W-033

Effects of Tocilizumab on DAS28 in Patients With Rheumatoid Arthritis (RA)

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INTRODUCTION

- Tocilizumab (TCZ; RO4877533) is a recombinant, humanized, antihuman interleukin-6 receptor (IL-6R) monoclonal antibody that specifically inhibits the binding of human IL-6 to its receptor (soluble and membrane-bound forms)
- TCZ, in intravenous (IV) and subcutaneous (SC) formulations, was shown to be effective in the treatment of patients with RA. The population pharmacokinetics–Disease Activity Score at 28 joints (PK-DAS28) model that describes the TCZ exposure-response relationship after IV doses was developed earlier.[1] In this analysis, the model was extended to investigate PK-DAS28 relationships after IV and SC administration of TCZ in studies WA22762 (SUMMACTA)[2] (**Figure 1**) and NA25220 (BREVACTA)[3] (**Figure 2**)

Figure 1. WA22762 study design.

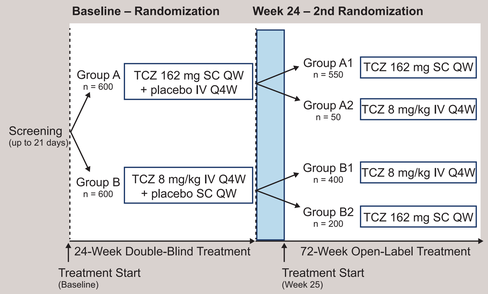
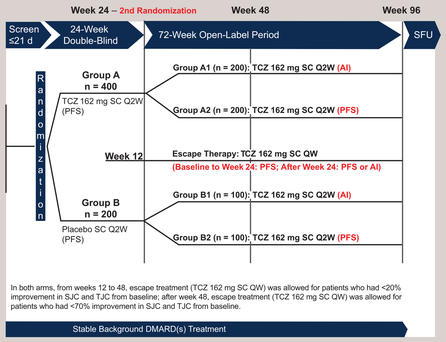


Figure 2. NA25220 study design.



AI, autoinjector; DMARD(s), disease-modifying antirheumatic drug(s); PFS, prefilled syringe; SFU, study follow-up; SJC, swollen joint count; TJC, tender joint count.

- The population PK model (poster W-026) was used to predict individual TCZ concentrations over time for the exposure-DAS28 analysis

OBJECTIVES

- The objectives of the present analysis were
  - To establish a predictive population PK-pharmacodynamics (PD) model that describes the DAS28 time course after TCZ IV and SC administration
  - To identify covariate factors that might influence the PK-PD relationship
  - To perform model-based simulations of DAS28 after clinically important dosing regimens

METHODS

- DAS28 data from two phase 3 studies, WA22762 and NA25220, were analyzed using NONMEM 7.2.0. Following the previously performed population PK-DAS28 modeling after TCZ IV administration,[1] the time course of DAS28 was described by an indirect-response model with inhibition of production driven by serum TCZ concentrations

$$\frac{d(\text{DAS28})}{d(\text{TIME})} = k_{in}(1 - \text{EFF}) - \text{DAS28} \times k_{out}$$

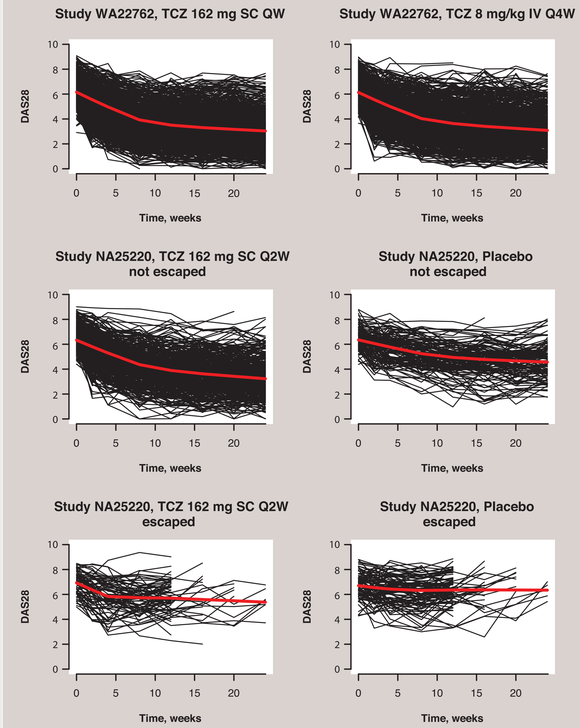
$$\text{EFF} = E_{max} \frac{(C + C_{DMARD})^{\gamma}}{EC_{50}^{\gamma} + (C + C_{DMARD})^{\gamma}}$$

