Exposure–Response Analyses of Ocrelizumab in Patients With Multiple Sclerosis

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CONCLUSIONS

- A greater depletion of circulating B cells was associated with higher exposure in patients with RMS and PPMS
- Clinical (ARR) and MRI outcomes were independent of exposure (potential ceiling effect)
- Higher ocrelizumab exposure was associated with a greater risk reduction in CDP (RMS and PPMS)
- The greater risk reduction in CDP observed with higher ocrelizumab exposure in patients with RMS or PPMS suggests that higher ocrelizumab exposure (and greater B-cell depletion) is important for control of disability progression
- These analyses are limited by confounding factors such as weight, region and sex on exposure; multivariate analyses will be reported in manuscript form (under preparation)

INTRODUCTION

- Ocrelizumab (OCR) is a CD20$^+$ B-cell–selective monoclonal antibody approved for treatment of relapsing multiple sclerosis (RMS) and primary progressive MS (PPMS)
- The efficacy and safety of OCR in patients with relapsing-remitting MS (RRMS),[1] RMS (OPERA I and OPERA II)[2] or PPMS (ORATORIO)[3] have been reported previously
- OCR population pharmacokinetics (popPK) fit a two-compartment model with time-dependent clearance and body weight as the main covariate[4]

OBJECTIVES

- The objectives of this presentation are to: **1.)** explore the relationship between popPK-based ocrelizumab exposure and circulating B-cell levels; **2.)** describe the population exposure–efficacy/safety relationships of OCR in Phase III studies in patients with MS; **3.)** investigate the correlation between circulating B-cell levels and disability progression in patients with MS

METHODS

Clinical Studies

- The methodologies of the Phase II study in patients with RRMS[1] and the Phase III studies in patients with RMS[2] or PPMS[3] have been reported previously
  - Data cut: February 2018

Population Pharmacokinetic Modelling

- Exposure quartiles (Q) are derived from the mean OCR concentration of individual patients across the treatment period from the popPK model[4]

Clinical Outcomes

- Exposure–response analyses are based on Phase III RMS[2] or PPMS[3] study endpoints:
  - Annualised relapse rate (ARR; RMS only); 24-week confirmed disability progression (CDP); MRI outcomes; safety
  - CDP defined as an increase from the baseline Expanded Disability Status Scale score of at least 1.0 point (or 0.5 points if the baseline score was >5.5)

RESULTS

Baseline Demographic Characteristics

- Predictable trends in baseline demographics correlating with exposure on a mg/kg basis (e.g. age, sex and body mass index [BMI]) were observed across OCR exposure-stratified quartiles in patients with RMS (**Table 1**) or PPMS (**Table 2**)
- There was a trend for a lower number of T1 gadolinium-enhancing lesions (RMS and PPMS) and T2 lesions (RMS only) in lower exposure quartiles

B-Cell Depletion

- The proportion of patients with peripheral B-cell levels <5 cells/µL correlated with higher OCR exposure in patients with RMS or PPMS (**Figure 1**)

MRI Outcomes

- OCR reduced T1 gadolinium-enhancing (**Figure 2**) and new/enlarging T2 MRI lesion counts (**QR Figure 3**) to nearly undetectable levels across exposure quartiles

Annualised Relapse Rate (RMS only)

- OCR reduced ARR to low levels (0.13–0.18) across exposure quartiles (**QR Figure 4**)

Disability Progression

- The effect of OCR on CDP was exposure dependent (**Figure 5**)
  - Sex, age and body weight/BMI were the main confounders of these analyses
- An exposure effect trend was observed in CDP stratified by BMI (**Figure 6**)
- Lower median peripheral B-cell levels in patients with RMS were associated with lower rates of CDP; no association in patients with PPMS was demonstrated (**Figure 7**)

Safety

- Safety parameters were similar across exposure quartiles (**QR Figure 8**)

Please scan here for ARR, T2 lesion and safety figures

Table 1. Baseline demographics and disease characteristics (RMS)

