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Title: ***Abatacept*** **reduces disease activity and power Doppler in ACPA negative undifferentiated arthritis:** ***a proof of concept clinical and imaging study***

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Short Title

Abatacept in ACPA negative poor prognosis undifferentiated arthritis

ABSTRACT: 250 words

Objectives: No proven treatment exists for anti-citrullinated peptide antibody (ACPA)-negative undifferentiated arthritis (UA). This study evaluated whether abatacept is effective in poor prognosis, ACPA-negative UA including its effect on ultrasound power Doppler (US PD)

Methods: A proof of concept, open-label, prospective study of 20 patients with DMARD-naïve, ACPA negative UA (≥ 2 joint synovitis) and PD ≥ 1 with clinical and 20 joint US [Grey Scale (GS)/PD] assessments at baseline, 6, 12, 18 and 24 months. All patients received 12 months of abatacept (monotherapy for minimum first 6 months). Primary endpoint was a composite of the proportion of patients that at 6 months achieved DAS44 remission, maximum of one swollen joint for at least 3 consecutive months and no radiographic progression (0-12months).

Results: 20/23 patients screened were enrolled [14 female; mean (SD) age 53.4 (11.2) years, symptom duration 7.5 (0.9) months]. Two (10%) achieved the composite primary endpoint. Reduction in mean(SD) DAS44 was observed from baseline value of 2.66(0.77) to 2.01(0.81) at 6 months and to 1.78(0.95) at 12 months. DAS44 remission rates were 6/20 (30%; 95%CI 15%, 51%) at 6 months and 8/20 (40%; 95%CI 22%,62%) at 12 months. A striking decrease in median(IQR) total PD score was noted from 10(4,23) at baseline to 3(2,12) and 3(0,5) at 6 and 12 months respectively.

Conclusions: This report is a first in potentially identifying an effective therapy, abatacept monotherapy, for poor prognosis ACPA negative UA, supported by a clear reduction in US PD. These data justify evaluation in a controlled study.

Keywords: Abatacept, Undifferentiated arthritis, Inflammatory arthritis, ACPA, Ultrasound

INTRODUCTION

An emerging aim in the management of rheumatoid arthritis (RA) is to identify patients at the pre-RA stage and intervene with immunomodulatory therapies to prevent its progression to RA. Undifferentiated arthritis (UA) is defined as an inflammatory oligo- or poly-arthritis, which does not fulfill criteria for a definitive diagnosis.

Rheumatoid factor (RF) and anti-citrullinated peptide antibody (APCA) are key elements that enable the classification of RA[1,2] with different rates of progression and response to treatment observed [3,4]. They are associated with persistence of inflammatory arthritis and are the best predictors of radiographic progression[5-7], thus considered poor prognosis factors. ACPA negative RA however is also associated at baseline with high level of disease activity, poor functional outcome and greater erosive disease [8,9]. Power Doppler (PD) on ultrasound (US) is a powerful predictive factor of persistent inflammatory arthritis in these autoantibody negative UA[10], and thus a poor prognosis factor that can be used as a tool to select ACPA negative UA at highest likelihood of persistence. The structural outcomes and pathological distinction between PD positive and negative, ACPA negative UA have however not been determined to date.

Several studies have suggested the ability of abatacept and/or methotrexate to delay progression of patients with ACPA positive UA [11,12] or improve outcomes [13]. There is no proven therapy for ACPA negative UA.

The hypothesis underlying this proof of concept study was that 12 months open-label abatacept would be effective in reducing persistent disease in adult subjects with ACPA negative UA, characterised by presence of PD, previously shown to be strongly predictive of persistence – the '*A*batacept in ACPA *S*ero-negative *U*ndifferentiated arthriti*S* (ASUS)' study .

PATIENTS AND METHODS

The study was sponsored by the University of Leeds (Sponsor Ref: RR08/8686; EudraCT: 2008-004878-41), approved by the appropriate research ethics committee and

conducted in accordance with International Conference on Harmonisation Good Clinical Practice and local regulations. All patients provided written informed consent for the 'ASUS' study.

Patients

Patients that satisfied the following key eligibility criteria were considered for this study: (i) patients with UA defined as symptomatic synovitis of 2 or more joints (who did not meet diagnostic criteria for any other rheumatic disease) (ii) symptom duration [defined as the time from the onset of symptoms (joint pain, swelling, or significant stiffness) of UA to enrolment] of > 12 weeks and $\leq$ 18 months (iii) being negative for ACPA (CCP2) (iv) US evidence of Power Doppler positive signal of $\geq$ 1 (in at least one of 20 joints scanned). To minimise the risk of including self-limiting UA, particularly in the absence of autoantibodies, the PD criterion was included as a poor prognosis factor of persistence[10], thus ensuring subjects with definite, active, synovitis with likelihood of persistence of arthritis were recruited. (v) no prior therapy with any DMARD therapy before screening (vi) no intramuscular or intra-articular steroid within 6 weeks prior to baseline was permitted.

