Received: 14 November 2019 | Revised: 8 April 2020 | Accepted: 21 April 2020

DOI: 10.1111/bcp.14330

ORIGINAL ARTICLE

Population pharmacokinetics of adalimumab biosimilar adalimumab-adbm and reference product in healthy subjects and patients with rheumatoid arthritis to assess pharmacokinetic similarity

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Funding information
Boehringer Ingelheim International GmbH

Aims: Adalimumab-adbm is a monoclonal antibody developed as a biosimilar to adalimumab (Humira, AbbVie Inc.). The key objectives of this study were using a population pharmacokinetic (PPK) approach to assess pharmacokinetic (PK) similarity between adalimumab-adbm and Humira in patients with active rheumatoid arthritis (RA), to quantify the effects of potential covariates on adalimumab PK and to assess the impact of switching treatment from Humira to adalimumab-adbm on PK.

Methods: A PPK model was firstly developed using intensive PK data from the phase-1 study in healthy subjects (NCT02045979). PPK models were developed separately for phase-3 base study (NCT02137226) and its extension study (NCT02640612) in patients with active RA.

Results: PPK models were developed for adalimumab from adalimumab-adbm and Humira treatment in healthy subjects and RA patients. Weight and anti-drug antibodies were found to be important predictors of adalimumab clearance. Adalimumab PK was similar between adalimumab-adbm and Humira. The estimated effect of Humira on clearance, relative to the adalimumab-adbm, was 1.02 (i.e., Humira has 0.02 greater clearance). Similarly, the effect of treatment arms (switching) on clearance was estimated to be 1.00 and 0.997 for Humira:Humira:BI and Humira:BI:BI arms, respectively, relative to the BI:BI:BI arm (BI refers to adalimumab-adbm) in the phase-3 extension study.

Conclusion: PK similarity between adalimumab-adbm and Humira in patients with active RA was demonstrated using PPK approach. Adalimumab PK was also similar when switching treatment from Humira to adalimumab-adbm at either week 24 or 48.

KEYWORDS

biosimilar, pharmacokinetics, rheumatoid arthritis

PI statement: In the current analysis, authors used data from several clinical studies to investigate new objectives that are difficult to investigate based on 1 single study. The clinical studies are already published with the principal investigators as authors and referenced in this manuscript.

1 | INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease presenting with synovial inflammation in the joints and progressive joint alteration and destruction. The biologic **tumour necrosis factor** (TNF) antagonists, including the human immunoglobulin G1 (IgG1) monoclonal antibody (mAb) **adalimumab** (Humira, AbbVie Inc.), are generally preferred as first-line biologic therapy and are endorsed in the current RA treatment recommendations of the American College of Rheumatology[1] and the European League Against Rheumatism.[2] Adalimumab binds specifically to **TNF**-α and blocks its interaction with the TNF receptors, **TNFR1** and **TNFR2**, and consequently reduces inflammation.

Adalimumab-adbm is a monoclonal antibody TNF antagonist that has been approved in USA and Europe (Cyltezo) as a biosimilar to Humira. During the development of a biosimilar product, establishing pharmacokinetic (PK) similarity is a key step to demonstrate the biosimilarity.[3,4] A phase-1 study was conducted in healthy male subjects to evaluate the 3-way bioequivalence, safety and immunogenicity of adalimumab-adbm compared to US-licensed and EU-approved Humira. PK similarity between adalimumab-adbm and Humira was demonstrated with the 90% confidence intervals (CIs) for the ratios of the maximum concentration and the area under the concentration–time curve being within the standard acceptance limits for bioequivalence (80%–125%) using noncompartmental analysis.[5] Concentration *vs* time profiles were similar between the study drugs as were the time course and frequency of immunogenic responses.

A phase-3 study was conducted in patients with active RA to demonstrate clinical equivalence of adalimumab biosimilar candidate adalimumab-adbm with Humira.[6] A phase-3 open-label extension study was also conducted where all the patients were switched to adalimumab-adbm to evaluate its long-term safety and efficacy. The current population PK (PPK) analysis was performed to evaluate PK similarity for adalimumab-adbm and Humira in patients with active RA. The PPK models were developed to (i) characterize adalimumab disposition in healthy subjects and in patients with active RA; (ii) quantify the effects of covariates on adalimumab clearance; (iii) assess if any relevant differences exist between adalimumab-adbm and Humira in terms of PK and the influence of anti-drug antibodies (ADA) on PK; and (iv) evaluate the long-term PK of adalimumab-adbm including effects of ADA and switching therapy from Humira to adalimumab-adbm.

What is already known about this subject

- Pharmacokinetic similarity and bioequivalence were established in healthy volunteers.
- Similarity in safety and efficacy was demonstrated in patients with rheumatoid arthritis.

What this study adds

- Pharmacokinetic similarity for adalimumab-adbm and Humira was demonstrated in patients with rheumatoid arthritis using a population pharmacokinetic approach.
- Switching treatments from Humira to adalimumab-adbm at either week 24 or 48 did not have an impact on adalimumab pharmacokinetics.

2 | METHODS

2.1 | Study design

The PPK analysis was conducted using data from a phase-1 study (NCT02045979) in healthy subjects, a phase-3 study (NCT02137226) in patients with active RA and the extension trial (NCT02640612) of this phase-3 study.

The phase-1 study was a randomized, double-blind, single-dose, parallel arm, active comparator study and was conducted to assess 3-way PK bioequivalence, safety and immunogenicity of adalimumab-adbm compared with US-licensed Humira and EU-approved Humira in healthy subjects.[5] Subjects were randomized 1:1:1 to receive a single subcutaneous 40 mg dose of adalimumab-adbm, US-licensed Humira or EU-approved Humira.

The phase-3 base study was a randomized, double-blind, parallel arm, multiple dose, active comparator trial to evaluate efficacy, safety and immunogenicity of adalimumab-adbm compared with US-licensed Humira with a 48-week treatment period in patients with active RA receiving background methotrexate treatment.[6] Subjects were randomized 1:1 to received 40 mg of adalimumab-adbm or US-licensed Humira every 2 weeks. At Week 24, all subjects were re-randomized. Subjects receiving Humira were re-randomized to either continue on Humira or to switch to adalimumab-adbm. Subjects who originally received adalimumab-adbm continued on adalimumab-adbm.

The phase-3 extension study was an open-label study with a 48-week adalimumab-adbm treatment for RA patients who have completed the previous phase-3 base study and were eligible for long-term treatment with adalimumab. This study was to assess long-term PK, safety, efficacy and immunogenicity of adalimumab-adbm in RA patients.

All study protocols and consent forms were approved by institutional review boards or ethics committees at the study sites, and studies were conducted in accordance with the principles of good clinical practice and the Declaration of Helsinki. All patients provided written informed consent before study participation.

2.2 | Sample collection and assay

In the phase-1 study,[5] blood samples for adalimumab concentration measurement were collected on Days 1–9, 14, 21, 28, 35, 44, 56 and 71 (end of study). ADA titres were measured prior to the dosing and during the

study up to Day 71. In the phase-3 base study,[6] blood samples for adalimumab concentration and ADA titre measurements were collected on Days 1, 7, 14, 28, 84, 168, 280, 336 and 406. In the extension study, blood samples for adalimumab concentration and ADA titre measurement were collected on Days 1, 95, 169, 337 and 407.

