## SAT0236 SAFETY AND DISEASE ACTIVITY CHANGES IN AN EXTENSION OF A PHASE IIB STUDY OF ATACICEPT IN PATIENTS WITH SLE (ADDRESS II)

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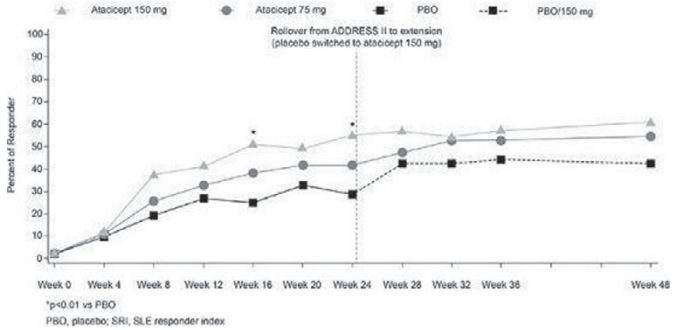
**Background:** We previously reported results of the 24-week phase IIb ADDRESS II study of atacicept, which demonstrated clinical response in patients with autoantibody-positive SLE, particularly those with high disease activity (HDA; SLEDAI 2K ≥10 at screening).
**Objectives:** This extension study of ADDRESS II evaluated safety and disease activity in patients with SLE given continued atacicept treatment to week 48 (NCT01972568).
**Methods:** Atacicept was given as weekly subcutaneous injection to completers of ADDRESS II on average for an additional ≥24 weeks (i.e. ≥48 weeks total from Day 1 of ADDRESS II). Patients already receiving atacicept continued on the same dose (75 mg or 150 mg); those receiving placebo (PBO) switched to atacicept 150 mg (PBO/150 mg).
**Results:** Of 262 patients completing ADDRESS II, 253 (95%) entered the extension (PBO/150 mg n=83; 75 mg n=82; 150 mg n=88). Demographics were balanced between groups, and most patients were female (91.3%) and white (70%). All three treatment groups had similar rates of treatment-emergent adverse events (TEAEs), TEAEs leading to treatment discontinuation, serious TEAEs, and serious/severe infection (Table 1). Two deaths occurred in the 150 mg arm, considered unrelated to treatment (reported events of stroke and abdominal pain with hematemesis). In the ITT population (n=253), SLE responder index (SRI)-4 rates were maintained between weeks 24 and 48 in the original atacicept groups (75 mg 56.9 vs 55.9%; 150 mg 53.8 vs 56.7%) and moderately increased in the PBO/150 mg group (44.0 vs 48.0%). This improvement was greater for SRI-6 in the HDA subpopulation (PBO/150 mg 28.8% at week 24 vs 42.3% at week 48; 75 mg 41.8 vs 54.5%; 150 mg 54.9 vs 60.8%; Figure 1). The proportion of HDA patients achieving SLEDAI scores ≤2 was also maintained in the atacicept groups (75 mg 20.0 vs 21.8%; 150 mg 37.3 vs 39.2%) and increased in the PBO/150 mg group (13.5 vs 19.2%). In the ITT and HDA populations, most flares occurred before week 24, with reduced risk of severe (BILAG A) and moderate/severe (BILAG A/2B) flares afterwards. Some increase in complement C3 and C4, and decrease in anti-dsDNA antibodies occurred after week 24. Serum IgG decreased moderately, without severe hypogammaglobulinemia (IgG <3 g/L) in any patients.

Table 1. Summary of adverse events

| Adverse events, n (%) | PBO/150 mg* (n=83) | Atacicept 75 mg (n=82) | Atacicept 150 mg (n=88) |
|---|---|---|---|
| Any TEAEs | 62 (74.7) | 63 (76.8) | 65 (73.9) |
| TEAEs leading to treatment discontinuation | 6 (7.0) | 4 (4.9) | 5 (5.7) |
| Infections and infestations | 27 (32.5) | 35 (42.7) | 43 (48.9) |
| Herpes zoster | 1 (1.2) | 0 | 1 (1.2) |
| Influenza | 1 (1.2) | 1 (1.2) | 2 (2.3) |
| Serious TEAEs | 15 (18.1) | 10 (12.2) | 10 (11.4) |
| Serious/severe infections | 4 (4.8) | 4 (4.9) | 5 (5.7) |
| Death | 0 | 0 | 2 (2.3%)† |

PBO, placebo; TEAE, treatment-emergent adverse event. *Patients receiving PBO in ADDRESS II who switched to atacicept 150 mg. †Due to 1) stroke and 2) hematemesis.