Parameter	Quartile 1 Min–15.4 µg/mL (N=194)	Quartile 2 15.4–18.7 µg/mL (N=197)	Quartile 3 18.7–22.2 µg/mL (N=196)	Quartile 4 22.2–Max µg/mL (N=197)
Age, mean (SD), years	38.2 (8.6)	37.8 (9.2)	36.6 (9.7)	36.4 (9.3)
Female, n (%)	109 (55.6)	107 (54.3)	132 (67.3)	163 (82.7)
Weight, median (range), kg	89.1 (48.9–170.0)	78.8 (48.9–123.0)	67.0 (46.0–108.0)	60.0 (38.0–96.6)
BMI, median (range), kg/m^2	29.4 (17.3–61.7)	26.3 (17.9–43.8)	23.4 (17.2–37.5)	21.8 (15.2–38.2)
Region, n (%)				
USA	64 (32.7)	49 (24.9)	48 (24.5)	37 (18.8)
RoW	132 (67.3)	148 (75.1)	148 (75.5)	160 (81.2)
T1 gadolinium-enhancing lesions present, n (%)	72 (37.1)	73 (37.4)	86 (44.1)	86 (44.6)
Non-enhancing T1 lesion volume, mean (SD), cm^3	3.78 (7.16)	2.86 (5.20)	3.80 (6.18)	3.59 (5.71)
T2 lesions, mean (SD), n	45.02 (37.25)	48.76 (37.13)	53.48 (40.52)	53.65 (40.06)
T2 lesion volume, mean (SD), cm^3	10.45 (14.30)	9.31 (12.72)	12.07 (14.94)	11.65 (14.81)

Table 2. Baseline demographics and disease characteristics (PPMS)

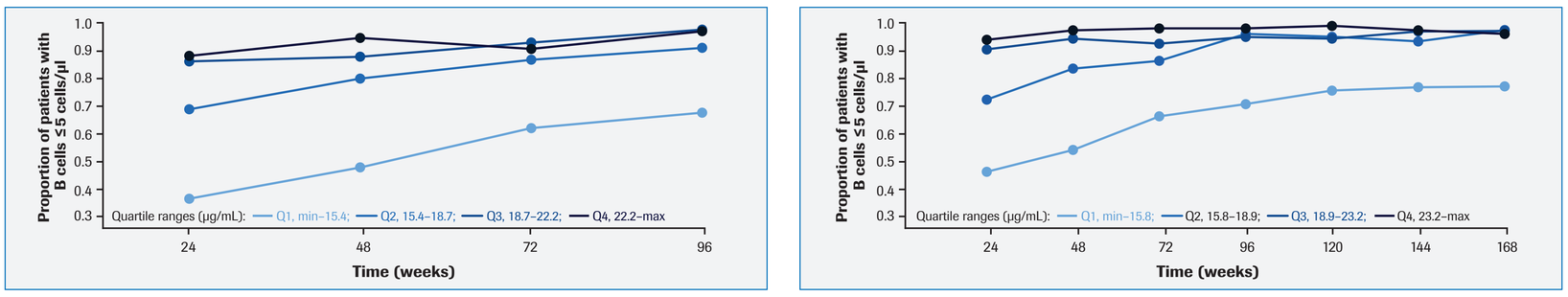
Parameter	Quartile 1 Min–15.8 µg/mL (N=120)	Quartile 2 15.8–18.9 µg/mL (N=121)	Quartile 3 18.9–23.2 µg/mL (N=120)	Quartile 4 23.2–Max µg/mL (N=121)
Age, mean (SD), years	45.3 (7.5)	44.2 (7.7)	45.3 (7.4)	44.1 (8.8)
Female, n (%)	32 (26.7)	58 (47.9)	57 (47.5)	89 (73.6)
Weight, median (range), kg	84.3 (46.0–135.9)	74.4 (45.8–125.0)	68.2 (45.9–115.5)	56.3 (40.2–93.5)
BMI, median (range), kg/m^2	27.6 (17.0–45.6)	25.2 (16.7–46.4)	23.6 (15.6–46.2)	21.3 (15.2–30.4)
Region, n (%)				
USA	24 (20.0)	16 (13.2)	16 (13.3)	9 (7.4)
RoW	96 (80.0)	105 (86.8)	104 (86.7)	112 (92.6)
T1 gadolinium-enhancing lesions present, n (%)	30 (25.4)	31 (25.6)	33 (27.7)	38 (31.7)
Non-enhancing T1 lesion volume, mean (SD), cm^3	6.19 (10.16)	4.90 (7.17)	5.23 (7.96)	4.40 (5.67)
T2 lesions, mean (SD), n	44.36 (35.19)	52.08 (41.23)	46.53 (39.06)	51.62 (37.12)
T2 lesion volume, mean (SD), cm^3	14.48 (19.43)	12.40 (14.63)	12.34 (14.12)	11.63 (11.59)

