


ORIGINAL ARTICLE

Risk of requiring a wheelchair in primary progressive multiple sclerosis: Data from the ORATORIO trial and the MSBase registry

Helmut Butzkueven¹  | Tim Spelman² | Dana Horakova³ | Stella Hughes^{4,5} | Claudio Solaro⁶ | Guillermo Izquierdo⁷ | Eva Kubala Havrdová⁸ | Francois Grand'Maison⁹ | Alexandre Prat¹⁰ | Marc Girard¹⁰ | Raymond Hupperts¹¹ | Marco Onofri¹² | Alessandra Lugaresi^{13,14} | Bruce Taylor¹⁵ | the MSBase Study Group | Gavin Giovannoni¹⁶ | Ludwig Kappos¹⁷ | Stephen L. Hauser¹⁸ | Xavier Montalban¹⁹ | Licinio Craveiro²⁰ | Rita Freitas²⁰ | Fabian Model²⁰ | James Overell²⁰ | Erwan Muros-Le Rouzic²⁰ | Annette Sauter²⁰ | Qing Wang²⁰ | David Wormser²⁰ | Jerry S. Wolinsky²¹

¹Department of Neuroscience, Central Clinical School, Monash University, Melbourne, Victoria, Australia

²Department of Medicine and Melbourne Brain Centre, The Royal Melbourne Hospital, University of Melbourne, Melbourne, Victoria, Australia

³Department of Neurology and Center of Clinical Neuroscience, First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic

⁴Department of Neurology, Craigavon Area Hospital, Craigavon, UK

⁵Belfast Health and Social Care Trust, Belfast, UK

⁶CRRF "Mons. Luigi Novarese", Moncrivello, (VC), Italy

⁷Vithas Nisa Hospital, Seville, Spain

⁸Department of Neurology and Center of Clinical Neuroscience, General University Hospital and Charles University, Prague, Czech Republic

⁹Neuro Rive-Sud, Quebec City, Quebec, Canada

¹⁰CHUM and Université de Montréal, Montreal, Quebec, Canada

¹¹Zuyderland Ziekenhuis, Sittard, The Netherlands

¹²University G. d'Annunzio, Chieti, Italy

¹³IRCCS Istituto delle Scienze Neurologiche di Bologna, UOSI Riabilitazione Sclerosi Multipla, Bologna, Italy

¹⁴Dipartimento di Scienze Biomediche e Neuromotorie, Università di Bologna, Bologna, Italy

¹⁵Royal Hobart Hospital, Hobart, Tasmania, Australia

¹⁶Queen Mary University of London, London, UK

¹⁷Research Center for Clinical Neuroimmunology and Neuroscience and MS Center, University Hospital Basel and University of Basel, Basel, Switzerland

¹⁸University of California, San Francisco, California, USA

¹⁹Department of Neurology-Neuroimmunology, Centre d'Esclerosi Múltiple de Catalunya (Cemcat), Hospital Universitari Vall d'Hebron, Barcelona, Spain

²⁰F. Hoffmann-La Roche Ltd, Basel, Switzerland

²¹McGovern Medical School, The University of Texas Health Science Center at Houston (UTHealth), Houston, Texas, USA

Correspondence

Helmut Butzkueven, Department of Neuroscience, Central Clinical School, Monash University, The Alfred Centre, Level 6, 99 Commercial Road, Melbourne, Vic 3004, Australia.

Email: helmut.butzkueven@monash.edu

Present address

During completion of the work related to this manuscript, R.Frietas was an employee of F.Hoffman-La Roche Ltd; her current affiliation is Novartis Pharma AG

During completion of the work related to this manuscript, D.Wormser was an employee of F.Hoffman-La Roche Ltd; his current affiliation is Novartis, Basel, Switzerland

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2021 The Authors. *European Journal of Neurology* published by John Wiley & Sons Ltd on behalf of European Academy of Neurology

Funding information

This work was financially supported by F. Hoffmann-La Roche Ltd., Basel, Switzerland for the study and publication of the article.

Abstract

Background and purpose: Reaching Expanded Disability Status Scale (EDSS) ≥ 7.0 represents the requirement for a wheelchair. Here we (i) assess the effect of ocrelizumab on time to EDSS ≥ 7.0 over the ORATORIO (NCT01194570) double-blind and extended controlled periods (DBP+ECP), (ii) quantify likely long-term benefits by extrapolating results, and (iii) assess the plausibility of extrapolations using an independent real-world cohort (MSBase registry; ACTRN12605000455662).

Methods: Post hoc analyses assessing time to 24-week confirmed EDSS ≥ 7.0 in two cohorts of patients with primary progressive multiple sclerosis (baseline EDSS 3.0–6.5) were investigated in ORATORIO and MSBase.

Results: In the ORATORIO DBP+ECP, ocrelizumab reduced the risk of 24-week confirmed EDSS ≥ 7.0 (hazard ratio = 0.54, 95% confidence interval [CI]: 0.31–0.92; $p = 0.022$). Extrapolated median time to 24-week confirmed EDSS ≥ 7.0 was 12.1 and 19.2 years for placebo and ocrelizumab, respectively (7.1-year delay [95% CI: –4.3 to 18.4]). In MSBase, the median time to 24-week confirmed EDSS ≥ 7.0 was 12.4 years.

