Selected abstracts on RA,SS EULAR 2015

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OP0029

BARICITINIB, AN ORAL JANUS KINASE (JAK)1/JAK2 INHIBITOR, IN PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS (RA) AND AN INADEQUATE RESPONSE TO TNF INHIBITORS: RESULTS OF THE PHASE 3 RA-BEACON STUDY

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Background: In ph 2 studies, baricitinib (bari) improved disease activity with an acceptable safety profile in patients (pts) with active RA naïve to biologic DMARDs (bDMARDs).[1,2]

Objectives: To report results from a ph 3 study of bari in pts with active RA and an inadequate response or intolerance to ≥1 TNF inhibitor (TNFi).

Methods: Pts with active RA (TJC & SJC ≥6, hsCRP ≥3mg/L) on conventional DMARDs (cDMARDs) were randomized 1:1:1 to placebo (PBO) or bari (2 or 4 mg) QD for 24 wks. All bDMARDs were discontinued ≥28d prior to treatment. Primary endpoint was ACR20 response at Wk 12 for bari 4 mg vs. PBO.

Results: Of 527 randomized pts, 57% had received ≥2 bDMARDs and 38% had received ≥1 non-TNFi bDMARD. Fewer pts discontinued treatment prior to Wk 24 on bari 2 or 4 mg vs. PBO (10%, 11%, 18%, respectively). ACR20 response at Wk 12 was higher with bari 4 mg vs. PBO (55% vs. 27%, $p \leq 0.001$). Improvements in ACR20, ACR50, ACR70, DAS28, CDAI, SDAI, and HAQ-DI were seen (Table), many as early as Wk 1. Treatment benefit was sustained through Wk 24 for the 4 mg dose. More TEAEs occurred in pts receiving bari 2 or 4 mg compared to PBO (71%, 77%, 64%, respectively) including infections (44%, 40%, 31%, respectively). SAE rates through 24 wks were similar among pts receiving bari 2 or 4 mg or PBO (4%, 10%, and 7%, respectively) including serious infections (2%, 3%, and 3%, respectively). There were no opportunistic

	Wk 12			Wk 24		
	PBO (N=176)	2 mg QD (N=174)	4 mg QD (N=177)	PBO (N=176)	2 mg QD (N=174)	4 mg QD (N=177)
ACR20	27	49***	55***	27	45***	46***
ACR50	8	20**	28***	13	23*	29***
ACR70	2	13***	11**	3	13***	17***
DAS28-hsCRP ≤3.2	9	24***	32***	11	20*	33***
DAS28-hsCRP <2.6	4	11**	16***	6	11	22***
DAS28-ESR ≤3.2	4	13**	12**	7	12	17**
DAS28-ESR <2.6	1	6**	6*	3	5	9*
CDAI ≤10	11	24**	28***	15	23	31***
CDAI ≤2.8	2	3	6	3	5	9*
SDAI ≤11	9	22***	28***	14	22*	31***
SDAI ≤3.3	2	2	5	2	5	9**
HAQ-DI MCID ≥0.22	43	59**	67***	30	50***	53***

Data are % patients achieving response (NRI); *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$ vs. PBO.

infections, TB, or GI perforations. Two non-melanoma skin cancers and 2 major adverse cardiovascular events, including 1 death (stroke), were seen with bari 4 mg. Lab findings were consistent with ph 2 studies. Abnormalities leading to discontinuation were infrequent.

Conclusions: In pts with active RA on cDMARDs and an inadequate response to bDMARDs, once daily oral bari was associated with rapid and sustained clinical improvements through 24 wks, with an acceptable safety and tolerability profile. The largest benefit was seen with the 4 mg dose. Additional ph 3 studies in bDMARD-naive pts are ongoing.