Figure 1. SRI-6 response rates over time up to week 48 in the HDA population




**Conclusions:** There were no new safety signals with atacicept between week 24 and 48, and clinical responses achieved during the first 24 weeks were maintained.
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## SAT0237 BONE MARROW AS A TARGET ORGAN OF SYSTEMIC LUPUS ERYTHEMATOSUS: ANALYSIS OF CASES WITH AUTOIMMUNE MYELOFIBROSIS

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**Background:** Cytopenia in the course of systemic lupus erythematosus (SLE) may be due to multiple factors. One of these factors can be SLE-associated autoimmune myelofibrosis (AIMF). However, the frequency of SLE-associated AIMF is not well known and the role of clinical and laboratory parameters in the development of AIMF is not clear.
**Objectives:** Our aim was to identify the frequency of SLE-associated AIMF and compared SLE-associated AIMF group with non-AIMF group in terms of clinical findings and morphological properties of the bone marrow (BM) in cytopenic SLE patients.
**Methods:** We retrospectively analyzed 224 SLE patients' files who met 1997 revised Classification criteria for SLE. BM aspirates and trephine biopsies were re-examinded. Patients were divided into two groups according to whether they had myelofibrosis or not (AIMF and non-AIMF groups). Concurrent SLE organ involvements, and drugs given pre- and post-AIMF were recorded. BM cellularity, the presence of fibrosis (reticulin or collagen) and grade of fibrosis, the presence of dysplasia, and lymphoid infiltration were recorded.
**Results:** 45 (20%) of 224 SLE patients were found to experienced BM biopsy due to cytopenia. Four patients were excluded from analyses (2 drug-induced cytopenia, 1 lymphoma, 1 insufficient BM biopsy samples). While AIMF was detected in 29 (70.7%) of the 41 patients, 12 patients did not have AIMF. All patients with AIMF had reticulin fibrosis, 2 patients (6.9%) had also collagen fibrosis. Between the AIMF and non-AIMF groups, no differences were identified in terms of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), SLEDAI, BM cellularity, or BM dysplastic changes (p=0.989, p=0.387, p=0.788, p=0.672, and p=0.494, respectively). In the AIMF group, 27 patients responded to immunosuppressive therapy and corticosteroids, but 2 patients were unresponsive. The response time was longer for the AIMF group compared to the non-AIMF group (3.3±3.1 months vs 1.7±1.2 months, p=0.091). Correlation analysis revealed that higher the grade of BM fibrosis, longer the response time (r=0.471, p=0.002).
**Conclusions:** AIMF may be underestimated in SLE patients. AIMF as an additional factor for cytopenia in SLE patients may lead to delayed response to appropriate therapy, which was dependent on the presence of high grade fibrosis.
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## SAT0238 GLUCOCORTICOID WITHDRAWAL IN AN INCEPTION COHORT OF LUPUS NEPHRITIS PATIENTS

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**Background:** Few studies have addressed glucocorticoid (GC) withdrawal in lupus nephritis (LN). Yet, this remains a pivotal issue due to GC-induced side effects on the one hand, and to the risk of relapse on the other hand.
**Objectives:** We reviewed the data of the Louvain Lupus Nephritis Inception Cohort (LOULUNIC) i): to determine the percentage of patients able to permanently or transiently stop GC; ii): to compare their baseline and follow-up characteristics to patients who never stopped; and iii): to assess the consequences of GC withdrawal.
**Methods:** Ninety patients with new-onset biopsy-proven LN were included. All were under the care of the same senior physician (FAH) during follow-up. Clinical, pathological and biological data were extracted from our data base. The SLICC/ACR-DI was assessed at last visit. Unpaired t-tests, Mann-Whitney tests and ANOVA were used, as appropriate.
**Results:** Out of 90 patients with incident LN, 43 (48%) ever stopped GC (group E), of which 32 permanently (group P). Median time to stop GC was 37 months. 47 patients (52%) never stopped GC (group N).
At *baseline*, serum creatinine, uP/C ratio, ISN/RPS classes, activity and chronicity indices did not differ between groups, nor did the mean initial dose of methylprednisolone (MP) (N: 28 mg/d; E: 32 mg/d; P: 31 mg/d), the use of IV MP pulses (82

