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

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RAG, DJA, JMT, SAVM, and EL are employees of/stockholder in GlaxoSmithKline
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MIRROR: MRI study In RRMS: evaluating Ofatumumab Regimen Study, also known as OMS112831
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Session S23: MS and CNS Inflammatory Disease: Novel Therapeutics

Disclosures (Bar-Or, A)

I have participated as a speaker at meetings sponsored by, received consulting fees, and/or grant support from:

Amplimmune, Biogen Idec, Diogenix, Genentech, Sanofi-Genzyme, GSK, Novartis, Ono Pharma, Teva Neuroscience, Receptos, Roche, Merck/EMDSerono

Investigational and off label agents will be discussed

Disclosures (Sorensen, PS)

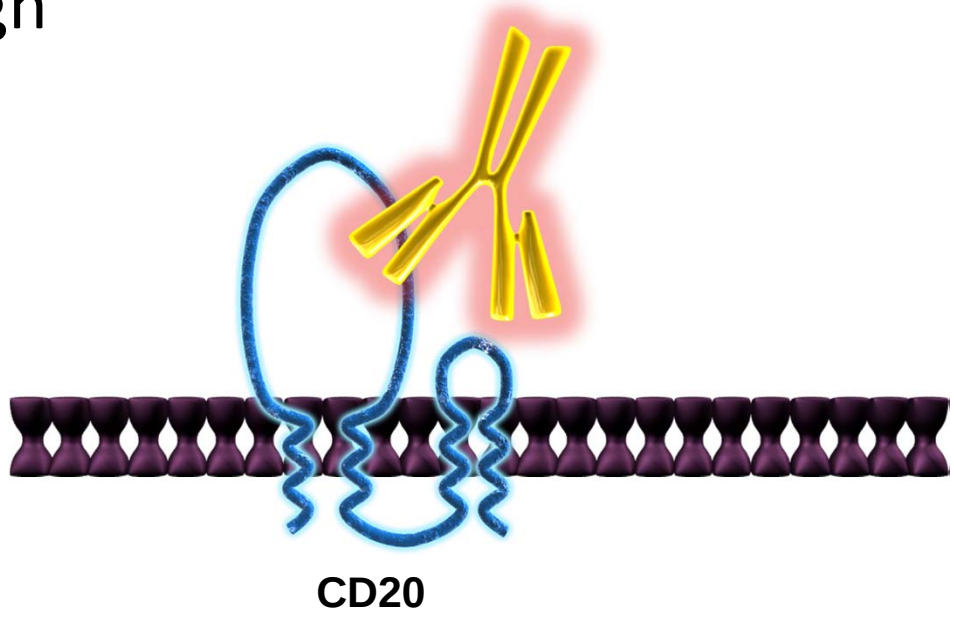
P. Sorensen has served on scientific advisory boards for Biogen Idec, Merck Serono, Novartis, Genmab, Teva Pharmaceutical Industries Ltd., Elan, and GlaxoSmithKline; has been on steering committees or independent data monitoring boards in clinical trials sponsored by Merck Serono, Genmab, Teva Pharmaceutical Industries Ltd., GlaxoSmithKline, and Bayer Schering, and has received funding of travel for these activities; has served as Editor-in-Chief of the European Journal of Neurology and is currently an editorial board member for Multiple Sclerosis Journal, European Journal of Neurology, and Therapeutic Advances in Neurological Disorders; and has received speaker honoraria from Biogen Idec, Merck Serono, Teva Pharmaceutical Industries Ltd., Bayer Schering, sanofi-aventis, Genzyme, and Novartis. His department has received research support from Biogen Idec, Bayer Schering, Merck Serono, Teva Pharmaceutical Industries Ltd., Baxter, sanofi-aventis, BioMS, Novartis, Bayer, RoFAR, Roche, and Genzyme, and from the Danish Multiple Sclerosis Society, the Danish Medical Research Council, and the European Union Sixth Framework Programme: Life Sciences, Genomics and Biotechnology for Health.