References:

[1] Keystone et al. Ann Rheum Dis 2015;24:333-340
[2] Tanaka et al. Arthritis Rheum 2013;65(S10):S765

OP0034

EFFICACY AND SAFETY OF MAVRILIMUMAB, A FULLY HUMAN GM–CSFR-ALPHA MONOCLONAL ANTIBODY IN PATIENTS WITH RHEUMATOID ARTHRITIS: PRIMARY RESULTS FROM THE EARTH EXPLORER 1 STUDY

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Background: Of patients with RA, ~40% of do not achieve a minimal acceptable improvement (ACR20) despite modern biologic therapy.[1,2,3] Granulocyte-macrophage colony-stimulating factor (GM–CSF) is implicated in RA pathogenesis via myeloid and granulocyte cell lineage activation. In a 12-week Phase IIa study, mavrilimumab, a first-in-class inhibitor of the GM–CSF receptor-α demonstrated a sustained effect via this novel therapeutic pathway in RA.[4]

Objectives: To evaluate the efficacy and safety of mavrilimumab in patients with moderate to severe, adult-onset RA in a 24-week, Phase IIb study.

Methods: Patients (18–80 yrs; inadequate response to ≥1 DMARDs; DAS28–CRP ≥3.2; ≥4 SJC) receiving MTX were randomized to receive 1 of 3 SC mavrilimumab dosages (150, 100, 30 mg every other week [eow]) or placebo

Endpoint	Mavrilimumab			PBO
	150 mg eow (N=79)	100 mg eow (N=85)	30 mg eow (N=81)	(N=81)
Week 12				
Mean (SE) change from BL in DAS28–CRP	-1.90 (0.136)	-1.64 (0.132)	-1.37 (0.136)	-0.68 (0.136)
p-value vs. PBO	<0.001	<0.001	<0.001	
Week 24				
ACR20 responders, % (SE)	73.42 (4.97)	61.18 (5.29)	50.62 (5.56)	24.69 (4.79)
p-value vs. PBO	<0.001	<0.001	<0.001	
ACR50 responders, % (SE)	40.51 (5.52)	25.88 (4.75)	28.40 (5.01)	12.35 (3.66)
p-value vs. PBO	<0.001	0.030	0.013	
ACR70 responders, % (SE)	13.92 (3.90)	10.59 (3.34)	12.35 (3.66)	3.70 (2.10)
p-value vs. PBO	0.026	0.133	0.079	

BL, baseline; eow, every other week; PBO, placebo; SE, standard error

(PBO) plus MTX (7.5–25.0 mg/week). Co-primary endpoints were change in DAS28–CRP (Day 1 to Week 12) and ACR20 response rate (Week 24). Safety and tolerability were measured through assessment of AEs and pulmonary parameters. Results were analyzed using the modified ITT population.

Results: 326 patients from Europe, South America, and South Africa (mean [SD] age, 51.8 [11.1] yrs; female, 86.5%; mean [SD] DAS28–CRP, 5.8 [0.9]; RF+/anti-CCP+, 81.9%) received mavrilimumab 150, 100 or 30 mg eow or PBO (N=79, 85, 81 and 81, respectively). At Week 12, a statistically significant difference in DAS28–CRP change from baseline ($p<0.001$) was observed for all dosages of mavrilimumab vs. PBO. At Week 24, a significantly greater percentage of all mavrilimumab-treated patients also met the ACR20 co-primary endpoint vs. PBO (table). A dosage response was observed across several secondary endpoints, with separation from PBO evident as early as Week 1 and first dose. The most common treatment-emergent AEs were headache (7.6%, 4.7%, 6.2%, 2.5%), nasopharyngitis (7.6%, 3.5%, 4.9%, 7.4%) and bronchitis (5.1%, 1.2%, 3.7%, 7.4%) for mavrilimumab 150, 100, 30 mg eow or PBO, respectively. There was no increase in pulmonary AEs for mavrilimumab vs. PBO (6.3%, 3.5%, 6.2% vs. 9.9%). No serious infections were observed in the 100 and 150 mg eow groups. Two cases of pneumonia were observed (one each in mavrilimumab 30 mg eow and PBO groups). There were no deaths or anaphylaxis, and no apparent dosage relationship for AEs. >90% of patients entered a long-term, open-label extension study.

