Methods: Pregnancies after cladribine treatment documented in the German Multiple Sclerosis and Pregnancy Registry (DMSKW) are presented. Information on pregnancy outcomes and disease course was collected with a standardized questionnaire during pregnancy and postpartum. For descriptive analysis, this cohort was stratified to last cladribine intake i) after last menstrual period (LMP), ii) between LMP and 6 months prior to LMP and iii) more than 6 months prior to LMP.
Results: 42 pregnancies in women with MS occurred after cladribine treatment, two with pregnancy exposure after LMP (median exposure duration 24 days; range 19 – 29), 16 with pregnancy exposure during the last 6 months prior to LMP (median days between CLAD and LMP 114,5 days; range 2 – 180) and 24 without pregnancy exposure (median days between CLAD and LMP 218 days; range 189 – 576). So far, 27 healthy babies and one elective abortion were reported. 11 pregnancies are ongoing and one woman is lost to follow up. One (2.6%) major and one minor (2.6%) congenital malformation were reported. Only one relapse occurred in 30 women with completed pregnancy follow-up (3.3%) and one postpartum relapse in 23 women with at least 3-months postpartum follow up (4.3%). Updated information will be presented at the time of the meeting.
Conclusions: Our data adds useful information on pregnancies with generally healthy newborns after cladribine treatment and excellent disease control during pregnancy and postpartum, but is limited by the small sample size.

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P288
Sustained low relapse rate with highly variable B cell re-population dynamics with extended rituximab dosing intervals in multiple sclerosis

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Background and Objectives: B cell depleting therapies are highly effective in relapsing-remitting multiple sclerosis (RRMS), but are associated with increased infection risk and blunted humoral vaccination responses. Extension of dosing intervals may mitigate such negative effects, but its consequences on MS disease activity is unknown. The objective of this study was to determine clinical and neuroradiological disease activity, as well as B cell re-population dynamics, after implementation of extended rituximab dosing in RRMS.
Methods: We conducted a prospective observational study in a specialized-care, single-center setting, including RRMS patients participating in the COMBAT-MS and MultipleMS observational drug trials, who had received at least two courses of rituximab (median follow up time 4.8 years, range 0.5 – 9.8). Using Cox regression, hazard ratios (HR) of clinical relapse and/or occurrence of contrast-enhancing lesions on MRI were calculated in relation to time since last administered dose of rituximab.
Results: A total of 3,904 dose intervals were accumulated in 718 patients and stratified into four intervals: <8 months, $\geqslant 8$ to 12, $\geqslant 12$ to 18 and $\geqslant 18$ months. We identified 24 relapses of which 20 occurred within 8 months since previous infusion and four with intervals over 8 months. HRs for relapse when comparing $\geqslant 8$ to 12, $\geqslant 12$ to 18, and $\geqslant 18$ months to <8 months since last dose were 0.28 (95% confidence interval (CI) 0.04-2.10), 0.38 (95%CI 0.05-2.94) and 0.89 (95%CI 0.20-4.04), respectively, and thus non-significant. Neuroradiological outcomes were in agreement with relapse rates. Dynamics of total B cell reconstitution varied considerably, but median total B cell counts reached lower level of normal (LLN) after 11 months. In contrast, median memory B cell counts remained below LLN.
Conclusions: In this prospective cohort of rituximab-treated RRMS patients exposed to extended dosing intervals we could not detect a relation between clinical or neuroradiological disease activity and time since last infusion. While memory B cell counts remained low in most patients, total B cell re-population kinetics varied considerably. These findings, relevant for assessing risk mitigation strategies with anti-CD20 therapies in RRMS, suggest that relapse risk remains low with extended infusion intervals. Further studies are needed to investigate the relation between B cell repopulation dynamics and adverse event risks associated with B cell depletion.

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EL, NR, MJ, IK, FAN and TF declare no competing interests.

P289
Efficacy and safety of ocrelizumab is maintained in patients with RRMS with suboptimal response to prior disease-modifying therapies: 4-year NEDA data from CASTING-LIBERTO