Ofatumumab is a Fully Human Anti-CD20 Monoclonal Antibody

Binds at low CD20 expression

Induces B-cell lysis through ADCC > CDC

Currently indicated for treatment of chronic lymphocytic leukemia.



CDC, complement-dependent cytotoxicity; IV, intravenous; ADCC, antibody-dependent cellular cytotoxicity

Ofatumumab has not been approved in any country for the treatment of MS

MIRROR Study

Overall Objective

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

Primary Endpoint

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

MIRROR Study Design

PBO, placebo; QM, every month.

MIRROR Study Design

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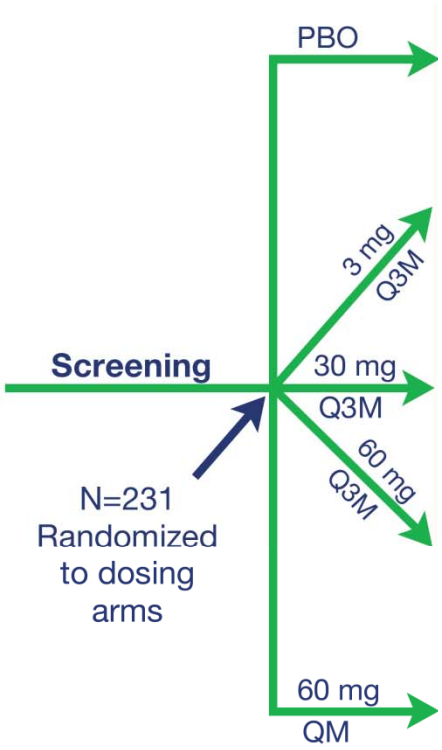

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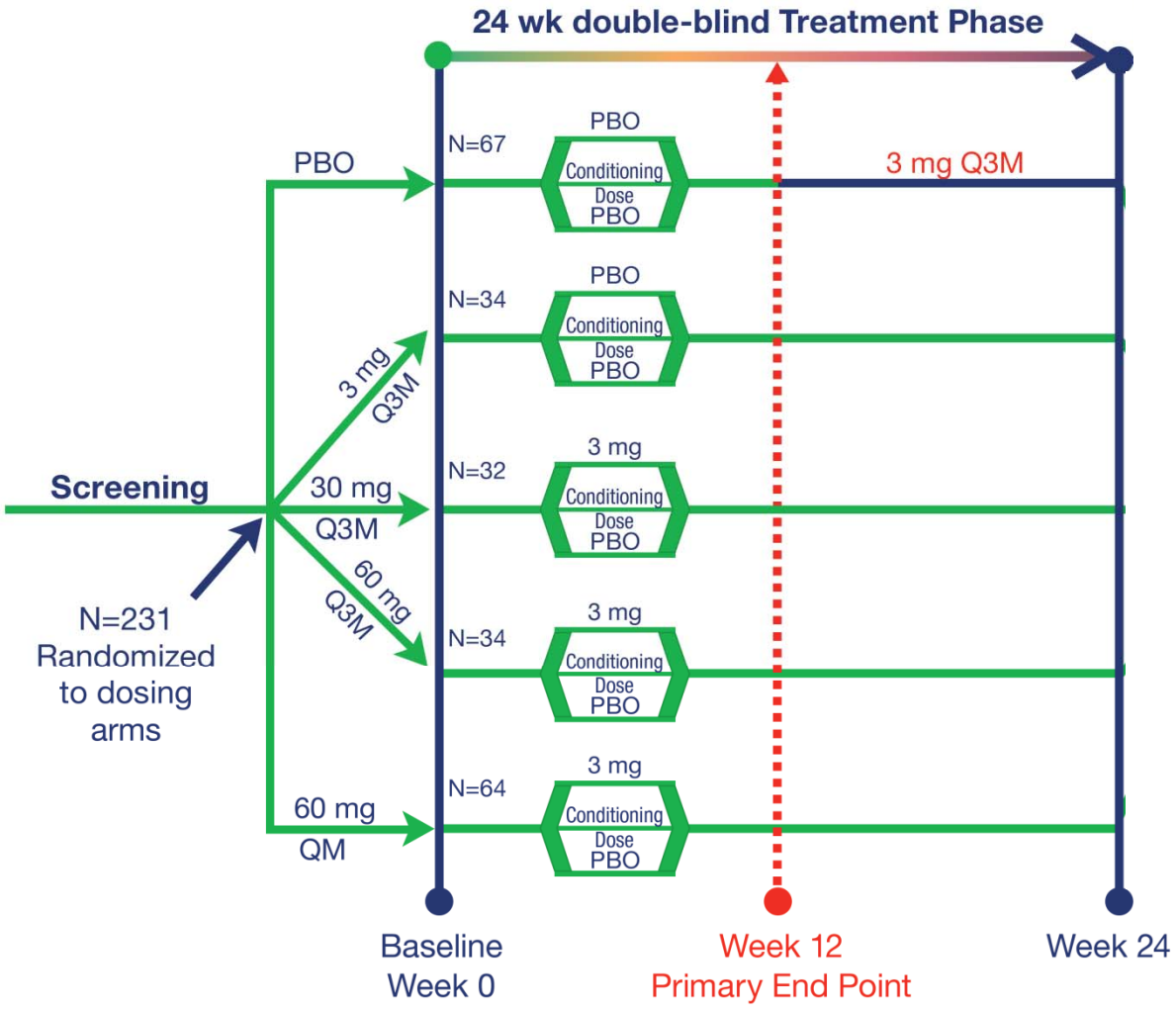
MIRROR Study Design