Conclusions: This Phase IIb study demonstrated the potential benefit of inhibiting macrophage activity via the GM–CSF receptor-α pathway on RA disease activity. The study met both co-primary endpoints with a clear dosage response. Mavrilimumb was well-tolerated over the 24-week study period.

References:

OP0031

A PHASE 2 STUDY EVALUATING THE EFFICACY AND SAFETY OF SUBCUTANEOUSLY ADMINISTERED USTEKINUMAB AND GUSELKUMAB IN PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS DESPITE TREATMENT WITH METHOTREXATE

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Objectives: To evaluate UST (anti-IL-12/23p40 mAb) and GUS (investigational anti-IL-23p19 mAb) in reducing signs and symptoms in active RA despite MTX.
Methods: In this Ph2, randomized, double-blind, multicenter, PBO-controlled, parallel-group study, patients (18-80yrs) with active RA (≥6 tender joint count [TJC] and 6 swollen joint count [SJC] and serum CRP≥0.80mg/dL) despite MTX, were randomized to the following through wk28 (with MTX): PBO wks 0,4, q8wks; UST90mg wks 0, 4, q8wks; UST90mg wks 0, 4, q12wks; GUS200mg wks 0, 4, q8wks; or GUS50mg wks 0, 4, q8wks. Patients were on MTX (10mg-25mg/wk) for ≥6 months with stable dose for a minimum of 12wks prior to randomization. Oral prednisone/equivalent (≤10 mg/day) and NSAIDs were permitted; previous and concomitant use of biologics not permitted. At wk16, PBO patients who failed to achieve ≥10% improvement (both TJC and SJC) received UST 90mg at wk16, 20, and 28. All patients were followed for safety through wk48. Primary endpoint was ACR20 response at wk28.

Results: 274 patients were enrolled; 22 (8.0%) d/c through wk28. Major reasons for d/c: lack of efficacy (10 [3.6%]);AEs (8 [2.9%]). Patient demographics were generally similar between groups. Baseline clinical disease characteristic were well balanced across groups except median disease duration (slightly longer in PBO [6.3yrs] vs UST [4.15 yrs] and GUS [4.30 yrs] groups). Baseline median CRP for all patients was 1.5mg/dL and median SJC and TJC were 14 and 24, resp. Proportion of patents with ACR20 did not differ significantly between groups; however some differences were observed for secondary endpoints (Table). Through wk48, 45.5% PBO, 50.4% combined UST, and 43.1% combined GUS had ≥1 treatment-emergent adverse events (TEAEs); serious TEAEs were reported in 5.5%, 6.4%, 2.8%, in PBO, combined UST and combined GUS,

Table. Primary and major secondary endpoints.

	PBO + MTX	UST + MTX			GUS +MTX		
		90mg q8w	90mg q12w	Combined	50mg q8w	200mg q8w	Combined
Patients randomized	55	55	55	110	55	54	109
ACR20 response Wk28 (*1° endpoint*) p value	40%	52.7% 0.184	54.5% 0.130	53.6% 0.101	38.2% 0.832	44.4% 0.642	41.3% 0.877
ACR20 response Wk12 p value	29.1%	37.0% 0.381	34.5% 0.543	35.8% 0.395	20.0% 0.273	33.3% 0.629	26.6% 0.737
Change from baseline in DAS28-CRP Wk28 (LS Means [±SE]) p value	-0.94(0.17)	-1.53(0.17) 0.019	-1.50(0.18) 0.025	-1.52(0.13) 0.006	-1.42(0.17) 0.045	-1.21(0.17) 0.248	-1.31(0.13) 0.074
Change from baseline in HAQ-DI Wk 28 (LS Means [±SE]) p value	-0.30(0.07)	-0.48(0.07) 0.060	-0.44(0.07) 0.134	-0.46(0.05) 0.068	-0.40(0.08) 0.345	-0.41(0.08) 0.280	-0.40(0.05) 0.230