Exposure quartiles are based on predicted individual patient mean OCR concentrations (ratio of AUC to the time of the last dose plus 24 weeks and the time from baseline until the last dose plus 24 weeks) across the treatment period. The mean OCR concentration (in patients receiving all planned doses) corresponds to the whole treatment period (RMS, 96 weeks; PPMS, duration varied due to the event-driven study design).
AUC, area under the exposure curve; BMI, body mass index; RoW, Rest of World.

Analyses in patients with RMS

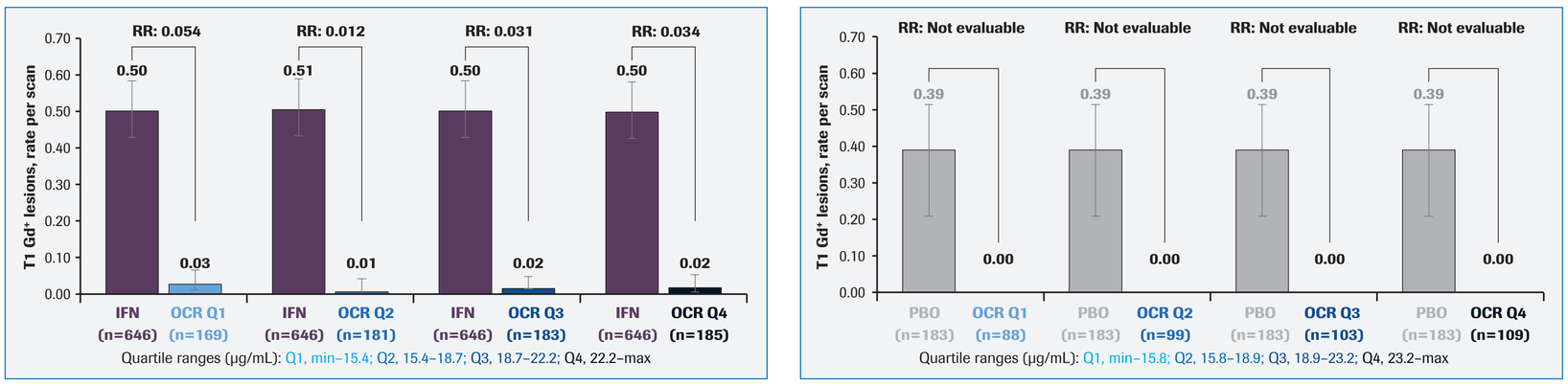