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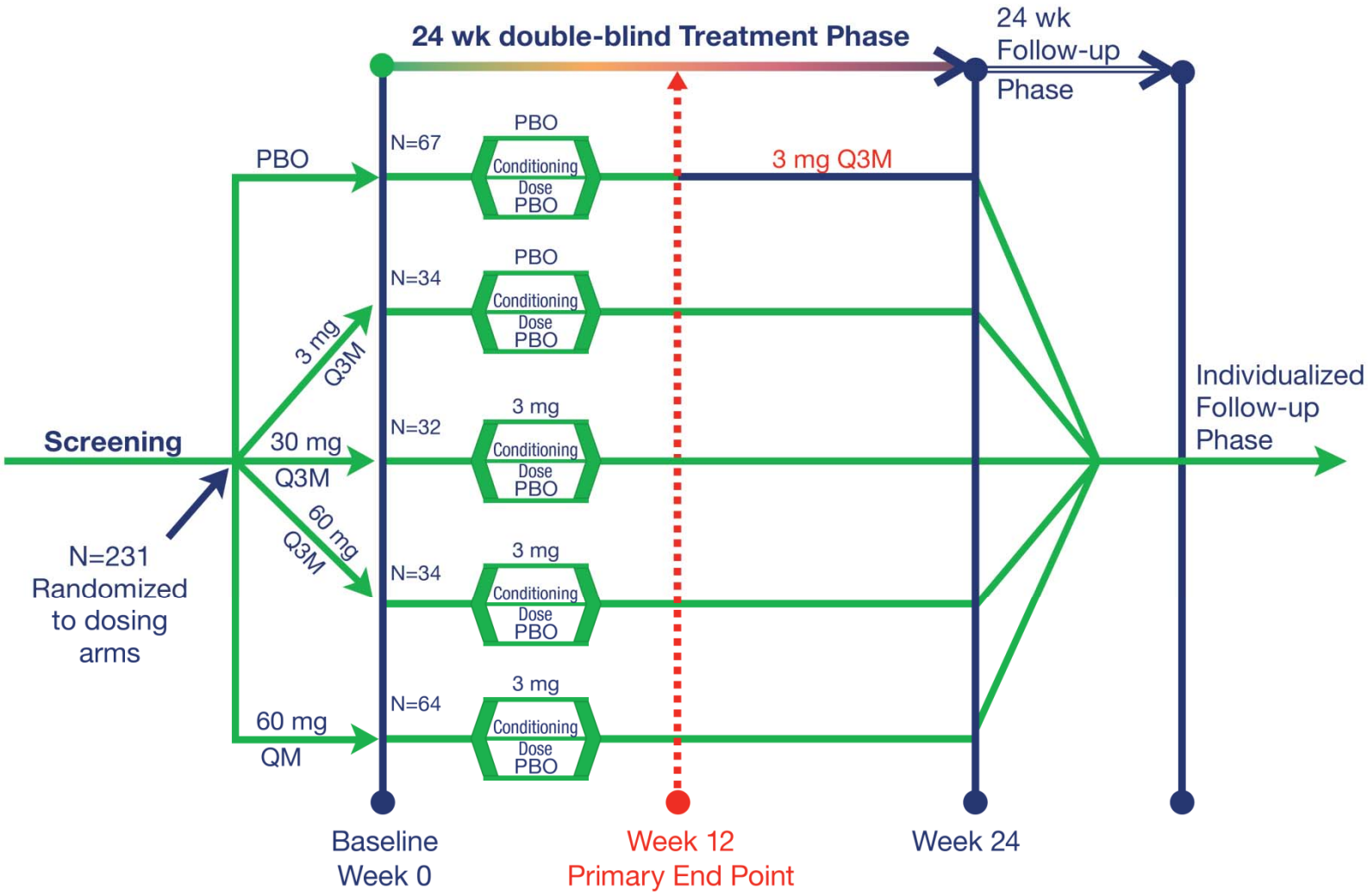
MIRROR Study Design



