withdrew from safety follow-up, B-cell monitoring, and observation periods were similar among treatment groups (Table 4).

Figure 3 Overview of Patient Disposition



Sources: Table 4, Table 5, Table 10

Table 4 Patient Disposition for the Treatment-Free Period by Treatment Group, TFP Intent-to-Treat Population

	Placebo Group C (N=49)	OCR 600mg Group B (N=48)	OCR 1000mg Group A (N=50)	Avonex Group D (N=49)
Entered Safety Follow-up	49 (100.0%)	48 (100.0%)	50 (100.0%)	49 (100.0%)
Ongoing Safety Follow-up	0	0	0	0
Withdrawn from Safety Follow-up	3 (6.1%)	2 (4.2%)	5 (10.0%)	1 (2.0%)
Completed Safety Follow-up	46 (93.9%)	46 (95.8%)	45 (90.0%)	48 (98.0%)
Entered B Cell Monitoring Period	33 (67.3%)	34 (70.8%)	35 (70.0%)	31 (63.3%)
Ongoing B Cell Monitoring Period	0	0	0	1 (2.0%)
Withdrawn from B Cell Monitoring Period	5 (10.2%)	8 (16.7%)	7 (14.0%)	6 (12.2%)
Completed B Cell Monitoring Period	28 (57.1%)	26 (54.2%)	28 (56.0%)	24 (49.0%)
Entered Observation Period	41 (83.7%)	38 (79.2%)	38 (76.0%)	41 (83.7%)
Ongoing Observation Period	0	0	0	0
Withdrawn from Observation Period	6 (12.2%)	6 (12.5%)	8 (16.0%)	7 (14.3%)
Completed Observation Period	35 (71.4%)	32 (66.7%)	30 (60.0%)	34 (69.4%)

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values).
Patients are summarized according to their randomized treatment group.
All percentages for reason for withdrawal are based on number withdrawn. All other percentages are based on N.
Withdrawals are included from withdrawal visits, completion pages and deaths; however reason for withdrawal is taken from the safety follow up completion forms only.

Program: /opt/BIOSTAT/prod/cdt3422z/z21493c/t_ds_tfp.sas
Output: /opt/BIOSTAT/prod/cdt3422z/z21493c/reports/t_ds_tfp_ITTFP.out
15DEC2015 9:49 [Modified by PDRD] Page 1 of 1
Group A: Dose 1 = OCR 1000 mg (Day 1 and 15); Dose 2 = OCR 1000 mg Day 1, placebo Day 15; Dose 3 = OCR 1000 mg; Dose 4 = OCR 600 mg.
Group B: Dose 1 = OCR 300 mg (Day 1 and 15); Dose 2 = OCR 600 mg Day 1, placebo Day 15; Dose 3 and Dose 4 = OCR 600 mg.
Group C: Dose 1 = Placebo (Day 1 and 15); Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg.
Group D: Dose 1 = Avonex 30 µg/week; Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg.
OCR = ocrelizumab

4.1.2 Patients Withdrawn from Treatment-Free Period

A total of 64 patients discontinued early from the TFP (Table 5). Four patients were withdrawn for safety reasons, including 3 deaths (see Section 4.4.4 for details) and the others discontinued the study for reasons such as withdrawal of consent, lost to follow-up, or other reasons unrelated to safety. Narratives are provided for these patients. A listing of patients who discontinued early from TFP is provided.

Table 5 Patients Withdrawn from Treatment-Free Period, TFP Intent-to-Treat Population

Status	Placebo Group C (N=49)	OCR 600mg Group B (N=48)	OCR 1000mg Group A (N=50)	Avonex Group D (N=49)
Completed TFP	35 (71.4%)	31 (64.6%)	30 (60.0%)	34 (69.4%)
Discontinued TFP	14 (28.6%)	16 (33.3%)	20 (40.0%)	14 (28.6%)
Safety	1 (2.0%)	1 (2.1%)	2 (4.0%)	0
ADVERSE EVENT	0	0	1 (2.0%)	0
DEATH	1 (2.0%)	1 (2.1%)	1 (2.0%)	0
Non-safety	13 (26.5%)	15 (31.3%)	18 (36.0%)	14 (28.6%)
LOST TO FOLLOW-UP	2 (4.1%)	2 (4.2%)	6 (12.0%)	2 (4.1%)
OTHER	8 (16.3%)	10 (20.8%)	8 (16.0%)	7 (14.3%)
WITHDRAWAL BY SUBJECT	3 (6.1%)	3 (6.3%)	4 (8.0%)	5 (10.2%)

Reason for withdrawal is taken from Safety Follow-up completion form only.
Patient [redacted] (Avonex group) is ongoing in the B-cell monitoring period, patient [redacted] (OCR 600mg group) has completed all three periods in TFP, but the CRF does not confirm that they completed nor withdrew from TFP.

Program: /opt/BIOSTAT/prod/cdt3422z/z21493c/t_ds_wd.sas
Output: /opt/BIOSTAT/prod/cdt3422z/z21493c/reports/t_ds_wd_ITTFP.out
15DEC2015 12:36 [Modified by PDRD] Page 1 of 1
Group A: Dose 1 = OCR 1000 mg (Day 1 and 15); Dose 2 = OCR 1000 mg Day 1, placebo Day 15; Dose 3 = OCR 1000 mg; Dose 4 = OCR 600 mg.
Group B: Dose 1 = OCR 300 mg (Day 1 and 15); Dose 2 = OCR 600 mg Day 1, placebo Day 15; Dose 3 and Dose 4 = OCR 600 mg.
Group C: Dose 1 = Placebo (Day 1 and 15); Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg.
Group D: Dose 1 = Avonex 30 µg/week; Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg.
OCR = ocrelizumab

4.1.3 Current (Concomitant) Diseases

The number of patients with current (concomitant) diseases (other than MS) during the TFP was higher in Group A compared with the other groups: 16 patients (32.0%) versus 7 patients (14.6%), 8 patients (16.3%), and 9 patients (18.4%) in Groups B, C, and D, respectively. The only current diseases reported at a frequency higher than 5% in any treatment group were depression and back pain.

4.2 CLINICAL AND IMAGING OUTCOME MEASURES: TREATMENT-FREE PERIOD

4.2.1 Assessment by Brain MRI

A listing of MRI outcomes is provided. This listing includes only unscheduled MRI assessments obtained during the TFP not included in the Primary CSR. There were two unscheduled MRI assessments and no lesions were detected.

4.2.2 Assessment of Relapse

4.2.2.1 Protocol-Defined Relapses

During the TFP, the annualized protocol-defined relapse rate adjusted by geographical region was 0.220, 95% CI [0.146, 0.333] in Group A, 0.058, 95% CI [0.028, 0.120] in Group B, 0.073, 95% CI [0.037, 0.144] in Group C, and 0.065, 95% CI [0.031, 0.136] in Group D (Table 6). The annualized protocol-defined relapse rate was higher in Group A compared with the other treatment groups. Sensitivity analysis where early discontinuations were considered as relapse free and the analysis where patients who

discontinued the TFP prematurely were assumed to have had a relapse are provided. Sensitivity analyses showed results consistent with this analysis.

Table 6 Annualized Protocol-Defined Relapse Rate (Poisson Model), TFP Intent-to-Treat Population

Efficacy Variable	Placebo Group C (N=49)	OCR 600mg Group B (N=48)	OCR 1000mg Group A (N=50)	Avonex Group D (N=49)
Total number of relapses	6	5	19	5
Total patient-years followed	65.0	72.4	71.9	62.9
Unadjusted annualized relapse rate	0.092	0.069	0.264	0.079
Adjusted annualized relapse rate*	0.073	0.058	0.220	0.065
95% CI of adjusted annualized relapse rate*	(0.037, 0.144)	(0.028, 0.120)	(0.146, 0.333)	(0.031, 0.136)
Overdispersion				0.7953

The total number of protocol defined relapses that occurred divided by the total number of subject-years followed in this period.
Log-transformed exposure time is included as offset variable.
*Adjusted for Geographical Region (Eastern Central Europe/Asia, North America and Western Europe).

Program: /opt/BIOSTAT/prod/cdt3422z/z21493c/t_pdr_arr_pois.sas
Output: /opt/BIOSTAT/prod/cdt3422z/z21493c/reports/t_pdr_arr_pois_TFP_ITTFP.out
14DEC2015 18:45 [Modified by PDRD]

Group A: Dose 1 = OCR 1000 mg (Day 1 and 15); Dose 2 = OCR 1000 mg Day 1, placebo Day 15; Dose 3 = OCR 1000 mg; Dose 4 = OCR 600 mg.
Group B: Dose 1 = OCR 300 mg (Day 1 and 15); Dose 2 = OCR 600 mg Day 1, placebo Day 15; Dose 3 and Dose 4 = OCR 600 mg.
Group C: Dose 1 = Placebo (Day 1 and 15); Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg.
Group D: Dose 1 = Avonex 30 µg/week; Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg.
OCR = ocrelizumab

4.2.2.2 Clinical Relapses

Annualized clinical relapse rate (including protocol-defined relapses, Poisson Model, adjusted for geographical region) was 0.342, 95% CI [0.233, 0.504] in Group A, 0.147, 95% CI [0.084, 0.257] in Group B, 0.095, 95% CI [0.046, 0.194] in Group C, and 0.111, 95% CI [0.057, 0.218] in Group D. The annualized clinical relapse rate was higher in Group A compared with the other treatment groups. Sensitivity analysis where early discontinuations were considered as relapse free and the analysis where patients who discontinued the TFP prematurely were assumed to have had a relapse are provided. Sensitivity analyses showed results consistent with this analysis.

A listing of relapse information during the TFP is provided.

4.2.3 Assessment of Disability

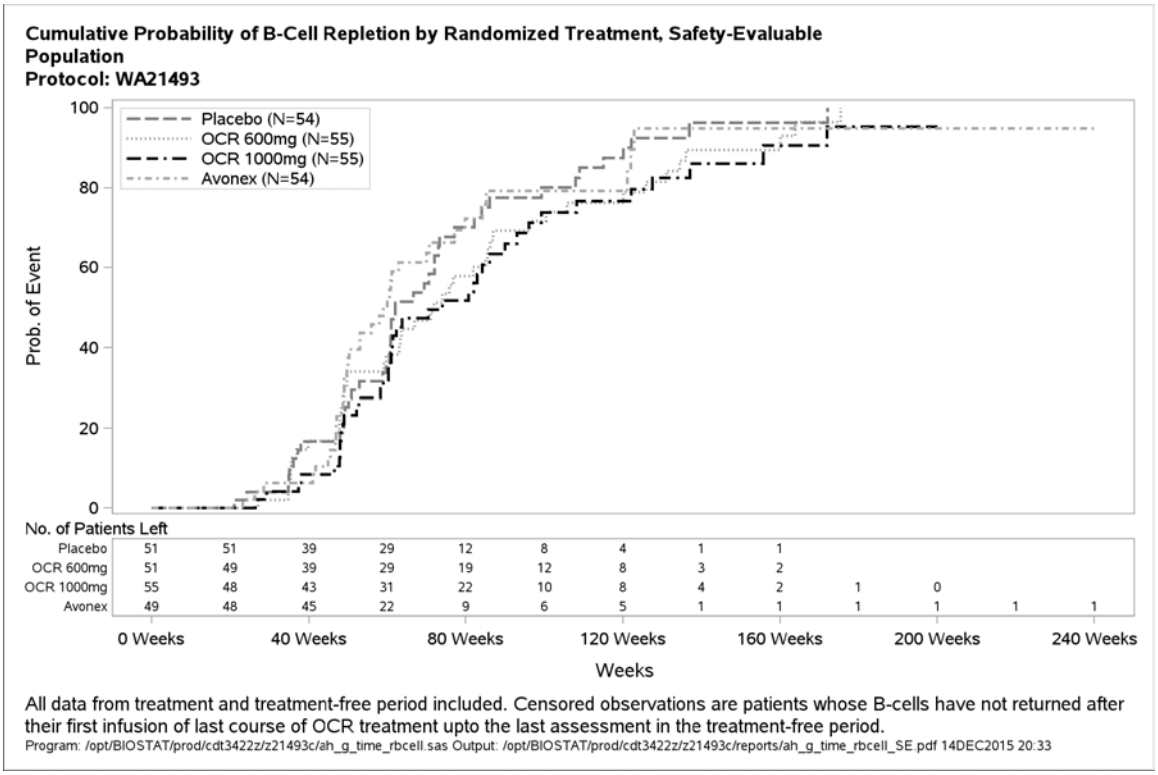
Mean and median EDSS were similar in all treatment groups (EDSS and FSS by Visit). There was little change in EDSS over time in any of the treatment groups.

4.3 PHARMACODYNAMICS: TREATMENT-FREE PERIOD

4.3.1 CD19+ B-Cells and Other FACS Results

Kaplan-Meier curves of cumulative probability of B-cell repletion are presented in Figure 4. Median times to B-cell repletion were numerically higher in Groups A and B (74.0 weeks and 71.9 weeks, respectively) compared with Groups C and D (62.0 weeks and 59.0 weeks, respectively); however the CIs were wide and overlapping.

Figure 4 Cumulative Probability of B-Cell Repletion



OCR 1000 mg group (Group A): Dose 1 = OCR 1000 mg (Day 1 and 15); Dose 2 = OCR 1000 mg Day 1, placebo Day 15; Dose 3 = OCR 1000 mg; Dose 4 = OCR 600 mg.

OCR 600 mg group (Group B): Dose 1 = OCR 300 mg (Day 1 and 15); Dose 2 = OCR 600 mg Day 1, placebo Day 15; Dose 3 and Dose 4 = OCR 600 mg.

Placebo group (Group C): Dose 1 = Placebo (Day 1 and 15); Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg.

Avonex group (Group D): Dose 1 = Avonex 30 μg/week; Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg.