Analyses in patients with PPMS

Figure 1. Peripheral CD19$^+$ B-cell depletion levels stratified by exposure



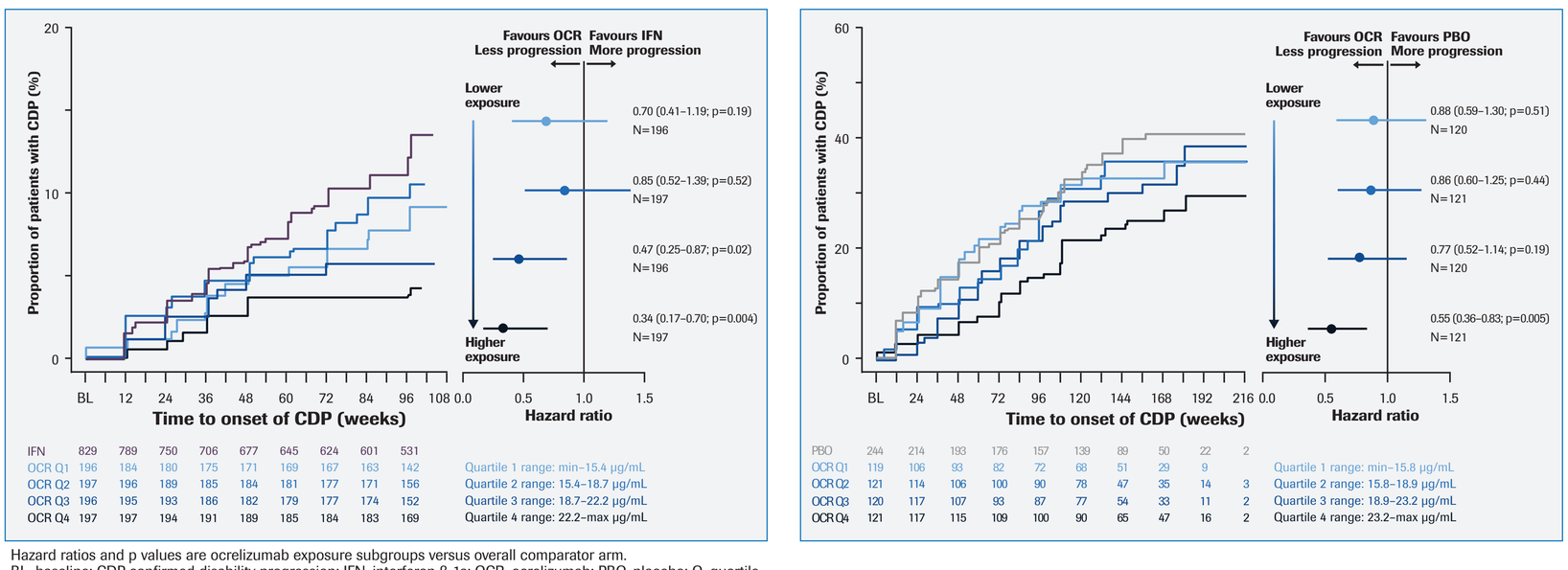
Peripheral B-cell levels in individual patients were determined by flow cytometry at trough ocrelizumab concentrations immediately prior to the next dose. The cut-off of ≤5 cells/µL relates to assay sensitivity limits.
Q, exposure quartile.

Figure 2. T1 gadolinium-enhancing lesions stratified by exposure



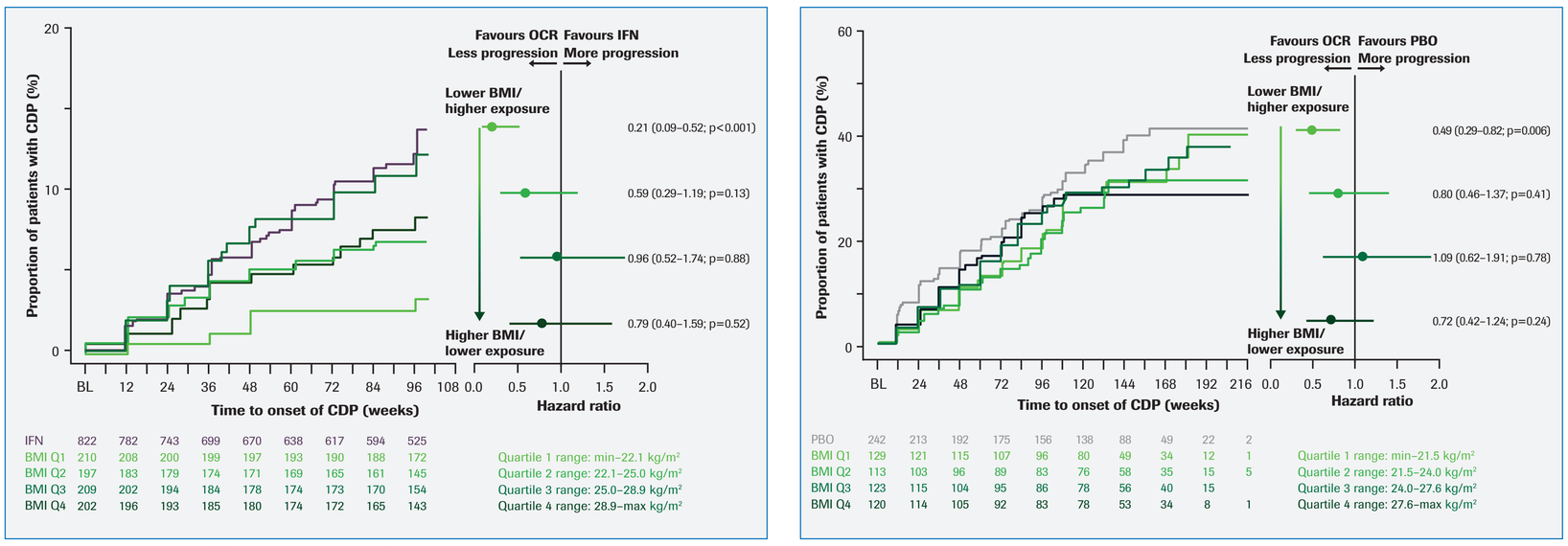
IFN, interferon β-1a; OCR, ocrelizumab; PBO, placebo; Q, exposure quartile; RR, rate ratio.

