Ocrelizumab Efficacy in PPMS Patients in the Presence/Absence of T1 Gadolinium-Enhancing Lesions at Baseline in a Phase III Placebo-Controlled Trial

J Wolinsky, DL Arnold, A Bar-Or, J de Seze, G Giovannoni, B Hemmer, K Rammohan, P Chin, P Fontoura, H Garren, D Masterman, A Sauter, X Montalban
on behalf of the ORATORIO clinical investigators

NCT01194570

The 2016 Annual Meeting of the Consortium of Multiple Sclerosis Centers
National Harbor, MD, USA, June 1-4, 2016
Oral Presentation DX06

Disclosures

Jerry Wolinsky has served on advisory boards, data monitoring or steering committees, held consulting agreements, or received speaker honoraria from the following commercial entities: AbbVie, AcademicCME, Alkermes, Antisense Therapeutics, Bayer HealthCare, Forward Pharma A/S, medDay, Mapi Scientific, Novartis, Roche/Genentech, Sanofi Genzyme, Takeda, Teva Pharmaceuticals, WebMD. Royalties are received for out licensed monoclonal antibodies through the UTHSCH to Millipore (Chemicon International) Corporation since 1993.

Douglas L Arnold reports equity interest in NeuroRx Research, which performed the MRI analysis for the trial, and consultation fees from Acorda Therapeutics, Biogen, Genzyme, F. Hoffmann-La Roche Ltd, Innate Immunotherapeutics, MedImmune, Mitsubishi Pharma, Novartis, Receptos, Sanofi Aventis, and Teva.

Amit Bar-Or has served on scientific advisory boards for F. Hoffmann-La Roche Ltd., Genentech, Biogen Idec, GlaxoSmithKline, Merck/EMD Serono, MedImmune, Mitsubishi Pharma, Ono Pharma, Receptos, Sanofi-Genzyme, and Guthy-Jackson/GGF; he has also received research support from Novartis and Sanofi-Genzyme.

Jérôme de Seze has received consultancy fees and served as an expert for advisory boards for Alexion, Allergan, Almiral, Bayer, Biogen, Chugai, CSL Behring, F. Hoffmann-La Roche Ltd., Genzyme, LFB, Merck, Novartis, and Teva.

Gavin Giovannoni has received honoraria from AbbVie, Bayer HealthCare, Biogen, Canbex Therapeutics, Five Prime Therapeutics, Genzyme, GSK, GW Pharma, Merck, Merck Serono, Novartis, Protein Discovery Laboratories, F. Hoffmann-La Roche Ltd., Synthon, Teva Neuroscience, UCB and Vertex; research grant support from Biogen, Ironwood, Merck Serono, Merz and Novartis; and compensation from Elsevier.

Bernhard Hemmer has served on scientific advisory boards for F. Hoffmann-La Roche Ltd., Novartis, Bayer Schering and Genentech; has received speaker honoraria from Biogen Idec and F. Hoffmann-La Roche Ltd.; has received research support from Chugai Pharmaceuticals; holds part of a patent for the detection of antibodies and T cells against KIR4.1 in a subpopulation of MS patients and genetic determinants of neutralising antibodies to interferon-beta.

Kottil Rammohan has received honoraria for participating in advisory boards and consulting for Acorda, Biogen, EMD Serono, Genentech, Inc./F. Hoffmann-La Roche Ltd., Genzyme and Teva; he has also received grants from Accera, Novartis and the United States Department of Defense.

Peter Chin is an employee and/or shareholder of Genentech, Inc.

Paulo Fontura is an employee and shareholder of F. Hoffmann-La Roche Ltd.

Hideki Garren is an employee and shareholder of F. Hoffmann-La Roche Ltd.

Donna Masterman is an employee and/or shareholder of Genentech, Inc.

Annette Sauter is an employee and shareholder of F. Hoffmann-La Roche Ltd.

Xavier Montalban has received speaking honoraria and travel expense reimbursement for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with Actelion, Almirall, Bayer, Biogen, Genzyme, Merck, Novartis, Octapharma, Receptos, F. Hoffmann-La Roche Ltd., Sanofi, Teva and Trophos.

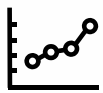
The study was sponsored by F. Hoffmann-La Roche Ltd.
Support for third-party writing assistance was provided by F. Hoffmann-La Roche Ltd, furnished by Articulate Science and Health Interactions.

