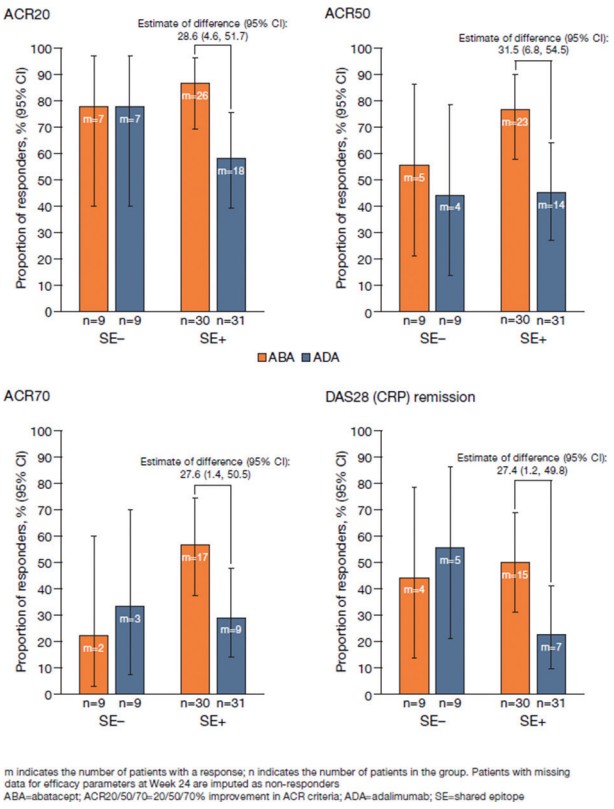
Figure 1. Clinical outcomes in ABA- vs ADA-treated pts at Wk 24 by SE genotype: as-treated analysis population



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

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).

Acknowledgement: Marianne Peluso (protocol manager); medical writing: Lola Parfitt (Caudex; funding: BMS)

Disclosure of Interests: William Rigby Consultant for: AbbVie, BMS, Genentech and Pfizer, Jane Buckner Grant/research support from: Janssen, Bristol-Myers Squibb (current); Novo Nordisk, Pfizer, Eli Lilly (past), Consultant for: Bristol-Myers Squibb, Eli Lilly, Lou Bridges: None declared, Marleen Nys Shareholder of: Bristol-Myers Squibb, Employee of: Bristol-Myers Squibb, Sheng Gao Shareholder of: Bristol-Myers Squibb, Employee of: Bristol-Myers Squibb, Martin Polinsky Shareholder of: Bristol-Myers Squibb, Employee of: Bristol-Myers Squibb, Alyssa Johnsen Shareholder of: Bristol-Myers Squibb, Employee of: Bristol-Myers Squibb, Neelanjana Ray Shareholder of: Bristol-Myers Squibb, Employee of: Bristol-Myers Squibb, Vivian Bykerk Grant/research support from: Mallinckrodt, BMS, Crescendo Biosciences, Sanofi/Regeneron., Consultant for: Amgen, Pfizer, UCB, Scipher, Sanofi/Genzyme/Regeneron

DOI: 10.1136/annrheumdis-2019-eular.8668

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 neuroimmune 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.
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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Disclosure of Interests: Mark C. Genovese Grant/research support from: Sanofi/Genzyme, Genentech/Roche, RPharm, Consultant for: Sanofi/Genzyme, Genentech/Roche, RPharm, Norman Gaylis Grant/research support from: Multiple clinical research trials, BMS, AbbVie, GSK, Janssen, Amgen, Pfizer, Regeneron, UCB, Sanofi, SetPoint, ImmunPharma, Astra Zeneca, Sandoz, Novartis, Gilead, Consultant for: electroCore, David Sikes Grant/research support from: SetPoint MedicalPfizerActelionAbbvieEli Lilly, Alan Kivitz Shareholder of: Novartis, Consultant for: Abbvie, Janssen, Pfizer, UCB, Genzyme, Sanofi, Regeneron, Boehringer Ingelheim, Sun Pharma Advanced Research, Flexion., Paid instructor for: Celgene, Horizon, Merck, Novartis, Pfizer, Genzyme, Sanofi, Regeneron, Speakers bureau: Celgene, Horizon, Merck and Genetech, Flexion, Diane M Horowitz Grant/research support from: SetPoint Medical, Charles Peterfy Shareholder of: Spire Sciences, Inc, Consultant for: AbbVie, Acerta, Amgen, AstraZeneca, Bristol-Myers Squibb, Centrexion, Daiichi Sankyu, Five Prime Therapeutics, Genentech, Hoffmann-La Roche, Janssen, Lilly USA, MedImmune, Merck, Novartis, Plexxikon, Pfizer, Sanofi, Salix-Santarus, Samsung, Employee of: Spire Sciences, Inc, Speakers bureau: Amgen, Yaakov Levine Shareholder of: SetPoint Medical, Employee of: SetPoint Medical, David Chernoff Shareholder of: SetPoint Medical, Consultant for: Crescendo BioScience, Employee of: SetPoint Medical