Conclusions: Compared with placebo, ocrelizumab significantly delayed time to 24-week confirmed wheelchair requirement in ORATORIO. The plausibility of the extrapolated median time to reach this milestone in the placebo group was supported by observed real-world data from MSBase. Extrapolated benefits for ocrelizumab over placebo could represent a truly meaningful delay in loss of ambulation and independence.

KEYWORDS

disease progression, ocrelizumab, primary progressive multiple sclerosis, wheelchair

INTRODUCTION

Approximately 10% to 15% of the multiple sclerosis (MS) population are classified as primary progressive MS (PPMS) [1]. PPMS is distinguished from more common relapsing forms of MS (i.e., relapsing–remitting MS and secondary progressive MS) by gradual worsening of neurological disability from disease onset [1]. Long-term disability is an important outcome for patients with MS [2], and is typically characterized using the Expanded Disability Status Scale (EDSS) [3]. Reaching EDSS ≥ 7.0 is a key clinical disability milestone, as this represents an inability to walk >5 meters, even with an aid, essentially leading to the requirement for a wheelchair. Progression to EDSS ≥ 7.0 is associated with a major reduction in patients' quality of life and a treatment cost increase [4].

Ocrelizumab is a humanized monoclonal antibody that selectively targets CD20⁺ B cells, while preserving the capacity for B-cell reconstitution and preexisting humoral immunity [5,6]. Ocrelizumab is the first CD20⁺ B-cell–selective monoclonal antibody approved for the treatment of relapsing MS and PPMS at a twice-yearly dose of 600 mg intravenously [7]. In the Phase III ORATORIO study (NCT01194570) [8] in patients with PPMS, the proportion of patients with 12-week confirmed disability progression (primary endpoint) was lower in patients receiving ocrelizumab

(32.9%) versus placebo (39.3%; hazard ratio [HR] = 0.76; 95% confidence interval [CI]: 0.59–0.98; $p = 0.03$) [8]. In the present analysis, we assessed the effect of ocrelizumab on time to EDSS ≥ 7.0 in the double-blind period (DBP) and extended controlled period (ECP) of ORATORIO, and extrapolated the potential long-term impact of ocrelizumab on time to requiring a wheelchair. We further assessed the plausibility of the extrapolations, using an independent real-world PPMS cohort from the MSBase registry [9] along with current observed data from the ongoing ORATORIO open-label extension (OLE) [10].

METHODS

ORATORIO trial design and patients

ORATORIO was a Phase III, randomized, parallel-group, double-blind, placebo-controlled trial investigating the efficacy and safety of ocrelizumab in patients with PPMS [8]. Key eligibility criteria included age 18 to 55 years, PPMS diagnosis (2005 revised McDonald criteria [11]), and an EDSS score of 3.0 to 6.5 at screening. ORATORIO consists of three treatment periods: the DBP (≥ 120 weeks), the ECP (3–9 months; the ECP provided approximately 3 additional months of blinded controlled data and

6 months of controlled follow-up, during which patients were gradually unblinded and entered the OLE period), and the currently ongoing OLE period. All patients completing DBP and ECP were eligible to enter the OLE period. In the ORATORIO DBP+ECP, which lasted approximately 3 years, post hoc analysis was carried out to assess the time to onset of 24-week confirmed EDSS ≥ 7.0 . Consistent with the original analyses [8], patients with an initial disability progression who discontinued treatment early and did not have a subsequent EDSS measurement were imputed as having a 24-week confirmed disability progression event. To further characterize the potential long-term impact of ocrelizumab treatment on the time to 24-week confirmed EDSS ≥ 7.0 , a Weibull regression analysis [12] was used to extrapolate observed data from the ORATORIO DBP+ECP into the future, estimating the time at which 50% of patients were expected to have reached EDSS ≥ 7.0 . The distribution of survival times was approximated by the Weibull distribution, which allows for monotonically increasing or decreasing hazard rates over time [12]. We performed sensitivity analyses using various parametric functions to estimate the delay in median time to requiring a wheelchair in patients treated with ocrelizumab versus placebo; sensitivity analyses were also performed after removal of imputed events. In addition, we analyzed the time to onset of 24-week confirmed EDSS ≥ 7.0 using data from the OLE period of ORATORIO in patients initially randomized to ocrelizumab (6 years total follow-up [312 weeks]) [10] to provide support for the extrapolation of the ORATORIO DBP+ECP ocrelizumab arm.

The ORATORIO trial protocol (NCT01412333)[8] was approved by the relevant institutional review boards/ethics committees. All patients provided written informed consent. The trial was conducted in accordance the Declaration of Helsinki.

MSBase registry

The MSBase registry (Australian New Zealand Clinical Trials Registry ID: ACTRN12605000455662) is a longitudinal, prospective, international, web-based database collecting standardized clinical outcomes in patients with MS [9]. MSBase was approved by the Melbourne Health Human Research Ethics Committee and by local ethics committees in all participating centers (or exemptions granted, according to local protocols). Written informed consent was provided by patients as required.

Using MSBase, a real-world cohort was created including adults (aged ≥ 18 years) with PPMS (2005 revised McDonald criteria [11]), a baseline EDSS score of 3.0 to 6.5 (same as ORATORIO), >2 EDSS assessments, and no disease-modifying therapy (DMT) use prior to diagnosis. Kaplan-Meier analyses were used to estimate time to 24-week confirmed EDSS ≥ 7.0 , similar to ORATORIO. Baseline EDSS was the first recorded EDSS in the PPMS untreated state. No imputation was done when EDSS measurements were not available after the initial progression (due to loss to follow-up, death, or analysis data cutoff). Findings from the MSBase cohort were then

superimposed onto the Weibull analysis extrapolation from the ORATORIO placebo arm.