PBO, placebo; QM, every month.

MIRROR Study Subject Disposition

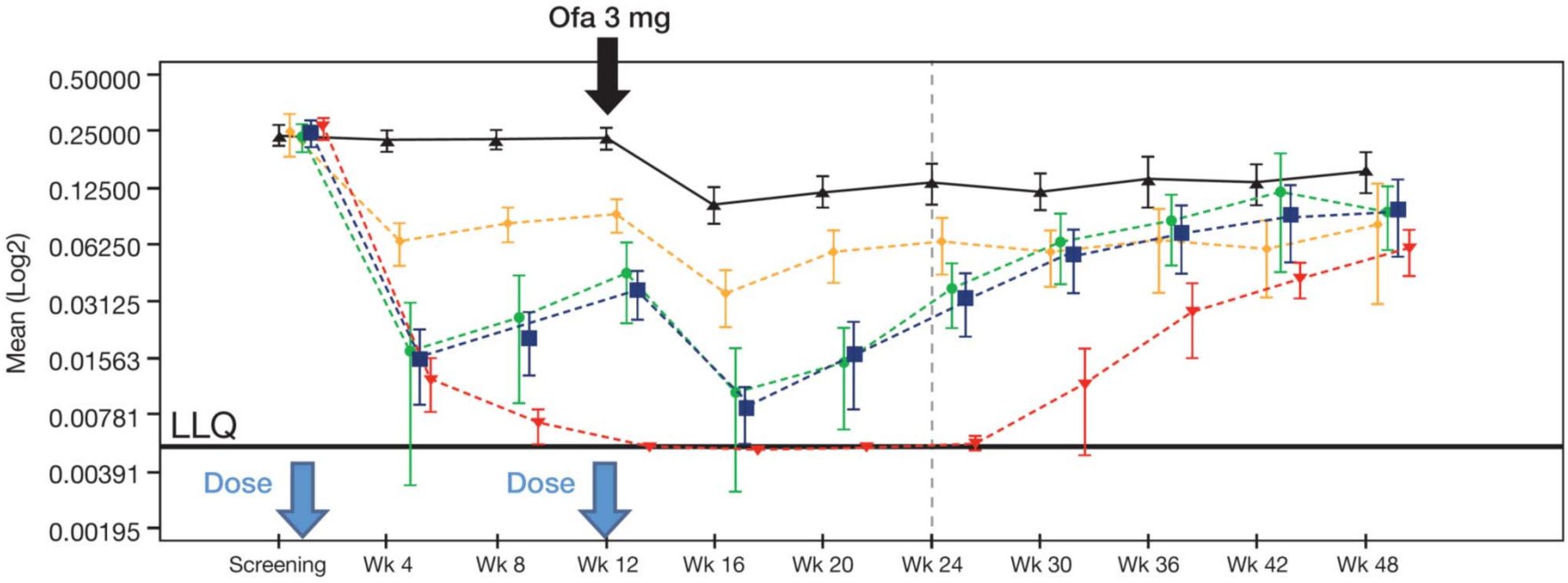
- Randomized, double-blind, placebo-controlled, parallel-group design
- Subjects with RRMS, aged 18-55 years, with a history of relapses, or new lesions and EDSS 0-5.5
- 231 randomized subjects who received at least one dose of study drug