DOI: 10.1136/annrheumdis-2019-eular.8716

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

case series even lower doses might be sufficient for maintenance treatment, potentially improving safety and decreasing costs.(1)

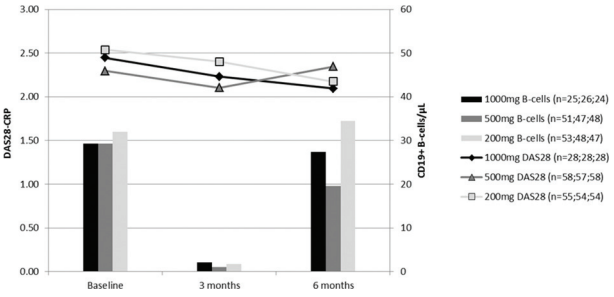
Objectives: To compare effectiveness of RTX retreatment with ultra-low doses (1 × 500mg or 1 × 200mg) to standard low dose (1 × 1000mg).

Methods: A 6-month double-blind randomised controlled non-inferiority trial (REDO study (2)) was performed in 5 centres in the Netherlands. Patients with RA responding well to RTX (based on DAS28-CRP<2.9 or clinical judgement) were randomised (1:2:2) to 1 × 1000mg, 1 × 500mg or 1 × 200mg RTX respectively. DAS28-CRP and peripheral CD19+ B-cells were measured at baseline, 3 and 6 months. Primary analysis (per protocol with LOCF) consisted of a hierarchical testing procedure comparing ultra-low doses (1 × 500mg at 3 and 6 months, then 1 × 200mg at 3 and 6 months) to 1 × 1000mg using a non-inferiority margin of 0.6 (on DAS28-CRP). DAS28-CRP change of study groups was compared using linear regression, adjusted for baseline DAS28-CRP, RF/ACPA status and concomitant csDMARD use.

Results: The projected inclusion was met (n=142, table 1a). In both ultra-low dose groups 2 patients received an extra dose of 1000mg RTX due to a flare. The 500mg dose was non-inferior to 1000mg at 3 months (-0.04 (95% CI -0.39 to 0.30)), but not at 6 months (0.31 (95% CI -0.05 to 0.68). The 200mg dose was non-inferior to 1000mg at both time points. Because of our pre-defined hierarchical testing, non-inferiority could not formally be inferred for the 200mg dose. Mean DAS28-CRP scores remained low in all groups throughout the study, and B-cell counts decreased similarly at 3 months (figure 1). In the 200mg group, more patients received intramuscular corticosteroid injection(s) compared to the 1000mg group (table 1b).

1a. Baseline characteristics (mean (sd) or n(%))			
	1000mg (n=29)	500mg (n=58)	200mg (n=55)
Age	63.8 (9.0)	64.0 (10.9)	64.2 (12.2)
Female	18 (62%)	37 (64%)	40 (73%)
Disease duration in years	17.1 (11.1)	14.9 (10.7)	13.5 (7.2)
RF/ACPA positive	27 (93%)	54 (93%)	49 (89%)
Concomitant csDMARD	18 (62%)	35 (60%)	32 (58%)
1b. Flares, co-medication and SAEs (n(%))			
Flare(s)	3 (10%)	14 (24%)	10 (18%)
Extra 1000mg RTX received*	0 (0%)	2 (3%)	2 (4%)
im gc injection(s)	4 (14%)	7 (12%)	16 (29%)
SAE(s)	3 (10%)	5 (9%)	5 (9%)

*2 patients with regular RTX accidently given before study end (protocol violation) not included



Conclusion: Non-inferiority of retreatment with 1 × 500mg or 1 × 200mg rituximab versus 1 × 1000mg after 6 months could not formally be established. However, ultra-low doses appear similarly effective in the majority of RA patients, judged by DAS28-CRP course over time and B-cell results, with use of slightly more co-medication.