ACR=American College of Rheumatology 20 response criteria, CRP=C-reactive protein, DAS28=disease activity score employing 28-joint count, MTX=methotrexate, PBO=placebo,UST=ustekinumab, GUS=guselkumab

respectively. Death occurred in 1 patient (UST90mg q8wk) (suspected pulmonary embolism or thoracic aorta aneurysm). Infections were reported in 29.1%, 29.6%, and 22.9% in the PBO, combined UST, and combined GUS groups, respectively; serious infections occurred in 1 PBO patient (appendicitis), 1 UST 90mg q8wk-treated patient (UTI) and 2 GUS 200mg q8wk-treated patients (1 lobar pneumonia and 1 gastroenteritis). No TB, opportunistic infections, MI or stroke were reported. A serious TEAE of unstable angina was reported in PBO. There were 2 cases of malignancy: squamous cell carcinoma of lung in UST 90mg q12wk group and breast cancer in GUS 200mg q8wk.

Conclusions: Neither UST nor GUS demonstrated significant efficacy in improving signs and symptoms of active RA based on ACR20 response at wk28. Improvements (based on nominal $p<0.05$) were observed in some secondary efficacy measures in both UST groups vs PBO. Both UST and GUS were generally well tolerated. Based on these results,inhibition of IL12 and/or IL23 does not appear to significantly alleviate signs and symptoms of active RA. These results provide additional insights into the differences between RA and psoriatic joint disease.

THU0179

TOFACITINIB, AN ORAL JANUS KINASE INHIBITOR, FOR THE TREATMENT OF RHEUMATOID ARTHRITIS: SAFETY AND EFFICACY IN OPEN-LABEL, LONG-TERM EXTENSION UP TO 6 YEARS

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Background: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA).

Objectives: To report tofacitinib safety, tolerability, and durability of response up to 72 months (mo) in long-term extension (LTE) studies.

Methods: Data were from 2, open-label studies: A3921024 (NCT00413699 [ongoing; database unlocked as of April 2014 data cut-off]) and A3921041 (NCT00661661). Patients (pts) had RA and participated in randomised Phases (P)1/2/3 tofacitinib studies. Treatment was initiated with tofacitinib 5 or 10 mg BID as monotherapy or with background DMARDs; data for both doses ± background DMARDs were pooled. Primary endpoints: AEs and laboratory safety. Confirmed data are reported for decreased haemoglobin (HgB), neutrophil, and lymphocyte counts, and increases >50% from baseline (BL) in creatinine. Secondary endpoints: ACR responses, DAS28-4(ESR), and HAQ-DI. Safety data were included over 84 mo and efficacy up to Mo 72 ($n \leq 29$ pts, post-Mo 72).

Results: 4858 pts were treated (mean [max] duration: 918 [2535] days). BL data were from index studies for 91% of pts. Total tofacitinib exposure was 12 359 pt-years (py). In total, 1747 pts (36.0%) discontinued (AEs: 882 [18.2%]; insufficient clinical response: 133 [2.7%]). Most common classes of AEs: infections and infestations (63.4%), musculoskeletal/connective tissue disorders (33.9%), and GI disorders (29.9%). Most frequently reported AEs: nasopharyngitis (16.3%), upper respiratory tract infection (14.5%), and urinary tract infection (10.3%). SAEs occurred in 23.0% of pts (incidence rate [IR] 9.9/100 py [95% confidence interval [CI]; 9.4, 10.5]) and serious infections in 7.2% (IR 2.9/100 py [95% CI; 2.6, 3.2]). Malignancies (excluding NMSC) were reported in 2.5% of pts (IR 1.0/100 py [95% CI; 0.8, 1.2]). IRs for SAEs, serious infections, and malignancies up to Mo 84 did not increase vs previously reported data (Mo 72).[1] Decreased Hgb (>2g/dL change from BL or Hgb <8 g/dL) occurred in 6.1% of pts and increased aminotransferases (>3× ULN) in 1.6% (ALT) and <1.0% (AST) of pts. Moderate to severe neutropenia (absolute neutrophil count [ANC] 0.5–1.5×10^3/mm^3) was reported in 1.3% of pts. No pts had ANC <0.5×10^3/mm^3. Absolute lymphocyte counts <0.5×10^3/mm^3 were reported in 1.1% of pts. Increases >50% from BL in creatinine occurred in 3.1% of pts. ACR20, ACR50 and ACR70 response rates for tofacitinib were sustained to Mo 72 (80.8%, 61.5% and 35.9%). Mean DAS28-4(ESR) was 6.29 at BL, 3.74 at LTE Mo 1 and 3.32 at Mo 72. Mean HAQ-DI score was 1.42 at BL, 0.81 at LTE Mo 1 and 0.77 at Mo 72.

