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Introduction: Elevations in neurofilament levels, as measured from blood and CSF samples, are associated with neuroaxonal damage, and may serve as a promising biomarker for disease activity and treatment response in multiple sclerosis. In the Phase 3 OPTIMUM study (NCT02425644), relapsing multiple sclerosis (RMS) patients treated with ponesimod (20 mg), a highly selective sphingosine 1-phosphate receptor 1 modulator, had greater reduction in the annualized relapse rate compared with patients treated with teriflunomide (14 mg).
Objective: To investigate the change in serum neurofilament light chain (NfL) concentration in the ponesimod and teriflunomide treatment groups after the 108-week treatment period in the OPTIMUM study.
Methods: Paired serum samples were collected at baseline (prior to treatment) and post-treatment (after the 108-week treatment period). Serum samples were analyzed for NfL concentrations using single molecule array (SIMOA) immunoassay (University of Basel, Switzerland). P-values for within group differences were based on paired t-tests. P-values for between treatment group comparisons were from an ANCOVA model with fixed effects for treatment, age, gender, baseline NfL value, EDSS strata ($\leqslant$3.5, $>$3.5), disease-modifying therapies within last 2 years (yes/no) and gadolinium-positive T1 lesions at baseline (present/absent) as covariates.
Results: 513/1123 randomized patients (ponesimod, n=247/567, teriflunomide, n=266/566) had serum samples collected at baseline and after the 108-week treatment period for NfL concentration analysis. Baseline serum NfL concentrations were similar in the ponesimod (mean 14.9 pg/mL, standard deviation [SD] 15.7 pg/mL) and teriflunomide (mean 15.7 pg/mL, SD 21.2 pg/mL) treatment groups. In the ponesimod treatment group, the mean percent change in serum NfL concentration from baseline to post-treatment was -23.8% (SD 38.03%) ($p<0.001$). In the teriflunomide treatment group, the mean percent change in serum NfL concentration from baseline to post-treatment was 5.4% (SD 75.60%) (p=0.243). Comparing ponesimod and teriflunomide treatment groups, there was a statistically significant difference in the least squares (LS) mean of the percent change in serum NfL concentration from baseline to post-treatment (difference in LS-mean -29.9%, standard error 4.91%, $p<0.001$).
Conclusion: In the OPTIMUM study, RMS patients treated with ponesimod for 108 weeks demonstrated significant reductions in serum NfL concentration.

Disclosure
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UBE3A inhibits remyelination by targeting ABCA1 for degradation

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Multiple sclerosis (MS) is a devastating neurological disease and one of the most prevalent autoimmune diseases in the Western world. Foamy macrophages loaded with myelin-derived lipids are a pathological hallmark of MS lesions. Our research group previously demonstrated that loss of the cholesterol efflux membrane transporter ABCA1 accounts for excessive accumulation of intracellular lipids, thereby skewing foamy phagocytes towards an inflammatory phenotype which hampers central nervous system (CNS) repair. Here, we show that the ubiquitin-proteasome system (UPS) is the main degradation pathway involved in the turnover of ABCA1 in myelin-loaded macrophages. Gain- and loss of function experiments demonstrated that the E3 ligase UBE3A was responsible for ABCA1 breakdown in foamy macrophages. Consistent with these findings, UBE3A was found to promote lipid overload, induce an inflammatory macrophage phenotype, and suppress remyelination *ex vivo*. By using RNA sequencing analysis, we further identified TIP30, an inhibitor of importin β-mediated nuclear import, as an essential regulator of cytosolic UBE3A levels. Altogether, our findings identify UBE3A as a novel therapeutic target to boost CNS repair. Importantly, this study is the first to link UBE3A to cellular lipid metabolism, thereby not only providing important new insight in MS, but in all diseases characterized by the presence of foamy macrophages.

Disclosure
Nothing to disclose