OCR = ocrelizumab

A listing of time to B-cell repletion is provided. Time to B-cell repletion was longer than 120 weeks in 8 patients in Group A, 8 patients in Group B, 4 patients in Group C, and 5 patients in Group D. The longest censored time to B-cell repletion was 200 weeks in Group A (patient No. [redacted]), 175.4 weeks in Group B (No. [redacted]), 172 weeks in Group C (No. [redacted]), and 241 weeks in Group D (No. [redacted] .

A summary of FACS results and change from baseline by visit for the TFP period is provided.

4.3.2 Serum Immunoglobulins Levels

Total serum Ig, IgG or IgA levels remained stable throughout the TFP (Immunoglobulin Results and Percent Change from Baseline by Visit, Immunoglobulin Results and Change from Baseline by Visit). Serum IgM levels were lower at the start of the TFP

compared with baseline values by approximately 35% in all treatment groups and remained stable during the TFP.

4.4 SAFETY: TREATMENT-FREE PERIOD

4.4.1 Overview of Safety

An overview of AEs is presented in Table 7. During the TFP, the proportion of patients with AEs was higher in Group A compared with the other treatment groups: 70.0% versus 50.0% in Group B, 36.7% in Group C, and 38.8% in Group D. This difference was mainly driven by MS relapses that were reported as AEs and occurred with a higher incidence in Group A compared with the other treatment groups. Sixteen patients (32.0%) in Group A had MS relapse AEs versus 9 (18.8%), 5 (10.2%), and 6 (12.2%) in Groups B, C, and D, respectively. The percentage of patients with at least one infection was also higher in Group A compared with the other treatment groups. Sixteen patients (32.0%) in Group A had an AE from the System Organ Class (SOC) Infections and Infestations versus 11 (22.9%), 11 (22.4%), and 9 (18.4%) in Groups B, C, and D, respectively. However, infection AE rate per 100 patient years was similar among the treatment groups: 34.77, 95% CI [23.49, 51.45] in Group A, 23.49, 95% CI [14.61, 37.79] in Group B, 33.84, 95% CI [22.28, 51.39] in Group C, and 22.25, 95% CI 13.18, 37.57 in Group D.

Most AEs were Grade 1 or Grade 2 in intensity. There were 2 Grade 3 AEs in each of the Groups B, C, and D, and 4 Grade 3 AEs in Group A. There were 2 Grade 4 AEs, both occurring in Group A: suicidal ideation and immune thrombocytopenic purpura. Two patients died during the TFP: 1 in Group B due to unknown cause, and 1 in Group C due to injury from accident.

A total of 12 patients had SAEs during the TFP. SAE rate per 100 patient years was 6.95, 95% CI [2.89, 16.71] in Group A, 5.53, 95% CI [2.07, 14.73] in Group B, 1.54, 95% CI [0.22, 10.92] in Group C, and 3.18, 95% CI [0.80, 12.71] in Group D. Two SAEs were considered related to the study drug by the investigator: breast cancer that resolved with sequelae and a life-threatening immune thrombocytopenic purpura that was unresolved at the time of the database lock. Both SAEs occurred in patients randomized to Group A. The patient who experienced immune thrombocytopenic purpura withdrew from the TFP due to this event. There were no other withdrawals due to AEs.

One pregnancy was reported in a patient randomized to Group B. No delivery complications were reported, and no congenital defects or infant AEs were reported.

There were no safety findings related to laboratory parameters, ECGs, vital signs or physical examination.

Table 7 Overview of Adverse Events

	Group C N=49	Group B N=48	Group A N=50	Group D N=49
Number and proportion of patients with at least one AE	18 (36.7%)	24 (50.0%)	35 (70.0%)	19 (38.8%)
Number and proportion of patients with Grade 3 or 4 AEs	2 (4.1%)	2 (4.2%)	5 (10.0%)	2 (4.1%)
Deaths	1	1	0	0
Number and proportion of patients with at least one SAE	1 (2.0%)	4 (8.3%)	5 (10.0%)	2 (4.1%)
Withdrawals due to AE	0	0	1[a]	0
Number and proportion of patients with selected AEs				
Infections	11 (22.4%)	12 (25.0%)	16 (32.0%)	9 (18.4%)
Pregnancy	0	1	0	0

Source: t_ae_TFP_SETFP, t_ae_int_TFP_SETFP, l_ae_TFP_SETFP, t_ae_IVSER_TFP_SETFP, t_ae_path_idespe_TFP_SETFP, l_preg_TFP_SETFP

[a] according to the withdrawal page of the CRF

Group A: Dose 1 = OCR 1000 mg (Day 1 and 15); Dose 2 = OCR 1000 mg Day 1, placebo Day 15; Dose 3 = OCR 1000 mg; Dose 4 = OCR 600 mg.

Group B: Dose 1 = OCR 300 mg (Day 1 and 15); Dose 2 = OCR 600 mg Day 1, placebo Day 15; Dose 3 and Dose 4 = OCR 600 mg.

Group C: Dose 1 = Placebo (Day 1 and 15); Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg.

Group D: Dose 1 = Avonex 30 μg/week; Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg.

OCR = ocrelizumab

4.4.2 Common Adverse Events

During the TFP, the proportion of patients with AEs was higher in Group A compared with the other treatment groups. The number of patients with at least one AE was 35 (70.0%) in Group A, 24 (50.0%) in Group B, 18 (36.7%) in Group C, and 19 (38.8%) in Group D. This difference was mainly driven by MS relapses that were reported as AEs and occurred with a higher incidence in Group A compared with the other treatment groups. Sixteen patients (32.0%) in Group A had MS relapse AEs versus 9 (18.8%), 5 (10.2%), and 6 (12.2%) in Groups B, C, and D, respectively. The percentage of patients with at least one infection was also higher in Group A compared with the other treatment groups. Sixteen patients (32.0%) in Group A had AEs belonging to the SOC Infections and Infestations versus 11 (22.9%), 11 (22.4%), and 9 (18.4%) in Groups B, C, and D, respectively. Infections are further discussed in Section 4.4.7.1 .

A listing of patients with AEs is provided.

A total of 34 patients (68.0%) had treatments for AEs in Group A versus 26 (54.2%) in Group B, 25 (51.0%) in Group C, and 24 (49.0%) in Group D. The most common treatments for AEs were non-steroidal anti-inflammatories, analgesics, penicillins, corticosteroids, and quinolone antibiotics.

4.4.3 Adverse Events by Intensity

Most AEs were Grade 1 or Grade 2 in intensity (Adverse Events by Intensity). There were 2 Grade 3 AEs in Groups B, C, and D, and 4 Grade 3 AEs in Group A. There were 2 Grade 4 AEs, both of them occurring in Group A: suicidal ideation and immune thrombocytopenic purpura. Two Grade 5 AEs were reported, 1 in Group B, and 1 in Group C (details provided in Section 4.4.4).

4.4.4 Deaths

Two patients died during the TFP. Note: Patient [redacted] (Group A) died during the treatment period; however this event was included in the listing of patient deaths. All three cases were reported in the Primary CSR. Full patient narratives are provided.

Patient [redacted]1 (Group B) was a [redacted]year-old white [redacted] who died due to unknown cause. The patient received the last infusion of ocrelizumab 600 mg on Day 505. On Day 1067 (1 week prior to death), [redacted] was hospitalized and received intrathecal corticosteroids due to progression of MS. On day 1074 (569 days after the last dose of study drug), the patient was found dead in bed in the morning by [redacted] The patient's [redacted] efused autopsy. The investigator considered the patient's death to be unrelated to the study drug and related to other (unknown). The investigator presumed as possible diagnoses myocardial infarction, pulmonary embolism or brain stem lesions affecting control of vital functions.

Patient [redacted](Group C) was a [redacted]-year-old white [redacted]who died due to injury from accident. The patient received placebo on Day 1 and 16 and then started ocrelizumab from Day 177. Last dose of ocrelizumab was received on Day 512. On Day 968, the patient had an accident as [redacted] experienced a life-threatening (Grade 4) traumatic injury. On the same day, the patient died. An autopsy revealed that the patient's death was caused by concomitant injury of the body accompanied by closed craniocerebral trauma and subarachnoid hemorrhage, hemorrhage in the brain matter, cerebral ventricles and non-penetrating trauma to the chest and abdomen. The investigator assessed the injury to be unrelated to the study drug and related to the accident.

4.4.5 Serious Adverse Events

A total of 12 patients had SAEs during the TFP:

- 5 patients (10.0%) in Group A (preferred terms: suicidal ideation, breast cancer, acute psychosis, muscular weakness, immune thrombocytopenic purpura)

- 4 patients (8.3%) in Group B (preferred terms: pregnancy, salivary duct inflammation, subileus, death)
- 1 patient (2.0%) in Group C (injury resulting in death)
- 2 patients (4.1%) in Group D (preferred terms: drug withdrawal syndrome, bronchitis).

A listing of patients with SAEs is provided. Full patient narratives for all reported SAEs are provided. Two SAEs were considered related to the study drug by the investigator and are described below. Both SAEs occurred in patients randomized to Group A.

Patient [redacted] a[redacted]-year-old[redacted] had breast cancer with onset on study Day 748. The diagnosis was based on clinical symptoms (palpable node) followed by biopsy. This patient's [redacted] (ongoing). A left[redacted]t partial resection was done on[redacted] due to [redacted]known since[redacted] [redacted] concurrent conditions included pineal gland cyst (since[redacted] and bilateral[redacted] (since[redacted]) that were ongoing without treatment. [redacted] eceived[redacted] last dose of ocrelizumab 600 mg on Day 491, completed the treatment period, and entered safety follow-up. On Day 748, the patient developed palpable indurated lump in the lateral side of[redacted] with intermittent blood secretion from the[redacted]. The histological examination revealed Grade 2, invasive ductal carcinoma (2.5 cm), Stage III clinical group 3, ICD: C 50+1. The intraductal carcinoma was cribriform papillary. Out of nine lymph nodes examined, three of them showed metastasis (0.2/4 cm) without capsule infiltration, PN1B receptor to[redacted] : 214 and receptor to progesterone:114. Immunohistochemical examination showed HER2 negative, ER and PR with 50% probability for chemotherapeutic response. The final diagnosis was[redacted] glandular mammary carcinoma. This SAE was considered by the investigator to be disabling, medically significant, possibly related to the study medication and pre-existing/underlying bilatera[redacted] status after partial[redacted]. This SAE was treated with surgery and chemotherapy. Radiological examination revealed no metastases. This SAE resolved with sequelae.

Patient [redacted] a[redacted]year-old[redacted] had life-threatening immune thrombocytopenic purpura. The patient did not have a relevant medical history. [redacted] concurrent conditions included osteochondrosis (since[redacted]) and hypertension (since[redacted] [redacted]),[redacted] previous medications included omeprazole, benfotiamine/ cyanocobalamin/ pyridoxine/ thiamine, midazolam and guaifenesin, and concomitant medications included amantadine, levonorgestrel, methylprednisolone, paracetamol and cetirizine. [redacted] received the last infusion of ocrelizumab 600 mg on Day 516, completed the treatment period, and entered safety follow-up. [redacted] had immune thrombocytopenic purpura on Day 1104 which was considered by the investigator to be serious and

remotely related to the study medication. This patient discontinued the study early due to this SAE. This SAE remained unresolved at the time of the database lock.

SAE rate per 100 patient years was 6.95, 95% CI [2.89, 16.71] in Group A, 5.53, 95% CI [2.07, 14.73] in Group B, 1.54, 95% CI [0.22, 10.92] in Group C, and 3.18, 95% CI [0.80, 12.71] in Group D (Table 8).

Table 8 Number of Serious Adverse Events per 100 Patient Years, TFP Safety-Evaluable Population

	Placebo Group C (N=49)	OCR 600mg Group B (N=48)	OCR 1000mg Group A (N=50)	Avonex Group D (N=49)
Total Patient-Years at Risk	65.0	72.4	71.9	62.9
Number of Adverse Events Observed	1	4	5	2
AE Rate per 100 Patient-Years	1.54	5.53	6.95	3.18
95% CI	(0.22, 10.92)	(2.07, 14.73)	(2.89, 16.71)	(0.80, 12.71)

Investigator text for AEs encoded using MedDRA version MedDRA v18.0
Serious is defined as 1) using "Is this a serious adverse event" (see protocol for definition)? ticked 'yes' from the Adverse Event CRF page or 2) Infections requiring IV Anti-Infective.
Multiple occurrences of the same event in one individual are counted multiple times.

Program: /opt/BIOSTAT/prod/cdt3422z/z21493c/t_ae_100py.sas
Output: /opt/BIOSTAT/prod/cdt3422z/z21493c/reports/t_ae_100py_IVSER_TFP_SETFP.out
14DEC2015 19:54 [Modified by PDRD] Page 1 of 1
Group A: Dose 1 = OCR 1000 mg (Day 1 and 15); Dose 2 = OCR 1000 mg Day 1, placebo Day 15; Dose 3 = OCR 1000 mg; Dose 4 = OCR 600 mg.
Group B: Dose 1 = OCR 300 mg (Day 1 and 15); Dose 2 = OCR 600 mg Day 1, placebo Day 15; Dose 3 and Dose 4 = OCR 600 mg.
Group C: Dose 1 = Placebo (Day 1 and 15); Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg.
Group D: Dose 1 = Avonex 30 µg/week; Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg.
OCR = ocrelizumab

4.4.6 Adverse Events Leading to Discontinuation from the Treatment-Free Period

Patient No. [redacted] andomized to Group A withdrew from the TFP due to an AE, immune thrombocytopenic purpura. This SAE was life-threatening and was considered remotely related to the study drug by the investigator. A narrative for this patient is provided.

4.4.7 Selected Adverse Events

4.4.7.1 Infections

During the TFP, infection AE rate per 100 patient years was similar among the treatment groups: 34.77, 95% CI [23.49, 51.45] in Group A, 23.49, 95% CI [14.61, 37.79] in Group B, 33.84, 95% CI [22.28, 51.39] in Group C, and 22.25, 95% CI 13.18, 37.57 in Group D (Table 9). The number of patients with at least one infection AE was 16 (32.0%) in Group A, 12 (25.0%) in Group B, 11 (22.4%) in Group C, and 9 (18.4%) in Group D (Infections by Dose and Identified or Suspected Pathogen).

