



Population Pharmacokinetics of Tofacitinib in Induction Studies for Moderate-to-Severe Ulcerative Colitis Patients

Camille Vong¹, Chenhui Deng²; Rujia Xie²; Steven W. Martin¹; Dahong Yu⁴; Deborah A Woodworth⁴; Wojciech Niezychowski ⁴; Chinyu Su⁴; Arnab Mukherjee³

¹Pfizer Inc, Cambridge, MA, USA; ²Pfizer Inc, Shanghai, China; ³Pfizer Inc, Groton, CT, USA; ⁴Pfizer Inc, Collegeville, PA, USA

Introduction

Current available therapies for patients with moderate to severe ulcerative colitis (UC) refractory to corticosteroids have often loss of response over time attributable to immunogenicity of biologics and need for therapeutic drug monitoring for treatment optimization. Tofacitinib is an oral, small molecule Janus kinase inhibitor that is being investigated for UC. The objectives of this analysis were to develop a population PK model of tofacitinib using pooled data from Phase 2 and 3 studies and evaluate the possible relationship between exposure and covariates.

Methods

Data from 1054 patients (median age: 41 years; median weight: 74 kg; median baseline Mayo score: 9) receiving tofacitinib either as 0.5, 3, 10 or 15 mg twice daily (BID) were analyzed using FOCE with Interaction in NONMEM. The following patient characteristics were assessed as covariates on PK parameters using a full model approach: race, sex, age, body weight, baseline creatinine clearance, baseline C-reactive protein, baseline albumin, ethnicity and use of concomitant medication (oral steroids and 5-ASA). Missing covariates were imputed using a single imputation method, based on the remaining available data. Inferences about clinical relevance of parameters were based on the resulting parameter estimates of the full model and measures of estimation precision (asymptotic standard errors, bootstrap 95% confidence intervals). Total BLQ concentrations were 4.5% of the total concentration measurements and were discarded in the analysis. Goodness of fit (GOF) plots and Visual Prediction Checks (VPC) were used for model selection and evaluation.

Results

Tofacitinib PK was characterized by a one-compartment pharmacokinetic model with first-order elimination, first-order absorption, an absorption lag time and an IIV on residual error. The following covariate relationships were significant, based on 95% bootstrap confidence intervals of the fixed effect for each covariate:

- CL/F increased with increasing BCCL, consistent with a renal elimination component (~30%) of tofacitinib clearance. The 25th, 50th, and 75th percentiles of BCCL in the analysis dataset were 91.45, 108.9, 128.7 mL/min, and corresponding predicted CL/F values were 23.3, 24.9, 26.5 L/hr, respectively;
- CL/F was 7.6% lower for Asians, and 8.5% lower for those identified as “other race”, compared to the rest of the study population;
- V/F decreased with increasing age. At the 25th, 50th, and 75th percentiles of age in the analysis dataset (30, 40, 51, years respectively) predicted V/F values were 111.3, 108, 105.3 L, respectively;
- V/F increased with increasing body weight. The 25th, 50th, and 75th percentile of body weight (61, 72, and 84 kg respectively) were 97.3, 108, 119.9 L, respectively.

Table 1: Parameter Estimates and corresponding 95% confidence intervals (N=1000) from PK analysis of pooled data from Phase 2 and Phase 3 studies

Parameter	Base Model	Full Model		
	Typical value (RSE %)	Typical value (RSE %)	Median	Bootstrap 95%CI
CL/F (L/hr)	24.8 (1.13)	24.9 (1.13)	24.93	24.21~ 25.65
V/F (L)	109 (1.14)	108 (1.12)	107.84	104.30 ~ 111.11
Ka (hr ⁻¹)	10.4 (9.71)	9.31 (8.63)	9.92	8.49 ~ 14.83
F1	1 FIX	1 FIX	1 FIX	NA
Lag Time (hr)	0.235 (0.62)	0.229 (0.40)	0.232	0.227 ~ 0.238
Effect _{black_CL}	--	1.18 (13.73)	1.18	1.04 ~ 1.34
Effect _{asian_CL}	--	0.924 (2.57)	0.924	0.879 ~ 0.965
Effect _{other_CL}	--	0.915 (5.39)	0.915	0.852 ~ 0.968
Effect _{BBCl_CL}	--	0.379 (8.44)	0.380	0.308 ~ 0.459
Effect _{Age_V}	--	-0.106 (-23.3)	-0.104	-0.162 ~ -0.038
Effect _{BWT_V}	--	0.659 (6.43)	0.660	0.586 ~ 0.734
IIV on CL (CV%)	25.30 (8.64)	24.57 (8.56)	24.50	21.54 ~ 27.61
IOV on Ka (CV%)	190.52 (7.99)	179.72 (7.49)	183.45	167.29 ~ 206.08
Scaling of IIV between CL-V	0.158 (27.40)	0.261 (15.47)	0.272	0.119 ~ 0.381
Proportional error (%)	50.5 (2.28)	48.2 (2.39)	48.39	45.19 ~ 51.68
IIV on error (CV%)	52.34 (5.04)	56.7 (4.66)	56.76	50.79 ~ 63.41