Trial registration

The ORATORIO trial was registered in the ClinicalTrials.gov registry (NCT01194570). MSBase registry was registered in the Australian New Zealand Clinical Trials Registry (ACTRN12605000455662).

RESULTS

Patient disposition, demographics, and characteristics

Baseline characteristics from the ORATORIO DBP ($n = 732$) have been reported previously [8] and are summarized in Table 1. Baseline characteristics were consistent between groups, with a median EDSS of 4.5. All patients ($n = 775$) in MSBase were treatment-naïve at baseline and remained untreated for most of the study. Baseline characteristics were similar to ORATORIO DBP, with a median EDSS of 4.5. Patient disposition is shown in Figure 1. In the ocrelizumab arm, 98.4% of patients who completed the DBP+ECP of ORATORIO transitioned into the OLE phase ($n/N = 367/373$; this represents 75.2% of those initially randomized ($n/N = 367/488$)).

Time to 24-week confirmed EDSS ≥ 7.0 during the DBP+ECP

In the ORATORIO DBP+ECP, ocrelizumab reduced the risk of 24-week confirmed EDSS ≥ 7.0 versus placebo by 46% (HR = 0.54, 95% CI: 0.31–0.92; $p = 0.02$; Figure 2a).

Extrapolation of time to 24-week confirmed EDSS ≥ 7.0 from the DBP+ECP

In the ORATORIO DBP+ECP, the extrapolated median time to 24-week confirmed EDSS ≥ 7.0 was 12.1 years for placebo and 19.2 years for ocrelizumab (Figure 2b). Similar to the placebo arm, the observed median time to 24-week confirmed EDSS ≥ 7.0 in real-world patients with PPMS from MSBase was 12.4 years (Figure 3). Extending the observation period for time to 24-week confirmed EDSS ≥ 7.0 in the ocrelizumab arm to include the OLE period of ORATORIO supports the extrapolation from the ORATORIO DBP+ECP for the ocrelizumab group (Figure 3). By comparing the extrapolated median time to 24-week confirmed EDSS ≥ 7.0 in the ORATORIO DBP+ECP for the placebo and ocrelizumab arms, ocrelizumab is predicted to delay 24-week confirmed EDSS ≥ 7.0 by 7.1 years (95% CI: -4.3 to 18.4) versus placebo. Sensitivity analyses performed without imputation indicated a similar delay of 7.5 years (data not shown).

Parameter	ORATORIO ITT		
	OCR 600 mg, n = 488	Placebo, n = 244	MSBase PPMS real-world cohort, n = 775 ^a
Age, mean (SD), years	44.7 (7.9)	44.4 (8.3)	43.4 (10.1)
Female, n (%)	237 (48.6)	124 (50.8)	437 (56.4)
Time since MS symptom onset, median (IQR), years	6.0 (3.8–8.7)	5.5 (3.3–8.3)	5.8 (3.0–10.8)
Time since MS diagnosis, median (IQR), years	1.6 (0.5–4.1)	1.3 (0.5–3.9)	0.4 (0–3.9)
Score on first eligible EDSS, median (IQR)	4.5 (3.5–6.0) ^b	4.5 (3.5–6.0) ^b	4.5 (3.5–6.0) ^c
Distribution of baseline EDSS scores, n (%)			
2.5	1 (0.2)	1 (0.4)	0
3.0	41 (8.4)	19 (7.8)	111 (14.3)
3.5	88 (18.0)	46 (18.9)	84 (10.8)
4.0	88 (18.0)	43 (17.6)	149 (19.2)
4.5	44 (9.0)	25 (10.2)	63 (8.1)
5.0	26 (5.3)	16 (6.6)	62 (8.0)
5.5	60 (12.3)	13 (5.3)	48 (6.2)
6.0	76 (15.6)	56 (23.0)	141 (18.2)
6.5	62 (12.7)	25 (10.2)	117 (15.1)
7.0	1 (0.2)	0	0
DMT exposure, n (%)			
Ever exposed in 2 years prebaseline	55 (11.3)	30 (12.3)	0 (0)
Never exposed in 2 years prebaseline	433 (88.7)	214 (87.7)	775 (100)
Time on DMT, mean (SD), years ^d	N/A	N/A	0.19 (1.04)
Time between consecutive EDSS visits, months			
Mean (SD)	3.0 ^e (N/A)	3.0 ^e (N/A)	11.0 (23.9)
Median (IQR)	N/A	N/A	6.8 (3.9–12.2)

Abbreviations: DMT, disease-modifying treatment; EDSS, Expanded Disability Status Scale; IQR, interquartile range; ITT, intent to treat; MS, multiple sclerosis; N/A, not applicable; OCR, ocrelizumab; PPMS, primary progressive multiple sclerosis.

^aBased on the MSBase registry definition of PPMS. Patient characteristics described at first recorded EDSS visit after PPMS diagnosis.

^bThe baseline EDSS value is the average score of the EDSS assessment at screening and Day 1 visit up to and including the date of randomization. If one of the values is missing, the non-missing values will be used as baseline.

^cBaseline EDSS was the first recorded EDSS in the PPMS untreated state.

^dBetween first and last recorded EDSS visits.

^eAs per schedule of assessments.