Learning objectives

- To review the primary and key secondary efficacy outcomes of ORATORIO, a randomized, parallel-group, double-blind, placebo-controlled Phase III study of ocrelizumab in primary progressive multiple sclerosis (PPMS)
- To explore the efficacy of ocrelizumab versus placebo in PPMS patients with and without T1 gadolinium-enhancing lesions at baseline
- To assess the overall safety and benefit-risk profile of ocrelizumab versus placebo in PPMS patients in ORATORIO

Primary progressive multiple sclerosis (PPMS): Epidemiology and unmet needs

- More than 2.3 million people worldwide affected by MS[1]
  - ≈10% have PPMS
- No cure for MS[2]



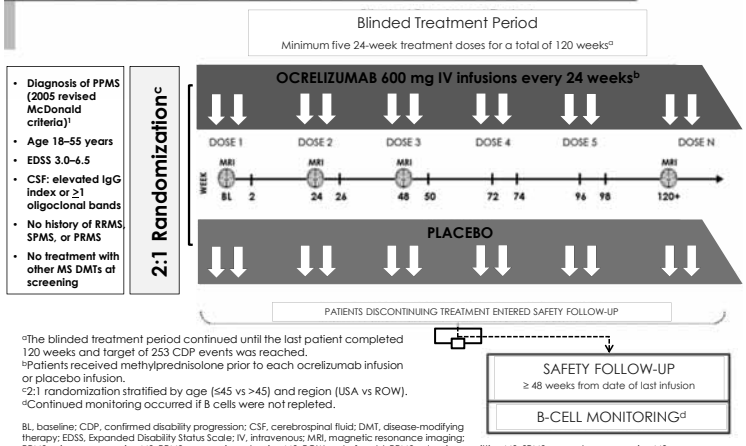
- PPMS is characterized by a progressive course from disease onset[3,4]
- Relapses and contrast-enhancing lesions may occur in PPMS[4]

- PPMS median age of onset ≈40 years[5]
- Men and women affected equally[5]
- No approved therapies for PPMS

- Previous trials have failed to demonstrate efficacy in slowing of disability progression in patients with PPMS
- PPMS is a disabling condition with very high unmet medical need

MS, multiple sclerosis.
1. http://www.msif.org/wp-content/uploads/2014/09/Atlas-of-MS.pdf; 2. Markowitz CE, ***et al. Am J Manag Care*** 2010;16:S211–S218;
3. Ebers GC. ***Mult Scler*** 2004;10 Suppl 1:S8–13; discussion S13–S15; 4. Miller DH, Leary SM. ***Lancet Neurol*** 2007;6:903–912;
5. Cottrell DA, ***et al. Brain*** 1999;122 :625–639.

ORATORIO: Phase III PPMS Study design



[a]The blinded treatment period continued until the last patient completed 120 weeks and target of 253 CDP events was reached.
[b]Patients received methylprednisolone prior to each ocrelizumab infusion or placebo infusion.
[c]2:1 randomization stratified by age (≤45 vs >45) and region (USA vs ROW).
[d]Continued monitoring occurred if B cells were not repleted.

BL, baseline; CDP, confirmed disability progression; CSF, cerebrospinal fluid; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; IV, intravenous; MRI, magnetic resonance imaging; PPMS, primary progressive MS; PRMS, progressive-relapsing MS; ROW, rest of world; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS.
1. Polman CH, *et al. Ann Neurol* 2005;58:840–6.

ORATORIO: Study objectives and endpoints

Objectives

- To evaluate the efficacy and safety of ocrelizumab compared with placebo in patients with PPMS

Primary endpoint

- 12-week confirmed disability progression (CDP)

Secondary endpoints

- 24-week CDP
- Change in timed 25-foot walk
- Change in T2 lesion volume
- Percent change in whole brain volume
- SF-36 Physical Component Score

PPMS, primary progressive multiple sclerosis; SF-36, short form (36).

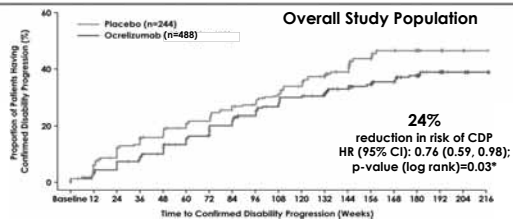
ORATORIO: MS disease history and baseline characteristics

	Placebo N=244	Ocrelizumab N=488
Age, years, mean (SD)	44.4 (8.3)	44.7 (7.9)
Female, n (%)	124 (50.8)	237 (48.6)
Time since MS symptom onset, years, mean (SD)	6.1 (3.6)	6.7 (4.0)
Time since MS diagnosis, years, mean (SD)	2.8 (3.3)	2.9 (3.2)
MS disease-modifying treatment naïve,* n (%)	214 (87.7)	433 (88.7)
EDSS, mean (SD)	4.7 (1.2)	4.7 (1.2)
MRI		
Patients with T1 Gd+ lesions, n (%)	60 (24.7)	133 (27.5)
Brain T2 hyperintense lesion volume, cm^3, mean (SD)	10.9 (13.0)	12.7 (15.1)
Normalized brain volume, cm^3, mean (SD)	1469.9 (88.7)	1462.9 (83.9)

