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.

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 ($\geq$30 IU/ml) and elevated BLyS ($\geq$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.


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 $\geq$4/11 ACR classification criteria) $\geq$6 months prior to screening, a SLEDAI-2K total score of $\geq$6 (including SLEDAI-2K clinical score $\geq$4) at screening, and
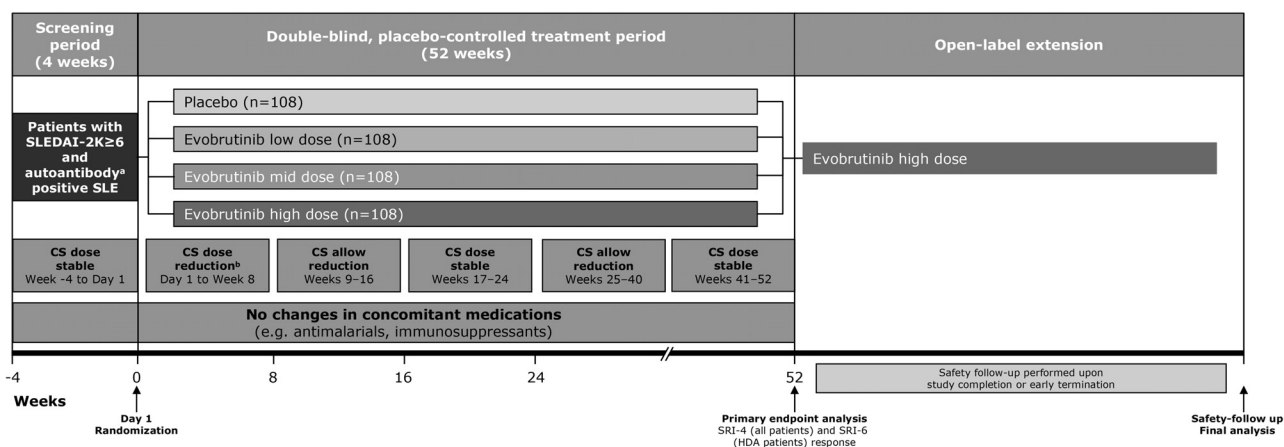
Abstract 212 Figure 1 Study design

are positive for anti-ds DNA, anti-Sm, and/or anti-nuclear antibodies. Exclusion criteria include: active, clinically significant, interstitial lung disease/pulmonary arterial hypertension; proteinuria >4 g/day and/or eGFR <45 mL/min/1.73 m²; recent acutely worsened renal function; and use of oral corticosteroids >30 mg/day prednisone equivalent, injectable corticosteroids, or change in dose of corticosteroids within 2 weeks prior to or during screening. The primary efficacy endpoint family comprises response based on SLE Responder Index (SRI)-4 among all patients and SRI-6 in patients with high disease activity (baseline SLEDAI-2K ≥10) at Week 52. Success on either endpoint will support a conclusion of efficacy. Primary safety endpoints include nature, severity, and incidence of adverse events (AEs) and serious AEs. Secondary endpoints include the time to first severe flare up to Week 52, SRI-4 and SRI-6 response at Week 52 in the serologically active subgroup, and disease activity over time, including attaining low disease activity, and change from baseline in Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI)-A at each study visit. The primary analysis is planned when all patients have completed the safety follow up for the 52-week blinded portion of the study, entered the OLE, or have discontinued prematurely from the study.

Results Recruitment is ongoing. Target enrolment is 432 to 468 participants. The first patient was randomized on 20 January 2017; study completion is expected end of 2019.

Conclusions This study will provide clinical proof of concept of the efficacy and safety of evobrutinib in SLE.

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| 213 | ASSOCIATION BETWEEN AGE OF SLE DIAGNOSIS AND DISEASE DAMAGE DIFFERS ACROSS RACIAL/ETHNIC GROUPS: RESULTS FROM THE CALIFORNIA LUPUS EPIDEMIOLOGY STUDY |

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Background Earlier age of SLE onset is associated with greater disease damage, even after taking into account the effects of current age and disease duration. We sought to determine if this association was consistent across racial and ethnic groups, given the differences in disease severity among these groups.

Methods Data derive from the baseline visit of the California Lupus Epidemiology Study (CLUES), an ongoing cohort of patients in the San Francisco Bay Area with confirmed SLE diagnoses, drawn from a variety of clinical sources and prior SLE studies. Participants provided access to medical records and had a visit with a study physician in which clinical labs were drawn. Disease damage was measured using the SLICC/ACR Damage Index (SDI), calculated at the study visit. Age of diagnosis was ascertained by the study physician or from the medical records. Race/ethnicity (White, African American, Hispanic of any race, and Asian) and educational attainment (high school or less, some college, college graduate) were determined by patient report. Due to the small sample size, patients from other racial groups were excluded from this analysis (n=5). Using multiple linear regression, we estimated a model of SDI as a function of race/ethnicity and age of diagnosis, plus terms for interaction between the variables. The model controlled for sex, current age, and education.
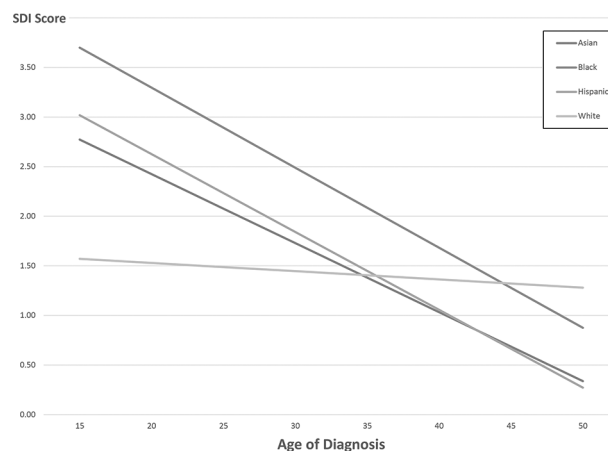
Abstract 213 Figure 1 SDI by race/ethnicity and age of diagnosis