Abstract 200 Table 1 Primary, key secondary, and subgroup efficacy analyses (mITT population)

	Belimumab (n=299) ^a	Placebo (n=149)
SRI-S2K response^b at Week 52, n (%)	145 (48.7)	62 (41.6)
Odds ratio (95% CI) vs placebo	1.40 (0.93–2.11)	
P-value	p=0.1068	
SRI response^c at Week 52, n (%)	146 (49.0)	62 (41.6)
Odds ratio (95% CI) vs placebo	1.42 (0.94–2.15)	
Number of patients with severe SFI flare over 52 weeks, n/n (%)	58 (19.4)	37 (24.8)
Hazard ratio (95% CI) vs placebo	0.77 (0.51–1.17)	
Patients who experienced a reduction in prednisone dose^d, n/n (%)	27/184 (14.7)	12/95 (12.6)
Adjusted odds ratio (95% CI)	1.30 (0.61–2.80)	
SRI-S2K^a response at Week 52 in subgroups		
Patients with baseline SS-S2K score ≤ 9, n/n (%)	62/140 (44.3)	24/56 (42.9)
Odds ratio (95% CI) vs placebo	0.97 (0.51–1.85)	
P-value	p=0.9198	
Patients with baseline SS-S2K score ≥ 10, n/n (%)	83/158 (52.5)	38/93 (40.9)
Odds ratio (95% CI) vs placebo	1.76 (1.03–3.00)	
P-value	p=0.0384	
Patients with low baseline C3 and/or C4 levels, n/n (%)	51/108 (47.2)	14/57 (24.6)
Odds ratio (95% CI) vs placebo	3.00 (1.45–6.23)	
P-value	p=0.0031	
Patients without low baseline C3 or C4 levels, n/n (%)	94/190 (49.5)	48/92 (52.2)
Odds ratio (95% CI) vs placebo	0.92 (0.55–1.54)	
P-value	p=0.7554	
Patients with low C3 and/or C4 and anti-dsDNA ≥ 30 IU/mL, n/n (%)	41/91 (45.1)	12/50 (24.0)
Odds ratio (95% CI) vs placebo	3.00 (1.35–6.68)	
p-value	p=0.0072	
Patients without low C3, C4 or anti-dsDNA ≥ 30 IU/mL, n/n (%)	104/207 (50.2)	50/99 (50.5)
Odds ratio (95% CI) vs placebo	1.01 (0.62–1.66)	
P-value	p=0.9556	
Patients from US/Canada, n/n (%)	49/131 (37.4)	25/65 (38.5)
Odds ratio (95% CI) vs placebo	0.97 (0.52–1.81)	
P-value	p=0.9334	
Patients from the rest of the world, n/n (%)	96/167 (57.5)	37/84 (44.0)
Odds ratio (95% CI) vs placebo	1.81 (1.05–3.13)	
P-value	p=0.0324	

^aOne patient in the belimumab group was excluded from the analyses as they did not have a baseline or screening PGA score; ^bmodified S2K scoring for proteinuria; ^cwith SELENA-SLEDAI scoring of proteinuria; ^dreduction in prednisone dose, in patients initially treated with >7.5 mg/day, by ≥25% to ≤7.5 mg/day during Weeks 40–52.

Anti-dsDNA, anti-double-stranded deoxyribonucleic acid; C, complement; CI, confidence interval; mITT, modified intent-to-treat; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus-SLE Disease Activity Index; SFI, SLE flare index; SRI-S2K, SLE Responder Index-SLEDAI-2000; SS, SELENA-SLEDAI.

screening. Patients were randomized (2:1) to monthly belimumab 10 mg/kg IV or placebo, plus SoC. The primary endpoint was the SLE Responder Index (SRI) response rate with modified SLEDAI-2K (S2K) scoring for proteinuria at Week 52 (SRI-S2K response required a 4 point reduction in the SELENA-SLEDAI (SS)-S2K, no worsening [increase of <0.3] in Physician's Global Assessment (PGA), and no new BILAG A or 2 new B organ domain scores). Key secondary endpoints included SRI response rate with SS scoring of proteinuria at

Week 52, time to first severe SFI flare, and reductions in prednisone dose by 25% to 7.5 mg/day during Weeks 40–52. Subgroup analyses of the primary endpoint were also conducted. Step-down sequential testing was utilized to control the overall type 1 error rate (2-sided, $\alpha=0.05$). Safety was assessed by monitoring adverse events (AEs).

Results The mITT population comprised 448 patients; 96.9% were female and mean (SD) age was 38.8 (11.42) years. Although the study did not achieve the primary endpoint, numerical trends were observed in favor of belimumab, and significant improvements were observed in subgroups with characteristics of high disease activity (HDA; table). Study withdrawals were similar between groups (belimumab 22.4%; placebo 24.2%) and AEs were the primary reason for withdrawals (belimumab 5.4%; placebo 6.7%). The percentage of patients who experienced an AE (belimumab 83.7%; placebo 87.3%) or serious AE (belimumab 10.9%; placebo 18.8%) was similar between groups. Two deaths occurred within the belimumab group (0.6%; pneumonia and meningitis); neither were established as directly related to belimumab.

Conclusions Whilst the primary endpoint of this study in black patients with SLE was not achieved, improvements in favor of belimumab were observed, with significant benefits in patients with HDA. The safety profile was acceptable and consistent with previous studies.

Funding Source(s): Study (BEL115471) funded by GSK.