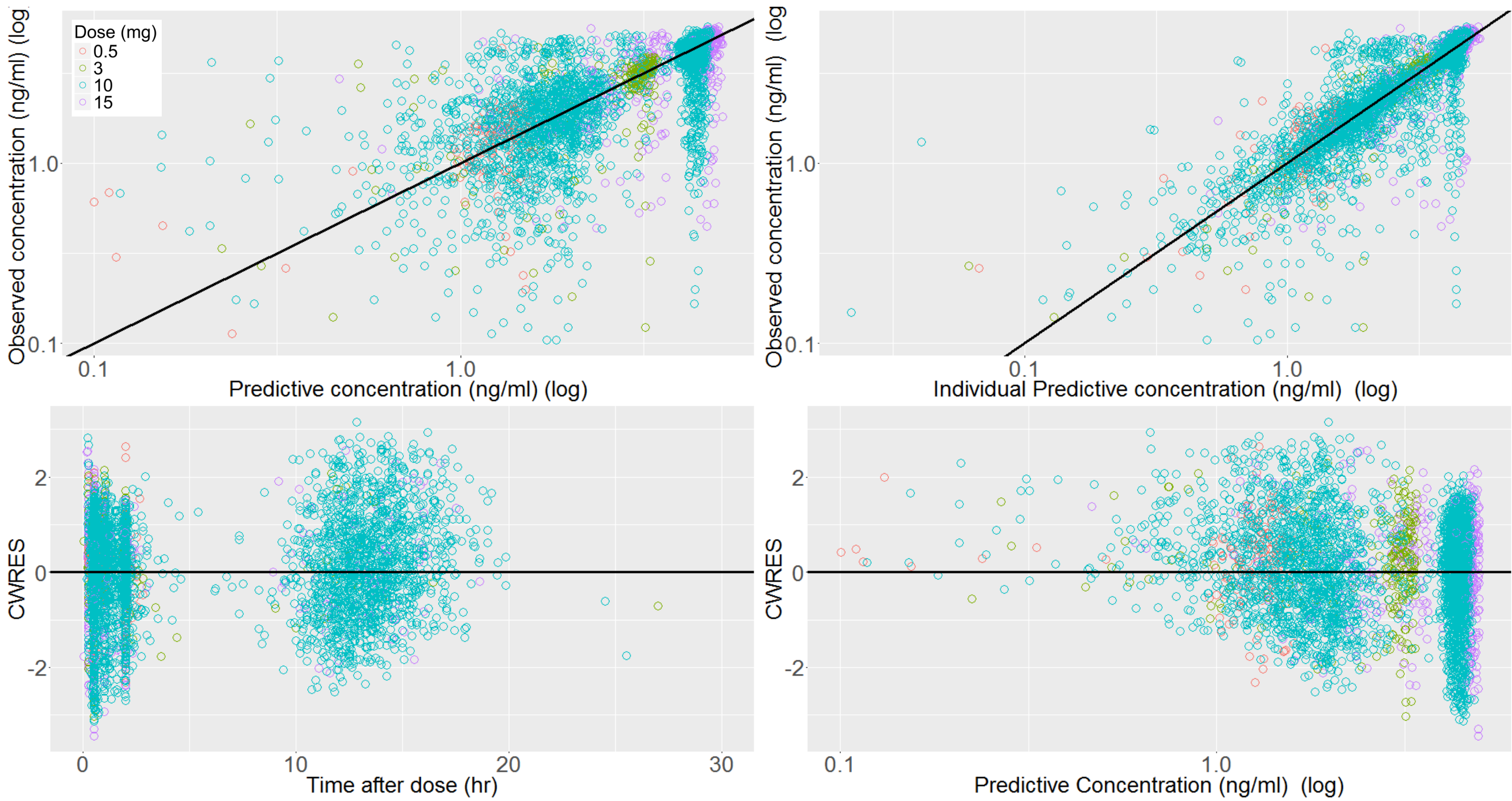


Figure1: Goodness of Fit plots per dose levels for phase 2 and 3 trials. Symbols represent observations and solid line represents the line of identity. Concentrations are log-transformed.