Study design

The study period was 24 months. Enrolled subjects received intravenous abatacept monotherapy (as per the standardised body weight-based dosing regimen of: <60kg: 500mg; 60-100Kg: 750mg; >100Kg: 1000mg) for the first twelve months of the study. Abatacept was administered on days 1, 15, 29 and every 28 days thereafter for a total of 14 doses with subsequent 12-month follow-up. Subjects were permitted to take non-steroidal anti-inflammatory drugs (NSAIDs) throughout the study. Single intramuscular (IM) or intra-articular (IA) corticosteroid medication could be utilised at a maximum frequency of 3-monthly during the trial, at the discretion of the investigator; but was not permitted within 8 weeks of a disease activity assessment.

Subjects with persistent UA after 6 months of study medication received additional DMARD treatment at the discretion of the investigator. Subjects who developed RA at

any point during the trial were discontinued from the study and allowed to receive DMARD at the discretion of the investigator.

Power Doppler ultrasound

Two rheumatologists (CR, JEF) performed blinded US PD; both received training in our Institution that included reproducibility and reliability testing before contributing to research studies. US scanning was performed (using a GE E9 machine equipped with a 6-15 MHz linear transducer) to determine the presence of synovitis at baseline and 6-monthly intervals to study completion (24 months). Specifically, grey scale (GS) and PD assessments, and erosions at baseline and 12 and 24 months were scored according to the OMERACT definition[14]. Bilateral wrist, knee and second to fifth MCP and PIP joints (twenty joints in total) were scanned, each assigned a GS and PD score (maximum of 3); giving maximum total scores of 60 for each.

Radiographic assessment

Plain radiographs of bilateral hands (carpal, MCP and PIP joints) were performed at baseline and 6, 12 and 24 months after the start of study medication to assess structural damage. Radiographs were scored as per the modified Genant-modified Sharp scoring system[15] by a single reader, with re-reading of baseline radiographs to ensure acceptable reproducibility. All time points for individual patients were viewed simultaneously but in random order and with the acquisition dates masked in order to blind the reader to chronology.

Patient-reported outcomes

Assessments to determine self-reported functional status (Disability Index of Health Assessment Questionnaire, HAQ) health status (EQ-5D) and health-related quality of life (RAQoL) were undertaken at the following time points: 3, 6, 12, 18 and 24 months following the start of open-label abatacept.

Statistical analysis

This was a proof of concept, open-label study. All available data from all subjects who

received at least one infusion of study medication at any time were included in the safety and efficacy analyses, unless otherwise specified.

The primary outcome of the study was the proportion of subjects that at 6 months achieved DAS44 remission (DAS44 < 1.6), had a maximum of one swollen joint for at least 3 consecutive months and no radiographic progression defined as change that did not exceed the smallest detectable difference (SDD) over the first year.

Secondary efficacy outcome measures included the proportion of subjects that achieved: DAS44 remission, DAS28 remission, ACR remission and modified remission and the mean DAS28 and 'Persistent Inflammatory Symmetrical Arthritis (PISA) score at 3, 6, 12, 18 and 24 months. Spearman's rank correlation (rho) was used to explore for an association between baseline PD score and DAS44 remission.

Adverse events (AEs) and serious AE (SAE) were summarised as the total number of events and number of unique events (with recurring events summarised per patient as the most severe occurrence of that event).

Handling of missing data

Screening values were imputed for missing baseline values. Patients who withdrew due to lack of efficacy were considered non-responders for the primary endpoint. Patients with missing data for an individual variable at any visit with the exception of the six-month visit were excluded from the analysis of that variable at that visit.

RESULTS

Baseline characteristics

Twenty-three patients were screened of which the target 20 patients were enrolled. One subject who was negative for ACPA prior to screening had a positive titre at screening and was inadvertently included, constituting a protocol violation. The data were analysed twice; first including all 20 patients, then repeated with this subject excluded. The other baseline characteristics and outcome of the analyses did not differ

significantly. Results from all 20 are thus presented (and the analyses with the CCP positive subject excluded are available in the supplemental file; tables S1-S5, corresponding to tables 1-5 in this report). Baseline characteristics are summarised in table 1. At the time of study protocol development and patient recruitment, the 2010 RA classification criteria[16] had not been established. Retrospectively applying these criteria to our cohort, nine patients would satisfy the criteria for RA classification.

Missing data

An ESR that was unavailable at 12 months for one subject and 18 months for another was imputed using a published nomogram (Paulus 1999) for converting CRP to ESR.

Withdrawals

Two patients withdrew after 6 and 12 months for an adverse event (AE) and serious AE (see 'Adverse events' later). A further three subjects were lost to follow-up after 12 months (reasons unknown).