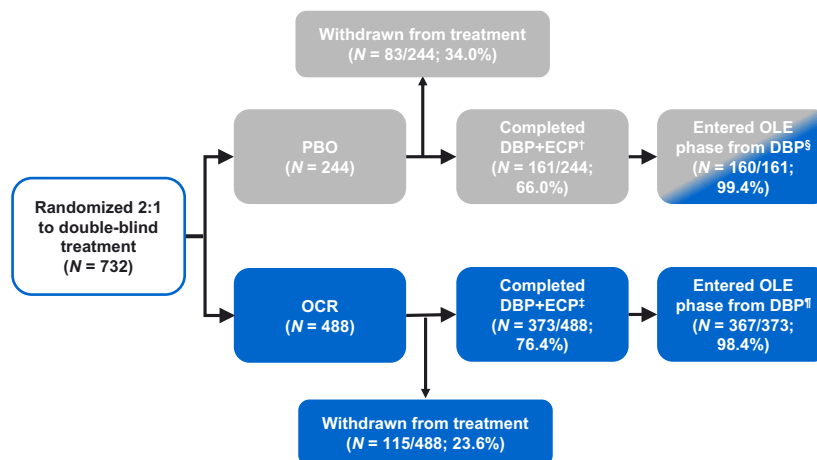
TABLE 1 Baseline characteristics of the ORATORIO ITT population and the MSBase natural history cohort

DISCUSSION

During the DBP and ECP of the ORATORIO trial, ocrelizumab significantly reduced the risk of requiring a wheelchair by 46% versus placebo. Extrapolated data from the DBP+ECP suggest ocrelizumab treatment delays the median time to requiring a wheelchair by 7.1 years versus placebo, indicating a meaningful long-term

benefit for patients with PPMS. Real-world data from the MSBase registry show a similar disability trajectory to that extrapolated from placebo-treated patients in ORATORIO, whereas initial data from the ocrelizumab arm of the ORATORIO OLE period show a similar trajectory to the extrapolation from ocrelizumab-treated patients in the DBP+ECP, supporting the plausibility of these extrapolations. Time to requiring a wheelchair is a well-defined outcome that

FIGURE 1 Patient disposition in the ORATORIO study period. [†]Forty-seven patients (19.3%) entered safety follow-up from DBP. [‡]Seventy-five patients (15.4%) entered safety follow-up from DBP. [§]One patient (0.6%) completed the DBP+ECP but did not enter the OLE period. [¶]Six patients (1.6%) completed the DBP+ECP but did not enter the OLE period. DBP, double-blind period; ECP, extended controlled period; OCR, ocrelizumab; OLE, open-label extension; PBO, placebo



allows comparisons to be made across studies and across cohorts. Furthermore, it is a clinically meaningful outcome for patients; high levels of disability are associated with a number of physical, emotional, and financial challenges, and an overall reduced quality of life [4,13,14]. Delaying time to EDSS ≥ 7.0 may alleviate some of these burdens. However, it is important to note that due to the restricted eligibility criteria for ORATORIO, patients were generally younger, had a shorter disease duration, and had lower levels of disability than a typical population; therefore, it may be difficult to generalize these results to a broad real-world PPMS population.

One study limitation is that the extrapolations from the ORATORIO DBP+ECP are based on relatively short observed periods, limiting the precision of the long-term extrapolation. Furthermore, the extrapolations are based on the assumption that the risk of disability progression is linear over time, which may not be the case; the disease course of MS is unpredictable and variable across individuals. However, as the study is based specifically on patients with PPMS, it is likely that the disease progression, through the accumulation of clinical deficit and disability, occurs steadily over time, characteristic of a linear model.

An additional limitation is that the data include the ECP of ORATORIO, in which gradual unblinding occurred; therefore, there may have been some bias introduced, for example informative censoring, causing results to be confounded. We cannot exclude the possibility that those patients who discontinued ocrelizumab had a more severe disease course, and thus, the median time to reach EDSS ≥ 7.0 in ocrelizumab-treated patients may be overestimated. However, 98.4% of patients in the ocrelizumab arm who completed the DBP+ECP of ORATORIO transitioned into the OLE period. This represents 75.2% of those initially randomized (Figure 1), and the low attrition rates in patients who completed the DBP reduces the possibility of selection bias.

Another limitation of this study is that the ORATORIO and MSBase populations could not be directly matched for baseline covariate differences. The MSBase cohort was instead restricted to patients with the same EDSS eligibility criteria as ORATORIO. As a result, the observed disease progression trajectories to EDSS ≥ 7.0 in MSBase may be affected by potential imbalances in some

baseline characteristics between the real-life MSBase cohort and the ORATORIO trial population. However, the populations were comparable for demographics, time since MS symptom onset, and median baseline EDSS scores. The distribution of EDSS 6.0 to 6.5 at baseline was similar between all groups (28.3% in ocrelizumab, 33.2% in placebo, 33.3% in MSBase), further suggesting that the cohorts had similar disability levels at baseline. Additionally, as there are currently no other treatments approved for PPMS, the comparison between the placebo arm and the untreated real-world MSBase cohort remains relevant. Some patients in the MSBase cohort did not remain DMT-free after the baseline EDSS assessment. However, off-label DMT usage remained low, with only 49/775 patients (6.3%) initiating DMTs and a mean of 0.19 years of DMT use between the first and last recorded EDSS visits. Additionally, off-label DMT use was not found to be effective in MSBase [15].