	Placebo then Ofa 3 mg at wk12	Ofa 3 mg q12w	Ofa 30 mg q12w	Ofa 60 mg q12w	Ofa 60 mg q4w
Randomized	67	34	32	34	64
Completed wk12	65 (97%)	31 (91%)	30 (94%)	33 (97%)	60 (94%)
Completed wk 24	64 (96%)	29 (85%)	30 (94%)	33 (97%)	58 (91%)
Withdrawn from Treatment	2 (3%)	5 (15%)	3 (9%)	1 (3%)	6 (9%)

MIRROR Study Baseline Characteristics

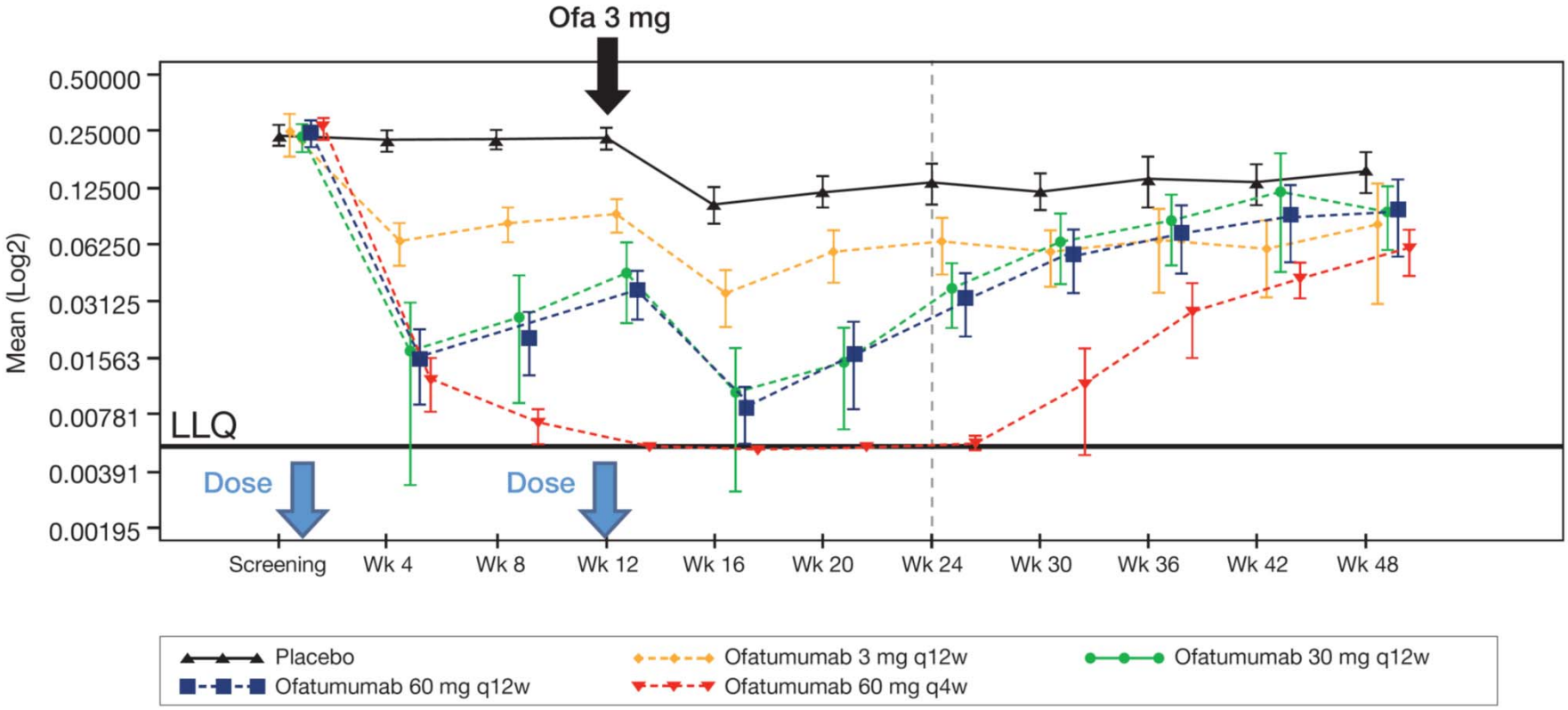
	Placebo (With 3 mg Ofa at Week 12) (N=67)	Ofa 3 mg q12w (N=34)	Ofa 30 mg q12w (N=32)	Ofa 60 mg q12w (N=34)	Ofa 60 mg q4w (N=64)	Total (N=231)
Sex Female, n (%)	46 (69)	22 (65)	24 (75)	22 (65)	41 (64)	155 (67)
Race White, n (%)	65 (97)	34 (100)	31 (97)	34 (100)	61 (95)	225 (97)
Age, y Mean (SD) Range	37.7 (9.38) 20-55	38.1 (8.29) 23-54	37.2 (10.04) 22-54	37.3 (9.67) 20-55	36.2 (9.57) 18-56	37.2 (9.36) 18-56
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) In last 24 months	1.8 (0.78)	1.7 (0.91)	1.9 (1.12)	1.9 (0.86)	1.8 (0.85)	
MRI in last 12 months with active lesion? Yes	29 (43%)	15 (45%)	11 (34%)	15 (45%)	28 (44%)	