and 77% in N and E groups, respectively) and of IV cyclophosphamide (81 and 77%, respectively).
During the *first year*, mean (SD) uP/C decreased statistically more in group E compared to group N ($p$=0.028 by ANOVA), with striking differences at month 3 (N: 1.73±1.87; E: 0.96±1.34; $p$=0.038 by unpaired t-test). This difference at month 3 was also noticed for group P patients (0.85±0.76; $p$=0.02 by unpaired t-test). Interestingly, the mean MP dose at month 3 was statistically higher in group E (19±8) and P (20±9) compared to group N (15±6) ($p$=0.005 by unpaired t-test).
At *last follow-up*, serum creatinine was statistically lower in E and P patients compared to N patients. Eight of the 11 patients from the T group suffered form a renal relapse, justifying restart of GC, after a median time of 30 months. Importantly, SLICC/ACR-DI was significantly lower in E and P patients, compared to N patients ($p$=0.0068 and 0.0027, respectively).
**Conclusions:** In half of LN patients, complete GC withdrawal is achievable and in one third it can be maintained long term. As expected, patients able to stop GC display less damage at last followup. Patients who were able to stop GC decreased their proteinuria much more promptly during the first year of treatment. Interestingly, they received more GC within the first 3 months of therapy, thereby suggesting that a higher dose of GC during the first 3 months of treatment might be associated with a higher probability of later GC withdrawal.
**Disclosure of Interest:** None declared
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## SAT0239 LATE-ONSET NEUTROPENIA FOLLOWING RITUXIMAB TREATMENT IN SYSTEMIC LUPUS ERYTHEMATOSUS – A ROLE OF THE BAFF/APRIL PATHWAY

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**Background:** Rituximab-mediated late-onset neutropenia (LON) has been studied in various diseases, but data from systemic lupus erythematosus (SLE) are limited.
**Objectives:** To study the prevalence and contributing factors for LON following treatment with rituximab in patients with SLE, including B cell related cytokines and growth factors of the myeloid lineage.
**Methods:** Patients from the Karolinska SLE cohort treated with rituximab (n=107) were enrolled in this observational study. Rituximab was given according to the lymphoma course (weekly for four weeks), the arthritis course (at week 0 and 2), or as a single infusion, with or without concomitant pulses of cyclophosphamide. LON was defined as an absolute neutrophil count $<$1,500 cells/$\mu$L, occurring four weeks to two years after initiation of rituximab treatment, provided that other apparent causes were excluded. Neutropenia occurring later than two years after treatment initiation but during sustained B cell depletion were also considered LON. B lymphocyte stimulator (BLyS/BAFF), a proliferation-inducing ligand (APRIL), interleukin 6 (IL-6), granulocyte colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF) were measured by ELISA prior to treatment (n=70) and either at the incidence of LON in patients who developed LON or after approximately the same median time following rituximab treatment in patients who did not develop LON (n=52).
**Results:** Thirty-four of 107 patients developed LON after a median time of 222 days (IQR: 105–355 days). BLyS levels increased from baseline (median: 0.62 ng/mL; IQR: 0.42–1.07 ng/mL) through the post-treatment measurement, both in patients who developed LON (median: 1.73 ng/mL; IQR: 1.03–2.13 ng/mL; P=0.005) and patients who did not (median: 1.03; IQR: 0.67–1.56 ng/mL; P$<$0.001), but the increase was greater in patients who developed LON, resulting in significantly higher post-treatment BLyS levels (P=0.029). BLyS levels did not differ between the two groups at baseline (P=0.745). We observed a numerical increase in APRIL levels from baseline (median: 1.29 ng/mL; IQR: 0.85–2.3 ng/mL) through the post-treatment measurement in patients who developed LON (median: 2.39; IQR: 1.08–5.16 ng/mL; P=0.074) and a numerical decrease in patients who did not (median: 1.11 ng/mL; IQR: 0.77–1.64 ng/mL; P=0.064), resulting in significantly higher post-treatment APRIL levels in the LON group (P=0.032), from being similar at baseline (P=0.125). We found no difference in levels of G-CSF, GM-CSF or IL-6 between patients who developed LON and patients who did not, either at baseline or at the post-treatment measurement. Higher prednisone dose administered concomitantly to rituximab (P=0.003) and younger age (P=0.001) were found to be associated with the development of LON, whereas neither the use nor the doses of cyclophosphamide were found to have any impact.
**Conclusions:** The prevalence of rituximab-mediated LON within the SLE patients of the current study (31.8%) was higher compared to previous reports on patients with lymphoma (3–27%), ANCA-associated vasculitis (11.9%) and rheumatoid arthritis (3%). Our results imply a role of the BAFF/APRIL pathway in the immunologic mechanisms underlying this phenomenon and demonstrate that LON following rituximab treatment is a common complication in SLE patients.
**Disclosure of Interest:** None declared
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## SAT0240 PHASE 3 TRIAL RESULTS WITH BLISIBIMOD, A SELECTIVE INHIBITOR OF B-CELL ACTIVATING FACTOR, IN SUBJECTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

