initial therapeutic strategies were oral methotrexate monotherapy 16% (site range 0%>55%), subcutaneous methotrexate monotherapy 15% (0%>45%), methotrexate-based combination therapy 30% (10%>47%), non-methotrexate DMARDs 19% (4%>44%), triple therapy 11% (0%>60%), and biologics 2% (0%>18%). At 60 months of follow-up, the frequency of use of these strategies was relatively stable except for biologics which increased to 21% (0%>80%). The mean and median time to DAS28 remission was 12.4 months (SD 12.1, range 8.6 to 17.2) and 9 (IQR 3, 18) months respectively. The mean and median time to CDAI remission was 14.8 (SD 13.5, range 10.3 to 21.2) and 9 (IQR 6, 18) months respectively. The frequency of sustained DAS28 remission was 50% (site range 20–70%), and CDAI 35% (12–58%). At the two sites with the highest rates of sustained remission and shortest time to remission, patients had fewer comorbidities and the initial treatment strategy was preferentially methotrexate-based combination therapies, and with eventual advancement to biologics in 7 and 39% in patients. In contrast, the patients at the site with the lowest rates of sustained remission and longest time to remission had long symptom duration at treatment initiation, highest body mass index and proportion with ≥2 comorbidities, worse socioeconomic status and higher baseline DAS28. This site also had the highest proportion of patients treated with biologics at the baseline visit, escalating to 80% by 60 months.

Conclusions: Treatment strategy and patient characteristics vary across CATCH sites and contribute to variable rate and frequency of achieving sustained remission.

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THU0086 THE USE OF A BLINDED TRUNCATED ULTRASOUND POWER DOPPLER JOINT COUNT VALIDATES EFFICACY DATA FROM AN EARLY PHASE OPEN LABEL DRUG STUDY TREATING RHEUMATOID ARTHRITIS

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Background: Small open label pilot trials generate important information on tolerability, toxicity, pharmacokinetics, and antigenicity in the early phase investigation of new compounds in the treatment of rheumatoid arthritis (RA). However, because the standard disease activity measures (DAMs), such as the disease activity score in 28 joints (DAS28) have a major subjective component, the efficacy data acquired in such trials is generally felt to be much less reliable than that obtained in blinded trials. Incorporating more objective DAMs, and performing them in a blinded fashion, might enhance the validity of efficacy data in such an early clinical setting.

One possible disease activity measure to fulfill this role would be an ultrasound power Doppler joint count (UPD) which has been shown to correlate with conventional clinical measures¹.

Objectives: To determine whether the blinded use of a truncated (low joint count) UPD in an early phase RA trial correlates with other DAMs in the trial and contributes to validation of efficacy of the drug.

Methods: The results of an open label trial in which Staph Protein A (PRTX-100, Protalex Inc.) was given to patients with active RA has been previously reported². Standard disease activity measurements were obtained. In addition, an UPD was performed utilizing a truncated methodology in which three sites at the dorsal wrist and three dorsal metacarpal sites were analyzed bilaterally for a total of twelve sites studied. There were a total of 117 UPDs performed on eleven patients. UPD were acquired in less than five minutes per study. These UPDs were stored digitally and subsequently read in duplicate in a blinded fashion after completion of the study by the investigator (CW). Each joint site was subjectively scored from 0 (normal) to 3 (severe) with a possible total score of 0–36. Intra-observer reliability was determined by two-way random intra-class correlations (ICC). Significant changes of UPD and clinical DAMs from baseline to single time points were assessed by the Wilcoxon signed rank test and correlations were performed by the Spearman's rho test (p). Effect size was determined by standardized mean difference (SMD). Clinical assessments and UPDs were obtained weekly for the first month, then monthly for five more months.

Results: Intra-observer UPD score reproducibility was high (ICC =0.886). Significant reductions (p<0.05) in UPD and the DAS28 were found at day 22 and on all subsequent visits. Correlations between UPD and DAMs total scores were moderate to strong. However, the total differences from baseline and visits did not correlate, except for CRP (n=67 p=0.471, p<0.001). Also, some individual time points showed differences such as baseline vs day 196 (see table). SRMs for both UPD and DAMs were high, but higher for the DAS28 (1.00–2.16) than for the UPD (0.83–1.10).

