SUPPLEMENTARY MATERIAL

SUPPLEMENTARY METHODS

Phase III Clinical Trial Simulations

The model describing OKZ exposure-response relationship was used to perform clinical trial simulations with DAS28(CRP) as the efficacy endpoint. 500 trials of 350 subjects per dose (placebo, 40, 60, 100, 120, 160, 200, 240, 300, 320, 400 and 480 mg) given Q2W or Q4W were simulated. Parameters were generated using *simpar* functionality within the MIfuns version 5.1 R-package, developed by Metrum Institute (http://metruminstitute.org). All simulations were performed in NONMEM.

SUPPLEMENTARY RESULTS

Immunogenicity Investigations

Despite the use of a study specific cut-off based on blinded analysis of all available baseline samples from the study, 13 subjects in OKZ groups, 5 subjects in the placebo groups and 2 subjects in the TCZ group were anti-OKZ antibody positive. Importantly, pre-dose samples for 4 of these 13 subjects in OKZ groups were also anti-OKZ Ab positive, suggesting a high level of false positives amongst these nominally anti-drug antibody positive samples.

In order to test the hypothesis of interference by non-specific immunoglobulins, anti-OKZ antibody positive samples from several subjects were pre-incubated with excess OKZ, isotype-matched control, different isotype control (IgG1), iv immune globulin (IVIG), or with infliximab. As expected, the anti-OKZ signal was reduced by excess OKZ, due to absorption of the anti-OKZ antibodies. However, a reduction of the signal was also observed in most of the samples pre-incubated with non-OKZ immunoglobulins, suggesting that not all of the anti-OKZ antibodies measured by the immunogenicity assay are specific to OKZ. Therefore, the true incidence of specific anti-OKZ antibodies were likely less than reported, due to inherent sensitivity issues within the assay.

In addition, graphical analysis of the PK profile of all the nominative anti-OKZ antibody positive subjects indicated that only 1 subject (120 mg Q4W group) fit the profile of true immunogenicity impact, including trough concentrations well below expectations, no signs of drug accumulation and steep drug plasma concentration declines. Incubation of samples from this patient with each of the aforementioned immunoglobulins revealed that only OKZ immunoglobulins could reduce the immunogenicity signal, indicating an OKZ-specific response and confirming the anti-OKZ antibody positive status of the patient.

Immunogenicity and efficacy evaluations

Of the 13 nominally anti-OKZ antibody positive patients from the OKZ treatment groups patients, 6 received OKZ Q2W and 7 received OKZ Q4W, from a total of 5 treatment arms. These patients included those who had received doses of 60 mg, 120 mg and 240 mg OKZ. Thus no effect of treatment dose or frequency was observed (Table S1).

These 13 patients also exhibited varied clinical efficacy (Table S1). One patient achieved an ACR70 response at Week 12, one achieved an ACR50 response and 4 achieved an ACR20 response. Change from baseline in DAS28(CRP) and DAS28(ESR) ranged from -3.84–0.85 and -4.00–0.35, respectively.

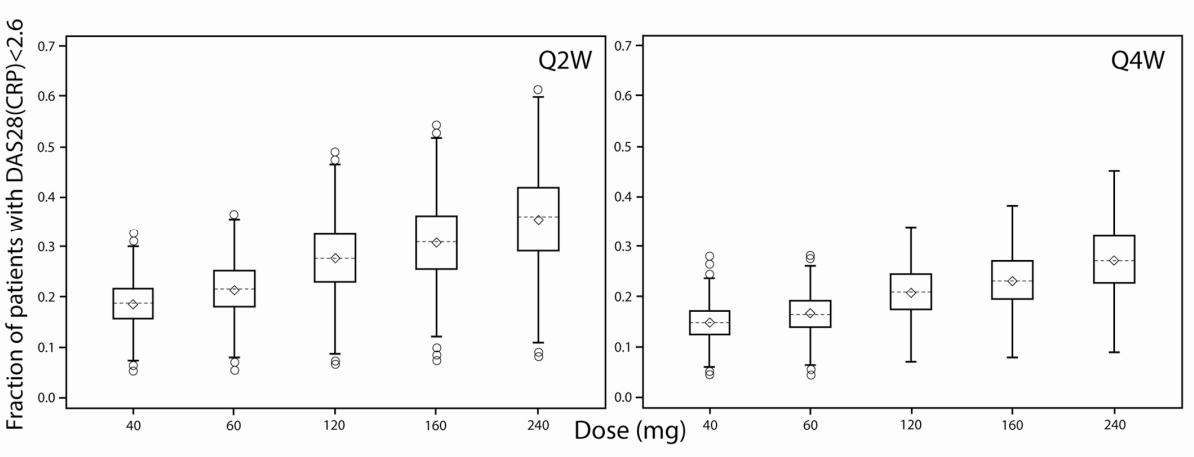
Table S1: Week 12 efficacy responses (ACR response rates and change from baseline in DAS28[CRP] and DAS28[ESR]) of the 13 nominally positive anti-OKZ antibody positive patients from OKZ treatment arms

Treatment Group	Pre-dose sample positive for anti-OKZ antibodies	Week 12 ACR20/50/70 response	Week 12 DAS28(CRP)/DAS28(ESR) change from baseline
60mg Q2W	Yes	Y/Y/Y	-2.83/-4.00
60mg Q2W	No	Y/N/N	-0.84/-1.30
60mg Q2W	Yes	-----[a]	------[a]
120mg Q4W	Yes	Y/N/N	-3.84/-3.89
120mg Q4W	No	N/N/N	-0.17/-0.50
120mg Q4W	No	N/N/N[b]	-1.86/---[b]
120mg Q4W	No	N/N/N	-2.16/-2.81
120mg Q4W	No	Y/N/N	-2.24/-3.32
120mg Q2W	Yes	N/N/N	0.85/0.35
240mg Q4W	No	Y/Y/N	-2.17/-3.68
240mg Q4W	No	N/N/N	-1.35/-3.16
240mg Q2W	No	N/N/N	-1.46/-2.00
240mg Q2W	No	Y/N/N	-2.39/-2.74

[a]Data not available due to early discontinuation; [b]Data represents Week 10 results, Week 12 not available

Figure S1: Phase III clinical trial simulation results based on dose exposure response model

Predicted DAS28(CRP) responder rate following **(A)** Q2W OKZ dosing and **(B)** Q4W OKZ dosing.



Diamonds represent the mean of 500 simulations, each of 350 patients; dashed bar represents median; box indicates 25% and 75% quantiles. Whiskers extend to distances computed as 75% quantile+1.5*(interquantile range) and 25% quantile-1.5*(interquantile range).