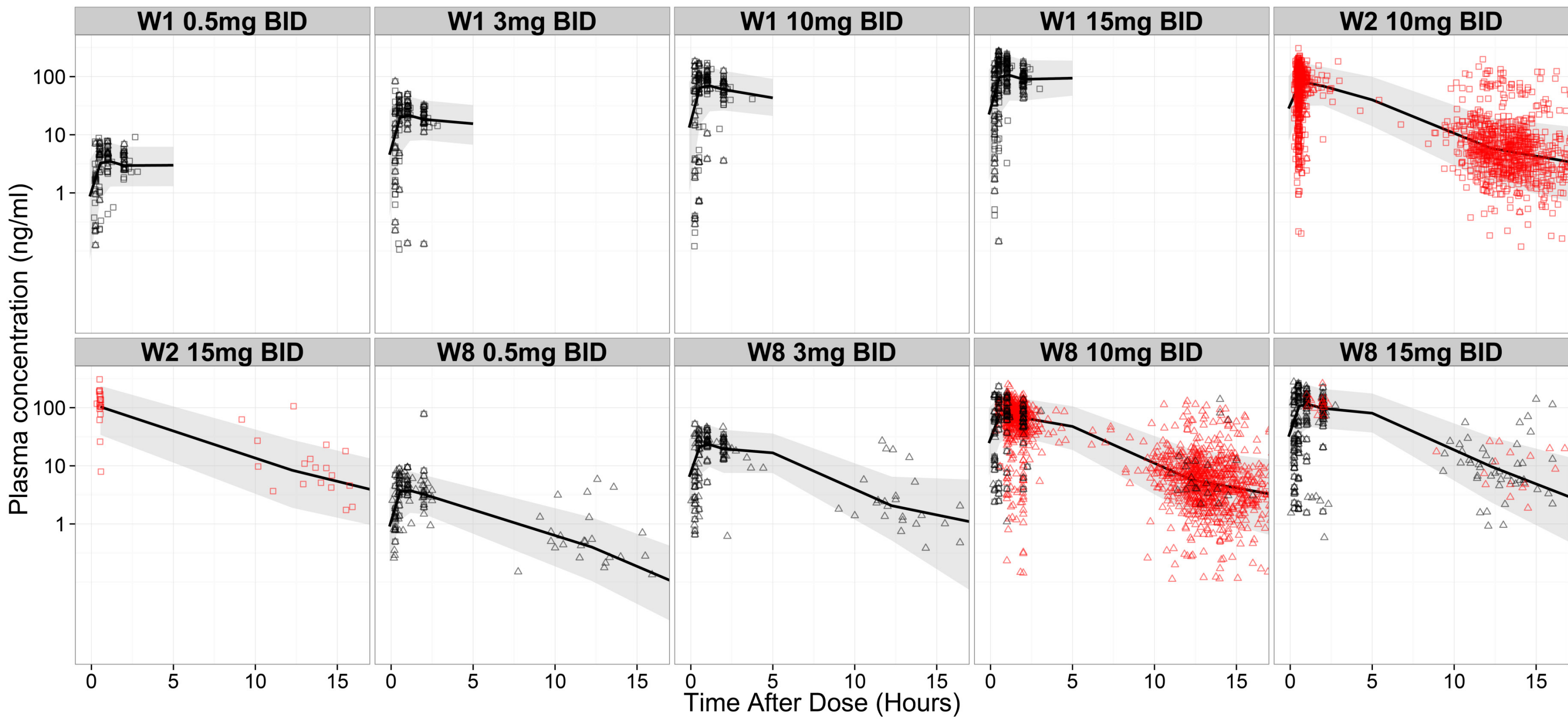


Figure 2: Log-transformed visual prediction check per dose and per week (W1, 2, 8) for model predicted and observed concentrations of tofacitinib. Symbols represent observed concentrations (Ph3:red/Ph2:black), predicted median values and corresponding 90% prediction interval defined as black solid and shaded region, respectively.