In all 3 studies, adalimumab (the analyte) serum concentrations from adalimumab-adbm and Humira were determined using a validated enzyme-linked immunosorbent assay which has been described in the phase-1 study.[5] The upper and lower limits of quantification of the assay were 2000 and 25 ng/mL, respectively, in neat human plasma. One batch of frozen quality control (QC) samples (QC1[low], QC2[mid] and QC3[high]) were prepared by spiking adalimumab-adbm into pooled naïve human plasma at concentrations 10 times greater than the working adalimumab-adbm concentrations (75, 230 and 1500 ng/mL).

ADAs were detected in human plasma samples by a bridging electrochemiluminescence method in 3 tiers. A positive response in the screening assay (Tier 1) was further characterized by a confirmatory assay (Tier 2). If a sample analysis at the minimum required dilution in the screening or confirmatory assay did not show a positive response, it was classified as ADA negative. If screening and confirmatory assay returned both a positive result, the sample was classified as ADA positive and the titre was investigated (Tier 3) analysing serial 2-fold dilution steps of the sample (in addition to minimum required dilution). The lowest dilution that still generated a positive response determined the titre of the sample. Therefore, the ADA titre values are generally the powers of 2 (i.e. 1, 2, 4, 8, 16, 32 etc.).

2.3 | PPK analysis

The current PPK analysis was conducted using the adalimumab (the analyte) concentration data from all treatment arms including adalimumab-adbm and Humira. PPK models were developed separately for the phase-1 study, phase-3 base study and phase-3 extension study using a nonlinear mixed effects modelling approach in NONMEM (version 7.3, ICON Development Solutions, Hanover, MD).[7]

For the phase-1 study with extensive PK data, the PPK model was developed using the first-order conditional estimation with η-ε interaction method. One apparent clearance (CL/F) was estimated for all treatment arms. Results from the phase-1 PPK model subsequently served as prior information to support parameter estimation in the phase-3 studies. The noninformative prior was given to CL/F in the phase-3 models, allowing the parameter estimation of the clearance to be driven by the phase-3 data rather than the phase-1 result. Given the sparse sampling in the phase-3 studies, the informative priors were given to other PK parameters (including apparent central volume of distribution, apparent intercompartmental clearance, apparent peripheral volume of distribution, first-order absorption rate constant and zero-order duration) to enable estimation of all these PPK parameters, which were not supported by sparse data.

PPK models were developed separately for phase-3 base and extension studies using a full Bayesian Markov Chain Monte Carlo method in NONMEM. Noninformative or informative prior was defined via the specification of hyperparameters of prior distribution in NONMEM. Data from the phase-3 base study were omitted in the analysis for the extension study to allow greater sensitivity of the model to possibly detect the differences in PPK analysis, which could be overlooked if the data from both phase-3 studies were combined. As with the phase-1 PPK model, phase-3 models estimated 1 CL/F for all treatment arms. Additional models were run to investigate the PK biosimilarity by estimating the effect of treatment on CL/F parameter (details are provided below; see also equation 4).

A 2-compartment PK model with first-order absorption and linear elimination was initially used. Different model structures were explored during model development. The interindividual random effects on PK parameters were modelled as an additive model in the log domain (Equation 1).

$$P_i = exp\left(\hat{P} + \eta_{Pi}\right) \quad (1)$$

where P_i is the estimated PK model parameter for individual i, $\hat{P}$ is the typical log-transformed value of the model parameter, η_{pi} are interindividual random effects for parameter P and are assumed to be normally distributed with a mean of 0 and a variance of ω^2 as $\eta \sim N(0, \omega^2)$.

Residual unexplained variability was described using a combined additive and proportional error model (Equation 2).

$$C_{ij} = \hat{C}_{ij} \cdot \left(1 + \varepsilon_{pij}\right) + \varepsilon_{aij} \quad (2)$$

where C_{ij} is the j^{th} measured concentration in individual i, $\hat{C}_{ij}$ is the j^{th} model predicted value in individual i, ε_{pij} and ε_{aij} are proportional and additive residual random errors, respectively, for measurement j in individual i, and are each assumed to be independently and identically distributed with a mean of 0 and variance of σ^2 as $\varepsilon \sim NID(0, \sigma^2)$.

A full covariate modelling approach was implemented to investigate covariate effects.[8] This approach emphasizes parameter estimation rather than stepwise hypothesis testing. Predefined covariate–parameter relationships were firstly identified based on scientific interest, exploratory graphics, mechanistic plausibility or prior knowledge. A full covariate model was built with care to avoid correlated predictors, and also guided by sufficiency of covariate data to support the estimation of covariate effects. Inferences about the clinical relevance of covariate effects were derived based on the resulting parameter estimates and estimation precision from the full model. No forward inclusion/backward deletion or hypothesis testing was performed. Covariates resulting in clearance changes >±20% compared to the clearance in the reference subject were considered as clinical meaningful in the current analysis.

In the current analysis, covariate effects, which were evaluated on adalimumab clearance, included body weight (WT), ADA titres, and disease-related variables including baseline rheumatoid factor (BRF), time-varying C-reactive protein (CRP) and albumin (ALB). BRF, CRP and ALB are associated with disease severity, which could potentially affect mAb PK. Disease-related variables were only evaluated in the phase-3 studies with RA patients. PK parameters were also allometrically scaled by WT to represent the physiological change due to the body size. Effects of these continuous covariates on PK

TABLE 1 Demographic and clinical covariates of study population by treatment arm for each study

Variable	Phase 1 study		Phase 3 base study			Phase 3 extension study		
Covariate*	BI	Humira	BI:BI	Humira:BI	Humira:Humira	BI:BI:BI	Humira:BI:BI	Humira:Humira:BI
Age (y)	30.5 (18.0, 55.0)	30.7 (18.0, 55.0)	53.2 (23.0, 80.0)	53.3 (21.0, 75.0)	52.9 (21.0, 77.0)	53.8 (24.0, 80.0)	54.6 (22.0, 76.0)	51.7 (28.0, 74.0)
WT (kg)	79.4 (55.0, 103)	78.3 (54.9, 110)	73.0 (40.1, 139)	76.6 (38.5, 128)	73.9 (40.1, 131)	72.9 (40.1, 137)	78.7 (53.0, 128)	71.6 (40.1, 118)
CRP (mg L^{-1})	3.72 (1.00, 107)	2.28 (1.00, 19.0)	13.2 (1.00, 141)	13.1 (1.00, 90.0)	13.7 (1.00, 141)	5.54 (1.00, 85.0)	4.61 (1.00, 44.0)	5.04 (1.00, 72.0)
BRF (IU mL^{-1})	NA	NA	130 (7.00, 1220)	129 (5.00, 1200)	182 (7.00, 6080)	82.9 (7.00, 790)	85.2 (7.00, 1100)	97.9 (7.00, 2780)
ALB (g L^{-1})	NA	NA	42.5 (32.0, 51.0)	42.6 (34.0, 52.0)	42.2 (32.0, 49.0)	43.4 (36.0, 53.0)	43.3 (37.0, 49.0)	43.1 (34.0, 49.0)
Sex, *n*/*N* (%)								
Male	108/108 (100%)	216/216 (100%)	57/323 (18%)	26/146 (18%)	26/175 (15%)	37/225 (16%)	18/102 (18%)	15/103 (15%)
Female	NA	NA	266/323 (82%)	120/146 (82%)	149/175 (85%)	188/225 (84%)	84/102 (82%)	88/103 (85%)
Race, *n*/*N* (%)								
White	88/108 (81%)	172/216 (80%)	308/323 (95%)	140/146 (96%)	164/175 (94%)	215/225 (96%)	100/102 (98%)	100/103 (97%)
Black	1/108 (1%)	3/216 (1%)	6/323 (2%)	3/146 (2%)	4/175 (2%)	3/225 (1%)	2/102 (2%)	NA
Asian	9/108 (8%)	14/216 (6%)	8/323 (2%)	2/146 (1%)	4/175 (2%)	7/225 (3%)	NA	2/103 (2%)
Native Hawaiian or other Pacific Islander	3/108 (3%)	3/216 (1%)	NA	NA	NA	NA	NA	NA
Others	7/108 (6%)	24/216 (11%)	1/323 (0.3%)	1/146 (1%)	3/175 (2%)	NA	NA	1/103 (1%)