Conclusions: A consistent safety profile and sustained efficacy up to 72 mo was observed in pts with RA receiving tofacitinib 5 or 10 mg BID in LTE studies.

OP0036

COMPARISON OF LOW- AND HIGH-DOSE RITUXIMAB FOR THE TREATMENT OF RHEUMATOID ARTHRITIS: AN UPDATED SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: In a previous systematic review (1), our group found no significant differences in most efficacy outcomes between low- (2x500 mg or 1x1,000mg) and high-dose (2x1,000 mg) rituximab (RTX) for the treatment of rheumatoid arthritis (RA).

Objectives: To update a systematic review and meta-analysis of randomized controlled trials (RCTs) comparing low- and high-dose RTX for the treatment of RA, considering the full publication of 2 important studies (2, 3).

Methods: The systematic literature review searching for RCTs was updated to November 6, 2014 using the Embase, PubMed, Cochrane Library, and Web of Science databases, and hand searching. The primary outcomes were the American College of Rheumatology (ACR) criteria for 20% improvement (ACR20), ACR50, and ACR70 responses and the Disease Activity Score in 28 joints (DAS28) at 24 and 48 weeks. The secondary outcomes were the EULAR (European League against Rheumatism) moderate/good and good responses, the change in Health Assessment Questionnaire (HAQ) score, the change in the radiographic modified Total Sharp Score (mTSS), levels of immunoglobulin G (IgG), and safety outcomes.

Results: In total, 7 RCTs (2-8) were identified; 5 RCTs (2,5-8) were included in the meta-analysis of efficacy and safety outcomes. There were no significant differences in the primary outcomes, EULAR responses, and change in HAQ. Mean change in mTSS was 0.25 units (95%CI: 0.01 to 0.49; P=0.04) higher in low-dose group at the end of week 52. Two RCTs (3, 4) did not demonstrate difference between the RTX regimens for maintaining clinical response (obtained initially using high-dose RTX) in anti-TNF-experienced patients. IgG levels were significantly lower in the high-dose group at week 24 (P=0.02). The low-dose RTX group presented a significantly lower incidence of first infusion reactions (P=0.02).

Conclusions: Our updated results further support the similar efficacy of low- and high-dose RTX in different subsets of RA patients, despite a small difference in radiographic progression favoring high-dose RTX. The low-dose regimen demonstrated a better clinical and laboratory safety profile.

FRI0155

RITUXIMAB ASSOCIATED LATE ONSET NEUTROPAENIA: SAFETY OF RETREATMENT RITUXIMAB THERAPY IN 900 PATIENTS

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Background: Neutropaenia is reported as a complication of rituximab (RTX) therapy for B cell malignancies with an incidence of 3-27%. [1] Data in rheumatic diseases are more limited and the optimal management of these patients has not been defined.