Primary endpoint

Only 2/20 (10%) subjects achieved the composite primary endpoint at 6 months i.e. DAS44 remission, a maximum of one swollen joint for at least 3 consecutive months and no radiographic progression defined.

Evaluating the individual components, the majority, 15/18 (83%; 95% CI 61%,94%) had no radiographic progression (baseline radiograph missing in 1 and follow-up radiographs missing in 2) and 12/20 (60%; 95% CI 39%,78%) had a maximum of one swollen joint or less for at least 3 consecutive months. Only 6/20 (30%; 95% CI 15%,52%) subjects achieved DAS44 remission.

Secondary endpoints

Clinical outcomes

Table 2 details the clinical efficacy variables over the 2-year study period.

Persistent synovitis

At 6 and 12 months, 25% (5/20) and 32% (6/19) patients demonstrated persistent clinical synovitis (2 or more tender and swollen joints).

Disease activity scores and remission rates

Reduction in mean (SD) DAS44/DAS28 was observed from baseline values of 2.66 (0.77) /4.26 (1.13) respectively to 2.01 (0.81) / 3.07 (1.26) at 6 months; with further notable reduction to 1.78 (0.95) / 2.64 (1.19) at 12 months respectively.

At 6 months, DAS28 remission was achieved in 6/20 (30%; 95% CI 14.5%,52%). At 12 months, DAS44 and DAS28 remission rates (withdrawal visit data from approximately 9 months imputed for 1 patient) were observed in 8/20 (40%; 95% CI22%,61%) and 10/20 (50%; 95% CI 30%,70%) subjects respectively.

PISA score

At baseline, 9/20 (40%) of patients had a PISA score of ≥ 3, consistent with poor prognosis; this reduced to 7/19 (36.8%) at month 6 and 6/19 (37.5%) at both months 12 and 24.

Changes in individual disease activity score components

Table 2 provides the values of all clinical variables at baseline and subsequent time points. Immediate suppression of median (IQR) CRP was observed from 9mg/L (0,21) at baseline to 0mg/L (0,15) at 3 months and 0mg/L (0,8) at 6 months [corresponding to 3 month change in median (IQR)/range CRP of -3 (-15,0)/-43 to 5; 6 months change of -1 (-14,0)/-90 to 7]. Similarly, effective reduction in joint counts was observed with median (IQR) swollen joint count 28 (SJC28) of 2(1,5) at baseline to 0(0,1) and 0(0,1) at 6 and 12

months respectively [corresponding to median (IQR/range) change in SJC28 at 6 months of -1 (-3,0/-10 to 8) and at 12 months of -1 (-5,0/-11 to 8)]. Median (IQR) tender joint count 28 (TJC28) changed from 7(5,15) at baseline to 3(1,9) and 2(1,5) at 6 and 12 months respectively [corresponding to median (IQR/range) change in TJC28 at 6 months of -5 (-7,-1/-13 to 10) and at 12 months of -6 (-9,-2/-17 to 6)]. Modest reduction was observed for the patient VAS General health with median (IQR) values of 49 (24,59) at baseline to 25 (9,50) and 16 (3-33) at 6 and 12 months respectively [corresponding to median (IQR/range) change in at 6 months of -14 (-35,-3/-40 to 52) and at 12 months of -19 (-43,-9/-58 to 62)].

Patient-reported outcomes

Reduction in median (IQR) HAQ-DI was noted from baseline value of 0.88 (0.32,1.63) to 0.69 (0,1.38) at 6 months and 0.57 (0,1.38) at 12 months. Similar to the general health, smaller reduction in median (IQR) patient VAS disease activity was observed from 52 (36,63) at baseline to 28 (18,41) and 24 (4,29) at 6 and 12 months respectively. Median (IQR) RAQoL improved from 12 at baseline to 8 (1,11) and 4 (0,15) at 6 and 12 months respectively.

Power Doppler ultrasound findings

A striking decrease in median (IQR) total PD score was noted from 10 (4,23) at baseline to 3 (2,12) and 3 (0,5) at 6 and 12 months respectively. More modest reduction in median (IQR) total GS score was recorded; 30 (18,40) at baseline and 22 (16,32) at 6 months and 19 (12,29) at 12 months. This was mainly attributable to reduction in median (IQR) total number of joints with GS>1 [from 10 (6,15) to 7 (6,12) and 7 (5,10) at baseline, 6 and 12 months respectively (table 3). Median (IQR) number of joints with GS>1 and PD>0 at baseline was 5 (2,11) and reduced to 2 (1,5) and 1 (0,3) at 6 and 12 months respectively. (Results are detailed in table 3.)

