The MIRROR Study: Treatment Phase Results for a Dose-Ranging Study of Ofatumumab in Subjects With Relapsing-Remitting Multiple Sclerosis

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ABSTRACT

OBJECTIVE: To determine the effects of several ofatumumab dosing regimens compared to placebo on cumulative number of new brain lesions assessed every 4 weeks for 12 weeks.

BACKGROUND: Benefits of anti-CD20 monoclonal antibody infusions have been demonstrated in RRMS. We investigated the safety and efficacy of four subcutaneous ofatumumab dosing regimens in RRMS patients.

DESIGN/METHODS: 232 subjects were randomized to one of 5 treatment groups: placebo, ofatumumab 3mg q12w, ofatumumab 30mg q12w, ofatumumab 60mg q12w, or ofatumumab 60mg q4w. Half of the subjects randomized to each of the 30mg and 60mg groups received a single initial 3mg dose at Week 0; all subjects were administered the first full dose at Week 1. At Week 12, placebo-randomized patients received a single 3mg ofatumumab dose. All subjects continued in the study for 24 weeks of treatment and in follow-up until B cell repletion.

RESULTS: Weeks 0-12 data analysis estimated 65% reductions compared to placebo in the cumulative number of new T1 gadolinium-enhancing lesions for each ofatumumab dose regimen [p < 0.001]; corresponding analysis of Weeks 4-12 data estimated ≥ 90% reductions for each dose ≥ 30mg [p < 0.001]. A dose dependent CD19 B cell depletion was seen across regimens. Dose dependent repletion was observed with q12 week but not q4 week dosing; rate of repletion of B cells following cessation of dosing was similar, with a delay of approximately 4 weeks in the 60mg q4 week group.

The most common adverse events during Weeks 0-12 were injection-related reactions (52% of ofatumumab-treated subjects; 15% of placebo). Five serious adverse events were reported during treatment; all had received a 60mg dose regimen of ofatumumab; no cases of PML or opportunistic infections were observed.

CONCLUSIONS: These results support further study of ofatumumab in longer studies of clinical efficacy in subjects with RRMS.

MIRROR: MRI study In RRMS: evaluating Ofatumumab Regimen, also known as OMS112831

ClinicalTrials.gov identifier: NCT01457924

Introduction

- Increasingly, the role of B cells in the immune-mediated histopathology of multiple sclerosis (MS)[1,2] has become clearer. B cells have essential functions in regulating immune response and may contribute to disease pathogenesis by serving as cellular adjuvants for CD4+ T-cell activation[3] and by regulating T-cell function and inflammation via cytokine production,[4] in addition to producing autoantibodies
- In experimental autoimmune encephalomyelitis mouse models of MS, B cells are required for autoantigen-specific CD4+ T-cell generation and encephalitogenic T-cell entry into the central nervous system during disease progression.[5] B cells are present in the chronic plaques, areas of demyelination, and cerebrospinal fluid of MS patients[6]
- Rituximab,[7] ocrelizumab,[8] and ofatumumab[9] have provided evidence of the therapeutic benefit of anti-CD20+ B-cell treatment in subjects with relapsing-remitting multiple sclerosis (RRMS)
- Ofatumumab is a fully human anti-CD20 monoclonal antibody that is able to bind at low CD20 expression and induces B-cell lysis through antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity
- Ofatumumab is indicated for the treatment of chronic lymphocytic leukemia. It has not been approved in any country for the treatment of MS

Objective

Study objective

- Determine magnetic resonance imaging (MRI) efficacy and the tolerability/safety of subcutaneous (SQ) ofatumumab doses of 3, 30, and 60 mg compared with placebo in subjects with RRMS

Other objectives

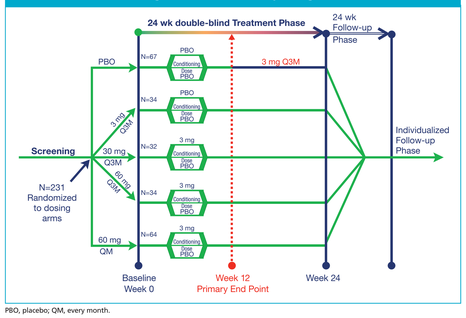
- To evaluate the safety and tolerability over a period of 24 weeks of a range of SQ ofatumumab doses in subjects with RRMS
- To determine the extent of B-cell depletion and repletion for a range of SQ doses of ofatumumab in subjects with RRMS
- To evaluate the immunogenicity of SQ ofatumumab in subjects with RRMS
- To evaluate the use of an initial conditioning dose (a subdepleting dose of ofatumumab given 1 week before a fully depleting dose to reduce postinjection systemic reactions to the SQ formulation)

Methods

Study design

- Global, randomized, double-blind, placebo-controlled, parallel group design

Figure 1. MIRROR Study Design



PBO, placebo; QM, every month.