Only one patient experienced a serious infection: patient [redacted] had bronchitis. This [redacted]-year-old [redacted] was randomized to Group D, received the last dose of ocrelizumab 600 mg on Day 493, completed the treatment period, and entered treatment-free follow-up. Patient's B cells repleted by Day 933. [redacted] completed treatment-free safety follow-up and entered the observation period. The SAE of bronchitis occurred on Day 1061, was considered unrelated to ocrelizumab by the investigator, and resolved without sequelae.

A listing of patients with infection AEs and a listing of patients with infection SAEs are provided).

Table 9 Number of Infections per 100 Patient Years, TFP Safety-Evaluable Population

	Placebo Group C (N=49)	OCR 600mg Group B (N=48)	OCR 1000mg Group A (N=50)	Avonex Group D (N=49)
Total Patient-Years at Risk	65.0	72.4	71.9	62.9
Number of Adverse Events Observed	22	17	25	14
AE Rate per 100 Patient-Years	33.84	23.49	34.77	22.25
95% CI	(22.28, 51.39)	(14.61, 37.79)	(23.49, 51.45)	(13.18, 37.57)

Investigator text for AEs encoded using MedDRA version MedDRA v18.0
Infections are identified either using the MedDRA Infections System Organ Class or where 'Is this event an infection?' on the CRF is ticked 'yes'.
Multiple occurrences of the same event in one individual are counted multiple times.

Program: /opt/BIOSTAT/prod/cdt3422z/z21493c/t_ae_100py.sas
Output: /opt/BIOSTAT/prod/cdt3422z/z21493c/reports/t_ae_100py_INFECT_TFP_SETFP.out
14DEC2015 20:08 [Modified by PDRD] Page 1 of 1
Group A: Dose 1 = OCR 1000 mg (Day 1 and 15); Dose 2 = OCR 1000 mg Day 1, placebo Day 15; Dose 3 = OCR 1000 mg; Dose 4 = OCR 600 mg.
Group B: Dose 1 = OCR 300 mg (Day 1 and 15); Dose 2 = OCR 600 mg Day 1, placebo Day 15; Dose 3 and Dose 4 = OCR 600 mg.
Group C: Dose 1 = Placebo (Day 1 and 15); Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg.
Group D: Dose 1 = Avonex 30 µg/week; Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg.
OCR = ocrelizumab

4.4.7.2 Pregnancies

One pregnancy was reported in patient [redacted] randomized to Group B (Listing of Pregnancy). No delivery complications were reported, and no congenital defects or infant AEs were reported. A narrative is provided for this patient.

4.4.8 Safety Laboratory Parameters

There were no safety findings related to laboratory parameters. A summary of safety laboratory results and change from baseline by visit is provided. A summary of single and replicated safety laboratory abnormalities is provided. A summary of antibody results is provided: Epstein-Barr virus, mumps, rubella, *S. pneumoniae*, and varicella.

4.4.9 Other Safety Tests

4.4.9.1 ECGs

There were no safety findings related to ECGs. A listing of ECG results is provided.

4.4.9.2 Vital Signs and Physical Examination

There were no safety findings related to vital signs or physical examinations. A summary of vital signs by study treatment is provided. Listings of vital signs and physical examination reports are also provided.

5. RESULTS: OPEN-LABEL EXTENSION

5.1 STUDY POPULATION: OPEN-LABEL EXTENSION PERIOD

5.1.1 Disposition of Patients

A total of 103 patients entered the OLE (Table 10). No patients had completed the OLE as this period was ongoing at the time of the cut-off. Six patients withdrew from the OLE period (see Section 5.1.2). Patients entering the OLE were from Central and Eastern Europe (62 patients, 60.2%), followed by North America (23 patients, 22.3%), and Western Europe (18 patients, 17.5%) (Enrollment by Region, Country, and Center).

Table 10 Patient Disposition for the Open-Label Extension Period, OLE Intent-to-Treat Population

	Placebo / OCR 600mg Group C (N=29)	OCR 600mg / OCR 600mg Group B (N=31)	OCR 1000mg / OCR 600mg Group A (N=19)	Avonex / OCR 600mg Group D (N=24)	All exposure for OLE (N=103)
Entered OLE Period	29 (100.0%)	31 (100.0%)	19 (100.0%)	24 (100.0%)	103 (100.0%)
Ongoing OLE Period	29 (100.0%)	28 (90.3%)	17 (89.5%)	23 (95.8%)	97 (94.2%)
Withdrawn from OLE Period	0	3 (9.7%)	2 (10.5%)	1 (4.2%)	6 (5.8%)
Completed OLE Period	0	0	0	0	0

n represents number of patients contributing to summary statistics.
Patients are summarized according to their randomized treatment group.
All percentages for reason for withdrawal are based on number withdrawn. All other percentages are based on N.
Withdrawals are included from withdrawal visits, completion pages and deaths; however reason for withdrawal is taken from the OLE completion forms only.
Only patients dosed in the OLE period are included.

Program: /opt/BIOSTAT/prod/cdt3422z/z21493c/t_ds_ole.sas / Output: /opt/BIOSTAT/prod/cdt3422z/z21493c/reports/t_ds_ole_ITOLE.out
15DEC2015 9:54 [Modified by PDRD] Page 1 of 1
Group A: Dose 1 = OCR 1000 mg (Day 1 and 15); Dose 2 = OCR 1000 mg Day 1, placebo Day 15; Dose 3 = OCR 1000 mg; Dose 4 = OCR 600 mg; OLE dose = 600 mg.
Group B: Dose 1 = OCR 300 mg (Day 1 and 15); Dose 2 = OCR 600 mg Day 1, placebo Day 15; Dose 3 and Dose 4 = OCR 600 mg; OLE dose = 600 mg.
Group C: Dose 1 = Placebo (Day 1 and 15); Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg; OLE dose = 600 mg.
Group D: Dose 1 = Avonex 30 µg/week; Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg; OLE dose = 600 mg.
OCR = ocrelizumab

The mean time between the last infusion of ocrelizumab in the 96-week treatment period and the first infusion in the OLE was 139.34 weeks (range: 89.0 – 184.0 weeks).

5.1.2 Patients Withdrawn Prematurely from Treatment

A total of six patients withdrew from treatment in the OLE (Table 11). All six patients withdrew for reasons other than safety: 2 patients withdrew consent, one patient was lost to follow-up, and 3 patients withdrew for administrative/other reasons. Narratives for those patients are provided. A listing of patients who discontinued early from treatment and/or study is provided.

Table 11 Patients Withdrawn from the Open-Label Period by Trial Treatment, OLE Intent-to-Treat Population

Status	Placebo / OCR 600mg Group C (N=29)	OCR 600mg / OCR 600mg Group B (N=31)	OCR 1000mg / OCR 600mg Group A (N=19)	Avonex / OCR 600mg Group D (N=24)	All exposure for OLE (N=103)
Discontinued OLE Period	0	3 (9.7%)	2 (10.5%)	1 (4.2%)	6 (5.8%)
Non-safety	0	3 (9.7%)	2 (10.5%)	1 (4.2%)	6 (5.8%)
LOST TO FOLLOW-UP	0	0	0	1 (4.2%)	1 (1.0%)
OTHER	0	3 (9.7%)	0	0	3 (2.9%)
WITHDRAWAL BY SUBJECT	0	0	2 (10.5%)	0	2 (1.9%)

Only patients dosed in the OLE period are included.
Reason for withdrawal is taken from OLE completion form only.

Program: /opt/BIOSTAT/prod/cdt3422z/z21493c/t_ds_wd.sas / Output:
/opt/BIOSTAT/prod/cdt3422z/z21493c/reports/t_ds_wd_ITOLE.out
15DEC2015 9:56 [Modified by PDRD] Page 1 of 1
Group A: Dose 1 = OCR 1000 mg (Day 1 and 15); Dose 2 = OCR 1000 mg Day 1, placebo Day 15; Dose 3 = OCR 1000 mg; Dose 4 = OCR 600 mg; OLE dose = 600 mg.
Group B: Dose 1 = OCR 300 mg (Day 1 and 15); Dose 2 = OCR 600 mg Day 1, placebo Day 15; Dose 3 and Dose 4 = OCR 600 mg; OLE dose = 600 mg.
Group C: Dose 1 = Placebo (Day 1 and 15); Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg; OLE dose = 600 mg.
Group D: Dose 1 = Avonex 30 µg/week; Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg; OLE dose = 600 mg.
OCR = ocrelizumab

5.1.3 Overview of Analysis Populations

All patients enrolled in the OLE were included in the ITT and Safety populations (Table 12).

Table 12 Analysis Populations for the Open-Label Extension Period, All OLE patients

Analysis Populations	Placebo / OCR 600mg Group C (N=29)	OCR 600mg / OCR 600mg Group B (N=31)	OCR 1000mg / OCR 600mg Group A (N=19)	Avonex / OCR 600mg Group D (N=24)	All exposure for OLE (N=103)
ITT Population					
Yes	29 (100.0%)	31 (100.0%)	19 (100.0%)	24 (100.0%)	103 (100.0%)
No	0	0	0	0	0
Safety Population					
Yes	29 (100.0%)	31 (100.0%)	19 (100.0%)	24 (100.0%)	103 (100.0%)
No	0	0	0	0	0

Patient Population : ITT=Intent-to-Treat.

Program: /opt/BIOSTAT/prod/cdt3422z/z21493c/t_pop.sas / Output:
/opt/BIOSTAT/prod/cdt3422z/z21493c/reports/t_pop_APOLE.out
14DEC2015 18:56 [Modified by PDRD] Page 1 of 1
Group A: Dose 1 = OCR 1000 mg (Day 1 and 15); Dose 2 = OCR 1000 mg Day 1, placebo Day 15; Dose 3 = OCR 1000 mg; Dose 4 = OCR 600 mg; OLE dose = 600 mg.
Group B: Dose 1 = OCR 300 mg (Day 1 and 15); Dose 2 = OCR 600 mg Day 1, placebo Day 15; Dose 3 and Dose 4 = OCR 600 mg; OLE dose = 600 mg.
Group C: Dose 1 = Placebo (Day 1 and 15); Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg; OLE dose = 600 mg.
Group D: Dose 1 = Avonex 30 µg/week; Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg; OLE dose = 600 mg.
OCR = ocrelizumab

5.1.4 Demographic Data and Baseline Characteristics

Demographic data and baseline disease characteristics for the subset of patients who entered OLE were consistent with the patient population enrolled in the main study [CSR 1034917]. A summary of demographic data for patients enrolled in the OLE (as recorded at the time of randomization to the study) is presented in Table 13. A summary of baseline disease history is provided. Summaries of baseline disease characteristics are provided for the following parameters: MRI assessments recorded at baseline, relapses, and EDSS/FSS.

Table 13 Summary of Demographic Data, OLE Intent-to-Treat Population

	Placebo / OCR 600mg Group C (N=29)	OCR 600mg / OCR 600mg Group B (N=31)	OCR 1000mg / OCR 600mg Group A (N=19)	Avonex / OCR 600mg Group D (N=24)	All exposure for OLE (N=103)
Age (years)					
n	29	31	19	24	103
Mean (SD)	39.8 (8.7)	35.1 (8.1)	39.8 (6.8)	37.8 (9.0)	37.9 (8.4)
Median	40.0	34.0	40.0	37.0	39.0
Min - Max	22 - 54	21 - 51	27 - 50	25 - 52	21 - 54
Age Group (years)					
n	29	31	19	24	103
< 40	13 (44.8%)	19 (61.3%)	9 (47.4%)	14 (58.3%)	55 (53.4%)
>= 40	16 (55.2%)	12 (38.7%)	10 (52.6%)	10 (41.7%)	48 (46.6%)
RMP Age Group Categories (years)					
n	29	31	19	24	103
<= 45	20 (69.0%)	27 (87.1%)	16 (84.2%)	17 (70.8%)	80 (77.7%)
> 45 to 65	9 (31.0%)	4 (12.9%)	3 (15.8%)	7 (29.2%)	23 (22.3%)
DSUR Age Group Categories (years)					
n	29	31	19	24	103
>= 18 to 65	29 (100.0%)	31 (100.0%)	19 (100.0%)	24 (100.0%)	103 (100.0%)
Sex					
n	29	31	19	24	103
Male	7 (24.1%)	14 (45.2%)	5 (26.3%)	13 (54.2%)	39 (37.9%)
Female	22 (75.9%)	17 (54.8%)	14 (73.7%)	11 (45.8%)	64 (62.1%)

Demographic characteristics as recorded at the time of randomization to the study.
DSUR and RMP Age Group Categories presented are standard defined categories.
n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values).
Percentages are not calculated if n=0.
Race values of 'Multiple' indicate that more than one Race value was selected. These values are assessed individually for inclusion in the Asian Race Subcategories.

Program: /opt/BIOSTAT/prod/cdt3422z/z21493c/t_dm.sas / Output: /opt/BIOSTAT/prod/cdt3422z/z21493c/reports/t_dm_ITOLE.out
14DEC2015 19:00 [Modified by PDRD]

Table 13 Summary of Demographic Data, OLE Intent-to-Treat Population (cont.)