- Here DAS28 is the disease activity score, k_{in} = BASE × k_{out} and k_{out} are the empirical zero-order production rate and the first-order elimination rate of DAS28, BASE is the baseline value of DAS28, E_{max} is the maximal effect of the drug, EC_{50} is the TCZ concentration at which 50% of the E_{max} is reached, γ is the sigmoidicity parameter, and C_{DMARD} is the background effect of concomitant disease-modifying antirheumatic drug therapies modeled in serum TCZ concentration units
- A full-model approach was implemented for development of the covariate model. Selection of the covariates for the investigation was based on earlier knowledge of the typical covariate relationships for monoclonal antibodies and on the previously developed TCZ population PK-DAS28 model for the IV data.[1] Small (clinically insignificant) and precisely estimated effects were excluded to arrive at a parsimonious model. Covariate effects not supported by the data (effects close to null value and/or with high relative standard error and/or with 95% confidence intervals that included the null value) were also excluded if they were not statistically significant at the α = 0.001 level. Extensive model evaluation using diagnostic plots and various visual predictive check (VPC) procedures was performed

RESULTS

- The data set contained 9430 DAS28 measurements from 1250 subjects in study WA22762 and 4568 measurements from 640 subjects in study NA25220. Of 1890 subjects, 629, 621, 353, and 126 subjects received, respectively, TCZ 8 mg/kg Q4W IV, TCZ 162 mg SC QW, TCZ 162 mg SC Q2W, or placebo TCZ doses. In addition, 90 and 71 subjects, respectively, were administered placebo or TCZ 162 mg SC Q2W doses for 12 weeks but escaped after week 12 by switching to 162 mg TCZ SC QW doses. For most escape subjects, DAS28 data were not available after week 12 (**Figure 3**)

Figure 3. Individual DAS28-time profiles.



Measurements of DAS28 versus nominal time (weeks).

- Parameters of the final model are presented in **Table 1**

Table 1. Parameter Estimates for the PK-DAS28 Final Model

Parameter	Estimate	%RSE	Parameter	Estimate	%RSE
EC_{50} (mg/mL)	1.86	12.8	$LE_{max,IL\text{-}6}$	–0.457	19.9
LE_{max}	0.77	3.46	ω^2	CV = 135%	12.1[a]
k_{out} (1/day)	0.0402	2.33	$R\omega_{EC_{50}}\omega_{BASE}$	R = 0.317	25.6[a]
BASE (DAS28)	6.67	0.289	ω^2_{BASE}	CV = 44.7%	9.18[a]
C_{DMARD}	0.581	16.7	$R\omega_{EC_{50}}\omega_{k_{out}}$	R = 0.455	19.3[a]
$BASE_{CRP}$	0.02	11.3	$R\omega_{k_{out}}\omega_{BASE}$	R = –0.622	9.37[a]
$BASE_{HAQ}$	0.0962	8.18	$\omega^2_{k_{out}}$	CV = 62.9%	7.56[a]
$BASE_{PAIN}$	0.103	7.95	$R\omega_{LE_{max}}\omega_{BASE}$	R = 0.176	34.5[a]
$BASE_{VASP}$	0.134	7.45	$R\omega_{LE_{max}}\omega_{k_{out}}$	R = 0.144	34.7[a]
$LE_{max,SEX}$	0.641	6.08	$\omega^2_{LE_{max}}$	CV = 81.4%	5.58[a]
$LE_{max,AGE}$	0.594	15.2	σ^2	SD = 0.676	1.09[a]
Derived parameter: E_{max} = 1/(1+LE_{max})					
$E_{max,females}$	0.565				
$E_{max,males}$	0.670				

"System-related" parameters: BASE = DAS28 score, k_{out} = rate constant of elimination of DAS28.
"Drug-related" parameters: E_{max} = maximal inhibition of K_{in}, EC_{50} = tocilizumab serum concentration at half the effect, C_{DMARD} = parameter describing the effect of DMARD medications.
[a]%RSE for the estimate of (co)variance.
CRP = C-reactive protein concentration at baseline, HAQ = baseline health assessment questionnaire, IL-6 = IL-6 concentration at baseline, PAIN = Patient's Assessment of Pain at baseline, VASP = Physician's Global Score of Disease Activity at baseline, RSE = relative standard error of estimate.