- **Treatment Phase:** 24 weeks
  - Stratified randomization based on presence or absence of gadolinium-enhanced (GdE) lesion on screening MRI
  - Equal numbers of subjects were randomized to placebo and ofatumumab 60 mg q4w, with half the number of subjects in the intermediate dosing groups
  - Half of the subjects randomized to each of the 30-mg and 60-mg groups were randomized to receive a conditioning dose, a single 3-mg dose administered as an initial dose 1 week before administration of a larger dose of ofatumumab
  - The first 12 weeks of the treatment phase were placebo controlled. At week 12, subjects randomized to placebo received a single 3-mg dose of ofatumumab
- **Follow-up Phase:** monitor safety upon completion of the treatment phase or upon any premature discontinuation of investigational product. Sites and subjects remain blinded to CD19+ B-lymphocyte counts during the follow-up phase
- **Individualized Follow-up Phase:** monitor repletion of CD19+ B-lymphocyte counts until they return to the limit of normal (LLN) or baseline (if < LLN); until the subject starts a disease modifying therapy (DMT); or after week 120, until circulating levels of immunoglobulin G were ≥LLN or baseline levels (if <LLN)

Investigational product dosing

- All subjects received placebo or the conditioning dose at week 0/randomization and the first full dose of investigational product (IP) at week 1
- Before each dose of IP, all subjects received treatment with acetaminophen and an antihistamine

Key inclusion/exclusion criteria

- Subjects with RRMS aged 18-55 years, with
  - 1 relapse in the previous year, or
  - 2 relapses within the previous 2 years, or
  - 1 relapse in the previous year with a GdE brain lesion on an MRI scan in the past year
- Expanded Disability Status Scale score at screening between 0 and 5.5
- Patients with prior use of experimental agents; monoclonal antibodies other than natalizumab; and immunosuppressive agents including, but not limited to, mitoxantrone, azathioprine, cyclosporine, cyclophosphamide, or tacrolimus were excluded from participation. Prior use of other DMTs was allowed

Independent Data Monitoring Committee and Progressive Multifocal Leukoencephalopathy Adjudication Committee

- An Independent Data Monitoring Committee reviewed study data on a regular basis during the conduct of the study to monitor the risk-to-benefit ratio of ofatumumab and evaluated the utility of the conditioning dose
- An Independent Progressive Multifocal Leukoencephalopathy (PML) Adjudication Committee reviewed and confirmed any potential cases of PML events

Statistical methods

- The null hypothesis is that there is no relationship between total ofatumumab dose received over a 12-week treatment period and the cumulative total of new GdE T1 lesions observed on monthly MRI scans in a 12-week treatment period, in the intent-to-treat (ITT) population; that is, there is a zero slope on the dose-response line of best fit
- Sample size calculations were performed by simulation based on the assumption of a 2-sided type I error of 5%. With the planned sample size of 196 subjects, the study had approximately 90% power to detect a reduction of at least 63% relative to placebo in the cumulative total of new GdE lesions observed up to week 12
- Four candidate statistical models for modeling the dose response were identified (linear model fitting cumulative dose as a categorical/continuous variable, E_{max} model, sigmoid Hill model); objective criteria were prespecified on how to select the model that best fit the data (lowest Bayesian information criterion score)

Primary end point

- Cumulative number of new GdE T1 brain lesions over a period of 12 weeks compared with placebo

Secondary end points

- Frequency and severity of adverse events (AEs) and serious adverse events (SAEs)
- Withdrawals due to AEs
- Changes in vital signs, hematology, chemistry, and urinalysis parameters
- Immunogenicity as measured by the incidence, titer, and type of human anti-human antibody immune response
- Pharmacodynamics (B-cell depletion and repletion) as measured by CD19+ peripheral blood B lymphocyte count via routine fluorescence-activated cell sorter (FACS) analysis