	Placebo / OCR 600mg Group C (N=29)	OCR 600mg / OCR 600mg Group B (N=31)	OCR 1000mg / OCR 600mg Group A (N=19)	Avonex / OCR 600mg Group D (N=24)	All exposure for OLE (N=103)
Race					
n	29	31	19	24	103
Asian	1 (3.4%)	0	0	0	1 (1.0%)
Black or African American	0	2 (6.5%)	1 (5.3%)	0	3 (2.9%)
White	27 (93.1%)	29 (93.5%)	18 (94.7%)	24 (100.0%)	98 (95.1%)
Other	1 (3.4%)	0	0	0	1 (1.0%)
Asian Race Subcategories					
n	1	0	0	0	1
INDIAN SUBCONTINENT	1 (100.0%)	0	0	0	1 (100.0%)
OTHER THAN INDIAN SUBCONTINENT	0	0	0	0	0
Ethnicity					
n	29	31	19	24	103
HISPANIC OR LATINO	4 (13.8%)	3 (9.7%)	2 (10.5%)	3 (12.5%)	12 (11.7%)
NOT HISPANIC OR LATINO	25 (86.2%)	28 (90.3%)	17 (89.5%)	21 (87.5%)	91 (88.3%)
Weight (kg)					
n	29	31	19	24	103
Mean (SD)	75.95 (17.86)	77.61 (21.33)	73.84 (19.24)	73.02 (16.42)	75.38 (18.73)
Median	76.70	74.00	71.20	76.25	75.00
Min - Max	50.8 - 126.5	51.0 - 133.6	40.0 - 110.0	43.0 - 106.2	40.0 - 133.6

Demographic characteristics as recorded at the time of randomization to the study.
DSUR and RMP Age Group Categories presented are standard defined categories.
n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values).
Percentages are not calculated if n=0.
Race values of 'Multiple' indicate that more than one Race value was selected. These values are assessed individually for inclusion in the Asian Race Subcategories.

Program: /opt/BIOSTAT/prod/cdt3422z/z21493c/t_dm.sas / Output: /opt/BIOSTAT/prod/cdt3422z/z21493c/reports/t_dm_ITOLE.out
14DEC2015 19:00 [Modified by PDRD]

Table 13 Summary of Demographic Data, OLE Intent-to-Treat Population (cont.)

	Placebo / OCR 600mg Group C (N=29)	OCR 600mg / OCR 600mg Group B (N=31)	OCR 1000mg / OCR 600mg Group A (N=19)	Avonex / OCR 600mg Group D (N=24)	All exposure for OLE (N=103)
Body Mass Index (kg/m2)					
n	29	31	19	24	103
Mean (SD)	26.19 (5.62)	26.04 (7.93)	25.06 (5.30)	24.32 (4.50)	25.50 (6.11)
Median	25.42	24.77	24.42	23.85	24.75
Min - Max	18.0 - 42.3	17.7 - 52.8	15.8 - 35.9	17.7 - 34.2	15.8 - 52.8
Region					
n	29	31	19	24	103
ROW	26 (89.7%)	25 (80.6%)	18 (94.7%)	20 (83.3%)	89 (86.4%)
USA	3 (10.3%)	6 (19.4%)	1 (5.3%)	4 (16.7%)	14 (13.6%)
Sub-Region					
n	29	31	19	24	103
EASTERN CENTRAL EUROPE/ASIA	17 (58.6%)	18 (58.1%)	12 (63.2%)	15 (62.5%)	62 (60.2%)
NORTH AMERICA	7 (24.1%)	8 (25.8%)	4 (21.1%)	4 (16.7%)	23 (22.3%)
WESTERN EUROPE	5 (17.2%)	5 (16.1%)	3 (15.8%)	5 (20.8%)	18 (17.5%)

Demographic characteristics as recorded at the time of randomization to the study.
DSUR and RMP Age Group Categories presented are standard defined categories.
n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values).
Percentages are not calculated if n=0.
Race values of 'Multiple' indicate that more than one Race value was selected. These values are assessed individually for inclusion in the Asian Race Subcategories.

Program: /opt/BIOSTAT/prod/cdt3422z/z21493c/t_dm.sas / Output: /opt/BIOSTAT/prod/cdt3422z/z21493c/reports/t_dm_ITOLE.out
14DEC2015 19:00 [Modified by PDRD] Page 3 of 3
Group A: Dose 1 = OCR 1000 mg (Day 1 and 15); Dose 2 = OCR 1000 mg Day 1, placebo Day 15; Dose 3 = OCR 1000 mg; Dose 4 = OCR 600 mg; OLE dose = 600 mg.
Group B: Dose 1 = OCR 300 mg (Day 1 and 15); Dose 2 = OCR 600 mg Day 1, placebo Day 15; Dose 3 and Dose 4 = OCR 600 mg; OLE dose = 600 mg.
Group C: Dose 1 = Placebo (Day 1 and 15); Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg; OLE dose = 600 mg.
Group D: Dose 1 = Avonex 30 µg/week; Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg; OLE dose = 600 mg.
OCR = ocrelizumab

5.1.5 Previous and Current Diseases and Treatments

One patient had previous diseases (other than MS): cyst and benign breast neoplasm. Previous diseases were defined as all diseases ongoing at the end of the TFP or with onset occurring before the first dose of ocrelizumab in OLE. A total of 15 patients (14.6%) had current diseases (other than MS) in the OLE. The most common current disease was hypercholesterolemia (3 patients, 2.9%).

Previous treatments were defined as all ongoing treatments at the end of the TFP and all later treatments up to the first ocrelizumab dose in OLE. The most common previous treatments were corticosteroids, analgesics, and antihistamines. A total of 32 patients (31%) received previous treatments for MS. The most common previous treatments for MS were vitamins and minerals, supplements and muscle relaxants.

The most common concomitant treatments were corticosteroids (mainly methylprednisolone), analgesics, and antihistamines. Note: this includes pre-medication received to reduce potential IRRs.

5.2 CLINICAL AND IMAGING OUTCOME MEASURES: OPEN-LABEL EXTENSION PERIOD

The population enrolled into the OLE was representative of the overall population of patients enrolled in the main study. However, due to the low number of patients and the fact that selection bias cannot be excluded, data should be interpreted with caution.

5.2.1 Assessment by Brain MRI

Brain volume at 2 years of the OLE was similar to OLE baseline (MRI by Visit). During this period, mean new/enlarging T2 lesion count decreased from 0.80 (SD=3.48) to 0.08 (SD=0.28), and the mean total number of Gadolinium-enhancing T1 lesions decreased from 0.13 (SD=1.12) to 0.00 (SD=0.00).

A listing of MRI outcomes is provided.

5.2.2 Assessment of Relapse

5.2.2.1 Protocol-Defined Relapses

A summary of annualized protocol-defined relapse rate for the OLE up to the cut-off (22 January 2015) is presented in Table 14 . The annualized protocol-defined relapse rate adjusted for geographical region for the all exposed population was 0.056, 95% CI [0.032, 0.097] (Table 14). This rate was higher in Group A: 0.245, 95% CI [0.142, 0.424]. In Group A, 5 patients had protocol-defined relapses: 3 patients with 1 relapse, 1 patient with 2 relapses during the OLE treatment period, and 1 patient with 3 relapses (listing of relapse information). In the other treatment groups, there were no patients with more than one protocol-defined relapse. Two patients had 1 protocol-defined relapse in each Group B and Group D, and 1 patient had 1 protocol-defined relapse in Group C.

Table 14 Annualized Protocol-Defined Relapse Rate (Poisson Model), OLE Intent-to-Treat Population

Efficacy Variable	Placebo / OCR 600mg Group C (N=29)	OCR 600mg / OCR 600mg Group B (N=31)	OCR 1000mg / OCR 600mg Group A (N=19)	Avonex / OCR 600mg Group D (N=24)	All exposure for OLE (N=103)
Total number of relapses	1	2	8	2	13
Total patient-years followed	50.2	49.6	32.0	39.9	171.8
Unadjusted annualized relapse rate	0.020	0.040	0.250	0.050	0.076
Adjusted annualized relapse rate*	0.019	0.039	0.245	0.052	0.056
95% CI of adjusted annualized relapse rate*	(0.005, 0.081)	(0.014, 0.108)	(0.142, 0.424)	(0.018, 0.144)	(0.032, 0.097)
Overdispersion					0.7211

The total number of protocol defined relapses that occurred divided by the total number of subject-years followed in this period.
Log-transformed exposure time is included as offset variable.
*Adjusted for Geographical Region (Eastern Central Europe/Asia, North America and Western Europe).

Program: /opt/BIOSTAT/prod/cdt3422z/z21493c/t_pdr_arr_pois.sas
Output: /opt/BIOSTAT/prod/cdt3422z/z21493c/reports/t_pdr_arr_pois_OLE_ITOLE.out
14DEC2015 18:45 [Modified by PDRD] Page 1 of 1
Group A: Dose 1 = OCR 1000 mg (Day 1 and 15); Dose 2 = OCR 1000 mg Day 1, placebo Day 15; Dose 3 = OCR 1000 mg; Dose 4 = OCR 600 mg; OLE dose = 600 mg.
Group B: Dose 1 = OCR 300 mg (Day 1 and 15); Dose 2 = OCR 600 mg Day 1, placebo Day 15; Dose 3 and Dose 4 = OCR 600 mg; OLE dose = 600 mg.
Group C: Dose 1 = Placebo (Day 1 and 15); Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg; OLE dose = 600 mg.
Group D: Dose 1 = Avonex 30 μg/week; Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg; OLE dose = 600 mg.
OCR = ocrelizumab

Up to Week 48 of OLE, 100 patients (97.1%) remained protocol-defined relapse-free, 2 patients (1.9%) had 1 relapse and 1 patient (1.0%) had 2 relapses.

Sensitivity analyses where patients who discontinued the study were assumed to have had a relapse showed similar results to the main analyses (Week 48, all data up to the cut-off).

5.2.2.2 Clinical Relapses

Annualized clinical relapse rate adjusted for geographical region in the all exposed population for the OLE up to the cut-off was 0.086, 95% CI [0.050, 0.147]. This rate was higher in Group A: 0.236, 95% CI [0.125, 0.449]. Up to the cut-off, 88 patients (85.4%) remained clinical relapse-free, 12 patients (11.7%) had 1 relapse, 1 patient (1.0%) had 2 relapses, and 2 patients (1.9%) had several relapses (Proportion of Patients who Remain Clinical Relapse-free).

Up to Week 48, 98 patients (95.1%) remained clinical relapse-free. Sensitivity analysis where patients who discontinued the study were assumed to have had a relapse showed similar results.

A summary of clinical MS relapse by dose, preferred term and sites/symptoms involved is provided. A listing of relapse information is provided.

5.2.3 Assessment of Disability

At OLE baseline, the mean EDSS in the all exposed population was 3.14 (SD=1.68) and the median was 3.50. No clinically relevant worsening in EDSS over time was observed during the OLE.

5.3 CLINICIAN-REPORTED OUTCOMES: OPEN-LABEL EXTENSION PERIOD

At OLE baseline, the mean value on the Karnofsky scale in the all exposed population was 80.5 (SD=14.1) and the median was 80.0. No major changes on the Karnofsky scale over time were observed during the OLE.

5.4 PHARMACODYNAMICS: OPEN-LABEL EXTENSION PERIOD

5.4.1 CD19+ B-Cells and Other FACS Results

A total of 86 patients (90.5%) enrolled in the OLE had repleted B cells at baseline. The proportion of patients with repleted B cells was similar between treatment groups. Treatment with ocrelizumab in the OLE led to B-cell depletion in all patients within 24 weeks after the first dose (FACS results and change from baseline by visit).

Memory B-cells ($CD19^{+}$, $CD38^{lo}$, $CD27^{+}$) were depleted efficiently after administration of ocrelizumab. No major 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 naïve B-cells ($CD19^{+}$, $CD21^{+}$, IgM^{+}, IgD^{+}).

5.4.2 Serum Immunoglobulin Levels

Small decreases from baseline in total Ig, IgA and IgG and larger decrease in IgM were observed following ocrelizumab treatment in the OLE (immunoglobulin results and percent change from baseline by visit, immunoglobulin results and change from baseline by visit). Serum IgM levels decreased from baseline after ocrelizumab treatment by approximately 25% and remained stable during the OLE.

5.5 SAFETY: OPEN-LABEL EXTENSION PERIOD

5.5.1 Overview of Safety: Open-Label Extension Period

An overview of AEs reported during the OLE is provided in Table 15. A total of 66 patients (64.1%) had at least one AE. Most AEs were Grade 1 or Grade 2 in intensity. Five patients had a total of 8 treatment-emergent Grade 3 AEs: bronchopneumonia, asthenia, sinusitis, headache, IRR, osteoarthritis, MS relapse, and non-alcoholic steatohepatitis. No Grade 4 or Grade 5 treatment-emergent AEs were reported. Three patients had SAEs: one patient had bronchopneumonia, one patient had hepatitis A, and one patient had uterine prolapse. Among those, only the SAE of bronchopneumonia was considered related to the study drug by the investigator. There were no AEs leading to permanent discontinuation of study drug.

The most common AEs were from the SOCs Infections and Infestations (42 patients, 40.8%), Nervous System Disorders, mainly MS relapse (15 patients, 14.6%), and IRRs (22 patients, 21.4%). Most IRRs occurred after first infusion and no IRRs were reported after the fourth and the subsequent doses. Most IRRs were Grade 1 or Grade 2 in intensity. Only one Grade 3 IRR was reported; it occurred after the first infusion. No serious, life-threatening or fatal IRRs were reported.

There were no safety findings related to laboratory parameters, ECGs, vital signs or physical examination.

Table 15 Overview of Adverse Events

	Group C N=29	Group B N=31	Group A N=19	Group D N=24	All exposure for OLE N=103
Number and proportion of patients with at least one AE	17 (58.6%)	19 (61.3%)	12 (63.2%)	18 (75.0%)	66 (64.1%)
Number and proportion of patients with Grade 3 AEs	1 (3.4%)	2 (6.5%)	1 (5.3%)	1 (4.2%)	5 (4.9%)
Deaths	0	0	0	0	0
Number and proportion of patients with at least one SAE	2 (6.9%)	0	0	1 (4.2%)	3 (2.9%)
Withdrawals due to AE	0	0	0	0	0
Number and proportion of patients with selected AEs					
Infections	10 (34.5%)	13 (41.9%)	8 (42.1%)	11 (45.8%)	42 (40.8%)
IRRs	4 (13.8%)	8 (25.8%)	3 (15.8%)	7 (29.2%)	22 (21.4%)
Pregnancy	0	0	0	0	0

Source: t_ae_OLE_SEOLE, t_ae_int_OLE_SEOLE, Table 17, t_ae_irr_inf_OLE_SEOLE, t_ae_INFECT_OLE_SEOLE, t_ae_IVSER_OLE_SEOLE, l_preg_OLESCR_SEOLE

Group A: Dose 1 = OCR 1000 mg on Day 1 and 15; Dose 2 = OCR 1000 mg Day 1, placebo Day 15; Dose 3 = OCR 1000 mg; Dose 4 = OCR 600 mg; OLE first dose = 300 mg on Day 1 and 15; subsequent OLE doses = 600 mg.