Ocrelizumab significantly delayed the time to requiring a wheelchair in the DBP and ECP of ORATORIO, and the extrapolated median time to reach this disability milestone for the placebo group was similar to that observed in a real-world MSBase cohort. Overall, the effect of ocrelizumab in significantly delaying the time to requiring a wheelchair likely translates to a meaningful long-term benefit for patients with PPMS.

ACKNOWLEDGMENTS

Eleanor Foy (Articulate Science, UK) drafted the manuscript based on input from the authors, funded by F. Hoffmann–La Roche Ltd. The authors had full editorial control of the manuscript and provided final approval. The authors thank all patients, their families, and the investigators who participated in the ORATORIO trial and MSBase registry.

CONFLICT OF INTERESTS

H.B.'s institution (Monash University) has received funding from Biogen, F. Hoffmann–La Roche Ltd., Merck, and Novartis; has carried out contracted research for Novartis, Merck, F. Hoffmann–La Roche Ltd., and Biogen; has taken part in speakers' bureaus for Biogen, Genzyme, F. Hoffmann–La Roche Ltd., and Merck; and has received personal grants from Oxford PharmaGenesis and Biogen (prior to

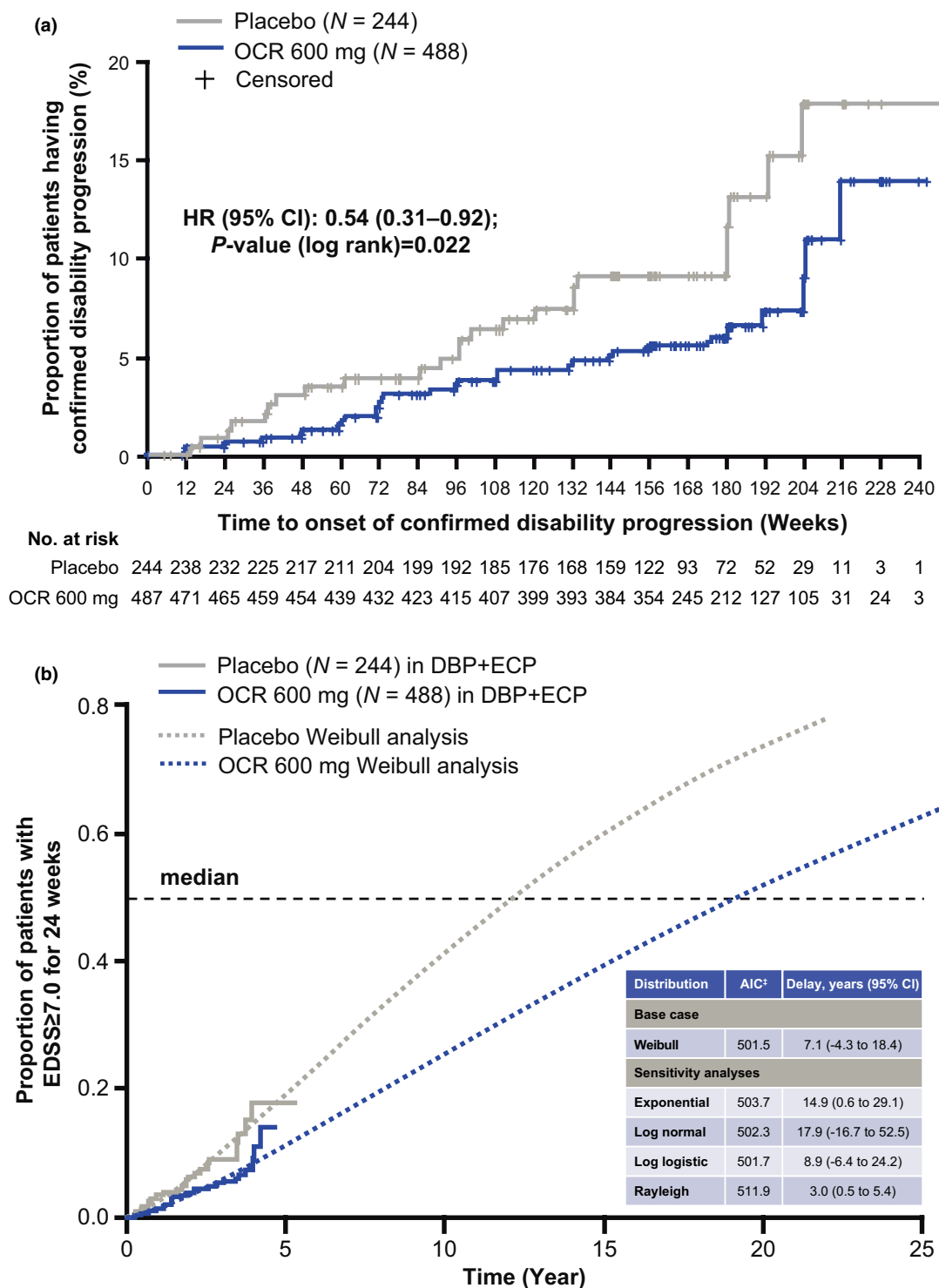


FIGURE 2 (a) Time to 24-week confirmed EDSS ≥ 7.0 during the DBP+ECP.[†] (b) Time to 24-week confirmed EDSS ≥ 7.0 extrapolation. Hazard ratios were estimated by Cox regression, stratified by geographical region (United States vs. ROW) and age (≤ 45 vs. >45 years). Patients with missing baseline EDSS ($n = 1$) were excluded from the analysis. Patients with a post-baseline EDSS ≥ 7.0 that is sustained for at least 24 weeks are considered as having an event. Patients with EDSS ≥ 7.0 at the time of treatment discontinuation with no further EDSS score are imputed as having an event. Parameters of the Weibull distribution were estimated based on the observed ORATORIO-DBP+ECP data, and these parameters applied to the extrapolated curve to enable estimation of the survival function beyond the observation period. [†]Data cutoff for DBP+ECP in ORATORIO: February 2017. [‡]The preferred model is the one with the minimum AIC value. AIC, Akaike information criterion; CI, confidence interval; DBP, double-blind period; ECP, extended controlled period; EDSS, Expanded Disability Status Scale; HR, hazard ratio; OCR, ocrelizumab; ROW, rest of world