*For continuous covariates, the number in each cell represents the mean (range) of data at baseline. BI refers to adalimumab-adbm. In the phase-3 base study, Humira:BI arm was for subjects who received Humira for 24 weeks, and then switched to adalimumab-adbm for the remaining 24 weeks. In the phase-3 extension study, Humira:BI:BI arm was for subjects who received Humira for 24 weeks, then switched to adalimumab-adbm during the base study and finally switched to open-label adalimumab-adbm during the extension, Humira:Humira:BI arm was for subjects who were treated with Humira for 48 weeks during the base study and switched to open-label adalimumab-adbm during the extension study.

parameters were modelled using a power function normalized by the reference values (Equation 3).

$$P_i = exp\left(\hat{P} + \theta_{Cov} \cdot log\left(\frac{Cov_i}{Cov_{ref}}\right)\right) \quad (3)$$

where P_i is the estimated PK model parameter for individual i, $\hat{P}$ is the typical log-transformed value of the model parameter, Cov_i is the covariate in individual i, Cov_{ref} is the reference value of the covariate (e.g. the median) and θ_{Cov} is the estimated covariate effect.

Differences between adalimumab-adbm and Humira disposition were initially investigated via model diagnostic plots stratified by treatment arm and via comparison of *posthoc* distributions of individual clearance between treatment arms. To further assess the PK similarity between 2 compounds, separate models were run to estimate the effect of treatment as an additional categorical covariate on adalimumab clearance only. There was no sufficient data in phase-3 studies to support the evaluation of covariates on other PK parameters. For phase-3 base study, the effect of Humira on adalimumab clearance was estimated with adalimumab-adbm considered as the reference. Similarly, effects of treatment arms (Humira:BI:BI and Humira:BI:BI) (switching effect) on adalimumab clearance relative to the reference BI:BI:BI arm (BI refers adalimumab-adbm) were estimated for phase-3 extension study (Equation 4).

$$CL/F_i = CL/F_{ref} \cdot (\theta)^{Trt_i} \quad (4)$$

where CL/F_{ref} is the apparent clearance of adalimumab from the reference treatment, θ is the estimated treatment effect, Trt_i is a categorical variable representing the treatment (e.g. with the value of 1 for Humira and 0 for adalimumab-adbm as reference in phase-3 base study).

The adequacy and predictive performance of the PPK model was assessed via a visual predictive check (VPC) method. Five hundred Monte Carlo simulation replicates of the original data set were generated using the PPK model and model parameter estimates. The 5th, 50th and 95th percentiles of the observed data were constructed, overlaid with the 95% prediction intervals of the 5th, 50th and 95th percentiles of the simulated data.

2.4 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY.

3 | RESULTS

3.1 | PK analysis data

The PPK data set consisted of 324 healthy subjects contributing 7255 measurable adalimumab concentrations from the phase-1 study, 644 patients with RA contributing 4342 measurable adalimumab concentrations from the phase-3 base study and 430 patients with RA contributing 2192 measurable adalimumab concentrations from the phase-3 extension study.

Baseline WT and disease characteristics of the study population included in the analysis are shown in Table 1, stratified by study and treatment. WT of the phase-1 study population ranges from 54.9 to 110 kg. The phase-3 study population was comprised of RA patients with baseline weight ranging from 38.5 to 139 kg, with baseline CRPs ranging from 1 to 141 mg L^{-1}, BRFs from 5 to 6080 IU mL^{-1} and baseline ALBs from 32 to 53 g L^{-1}. All patients received a methotrexate background treatment. Most study subjects had negative ADA test at baseline (95%) with the absence of ADA. As the treatment proceeded, ADA appeared in all treatment arms (55% of subjects in the phase-3 base study and 52% of

TABLE 2 Parameter estimates from population pharmacokinetic model for the phase-1 study

Parameter	Estimate	95% CI*
CL/F (L h^{-1})	0.0278	(0.0264, 0.0292)
(WT/70)$^{0.75}$		
(ADA–) * exp(θ_7)	0.421	(0.399, 0.444)
(ADA/16)$^{\theta 8}$	0.242	(0.229, 0.255)
Vc/F (L)	2.49	(2.24, 2.78)
(WT/70)^{1}		
Q/F (L h^{-1})	0.0708	(0.0609, 0.0825)
(WT/70)$^{0.75}$		
Vp/F (L)	3.74	(3.53, 3.96)
(WT/70)^{1}		
k_a (h^{-1})	0.0108	(0.00981, 0.0119)
D_1 (h)	2.96	(2.75, 3.19)
IIV CL/F	0.137 (CV = 38.4%)	(0.116, 0.159)
IIV Vc/F	0.533 (CV = 83.9%)	(0.412, 0.653)
$COV_{Vc/F\text{-}CL/F}$	0.0388 (corr = 0.143)	(0.00227, 0.0753)
IIV Q/F	0.992 (CV = 130%)	(0.761, 1.22)
$COV_{Q/F\text{-}CL/F}$	0.0306 (corr = 0.0828)	(–0.0289, 0.0901)
$COV_{Q/F\text{-}Vc/F}$	–0.108 (corr = –0.149)	(–0.246, 0.0305)
IIV Vp/F	0.124 (CV = 36.3%)	(0.0941, 0.154)
$COV_{Vp/F\text{-}CL/F}$	–0.0272 (corr = –0.208)	(–0.0470, –0.00731)
$COV_{Vp/F\text{-}Vc/F}$	–0.0693 (corr = –0.270)	(–0.125, –0.0139)
$COV_{Vp/F\text{-}Q/F}$	0.217 (corr = 0.618)	(0.148, 0.285)
IIV ka	0.345 (CV = 64.2%)	(0.246, 0.444)
$COV_{ka\text{-}CL/F}$	–0.0219 (corr = –0.100)	(–0.0609, 0.0171)
$COV_{ka\text{-}Vc/F}$	0.0861 (corr = 0.201)	(0.00709, 0.165)
$COV_{ka\text{-}Q/F}$	0.404 (corr = 0.690)	(0.265, 0.543)
$COV_{ka\text{-}Vp/F}$	0.101 (corr = 0.490)	(0.0589, 0.144)
Proportional residual error	0.00668 (CV = 8.18%)	(0.00642, 0.00695)
Additive residual error	0.0198 (SD = 0.141 mg L^{-1})	(0.0187, 0.0208)

*95%CI was derived from standard errors obtained from the NONMEM $COVARIANCE step. ADA = anti-drug antibodies; ADA– = absence of ADA; CV = coefficient of variation; corr = correlation; IIV = interindividual variability (variance); COV = covariance of interindividual variability; SD = standard deviation; CL/F = apparent clearance; Vc/F = apparent central volume of distribution; Q/F = apparent intercompartmental clearance; Vp/F = apparent peripheral volume of distribution; k_a = first-order absorption rate constant; D_1 = zero-order duration.

subjects in the extension study). To facilitate the model estimation (convergence of runs), the commonly observed titre value of 16 was chosen as the reference value to estimate the ADA effect in the covariate model. The effect of having ADA negative test was also estimated as a factor compared to the reference titre value of 16.