Objectives: The aims of this study were to determine the (1) incidence of rituximab-associated neutropaenia; (2) rates of infection; (3) time for recovery; (4) safety of retreatment with RTX, as a basis for management guidelines.

Methods: We conducted an observational study on all patients treated with RTX in a single centre between 2003 and 2014. Each cycle consisted of 2x1000mg (with a small percentage receiving half dose if in remission), repeated either on clinical relapse or pre-emptively. RAN was defined as an absolute neutrophil count $<2.0\times10^9$/L occurring at least 4 weeks after RTX excluding chronic neutropaenia or alternative plausible explanation (e.g. Felty's syndrome).

Results: Rituximab-associated neutropaenia was identified in 23 patients (2.5%) from a cohort of 912, and in 36 cycles (1.2%) out of 3062 administered. 20 patients were female; median (IQR) age 61 (54-68,2) years. 19 had rheumatoid arthritis (RA) (2.72% of all RA patients in this cohort), 1 SLE, 1 cryoglobulinemia, 1 Sjogren's syndrome and 1 GPA. 21 patient received concomitant methotrexate, 1 SLE patient received cyclophosphamide and 1 RA patient received hydroxychloroquine. Neutropaenia occurred at median 17 weeks (range 4-31) following RTX infusion and median 3nd cycle (range 1-9). The majority of neutropenic episodes were transient; neutrophil count was normal on the first repeat test in 24 (66.7%) of the episodes. The frequency of mild ($>1.0\times10^9$/L), moderate (0.5-1.0$\times10^9$/L) and severe ($<0.5\times10^9$/L) neutropaenia were 18 (50%), 6 (16.7%) and 12 (32.3%) episodes respectively. Of these, 10 infections requiring antibiotics were recorded in severe neutropenia cases, most commonly chest infection (6 also required granulocyte-colony stimulating factor (GCSF)). No case of neutropaenia >0.5 x 10^9/L was associated with infection. Irrespective of the degree of neutropaenia, all patients responded to RTX for the original indication. 26 (72.2%) of the episodes had complete B cell depletion as assessed by highly sensitive FACS. Of the patients who were retreated with RTX 2x1000mg: 11/19 had no recurrence of neutropaenia, 8/19 had mild neutropaenia in next cycle, and 4 patients had again recurrence of mild neutropenia. All the subsequent episodes were without associated infection or requirement for GCSF.
Conclusions: This is the largest cohort analysed for rituximab-associated neutropaenia. It can be concluded: (1) at <3%, it is less common in rheumatic disease than lymphoma; (2) monitoring alone is appropriate unless there is evidence of infection, when GCSF may be required; (3) the majority of the neutropenia cases recovered promptly; (4) counts >0.5 x109/L had no infections; (5) on retreatment, mild neutropaenia recurred in less than half with few consequences, with no evidence for neutropaenia becoming more severe on repeat cycles; (6) it therefore appears retreatment with monitoring is appropriate with caution only in severely neutropenic patients. The aetiology of rituximab-associated neutropaenia needs further investigation.

THU0094

IMPACT OF BIOLOGIC DISCONTINUATION IN PATIENTS WITH RHEUMATOID ARTHRITIS: OBSERVATION FROM THE CORRONA REGISTRY

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Background: Biologic agents are effective therapies for rheumatoid arthritis (RA). It has been suggested that biologic taper and discontinuation may be a viable option for a subset of RA patients whose disease activity is in control.
Objectives: The objective of this study was to describe the outcomes of biologic withdrawal in RA in the real world setting.
Methods: Data from the Corrona registry were used. RA patients who discontinued biologic therapies after ≥1 year of continuous use, and who had no additional biologic use for the subsequent 12 months were included. Disease activity were evaluated at baseline (time of biologic discontinuation), 3, 6 and 12 months post biologic discontinuation. The percentage of patients who had at least 1 flare (i.e. an increase in Clinical Disease Activity Index (CDAI) by ≥16.11, 2) off biologic therapy was assessed.
Results: Of the 120 included patients: 97 (80.8%) were female; age (mean ± SD) was 58.7±12.5 years, CDAI was 15.2±15.1, ESR was 48.7±34.3, CRP was 9.1±10.2 and HAQ 1.0±0.7, all at baseline. After biologic discontinuation, 8.3% of patients had at least 1 flare by 3 months, 30% by 6 months and 41.7% by 12 months.
Conclusions: In the current study using data from Corrona, biologic discontinuation in RA was associated with flares whose rates increase over time.