Evaluation of efficacy in patient subgroups with and without T1 gadolinium-enhancing lesions at baseline is a key area of interest

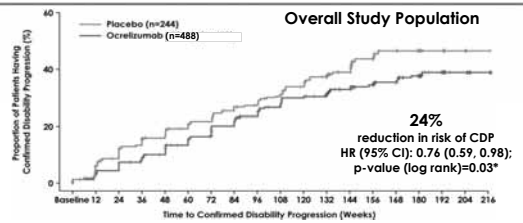
*No disease-modifying treatments in the previous 2 years.
EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; MRI, magnetic resonance imaging; MS, multiple sclerosis; SD, standard deviation.

Significant reduction in risk of 12-week confirmed disability progression



Primary endpoint
*Analysis based on ITT population; p-value based on log-rank test stratified by geographic region and age. Patients with initial disability progression who discontinued treatment early with no confirmatory EDSS assessment were considered as having confirmed disability progression.
CDP, confirmed disability progression; CI, confidence interval; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; HR, hazard ratio; ITT, intent-to-treat.

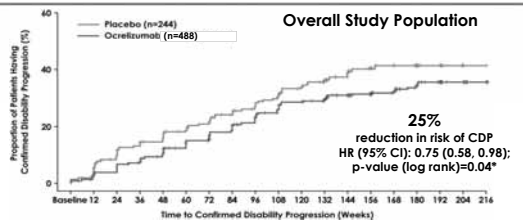
Significant reduction in risk of 12-week confirmed disability progression



	Placebo (N=244)		Ocrelizumab (N=488)		Hazard Ratio	95% CI
	n	Events	n	Events		
Overall population	244	96	487	160	0.76	(0.59, 0.98)
With T1 Gd+ lesions	60	27	133	43	0.65	(0.40, 1.06)
Without T1 Gd+ lesions	183	68	350	115	0.84	(0.62, 1.13)

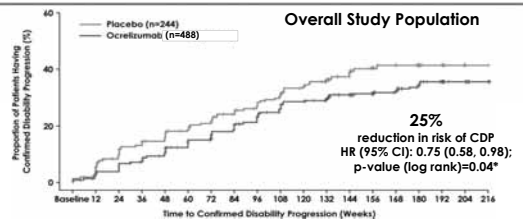
Primary endpoint
*Analysis based on ITT population; p-value based on log-rank test stratified by geographic region and age. Patients with initial disability progression who discontinued treatment early with no confirmatory EDSS assessment were considered as having confirmed disability progression.
CDP, confirmed disability progression; CI, confidence interval; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; HR, hazard ratio; ITT, intent-to-treat.

Significant reduction in risk of 24-week confirmed disability progression



Secondary endpoint
*Analysis based on ITT population; p-value based on log-rank test stratified by geographic region and age. Patients with initial disability progression who discontinued treatment early with no confirmatory EDSS assessment were considered as having confirmed disability progression.
CDP, confirmed disability progression; CI, confidence interval; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; HR, hazard ratio; ITT, intent-to-treat.

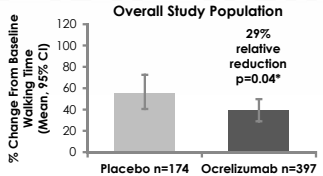
Significant reduction in risk of 24-week confirmed disability progression



	Placebo (N=244)		Ocrelizumab (N=488)		Hazard Ratio	95% CI
	n	Events	n	Events		
Overall population	244	87	487	144	0.75	(0.58, 0.98)
With T1 Gd+ lesions	60	23	133	39	0.67	(0.40, 1.14)
Without T1 Gd+ lesions	183	63	350	103	0.81	(0.59, 1.10)

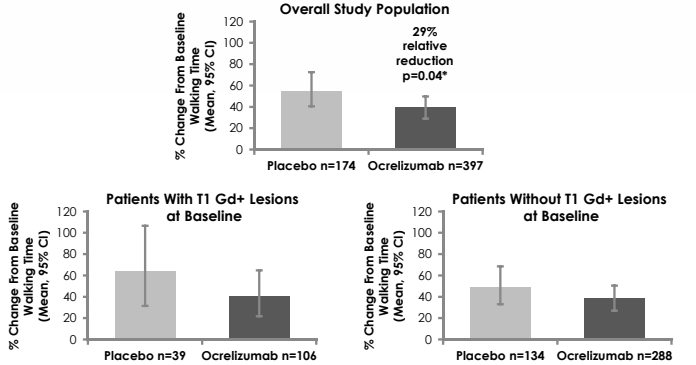
Secondary endpoint
*Analysis based on ITT population; p-value based on log-rank test stratified by geographic region and age. Patients with initial disability progression who discontinued treatment early with no confirmatory EDSS assessment were considered as having confirmed disability progression.
CDP, confirmed disability progression; CI, confidence interval; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; HR, hazard ratio; ITT, intent-to-treat.