MIRROR Study Pharmacological response: Sub-maximal 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

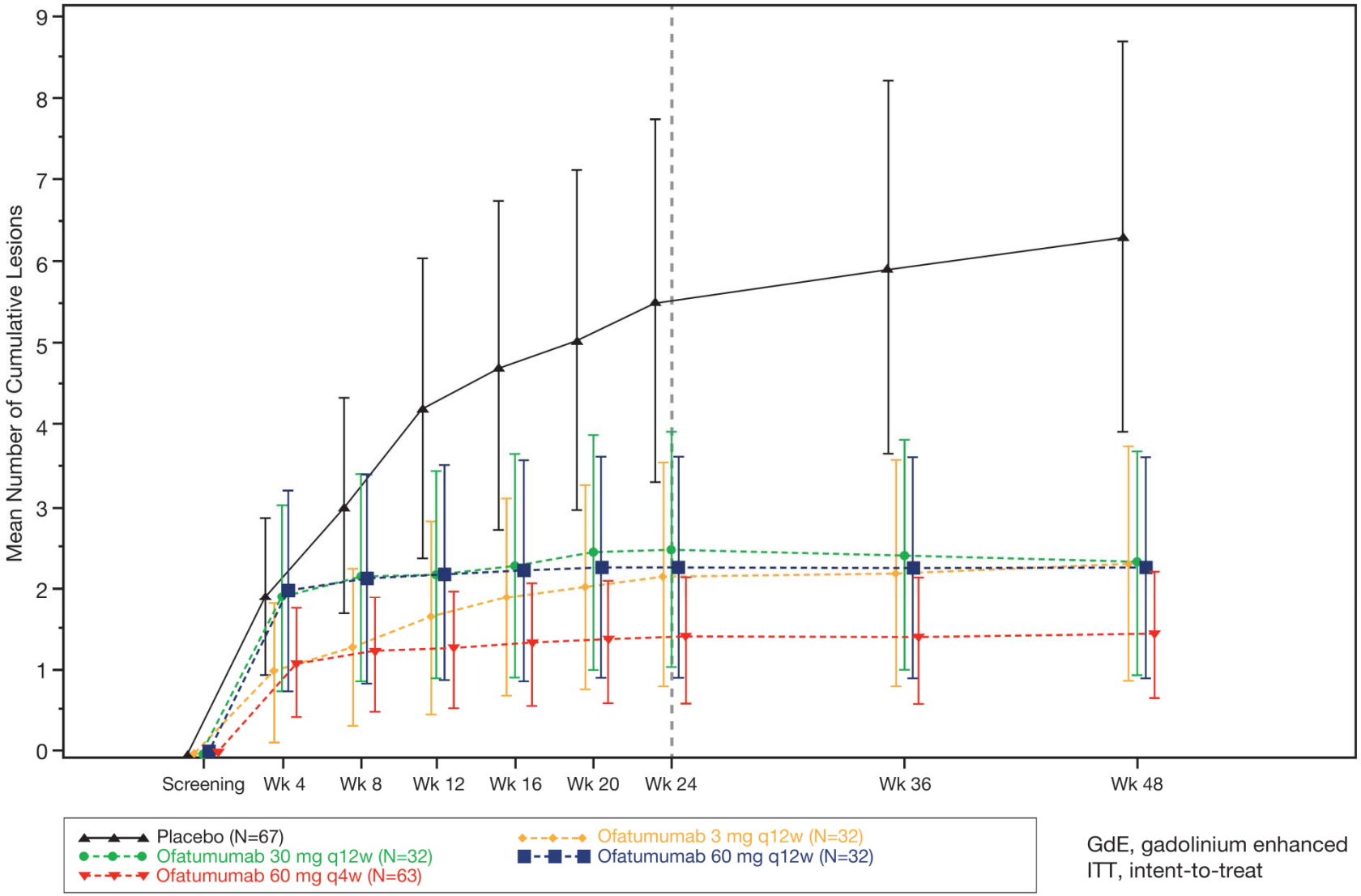
MIRROR Study Pharmacological response: Sub-maximal depletion of CD19 B cells