THU0392

EFFICACY AND SAFETY OF BELIMUMAB GIVEN FOR 12 MONTHS IN PRIMARY SJÖGREN'S SYNDROME: THE BELISS OPEN-LABEL PHASE II STUDY

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Background: Belimumab, a monoclonal antibody against BAFF registered for the treatment of systemic lupus erythematosus (SLE), was recently employed in primary SS in the BELISS trial (1), with encouraging results reported at 6 months of treatment.

Objectives: To report the efficacy and safety of long term treatment of Sjögren's syndrome (SS) with belimumab, targeting the B-cell activating factor.

Methods: Patients with primary SS were included in this 1-year open-label trial if they were positive for anti-SSA or anti-SSB antibodies and had systemic complications or persistent salivary gland enlargement or early disease or biomarkers of B-cell activation. Efficacy and safety were analyzed during the 1-year period of treatment. Limitedly to the Italian BELISS protocol, to evaluate a possible delayed response, treatment with belimumab could be also continued up to W48 if both the clinician and the patient agreed to complete the study despite the lack of response at W28, but in the absence of clinical worsening or side effects. A final evaluation was scheduled at W52. Response was defined as the improvement in at least 2 of the 5 following items: ≥30% reduction in dryness score on a visual analogue scale (VAS), ≥30% reduction in fatigue score on a VAS, ≥30% reduction in musculoskeletal pain score on a VAS, ≥30% reduction in systemic activity score on a VAS assessed by the physician, and/or ≥25% reduction in serum levels of any of the following B-cell activation biomarkers (free light chains of immunoglobulin, beta2-microglobulin, immunoglobulin monoclonal component, cryoglobulins, IgG) or ≥25% increase in C4 level.

Results: Nineteen out of 30 patients terminated the 52-week study, 15 of them being responders while 4 non-responders at W28. Thirteen of the 15 responders at W28 also responded at W52 (86.7%). Overall, fatigue, and pain appeared to improve with time from W28 to W52, although without any statistical significance, while dryness symptoms remained stable. However, a significant improvement in the physician VAS systemic activity score was recorded (3.2±1.2 at W28 vs. 2.5±1.1 at W52; p=0.04). In the 15 responders at W28, the ESSDAI was 7.5±4.0 at baseline, 3.9±3.1 at W28 ($p<0.0001$ vs. baseline), with a trend of further improvement at W52, i.e., 3.1±3.2 ($p<0.0001$ vs. baseline). In the same 15 responders, the ESSPRI was 6.0±1.0 at baseline, 4.5±1.8 at W28 (p=0.003 vs. baseline), and 4.3±2.3 at W52 (p=0.01 vs. baseline) (p=0.7, between W28 and W52). A moderate disease activity (i.e., an ESSDAI score ≥ 5) was observed in 5/15 (33.3%) patients at W52 vs. 6/15 (40%) at W28 and vs. 10/15 (66.7%) at baseline. Decreases of B-cell biomarkers observed at W28 persisted unchanged until W52, with the exception of the rheumatoid factor, which appeared to further decrease [64.8±78.7 IU/mL at baseline, 51.1±56.8 IU/mL at W28 (p=0.028, W28 vs. baseline) and 42.6±47.3 IU/ml at W52 (p=0.048, W52 vs. baseline)]. The safety of treatment was good at W52.

Conclusions: Long-term treatment with belimumab may be beneficial in SS. Randomised, controlled studies in larger populations are encouraged.