Significant reduction in change in timed 25-foot walk from baseline to Week 120



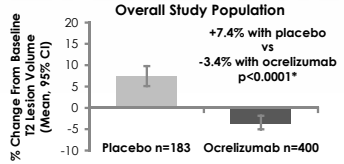
Secondary endpoint
*Analysis based on ITT population; p-value based on ranked ANCOVA at 120-week visit adjusted for baseline timed 25-foot walk, geographic region and age with missing values imputed by LOCF. Point estimates and 95% CIs based on MMRM analysis on log-transformed data adjusted for baseline timed 25-foot walk, geographic region and age.
CI, confidence interval; Gd+, gadolinium-enhancing; ITT, intent to treat; LOCF, last observation carried forward;
MMRM; mixed-effect model repeated measure.

Significant reduction in change in timed 25-foot walk from baseline to Week 120



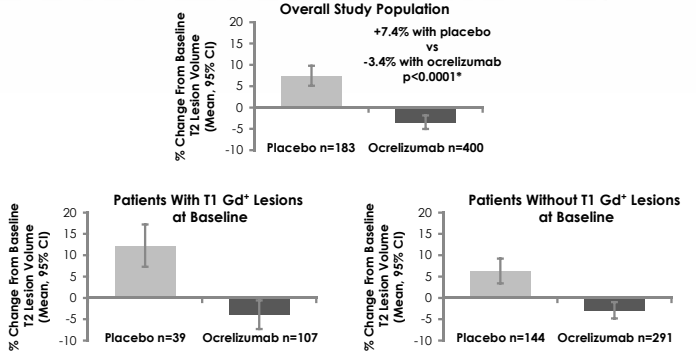
Secondary endpoint
*Analysis based on ITT population; p-value based on ranked ANCOVA at 120-week visit adjusted for baseline timed 25-foot walk, geographic region and age with missing values imputed by LOCF. Point estimates and 95% CIs based on MMRM analysis on log-transformed data adjusted for baseline timed 25-foot walk, geographic region and age.
CI, confidence interval; Gd+, gadolinium-enhancing; ITT, intent to treat; LOCF, last observation carried forward; MMRM; mixed-effect model repeated measure.

Significant reduction in T2 hyperintense lesion volume from baseline to Week 120



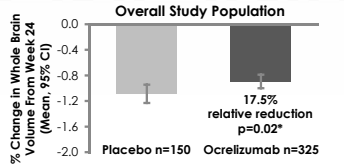
Secondary endpoint
*Analysis based on ITT population; p-value based on ranked ANCOVA at 120-week visit adjusted for baseline T2 lesion volume, geographic region and age with missing values imputed by LOCF. Point estimates and 95% CIs based on MMRM analysis on log-transformed data adjusted for baseline T2 lesion volume, geographic region and age.
ANCOVA, analysis of covariance; CI, confidence interval; Gd+, gadolinium-enhancing; ITT, intent-to-treat; LOCF, last observation carried forward; MMRM; mixed-effect model repeated measure.

Significant reduction in T2 hyperintense lesion volume from baseline to Week 120



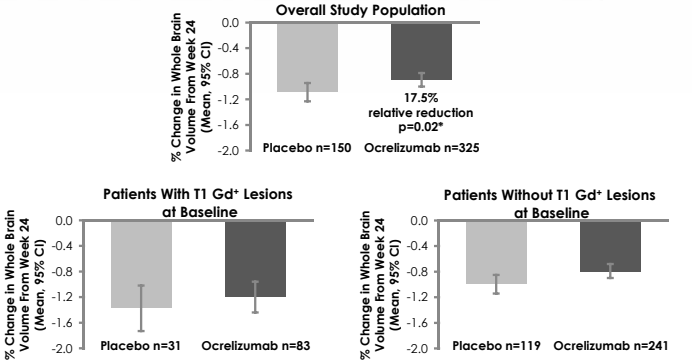
Secondary endpoint
*Analysis based on ITT population; p-value based on ranked ANCOVA at 120-week visit adjusted for baseline T2 lesion volume, geographic region and age with missing values imputed by LOCF. Point estimates and 95% CIs based on MMRM analysis on log-transformed data adjusted for baseline T2 lesion volume, geographic region and age.
ANCOVA, analysis of covariance; CI, confidence interval; Gd+, gadolinium-enhancing; ITT, intent-to-treat; LOCF, last observation carried forward; MMRM; mixed-effect model repeated measure.