3.2 | PPK analysis

3.2.1 | Phase 1 analysis

A 2-compartment model with sequential zero- and first-order absorption and linear elimination was chosen as the best structural model to describe the adalimumab PK. The clearance- and volume-related PK parameters were allometrically scaled by WT with the coefficients fixed at 0.75 for clearance-related PK parameters and 1 for volume-related parameters.[9] The typical estimate (95% CI) of the CL/F given the reference covariates (70 kg WT and ADA titre value of 16) was 0.0278 (0.0264, 0.0292) L h^{-1}. Parameter estimates indicated that adalimumab CL/F increased as ADA titre value increased. Subjects with negative ADA test had approximately 42.1% (39.9%, 44.4%) of CL/F in subjects with ADA titre value of 16. PK parameter estimates and 95% CIs from the final phase-1 PPK model are presented in Table 2. The goodness-of-fit plots showed the final model provided an adequate description of the observed adalimumab data (Figure 1A). The VPC plots also demonstrated the overall agreement between the observed and simulated data for both adalimumab-adbm and Humira treatment arms in the phase-1 study (Figure S1).

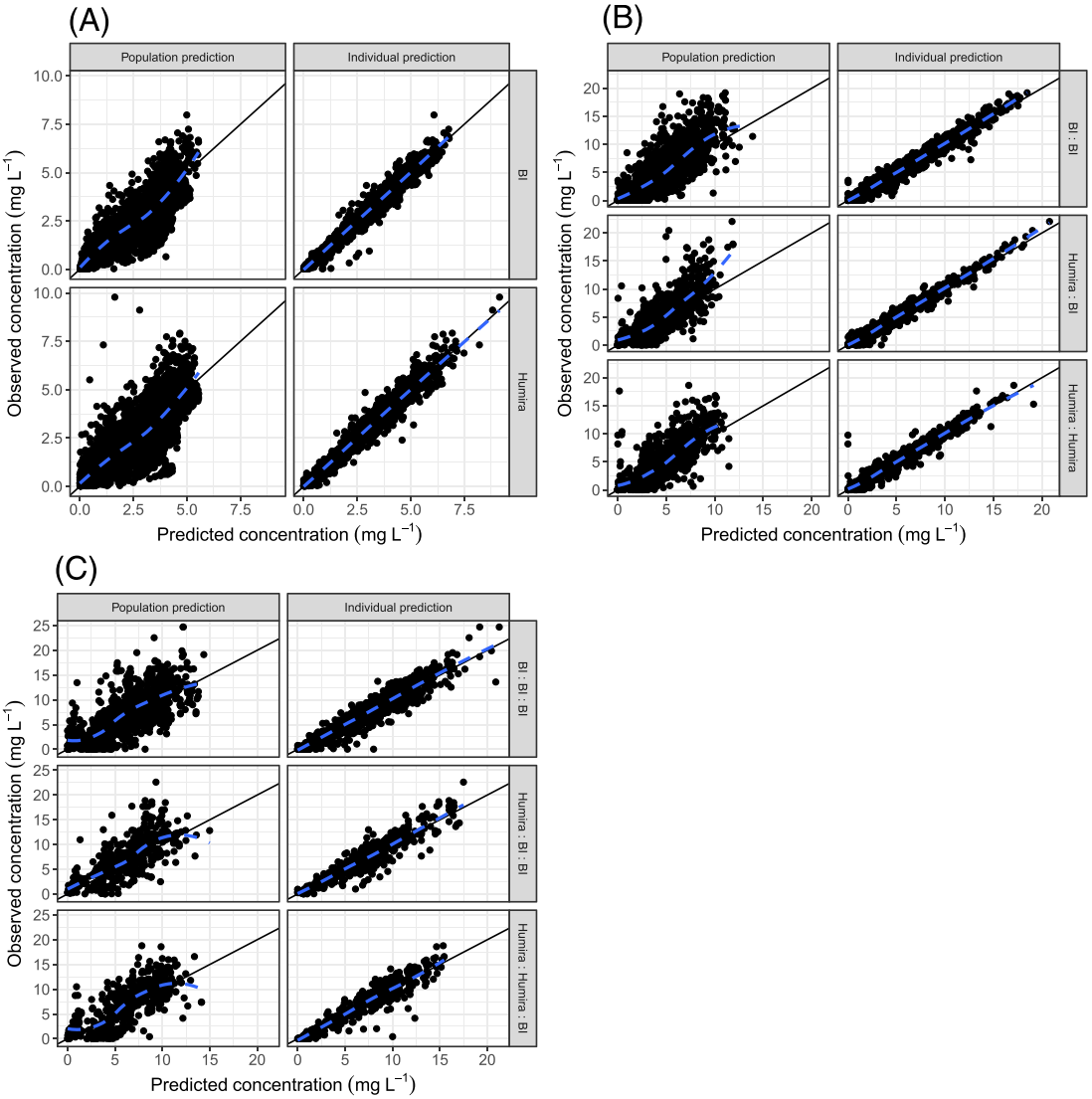

FIGURE 1 Diagnostic plots of observed *vs* individual and population predicted concentrations from the final population pharmacokinetic models by treatment arm for the phase-1 study (A), phase-3 base study (B) and phase-3 extension study (C). BI refers to adalimumab-adbm. The black line of identity is included as reference. The blue dashed line represents a loess smooth line. In the phase-3 base study, Humira:BI arm was for subjects who received Humira for 24 weeks and then switched to adalimumab-adbm for the remaining 24 weeks. In the phase-3 extension study, Humira:BI:BI arm was for subjects who received Humira for 24 weeks, then switched to adalimumab-adbm during the base study and finally switched to open-label adalimumab-adbm during the extension, Humira:Humira:BI arm was for subjects who were treated with Humira for 48 weeks during the base study and switched to open-label adalimumab-adbm during the extension study

TABLE 3 Parameter estimates from population pharmacokinetic model for the phase-3 base study