Group B: Dose 1 = OCR 300 mg on Day 1 and 15; Dose 2 = OCR 600 mg Day 1, placebo Day 15; Dose 3 and Dose 4 = OCR 600 mg; OLE first dose = 300 mg on Day 1 and 15; subsequent OLE doses = 600 mg.

Group C: Dose 1 = Placebo (Day 1 and 15); Dose 2 = OCR 300 mg on Day 1 and 15; Dose 3 and Dose 4 = OCR 600 mg; OLE first dose = 300 mg on Day 1 and 15; subsequent OLE doses = 600 mg.

Group D: Dose 1 = Avonex 30 μg/week; Dose 2 = OCR 300 mg on Day 1 and 15; Dose 3 and Dose 4 = OCR 600 mg; OLE first dose = 300 mg on Day 1 and 15; subsequent OLE doses = 600 mg.

OCR = ocrelizumab

5.5.2 Extent of Exposure to Study Treatment

Exposure to ocrelizumab during the OLE is presented in Table 16 . All patients enrolled in the OLE received at least one infusion of ocrelizumab. The median number of infusions was 5, which corresponds to 4 doses of 600 mg, and the median total cumulative dose was 2400 mg. A listing of exposure to ocrelizumab by infusion is provided. Over 90% of patients received the intended dose of ocrelizumab and steroids.

Table 16 Exposure to Ocrelizumab (mg) during the Open-Label Extension Treatment Period, OLE Safety-Evaluable Population

	Placebo / OCR 600mg Group C (N=29)	OCR 600mg / OCR 600mg Group B (N=31)	OCR 1000mg / OCR 600mg Group A (N=19)	Avonex / OCR 600mg Group D (N=24)	All exposure for OLE (N=103)
Treatment duration (W)					
n	29	31	19	24	103
0 - <24	0	1 (3.2%)	0	1 (4.2%)	2 (1.9%)
24 - <48	0	2 (6.5%)	1 (5.3%)	0	3 (2.9%)
48 - <72	9 (31.0%)	6 (19.4%)	4 (21.1%)	6 (25.0%)	25 (24.3%)
72 - <96	7 (24.1%)	10 (32.3%)	5 (26.3%)	6 (25.0%)	28 (27.2%)
96 - <120	6 (20.7%)	7 (22.6%)	6 (31.6%)	5 (20.8%)	24 (23.3%)
120- <144	7 (24.1%)	5 (16.1%)	3 (15.8%)	6 (25.0%)	21 (20.4%)
Number of Infusions					
n	29	31	19	24	103
Mean (SD)	5.5 (1.3)	5.3 (1.3)	5.3 (1.2)	5.4 (1.4)	5.4 (1.3)
Median	5.0	5.0	5.0	5.5	5.0
Min - Max	4 - 8	2 - 8	3 - 7	1 - 7	1 - 8
Total cumulative dose (mg)					
n	29	31	19	24	103
Mean (SD)	2689.7 (762.7)	2559.1 (811.4)	2558.9 (718.3)	2637.5 (825.0)	2614.1 (775.3)
Median	2400.0	2400.0	2400.0	2700.0	2400.0
Min - Max	1800 - 4200	600 - 4200	1200 - 3620	300 - 3600	300 - 4200

Patients are summarized according to first treatment actually received (if a patient switches treatment they are summarized in the original treatment group).
Treatment duration is the date of the last recorded observation during the Open Label Treatment Period minus the date of first infusion of Open Label treatment.

Program: /opt/BIOSTAT/prod/cdt3422z/z21493c/t_ex_ocr.sas
Output: /opt/BIOSTAT/prod/cdt3422z/z21493c/reports/t_ex_ocr_OLE_SEOLE.out
15DEC2015 9:46 [Modified by PDRD] Page 1 of 1
Group A: Dose 1 = OCR 1000 mg on Day 1 and 15; Dose 2 = OCR 1000 mg Day 1, placebo Day 15; Dose 3 = OCR 1000 mg; Dose 4 = OCR 600 mg; OLE first dose = 300 mg on Day 1 and 15; subsequent OLE doses = 600 mg.
Group B: Dose 1 = OCR 300 mg on Day 1 and 15; Dose 2 = OCR 600 mg Day 1, placebo Day 15; Dose 3 and Dose 4 = OCR 600 mg; OLE first dose = 300 mg on Day 1 and 15; subsequent OLE doses = 600 mg.
Group C: Dose 1 = Placebo (Day 1 and 15); Dose 2 = OCR 300 mg on Day 1 and 15; Dose 3 and Dose 4 = OCR 600 mg; OLE first dose = 300 mg on Day 1 and 15; subsequent OLE doses = 600 mg.
Group D: Dose 1 = Avonex 30 µg/week; Dose 2 = OCR 300 mg on Day 1 and 15; Dose 3 and Dose 4 = OCR 600 mg; OLE first dose = 300 mg on Day 1 and 15; subsequent OLE doses = 600 mg.
OCR = ocrelizumab

5.5.3 Common Adverse Events and Treatments for Adverse Events

A total of 66 patients (64.1%) had at least one AE during the OLE. The most common AEs were from the SOCs of Infections and Infestations (42 patients, 40.8%), Nervous System Disorders, mainly MS relapse (15 patients, 14.6%), and IRRs (22 patients, 21.4%). The listing of patients with AEs is provided.

A total of 53 patients (51.5%) received treatments for AEs. The most common treatments for AEs were non-steroidal anti-inflammatories (12 patients, 11.7%), penicillins (10 patients, 9.7%), and corticosteroids (8 patients, 7.8%).

5.5.4 Adverse Events by Intensity

Most AEs occurring during the OLE were Grade 1 or Grade 2 in intensity (Adverse Events by Intensity). Five patients had a total of 8 treatment-emergent Grade 3 AEs: bronchopneumonia, asthenia, sinusitis, headache, IRR, osteoarthritis, MS relapse, and

non-alcoholic steatohepatitis. No Grade 4 or Grade 5 treatment-emergent AEs were reported.

5.5.5 Deaths

No deaths occurred during the OLE.

5.5.6 Serious Adverse Events

Three patients had SAEs during the OLE (Table 17). One patient had bronchopneumonia, one patient had hepatitis A, and one patient had uterine prolapse. The bronchopneumonia that occurred in patient No. [redacted] randomized to Group C was considered related to the study drug by the investigator; the two other SAEs were considered unrelated. All three SAEs resolved without sequelae (listing of patients with SAEs). Narratives are provided for those patients. The SAE rate per 100 patient years was 1.75, 95% CI [0.56, 5.42].

Table 17 Serious Adverse Events by Body System Class and Preferred Term, OLE Safety-Evaluable Population

MedDRA System Organ Class MedDRA Preferred Term	Group C Placebo / OCR 600mg (N=29)	Group B OCR 600mg / OCR 600mg (N=31)	Group A OCR 1000mg / OCR 600mg (N=19)	Group D Avonex / OCR 600mg (N=24)	All exposure for OLE (N=103)
Total number of patients with at least one adverse event	2 (6.9%)	0	0	1 (4.2%)	3 (2.9%)
Overall total number of events	2	0	0	1	3
INFECTIONS AND INFESTATIONS					
Total number of patients with at least one adverse event	1 (3.4%)	0	0	1 (4.2%)	2 (1.9%)
Total number of events	1	0	0	1	2
BRONCHOPNEUMONIA	1 (3.4%)	0	0	0	1 (1.0%)
HEPATITIS A	0	0	0	1 (4.2%)	1 (1.0%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS					
Total number of patients with at least one adverse event	1 (3.4%)	0	0	0	1 (1.0%)
Total number of events	1	0	0	0	1
UTERINE PROLAPSE	1 (3.4%)	0	0	0	1 (1.0%)

Investigator text for AEs encoded using MedDRA version MedDRA v18.0
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Serious is defined as 1) using "Is this a serious adverse event" (see protocol for definition)? ticked 'yes' from the Adverse Event CRF page or 2) Infections requiring IV Anti-Infective.

Program: /opt/BIOSTAT/prod/cdt3422z/z21493c/t_ae.sas
Output: /opt/BIOSTAT/prod/cdt3422z/z21493c/reports/t_ae_IVSER_OLE_SEOLE.out
14DEC2015 19:42 [Modified by PDRD] Page 1 of 1
Group A: Dose 1 = OCR 1000 mg on Day 1 and 15; Dose 2 = OCR 1000 mg Day 1, placebo Day 15; Dose 3 = OCR 1000 mg; Dose 4 = OCR 600 mg; OLE first dose = 300 mg on Day 1 and 15; subsequent OLE doses = 600 mg.
Group B: Dose 1 = OCR 300 mg on Day 1 and 15; Dose 2 = OCR 600 mg Day 1, placebo Day 15; Dose 3 and Dose 4 = OCR 600 mg; OLE first dose = 300 mg on Day 1 and 15; subsequent OLE doses = 600 mg.
Group C: Dose 1 = Placebo (Day 1 and 15); Dose 2 = OCR 300 mg on Day 1 and 15; Dose 3 and Dose 4 = OCR 600 mg; OLE first dose = 300 mg on Day 1 and 15; subsequent OLE doses = 600 mg.
Group D: Dose 1 = Avonex 30 µg/week; Dose 2 = OCR 300 mg on Day 1 and 15; Dose 3 and Dose 4 = OCR 600 mg; OLE first dose = 300 mg on Day 1 and 15; subsequent OLE doses = 600 mg.
OCR = ocrelizumab

A listing of patients with SAEs is provided. In addition to the SAEs presented in Table 17, this listing also contains SAEs occurring during the OLE screening period. One patient experienced vertigo and another patient experienced depression during the OLE screening period.

5.5.7 Adverse Events Leading to Discontinuation from Study Treatment or Study Withdrawal

There were no discontinuations from study treatment due to AEs.

5.5.8 Adverse Events That Led to Dose Modification

Four patients (3.9%) had AEs leading to modification or interruption of study drug. Among those, 3 patients had IRRs and one patient had non-alcoholic steatohepatitis.

5.5.9 Selected Adverse Events

5.5.9.1 Infections

During the OLE, the rate of infections per 100 patient years in the all exposed population was 51.81, 95% CI [42.09, 63.78] (Table 18). This rate was higher in Group A: 74.94, 95% CI [50.23, 111.80]. However, the percentage of patients who experienced an infection was similar in Group A (42.1%) compared to the all exposed population (40.8%). The higher rate of infections in Group A can be explained by a high number of infections in patient No. [redacted] This patient had a total of 9 infections during the OLE (listing of patients with infection AEs): infectious mononucleosis, 4 urinary tract infection AEs, pharyngitis, upper respiratory tract infection, and 2 oral herpes AEs. All infections experienced by this patient were non serious, Grade 1 or 2, were considered unrelated to study drug by the investigator, and resolved without sequelae. Study drug was not discontinued as the result of those infection AEs.

Two serious infections were reported during the OLE. One patient in Group C had bronchopneumonia and one patient in Group D had hepatitis A. The bronchopneumonia was considered related to study drug by the investigator and hepatitis A was considered unrelated (listing of patients with infection SAEs). Both SAEs resolved without sequelae. Patient narratives are provided for both cases.

Table 18 Number of Infections per 100 Patient Years, OLE Safety-Evaluable Population

	Placebo / OCR 600mg Group C (N=29)	OCR 600mg / OCR 600mg Group B (N=31)	OCR 1000mg / OCR 600mg Group A (N=19)	Avonex / OCR 600mg Group D (N=24)	All Exposure for OLE (N=103)
Total Patient-Years at Risk	50.2	49.6	32.0	39.9	171.8
Number of Adverse Events Observed	25	23	24	17	89
AE Rate per 100 Patient-Years	49.76	46.35	74.94	42.62	51.81
95% CI	(33.63, 73.65)	(30.80, 69.75)	(50.23, 111.80)	(26.49, 68.56)	(42.09, 63.78)

Investigator text for AEs encoded using MedDRA version MedDRA v18.0
Infections are identified either using the MedDRA Infections System Organ Class or where 'Is this event an infection?' on the CRF is ticked 'yes'.
Multiple occurrences of the same event in one individual are counted multiple times.