Significant reduction in rate of whole brain volume loss from Week 24 to Week 120



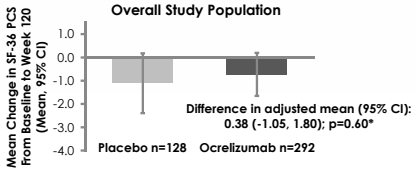
Secondary endpoint
*Analysis based on ITT population with Week 24 and at least one post-Week 24 assessment; p-value based on MMRM at 120-week visit adjusted for Week 24 brain volume, geographic region and age.
CI, confidence interval; Gd+, gadolinium-enhancing; ITT, intent-to-treat; MMRM; mixed-effect model repeated measure.

Significant reduction in rate of whole brain volume loss from Week 24 to Week 120



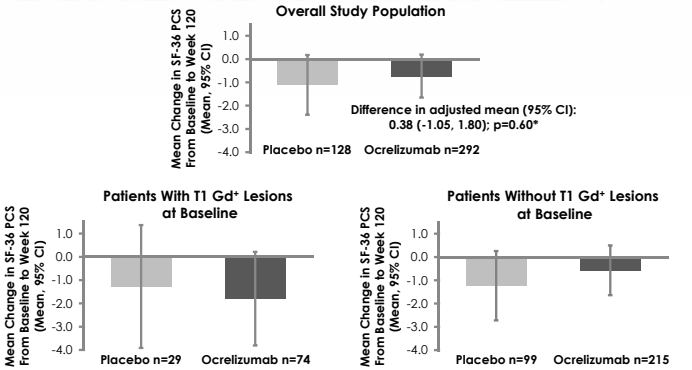
Secondary endpoint
*Analysis based on ITT population with Week 24 and at least one post-Week 24 assessment; p-value based on MMRM at 120-week visit adjusted for Week 24 brain volume, geographic region and age.
CI, confidence interval; Gd+, gadolinium-enhancing; ITT, intent-to-treat; MMRM; mixed-effect model repeated measure.

Change in SF-36 Physical Component Summary score from baseline to Week 120



Secondary endpoint
*Analysis based on ITT population with assessment at baseline and at least one post-baseline value; p-value based on MMRM at the 120-week visit adjusted for baseline SF-36 PCS score, geographic region and age.
CI, confidence interval; Gd+, gadolinium-enhancing; ITT, intent-to-treat; MMRM, mixed-effect model of repeated measures;
PCS, physical component summary; SF-36, short form (36).

Change in SF-36 Physical Component Summary score from baseline to Week 120



Secondary endpoint
*Analysis based on ITT population with assessment at baseline and at least one post-baseline value; p-value based on MMRM at the 120-week visit adjusted for baseline SF-36 PCS score, geographic region and age.
CI, confidence interval; Gd+, gadolinium-enhancing; ITT, intent-to-treat; MMRM, mixed-effect model of repeated measures;
PCS, physical component summary; SF-36, short form (36).

AEs by system organ class reported by ≥10% of patients in either treatment arm until clinical cut-off date

n (%)	Placebo (n=239)	Ocrelizumab (n=486)
Overall patients with ≥1 AE	215 **(90.0)**	462 **(95.1)**
Infections and Infestations*	162 **(67.8)**	339 **(69.8)**
Nasopharyngitis	65 **(27.2)**	110 **(22.6)**
Urinary tract infection	54 **(22.6)**	96 **(19.8)**
Influenza	21 **(8.8)**	56 **(11.5)**
Upper respiratory tract infection	14 **(5.9)**	53 **(10.9)**
Bronchitis	12 **(5.0)**	30 **(6.2)**
Gastroenteritis	12 **(5.0)**	20 **(4.1)**
Injury, Poisoning and Procedural Complications	104 **(43.5)**	263 **(54.1)**
Musculoskeletal and Connective Tissue Disorders	98 **(41.0)**	181 **(37.2)**
Nervous System Disorders	79 **(33.1)**	174 **(35.8)**
General Disorders and Administration-Site Conditions	60 **(25.1)**	130 **(26.7)**
Gastrointestinal Disorders	60 **(25.1)**	126 **(25.9)**
Psychiatric Disorders	59 **(24.7)**	89 **(18.3)**
Skin and Subcutaneous Tissue Disorders	44 **(18.4)**	99 **(20.4)**
Respiratory, Thoracic and Mediastinal Disorders	35 **(14.6)**	87**(17.9)**
Metabolism and Nutrition disorders	28 **(11.7)**	56 **(11.5)**
Renal and Urinary Disorders	30 **(12.6)**	51 **(10.5)**
Vascular Disorders	26 **(10.9)**	54 **(11.1)**
Investigations	20 **(8.4)**	58 **(11.9)**