Analysis of Power Doppler ultrasound by joint site (table 4)

Table 4 details the maximum GS and PD scores by each joint site. The wrist joint was most resistant to reduction in GS and PD. All patients had GS of 2 or more in the wrist at baseline and 12 months. One patient achieved GS of 0 by 24 months. Reduction in wrist PD score was observed in a small proportion. At baseline, 45% (9/20) and 25% (5/20) had PD of 2 and 1 respectively in the wrist; with 32% (6/19) and 37% (7/19) respectively by 12 months. By contrast, notable reduction in both GS and particularly PD were seen in the MCPs and PIPs by 6 months; with continued improvement by 12 months. At 6 and 12 months, PD=0 in the wrist, MCP, PIP and knee joints was observed in 30%, 40%, 65% 70% and 32%, 58%, 79% 68% of subjects respectively (compared to 30%, 20%, 45% and 55% at baseline respectively). Absence of GS was infrequent except in the PIP joint in 9 subjects; none in the wrist, 1 subject in the MCP and 2 in the knee.

Baseline PD and DAS44 remission

There was no evidence of an association between baseline PD score and change in DAS44 (Spearman's rho=-0.16, n=19). Baseline PD score was slightly lower in those who achieved DAS44 remission at 6 months [median (IQR) 9 (3, 14), n=6] than in those who did not [12 (5, 23), n=13].

Radiographic progression

The re-read of baseline radiographs for reproducibility was excellent (ICC=0.98 [0.95, 0.99]). The mean and median joint space narrowing (JSN), erosion and Genant-modified Sharp scores at baseline, months 6, 12 and 24 are presented in table 5. Of note, 18/20 patients had baseline radiographs with only half the patients having repeat evaluation at month 24. Median JSN and erosion scores remained unchanged throughout. Mean and median total modified Sharp scores remained stable throughout the study period.

Additional medication

None of the patients were prescribed oral steroids within the first 12 months and no additional synthetic DMARDs were commenced in the first 6 months of the study, in line with the study protocol.

Months 0-6

One patient received an intra-articular shoulder injection at week 11 by their GP, which constituted a protocol violation.

Months 6-12

One patient received two IA injections (80mg depomedrone each time) for a Baker's cyst/right knee effusion at weeks 25 and 28. Two patients required synthetic DMARDs within the first 12 months; one subject was prescribed methotrexate (20 mg weekly) at week 32 who withdrew 3 weeks later and the second received hydroxychloroquine (HCQ, 400 mg daily) at week 29.

Months 12-24 (following abatacept cessation)

Ten patients received synthetic DMARDs after abatacept was stopped at 12 months. Seven of these were prescribed MTX (one of whom was the subject already taking HCQ prescribed at week 29 as indicated above) and the other 3 received HCQ.

Outcomes following cessation of abatacept

<u>Disease activity outcomes</u>

By 24 months, 47% (7/15) of patients with evaluable data had persistent clinical synovitis. Following cessation of abatacept small increases in DAS44/28 values were observed but with plateau at 24 months (similar values to that seen 6 months into the study). The DAS44 and DAS28 remission states were broadly maintained at 18 and 24 months (see table 2). The CRP reduction described above in the first year was maintained throughout the follow-up time points; as were joint counts (table 2).

Adverse events

There were no serious adverse events during the first 12 months. Subsequent to abatacept cessation, one patient was diagnosed with upper right lobe lung tumour shortly after the 12-month infusion. This SAE was thought unrelated to study medication. Surgery to remove the tumour was successful. There were no infections requiring IV treatment/hospitilisation and no abnormal liver enzyme tests. Another patient was found to be neutropaenic at 1.3 after starting MTX. In total there were 131 adverse events (with 102 unique AE) during the course of the 2-year study. These are detailed in table 6.

DISCUSSION

This proof-of-concept, open-label study is the first to evaluate the scope for biological immunomodulatory therapy in poor prognosis ACPA negative UA, an important but under-studied group. The findings suggest abatacept monotherapy confers clinical improvement in poor prognosis ACPA negative UA and demonstrates the ability of abatacept to reduce US PD signal.

ACPA negative UA when persistent is also associated with functional impairment and erosive damage[17]. We have previously demonstrated the utility of US PD in identifying persistence in seronegative disease[10]. Studies to date in an UA patient group have been relatively limited; although an earlier study in early oligoarthritis by our group demonstrated that disease modifying intervention (intra-articular corticosteroid and sulphasalazine) reduced clinical synovitis [18]. The PROMPT study failed to indicate any benefit of MTX in seronegative UA on any outcome (preventing the development of RA, the signs and symptoms or radiographic progression)[12]. Thus, there is a lack of effective therapies in this group. The 'ADJUST' study suggested abatacept could delay progression from ACPA positive UA to RA[11]. These observations stimulated the basis for this study in a similar ACPA negative group; with a proof-of-concept study designed to support our hypothesis before embarking on a larger, randomised study.

Interestingly, almost two-thirds of our cohort was SE positive, and half of those tested positive for HLA–DRB1*0401; that confers the highest risk in predisposition to anti-CCP antibodies [19] The basis for this remains unclear.