Parameter	Estimate	95% CI*
CL/F (L h^{-1})	0.0244	(0.0233, 0.0257)
$(WT/70)^{0.75}$		
(ADA–) * $\exp(\theta_7)$	0.560	(0.537, 0.580)
$(ADA/16)^{\theta 8}$	0.178	(0.163, 0.194)
$(CRP/3)^{\theta 9}$	0.0867	(0.0645, 0.108)
$(ALB/43)^{\theta 10}$	−0.693	(−1.03, −0.385)
$(BRF/47)^{\theta 11}$	0.0278	(0.00488, 0.0432)
Vc/F (L)	2.96	(2.64, 3.42)
$(WT/70)^{1}$		
Q/F (L h^{-1})	0.0766	(0.0672, 0.0872)
$(WT/70)^{0.75}$		
Vp/F (L)	4.27	(4.01, 4.53)
$(WT/70)^{1}$		
k_a (h^{-1})	0.0117	(0.0108, 0.0129)
D_1 (h)	2.82	(2.61, 3.03)
IIV CL/F	0.122 (CV = 36.0%)	(0.106, 0.139)
IIV Vc/F	0.927 (CV = 124%)	(0.721, 1.18)
$COV_{Vc/F\text{-}CL/F}$	−0.0139 (corr = −0.0412)	(−0.0656, 0.0455)
IIV Q/F	1.15 (CV = 147%)	(0.857, 1.54)
$COV_{Q/F\text{-}CL/F}$	0.00861 (corr = 0.0230)	(−0.0458, 0.066)
$COV_{Q/F\text{-}Vc/F}$	−0.209 (corr = −0.202)	(−0.429, 0.123)
IIV Vp/F	0.205 (CV = 47.7%)	(0.143, 0.286)
$COV_{Vp/F\text{-}CL/F}$	−0.0378 (corr = −0.239)	(−0.0658, −0.0126)
$COV_{Vp/F\text{-}Vc/F}$	−0.233 (corr = −0.534)	(−0.380, −0.123)
$COV_{Vp/F\text{-}Q/F}$	0.305 (corr = 0.629)	(0.191, 0.414)
IIV ka	0.561 (CV = 86.7%)	(0.369, 0.869)
$COV_{ka\text{-}CL/F}$	−0.0468 (corr = −0.179)	(−0.0822, −0.0119)
$COV_{ka\text{-}Vc/F}$	0.142 (corr = 0.197)	(−0.0423, 0.382)
$COV_{ka\text{-}Q/F}$	0.560 (corr = 0.698)	(0.371, 0.919)
$COV_{ka\text{-}Vp/F}$	0.140 (corr = 0.413)	(0.0551, 0.221)
IOV	0.0479 (CV = 22.1%)	(0.0401, 0.0568)
Proportional residual error	0.0112 (CV = 10.6%)	(0.00877, 0.0141)
Additive residual error	0.529 (SD = 0.727 mg L^{-1})	(0.481, 0.574)

*95%CI was derived from posterior distribution obtained from the NONMEM BAYES estimation method. ADA = anti-drug antibodies; ADA– = absence of ADA, CV = coefficient of variation, corr = correlation, IIV = interindividual variability (variance), COV = covariance of interindividual variability, IOV = interoccasion variability (variance) on relative bioavailability, SD = standard deviation; CL/F = apparent clearance; Vc/F = apparent central volume of distribution; Q/F = apparent intercompartmental clearance; Vp/F = apparent peripheral volume of distribution; k_a = first-order absorption rate constant; D_1 = zero-order duration.

TABLE 4 Parameter estimates from population pharmacokinetic model for the phase-3 extension study

Parameter	Estimate	95% CI*
CL/F (L h^{-1})	0.0195	(0.0187, 0.0202)
$(WT/70)^{0.75}$		
(ADA–) * $\exp(\theta_7)$	0.654	(0.619, 0.69)
$(ADA/16)^{\theta 8}$	0.165	(0.145, 0.187)
$(CRP/3)^{\theta 9}$	0.0747	(0.0538, 0.095)
$(ALB/43)^{\theta 10}$	−0.655	(−0.95, −0.372)
$(BRF/47)^{\theta 11}$	0.0562	(0.031, 0.0802)
Vc/F (L)	2.67	(2.44, 2.94)
$(WT/70)^{1}$		
Q/F (L h^{-1})	0.0709	(0.0614, 0.0821)
$(WT/70)^{0.75}$		
Vp/F (L)	3.94	(3.71, 4.18)
$(WT/70)^{1}$		
k_a (h^{-1})	0.0109	(0.0102, 0.0119)
D_1 (h)	2.91	(2.72, 3.1)
IIV CL/F	0.114 (CV = 34.8%)	(0.0976, 0.134)
IIV Vc/F	0.585 (CV = 89.2%)	(0.462, 0.741)
$COV_{Vc/F\text{-}CL/F}$	0.0525 (corr = 0.203)	(0.0144, 0.0924)
IIV Q/F	1.31 (CV = 165%)	(0.936, 1.92)
$COV_{Q/F\text{-}CL/F}$	0.0358 (corr = 0.0924)	(−0.0318, 0.105)
$COV_{Q/F\text{-}Vc/F}$	−0.205 (corr = −0.233)	(−0.376, −0.0537)
IIV Vp/F	0.150 (CV = 40.3%)	(0.114, 0.199)
$COV_{Vp/F\text{-}CL/F}$	−0.0298 (corr = −0.227)	(−0.0509, −0.0103)
$COV_{Vp/F\text{-}Vc/F}$	−0.138 (corr = −0.465)	(−0.208, −0.0839)
$COV_{Vp/F\text{-}Q/F}$	0.287 (corr = 0.646)	(0.187, 0.429)
IIV ka	0.439 (CV = 74.2%)	(0.295, 0.603)
$COV_{ka\text{-}CL/F}$	−0.00761 (corr = −0.0340)	(−0.0495, 0.0298)
$COV_{ka\text{-}Vc/F}$	0.0438 (corr = 0.0863)	(−0.0506, 0.139)
$COV_{ka\text{-}Q/F}$	0.559 (corr = 0.736)	(0.343, 0.831)
$COV_{ka\text{-}Vp/F}$	0.119 (corr = 0.463)	(0.0589, 0.19)
Proportional residual error	0.0367 (CV = 19.2%)	(0.0318, 0.042)
Additive residual error	0.399 (SD = 0.632 mg L^{-1})	(0.292, 0.542)

*95%CI was derived from posterior distribution obtained from the NONMEM BAYES estimation method. ADA = anti-drug antibodies; ADA– = absence of ADA; CV = coefficient of variation; corr = correlation; IIV = interindividual variability (variance); COV = covariance of interindividual variability; SD = standard deviation; CL/F = apparent clearance; Vc/F = apparent central volume of distribution; Q/F = apparent intercompartmental clearance; Vp/F = apparent peripheral volume of distribution; k_a = first-order absorption rate constant; D_1 = zero-order duration.

3.3 | Phase-3 analysis

The same structural PK model from the phase-1 study was applied to the phase-3 base and extension studies.

Like the phase-1 model, the clearance- and volume-related PK parameters were allometrically scaled by WT with the fixed coefficients. Additionally, effects of BRF, ADA, CRP and ALB on CL/F were evaluated in the full covariate model (Equation 5). The same full covariate model was fit to the phase-3 studies. Inter-occasion variability on relative bioavailability (F) was estimated in the phase-3 base study to account for within-subject variability upon multiple dosing over time.

$$CL/F_{i,t} = \exp\left(\theta_1 + 0.75 \cdot log\left(\frac{WT_i}{70}\right) + \theta_7 \cdot (ADA-_{i,t}) + \theta_8 \cdot log\left(\frac{ADA_{i,t}}{16}\right) + \theta_9 \cdot log\left(\frac{CRP_{i,t}}{3}\right) + \theta_{10} \cdot log\left(\frac{ALB_{i,t}}{43}\right) + \theta_{11} \cdot log\left(\frac{BRF_i}{47}\right) + \eta_{CL/F,i}\right) \quad (5)$$

where $CL/F_{i,t}$ is the estimated apparent clearance for individual *i* at time *t*, WT_i represents WT in individual *i*, $ADA-_{i,t}$ represents the time-varying indictor in individual *i* at time *t* with value of 1 for negative ADA test and 0 for positive ADA test, $ADA_{i,t}$ represents the time-varying ADA in individual *i* at time *t*, $CRP_{i,t}$ represents the time-varying CRP in individual *i* at time *t*, $ALB_{i,t}$ represents the time-varying ALB in individual *i* at time *t* BRF_i represents BRF in individual *i, and* $\eta_{CL/F,i}$ is the individual-specific random effect for apparent clearance in individual *i*.