***For Infections and Infestations SOC only: events reported by at least 5% of patients in one treatment arm are presented**

Safety-evaluable population
AE, adverse event; SOC, system organ class.

SAEs by system organ class reported by ≥1% of patients in either treatment arm until clinical cut-off date

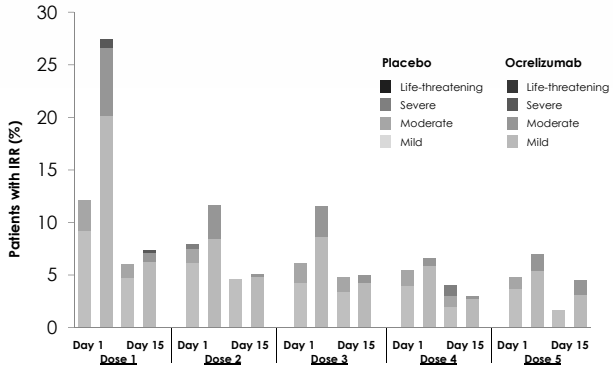
n (%)	Placebo (n=239)	Ocrelizumab (n=486)
Overall patients with ≥1 SAE	53 **(22.2)**	99 **(20.4)**
Infections and Infestations	14 **(5.9)**	30 **(6.2)**
Injury, Poisoning, and Procedural Complications	11 **(4.6)**	19 **(3.9)**
Nervous System Disorders	9 **(3.8)**	18 **(3.7)**
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)	7 **(2.9)**	8 **(1.6)**
Gastrointestinal Disorders	3 **(1.3)**	10 **(2.1)**
Musculoskeletal and Connective Tissue Disorders	6 **(2.5)**	6 **(1.2)**
General Disorders and Administration-Site Conditions	3 **(1.3)**	6 **(1.2)**
Renal and Urinary Disorders	3 **(1.3)**	5 **(1.0)**

Five deaths were reported:
- 0.4% in the placebo arm: road traffic accident
- 0.8% in the ocrelizumab arm: pulmonary embolism, pneumonia, pancreas carcinoma, pneumonia aspiration

Thirteen malignancies were reported:
- 0.8% in the placebo arm: one cervix adenocarcinoma *in situ* and one basal cell carcinoma
- 2.3% in the ocrelizumab arm: four breast cancers, one endometrial adenocarcinoma, one anaplastic lymphoma, one histiocytoma, one metastatic pancreas cancer, and three basal cell carcinomas

Safety-evaluable population
SAE, serious adverse event.

Infusion-related reactions (IRRs) by dose and severity until clinical cut-off date



- 1 patient (0.2%) withdrew from ocrelizumab treatment due to an IRR at the first infusion

Ocrelizumab is the first treatment to show efficacy in PPMS

- Ocrelizumab met the primary and key secondary clinical and MRI endpoints
- Efficacy of ocrelizumab versus placebo in patients with and without T1 Gd+ lesions at baseline was consistent with that in the overall study population
  - However, the ORATORIO study was not powered to demonstrate efficacy differences between these subgroups
- Overall, the proportion of patients experiencing AEs and SAEs associated with ocrelizumab, including serious infections, was similar to placebo
  - As expected with IV monoclonal antibodies, a higher proportion of patients in the ocrelizumab group reported infusion-related reactions, the majority of which were mild to moderate in severity
  - The imbalance observed in the incidence of malignancies needs to be contextualized with the totality of MS data and epidemiology data; no conclusion can be made based on this low number
- The benefit:risk profile of ocrelizumab in ORATORIO supports it as a potential therapeutic approach in PPMS

AE, adverse event; Gd+, gadolinium-enhancing; IV, intravenous; MS, multiple sclerosis; PPMS, primary progressive MS; SAE, serious adverse event.