A 3-composite primary endpoint (encompassing clinical, disease activity composite and radiographic components) was chosen to acknowledge the modern expectations of treatment of inflammatory arthritis. A low proportion (n=2) achieved this with abatacept therapy and under half achieved DAS28/44 remission rates at 6 months (30-40%), albeit with half achieving these outcomes by 12 months. This appears to have been driven by more modest reduction in patient-reported outcomes (PRO) compared to the more objective indicators of synovitis. Incremental reduction in disease activity over time was observed with efficient reduction in swollen joint counts and ESR and CRP recorded.

The blinded US PD assessments provide further evidence of a significant effect on synovial inflammation. A considerable reduction in PD was observed within 6 months and maintained over the 2-year period including following cessation of abatacept. Improvements in GS were more modest, consistent with prior reports of a relative lack of correlation[20,21] (even at this early stage). Limited radiographic data were available but suggested no change over the study period, including following abatacept cessation; in line with early use in ACPA positive disease[11].

The open-label nature of the study is a potential weakness, introducing a bias that could have influenced the apparent discrepancy between PRO and SJC. However, the rapid suppression of inflammation markers (and small deterioration after abatacept cessation) implies a clear biological effect. The absence of a control group means it is not possible to determine whether these improvements would also be seen in a placebo +/- synthetic DMARD arm. However, the poor outcomes observed in UA cohorts[8], together with the selection of poor prognostic (power Doppler positive) UA in this study,

which in a comparable cohort had inferior outcome[10], is suggestive of a benefit over and above placebo. Finally, the distinct genetic associations of ACPA negative (and positive) disease means these data could not necessarily be applied to other ethnic populations.

The clinical, ultrasound and radiographic outcomes were maintained in the second year of the study, following cessation of 12 months of abatacept therapy although half the patients required a synthetic DMARD to maintain this state. Overall, these data suggest that in the vast majority (18/20), abatacept therapy prevented further progression of disease but on cessation, additional therapy was indicated to maintain this. The proportion that did not require additional therapy following abatacept cessation might imply the possibility of drug-free disease control; additional follow-up would be able to clarify longer-term outcomes.

In established RA an association between autoantibody positive RA and abatacept response has been recently reported in registry data (albeit with relatively marginal differences). Whether this is causal and any mechanistic basis for this remains speculative but relies on the B-cell antibody response with enhanced B-cell antigen presentation and T-dependent B-cell activation. An autoantibody-mediated interaction however is not solely required for T-cell effector function and development of inflammatory pathology. The anticipated reduction in T-cell activated cytokine production and abrogated activation of other key effector cells such as dendritic cell, monocyte and synovial fibroblasts; leading to reduced cytokine, chemokine, matrix metalloproteinase production and so on would be postulated to underlie the benefits we observed in our cohort. It might also be possible that some of our cohort have an as of yet undetermined autoantibody status.

In summary, this first report of abatacept therapy in power Doppler positive ACPA negative UA provides an initial indication of its ability to improve both clinical disease

activity and ultrasound parameters of synovial inflammation. These data justify evaluation in a larger, controlled cohort. Further work may also identify biomarkers predictive of greater therapeutic responsiveness.

Key messages

1. In ACPA-negative UA abatacept leads to clinical improvements, particularly swollen joint count and CRP
2. Reduction in ultrasound PD is observed within 6 months of commencing abatacept
3. Following abatacept withdrawal, clinical and ultrasound measures are maintained in a proportion, implying a possible modulatory role.

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Competing interests

MHB has received consultancy fees/been on advisory boards for Abbvie, Bristol Myers Squibb, Pfizer Ltd, Roche-Chugai and received grant funding from Pfizer and Roche-Chugai. RJW has received honoraria from Abbvie. PE has received consultancy fees/been on advisory boards for Abbvie, Astrazeneca, Bristol Myers Squibb, Janssen, Merck, Novartis, Pfizer Ltd, Roche-Chugai, Samsung, UCB and received grant funding from Abbvie, Bristol Myers Squibb, Merck, Pfizer and Roche-Chugai. CP is owner of Spire Sciences, Inc., which performs image analyses services for multiple pharmaceutical and

biotechnology companies, has received consultancy fees/been on advisory boards for Abbvie, Acerta, Amgen, AstraZeneca, Bristol Myers Squibb, Celgene, Daiichi-Sankyo, Five Prime, Genentech, Janssen, Medimmune, Merck, Novartis, Pfizer Ltd, Roche, Salix-Santarus and Samsung, and is a member of the Amgen Speaker Bureau.