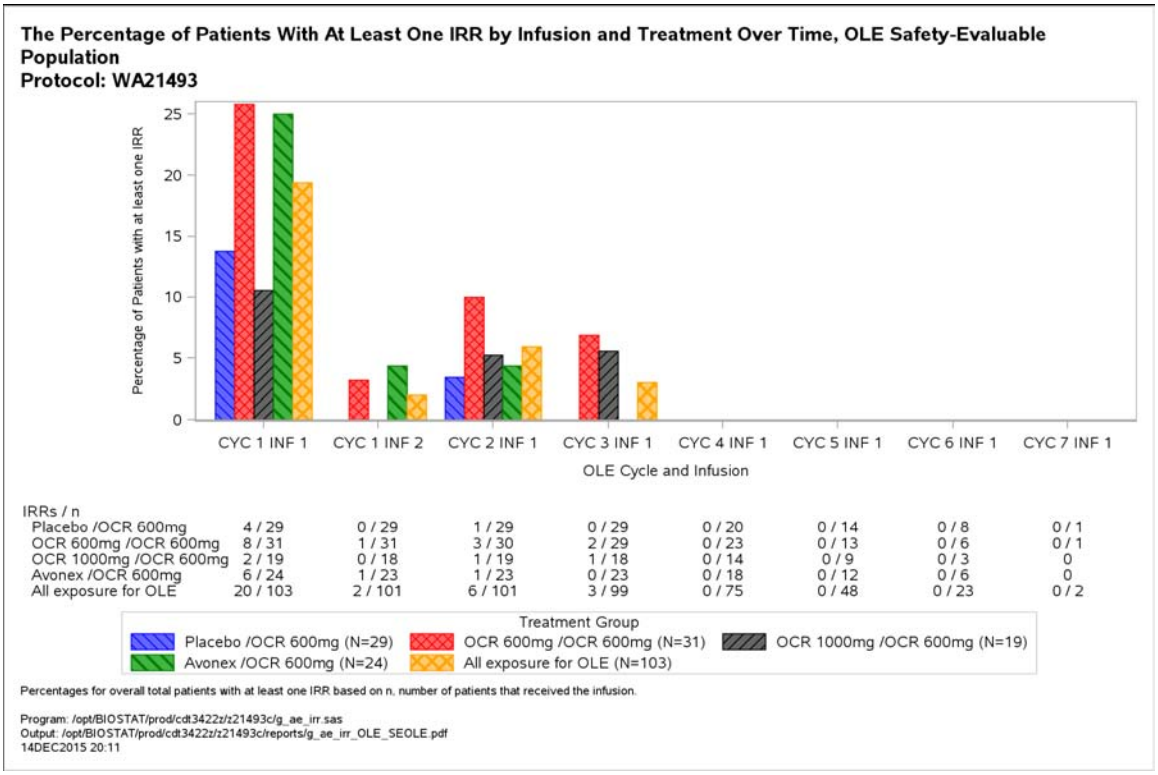
Program: /opt/BIOSTAT/prod/cdt3422z/z21493c/t_ae_100py.sas
Output: /opt/BIOSTAT/prod/cdt3422z/z21493c/reports/t_ae_100py_INFECT_OLE_SEOLE.out
14DEC2015 20:08 [Modified by PDRD] Page 1 of 1
Group A: Dose 1 = OCR 1000 mg (Day 1 and 15); Dose 2 = OCR 1000 mg Day 1, placebo Day 15; Dose 3 = OCR 1000 mg; Dose 4 = OCR 600 mg; OLE dose = 600 mg.
Group B: Dose 1 = OCR 300 mg (Day 1 and 15); Dose 2 = OCR 600 mg Day 1, placebo Day 15; Dose 3 and Dose 4 = OCR 600 mg; OLE dose = 600 mg.
Group C: Dose 1 = Placebo (Day 1 and 15); Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg; OLE dose = 600 mg.
Group D: Dose 1 = Avonex 30 µg/week; Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg; OLE dose = 600 mg.
OCR = ocrelizumab

5.5.9.2 Infusion-Related Reactions

A total of 22 patients (21.4%) had at least one IRR during the OLE (Infusion Related Reactions and Symptoms Overall and by Infusion). The most common symptoms were rash, throat itching, and laryngeal/throat irritation. Most IRRs were of Grade 1 or Grade 2 intensity. Only one Grade 3 IRR was reported after the first infusion (patient No. [redacted]). This patient experienced an IRR on Day 1311 (first infusion of Dose 1 of OLE) with the following symptoms: severe flushing (Grade 3). [redacted] was treated with oral cetirizine 10 mg and intravenous methylprednisolone 100 mg. The infusion of study drug was discontinued. The IRR was considered resolved without sequelae on the same day. The event was considered to be non-serious by the investigator and related to the study medication. Due to this event, study drug administration was not changed. This patient experienced another IRR on Day 1479; it was non serious and resolved without sequelae. A full narrative is provided for this patient.

No serious IRRs were reported. There were no premature withdrawals from study due to IRRs. Three patients had dose modifications or interruptions due to IRRs. Fifteen patients (14.6%) received concomitant treatments for IRRs, mainly antihistamines (13 patients, 12.6%). Most IRRs occurred after first infusion and no IRRs were reported after the fourth and the subsequent doses (Figure 5).

Figure 5 Percentage of Patients with IRR by Infusion and Treatment Over Time, OLE Safety-Evaluable Population



5.5.9.3 Pregnancies

No pregnancies were reported during the OLE.

5.5.10 Safety Laboratory Parameters

There were no safety findings related to laboratory parameters. A summary of safety laboratory results and change from baseline by visit and a summary of single and replicated safety laboratory abnormalities are provided.

5.5.11 Immunogenicity

The prevalence of ADAs at baseline of the OLE was 1.0% (1 patient out of 103, Table 19), and the ADA titers of this patient did not increase post baseline The post-baseline incidence of treatment-induced ADAs was 1.9% (2 patients out of 103). A summary of ADA sample status by visit during the OLE is provided.

Table 19 Baseline Prevalence and Post-Baseline Incidence of ADAs – Open-Label Extension Period

	Placebo / OCR 600mg Group C (N=29)	OCR 600mg / OCR 600mg Group B (N=31)	OCR 1000mg / OCR 600mg Group A (N=19)	Avonex / OCR 600mg Group D (N=24)	All exposure for OLE (N=103)
Baseline Prevalence of ADAs					
Baseline evaluable patients	29	31	19	24	103
Patients with a positive sample at baseline	1 (3.4%)	0	0	0	1 (1.0%)
Patients with no positive samples at baseline	28	31	19	24	102
Post-Baseline Incidence of ADAs					
Post-baseline evaluable patients	29	31	19	24	103
Patients positive for ADA	1 (3.4%)	1 (3.2%)	0	0	2 (1.9%)
Treatment-induced ADA	1	1	0	0	2
Treatment-enhanced ADA	0	0	0	0	0
Patients negative for ADA	28	30	19	24	101
Treatment unaffected	1	0	0	0	1

ADA = Anti-Therapeutic Antibodies. Baseline is the last evaluable ADA assessment prior to the first infusion of Ocrelizumab in OLE.
All data from the OLE Treatment and OLE Safety-follow up included.
Baseline evaluable patient = a patient with an ADA assay result from a baseline sample(s).
Post-baseline evaluable patient = a patient with an ADA assay result from at least one post-baseline sample.
Number of patients positive for ADA = the number (and percentage) of post-baseline evaluable patients determined to have treatment-induced ADA or treatment-enhanced ADA during the study period.
Treatment-induced ADA = a patient with negative or missing baseline ADA result(s) and at least one positive post-baseline ADA result
Treatment-enhanced ADA = a patient with positive ADA result at baseline who has one or more post-baseline titer results that are at least 0.60 t.u. greater than the baseline titer result.
Number of patients negative for ADA = number of post-baseline evaluable patients with negative or missing baseline ADA result(s) and all negative post-baseline results, or a patient who is treatment unaffected.
Treatment unaffected = A post-baseline evaluable patient with a positive ADA result at baseline and (a)where all post-baseline titer results are less than 0.60 t.u. greater than the baseline titer result, OR (b) where all post-baseline results are negative or missing. For any positive sample with titer result less than the minimum reportable titer or any positive sample where a titer cannot be obtained, titer value is imputed as equal to the minimum reportable titer.
The percentage (%) is calculated by the number of evaluable patients at baseline or post-baseline respectively.

Program: /opt/BIOSTAT/prod/cdt3422z/z21493c/t_ada_previnci.sas
Output: /opt/BIOSTAT/prod/cdt3422z/z21493c/reports/t_ada_previnci_OLE_SEOLE.out
14DEC2015 20:19 [Modified by PDRD] Page 1 of 1
Group A: Dose 1 = OCR 1000 mg (Day 1 and 15); Dose 2 = OCR 1000 mg Day 1, placebo Day 15; Dose 3 = OCR 1000 mg; Dose 4 = OCR 600 mg; OLE dose = 600 mg.
Group B: Dose 1 = OCR 300 mg (Day 1 and 15); Dose 2 = OCR 600 mg Day 1, placebo Day 15; Dose 3 and Dose 4 = OCR 600 mg; OLE dose = 600 mg.
Group C: Dose 1 = Placebo (Day 1 and 15); Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg; OLE dose = 600 mg.
Group D: Dose 1 = Avonex 30 μg/week; Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg; OLE dose = 600 mg.
OCR = ocrelizumab

5.5.12 Other Safety Tests

5.5.12.1 ECGs

There were no safety findings related to ECG results. A listing of ECG results is provided.

5.5.12.2 Vital Signs and Physical Examination

No clinically meaningful changes in vital signs and in physical examination findings were observed. A summary of vital signs by trial treatment is provided. Listings of vital signs and physical examination reports are provided.

6. DISCUSSION

6.1 TREATMENT-FREE PERIOD

Overall the safety profile of ocrelizumab during the TFP was consistent with the main treatment period, with the exception of the incidence of AEs, mainly driven by MS relapses, that was higher in Group A compared with the other treatment groups. However, the sample size was small and therefore data should be interpreted with caution. Of note, more patients randomized to Group A had current (concomitant) diseases compared with the other groups. The number of patients with current (concomitant) diseases during the TFP was 16 patients (32.0%) in Group A compared with 7 patients (14.6%) in Group B, 8 patients (16.3%) in Group C, and 9 patients (18.4%) in Group D. This difference was not driven by any particular preferred terms. This imbalance may have contributed to a higher incidence of AEs in Group A compared with the other groups.

Median times to B-cell repletion were numerically higher in Groups A and B (74.0 weeks and 71.9 weeks, respectively) compared with Groups C and D (62.0 weeks and 59.0 weeks, respectively); however the CIs were wide and overlapping.

The percentage of patients with at least one infection was higher in Group A compared with the other groups; however, the infection AE rate per 100 patient years was similar between the treatment groups. One patient in Group D experienced a serious infection (bronchitis) considered unrelated to study drug by the investigator that resolved without sequelae.

6.2 OPEN-LABEL EXTENSION

The population enrolled into the OLE was representative of the population of patients enrolled into the main study in terms of demographic and baseline disease characteristics. However, as only 47% of patients who were enrolled in the main study entered the OLE and a selection bias cannot be excluded, comparisons between the main study and the OLE in terms of treatment effects should be interpreted with caution. Patients who agreed to participate in the OLE had relatively low MS disease activity as evidenced by a low number of MRI lesions at baseline. During the OLE treatment period, their annualized relapse rate was also low (0.056 for protocol-defined relapses and

0.086 for clinical relapses). The majority of patients remained relapse-free during the reporting period of this CSR.

Patients in Group A had higher annualized relapse rates compared with the average for the all exposed population. This is likely to be a chance finding as the number of patients who enrolled in the OLE was small: 103 patients in total, and only 19 patients were randomized to Group A.

The safety profile of ocrelizumab during the OLE was consistent with the main treatment period. There were no new safety findings compared with the main study. There were no deaths or withdrawals from treatment due to AEs. The SAE rate per 100 patient years was 1.75, 95% CI [0.56, 5.42], which is similar to the main treatment period and the TFP.

The percentage of patients with at least one infection (40.8%) and the rate of infections per 100 patient years in the all exposed population (51.81, 95% CI [42.09, 63.78]) were similar in the OLE to the main treatment period and the TFP. The rate of infections per 100 patient years was higher in Group A: 74.94, 95% CI [50.23, 111.80]. However, the percentage of patients with at least one infection was similar in this group compared to the all exposed population. The higher rate of infections in Group A can be explained by a high number of infections in one patient who experienced a total of 9 infections during the OLE. All infections experienced by this patient were non serious, Grade 1 or 2 severity, were considered unrelated to study drug by the investigator and resolved without sequelae. Study drug was not discontinued as the result of those infection AEs. Two serious infections were reported during the OLE: one patient in Group C had bronchopneumonia and one patient in Group D had hepatitis A. The bronchopneumonia was considered related to study drug by the investigator and hepatitis A was considered unrelated. Both SAEs resolved without sequelae.

A total of 22 patients (21.4%) had at least one IRR during the OLE, most IRRs being Grade 1 or 2 in intensity. Only one Grade 3 IRR was reported after the first infusion and no Grade 4, Grade 5 or serious IRRs were reported. There were no premature withdrawals from treatment due to IRRs. Three patients had dose modifications or interruptions due to IRRs. Most IRRs occurred after the first infusion and no IRRs were reported after the fourth and the subsequent doses. The incidence, severity, and symptoms of IRRs reported during the OLE were similar to the main treatment period. The pattern was also similar, i.e. most IRRs occurred after first infusion and the incidence of IRRs decreased over the subsequent doses. IRRs were manageable with symptomatic treatment and adjustment of infusion rate. Similarly to the main treatment period, the most common concomitant medications given for IRRs were antihistamines. Overall, the IRR profile observed during the OLE was consistent with main treatment period.

7. CONCLUSIONS

No new safety findings were identified during the TFP or the OLE. No increase in the rate or incidence of infections or serious infections was observed during the TFP or the OLE period compared with the main 96-week treatment period. The IRR profile observed during the OLE was consistent with the main 96-week treatment period in terms of severity and nature of AEs.

8. ADDENDUM TO THE PRIMARY CSR

This is an addendum to the Primary CSR for study WA21493/ACT4422g reporting the data collected during the main part of this study up to Week 144 [CSR 1034917]. This addendum provides a listing of AEs that occurred during the main treatment period with onset up to Week 96 that were missing from the clinical database at the time of the preparation of the Primary CSR. Post-hoc analyses using the data from the main (96-weeks) study period described in Section 3.8.8 are also presented in this section. These analyses were conducted to better understand and describe the study results.

The data presented in this addendum replaces the data presented in the Primary CSR. The conclusions of the Primary CSR remain unchanged based on the data presented in this addendum.

8.1 PREVIOUS MULTIPLE SCLEROSIS TREATMENTS

This section presents new information and a new analyses (Table 20) to clarify patient populations in regard to prior use of MS therapies (i.e., patients who used any prior therapy for MS versus patients who used any prior disease modifying therapy for MS).

Prior disease modifying therapy for MS was given in 42% of the ITT population with 58% of patients considered treatment naïve (those who had not received any therapy for MS within 2 years of entry into the study). There was an imbalance across treatment groups in the percentage of patients receiving previous disease modifying therapy, with fewer patients in Group C (29.6%) compared to Group A (50.9%), Group B (45.5%), and Group D (42.6%). The most frequently used disease modifying therapy for MS were interferons followed by glatiramer acetate and natalizumab. One patient (Group D) had previously received rituximab. A summary of previous MS treatments for the safety population is provided.