Acknowledgements: Investigators and patients involved in the ORATORIO study

AUSTRALIA
St Vincent's Hospital Melbourne
Royal Hobart Hospital

AUSTRIA
Landes-Nervenklinik Wagner-Jauregg
Medizinische Universität Wien
Universitätsklinikum Innsbruck
Kepler Universitätsklinikum Linz
Christian-Doppler-Klinik Salzburg

BELGIUM
AZ Sint-Jozef
AZ Alma

BRAZIL
Hospital São Lucas da PUCRS
Hospital das Clínicas da Universidade Federal de Goias
Santa Casa de Misericordia de Belo Horizonte
Hospital Universitário Clementino Fraga Filho (UFRJ)

BULGARIA
Multiprofile Hospital for Active Treatment "National Cardiology Hospital"
Multiprofile Hospital for Active Treatment of Neurology and Psychiatry "Dr. Nikolay"

CANADA
Montreal Neurological Institute and Hospital
Ottawa Hospital
Recherche Sepmus, Inc.
Health Sciences Centre
St. Michael's Hospital
University Of British Columbia Hospital
Foothills Medical Centre

CZECH REPUBLIC
Fakultní nemocnice Brno
Všeobecná fakultní nemocnice v Praze
Krajská zdravotní, a.s. – Nemocnice Teplice, o.z.

FINLAND
Turun yliopistollinen keskussairaala
Tampereen yliopistollinen sairaala
Helsingin yliopistollinen keskussairaala / Meilahti

FRANCE
Centre Hospitalier Universitaire de Bordeaux, Hopital Pellegrin
CHU de Nice-Cimiez
Centre hospitalo-universitaire Caremeau
Hopital Purpan
Hopital Gabriel Montpied
Hôpital de Haute-Pierre
CHRU Nancy
Hôpital Côte de Nacre
Fondation Rothschild
Hôpital de Poissy
Hôpital Guillaume et René Laënnec
Hôpital Pasteur
Groupe Hospitalier Pitié- Salpêtrière
Hôpitaux de La Timone
Hôpital Maison Blanche
Hôpital Roger Salengro
Hôpital Pierre Wertheimer – Hôpital Neurologique

GERMANY
Medizinische Einrichtungen des Bezirks Oberpfalz GmbH
Universitätsklinikum Gießen und Marburg GmbH
Universitätsklinikum Frankfurt
Heinrich Heine Universität Düsseldorf
C/O Jüdisches Krankenhaus
Charité – Universitätsmedizin Berlin
Klinikum rechts der Isar der Technische Universität München
Ruhr-Universität Bochum
Marienne-Straß-Klinik
Deutsche Klinik für Diagnostik GmbH
Klinikum der Stadt Köln gGmbH
Carl-Thiem-Klinikum Cottbus
Klinikum Bayreuth GmbH
Universität Heidelberg
Universitätsklinikum Leipzig
Universitätsklinikum Ulm
Universitätsklinikum Tübingen
Universitätsklinikum Carl Gustav Carus an der TU Dresden

GREECE
401 Military Hospital of Athens
"AHEPA" University General Hospital of Thessaloniki
"Georgios Papanikolaou" General Hospital of Thessaloniki

HUNGARY
Uzsoki Utcai Kórház
Pécsi Tudományegyetem
John Ferenc Dél-Pest Kórház és Rendelőintézet
Vasasy Kolos Kórház
Clinexpert Egészségügyi Szolgáltató és Kereskedelmi Kft.
Szegedi Tudományegyetem Szent-Györgyi Albert Klinikai Központ

ISRAEL
The Chaim Sheba Medical Center
Rabin Medical Center
Tel Aviv Sourasky Medical Center
Hadassah University Hospital Ein Kerem
Meir Medical Center
Ziv Medical Center

ITALY
Azienda Sanitaria Ospedaliera S. Luigi Gonzaga
Ospedale San Raffaele S.r.l.
Ospedale Binaghi
Azienda Ospedaliero Universitaria San Martino

LITHUANIA
Klaipeda University Hospital
Hospital of Lithuanian University of Health Sciences Kaunas Clinics
Republican Siauliai Hospital

MEXICO
Grupo Médico Camino
Centro de Estudios Clínicos y Especialidades Medicas SC
Instituto Nacional de Neurologia y Neurocirugia
Instituto Biomédico de Investigación A.C.