PK parameter estimates and 95% CIs from the final PPK models were presented in Table 3 for the phase-3 base study and Table 4 for the extension study. The typical estimate (95% CI) of CL/F given the reference covariates (70 kg WT, ADA titre value of 16, 3 mg L^{-1} CRP, 43 g L^{-1} ALB, 47 IU mL^{-1} BRF) was 0.0244 (0.0233, 0.0257) L h^{-1} for the phase-3 base study and 0.0195 (0.0187, 0.0202) L h^{-1} from the extension study. The goodness-of-fit plots showed the final PPK models provided an adequate description of the observed adalimumab data in the phase-3 studies (Figures 1B and 1C). The VPC plots demonstrated overall good agreement between the observed and simulated data for both adalimumab-adbm and Humira treatment arms (Figures S2 and S3).

PK similarity between 2 compounds was initially graphically investigated based on goodness-of-fit plots stratified by treatment arm. The plot (Figure 1B) did not show any obvious difference when comparing treatment arms. The estimated effect of Humira on clearance (in a separate PPK model) was 1.02 (95% CI: 0.981, 1.05), which means that Humira has 0.02 greater clearance than adaliumumab-adbm. The estimate indicated that there was no relevant difference in adalimumab CL/F between Humira and adalimumab-adbm which further concluded adalimumab-adbm PK was similar to Humira in RA patients.

The effect of switching from long-term treatment with Humira to adalimumab-adbm on adalimumab PK was assessed in the phase-3 extension study. The goodness-of-fit for this study (Figure 1C) demonstrated that the model fit the adalimumab data similarly in all treatment arms including those switching therapy from Humira to

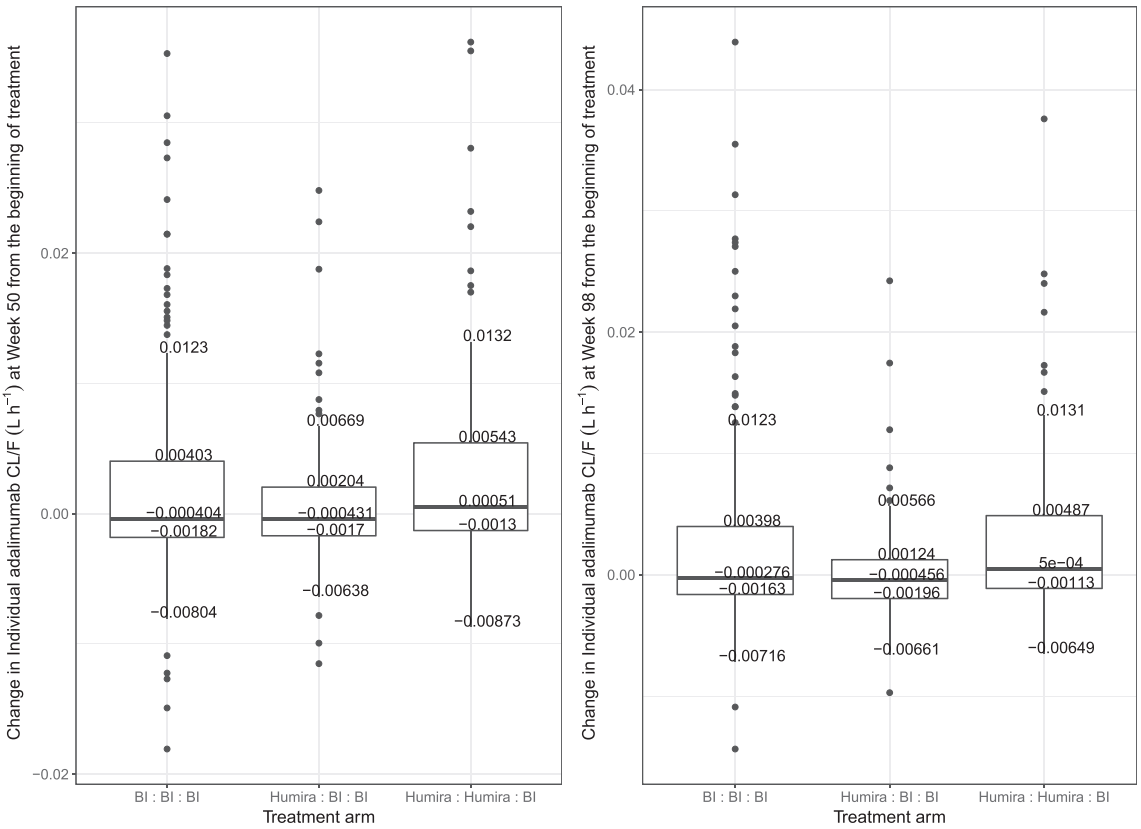

FIGURE 2 Changes in individual estimates of apparent clearance (CL/F) at week 50 and 98 are plotted *vs* treatment arm using boxplots. BI refers to adalimumab-adbm

adalimumab-adbm at week 24 or 48 of treatment. Furthermore, the effect of switching treatment was evaluated by estimating an additional 'treatment arm' covariate of CL/F (in a separate PPK model). The effect of treatment arms on CL/F was estimated (95% CI) to be 1.00 (0.940, 1.08) and 0.997 (0.922, 1.08) for Humira:Humira:BI and Humira:BI:BI arms, respectively, relative to the reference BI:BI:BI arm (BI refers to adalimumab-adbm). These estimates being at or close to 1 indicated that switching treatments from Humira to adalimumab-adbm at either week 24 or 48 of treatment had effectively no impact on long-term overall adalimumab CL/F. This was also demonstrated in plots of change from the start treatment in individual CL/F estimates for each of the treatment groups at weeks 50 and 98 (Figure 2). Almost no change in CL/F was observed at these timepoints compared to the start of treatment.

Parameter estimates from phase-3 studies indicated that CL/F increased with increasing CRP and BRF, and decreasing ALB. CL/F was greater with higher ADA titre values. With the presence of ADA, clearance was approximately 28% greater (the base study) with ADA titre value of 64 than that with ADA titre value of 16. With the absence of ADA, clearances would be approximately 44.0% (the base study) and 34.6% (the extension study) lower than that with the ADA titre value of 16.

Covariate effects on CL/F were further evaluated by calculating clearances based on representative values of the covariates and estimated covariate effects, and comparing these calculated clearances to the typical estimate of CL/F with in a typical patient with reference covariate values (70 kg WT, ADA titre value of 16, 3 mg L^{-1} CRP, 43 g L^{-1} ALB, 47 IU mL^{-1} BRF). Figure 3 showed that some portion of 95% CI of CL/F relative to the typical CL/F fell outside the region (±20%) at small and large values of WT and ADA titre, suggesting possibly clinical meaningful changes. Effects of ALB, BRF and CRP on CL/F were not clinically meaningful based on the median covariate effect sizes of <±20% from the typical CL/F.

In the phase-3 studies, all adalimumab-adbm and Humira arms had similar patterns of the observed ADA titre values over the time on treatment (Figure 4). Plots of weighted residuals from the PPK models *vs* time-varying ADA titre values did not show any obvious trend and were similar across treatment arms (Figure S4).