Conclusions: The use of a truncated UPD in this small open label trial was feasible, reproducibly read, and significantly correlated with conventional disease activity measure.

The inclusion of UPD in this open label pilot trial adds validation to the efficacy data.

References:

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Absolute Numbers UPD vs Disease Activity Measures				Differences UPD vs Disease Activity Measures on Visit Day 196			
	N	USP vs	Prob	N	USP vs		
DAS28CRP	71	p=.555	***	11	p=.639		*
DAS28ESR	98	p=.521	***	11	p=.542		*
ESR	97	p=.440	***	11	p=.043		NS
CRP	63	p=.540	***	11	p=.588		*
Jt Pain	111	p=.466	***	11	p=.152		NS
Jt Swelling	113	p=.468	***	11	p=.509		*
Pt. Global	113	p=.313	***	11	p=.422		NS
Dr Global	113	p=.634	***	11	p=.342		NS
CDAI	113	p=.502	***	11	p=.365		NS
Vectra	33	p=.525	***	11	p=.093		NS
prob <0.05 *				prob <0.01 **		prob <0.001 ***	

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THU0087 DAILY AND DIURNAL VARIATION AND DETERMINATION OF THE MINIMALLY IMPORTANT DIFFERENCE IN RHEUMATOID ARTHRITIS PATIENTS WITH MODERATE TO HIGH MULTI-BIOMARKER DISEASE ACTIVITY SCORES

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Background: The Multi-Biomarker Disease Activity (MBDA) score has been validated as a disease activity metric in rheumatoid arthritis (RA) patients. Patients initiating new therapy or changing therapy frequently have moderate to high MBDA scores. Understanding short term biological variation of MBDA scores in these patients is important in order to determine a minimally important difference (MID).

Objectives: To evaluate biological variation in MBDA scores over a 24-hour period and from day to day in patients with clinically stable RA with moderate to high MBDA scores at baseline and to determine the MID in these patients.

Methods: We performed an analysis of 22 RA patients with moderate or high baseline MBDA scores. Adults with clinically stable seropositive RA (>8 weeks without DMARD and/or biologic medication changes and ≤10 mg prednisone per day) who had MBDA scores of moderate (MBDA 30–44) or high (MBDA >44) were eligible. Serum samples were obtained 5 times over the first 24-hour period (8 AM, 12 PM, 4 PM, 8 PM, and 8 AM); at 12 PM in the next 24-hour period; and at 8 AM the next 2 consecutive days, for a total of 8 timepoints. An additional midnight sample was excluded from the analysis because this timepoint is not relevant to normal clinical practice hours. Diurnal variation was calculated using 5 timepoints over the first 24 hours. Daily variation was determined using 4 timepoints taken at 8 AM on successive days. Combined diurnal and daily variation was calculated using 8 timepoints over 4 days. For each patient, absolute changes in MBDA scores were calculated for all possible pairs of timepoints for: a) diurnal variation (total 220 pairs), b) daily variation (total 132 pairs) and c) diurnal and daily variation (total 616 pairs). MID was calculated as the 90th percentile of absolute

Figure 1. Mean (SE) MBDA Scores over Four Days for Patients with Moderate (n=13) or High (n=9) MBDA Scores at Baseline

changes using all diurnal and daily variation data. Bootstrapping was used to validate the result.

Results: Of patients included in the analysis, 13 had moderate MBDA scores and 9 had high MBDA scores at baseline. Baseline demographics were: 73% women, mean age 61.8 (SD: 12.1) years, mean MBDA score 43.9 (SD: 8.3), and mean CDAI 20.2 (SD: 17.1). No patients were on glucocorticoids. Based on the analysis of the absolute change of MBDA score in the data with daily and diurnal variation combined, the mean was 3.4 (SD: 3.8), the median (Q1, Q3) was 2 (1, 5), and the MID was calculated as 7. Similar results were obtained using a bootstrap method. Minimal variability in mean MBDA scores was observed over 4 days for patients with moderate and high baseline MBDA scores (Figure 1).

Conclusions: Based upon the short term biologic variability of moderate and high MBDA scores, the MID was 7 units. An absolute change exceeding this threshold is unlikely due to diurnal and daily biological variation of the MBDA scores.