- The following covariates were included in the final model: baseline C-reactive protein (CRP), Health Assessment Questionnaire (HAQ), Patient's Assessment of Pain (PAIN), and Physician's Global Score of Disease Activity (VASP) on BASE; age, sex, and baseline IL-6 on E_{max}. The magnitude of the covariate effects on model parameters is illustrated in **Table 2**

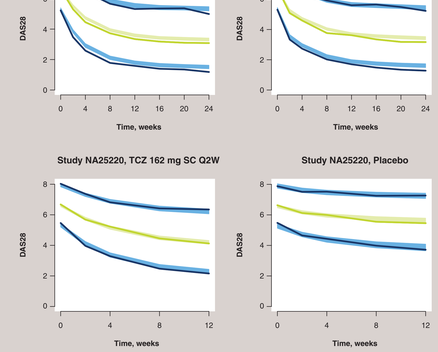
Table 2. Covariate Effects as Predicted by the Final Model

Parameter	Covariate				Effect, % (95% CI)
	Name	Median (range) or Level	Reference	Value	
BASE	CRP, mg/L	13.5 (0.2-205)	10	1	–20.9 (–23.0, –18.8)
				100	26.5 (23.1, 29.9)
	PCOR	PCOR: Yes/No	No	Yes	22.9 (19.3, 26.4)
	Smoker	Nonsmoker/Smoker	Nonsmoker	Smoker	17.5 (13.2, 21.9)
k_{out}	Age, years	54 (18-86)	50	20	–46.2 (–55.9, –34.3)
				80	37.4 (24.1, 52.1)
EC_{50}	Sex	Females/Males	Females	Males	–22.0 (–39.2, –4.7)
E_{max}	CRP, mg/L	13.5 (0.2-205)	10	1	–13.6 (–19.7, –7.1)
				100	15.7 (7.6, 24.5)
	Log(10 × IL-6, pg/mL)	5.14 (1.39-10.7)	Log(10 × 20)	Log(10 × 1)	–42.5 (–48.1, –36.4)
				Log(10 × 10^3)	44.4 (35.1, 54.5)

PCOR, previous corticosteroid therapy.

- Consistent with the earlier model, DAS28 values at baseline were higher in patients with higher HAQ, PAIN, and VASP, and E_{max} parameters were higher in males. In addition, patients with high CRP had higher baseline values of DAS28, whereas younger patients and patients with high baseline IL-6 had higher E_{max} values. Overall, for all covariates (except CRP on the 162 mg SC Q2W regimen) the differences were small, and none of the covariates had a clinically meaningful influence on the time course of DAS28
- Results of the VPC evaluations (**Figure 4**) indicated that the model correctly captured both the central tendency and the inter-individual variability of DAS28 measurements, as well as the dependence of the TCZ PK-PD parameters on covariates

Figure 4. VPC for the final model: DAS28 versus time, by study and route of administration.



Lines show the median (green) and the 10th and 90th percentiles (blue) of the observed values. Shaded regions show the 80% confidence intervals of these quantities obtained by simulations. Simulated values were computed from 500 trials simulated using dosing, sampling, PK parameters, and the covariate values of the analysis data set.

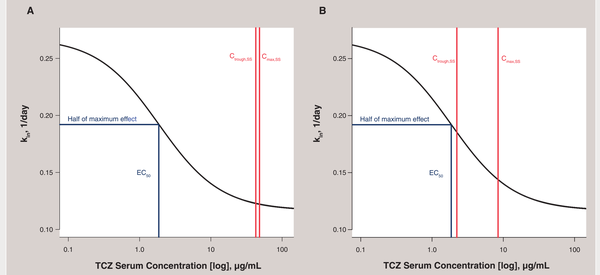
- Simulations of response characterized by European League Against Rheumatism (EULAR) criteria (**Table 3**) indicated that the model correctly captured the fraction of nonresponders but mischaracterized 5% to 6% of good responders as moderate responders
- Similarly, the model underestimated the remission rate by approximately 5% to 7% (**Table 3**)

