of adverse events (AEs) and discontinuations due to AEs were similar across groups, though serious AEs occurred more frequently in both tanezumab groups relative to placebo. Two deaths in the 5 mg tanezumab group were deemed unrelated to treatment. The only AE occurring in =3% of patients in any group, and more frequently (>1% difference) in both tanezumab groups relative to placebo, was OA. Total joint replacements (TJR) occurred in 6.7%, 7.8%, and 7.0% of patients in the placebo, tanezumab 2.5 mg, and tanezumab 5 mg groups, respectively. Joint safety events, including TJRs, were mostly adjudicated as normal progression of OA (58/79; 73.4%). Pre-specified joint safety events occurred in 0% and 2.5% (n = 14) of patients in the placebo and tanezumab (2.5 mg = 1.8%; 5 mg = 3.2%) groups, respectively. These 14 events in the tanezumab groups included rapidly progressive OA (2.5 mg n = 4; 5 mg n = 8), subchondral insufficiency fracture (2.5 mg n = 1), and primary osteonecrosis (5 mg n = 1).

Figure 1. Change from baseline in WOMAC Pain, WOMAC Physical Function, and Patient Global Assessment of OA scores at Week 24.
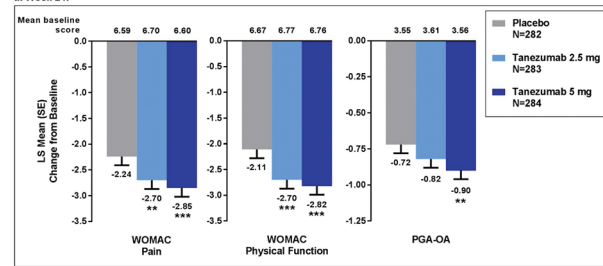
**p ≤ 0.01; ***p ≤ 0.001

Table 2. Treatment-Emergent AEs During the Treatment Period (All Causalities)

	Placebo	Tanezumab 2.5 mg	Tanezumab 5 mg
N (%) of patients	N=282	N= 283	N= 284
AE	155 (55.0)	150 (53.0)	162 (57.0)
Serious AE	3 (1.1)	8 (2.8)	9 (3.2)
Discontinued study due to AE	2 (0.7)	5 (1.8)	1 (0.4)
Discontinued treatment but continued study	7 (2.5)	3 (1.1)	4 (1.4)
Common AEs[a]			
Arthralgia	34 (12.1)	27 (9.5)	23 (8.1)
Nasopharyngitis	25 (8.9)	31 (11.0)	22 (7.7)
Back pain	15 (5.3)	16 (5.7)	17 (6.0)
Headache	18 (6.4)	15 (5.3)	14 (4.9)
Osteoarthritis	5 (1.8)	9 (3.2)	13 (4.6)
Paraesthesia	5 (1.8)	5 (1.8)	12 (4.2)
Influenza	5 (1.8)	5 (1.8)	9 (3.2)
Fall	8 (2.8)	12 (4.2)	7 (2.5)
Pain in extremity	7 (2.5)	9 (3.2)	5 (1.8)

[a] Occurring in ≥3% of patients in any group.

Conclusion: Tanezumab 5 mg significantly improved all co-primary endpoints of pain, physical function, and PGA-OA. Tanezumab 2.5 mg significantly improved pain and physical function, but did not reach significance on PGA-OA. AEs are consistent with previous studies of tanezumab in OA. A similar number of TJRs were reported across groups, though overall joint safety events were more frequent with tanezumab than placebo.

LB0008

THE EFFECT OF HLA-DRB1 RISK ALLELES ON THE CLINICALEFFICACY OF ABATACEPT AND ADALIMUMAB IN SEROPOSITIVE BIOLOGIC-NAÏVE PATIENTSWITH EARLY, MODERATE-TO-SEVERE RA: DATA FROM A HEAD-TO-HEAD SINGLE-BLINDEDTRIAL

