Background Low disease activity (LDA) and remission are important goals in the treatment of patients with SLE.[1 2] Lupus Low Disease Activity State (LLDAS) is associated with reduced damage accrual,[2] and has been shown to be a feasible clinical trial endpoint.[3] In patients with high disease activity (HDA; SLEDAI-2K ≥10) enrolled in the ADDRESS II study, atacicept improved SLE responder index (SRI)-6 response rates and flare prevention at Week 24 vs placebo. Atacicept also demonstrated an acceptable safety profile.[4] We present a post-hoc analysis of data from ADDRESS II and its long-term extension, describing 48-week LDA and remission rates in patients with HDA at Screening.

Methods In ADDRESS II, patients were randomized (1:1:1) to weekly subcutaneous atacicept 75 or 150 mg or placebo for 24 weeks. Atacicept-completers continued at the same dose in the extension study, while placebo-treated patients were switched to atacicept 150 mg (placebo/atacicept 150 mg). This post-hoc analysis assessed: LDA (SLEDAI-2K ≤2), LLDAS (SLEDAI-2K ≤4 without major organ activity, no new disease activity vs previous visit, Physician's Global Assessment [PGA] ≤1, prednisone-equivalent ≤7.5 mg/day, and stable immunosuppressants),[2] and remission (clinical SLEDAI-2K=0, PGA <0.5, prednisone ≤5 mg/day), as proposed by the task force on definitions of remission in SLE (DORIS).[1]

Results Of 306 ADDRESS II patients, 158 (51.6%) had HDA at Screening. At Week 24, 42.4% achieved SRI-6, 23.4% attained LDA, 15.8% LLDAS and 10.8% remission. At Week 48, 52.5% achieved SRI-6, 26.6% attained LDA, 19.0% LLDAS and 10.8% remission. Among 83 patients with HDA at Screening who had an SRI-6 response at Week 48, 49.4% (n=41) attained LDA, 34.9% (n=29) LLDAS and 20.5% (n=17) remission. At 48 weeks, LDA, LLDAS and remission rates were higher in patients treated with atacicept 150 mg vs atacicept 75 mg and vs placebo/atacicept 150 mg (figure 1).

Conclusions ADDRESS II patients with HDA at Screening who received atacicept 150 mg were more likely to attain LDA, LLDAS and remission at Week 48 than those treated with atacicept 75 mg or placebo/atacicept 150 mg. These endpoints were more stringent and discriminatory than SRI-6, confirming LLDAS, LDA, and remission to be robust and meaningful endpoints for SLE trials. In addition, these data further support future studies of atacicept in SLE.

Funding Source(s): Merck KGaA, Darmstadt, Germany

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210 INTEGRATED SAFETY PROFILE OF ATACICEPT FROM ALL CLINICAL STUDIES TO DATE

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Background We conducted an integrated analysis of pooled safety data from all 17 atacicept clinical studies across

Abstract 210 Table 1 Exposure-adjusted TEAE rates by dose (DBPC set)