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**Background:** Targeted, biologic inhibitors of B-cell Activating Factor (BAFF) have been evaluated in Phase 3 trials in over 5000 patients with SLE. Post hoc analyses of these studies identify lower placebo response and greater treatment effect using more stringent endpoints in patients entering with higher disease activity, greater corticosteroid doses, and/or anti-double-stranded DNA (dsDNA) and low complement C3 or C4[1,2].
**Objectives:** The Phase 3 CHABLIS-SC1 trial evaluated blisibimod, an inhibitor of B-cell activating factor (BAFF), in a "responder population" identified from prior studies with this drug class.
**Methods:** 442 SLE patients with anti-nuclear antibodies or anti-dsDNA, SELENA-SLEDAI score $\geq$10 on standard of care medications were randomized to receive weekly subcutaneous blisibimod (200 mg) or placebo. Corticosteroid taper was encouraged from Week 8 with the goal to reach $\leq$7.5 mg prednisone/day. The primary endpoint at Week 52 was the SLE Responder Index-6 (SRI-6): $\geq$6-point improvement in SELENA-SLEDAI, no new BILAG 1A or 2B domain scores, and $<$0.3-point increase in Physician's Global Assessment.
**Results:** This study did not meet its primary endpoint at Week 52. Response rates to blisibimod were equivalent to past trials of BAFF inhibitors, but the placebo response was greater. A slightly higher proportion of subjects on blisibimod met the SRI-6 and SRI-4 criteria at most timepoints and more blisibimod-treated subjects achieved corticosteroid taper to prednisone $\leq$7.5 mg/day from Week 40 through Week 52 (p=0.04 at Week 44). Reductions in peripheral B cell lineages, anti-dsDNA, anti-phospholipid antibodies, and serum immunoglobulins, and increases in complement C3 and C4 were observed with blisibimod (see Table).
Blisibimod was well-tolerated. The most common adverse events were upper respiratory tract infection (10.6% vs 14.3% on placebo), urinary tract infection (6.9% vs 10.7%), injection site erythema (7.8% vs 2.0%), injection site reaction (7.3% vs 2.6%), and diarrhea (7.3% vs 2.6%).

Table of Results

| | Blisibimod (N=245) | Placebo (N=197) |
|---|---|---|
| Disease characteristics at baseline | | |
| SELENA-SLEDAI mean score | 13.4 | 13.5 |
| Low C3/C4 & anti-dsDNA, % | 62.4 | 61.7 |
| Proteinuria $\geq$0.5 g/g, % | 32.7 | 27.9 |
| Mean prednisone dose, mg | 15.6 | 15.6 |
| Oral immunosuppressant use, % | 42.4 | 41.6 |
| Antimalarial use, % | 61.2 | 62.2 |
| Results at Week 52 (*p$<$0.05, **p$<$0.01) | | |
| SRI-6 (primary), % | 46.9 | 42.3 |
| SRI-4, % | 56.7 | 52.0 |
| Taper to $\leq$7.5 mg prednisone/day, % | 23.3 | 16.9 |
| Total B cell change from baseline, counts | -3.30** | -1.58 |
| Anti-dsDNA change from baseline, IU | -134.8 | -75.5 |
| C3 and C4 change from baseline, mg/dL | 0.11**, 0.03** | 0.03, -0.002 |
| Anticardiolipin IgG % change from baseline | -12.7* | 9.3 |

**Conclusions:** With a deliberate focus on a "responder population" for whom lower placebo rates were observed in previous trials, much higher placebo response rates were observed in the CHABLIS-SC1 trial. Modest benefits of blisibimod were observed on serological effects and corticosteroid tapering.
**References:**
[1] van Vollenhoven RF et al. Ann Rheum Dis. 2012;71:1343.
[2] Merrill JT et al. Ann Rheum Dis. 2016;75(2):332–40.
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## SAT0241 EARLY RESPONSE TO BELIMUMAB IN SLE-RELATED JOINT INVOLVEMENT EVALUATED BY ULTRASONOGRAPHIC ASSESSMENT

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**Background:** Belimumab (BLM), a fully human monoclonal antibody directed against B lymphocyte stimulator (BLyS), is currently the only biological drug