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Background: Mechanistic differences between biologics are poorly understood. *HLA-DRB1* alleles containing the shared epitope (SE), which are strongly associated with RA, are present in 85% of anti-cyclic citrullinated protein 2 (anti-CCP2) + patients (pts) with RA (Jiang *et al. Arthritis Rheumatol* 2015). In a prior retrospective exploratory analysis, abatacept (ABA) was more effective in SE+ vs SE- pts (Oryoji *et al. Ann Rheum Dis* 2017). Head-to-head (H2H) comparisons with other agents are lacking.
Objectives: This H2H, single-blinded trial (NCT02557100) in biologic-naïve pts with early, active RA prospectively explored the relationship between *HLA-DRB1* SE and the clinical efficacy of ABA or adalimumab (ADA).
Methods: Adults with early (=12 mths from symptom onset), moderate-to-severe RA (ACR/EULAR 2010 criteria) seropositive for anti-CCP2 (>3x ULN) and RF, were randomised 1:1 to SC ABA 125mg wkly or SC ADA 40mg every 2 wks (both with stable, oral MTX wkly) for 24 wks. Pts were grouped by SE status (+/-) based on *HLA-DRB1* genotype (-: no SE allele; +: =1 SE allele). Safety was analysed throughout the trial and up to 8 wks post last study drug dose. Clinical efficacy was assessed at Wk24 to determine the proportion of ACR20/50/70 responders in ABA vs ADA arms, and the adjusted mean changes from baseline in DAS28 (CRP), SDAI and CDAI. Treatment (tmt) differences between ABA and ADA in SE + and SE− pts were assessed for ACR20/50/70 responders and DAS28 (CRP) remission at Wk24.
Results: 80 pts were treated: 40 ABA (9 SE-, 30 SE+, 1 SE unknown) and 40 ADA (9 SE-, 31 SE+). Baseline characteristics were balanced. Mean (SD) age, disease duration and DAS28 (CRP) were 46.0 (14.4) years, 5.5 (2.6) mths and 5.2 (1.1), respectively; 75% were female. No new safety signals were identified. In each arm, related AEs (ABA: 12 [30%]; ADA: 11 [27.5%]) and related serious AEs (ABA: 0; ADA: 1 [2.5%]) were similar. Numerically higher efficacy responses were seen with ABA vs ADA at Wk24 (Table 1). Similar results were observed for DAS28 (CRP), SDAI and CDAI. In SE+ pts, numerically higher efficacy responses were seen with ABA vs ADA at Wk24; 95% CI for estimated tmt differences for ACR20/50/70 responses and DAS28 (CRP) remission did not cross 0 (Figure 1).
Conclusion: In this seropositive early RA population, numerically higher efficacy responses were seen with abatacept vs adalimumab after 24wks of tmt, with more pronounced tmt differences in SE+ pts. Results are consistent with a previous

Table 1. Clinical outcomes at Wk24: as-treated analysis population

Clinical outcome	ABA (n=40)	ADA (n=40)	Estimate of difference for ABA vs ADA (95% CI)
ACR responses			
ACR20	83 (67, 93)	63 (46, 77)	20 (−3, 42)
ACR50	70 (54, 83)	45 (29, 62)	25 (2, 46)
ACR70	48 (32, 64)	30 (17, 47)	17.5 (−6, 39)
DAS28 (CRP)			
Adjusted mean change* (95% CI)	−2.6 (−2.9, −2.2)	−2.4 (−2.7, −2.1)	0.2 (−0.6, 0.3)†
Remission	48 (32, 64)	30 (17, 47)	17.5 (−6, 39)
SDAI			
Adjusted mean change* (95% CI)	−27.4 (−29.9, −24.9)	−26.1 (−28.7, −23.5)	−1 (−5, 2)†
Remission	35 (21, 52)	23 (11, 39)	12.5 (−11, 35)
CDAI			
Adjusted mean change* (95% CI)	−27.1 (−29.5, −24.7)	−25.0 (−27.5, −22.6)	−2 (−5.5, 1)†

Data are % (95% CI) unless stated otherwise. Estimates of adjusted mean change are from a repeated measures mixed model which includes baseline value, treatment group, time and time by treatment group interaction. Missing values were imputed as non-responders. DAS28 (CRP) remission: DAS28 (CRP) <2.6. SDAI remission: SDAI ≤3.3. *From baseline. †Adjusted mean difference for ABA vs ADA (95% CI). ABA=abatacept; ACR20/50/70=20/50/70% improvement in ACR criteria; ADA=adalimumab

Figure 1. Clinical outcomes in ABA- vs ADA-treated pts at Wk 24 by SE genotype: as-treated analysis population
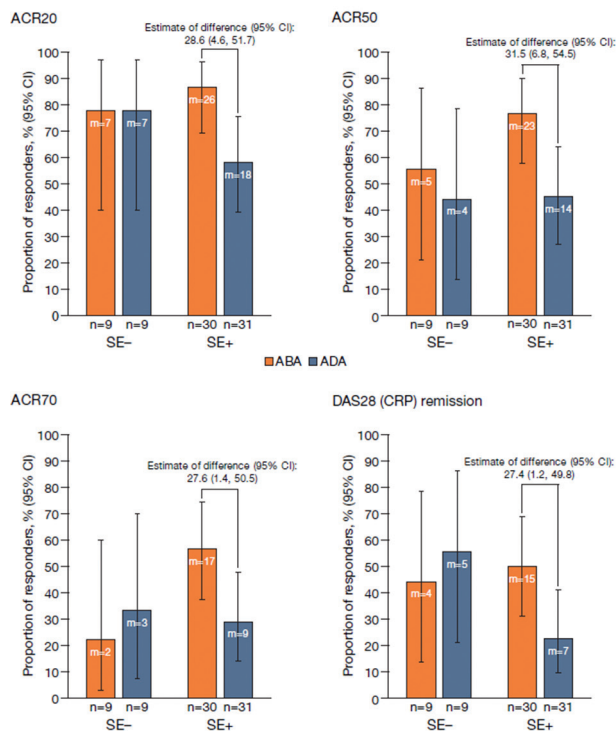
m indicates the number of patients with a response; n indicates the number of patients in the group. Patients with missing data for efficacy parameters at Week 24 are imputed as non-responders
ABA=abatacept; ACR20/50/70=20/50/70% improvement in ACR criteria; ADA=adalimumab; SE=shared epitope