		Atacicept				
	Placebo, n=483	25 mg, n=129	75 mg, n=384	150 mg, n=572	All, n=1085	Total, n=1568
Total number of patient-years	278.3	51.5	225.0	286.7	563.2	841.4
TEAE, n (per 100 patient-years)						
Hypersensitivity*	37 (13.9)	8 (15.7)	40 (19.1)	55 (20.4)	103 (19.4)	140 (17.6)
Infections	211 (107.8)	43 (104.4)	180 (118.7)	281 (141.3)	504 (128.7)	715 (121.7)
Herpes zoster	13 (4.7)	2 (3.9)	10 (4.5)	17 (6.1)	29 (5.2)	42 (5.1)
Serious infection	20 (7.3)	1 (1.9)	23 (10.5)	22 (7.7)	46 (8.3)	66 (7.9)
Severe infection	9 (3.2)	0	11 (4.9)	16 (5.6)	27 (4.8)	36 (4.3)
Injection site reactions	54 (20.9)	27 (64.8)	109 (63.0)	156 (72.4)	292 (67.9)	346 (50.2)
Severe hypogammaglobulinemia (IgG <3 g/L)	0	0	2 (0.9)	4 (1.4)	6 (1.1)	6 (0.7)
Cardiac arrhythmias [all]*	18 (6.6)	11 (22.4)	23 (10.6)	25 (8.9)	59 (10.8)	77 (9.4)
Ventricular arrhythmias	5 (1.8)	0	4 (1.8)	6 (2.1)	10 (1.8)	15 (1.8)
Ischemic heart disorders*	11 (4.0)	3 (5.9)	13 (5.9)	11 (3.9)	27 (4.9)	38 (4.6)
Embolic and thromboembolic events*	11 (4.0)	1 (2.0)	6 (2.7)	9 (3.2)	16 (2.9)	27 (3.2)
Vestibular disorders*	19 (7.0)	5 (9.9)	18 (8.3)	26 (9.3)	49 (8.9)	68 (8.3)
Demyelination*	1 (0.4)	1 (1.9)	0	5 (1.7)	6 (1.1)	7 (0.8)
Depression*	14 (5.1)	3 (5.8)	8 (3.6)	11 (3.9)	22 (3.9)	36 (4.3)
Malignant tumor*	0	1 (1.9)	1 (0.4)	3 (1.1)	5 (0.9)	5 (0.6)
Serious TEAE	51 (18.9)	15 (30.0)	51 (23.9)	61 (21.8)	127 (23.4)	178 (21.9)
Severe TEAE	28 (10.2)	10 (19.6)	45 (20.9)	56 (20.0)	111 (20.3)	139 (17.0)
Discontinuation of treatment due to TEAE	30 (10.9)	14 (27.6)	30 (13.4)	46 (16.1)	90 (16.1)	120 (14.3)
Deaths related to infections, n (%)						
Deaths	0	0	0	2 (0.3)†	0	0

*Programmatically determined (crude results of the search) from a predefined list of MedDRA preferred terms according to the Standardized MedDRA Query (SMQ) or Customized MedDRA Query (CMQ) classification of the corresponding MedDRA version
†Acute respiratory failure and probable leptospirosis (n=1); pneumonia and pulmonary alveolar hemorrhage (n=1)

multiple indications to date, to characterize the safety profile of atacicept.

Methods Analyses were based on 3 pooled datasets: double-blind placebo-controlled (DBPC) set (n=1568; key endpoint: treatment-emergent AEs [TEAEs]); SLE set (n=761; key endpoint: IgG change and serious infection rates); and full analysis set (n=1845; key endpoint: exposure-adjusted mortality).

Results Of 1568 patients in the DBPC set, 30.8% received placebo, 8.2% atacicept 25 mg, 24.5% atacicept 75 mg and 36.5% atacicept 150 mg. Overall, baseline characteristics were balanced across treatment arms. Treatment exposure was similar with placebo and atacicept 75 and 150 mg (278.3, 225.0 and 286.7 patient-years, respectively), but was lower with atacicept 25 mg (51.5 patient-years). Exposure-adjusted TEAE rates were generally higher with atacicept vs placebo, with no consistent association between atacicept dose and cardiac arrhythmias, serious and severe infections or injection site reactions (table 1). Serious infection and serious TEAE rates were similar between atacicept and placebo. TEAE-related discontinuation rates were higher with atacicept vs placebo (16.1 vs 10.9 per 100 patient-years). In the SLE set, there was no association between reduced IgG levels and increased infection rates. Across all studies (full analysis set), 11 patients died during treatment (10 atacicept [0.5%], 1 placebo [0.1%]). Infection-related deaths in the DBPC set are shown in the table 1. Exposure-adjusted mortality rates per 100 patient-years were 3.60 (95% CI: 0.90–14.38) with atacicept 25 mg, 0.34 (95% CI: 0.05–2.43) with 75 mg, 1.18 (95% CI: 0.49–2.82) with 150 mg, and 0.44 (95% CI: 0.06–3.12) with placebo.