Figure 5. Disability progression stratified by exposure



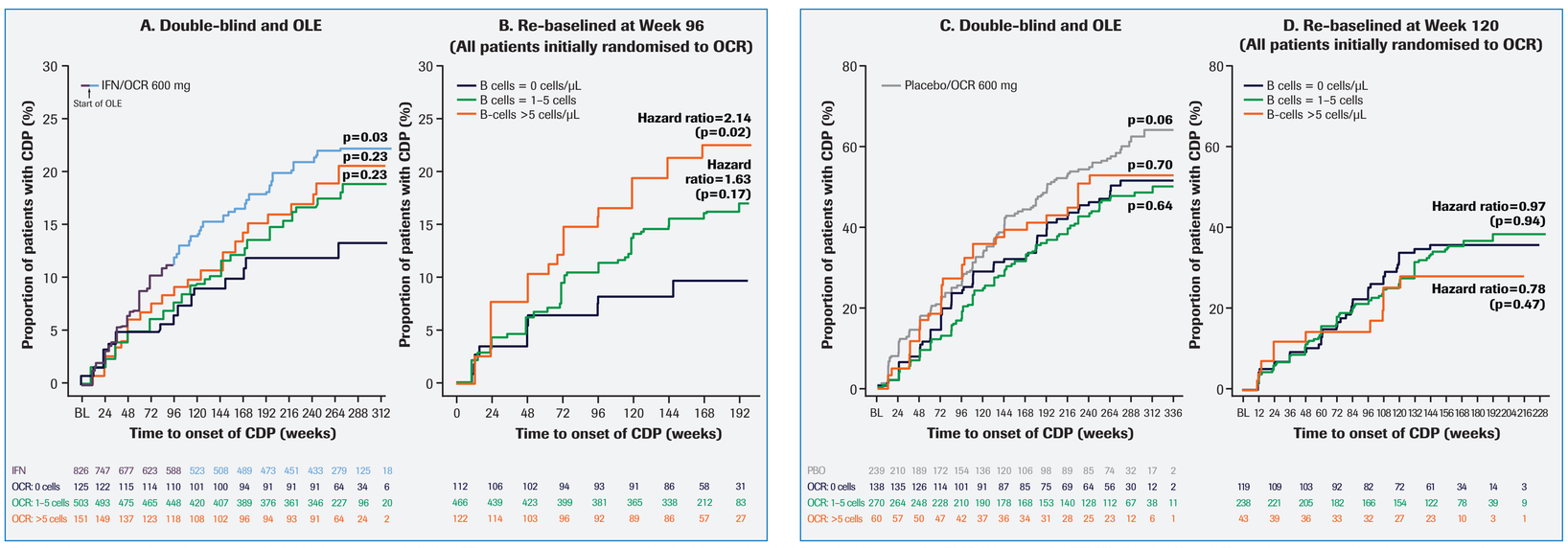
Hazard ratios and p values are ocrelizumab exposure subgroups versus overall comparator arm.
BL, baseline; CDP, confirmed disability progression; IFN, interferon β-1a; OCR, ocrelizumab; PBO, placebo; Q, quartile.