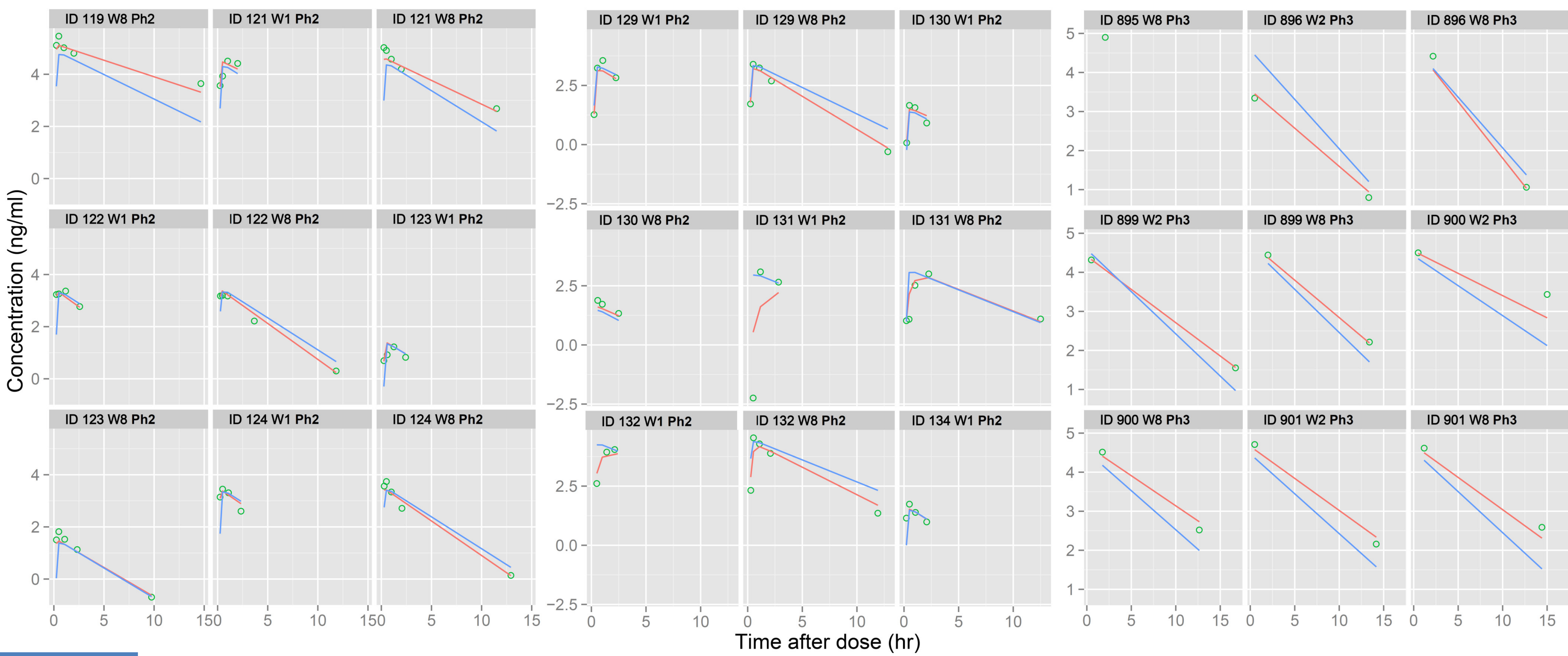


Figure 3: Observations (circle), and population (blue line) and individual (red line) predicted concentrations for time after dose for Phase 2 and Phase 3 studies

Conclusions

The proposed model adequately describes tofacitinib plasma PK that was found consistent between phase 2 and 3 studies. This model will be used in the next step to evaluate the exposure-response correlation between tofacitinib exposure and primary and secondary endpoints of remission and mucosal healing at Week 8 (central read) based on Mayo scores.

References

[1] Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults: American College of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol 2010; 105:501-23.
[2] Meyer DM, et al., Anti-inflammatory activity and neutrophil reductions mediated by the JAK1/JAK3 inhibitor, CP-690,550, in rat adjuvant-induced arthritis. J Inflamm (Lond). 2010. 11; 7:41.
[3] Murray PJ, The JAK-STAT signaling pathway: input and output integration. J Immunol. 2007. 178(5): 2623-9.
[4] Gastonguay MR, A Full Model Estimation Approach for Covariate Effects: Inference Based on Clinical Importance and Estimation Precision. Abstract at 2004 AAPS Annual Meeting.