Conclusions Results from this pooled analysis clarify the benefit-risk relationship for atacicept, which is being further evaluated in additional clinical studies in IgA nephropathy and SLE.

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211 IDENTIFYING LUPUS PATIENT SUBSETS AND SPECIFIC PHARMACODYNAMIC CHANGES THROUGH IMMUNE CELL DECONVOLUTION OF GENE EXPRESSION DATA IN ATACICEPT-TREATED PATIENTS IN THE APRIL-SLE STUDY

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Background The Phase II/III APRIL-SLE study evaluated the safety and efficacy of atacicept in systemic lupus erythematosus (SLE). The goal of this post-hoc analysis was to use cell-based gene signatures on the APRIL-SLE gene expression data to identify clusters of patients with potential to flare and to assess for difference in treatment effect of atacicept vs placebo.

Methods A published immune cell deconvolution algorithm was applied to whole-blood gene expression data from APRIL-SLE to identify relative proportions of 17 immune cell types. Patients were then grouped into clusters based on these immune cell profiles using a k-medoid clustering algorithm, and were compared to each other based on patient characteristics, biomarkers and clinical efficacy. In addition, the baseline expression and change in expression of putative APRIL-responder genes were compared among the clusters. APRIL-responder genes were identified by combining differential expression results from the APRIL-SLE study (Week 52 vs. Day 1 randomization) and tabalumab Phase III studies (Week 52 vs. Baseline; GSE88887).

Results Patient gene expression data (N=105; Placebo: N=30; atacicept 75 mg: N=40; atacicept 150 mg N=35) was used to group patients into 5 main clusters (P1-P5) by predominant characteristic cells: P1, T helper cells; P2, plasma cells; P3, neutrophils and B cells; P4, B cells; P5, activated dendritic cells. Patients in P2 and P5 were more likely to have positive anti-dsDNA antibodies (≥30 IU/ml) and elevated BLyS (≥1.6 ng/ml), as well as high IFN gene signature in the blood. Patients in P2 were more likely to have low complement C3 and C4 levels. In P2, P4, and P5 clusters the flare rate in the placebo group was significantly higher than in P1 and P3. In P2 and P4, atacicept 150mg treatment group showed delayed time to flare and reduced flare rate as compared with the placebo group. A comparison of differentially-expressed genes from clinical studies of SLE patients on atacicept (targets BLyS & APRIL) vs tabalumab (targets BLyS) revealed possible APRIL-responder genes: SDC1, PARM1 and MZB1. These genes have a higher baseline expression in the P2 and P4 compared to other clusters. SDC1 was reduced more in P2, P4, and P5 after atacicept treatment, while PARM1 and MZB1 decreased after atacicept treatment in P2 and P4.

Conclusions These post-hoc analyses revealed different subsets of SLE patients based on their molecular profiles, which identified patient subsets that might have differential treatment effect of atacicept vs placebo, and provided insights into potential mechanisms of flare.

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212 PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, DOSE-FINDING STUDY, EVALUATING THE BRUTON'S TYROSINE KINASE INHIBITOR EVOBRUTINIB IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS: STUDY DESIGN

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Background Evobrutinib is a highly specific, oral inhibitor of Bruton's tyrosine kinase, a key regulator of B cell and macrophage functions implicated in SLE. Evobrutinib was shown to be well tolerated in healthy volunteers in a phase 1b study and subsequently advanced to phase 2.

Methods In this double-blind, placebo-controlled, potentially pivotal, 52-week dose-finding study with an optional open-label extension (OLE) and a 4-week safety follow-up period (NCT02975336), patients are randomized 1:1:1:1 to receive low, mid or high dose evobrutinib, or placebo (figure 1). Eligible patients are aged 18–75 years, with an SLE diagnosis (SLICC criteria or ≥4/11 ACR classification criteria) ≥6 months prior to screening, a SLEDAI-2K total score of ≥6 (including SLEDAI-2K clinical score ≥4) at screening, and