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Table 1: Baseline characteristics

Characteristic	ACPA negative UA (n=20)
Age at baseline, years	53.4 (11.2)
Female (n/N)	70% (14/20)
RF positive (n/N)	5% (1/20)
ACPA positive (n/N)	5% (1/20)*
SE positive^, (n/N) Single allele: 01 Single allele: 04 Single allele: 10 Double allele 01/04 Double allele 01/10 Double allele 04/10	61.1% (11/18)" 11.1% (2/18) 33.3% (6/18) 0 11.1% (2/18) 0 5.6% (1/18)
TJC28/RAI	7 (0-18) / 6 (0-18)
SJC28/44	2 (0-12) / 2 (0-14)
CRP, mg/L	9 (0-117)
DAS28-ESR	4.22 (1.12)
DAS44-ESR	2.65 (0.75)
Baseline total median (IQR) GS	30.5 (18,40)
Baseline total median (IQR) PD	10 (4,23)

* 1 subject that was negative for ACPA prior to screening had a positive titre at screening and was inadvertently included. This was not the same patient who was RF positive (which was not an exclusion criterion)
^ HLADR 1, 4 and 10 serotypes that recognize HLADRB1*01, HLADRB1*04 and HLADR10*1001 genes respectively were tested. Patients that tested positive for any of these three genotypes were assigned shared epitope (SE) positive status.

"Sample not taken (n=1); incorrect sample sent for processing (n=1)

All values are presented as mean (SD, standard deviation) aside from baseline total median (IQR, inter-quartile range) grey scale and baseline total median (IQR) power Doppler where median (range) are presented
RF = Rheumatoid factor, positive>20u/ml; SE= shared epitope; TJC= tender joint count; SJC= Swollen joint count; CRP= C-reactive protein; GS= grey scale; PD= power doppler

Table 2 Clinical efficacy variables over 2-year study*

Variable		Baseline	3 months	6 months	12 months**	18 months	24 months
DAS44-ESR rem (<1.6)	% (n/N)	10.0% (2/20)	22.2% (4/18)	30.0% (6/20)	40.0% (8/20)	41.2% (7/17)	40.0% (6/15)
	95% CI	2.8%, 30.1%	9.0%, 45.2%	14.5%, 51.9%	21.9%, 61.3%	21.6%, 64.0%	19.8%, 64.3%
DAS28-ESR rem (<2.6)	% (n/N)	0% (0/20)	27.8% (5/18)	30.0% (6/20)	50.0% (10/20)	47.1% (8/17)	40.0% (6/15)
	95% CI	0%, 16.1%	12.5%, 50.9%	14.5%, 51.9%	29.9%, 70.1%	26.2%, 69.0%	19.8%, 64.3%
mACR rem (Boolean)	% (n/N)	5.0% (1/20)	10.0% (2/20)	20.0% (4/20)	20.0% (4/20)	17.6% (3/17)	20.0% (3/15)
	95% CI	0.9%, 23.6%	2.8%, 30.1%	8.1%, 41.6%	8.1%, 41.6%	6.2%, 41.0%	7.0%, 45.2%
DAS44-ESR	Mean	2.65	2.16	2.04	1.82	1.84	2.07
	SD	0.75	0.85	0.84	0.94	0.86	1.07
	n	20	18	20	20	17	15
DAS28-ESR	Mean	4.22	3.25	3.08	2.71	2.90	3.03
	SD	1.12	1.31	1.22	1.20	1.31	1.40
	n	20	18	20	20	17	15
SJC44	Median	2	0	0	0	0	1
	IQR	1,6	0,3	0,1	0,1	0,1	0,4
	n	20	19	20	20	17	15
SJC28	Median	2	0	0	0	0	0
	IQR	1,5	0,2	0,0	0,1	0,1	0,4
	n	20	19	20	20	17	15
RAI	Median	6	3	4	3	4	4
	IQR	4,10	1,9	1,8	1,6	1,6	0,13
	n	20	19	20	20	17	15
TJC28	Median	7	3	3	3	4	4

	IQR		5,15	1,6	1,9	1,5	1,7	0,8
	n		20	19	20	20	17	15
Symptomatic Synovitis	% (n/N)		75.0% (15/20)	42.1% (8/19)	25.0% (5/20)	30.0% (6/20)	35.3% (6/17)	46.7% (7/15)
	95% CI		53.1%, 88.8%	23.1%, 63.7%	11.2%, 46.9%	14.5%, 51.9%	17.3%, 58.7%	24.8%, 70.0%
CRP mg/L								
	Median		9	0	0	0	0	0
	IQR		0,21	0,15	0,8	0,6	0,7	0,0
	n		20	19	20	20	16	15
ESR, mm/hr								
	Median		12	7	8	8	5	10
	Range		5,27	3,16	7,11	4,12	4,14	4,14
	n		20	19	20	20	17	15
PISA score	% (n/N)	0	5.0% (1/20)	5.0% (1/20)	5.3% (1/19)	5.3% (1/19)	6.3% (1/16)	7.1% (1/14)
		1	30.0% (6/20)	30.0% (6/20)	26.3% (5/19)	31.6% (6/19)	25.0% (4/16)	28.6% (4/14)
		2	20.0% (4/20)	30.0% (6/20)	31.6% (6/19)	31.6% (6/19)	25.0% (4/16)	35.7% (5/14)
		3	30.0% (6/20)	25.0% (5/20)	26.3% (5/19)	31.6% (6/19)	37.5% (6/16)	28.6% (4/14)
		4	15.0% (3/20)	10.0% (2/20)	10.5% (2/19)	-	6.3% (1/16)	-