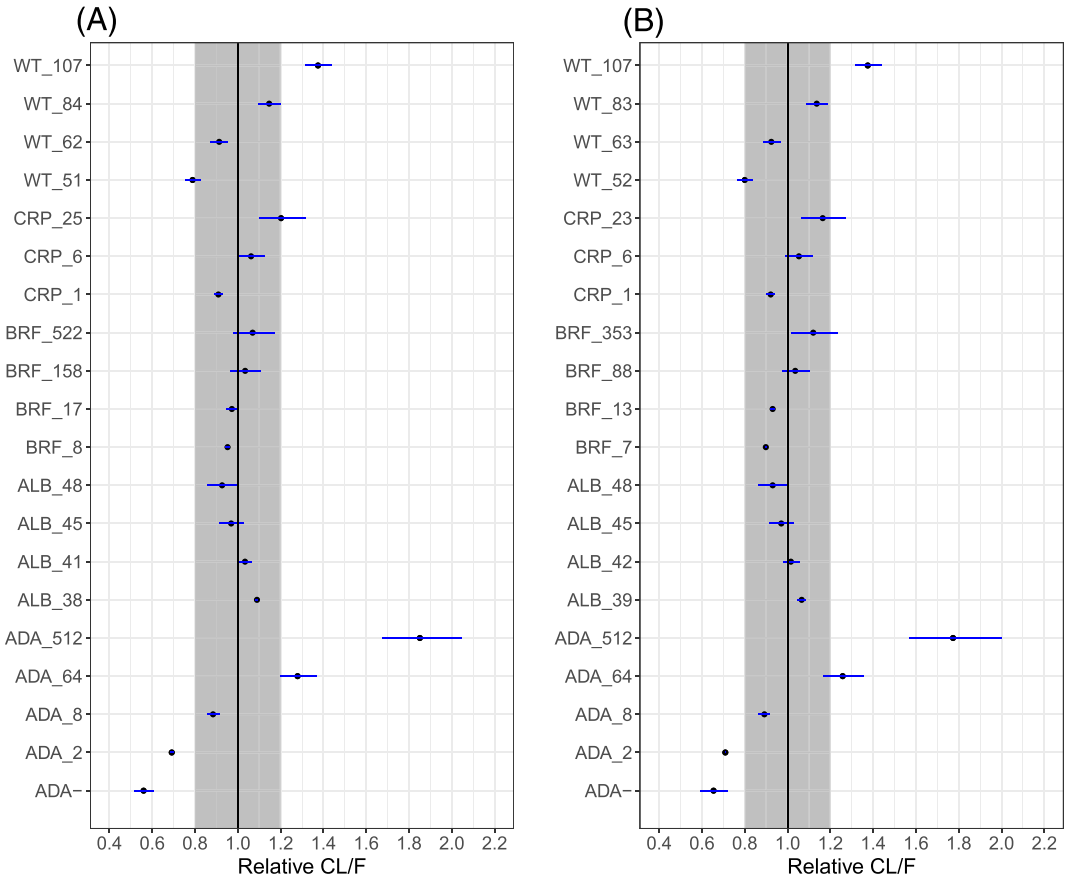

FIGURE 3 Plots of covariate effects on apparent clearance (CL/F) for the phase-3 base study (A) and the phase-3 extension study (B). CL/F relative to the typical patient with reference covariates (70 kg body weight [WT], anti-drug antibody [ADA] titre value of 16, 3 mg/L C-reactive protein [CRP], 43 g/L albumin [ALB], 47 IU/mL baseline rheumatoid factor [BRF]) is plotted by representative covariate value. Different cuts of WT, CRP, ALB, ADA and BRF represent the 5th, 25th, 75th and 95th percentiles of the observed covariate values during the treatment in the study. The black dot represents the clearance evaluated at the representative values of covariates and point estimates of the covariate parameter, compared to the CL/F in the typical patient. The blue line represents the clearance at the representative values of covariates and 95% CIs of the covariate parameter estimate relative to CL/F in the typical patient. The black solid line represents the CL/F in the typical patient with reference covariate values. The grey shaded region represents covariate effect size <±20% of the typical CL/F, which is considered not clinical meaningful

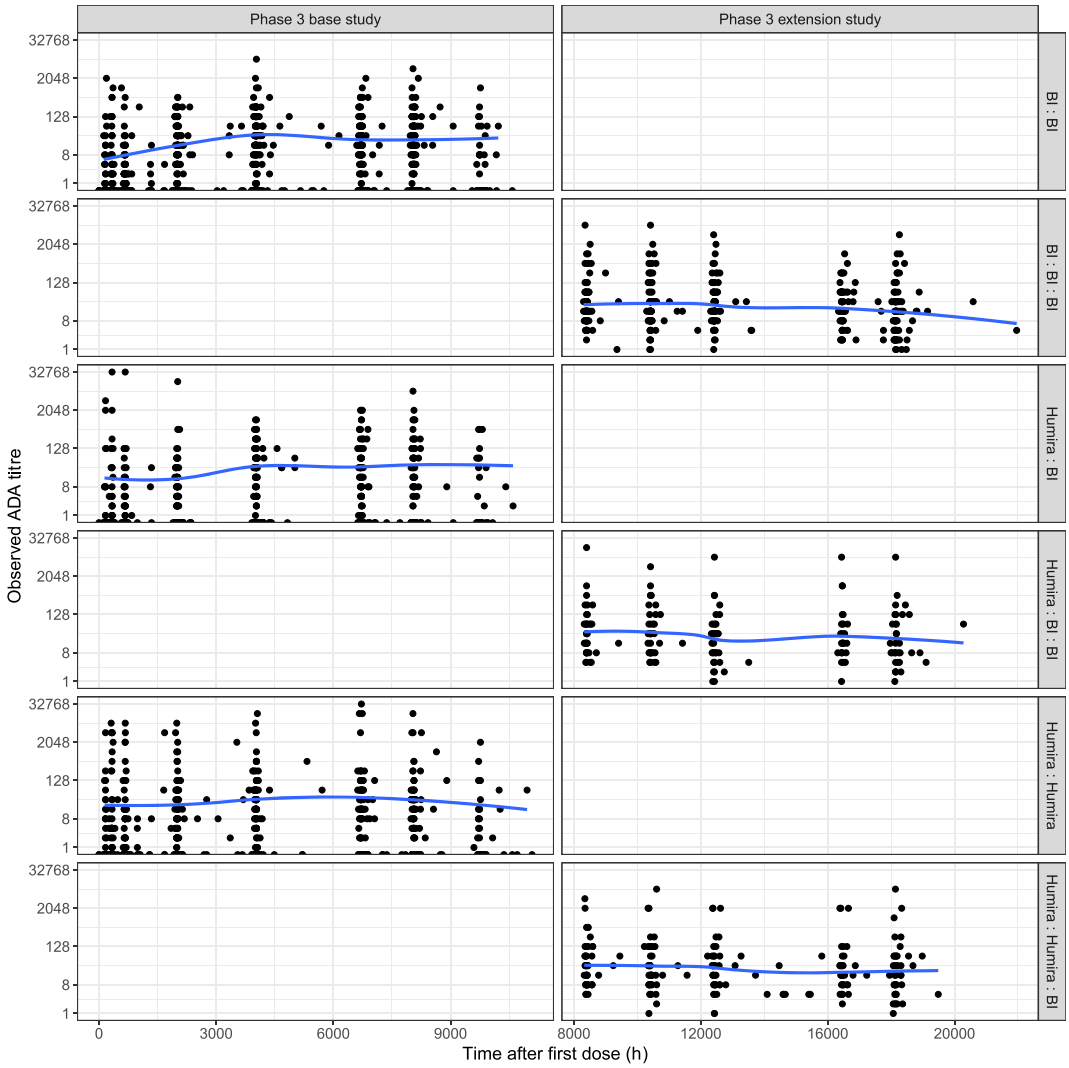

FIGURE 4 Plots of observed anti-drug antibody [ADA] titre (in log 2 scale) *vs* time after the first dose by treatment arm and study. BI refers to adalimumab-adbm. Black dots represent observed ADA titre value with blue loess smoothing trend line

4 | DISCUSSION

4.1 | PPK analysis

In the current investigation, we performed PPK analysis for adalimumab from adalimumab-adbm and Humira. The PK of adalimumab from adalimumab-adbm and Humira was well described by a 2-compartment model with sequential zero- and first- order absorption and linear elimination in healthy subjects and patients with active RA. Potential covariate effects on adalimumab CL/F were evaluated in the final PPK models for 2 phase-3 studies.