Populations and data sets

- The safety population (SP) includes all subjects who took at least one dose of IP
- The ITT population includes all subjects randomized to treatment who have taken at least one dose of IP and who have at least one postscreening MRI assessment
- All-evaluable-scans data set includes all on-treatment MRI scans for each subject included in the analysis, thus allowing estimates of lesion rates to be calculated across the entire 12-week treatment phase for all subjects

Results

Subject disposition

- The safety population included 231 subjects who were enrolled in the study and received at least one dose of IP
- As of the data cutoff for this report, July 31, 2013, all subjects had completed the treatment phase of the study and 88 subjects (38%) had completed the follow-up phase
- The proportion of subjects completing the Treatment Phase was high and generally comparable across treatment groups
- There was a higher number of withdrawals from treatment due to AEs in the ofatumumab groups (7/164, 4.3% of subjects) compared with placebo (0 subjects), but no evidence of a relationship to dose

Table 1. Subject Disposition at Completion of the Treatment Phase (Safety Population)

	Placebo (with 3 mg Ofa at Week 12)(N=67)	Ofa 3 mg q12w (N=34)	Ofa 30 mg q12w (N=32)	Ofa 60 mg q12w (N=34)	Ofa 60 mg q4w (N=64)
Completed to week 12	65 (97%)	31 (91%)	30 (94%)	33 (97%)	60 (94%)
Completed to week 24	64 (96%)	29 (85%)	30 (94%)	33 (97%)	58 (91%)
Withdrawn from treatment	3 (4%)	5 (15%)	2 (6%)	1 (3%)	6 (9%)
Primary reason for withdrawal from Treatment Phase					
Adverse event	0	4 (12%)	1 (3%)	0	2 (3%)
Subject met protocol-defined stopping criteria	1 (1%)	1 (3%)	0	0	2 (3%)
Protocol deviation	1 (1%)	0	1 (3%)	0	0
Withdrew consent	0	0	0	1 (3%)	1 (2%)
Lack of efficacy	1 (1%)	0	0	0	0
Investigator discretion	0	0	0	0	1 (2%)
Study closed/terminated	0	0	0	0	0
Lost to follow-up	0	0	0	0	0

Subject demographics

- Sixty-seven percent of the subjects were female and 97% were white, with an average age of 37.2 years
- Demographic characteristics and MS medical history were generally similar across all treatment groups and are consistent with reports of other clinical studies in subjects with RRMS

Table 2. MIRROR Study Disease History at Screening (ITT Population)

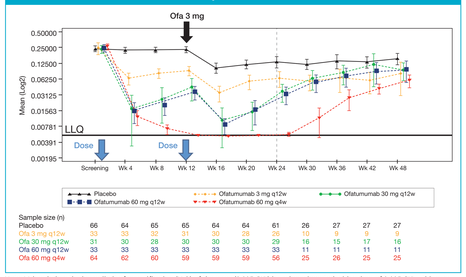
	Placebo (with 3 mg Ofa at Week 12) (N=67)	Ofa 3 mg q12w (N=33)	Ofa 30 mg q12w (N=32)	Ofa 60 mg q12w (N=33)	Ofa 60 mg q4w (N=63)
Disease duration, mean (SD), y	3.9 (5.29)	3.9 (6.19)	6.1 (6.03)	3.6 (4.41)	4.7 (5.64)
Number of relapses, mean (SD)					
Total	3.5 (2.69)	3.2 (2.35)	4.2 (2.84)	4.0 (2.47)	3.3 (1.92)
In last 12 months	1.3 (0.58)	1.4 (0.61)	1.3 (0.67)	1.3 (0.60)	1.3 (0.70)
In last 24 months	1.8 (0.78)	1.7 (0.91)	1.9 (1.12)	1.9 (0.86)	1.8 (0.85)
Number of days					
Since last relapse, mean (SD)	150 (102)	129 (78)	185 (127)	166 (112)	140 (118)
Since last steroid use, median (range)	96 (33-10,522)	72 (36-3182)	138 (34-2385)	105 (30-2506)	71 (29-4404)
MRI in last 12 months with active lesion? Yes	29 (43%)	15 (45%)	11 (34%)	15 (45%)	28 (44%)

ITT, intent-to-treat.