Disclosure of Interest: D. Chernoff Shareholder of: Myriad Genetics, Inc., Employee of: Crescendo Bioscience Inc., R. Bolce Shareholder of: Myriad Genetics, Inc., Employee of: Crescendo Bioscience Inc., C. Hwang Shareholder of: Myriad Genetics, Inc., Employee of: Crescendo Bioscience Inc., X. Wang Shareholder of: Myriad Genetics, Inc., Employee of: Crescendo Bioscience Inc., A. Kivitz Consultant for: Genentech, Pfizer, UCB, Janssen, J. Curtis Grant/research support from: Crescendo Bioscience Inc., Consultant for: Crescendo Bioscience Inc.

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THU0088 STRUCTURAL DAMAGE PROGRESSION IN PATIENTS TREATED WITH METHOTREXATE, BARICITINIB MONOTHERAPY OR BARICITINIB + METHOTREXATE BASED ON THEIR LEVEL OF CLINICAL RESPONSE IN THE PHASE 3 RA-BEGIN STUDY

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Background: Baricitinib (BARI), an oral inhibitor of Janus kinase (JAK) 1 and JAK 2, is being developed for the treatment of rheumatoid arthritis (RA). RA-BEGIN was a phase 3 double-blind, three-arm multicentre study of BARI administered as monotherapy or in combination with methotrexate (MTX) to patients (pts) with early active RA who had no or limited treatment with DMARDs. Methotrexate (MTX) monotherapy was the active comparator.

Objectives: To evaluate the proportion of pts with structural damage progression, defined as change from baseline (CFB) greater than the smallest detectable change (SDC) in mTSS at week (wk) 52, depending on their disease state as measured by DAS28-CRP.

Methods: Pts were classified into two groups based on DAS28-CRP. Group A included pts who achieved sustained DAS28-CRP ≤ 3.2 at weeks 16, 20 and 24. Pts who did not achieve DAS28-CRP ≤ 3.2 consecutively at weeks 16, 20 and 24 and pts with missing DAS28-CRP at any of those 3 visits were included in Group B. The proportion of pts with CFB mTSS > SDC at wk 52 was estimated for each treatment arm for the two defined groups of response. The SDC in mTSS in the RA-BEGIN population at wk 52 was 1.4. Missing mTSS at wk 52 were imputed using linear extrapolation based on baseline data and the most recent radiographic data prior to the missed radiograph. No formal statistical tests were performed and comparisons are merely descriptive. All analyses were post-hoc.

Results: Out of the 584 pts of the modified-ITT population (all randomised pts who received at least 1 dose of study drug) in the RA-BEGIN study, 212 were classified in Group A: 21.4% (45/210), 42.1% (67/159), and 46.5% (100/215) for MTX, BARI and BARI+MTX, respectively. The odds ratios for sustained DAS28-CRP ≤ 3.2 response (weeks 16, 20 and 24) to BARI and BARI+MTX vs. MTX, were respectively 2.8 (95% CI 1.7–4.4) and 3.3 (95% CI 2.1–5.1). Pts classified in Group A maintained an adequate level of response up to wk 52. Further, pts in Group A (sustained DAS28-CRP ≤ 3.2) on either BARI + MTX or BARI, were less likely to show structural progression than patients who achieved sustained DAS28-CRP ≤ 3.2 on MTX. Pts in Group B on MTX or BARI monotherapy were more likely to show structural progression than patients who did not achieve a sustained DAS28-CRP ≤ 3.2 response on BARI + MTX (Figure 1).

Footnote: Group A: Patients who achieved sustained DAS28-CRP ≤ 3.2 (NRI) at weeks 16, 20 and 24 (N=212); Group B: Complement group

Conclusions: In patients who achieved sustained low DAS28-CRP scores, progression rates compared to MTX were reduced to a similar degree with BARI as monotherapy or in combination with MTX. Compared to MTX in patients who did not achieve sustained low DAS28-CRP scores, progression rates were reduced most markedly with combination therapy.