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Disclosure of Interests: L.M. Verhoef: None declared, Nathan den Broeder: None declared, R.M. Thurlings Grant/research support from: Congress invitations: Roche, Abbvie, Cellgene, W.H. van der Laan: None declared, W. van der Weele: None declared, Marc Kok: None declared, H.J. Bernelot Moens: None declared, Thasia Woodworth: None declared, Bart van den Bemt Grant/research support from: UCB, Pfizer, Abbvie, Bristol-Myers Squibb, Consultant for: UCB, Novartis and Pfizer, Speakers bureau: Pfizer, AbbVie, UCB, Biogen, Sandoz, Frank van den Hoogen Grant/research support from: Grants, speakers fee, advisory boards: AbbVie, Actelion, Amgen, Boehringer Ingelheim, Biogen, BMS, Celgene, Celltrion Healthcare, Corbus, Janssen, Eli Lilly, Mundipharma, Novartis, Pfizer, Roche, Sandoz, Sanofi Genzyme., Alfons den Broeder Grant/research support from: Congress invitations: Roche, Cellgene, Abbvie, Biogen, Consultant for: Expert Witness for Fresenius, BI, BMS, Amgen

DOI: 10.1136/annrheumdis-2019-eular.8658

LB0011 A PHASE II SINGLE ARM (ADAPTIVE DESIGN) TRIAL OF TOCILIZUMAB IN ANTI-TNF REFRACTORY PATIENTS WITH JIA-ASSOCIATED UVEITIS (APTITUDE TRIAL)

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Background: Children with severe uveitis or those who have not responded to anti-tumour necrosis factor agents and methotrexate (MTX) are at significant risk of sight loss[1-3]. Evidence on alternative therapies is needed.

Objectives: To evaluate the clinical response to Tocilizumab with MTX in children with Juvenile Idiopathic Arthritis (JIA)-associated uveitis who failed anti-TNF therapy to determine the need for further research.

Methods: Multi-centre, open label, single arm trial using a two-stage Simon design[4].

Setting: 7 UK sites

Participants: Children aged 2-18 years with JIA-associated uveitis defined as "2 readings of cellular infiltrate in anterior chamber of SUN criteria grade ≤1+ or more during the preceding 6 weeks, the latest reading must be at the time of screening."

Intervention: Treatment with MTX and those weighing ≤30 kg treated with 162 mg of Tocilizumab every 2 weeks and those weighing <30 kg every 3 weeks.

Main Outcome Measures: Primary outcome was treatment response at 12 weeks defined as per SUN criteria as a 2 step decrease in the level of inflammation or decrease to 0 between baseline and 12 weeks of treatment. Data on safety, topical corticosteroid usage, tolerability, compliance, optic and ocular measurements, American College of Rheumatology Pedi core set criteria measurements, changes in biologic/Disease-modifying anti-rheumatic drugs therapy and flares of arthritis collected.

Results: 22 participants were registered; 1 was removed as found to be ineligible soon after registration. A total of 7 were classified as a pre-specified treatment response, the median unbiased estimate of proportion was 34% 95% CI (25% to 57%), p=0.11. 4 had macular oedema at baseline and this was resolved in 3 participants. Post-hoc analysis showed that there were 4 (19%) who were classified as a non-treatment response but had at least a one-step improvement at 3 months, leaving 10 (48%) showing no response, the mean (SD) number of steroid drops at baseline was 4.48 (3.11) and which reduced to 4.33 (2.29) at 12 weeks. Safety results were consistent with the known safety profile of Tocilizumab; no SAEs were reported.

Conclusion: Whilst this study did not pass the pre-specified criterion, the data shows almost a half of the participants including 7 (33%) with a 2-step improvement, and a further 3 (14%) with 1-step improvement, responded to Tocilizumab.

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Acknowledgement: This trial is funded by Versus Arthritis (project reference number 20659)

Disclosure of Interests: Athimalaipet Ramanan Consultant for: AbbVie, UCB, Sobi, Eli Lilly, Speakers bureau: Speaker fees/ honoraria from Abbvie, SOBI, Eli Lilly and UCB, AbbVie, UCB, Sobi, Eli Lilly, Andrew Dick: None declared, Ashley Jones: None declared, Andrew McKay: None declared, Catherine Guly: None declared, Ben Hardwick: None declared, Richard Lee: None declared, Matthew Smyth: None declared, Michael Beresford: None declared

DOI: 10.1136/annrheumdis-2019-eular.8744