Table 3. Predictive Check Simulations for the Final Model: Week 12 or Week 24 Response

Dosing Regimen	Time, weeks	DAS28, mean (SD)	Remission Rate	Response Rate According to EULAR		
				No Response	Moderate Response	Good Response
Observed						
TCZ 162 mg SC QW	24	3.28 (1.58)	0.35	0.08	0.41	0.51
TCZ 162 mg SC Q2W	12	4.14 (1.62)	0.19	0.16	0.54	0.30
TCZ 8 mg/kg IV Q4W	24	3.35 (1.57)	0.34	0.08	0.45	0.48
Placebo SC Q2W	12	5.49 (1.44)	0.03	0.51	0.44	0.05
Simulated						
TCZ 162 mg SC QW	24	3.45 (1.51)	0.30	0.08	0.47	0.45
TCZ 162 mg SC Q2W	12	4.26 (1.52)	0.14	0.18	0.57	0.25
TCZ 8 mg/kg IV Q4W	24	3.58 (1.52)	0.27	0.09	0.50	0.42
Placebo SC Q2W	12	5.61 (1.33)	0.02	0.55	0.41	0.04

- The relationship between DAS28 production rate (k_{in}) and TCZ concentrations along with the mean concentration range at steady state ($C_{min,ss} - C_{max,ss}$) for the 162 mg SC QW and Q2W dose regimens are shown in **Figure 5**

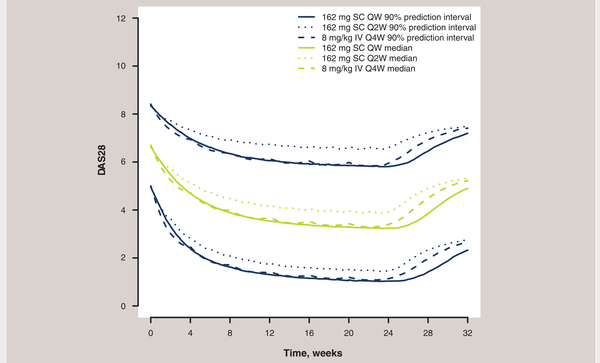
Figure 5. Relationship between DAS28 production rate (k_{in}) and TCZ concentration and typical TCZ steady state concentration range for (A) 162 mg SC QW and (B) 162 mg SC Q2W dosing.



The relationship between k_{in} and TCZ concentration does not include the placebo effect.

- A more pronounced effect was achieved for the QW regimen compared with the Q2W regimen because of the exposure difference: the TCZ effect ranged from 95.8% to 96.3% of the maximum effect compared with 54.5% to 81.9% for concentrations achieved with QW and Q2W regimens, respectively
- Median and 90% prediction intervals of the simulated DAS28 scores for all patients in each dosing regimen are presented in **Figure 6**

Figure 6. Simulated DAS28 over time, by TCZ dosing regimen.



Simulations were performed 100 times for each subject in the analysis data set using subject's covariates, PK parameters, and nominal dosing.

SUMMARY/CONCLUSIONS

- The indirect response model with an inhibitory effect on DAS28 production rate by TCZ serum concentrations adequately described the magnitude and time course of DAS28 score reduction
- TCZ inhibited the production of DAS28 by way of an E_{max} function. The population mean of the maximum effect of TCZ corresponded to a 56.5% reduction of DAS28 from baseline
- The relationship between TCZ concentration and DAS28 was independent of the route of administration
- Similar to the PK-safety relationship (shown on another poster at this conference [poster W-026]), the PK-efficacy relationship of TCZ was similar for the 8 mg/kg IV Q4W and 162 mg SC QW regimens)
- The efficacy of TCZ was similar for the 8 mg/kg IV Q4W and 162 mg SC QW dosing regimens and was higher than that of the 162 mg SC Q2W dosing regimen
- After 24 weeks of treatment, DAS28 reduction from baseline was predicted to be 50% for the 8 mg/kg IV Q4W and 162 mg SC QW dosing regimens and 41% for the 162 mg SC Q2W dosing regimen
- No covariate, including the presence of neutralizing anti-TCZ antibodies, was found to have a clinical impact on the effect of TCZ on DAS28

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