WT was an important covariate on adalimumab CL/F, which was also identified in Humira PPK analysis.[10] Body size is commonly identified covariate influencing the PK of therapeutic mAbs.[11,12] Another important covariate was ADA. Immunogenicity has been frequently evaluated for its potential impact on mAb disposition and efficacy.[13,14] The current analysis demonstrated adalimumab CL/F increased with the appearance of ADA and was elevated further with higher ADA titre values. This is consistent with what was reported in the Humira PPK analyses[3,10,15,16] and also in other mAbs.[11] Disease-related variables including ALB, CRP and BRF, are associated with disease severity and inflammatory status, which could affect proteolytic degradation of mAbs and consequently impact the elimination pathways of mAbs.[17] High albumin may indicate the increasing neonatal Fc receptors, which can protect immunoglobulin G and mAb from catabolism by recycling them back to the systemic circulation.[18] Therefore, high albumin could be associated with the reduced mAb clearance.[19] CRP was found to have a positive effect on mAb clearance.[20] Similarly, the current analysis found that adalimumab CL/F increased with increasing CRP and BRF, and decreasing ALB. However, these covariate effects appeared to be minor and were judged not clinically important when comparing to the clearance in a typical subject with reference covariates. Minor increases in the Humira CL/F were also reported in patients with higher BRF and CRP and were considered not clinically important.[3] The estimate of adalimumab CL/F from the phase-3 base study was similar to the estimate from the extension study (0.0244 *vs* 0.0195 L h^{-1}), and was comparable to those reported in other indications (hidradenitis suppurativa: 0.028 L h^{-1}, psoriasis: 0.021 L h^{-1}).[10]

The slightly lower CL/F in the extension study may be attributable to selection of responder patients with low clearance and drop out of nonresponders which is correlated to patients with high ADA and high CL/F.

When using the phase-1 results as the prior information for the phase-3 analysis, we were aware of differences between the phase-1 study and the phase-3 studies, such as study population (healthy subjects *vs* RA patients), study design (rich sampling *vs* sparse sampling), dosage regimen (single dose *vs* multiple doses) and background therapy with methotrexate for RA patients. However, it was difficult to characterize the adalimumab PK adequately if only using the sparse data from the phase-3 studies. The structural PK model was well supported by the intensive PK data from the phase-1 study. The application of assigning informative priors to a subset of model parameters allowed the phase-3 analysis to focus on the estimation of clearance and covariate effects on the clearance by stabilizing the parts of the model that were not being informed by the sparse data. A vague prior was used for clearance in the phase-3 models, allowing the parameter estimation to be driven by the phase-3 data. This approach has been used in the PPK analysis of another mAb when there was rich phase-1 data and sparse phase-3 data.[21] In the phase-3 base study analysis, a discrepancy was seen between the model-simulated and the observed medians for all treatment arms in the VPC plot (Figure S2). This discrepancy was significantly reduced in the PPK model from the phase-3 extension study (Figure S3). Several different PK models were explored in attempt to account for the bias in the PPK model for the phase-3 base study, but none of these was successful in correcting this bias. For the key objective, which was to demonstrate PK similarity, the bias was not considered relevant, as it was identical between treatment arms.

4.2 | PK similarity between adalimumab-adbm and Humira

In the current analysis, the PK similarity was evaluated in patients with active RA using a PPK approach, which does not require extensive PK data and is suitable for sparse phase-3 data. The PPK approach can make use of all PK observations independent of sampling scheme and also can simultaneously account for covariate effects. This method has been used to evaluate bioequivalence and PK similarity.[22–25]

Using the developed PPK models, PK similarity between adalimumab-adbm and Humira were graphically investigated based on goodness-of-fit plots stratified by treatment arm, which demonstrated the model fit the adalimumab data similarly in adalimumab-adbm, Humira or switching treated arms. The adalimumab CL/F did not show any difference among these treatment arms when the treatment arm was evaluated as a covariate on CL/F. The changes in CL/F at different timepoints during the treatment were minor compared to the start of treatment, suggesting switching treatment from Humira to adalimumab-adbm at either week 24 or 48 did not have an impact on long-term overall adalimumab CL/F. The ADA effect on adalimumab PK was also similar between adalimumab-adbm and Humira.

In conclusion, PPK models were developed to adequately describe PK of adalimumab from adalimumab-adbm and Humira in healthy subjects and RA patients, and indicated that the adalimumab PK was similar between adalimumab-adbm and Humira. WT and ADA were found to be important predictors of the adalimumab clearance. Both long-term effects of mAb PK and ADA effect on mAb PK were consistent with short-term treatment, being similar between adalimumab-adbm and Humira-treated arms in RA patients. Switching treatment from Humira to adalimumab-adbm at either week 24 or 48 did not have an impact on adalimumab PK.

ACKNOWLEDGEMENTS

The authors acknowledge all patients, investigators and site research professionals and staff who took part in the conduct of the reported trials. This includes the medical staff of Boehringer Ingelheim, and the staff conducting the bioanalytical portion of the studies. This work was funded by Boehringer Ingelheim International GmbH. The sponsor was given the opportunity to review the manuscript for medical and scientific accuracy as well as intellectual property considerations.

COMPETING INTERESTS

There are no competing interests to declare. G.J. and K.-H.L. are employees of Boehringer Ingelheim. J.K., R.J.E.-B., J.M. and W.K. are employees of Metrum Research Group, which was contracted by Boehringer Ingelheim to perform these analyses and support preparation of this manuscript.

CONTRIBUTORS

J.M., W.K., G.J. and K.-H.L. made substantial contributions to the conceptualization and project supervision. J.K. and R.J.E.-B. performed formal analyses. J.K. wrote the original draft of the manuscript. R.J.E.-B., J.M., W.K., G.J. and K.-H.L. contributed to scientific review and revision of the manuscript.

DATA AVAILABILITY STATEMENT

To ensure independent interpretation of clinical study results, Boehringer Ingelheim grants all external authors access to all relevant material, including participant-level clinical study data, and relevant material as needed by them to fulfil their role and obligations as authors under the ICMJE criteria.

Furthermore, clinical study documents (e.g. study report, study protocol, statistical analysis plan) and participant clinical study data are available to be shared after publication of the primary manuscript in a peer-reviewed journal and if regulatory activities are complete and other criteria met per the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data: https://trials.boehringer-ingelheim.com/transparency_policy.html

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Kang J, Eudy-Byrne RJ, Mondick J, Knebel W, Jayadeva G, Liesenfeld K-H. Population pharmacokinetics of adalimumab biosimilar adalimumab-adbm and reference product in healthy subjects and patients with rheumatoid arthritis to assess pharmacokinetic similarity. *Br J Clin Pharmacol*. 2020;86:2274–2285. https://doi.org/10.1111/bcp.14330