NETHERLANDS
Erasmus MC
Orbis Medisch Centrum

NEW ZEALAND
Waikato Hospital
Wellington Hospital

NORWAY
Oslo universitetssykehus HF, Ullevål

PERU
Clínica Anglo Americana
Hospital Dos de Mayo
Hospital IV Alberto Sabogal Sologuren

POLAND
Aleson Clinical Research Maciejowski-Bielecki Sp. j.
Zespol Opieki Zdrowotnej w Konskich
Niepubliczny Zaklad Opieki Zdrowotnej KENDRON
M.A. - LEK A.M. Maciejowscy SC. Centrum Terapii SM
SPZOZ Uniwersytecki Szpital Kliniczny nr 1 im. Norberta Barlickiego Uniwersytetu Medycznego w Lodzi
Centrum Medyczne Promedicus Sp. z o.o.
Samodzielny Publiczny Szpital Kliniczny nr 4
Niepubliczny Zaklad Opieki Zdrowotnej NEURO-MEDIC

PORTUGAL
Centro Hospitalar e Universitário de Coimbra, EPE
Hospital Garcia de Orta
Centro Hospitalar Lisboa Norte, E.P.E.
Hospital Fernando Fonseca
Centro Hospitalar do Porto – Hospital de Santo António

ROMANIA
SCPCL Mures Emergency County Clinical Hospital
"Dr. Carol Davila" Central Military Emergency Teaching Hospital SRL
"Elias" Emergency University Hospital
Timisoara Emergency County Clinical Hospital

RUSSIA
Research Medical Complex "Vrache Zdorovie"

SPAIN
Hospital Universitario Ramón y Cajal
Hospital Clínico San Carlos
Hospital de la Santa Creu i Sant Pau
Hospital Regional Universitario de Malaga – Hospital General
Hospital Universitario Virgen Macarena
Hospital Son Llatzer
Hospital Universitario de La Princesa
Hospital Universitario Vall d'Hebron
Hospital Universitario de Donostia
Hospital General Universitario de Alicante
Hospital Clínico Universitario de Santiago
Hospital Universitari de Girona Dr. Josep Trueta
Organización Sanitaria Integrada Bilbao Basurto
Hospital Clínic de Barcelona

SWITZERLAND
Ospedale Regionale Lugano Civico
Universitätsspital Basel

UKRAINE
Municipal Institution of Kyiv Regional Council "Kyiv Regional Clinical Hospital"
Municipal Institution "Odessa Regional Clinical Hospital"
State Treatment and Prevention Institution "Central Clinical Hospital of Ukrzaliznytsya"
SI "Ukrainian State Research Institute of Medical and Social Problems of Disability" MOH of Ukraine
Vinnytsya National Medical University n.a. M.I. Pyrohov
Kyiv Regional Clinical Hospital
Lviv National Medical University
Municipal Institution "Dnipropetrovsk Regional Clinical Hospital n.a. I.I. Mechnikov"
Volyn Regional Clinical Hospital
Kyiv City Clinical Hospital #4
"State Institution "Institute of Neurology, Psychiatry and Narcology of NAMS of Ukraine"

UNITED KINGDOM
King's College Hospital
Queen's Medical Centre
Royal Victoria Infirmary
Barts and the London NHS Trust
The Walton Centre For Neurology And Neurosurgery

USA
University of California, Davis
Legacy Health System
Multiple Sclerosis Center of California
Wayne State University
Swedish Neuroscience Center
University of Minnesota
Mayo Clinic- Scottsdale
Henry Ford Health System
Carolinas Medical Center
Sutter East Bay Medical Foundation
Washington University
MS Specialty Clinic University of New Mexico
Central Texas Neurology
Raleigh Neurology Associates, PA
University of Texas Southwestern
Center for Neurology and Spine
Worthrop University Hospital
Comprehensive Multiple Sclerosis Care Center at South Shore Neurologic Associates, P.C.
Phoenix Neurological Associates
Maxine Meisinger MS Clinic/Baylor College of Medicine
Neurology Associates Of Stony Brook
University of Kansas Medical Center
Trustees of the University of Pennsylvania
Indiana University Cancer Center
Icahn School of Medicine at Mount Sinai
University of Colorado
St Joseph's Hospital Barrow Neurology Clinics
Weill Medical College of Cornell University
Oklahoma Medical Research Foundation
Ohio Health Physicians
Ohio State University Medical Center
The Neurology Foundation, Inc.
Michigan Institute For Neurological Disorders
MidAmerica Neuroscience Institute
Neurological Associates, Inc.
MS Center of Vero Beach
University Of Miami
Neurology Clinic, P.C.
University of California San Francisco

We would also like to thank NeuroRx Research (Montreal, QC, Canada) for evaluation of MRI scans and the following members of the independent data monitoring committee for performing data analysis and safety monitoring:
Stephen C. Reingold, PhD (Chair)
Magnhild Sandberg-Wollheim, M.D., PhD (Vice Chair)
Gary R. Cutter, Ph.D.
Israel Steiner, M.D.
Scott Evans, PhD
Henry F. McFarland, M.D.
Thomas Dämer, M.D.