Sample size (n)											
Placebo	66	64	65	65	64	64	61	26	27	27	27
Ofa 3 mg q12w	33	33	32	31	30	28	26	10	9	9	9
Ofa 30 mg q12w	31	30	28	30	30	30	29	16	15	17	16
Ofa 60 mg q12w	33	33	33	33	33	33	33	11	11	11	11
Ofa 60 mg q4w	64	62	60	59	59	59	56	25	26	25	25

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

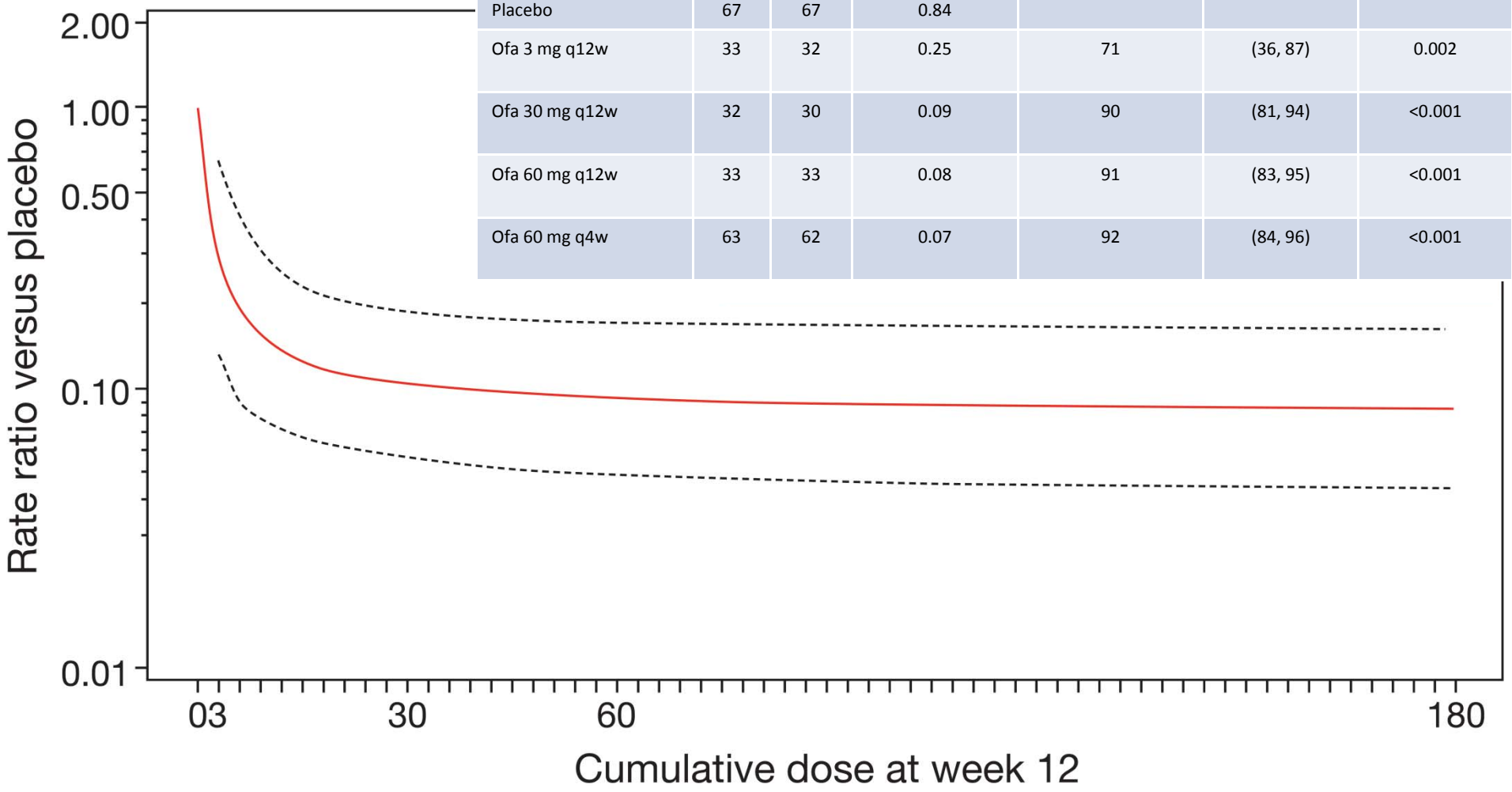
MIRROR Study Cumulative T1 GdE Lesions Over Time (ITT Population/AES Dataset)



GdE, gadolinium enhanced
ITT, intent-to-treat

MIRROR Study New T1 GdE Lesions Weeks 4-12

	N	n	Mean Rate (Lesions /Scan)	% Reduction vs. Placebo	95% CI	*P* Value
Placebo	67	67	0.84			
Ofa 3 mg q12w	33	32	0.25	71	(36, 87)	0.002
Ofa 30 mg q12w	32	30	0.09	90	(81, 94)	<0.001
Ofa 60 mg q12w	33	33	0.08	91	(83, 95)	<0.001
Ofa 60 mg q4w	63	62	0.07	92	(84, 96)	<0.001



Based upon results of E_{max} model

Safety Data

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 q12w (N=34)	Ofa 60 mg q4w (N=64)	Total Ofa (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

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

Preferred Term	Placebo (With 3 mg Ofa at Wk 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.

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: $\geq$5% in any ofa dose group and more than 2 times the rate observed for placebo

MIRROR Study Additional Safety Findings

- No evidence of clinically meaningful changes in laboratory parameters or vital signs
- No evidence of clinically meaningful immunogenicity (human anti-human antibodies)
- No cases of progressive multifocal leukoencephalopathy or opportunistic infections

Conclusions

- Ofatumumab depletes B cells quickly and in a dose-dependent and frequency-dependent manner
- Ofatumumab effectively reduces new T1 GdE 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

MIRROR Study

Thank You to IDMC and PML Committee Members and Participating Sites and Subjects

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Poster number 009. Daren Austin et al. `The Relationship Between Peripheral B-Cell Levels and MRI Disease Activity in Relapsing Remitting Multiple Sclerosis (RRMS)'. April 30 at 6:39 pm