Pharmacologic response

- Dose-dependent depletion of B cells was observed, with greater depletion for the 30-mg and 60-mg doses than for the 3-mg dose
- Monthly dosing showed no signs of B-cell repletion during the interdosing interval, whereas both 30-mg and 60-mg q12 weeks showed some repletion of B cells before redosing

Figure 2. MIRROR Study Pharmcologic Response: Submaximal Depletion of CD19 B Cells

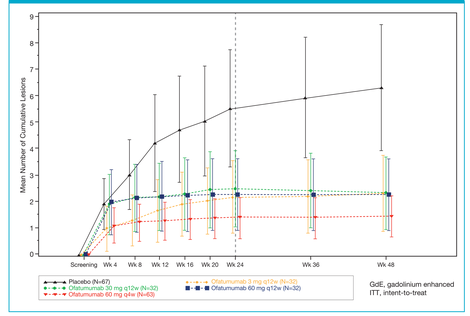


Note: Values below the lower limit of quantification (LLQ) of the assay (0.005 GI/L) have been imputed with values of 0.005 GI/L—this may underreport true depletion.

Efficacy

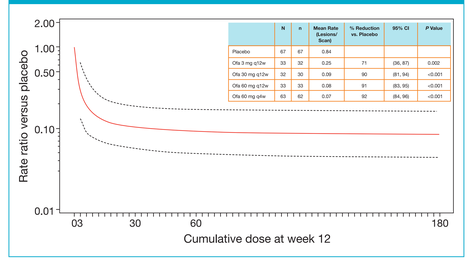
- The study met the primary end point, a significant reduction in the cumulative number of new GdE T1 lesions at week 12, for ofatumumab compared with placebo. There was a statistically significant reduction (65%) in the mean rate of cumulative new GdE T1 lesions for all ofatumumab groups compared with placebo at week 12 (P<0.001 for all dose groups; data not shown)

Figure 3. MIRROR Study Cumulative GdE T1 Lesions Over Time (ITT Population/All Evaluable Scans Data Set)



- MRI activity continued across all treatment groups during weeks 0-4 with a mean of 1 to 2 new GdE lesions observed for all groups during this period
- The mean rate of cumulative new GdE T1 lesions for the weeks 4-12 observation period shows a dose-dependent reduction in the mean rate of new GdE T1 lesions ranging from 71% to 92% for the ofatumumab dose groups compared with placebo (statistically significant for all dose groups, P≤ 0.002)
- The analysis of dose response, using an E_{max} model, for cumulative number of new GdE T1 lesions, based on the cumulative ofatumumab dose at week 12, showed that the median effective dose for half-maximal lesion suppression was poorly estimated at approximately 1 mg cumulative dose over 12 weeks; the lowest dose of 3 mg was not maximal; and a cumulative dose of approximately 60 mg of ofatumumab administered over 12 weeks provided maximal benefit, with no additional suppression of GdE T1 lesions at higher cumulative doses

Figure 4. MIRROR Study: New GdE T1 Lesions Weeks 4-12 (ITT Population/All Evaluable Scans Data Set)



Based upon results of E_{max} model.

Safety

- Most AEs were mild to moderate in intensity
  - Injection-related reactions were similar among those with and without a conditioning dose and were primarily associated with first dose of ofatumumab (data not shown)
- There was no evidence of a relationship between dose and occurrence or severity of AEs
- The rate of infections was similar across all treatment groups
- There were few SAEs or AEs leading to withdrawal
- There was no evidence of clinically meaningful changes in laboratory parameters or vital signs, including cytopenias
- There was no evidence of clinically meaningful immunogenicity (human anti-human antibodies)
- There were no cases of PML, opportunistic infections, or reactivation of hepatitis B