CRP C-Reactive Protein; DAS28-ESR Disease Activity Score incorporating 28-joint counts and ESR; DAS44 Disease Activity Score incorporating SJC44, RAI and ESR; EMS Early Morning Stiffness; ESR Erythrocyte Sedimentation Rate; IQR Inter Quartile Range; mACR modified American College of Rheumatology; Max Maximum; Min Minimum; Phys Physician; RAI Ritchie Articular Index; Rem remission; SJC28 28-Swollen Joint Count; SJC44 44-Swollen Joint Count; TJC28 28-Tender Joint Count; VAS Visual Analogue Scale

* Abatacept stopped at month 12

**Imputing withdrawal values for one patient who withdrew after 35 weeks due to AE

Table 3 Power Doppler ultrasound findings over the 2-year study period

Variable					
	Baseline	**6 months**	**12 months**	**18 months**	**24 months**
Total GS score					
Median	30	22	19	18	20
IQR	18,40	16,32	12,29	13,29	13,30
N	20	20	19	14	14
Total number of joints scoring GS>0					
Median	14	12	13	14	14
IQR	10,22	10,19	8,17	8,16	8,19
N	20	20	19	14	14
Total number of joints scoring GS>1					
Median	10	7	7	5	6
IQR	6,15	6,12	5,10	4,11	3,12
N	20	20	19	14	14
Total PD score					
Median	10	3	3	3	2
IQR	4,23	2,12	0,5	0,7	1,5
N	20	20	19	14	14
Total number of joints scoring PD>0					
Median	6	2	2	2	2
IQR	4,12	2,6	0,4	0,5	1,3
N	20	20	19	14	14
Total number of joints scoring GS>1&PD>0					
Median	5	2	1	1	1
IQR	2,11	1,5	0,3	0,3	0,3
N	20	20	19	14	14
Total number of joints with erosions					
Median	1		1		2

IQR	0,3		0,4		0,2
N	20		19		14
Total erosion count					
Median	1		1		2
IQR	0,3		0,5		0,3
N	20		19		14

Table 4 Individual joint (maximum) power Doppler ultrasound scores over 2-year study period

Variable		Baseline	6 months	12 months	18 months	24 months
Wrist (maximum)						
GS score	0	-	-	-	-	7.1% (1/14)
	1	20.0% (4/20)	25.0% (5/20)	31.6% (6/19)	57.1% (8/14)	35.7% (5/14)
	2	45.0% (9/20)	50.0% (10/20)	57.9% (11/19)	42.9% (6/14)	50.0% (7/14)
	3	35.0% (7/20)	25.0% (5/20)	10.5% (2/19)	-	7.1% (1/14)
PD score	0	30.0% (6/20)	30.0% (6/20)	31.6% (6/19)	64.3% (9/14)	71.4% (10/14)
	1	25.0% (5/20)	25.0% (5/20)	36.8% (7/19)	28.6% (4/14)	14.3% (2/14)
	2	45.0% (9/20)	45.0% (9/20)	31.6% (6/19)	7.1% (1/14)	14.3% (2/14)
	3	-	-	-	-	-
Erosion present		35.0% (7/20)		57.9% (11/19)		50.0% (7/14)
Erosion count	0	65.0% (13/20)		42.1% (8/19)		50.0% (7/14)
	1	25.0% (5/20)		36.8% (7/19)		35.7% (5/14)
	2	5.0% (1/20)		21.1% (4/19)		14.3% (2/14)
	3	5.0% (1/20)		-		-
MCP (maximum)						
GS score	0	5.0% (1/20)	-	5.3% (1/19)	-	7.1% (1/14)
	1	20.0% (4/20)	10.0% (2/20)	-	14.3% (2/14)	28.6% (4/14)
	2	25.0% (5/20)	75.0% (15/20)	89.5% (17/19)	64.3% (9/14)	28.6% (4/14)
	3	50.0% (10/20)	15.0% (3/20)	5.3% (1/19)	21.4% (3/14)	35.7% (5/14)
Total PD score	0	20.0% (4/20)	40.0% (8/20)	57.9% (11/19)	57.1% (8/14)	71.4% (10/14)
	1	25.0% (5/20)	25.0% (5/20)	21.1% (4/19)	14.3% (2/14)	7.1% (1/14)
	2	30.0% (6/20)	25.0% (5/20)	21.1% (4/19)	21.4% (3/14)	14.3% (2/14)
	3	25.0% (5/20)	10.0% (2/20)	-	7.1% (1/14)	7.1% (1/14)
Erosion present		25.0% (5/20)		26.3% (5/19)		28.6% (4/14)