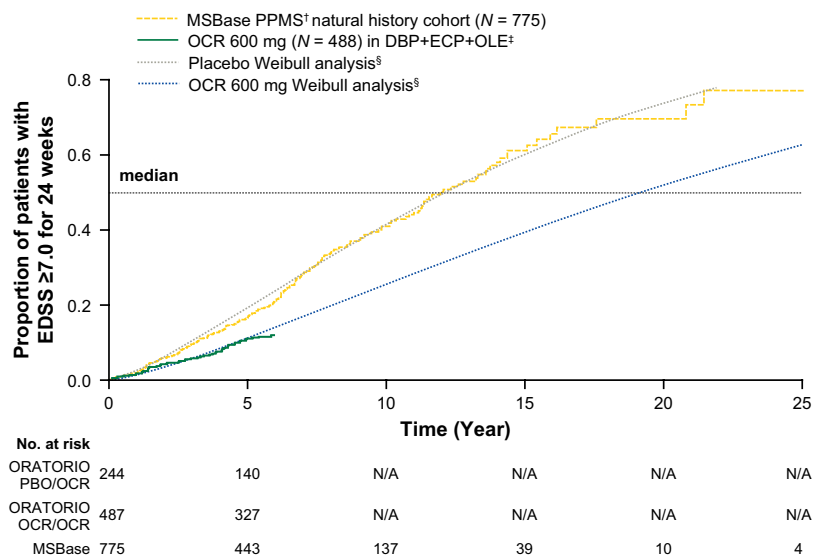


FIGURE 3 Time to 24-week confirmed EDSS ≥ 7.0 in MSBase[†] and the ORATORIO DBP+ECP+OLE,[‡] superimposed onto extrapolated results. Patients with a post-baseline EDSS ≥ 7.0 , which is sustained for at least 24 weeks, are considered as having an event. Patients with EDSS ≥ 7.0 at the time of treatment discontinuation with no further EDSS score are imputed as having an event in ORATORIO but are not imputed in MSBase. [†]Patients with PPMS with baseline EDSS 3.0–6.5 (N = 775). [‡]Data presented up to 312 weeks; OLE data cutoff from January 2019. In ORATORIO, patients with missing baseline EDSS (n = 1) were excluded from the analysis. [§]Results extrapolated from the DBP+ECP, data cutoff from February 2017.

DBP, double-blind period; ECP, extended controlled period; EDSS, Expanded Disability Status Scale; N/A, not applicable; OCR, ocrelizumab; OLE, open-label extension; PBO, placebo; PPMS, primary progressive multiple sclerosis

June 30, 2018). **T.S.** has received compensation for serving on steering committees and advisory boards from Biogen. **D.H.** received compensation for travel, speaker honoraria, and consultant fees from Biogen, Novartis, Merck, Bayer, Sanofi, Roche, and Teva; as well as support for research activities from Biogen. She was also supported by the Czech Ministry of Education project Progress Q27/LF1. **S.H.** has received previous travel/conference support and speaking honoraria from Biogen, Sanofi-Genzyme, Merck, Novartis, and Roche. **C.S.** has received honoraria/research support from Biogen, Merck Serono, Novartis, Roche, Almirall, Amgen, and Teva; and has been supported by the Italian MS Foundation. **G.I.** has received personal fees from Bayer, Biogen-IDec, Novartis, Sanofi, Merck Serono, Roche, Actelion, Celgene, and Teva. **E.K.H.** has received honoraria/research support from Biogen, F. Hoffmann-La Roche Ltd., Merck Serono, Novartis, Sanofi Genzyme, and Teva; has served on advisory boards for Actelion, Biogen, Celgene, Merck Serono, Novartis, and Sanofi Genzyme; and has been supported by the Czech Ministry of Education project Progress Q27/LF1. **F.G.** received honoraria or research funding from Biogen, Genzyme, Novartis, Teva Neurosciences, Mitsubishi, and ONO Pharmaceuticals. **A.P.** does not declare any competing interests. **M.G.** received consulting fees from Teva Canada Innovation, Biogen, Novartis, and Genzyme Sanofi; lecture payments from Teva Canada Innovation, Novartis, and EMD; and has also received a research grant from Canadian Institutes of Health Research. **R.H.** received research grants from Merck, Biogen, and Sanofi; and received honoraria from Merck, Roche, and Sanofi