Table 20 Previous Multiple Sclerosis Treatments by Preferred Term, Intent-to-Treat Population

	Placebo Group C (N=54)	OCR 600mg Group B (N=55)	OCR 1000mg Group A (N=55)	Avonex Group D (N=54)
Number of patients untreated with any MS medication	38 (70.4%)	30 (54.5%)	27 (49.1%)	31 (57.4%)
Number of patients treated with any MS medication	16 (29.6%)	25 (45.5%)	28 (50.9%)	23 (42.6%)
Number of patients treated with the following				
INTERFERON BETA-1A I.M.	2 (3.7%)	7 (13.0%)	7 (13.0%)	6 (11.1%)
INTERFERON BETA-1A S.C.	0	6 (11.1%)	9 (16.7%)	4 (7.4%)
INTERFERON BETA-1B S.C.	4 (7.4%)	6 (11.1%)	7 (13.0%)	5 (9.3%)
INTERFERON BETA NOS/INTERFERON NOS/INTERFERON BLINDED	3 (5.6%)	3 (5.6%)	2 (3.7%)	4 (7.4%)
GLATIRAMER ACETATE	6 (11.1%)	7 (13.0%)	9 (16.7%)	5 (9.3%)
NATALIZUMAB	1 (1.9%)	2 (3.7%)	3 (5.6%)	3 (5.6%)
FINGOLIMOD	1 (1.9%)	1 (1.9%)	0	0
DIMETHYL FUMARATE	0	0	0	0
TERIFLUNOMIDE	0	0	0	0
ALEMTUZUMAB	0	0	0	0
BLINDED DIMETHYL FUMARATE	0	1 (1.9%)	0	0
Any of above medications	15 (27.8%)	24 (44.4%)	26 (48.1%)	20 (37.0%)
Other:				
MITOXANTRONE	1 (1.9%)	1 (1.9%)	1 (1.9%)	0
RITUXIMAB	0	0	0	1 (1.9%)
NORMAL IMMUNOGLOBULIN	0	1 (1.9%)	2 (3.7%)	0
MYCOPHENOLATE MOFETIL	0	0	0	1 (1.9%)
AZATHIOPRINE	0	0	1 (1.9%)	2 (3.7%)
IMMUNOTHERAPY NOS	0	0	0	0
Any of above medications	1 (1.9%)	2 (3.7%)	4 (7.4%)	4 (7.4%)

Only data from 2 years prior to study entry is collected and analyzed.
A patient can be counted in several categories.
Number of patients treated with any MS medication includes patients who received any of the listed medications.

Program: /opt/BIOSTAT/prod/cdt3422z/z21493c/ah_t_cm_pt_ms.sas / Output: /opt/BIOSTAT/prod/cdt3422z/z21493c/reports/ah_t_cm_pt_ms_IT.out
11JAN2016 13:36 [Modified by PDRD]

Group A: Dose 1 = OCR 1000 mg (Day 1 and 15); Dose 2 = OCR 1000 mg Day 1, placebo Day 15; Dose 3 = OCR 1000 mg; Dose 4 = OCR 600 mg.
Group B: Dose 1 = OCR 300 mg (Day 1 and 15); Dose 2 = OCR 600 mg Day 1, placebo Day 15; Dose 3 and Dose 4 = OCR 600 mg.
Group C: Dose 1 = Placebo (Day 1 and 15); Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg.
Group D: Dose 1 = Avonex 30 µg/week; Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg.
OCR = ocrelizumab

8.2 CONFIRMED DISABILITY IMPROVEMENT

A post hoc analysis of CDI was conducted using the data collected during the entire study. The proportion of patients who had CDI was higher in Groups A and B compared with Groups C and D (Table 21, Table 22). However, 95% CIs were wide and overlapping.

The mean duration (± standard error) of CDI for at least 12 weeks (Kaplan-Meier estimate) was 86.7 weeks (±24.17) in Group A, 164.7 weeks (±32.44) in Group B, 59.9 weeks (±14.83) in Group C, and 143.7 weeks (±45.06) in Group D. The mean duration (± standard error) of CDI for at least 24 weeks (Kaplan-Meier estimate) was 105.4 weeks (±28.39) in Group A, 164.7 weeks (±32.44) in Group B, 71.1 weeks (±12.51) in Group C, and 166.9 weeks (±47.35) in Group D.

Table 21 Proportion of Patients who have Confirmed Disability Improvement for at Least 12 Weeks During the Treatment Period, Intent-to-Treat Population

Parameter	Placebo Group C (n=47)	OCR 600mg Group B (n=46)	OCR 1000mg Group A (n=49)	Avonex Group D (n=42)
Cycle 1: Day 169 (+/- 14 days)				
Number of patients with CDI	1	5	8	2
Proportion	2.1%	10.9%	16.3%	4.8%
95% CI of Proportion	(0.1%, 11.3%)	(3.6%, 23.6%)	(7.3%, 29.7%)	(0.6%, 16.2%)
Cycle 1 to 4:				
Number of patients with CDI	5	10	14	6
Proportion	10.6%	21.7%	28.6%	14.3%
95% CI of Proportion	(3.5%, 23.1%)	(10.9%, 36.4%)	(16.6%, 43.3%)	(5.4%, 28.5%)

95% CI of proportion were constructed using Pearson-Clopper method.
Patients with missing EDSS or no confirmation after onset of disability improvement are counted as not having confirmed disability improvement.
Patients with Baseline EDSS Score >=2.0 included only.

Program : $PROD/cdt3422z/z21493c/t_cdi_prop.sas
Output : $PROD/cdt3422z/z21493c/reports/t_cdi_prop_CDI12TE_IT.out
14DEC2015 18:39 [Modified by PDRD]

Group A: Dose 1 = OCR 1000 mg (Day 1 and 15); Dose 2 = OCR 1000 mg Day 1, placebo Day 15; Dose 3 = OCR 1000 mg; Dose 4 = OCR 600 mg.
Group B: Dose 1 = OCR 300 mg (Day 1 and 15); Dose 2 = OCR 600 mg Day 1, placebo Day 15; Dose 3 and Dose 4 = OCR 600 mg.
Group C: Dose 1 = Placebo (Day 1 and 15); Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg.
Group D: Dose 1 = Avonex 30 µg/week; Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg.
OCR = ocrelizumab

Table 22 Proportion of Patients who have Confirmed Disability Improvement for at Least 24 Weeks During the Treatment Period, Intent-to-Treat Population

Parameter	Placebo Group C (n=47)	OCR 600mg Group B (n=46)	OCR 1000mg Group A (n=49)	Avonex Group D (n=42)
Cycle 1: Day 169 (+/- 14 days)				
Number of patients with CDI	0	5	5	1
Proportion		10.9%	10.2%	2.4%
95% CI of Proportion		(3.6%, 23.6%)	(3.4%, 22.2%)	(0.1%, 12.6%)
Cycle 1 to 4:				
Number of patients with CDI	4	10	11	5
Proportion	8.5%	21.7%	22.4%	11.9%
95% CI of Proportion	(2.4%, 20.4%)	(10.9%, 36.4%)	(11.8%, 36.6%)	(4.0%, 25.6%)

95% CI of proportion were constructed using Pearson-Clopper method.
Patients with missing EDSS or no confirmation after onset of disability improvement are counted as not having confirmed disability improvement.
Patients with Baseline EDSS Score >=2.0 included only.

Program : $PROD/cdt3422z/z21493c/t_cdi_prop.sas
Output : $PROD/cdt3422z/z21493c/reports/t_cdi_prop_CDI24TE_IT.out
14DEC2015 18:40 [Modified by PDRD]

Group A: Dose 1 = OCR 1000 mg (Day 1 and 15); Dose 2 = OCR 1000 mg Day 1, placebo Day 15; Dose 3 = OCR 1000 mg; Dose 4 = OCR 600 mg.
Group B: Dose 1 = OCR 300 mg (Day 1 and 15); Dose 2 = OCR 600 mg Day 1, placebo Day 15; Dose 3 and Dose 4 = OCR 600 mg.
Group C: Dose 1 = Placebo (Day 1 and 15); Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg.
Group D: Dose 1 = Avonex 30 µg/week; Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg.
OCR = ocrelizumab

8.3 ADVERSE EVENTS

Several AEs had onset before the clinical cut-off date for the Primary CSR, but were reported afterwards. A listing of those AEs is provided. There were 20 additional AEs occurring in 17 patients. The nature of those AEs is consistent with the known safety profile of ocrelizumab.

8.4 INFUSION-RELATED REACTIONS

This section provides updated analyses of IRR data for the main (96-week) treatment period.

The most common AE were IRRs which were reported more often in patients receiving their first ocrelizumab infusion relative to subsequent ocrelizumab doses (Figure 6, Table 23). IRRs were reported both in patients receiving ocrelizumab and in patients receiving placebo. During the initial infusion of the placebo-controlled period (Dose 1 Day 1), IRRs were reported in 43.6% and 36.4% of patients receiving ocrelizumab (Groups A and B, respectively) compared with 9.3% of patients in Group C (placebo). After the second infusion (Dose 1, Day 15), the percentage of patients experiencing IRRs was similar in the ocrelizumab groups (Groups A and B) compared with Group C (placebo) (9.4% in Group A, 3.8% in Group B, and 11.1% in Group C). Similar results were observed during the open-label treatment period when patients randomized to Group C (placebo) and Group D (Avonex) received their first infusion of ocrelizumab. After the initial ocrelizumab infusion (Dose 2, Day 1) in these groups, IRRs were reported in 41.5% and 30.0% of patients in Groups C and D, respectively, and fell to 3.8% and 2.1%, respectively, following their second OCR infusion (Dose 2, Day 15).

Figure 6 Percentage of Patients with IRR by Infusion and Treatment Over Time, Safety-Evaluable Population

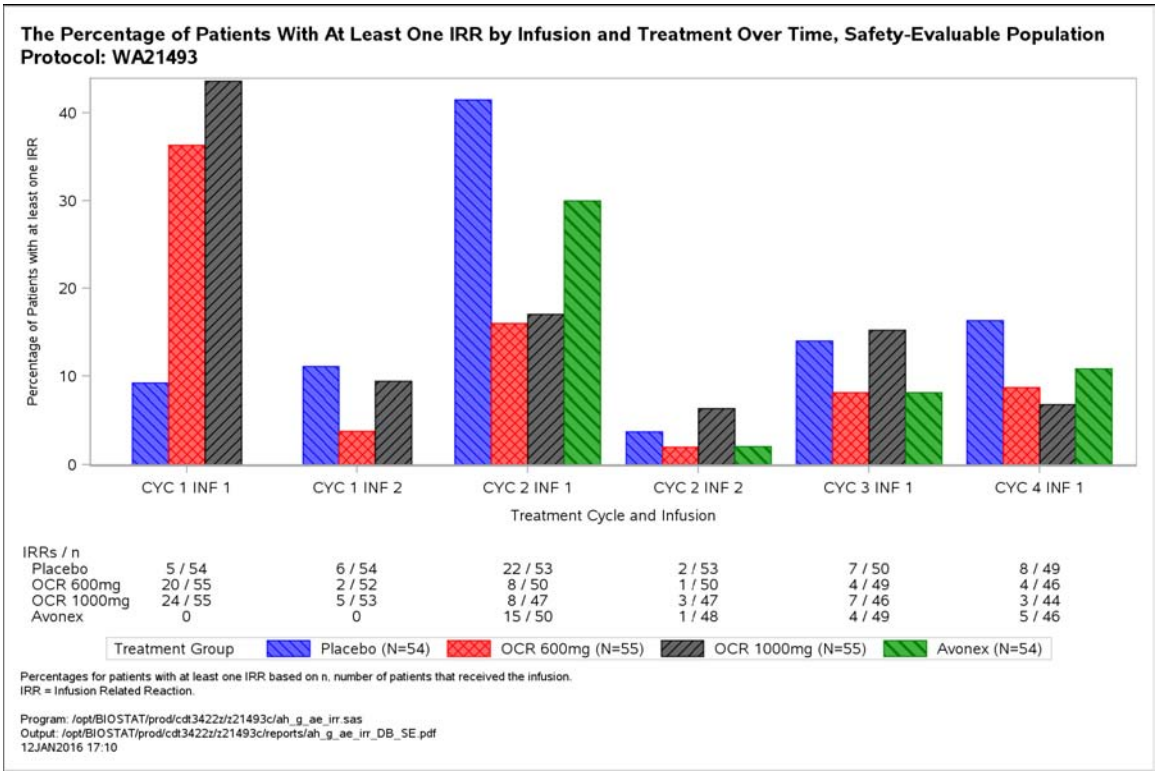


Table 23 Proportion of Patients with IRR by Infusion and Severity, Safety-Evaluable Population

	Placebo Group C (N=54)	OCR 600mg Group B (N=55)	OCR 1000mg Group A (N=55)	Avonex Group D (N=54)
Overall				
Total pts with at least one IRR	26 (48.1%)	22 (40.0%)	27 (49.1%)	16 (29.6%)
Total number of IRR	53	45	54	26
Grade				
1	9 (16.7%)	11 (20.0%)	10 (18.2%)	6 (11.1%)
2	15 (27.8%)	11 (20.0%)	15 (27.3%)	8 (14.8%)
3	2 (3.7%)	0	2 (3.6%)	1 (1.9%)
4	0	0	0	1 (1.9%)
5	0	0	0	0
CYCLE 1 INFUSION 1	54	55	55	
Total pts with at least one IRR	5 (9.3%)	20 (36.4%)	24 (43.6%)	
Total number of IRR	5	23	27	
Grade				
1	4 (7.4%)	10 (18.2%)	8 (14.5%)	
2	1 (1.9%)	10 (18.2%)	15 (27.3%)	
3	0	0	1 (1.8%)	
4	0	0	0	
5	0	0	0	

Percentages of Overall are based on N; percentages of by infusion are based on the number of patients who received that infusion.
For summaries by grade multiple events in one individual are counted only once (AE with most extreme intensity is used).
Grade: 1=Mild, 2=Moderate, 3=Severe, 4=Life Threatening, 5=Death.
IRR = Infusion Related Reaction.

