arthritis domain both at month 6 ($p<0.001$) and 12 ($p<0.001$). From baseline to month 6, the mean tender joints count decreased from 5.7 to 2.7 ($p=0.010$), and the swollen joints count from 3.6 to 0.7 ($p<0.001$); the decreases were sustained through month 12 ($p=0.001$ for both counts). No impact of smoking habits on treatment outcomes in relation to articular SLE was observed.

Conclusion In line with previous reports, belimumab treatment was effective in limiting mucocutaneous and articular symptoms in patients with SLE. A history of past or current smoking was found to reduce the efficacy of belimumab in mucocutaneous manifestations. Further survey on the impact of smoking on the efficacy of belimumab at a mechanistic level is merited.

PS7:133 EXPOSURE-RESPONSE MODELLING AND EXPOSURE-SAFETY MODELLING ANALYSES IN TWO PHASE II STUDIES OF ATACICEPT IN SLE

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Purpose Atacicept targets the B-cell stimulating factors BLyS and APRIL, and has been shown to reduce SLE disease activity.

Methods APRIL-SLE (NCT00624338) and ADDRESS II (NCT01972568) were phase II, multicenter studies in patients (pts) with autoantibody-positive SLE randomised (1:1:1) to weekly SC injections of atacicept (75 or 150 mg) or placebo (PBO). In APRIL-SLE, pts had BILAG A/B flare at Screening that was reduced to BILAG C/D before randomization using corticosteroids; the primary endpoint was BILAG A/B flare over 52 weeks. In ADDRESS II, pts had SLEDAI-2K$\geq$6 at Screening; the primary endpoint was SRI-4 response at Week 24. SLE responder index (SRI)−6 response was analysed post-hoc in high disease activity (HDA; SLEDAI-2K$\geq$10) pts. Population pharmacokinetic (PK) model-derived exposure vs the probability of response (BILAG A/B flare, SRI-4, SRI-6), exploratory analysis of exposure vs safety, and population model simulations of serum IgG were analysed.

Results Exposure-response modelling suggests a relationship between atacicept exposure and SLE clinical response [figure 1], including serum IgG changes from baseline. The optimal atacicept exposure was AUCtau,ss $\geq\sim$1 mg.hr/mL, which is more achievable with weekly SC doses of atacicept 150 mg than 75 mg across a range of body weights. Body weight-based dosing is unlikely to offer any value over a fixed 150 mg dose, based on comparable predicted clinical response. In HDA pts, greater reductions in serum IgG from baseline corresponded to a higher probability of SRI-6 response. Greater IgG reductions from baseline were associated with higher atacicept exposure; however, even at the highest exposure range, mean IgG reductions did not exceed ~40%. There was no association between serious/severe infections and exposure by PK quartile.

Conclusions Exposure-response modelling indicated robust relationships between atacicept exposure and clinical response or IgG levels, supporting the proposed mechanism of action for atacicept. Atacicept 150 mg weekly SC is likely to provide an effective level of exposure with an acceptable safety profile. There was no evidence of an increased risk of severe or serious infections at higher exposures. Based on these results, the 150 mg dose merits further evaluation.

PS7:134 RITUXIMAB-MEDIATED LATE-ONSET NEUTROPENIA IN SYSTEMIC LUPUS ERYTHEMATOSUS – DISTINCT ROLES OF BAFF AND APRIL

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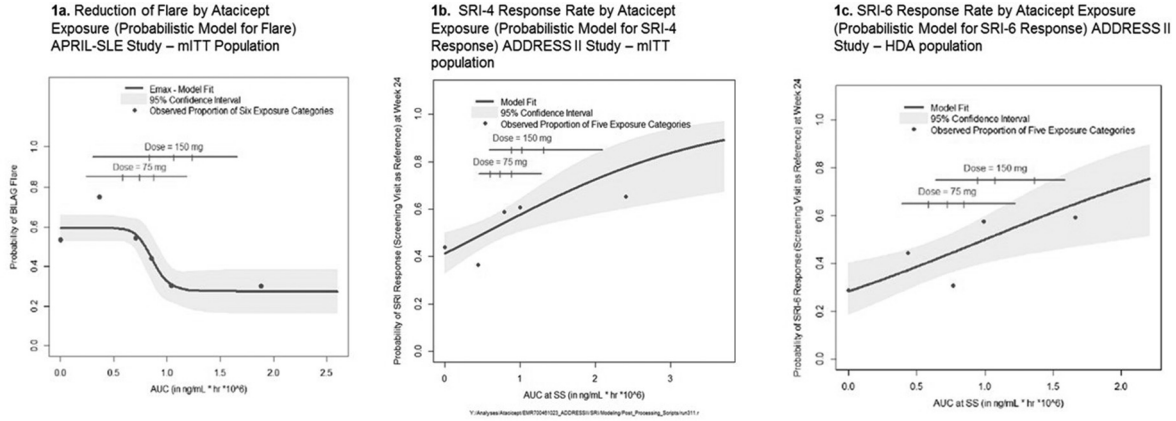
Background Rituximab-mediated late-onset neutropenia (LON) has been described in various diseases. We investigated its prevalence and contributing factors, including B cell related cytokines and growth factors of the myeloid lineage, in patients with systemic lupus erythematosus (SLE).



Exposure categories correspond to placebo (AUCtau=0) and quintiles (APRIL-SLE – 1a) or quartiles (ADDRESS II – 1b and c) of the AUCtau distribution for subjects on atacicept. Observed proportions (blue points) are plotted at the mid-point of the corresponding AUCtau exposure group. Solid blue lines are predicted mean profiles with shaded areas for 95% confidence intervals.
Horizontal lines correspond to the 95% of the distribution of AUCtau by dose. The 3 ticks are the 1st, 2nd (median) and 3rd quartiles.

AUCtau, area under the concentration curve over 1 dosing interval, ie, 1 week; BILAG, British Isles Lupus Assessment Group; BLyS, B lymphocyte stimulator; Emax, maximum response achievable; HDA, high disease activity (SLEDAI-2K ≥10 at Screening); mITT, modified Intention-to-Treat (all randomized subjects who received at least 1 dose of investigational medicinal product); SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SRI-6, Systemic Lupus Erythematosus Responder Index 6

Abstract PS7:133 Figure 1 Probabilistic models of clinical response by atacicept exposure