Figure 6. Disability progression stratified by BMI



Hazard ratios and p values are BMI subgroups versus overall comparator arm.
BL, baseline; BMI, body mass index; CDP, confirmed disability progression; IFN, interferon β-1a; OCR, ocrelizumab; PBO, placebo; Q, quartile.

Figure 7. Disability progression stratified by B-cell depletion level



B-cell subgroups are based on median individual patient pre-infusion CD19 measurements during the double-blind period (baseline–Week 96 for RMS; Week 120 for PPMS). Graphs A) and C): p values are based on log-rank test of: a) IFN/OCR (RMS) and >0 B-cell subgroups or b) PBO (PPMS) and >0 B-cell subgroups, respectively, versus 0 B-cell subgroup. Graphs B) and D): Hazard ratios and p values are >0 B-cell subgroups versus 0 B-cell subgroup from the double-blind period. BL, baseline; CDP, confirmed disability progression; IFN, interferon β-1a; OCR, ocrelizumab; OLE, open-label extension; PBO, placebo.

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ACKNOWLEDGEMENTS

We would like to thank all patients, their families, and the investigators who participated in these trials. This research was funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland. Writing and editorial assistance for this presentation was provided by Articulate Science, UK, and funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland.

DISCLOSURES

SL Hauser serves on the board of trustees for Neurona and on scientific advisory boards for Alector, Annexon, Bionure, Molecular Stethoscope and Symbiotix, and has received travel reimbursement and writing assistance from F. Hoffmann-La Roche Ltd for CD20-related meetings and presentations. **A Bar-Or** has received consulting fees from Actelion, Atara Biotherapeutics, Biogen Idec, Celgene/Receptos, Genentech/Roche, MAPI, MedImmune, Merck/EMD Serono, Novartis, Sanofi Genzyme, GlaxoSmithKline and Brainstorm. He has carried out contracted research for Genentech and Biogen. He receives a salary from The University of Pennsylvania, Perelman School of Medicine. **MS Weber** receives research support from the Deutsche Forschungsgemeinschaft (DFG; WE 3547/5-1), from Novartis, Teva, Biogen Idec, Roche, Merck and the ProFutura Program of the Universitätsmedizin Göttingen. He is serving as an editor for *PLoS One*. He has received travel funding and/or speaker honoraria from Biogen Idec, Merck Serono, Novartis, Roche, Teva, Bayer and Genzyme. **E Gibiansky** is a paid consultant for F. Hoffmann-La Roche Ltd. **H Kletzl** is an employee of F. Hoffmann-La Roche Ltd. **C Petry** is an employee and shareholder of F. Hoffmann-La Roche Ltd. **F Mercier** is an employee of F. Hoffmann-La Roche Ltd. **A Guenther** is an employee of Genentech, Inc., and a shareholder of F. Hoffmann-La Roche Ltd. **F Model** is an employee and shareholder of F. Hoffmann-La Roche Ltd. **Q Wang** is an employee of F. Hoffmann-La Roche Ltd. **G-A Thanei** is an employee and shareholder of F. Hoffmann-La Roche Ltd. **H Koendgen** is an employee and shareholder of F. Hoffmann-La Roche Ltd. **L Kappos**'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, Vianex and licence 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, Innosswiss, the European Union and Roche Research Foundations. In the last year, his institution (The Research of the MS Center in Basel) has been supported by grants and support (Actelion, Bayer, Baxalta, Biogen, Celgene/Receptos, CSL Behring, Desitin, Genzyme, Japan Tobacco, Merck, Novartis, Pfizer, Roche, Sanofi, Santhera and Teva).

Presented at the 27th Annual Meeting of the European Charcot Foundation (ECF); 21–23 November 2019; Baveno, Italy

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