201

USTEKINUMAB TARGETS A NOVEL MECHANISM OF ACTION TO TREAT PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

¹Ronald van Vollenhoven*, ²Bevra H Hahn, ³George C Tsokos, ⁴Shawn Rose. ¹Amsterdam Rheumatology and Immunology Center; ²University of California, Los Angeles; ³Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School; ⁴Janssen Research and Development, LLC

10.1136/lupus-2019-lsm.201

Background Both IL-12 and IL-23 have been implicated in the pathogenesis of human and experimental lupus,^{1–6} and in a drug repositioning analysis, the anti-IL-12/23 monoclonal antibody ustekinumab (UST) was identified as a high-priority candidate for the treatment of patients with SLE.⁷ We evaluated the efficacy, safety, and molecular effects of UST in a Ph2 trial.⁸

Methods A Ph2, placebo (PBO)-controlled study was conducted in 102 adults with seropositive (ANA, anti-dsDNA, and/or anti-Smith autoantibodies) SLE by SLICC criteria and active (SLEDAI 6 and 1 BILAG A and/or 2 BILAG B) disease. Patients were randomized (3:2) to receive UST IV ~6 mg/kg or PBO at wk0, followed by SC injections of UST 90 mg q8w or PBO, both added to standard care. PBO patients crossed over to SC UST at wk24. The primary endpoint was proportion of patients achieving SLE Responder Index (SRI)–4 response at wk24. Circulating levels of type I (IFN-I) and type II interferon (IFN-II) were assessed by microarray of whole blood RNA samples and serum protein ELISA analyses.

Results SRI-4 response at wk24 was significantly greater ($p=0.0057$) in the UST group (62%) vs PBO (33%). UST also demonstrated greater improvement in musculoskeletal and mucocutaneous disease features vs PBO at wk24. The risk of a new BILAG flare (1 new BILAG A or 2 new BILAG B) was significantly lower in the UST group vs. PBO (HR 0.11 [95% CI 0.01–0.94]; $p=0.0078$; wk12 to wk24 prespecified

analysis). Between wk24 and wk48, response rates across disease measures were either sustained (e.g. SRI-4, 62% at wk24 vs 63% at wk48; joint response 87% at wk24 vs 87% at wk48) or increased (CLASI response, 53% at wk24 vs 69% at wk48) in those randomized to UST. Following crossover at wk 24, an additional 10%–20% of PBO patients responded to UST (n=33) in the outcomes studied. Clinical response to UST was associated with decreases in IFN- protein and gene signature. In contrast, IFN-I levels were stable over time and were not associated with UST response. Safety events were consistent with the known UST safety profile.

Conclusions UST provided sustained clinical benefit in global and organ (mucocutaneous and joint disease)-specific SLE activity measures with a safety profile consistent with approved indications. Thus, UST may be an effective biologic therapy for SLE by blocking IL-12 and IL-23-driven pathogenic mechanisms which are independent of the IFN-I pathway.

Funding Source(s): Janssen Research and Development, LLC supported this study.

REFERENCES

1. Relle M, et al. *Autoimmun Rev*. 2015;**14**:1005.
2. Kikawada E, et al. *J Immunol*. 2003;**170**:3915.
3. Dai J, et al. *Eur J Immunol*. 2007;**37**:706.
4. Dai H, et al. *J Immunol*. 2017;**199**:903.
5. Martin JC, et al. *Clin Immunol*. 2014;**154**:1.
6. Mesquita D, et al. *Clin Exp Immunol*. 2018;**191**:50.
7. Grammer AC, et al. *Lupus* 2016;**25**:1150.
8. van Vollenhoven RF, et al. *Lancet* 2018;**392**:1330.

202

TARGETED SEQUENCING IN 1200 SLE PATIENTS REVEAL DAP1 REGULATORY HAPLOTYPE THAT POTENTIATE AUTOIMMUNITY

¹Prithvi Raj*, ²Ran Song, ²Linley Riediger, ²Dong-Jae Jun, ²Igor Dozmorov, ²Chaoying Liang, ²Bo Zhang, ²Benjamin Wakeland, ²Carlos Arana, ²Jinchun Zhou, ²David R Karp, ²Quan Li, ²Edward K Wakeland. ¹University of Texas Southwestern Medical Center, ²UT Southwestern Medical Center

10.1136/lupus-2019-lsm.202

Abstract 202 Figure 1 SLE associated DAP1 haplotype in Caucasian, African American and Asian population. Panel a: shows the sequencing depth across DAP1 gene locus on chromosome 5. Panel b: shows the 62kb LD (Linkage Disequilibrium) block that contain top 19 SLE associated variants (rsIDs shown). The peak SLE associated SNP rs267985 and strongest DAP1 eQTL rs2930047 are shown. Panel c: Median-joining (MJ) network analysis on most common DAP1 haplotypes in Caucasian SLEs and healthy controls. Spheres (termed nodes) represent the locations of each haplotype (from Table 2) within the network and the size of the node is proportional to the overall frequency of that haplotype in the dataset. Each node is overlaid with a pie chart that reflects the frequency of that haplotype in SLE group (yellow) versus healthy group (black). The lines connecting the nodes are labeled with the variants that distinguish the connected nodes and the length is proportional to the number of variants. Odds ratio (OR) are shown for two most significant alleles. Red highlighted nodes indicate SLE risk clades. . Panel d: Median-joining (MJ) network analysis on most common DAP1 haplotypes in African American SLEs and healthy controls. . Panel e: Median-joining (MJ) network analysis on most common DAP1 haplotypes in Asian SLEs and healthy controls.