for invited speaker's activities. **M.O.** does not declare any competing interests. **A.L.** has received personal compensation for consulting, serving on a scientific advisory board, speaking or other activities from Biogen, Merck Serono, Mylan, Novartis, Roche, Sanofi/Genzyme, and Teva. Her institutions have received research grants from Novartis (in the last 4 years). **B.T.** received funding for travel and speaker honoraria from Bayer Schering Pharma, CSL Australia, Biogen, and Novartis; and has served on advisory boards for Biogen, Novartis, Roche, and CSL Australia. **G.G.** received personal compensation in the past for serving as a consultant for AbbVie, Actelion, Atara Bio, Biogen, Celgene, Sanofi Genzyme, Genentech, GlaxoSmithKline, Merck Serono, Novartis, Roche, and Teva; has received personal compensation from Elsevier for serving as an editor on *Multiple Sclerosis and Related Disorders*; and has received financial support for research activities from Biogen, Roche, Merck, Merck Serono, Novartis, Sanofi Genzyme, and Takeda. **L.K.'s** institution (University Hospital Basel) received in the last 3 years and used exclusively for research support at the department: steering committee, advisory board, and consultancy fees from Actelion, Alkermes, Almirall, Bayer, Biogen, Celgene/Receptos, df-mp, Excemed, GeNeuro SA, Genzyme, Japan Tobacco, Merck, Minoryx, Mitsubishi Pharma, Novartis, F. Hoffmann-La Roche Ltd., Sanofi-Aventis, Santhera, Teva, and Vianex; and license fees for Neurostatus-UHB products; the Research of the MS Center in Basel has been supported by grants from Bayer, Biogen, Novartis, the Swiss MS Society, the Swiss National Research Foundation, Innoswiss, the

European Union, and Roche Research Foundations. **S.L.H.** serves on the board of trustees for Neurona and on scientific advisory boards for Alektor, Annexon, Bionure, and Molecular Stethoscope; and has received travel reimbursement and writing assistance from F. Hoffmann-La Roche Ltd. and Novartis for CD20-related meetings and presentations. **X.M.** has received speaking honoraria and travel expenses 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, Alexion, Bayer, Biogen, Celgene, EMD Serono, Genzyme, Immunic, Medday, Merck, Mylan, Nervgen, Novartis, Roche, Sanofi-Genzyme, Teva Pharmaceutical, TG Therapeutics, Excemed, MSIF, and NMSS. **L.C.** is an employee of F. Hoffmann-La Roche Ltd. **R.F.** is an employee of F. Hoffmann-La Roche Ltd. **F.M.** is an employee and shareholder of F. Hoffmann-La Roche Ltd. **J.O.** is currently an employee and shareholder of F. Hoffmann-La Roche Ltd. During his previous employment he received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Teva, Biogen, Celgene, EMD Serono, MedDay, Novartis, Roche, Sanofi Genzyme, WebMD Global, and Allergan. His research and department were supported by grants from Sanofi Genzyme, Biogen, Novartis, and Roche. **E.M.-L.R.** is an employee and shareholder of F. Hoffmann-La Roche Ltd. **A.S.** is an employee and shareholder of F. Hoffmann-La Roche Ltd. **Q.W.** is an employee of F. Hoffmann-La Roche Ltd. **D.W.** is an employee of Novartis and shareholder of F. Hoffmann-La Roche Ltd. and Novartis. **J.S.W.** has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Acorda Therapeutics, Alkermes, Brainstorm Cell Therapeutics, EMD Serono, GeNeuro, GW Pharma Ltd., MedDay Pharmaceuticals, NervGen Pharma Corp, Novartis, Roche/Genentech, and Sanofi Genzyme; royalties are received for out-licensed monoclonal antibodies through UTherapeutics from Millipore Corporation.

AUTHOR CONTRIBUTIONS

Helmut Butzkueven: Conceptualization (lead); investigation (equal); methodology (lead); validation (lead); writing-original draft (equal); writing-review & editing (equal). **Tim Spelman:** Conceptualization (equal); formal analysis (lead); methodology (equal); validation (equal); writing-original draft (equal); writing-review & editing (equal). **Dana Horakova:** Conceptualization (supporting); investigation (equal); methodology (supporting); validation (equal); writing-review & editing (equal). **Stella Hughes:** Conceptualization (supporting); investigation (equal); methodology (supporting); validation (equal); writing-review & editing (equal). **Claudio Solaro:** Conceptualization (supporting); investigation (equal); methodology (supporting); validation (equal); writing-review & editing (equal). **Guillermo Izquierdo:** Conceptualization (supporting); investigation (equal); methodology (supporting); validation (equal); writing-review & editing (equal). **Eva Kubala Havrdova:** Conceptualization (supporting); investigation (equal); methodology (supporting); validation (equal); writing-review & editing (equal). **Francois Grand'Maison:** Conceptualization (supporting); investigation (equal); methodology (supporting); validation (equal); writing-review