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Background: Despite treatment with disease-modifying therapies (DMTs), patients with relapsing-remitting multiple sclerosis (RRMS) frequently experience disease activity. The Phase IIIb CASTING study (NCT02861014) examined the efficacy and safety of ocrelizumab (OCR) in patients with RRMS with previous suboptimal response to ⩾6 months DMTs. Eligible CASTING patients enrolled into LIBERTO (NCT03599245), an open-label extension study assessing the efficacy and safety of OCR in patients previously registered in OCR Phase IIIb/IV trials.
Aims: To assess the efficacy and safety of OCR over 4 years in patients with RRMS with a suboptimal response to prior DMTs from CASTING-LIBERTO.
Methods: Patients who completed the 2-year CASTING study were offered to rollover to LIBERTO and continue intravenous OCR 600 mg every 24 weeks for 2 years. Efficacy endpoint was no evidence of disease activity (NEDA; defined as no protocol-defined relapses, 24-week confirmed disability progression [24W-CDP], contrast-enhancing T1-weighted and new/enlarging T2-weighted lesions [T1w-CEL and N/E T2w-L], with MRI rebaselining at Week 8). Safety objectives included the rate and nature of adverse events (AEs).
Results: Overall, 12 out of 17 countries that participated in CASTING entered LIBERTO, resulting in a rollover of 439/680 patients from CASTING to LIBERTO. Patient baseline demographics were consistent between trials (CASTING/LIBERTO: Age [years], 34.2/36.0; % female, 64.1/62.9; mean Expanded Disability Status Scale, 2.1/2.0). During 4 years in CASTING-LIBERTO, 56.8% of patients had NEDA, 64.6% had no clinical activity (84.1% no relapses and 73.9% no 24W-CDP), 87.2% had no MRI activity (96.8% no T1w-CEL and 87.2% no N/E T2w-L). Of the 71 CASTING-LIBERTO patients who had EDA during CASTING, 45 (63.4%) achieved NEDA during LIBERTO. Of the 246 CASTING-LIBERTO patients who had NEDA during CASTING, 189 (76.8%) maintained NEDA during LIBERTO. AEs were reported in 92.7% of patients and serious AEs in 8.7%. Infections were observed in 72.2% patients. In total, 3 patients withdrew from LIBERTO due to AEs (0.7%); no deaths occurred in LIBERTO.
Conclusions: The majority of patients with RRMS with a suboptimal response to prior DMTs who switched to OCR showed NEDA during the 4-year follow-up of CASTING-LIBERTO, based on clinical and MRI measures. A high proportion of patients with EDA during the first 2 years of treatment achieved NEDA over 2 years in LIBERTO. No new safety signals were observed.

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P290

Functional systems scores and expanded disability status scale score evaluations in the ultimate I and II studies of ublituximab versus teriflunomide in participants with relapsing multiple sclerosis

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Introduction: Ublituximab is a novel monoclonal antibody targeting a unique epitope of CD20. Ublituximab is glycoengineered for enhanced antibody-dependent cellular cytotoxicity and is administered in 1-hour maintenance infusions after the first infusion. In ULTIMATE I and II, ublituximab significantly improved annualised relapse rate as well as number of gadolinium-enhancing T1 lesions and new/enlarging T2 lesions, and a higher proportion of participants achieved no evidence of disease activity versus teriflunomide in participants with relapsing multiple sclerosis (RMS).
Objectives/Aims: To evaluate Functional Systems Scores (FSS) and Expanded Disability Status Scale (EDSS) score with ublituximab versus teriflunomide in pooled post hoc analyses of ULTIMATE I and II.
Methods: The Phase 3 ULTIMATE I (N=549) and II (N=545) studies evaluated ublituximab 450 mg intravenous infusion every 24 weeks or teriflunomide 14 mg oral once daily for 96 weeks in participants with RMS. Clinical evaluations were performed at baseline and every 12 weeks. Pooled post hoc analyses evaluated the change from baseline in EDSS score and FSS at each visit. A repeated measures proportional odds model was used to estimate the odds ratio (OR) between the two arms for the change from baseline across all visits during the studies.
Results: Across all visits, significant improvements (OR [95% confidence interval]) with ublituximab versus teriflunomide were seen in: EDSS score, 1.7 (1.2-2.4), P=0.0010; bowel/bladder functions, 1.4 (1.0-1.8), P=0.0222; and sensory functions, 1.4 (1.1-1.9), P=0.0052. By individual visits, significant improvements were seen with ublituximab versus teriflunomide in EDSS score (Weeks 48-96), bowel/bladder (Weeks 24-96), sensory (Weeks 48-96), cerebellar (Weeks 48, 84, 96), cerebral/mental (Weeks 48, 72, 84), and ambulation and pyramidal (Week 96) functions ($P<0.05$).
Conclusions: Pooled post hoc analyses of ULTIMATE I and II demonstrated significant improvements with ublituximab versus teriflunomide in EDSS score and multiple FSS. These results further support prior data on improved disability outcomes with ublituximab versus teriflunomide in participants with RMS.

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