Disclosure of Interest: D. van der Heijde Consultant for: Abbvie, Amgen, Astellas, AstraZeneca, BMS, Boehringer Ingelheim, Celgene, Daiichi Sankyo, Eli Lilly and Company, Galapagos, Janssen, Merck, Novartis, Pfizer, Roche, Sanofi-Aventis, UCB, P. Durez: None declared, G. Schett: None declared, E. Naredo: None declared, M. Østergaard Consultant for: Abbvie, BMS, Boehringer-Ingelheim,

Celgene, Eli-Lilly, Centocor, GSK, Hospira, Janssen, Merck, Mundipharma, Novartis, Novo, Orion, Pfizer, Regeneron, Schering-Plough, Roche, Takeda, UCB, and Wyeth. G. Meszaros Employee of: Eli Lilly & Company, N. Bello Employee of: Eli Lilly & Company, I. De la Torre Employee of: Eli Lilly and Company, P. Lopez-Romero Employee of: Eli Lilly & Company, D. Schlichting Employee of: Eli Lilly and Company, E. Nantz Employee of: Eli Lilly and Company, R. Fleischmann Consultant for: Abbvie, Amgen, Astra Zeneca, BMS, Celgene, Janssen, Eli Lilly and Company, Novartis, Roche, Sanofi-Aventis, Pfizer, UCB

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THU0089 M-DAS28, DAS28 (CRP) AND RAPID3 SCORES AT BASELINE ARE GOOD PREDICTORS OF RADIOGRAPHIC DISEASE PROGRESSION AT 1 AND 2 YEARS: DATA FROM THE AMPLE TRIAL

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Background: Clinicians rely on time-efficient, validated disease activity assessments to help predict disease progression accurately in patients (pts) with RA. The utility in predicting structural damage progression for the Routine Assessment of Patient Index Data 3 (RAPID3)¹ is largely unknown, while that of DAS28 (CRP)² and modified (M-)DAS28 have been previously reported.³

Objectives: This *post hoc* analysis examined the relationship between baseline disease activity measures and their ability to predict structural damage progression in the Phase III AMPLE (NCT00929864) trial.⁴

Methods: AMPLE was a randomized, investigator-blinded study in which MTX-experienced pts with active RA ≤ 5 years received SC abatacept 125 mg weekly or adalimumab 40 mg every 2 weeks in combination with stable-dose MTX. Logistic regression analysis was used to correlate the effect of disease activity at baseline on radiographic (X-ray) progression at Months (M) 12 and 24. Disease activity was assessed using M-DAS28,³ DAS28 (CRP), RAPID3, CDAI and SDAI. Radiographs were scored using the modified Sharp/van der Heijde scoring system; progression was defined as change from baseline in total score greater than the smallest detectable change, which was calculated as SD/square root (2) $\times$ 1.96 (where SD is standard deviation of paired differences of change from baseline in total score between two readers).

Results: Logistic regression analysis was carried out for all randomized and treated pts (abatacept, n=318; adalimumab, n=328). For these patients, M-DAS28, DAS28 (CRP) and RAPID3 at baseline were significant predictors of radiographic progression at M12 and M24, baseline SDAI was a significant predictor at M12 but not M24 and baseline CDAI was not a significant predictor at either time point

Logistic regression model and area under ROC curves for the impact of disease activity at baseline on radiographic progression at M12 and M24 (all randomized and treated patients)

Disease activity measure	M12			M24		
	OR (95% CI)	p value	AUC	OR (95% CI)	p value	AUC
CDAI	1.02 (1.00, 1.04)	NS	0.5762	1.01 (0.99, 1.03)	NS	0.5416
SDAI	1.02 (1.00, 1.04)	<0.05	0.5963	1.02 (1.00, 1.03)	NS	0.5634
DAS28 (CRP)	1.47 (1.15, 1.90)	<0.01	0.6271	1.31 (1.03, 1.67)	<0.05	0.5911
RAPID3	1.26 (1.08, 1.47)	<0.01	0.6270	1.16 (1.01, 1.34)	<0.05	0.5871
M-DAS28	1.51 (1.25, 1.83)	<0.001	0.6624	1.36 (1.13, 1.63)	<0.01	0.6208

AUC = area under the curve; M = month; NS = not statistically significant; OR = odds ratio; ROC = receiver operating characteristic.