Program: /opt/BIOSTAT/prod/cdt3422z/z21493c/ah_t_ae_irr_int_inf.sas
Output: /opt/BIOSTAT/prod/cdt3422z/z21493c/reports/ah_t_ae_irr_int_inf_DB_SE.out
12JAN2016 17:11[Modified by PDRD] Page 1 of 4
Group A: Dose 1 = OCR 1000 mg (Day 1 and 15); Dose 2 = OCR 1000 mg Day 1, placebo Day 15; Dose 3 = OCR 1000 mg; Dose 4 = OCR 600 mg.
Group B: Dose 1 = OCR 300 mg (Day 1 and 15); Dose 2 = OCR 600 mg Day 1, placebo Day 15; Dose 3 and Dose 4 = OCR 600 mg.
Group C: Dose 1 = Placebo (Day 1 and 15); Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg.
Group D: Dose 1 = Avonex 30 µg/week; Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg.
OCR = ocrelizumab

Table 23 Proportion of Patients with IRR by Infusion and Severity, Safety-Evaluable Population (cont.)

	Placebo Group C (N=54)	OCR 600mg Group B (N=55)	OCR 1000mg Group A (N=55)	Avonex Group D (N=54)
CYCLE 1 INFUSION 2	54	52	53	
Total pts with at least one IRR	6 (11.1%)	2 (3.8%)	5 (9.4%)	
Total number of IRR	7	3	5	
Grade				
1	3 (5.6%)	2 (3.8%)	3 (5.7%)	
2	3 (5.6%)	0	2 (3.8%)	
3	0	0	0	
4	0	0	0	
5	0	0	0	
CYCLE 2 INFUSION 1	53	50	47	50
Total pts with at least one IRR	22 (41.5%)	8 (16.0%)	8 (17.0%)	15 (30.0%)
Total number of IRR	24	10	8	16
Grade				
1	9 (17.0%)	5 (10.0%)	7 (14.9%)	7 (14.0%)
2	11 (20.8%)	3 (6.0%)	0	6 (12.0%)
3	2 (3.8%)	0	1 (2.1%)	1 (2.0%)
4	0	0	0	1 (2.0%)
5	0	0	0	0

Percentages of Overall are based on N; percentages of by infusion are based on the number of patients who received that infusion.
For summaries by grade multiple events in one individual are counted only once (AE with most extreme intensity is used).
Grade: 1=Mild, 2=Moderate, 3=Severe, 4=Life Threatening, 5=Death.
IRR = Infusion Related Reaction.

Program: /opt/BIOSTAT/prod/cdt3422z/z21493c/ah_t_ae_irr_int_inf.sas
Output: /opt/BIOSTAT/prod/cdt3422z/z21493c/reports/ah_t_ae_irr_int_inf_DB_SE.out
12JAN2016 17:11 [Modified by PDRD]

Group A: Dose 1 = OCR 1000 mg (Day 1 and 15); Dose 2 = OCR 1000 mg Day 1, placebo Day 15; Dose 3 = OCR 1000 mg; Dose 4 = OCR 600 mg.
Group B: Dose 1 = OCR 300 mg (Day 1 and 15); Dose 2 = OCR 600 mg Day 1, placebo Day 15; Dose 3 and Dose 4 = OCR 600 mg.
Group C: Dose 1 = Placebo (Day 1 and 15); Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg.
Group D: Dose 1 = Avonex 30 μg/week; Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg.
OCR = ocrelizumab

Table 23 Proportion of Patients with IRR by Infusion and Severity, Safety-Evaluable Population (cont.)

	Placebo Group C (N=54)	OCR 600mg Group B (N=55)	OCR 1000mg Group A (N=55)	Avonex Group D (N=54)
CYCLE 2 INFUSION 2	53	50	47	48
Total pts with at least one IRR	2 (3.8%)	1 (2.0%)	3 (6.4%)	1 (2.1%)
Total number of IRR	2	1	3	1
Grade				
1	1 (1.9%)	1 (2.0%)	3 (6.4%)	1 (2.1%)
2	1 (1.9%)	0	0	0
3	0	0	0	0
4	0	0	0	0
5	0	0	0	0
CYCLE 3 INFUSION 1	50	49	46	49
Total pts with at least one IRR	7 (14.0%)	4 (8.2%)	7 (15.2%)	4 (8.2%)
Total number of IRR	7	4	8	4
Grade				
1	4 (8.0%)	2 (4.1%)	6 (13.0%)	2 (4.1%)
2	2 (4.0%)	2 (4.1%)	1 (2.2%)	2 (4.1%)
3	1 (2.0%)	0	0	0
4	0	0	0	0
5	0	0	0	0

Percentages of Overall are based on N; percentages of by infusion are based on the number of patients who received that infusion.
For summaries by grade multiple events in one individual are counted only once (AE with most extreme intensity is used).
Grade: 1=Mild, 2=Moderate, 3=Severe, 4=Life Threatening, 5=Death.
IRR = Infusion Related Reaction.

Program: /opt/BIOSTAT/prod/cdt3422z/z21493c/ah_t_ae_irr_int_inf.sas
Output: /opt/BIOSTAT/prod/cdt3422z/z21493c/reports/ah_t_ae_irr_int_inf_DB_SE.out
12JAN2016 17:11 [Modified by PDRD]

Group A: Dose 1 = OCR 1000 mg (Day 1 and 15); Dose 2 = OCR 1000 mg Day 1, placebo Day 15; Dose 3 = OCR 1000 mg; Dose 4 = OCR 600 mg.
Group B: Dose 1 = OCR 300 mg (Day 1 and 15); Dose 2 = OCR 600 mg Day 1, placebo Day 15; Dose 3 and Dose 4 = OCR 600 mg.
Group C: Dose 1 = Placebo (Day 1 and 15); Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg.
Group D: Dose 1 = Avonex 30 μg/week; Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg.
OCR = ocrelizumab

Table 23 Proportion of Patients with IRR by Infusion and Severity, Safety-Evaluable Population (cont.)

	Placebo Group C (N=54)	OCR 600mg Group B (N=55)	OCR 1000mg Group A (N=55)	Avonex Group D (N=54)
CYCLE 4 INFUSION 1	49	46	44	46
Total pts with at least one IRR	8 (16.3%)	4 (8.7%)	3 (6.8%)	5 (10.9%)
Total number of IRR	8	4	3	5
Grade				
1	2 (4.1%)	3 (6.5%)	2 (4.5%)	3 (6.5%)
2	6 (12.2%)	1 (2.2%)	1 (2.3%)	2 (4.3%)
3	0	0	0	0
4	0	0	0	0
5	0	0	0	0

Percentages of Overall are based on N; percentages of by infusion are based on the number of patients who received that infusion.
For summaries by grade multiple events in one individual are counted only once (AE with most extreme intensity is used).
Grade: 1=Mild, 2=Moderate, 3=Severe, 4=Life Threatening, 5=Death.
IRR = Infusion Related Reaction.

Program: /opt/BIOSTAT/prod/cdt3422z/z21493c/ah_t_ae_irr_int_inf.sas
Output: /opt/BIOSTAT/prod/cdt3422z/z21493c/reports/ah_t_ae_irr_int_inf_DB_SE.out
12JAN2016 17:11 [Modified by PDRD] Page 4 of 4
Group A: Dose 1 = OCR 1000 mg (Day 1 and 15); Dose 2 = OCR 1000 mg Day 1, placebo Day 15; Dose 3 = OCR 1000 mg; Dose 4 = OCR 600 mg.
Group B: Dose 1 = OCR 300 mg (Day 1 and 15); Dose 2 = OCR 600 mg Day 1, placebo Day 15; Dose 3 and Dose 4 = OCR 600 mg.
Group C: Dose 1 = Placebo (Day 1 and 15); Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg.
Group D: Dose 1 = Avonex 30 µg/week; Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg.
OCR = ocrelizumab

Most IRRs were Grade 1 or 2 in intensity (Table 23). A total of 7 IRR events of Grade ≥ 3 were reported in 6 patients and 3 were considered to be serious. All but one occurred during the first infusion of ocrelizumab. Six Grade 3 IRRs were reported in 5 patients (two in Group A, 1 in Group B, and 2 in Group C) and all were considered resolved without sequelae. One patient randomized to Group D experienced an IRR of Grade 4 when receiving the first dose of ocrelizumab. This patient developed life-threatening hypotension and was hospitalized. Due to the severity of the IRR, study drug was permanently discontinued as required by the protocol. Infusions were adjusted in 3 patients due to IRRs, all in patients receiving ocrelizumab: 1 patient in Group B (Dose 1, Day 1), 1 patient in Group A (Dose 1, Day 15), and 1 patient in Group C (Dose 2, Day 1).

Narratives are provided for all patients who experienced Grade ≥ 3 IRRs.

Listings of IRR symptoms by the first infusion of ocrelizumab and placebo are provided. The most common IRR symptoms were rash, throat irritation, pruritus, flushing, headache, tachycardia, and pyrexia.

8.5 MALIGNANCIES AND PREMALIGNANT DISORDERS

Listings of malignancies and premalignant disorders are provided. These listings cover the entire duration of the main study, including screening, the treatment period, and the TFP.

Malignancies were reported in two patients. Patient [redacted] had breast cancer during the TFP (see Section 4.4.5 for details). Patient [redacted] had squamous cell carcinoma during the screening period, i.e. before the first dose of ocrelizumab. This AE was considered serious and unrelated to the study drug. This patient was randomized to Group A and permanently discontinued the study due to this SAE.

One premalignant disorder was reported. Patient [redacted] randomized to Group A had a large intestine polyp, considered by the investigator to be serious and unrelated to study drug. This SAE occurred during the TFP and resolved without sequelae. This patient was not withdrawn from the study due to this SAE and completed the TFP.

Full patient narratives for all three cases of malignancy or premalignant disorder are provided.

8.6 IMMUNOGENICITY

The prevalence of ADAs at baseline was 0.0% in Group A, 2.0% (1 patient) in Group B, 3.8% (2 patients) in Group C, and 4.3% (2 patients) in Group D (Table 24). Overall the prevalence of ADAs at baseline (prior to first exposure to ocrelizumab) was 2.5% (5 out of 199 patients). The ADA titers of these patients did not increase after treatment. No patients had treatment-induced or treatment-enhanced ADAs. A summary of ADA sample status by visit during the TFP is provided.

Table 24 Baseline Prevalence and Post-Baseline Incidence of ADAs – 96-week Treatment Period and Treatment-Free Period

	Placebo Group C (N=54)	OCR 600mg Group B (N=55)	OCR 1000mg Group A (N=55)	Avonex Group D (N=54)
Baseline Prevalence of ADAs				
Baseline evaluable patients	53	51	49	46
Patients with a positive sample at baseline	2 (3.8%)	1 (2.0%)	0	2 (4.3%)
Patients with no positive samples at baseline	51	50	49	44
Post-Baseline Incidence of ADAs				
Post-baseline evaluable patients	53	52	54	49
Patients positive for ADA	0	0	0	0
Treatment-induced ADA	0	0	0	0
Treatment-enhanced ADA	0	0	0	0
Patients negative for ADA	53	52	54	49
Treatment unaffected	2	1	0	2

ADA= Anti-Therapeutic Antibodies. Baseline is the ADA assessment with the highest titre prior to the first infusion of Ocrelizumab.
All data from the treatment and treatment-free period included.
Baseline evaluable patient = a patient with an ADA assay result from a baseline sample(s).
Post-baseline evaluable patient = a patient with an ADA assay result from at least one post-baseline sample.
Number of patients positive for ADA = the number (and percentage) of post-baseline evaluable patients determined to have treatment-induced ADA or treatment-enhanced ADA during the study period.
Treatment-induced ADA = a patient with negative or missing baseline ADA result(s) and at least one positive post-baseline ADA result
Treatment-enhanced ADA = a patient with positive ADA result at baseline who has one or more post-baseline titer results that are at least 0.60 t.u. greater than the baseline titer result.
Number of patients negative for ADA = number of post-baseline evaluable patients with negative or missing baseline ADA result(s) and all negative post-baseline results, or a patient who is treatment unaffected.
Treatment unaffected = A post-baseline evaluable patient with a positive ADA result at baseline and (a)where all post-baseline titer results are less than 0.60 t.u. greater than the baseline titer result, OR (b) where all post-baseline results are negative or missing. For any positive sample with titer result less than the minimum reportable titer or any positive sample where a titer cannot be obtained, titer value is imputed as equal to the minimum reportable titer.
The percentage (%) is calculated by the number of evaluable patients at baseline or post-baseline respectively.

Program: /opt/BIOSTAT/prod/cdt3422z/z21493c/t_ada_previnci.sas
Output: /opt/BIOSTAT/prod/cdt3422z/z21493c/reports/t_ada_previnci_DBTFU_SE.out
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Group A: Dose 1 = OCR 1000 mg (Day 1 and 15); Dose 2 = OCR 1000 mg Day 1, placebo Day 15; Dose 3 = OCR 1000 mg; Dose 4 = OCR 600 mg.
Group B: Dose 1 = OCR 300 mg (Day 1 and 15); Dose 2 = OCR 600 mg Day 1, placebo Day 15; Dose 3 and Dose 4 = OCR 600 mg.
Group C: Dose 1 = Placebo (Day 1 and 15); Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg.
Group D: Dose 1 = Avonex 30 µg/week; Dose 2 = OCR 300 mg (Day 1 and 15); Dose 3 and Dose 4 = OCR 600 mg.
OCR = ocrelizumab

9. REFERENCES

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.

Shankar G, Arkin S, Cocea L, et al. Assessment and Reporting of the Clinical Immunogenicity of Therapeutic Proteins and Peptides—Harmonized Terminology and Tactical Recommendations. The AAPS Journal 2014: DOI: 10.1208/s12248-014-9599-2.