Erosion count	0	75.0% (15/20)		73.7% (14/19)		71.4% (10/14)
	1	15.0% (3/20)		21.1% (4/19)		28.6% (4/14)
	2	10.0% (2/20)		5.3% (1/19)		-
PIP (maximum)						
GS score	0	30.0% (6/20)	40.0% (8/20)	47.4% (9/19)	42.9% (6/14)	28.6% (4/14)
	1	5.0% (1/20)	-	-	14.3% (2/14)	28.6% (4/14)
	2	10.0% (2/20)	15.0% (3/20)	36.8% (7/19)	14.3% (2/14)	14.3% (2/14)
	3	55.0% (11/20)	45.0% (9/20)	15.8% (3/19)	28.6% (4/14)	28.6% (4/14)
Total PD score	0	45.0% (9/20)	65.0% (13/20)	78.9% (15/19)	85.7% (12/14)	78.6% (11/14)
	1	20.0% (4/20)	5.0% (1/20)	15.8% (3/19)	-	-
	2	10.0% (2/20)	25.0% (5/20)	5.3% (1/19)	14.3% (2/14)	21.4% (3/14)
	3	25.0% (5/20)	5.0% (1/20)	-	-	-
Erosion present		30.0% (6/20)		31.6% (6/19)		14.3% (2/14)
Erosion count	0	70.0% (14/20)		68.4% (13/19)		85.7% (12/14)
	1	25.0% (5/20)		31.6% (6/19)		7.1% (1/14)
	2	5.0% (1/20)		-		7.1% (1/14)
Knee (maximum)						
GS score	0	10.0% (2/20)	-	10.5% (2/19)	-	7.1% (1/14)
	1	10.0% (2/20)	30.0% (6/20)	10.5% (2/19)	28.6% (4/14)	35.7% (5/14)
	2	55.0% (11/20)	50.0% (10/20)	73.7% (14/19)	57.1% (8/14)	42.9% (6/14)
	3	25.0% (5/20)	20.0% (4/20)	5.3% (1/19)	14.3% (2/14)	14.3% (2/14)
Total PD score	0	55.0% (11/20)	70.0% (14/20)	68.4% (13/19)	78.6% (11/14)	78.6% (11/14)
	1	25.0% (5/20)	15.0% (3/20)	21.1% (4/19)	14.3% (2/14)	14.3% (2/14)
	2	20.0% (4/20)	10.0% (2/20)	10.5% (2/19)	7.1% (1/14)	7.1% (1/14)
	3	-	5.0% (1/20)	-	-	-

All values presented are % (n/N)

Table 5 Radiographic scores over 2-year study period

Variable		Visit			
		Baseline (n=18)	**6 months (n=16)**	**12 months (n=17)**	**24 months (n=10)**
JSN score	Mean	3.4	3.7	3.9	3.7
	SD	6.0	6.4	7.0	4.8
	Median	1	1	0.5	2
	IQR	0,5	0,5	0,5	0,5
Erosion score	Mean	4.3	4.7	4.6	3.5
	SD	5.2	6.6	6.6	3.0
	Median	3	3	3	3
	IQR	0,6	0,4	0,5	1,5
Total Genant-modified Sharp score	Mean	7.5	8.1	8.3	7.2
	SD	10.9	12.6	13.2	7.1
	Median	4	4	4	4
	IQR	1,9	1,9	1,8	3,11

IQR: Inter Quartile Range; JSN: Joint Space Narrowing

Table 6 **Summary of adverse events**

Total number of AEs:		131
Number of unique AEs:		102
Severity	Mild:	49% (50/102)
	Moderate:	49% (50/102)
	Severe:	2% (2/52)

AE type by relation to study drug (all events):	Possible	Probable	Unlikely	Unrelated	Total
Endocrine disorders	0	0	0	1	1
Eye disorders	0	0	0	2	2
Gastrointestinal disorders	6	0	1	15	22
General disorders	1	0	0	1	2
Immune system disorders	0	0	0	1	1
Infections and infestations	35	0	0	14	49
Injury, poisoning and procedural	0	0	0	1	1
Investigations	0	0	0	1	1
Musculoskeletal	3	0	0	15	18
Neoplasms benign, malignant and unspecified	0	0	0	1	1
Nervous system disorders	4	3	0	5	12
Reproductive system and breast disorders	2	0	0	0	2
Respiratory, thoracic and mediastinal disorders	5	0	0	2	7
Skin and subcutaneous tissue disorders	5	0	0	5	10
Vascular disorders	0	0	0	2	2
Total	61	3	1	66	131