CONCLUSIONS
A direct correlation of CD4+ T-cell levels was associated with higher exposure in patients with RMS and PPMS.
- Clinical RMS and PPMS outcomes were independent of exposure (potential ceiling effect).
- Higher exposure–response was associated with a greater risk reduction in CD3+ (RMS) and CD4+ (PPMS).
- The greater reduction in CD4+ observed with higher exposure–response in patients with RMS or PPMS suggests that higher exposure–response could be better interpreted for control of disability progression.

OBJECTIVES
- The current study analyses the impact of exposure–response on the demographic and disease activity in patients treated with ocrelizumab (OCR) for relapsing-remitting multiple sclerosis (RMS) and primary progressive multiple sclerosis (PPMS) in the clinical trials and clinical development program.

METHODS
Clinical Studies
- The clinical trials of the Phase II study in patients with RMS and the Phase II study in patients with PPMS have been reported previously.

Population Pharmacokinetic Modelling
- Exposure quartiles (EQ) are defined from the mean OCR concentration of individual patients across the treatment period from the popPK model.

Clinical Outcomes
- Exposure-response analyses are based on Phase II (RMS) or popPK study endpoint:
  - Annualised relapse rate (ARR) RMS only: 24-week confirmed disability progression (CDP) risk reduction.
- CDP defined as an increase from the baseline Expanded Disability Status Scale score of at least 1.0 points (or 0.5 points if the baseline score was ≥ 5).

RESULTS
Baseline Demographic Characteristics
- Predictable trends in baseline demographics correlating with exposure at a median time are age and body mass index (BMI) were observed across OCR exposure-stratified quartiles in patients with RMS (Table 1) or PPMS (Table 2).

MHI Outcomes
- OCR reduced T1 gadolinium-enhancing (Gd+) lesions (Figure 2) and T2 MRI lesion counts (Figure 3) in treated patients with better exposure.

Annualised Relapse Rate (RMS only)
- OCR reduced ARR in low levels (1.3–1.8) across exposure quartiles (QR Figure 4).

Disability Progression
- The effect of OCR on CDP was exposure-dependent (Figure 5).
- Age, age and BMI/weight were the main confounders of these analyses.

An exposure effect trend was observed in CDP stratified by BMI (Figure 6).

Lower progression rate trend is observed with lower exposure in patients with PPMS was demonstrated (Figure 7).

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

DISCLOSURES
SL Hauser serves on the board of directors for Teva and an advisory board for Baxalta, Aventis, Alexion, Roche, Mitsubishi, Biogen, and has received travel grants and research funding from Teva, Aventis, Alexion, Roche, Biogen, and Mitsubishi.

REFERENCES
1. Hauser SL. et al. Neurology 2017;89;1210-1219

Table 1. Baseline demographics and disease characteristics (RMS)

Table 2. Baseline demographics and disease characteristics (PPMS)

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Poster 93