& editing (equal). **Alexandre Prat:** Conceptualization (supporting); investigation (equal); methodology (supporting); validation (equal); writing-review & editing (equal). **Marc Girard:** Conceptualization (supporting); investigation (equal); methodology (supporting); validation (equal); writing-review & editing (equal). **Raymond Hupperts:** Conceptualization (supporting); investigation (equal); methodology (supporting); validation (equal); writing-review & editing (equal). **Marco Onofri:** Conceptualization (supporting); investigation (equal); methodology (supporting); validation (equal); writing-review & editing (equal). **Alessandra Lugaresi:** Conceptualization (supporting); investigation (equal); methodology (supporting); validation (equal); writing-review & editing (equal). **Bruce Taylor:** Conceptualization (supporting); investigation (equal); methodology (supporting); validation (equal); writing-review & editing (equal). **Gavin Giovannoni:** Conceptualization (supporting); investigation (equal); methodology (supporting); validation (equal); writing-review & editing (equal). **Ludwig Kappos:** Conceptualization (supporting); investigation (equal); methodology (supporting); validation (equal); writing-review & editing (equal). **Stephen L. Hauser:** Conceptualization (supporting); investigation (equal); methodology (supporting); validation (equal); writing-review & editing (equal). **Xavier Montalban:** Conceptualization (supporting); investigation (equal); methodology (supporting); validation (equal); writing-review & editing (equal). **Licinio Craveiro:** Conceptualization (supporting); methodology (equal); validation (equal); writing-original draft (equal); writing-review & editing (equal). **Rita Freitas:** Conceptualization (lead); methodology (lead); validation (equal); writing-review & editing (equal). **Fabian Model:** Conceptualization (lead); formal analysis (equal); methodology (lead); validation (lead); writing-original draft (lead); writing-review & editing (lead). **James Overell:** Conceptualization (supporting); methodology (equal); validation (equal); writing-original draft (equal); writing-review & editing (equal). **Erwan Muros-Le Rouzic:** Conceptualization (supporting); methodology (equal); validation (equal); writing-original draft (lead); writing-review & editing (lead). **Annette Sauter:** Conceptualization (equal); formal analysis (equal); methodology (equal); validation (equal); writing-original draft (equal); writing-review & editing (equal). **Qing Wang:** Conceptualization (equal); formal analysis (lead); methodology (lead); validation (lead); writing-original draft (lead); writing-review & editing (lead). **David Wormser:** Conceptualization (lead); methodology (lead); validation (equal); writing-review & editing (equal). **Jerry S. Wolinsky:** Conceptualization (lead); investigation (equal); methodology (equal); validation (equal); writing-review & editing (equal).

STATISTICAL ANALYSIS

ORATORIO statistical analyses were conducted by Qing Wang (F. Hoffmann-La Roche Ltd., Basel, Switzerland); MSBase statistical analyses were conducted by Tim Spelman (Department of Medicine and Melbourne Brain Centre, The Royal Melbourne Hospital, University of Melbourne, Melbourne, Australia).

DATA AVAILABILITY STATEMENT

For ORATORIO, qualified researchers can request access to individual patient-level data through the clinical study data request

platform (<https://vivli.org/>). Further details on Roche's criteria for eligible studies are available here: <https://vivli.org/members/ourmembers/>. For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here: https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm. For MSBase, data are available from individual investigators upon request to the corresponding author.

ORCID

Helmut Butzkueven  <https://orcid.org/0000-0003-3940-8727>

REFERENCES

1. Miller DH, Leary SM. Primary-progressive multiple sclerosis. *Lancet Neurol.* 2007;6(10):903-912.
2. Wilson LS, Loucks A, Gipson G, et al. Patient preferences for attributes of multiple sclerosis disease-modifying therapies: development and results of a ratings-based conjoint analysis. *Int J MS Care.* 2015;17(2):74-82.
3. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology.* 1983;33(11):1444-1452.
4. Kobelt G, Thompson A, Berg J, Gannedahl M, Eriksson J. New insights into the burden and costs of multiple sclerosis in Europe. *Mult Scler.* 2017;23(8):1123-1136.
5. DiLillo DJ, Hamaguchi Y, Ueda Y, et al. Maintenance of long-lived plasma cells and serological memory despite mature and memory B cell depletion during CD20 immunotherapy in mice. *J Immunol.* 2008;180(1):361-371.
6. Klein C, Lammens A, Schäfer W, et al. Epitope interactions of monoclonal antibodies targeting CD20 and their relationship to functional properties. *MAbs.* 2013;5(1):22-33.
7. Genentech. Ocrevus (Ocrelizumab) [Full Prescribing Information]. https://www.gene.com/download/pdf/ocrevus_prescribing.pdf. Accessed January 20, 2020.
8. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. *N Engl J Med.* 2017;376(3):209-220.
9. Butzkueven H, Chapman J, Cristiano E, et al. MSBase: an international, online registry and platform for collaborative outcomes research in multiple sclerosis. *Mult Scler.* 2006;12(6):769-774.
10. Wolinsky JS, Arnold DL, Brochet B, et al. Long-term follow-up from the ORATORIO trial of ocrelizumab for primary progressive multiple sclerosis: a post-hoc analysis from the ongoing open-label extension of the randomised, placebo-controlled, phase 3 trial. *Lancet Neurol.* 2020;19:998-1009.
11. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". *Ann Neurol.* 2005;58(6):840-846.
12. Carroll KJ. On the use and utility of the Weibull model in the analysis of survival data. *Control Clin Trials.* 2003;24(6):682-701.
13. Sutcliffe MH. Contribution of impaired mobility to patient burden in multiple sclerosis. *Curr Med Res Opin.* 2010;26(1):109-119.
14. Jones KH, Jones PA, Middleton RM, et al. Physical disability, anxiety and depression in people with MS: an internet-based survey via the UK MS register. *PLoS ONE.* 2014;9(8):e104604.
15. Lorscheider J, Kuhle J, Izquierdo G, et al. Anti-inflammatory disease-modifying treatment and disability progression in primary progressive multiple sclerosis: a cohort study. *Eur J Neurol.* 2019;26(2):363-370.

How to cite this article: Butzkueven H, Spelman T, Horakova D, et al. Risk of requiring a wheelchair in primary progressive multiple sclerosis: Data from the ORATORIO trial and the MSBase registry. *Eur J Neurol.* 2021;00:1-9. <https://doi.org/10.1111/ene.14824>