Methods: The MR was implanted in 14 patients with active RA and prior insufficient response to =2 bDMARDS or JAK inhibitors with =2 different modes of action; all patients remained on stable background of methotrexate. Three weeks after implantation, the first 3 subjects were stimulated 1 min QD and, following safety review board approval, the remaining 11 patients were implanted with the MR and randomized to 1 min of sham, QD, or QID stimulations for 12 weeks. Patients, rheumatologists, joint assessors and monitors were fully blinded to treatment arm. Subjects randomized to sham had their devices activated after the primary endpoint at 12 weeks. Clinical efficacy was measured by DAS28-CRP response and contrast-enhanced MRI (RAMRIS OMERACT). The pharmacodynamic response to VNS was assessed in blood using cytokine production in an ex-vivo bioassay (TruCulture).

Results: 14 patients were enrolled (mean prior bDMARDs= 4.8, mean DAS28-CRP= 5.94). Implantation and stimulation were generally well tolerated. There were no device or treatment-related SAEs and 2 surgery related adverse events (left vocal cord paralysis, Horner's syndrome) that resolved without clinically significant sequelae. DAS28-CRP change at week 12 was (mean ± SEM): Open label QD= -1.44 ± 0.64, QD= -1.24 ± 0.88, QID= 0.38 ± 0.71, Sham=0.16 ± 0.21. Of QD stimulated patients, 4 of 6 had a EULAR good or moderate response. MRI measures of synovitis or osteitis did not change after 12 weeks of stimulation. RAMRIS erosion scores correlated with EULAR response (change ± SEM in erosion scores in EULAR responders = -2.2 ± 1.4 vs. 2.4 ± 0.96 in EULAR non-responders). The pharmacodynamic response to VNS was confirmed in actively stimulated groups with >30% decrease from baseline in bioassay levels of IL-1β, IL-6, and TNF-a at week 12.

Conclusion: The novel MR device and stimulation was well tolerated independent of the two surgery-related events. MR associated stimulation reduced signs and symptoms of RA in a meaningful number of highly drug-refractory subjects. No clinical improvement was observed in the sham group. These initial pilot data support the use of the MR in a larger blinded sham-controlled study in patients who have failed biologics or targeted oral therapies as a novel approach for treatment of RA and other chronic inflammatory diseases.

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study in which greater efficacy was seen with abatacept, but not TNF inhibitors, in anti-CCP2+ vs anti-CCP2- pts with RA (Harrold *et al. J Rheumatol* 2018).

LB0009   **FIRST-IN-HUMAN STUDY OF NOVEL IMPLANTED VAGUS NERVE STIMULATION DEVICE TO TREAT RHEUMATOID ARTHRITIS**

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Background: The inflammatory reflex plays a role in regulating innate and adaptive immunity through cellular and molecular pathways[1]. Activation of this neuro-immune reflex by electrical vagus nerve stimulation (VNS) reduced systemic inflammation and improved disease activity in a 17 subject rheumatoid arthritis (RA) proof-of-concept study using a reprogrammed epilepsy stimulator[2]. A novel miniaturized neurostimulator, the "MicroRegulator" (MR), was developed for a first-in-human pilot study in multi-drug refractory RA.

Objectives: To assess the safety and efficacy of the MR in a double-blind study in active RA patients.

LB0010   **ULTRA-LOW DOSES OF RITUXIMAB OR RETREATMENT OF RHEUMATOID ARTHRITIS: A RANDOMISED CONTROLLED NON-INFERIORITY TRIAL**

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Background: Rituximab (RTX) is an effective treatment for patients with Rheumatoid Arthritis (RA). 1000mg (1 × 1000mg or 2 × 500mg) has similar 6-month efficacy as the registered dose of 2 × 1000mg. Based on several case reports and a