Treatment phase

Table 3. MIRROR Study Summary of AE/SAE Data: Weeks 0-24

	Placebo (with 3 mg Ofa at Week 12)(N=67)	Ofa 3 mg q12w (N=34)	Ofa 30 mg q12w (N=32)	Ofa 60 mg q4w (N=34)	Ofa 60 mg q4w (N=64)	Total (N=231)
Any AE	53 (79%)	25 (74%)	25 (78%)	27 (79%)	55 (86%)	173 (75%)
Mild	21 (31%)	11 (32%)	12 (38%)	12 (35%)	28 (44%)	83 (36%)
Moderate	30 (45%)	13 (38%)	12 (38%)	14 (41%)	23 (36%)	81 (35%)
Severe	2 (3%)	1 (3%)	1 (3%)	1 (3%)	4 (6%)	9 (4%)
AE leading to withdrawal	0	3 (9%)	1 (3%)	0	2 (3%)	6 (3%)
Related AEs[a]	29 (43%)	19 (56%)	18 (56%)	19 (56%)	46 (72%)	119 (52%)
Any SAEs	0	1 (3%)	0	1 (3%)	4 (6%)	6 (3%)
Any infection AEs	28 (42%)	11 (32%)	10 (31%)	17 (50%)	22 (34%)	80 (35%)

[a]Related AEs were AEs judged by the investigator to be related to investigational product.
AEs, adverse events; SAEs, serious adverse events.

Table 4. MIRROR Study SAEs: Weeks 0-12 Placebo-Controlled Treatment Period

Preferred Term	Placebo (with 3 mg Ofa at Week 12) (N=67)	Ofa 3 mg q12w (N=34)	Ofa 30 mg q12w (N=32)	Ofa 60 mg q12w (N=34)	Ofa 60 mg q4w (N=64)
Any SAE	0	0	0	1 (3%)	4 (6%)
Injection-related reaction	0	0	0	0	2 (3%)
Cholelithiasis	0	0	0	0	1 (2%)
Cytokine release syndrome	0	0	0	1 (3%)	0
Hypokalemia	0	0	0	0	1 (2%)

One additional SAE of angioedema of periorbital region and urticaria was reported for a subject randomized to 3 mg ofatumumab administered every 12 weeks between Weeks 12 and 24.

- The most common AE reported during the placebo-controlled period of the treatment phase was injection-related reactions
- Injection-related reactions were more common in ofatumumab-treated subjects than in placebo-treated subjects

Table 5. MIRROR Study Common AEs: Placebo-Controlled Treatment Period Weeks 0-12

Preferred Term	Placebo (with 3 mg Ofa at Week 12) (N=67)	Ofa 3 mg q12w (N=34)	Ofa 30 mg q12w (N=32)	Ofa 60 mg q12w (N=34)	Ofa 60 mg q4w (N=64)	Total Ofa (N=164)
Injection-related reaction	10 (15%)	16 (47%)	13 (41%)	15 (44%)	42 (66%)	86 (52%)
Nasopharyngitis	4 (6%)	1 (3%)	2 (6%)	6 (18%)	6 (9%)	15 (9%)
Dizziness	0	0	1 (3%)	0	4 (6%)	5 (3%)
Urinary tract infection	2 (3%)	1 (3%)	3 (9%)	0	0	4 (2%)
Anxiety	2 (3%)	1 (3%)	2 (6%)	0	0	3 (2%)
Pyrexia	0	1 (3%)	2 (6%)	0	1 (2%)	4 (2%)
Respiratory tract infection	1 (1%)	1 (3%)	0	2 (6%)	0	4 (2%)
Ecchymosis	0	2 (6%)	0	0	0	2 (1%)
Neuralgia	0	0	2 (6%)	0	0	2 (1%)

Common: ≥5% in any ofatumumab group and more than 2 times the rate observed for placebo.

Follow-up phase

- As of July 31, 2013, the data cutoff, 88 (38%) subjects had completed and are included in the follow-up phase reporting
- 16% of subjects experienced any AE; most were mild to moderate in intensity
- 3 subjects experienced SAEs
- 19 subjects experienced an infection, with no apparent dose relationship

Conclusions

- Ofatumumab depletes B cells quickly and in a dose-dependent and frequency-dependent manner; dose-dependent repletion was also seen in several ofatumumab regimens
- Ofatumumab effectively reduces new GdE T1 lesions relative to placebo
  - Over 90% reduction from weeks 4 to 12 for cumulative doses ≥30 mg over 12 weeks
  - The dose for half-maximal effect is less than 3 mg
- There were no new or unexpected safety findings

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Disclosures

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