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A mechanistic pharmacokinetic model with drug and antidrug antibody interplay, and its application for assessing the impact of immunogenicity response on bioequivalence testing

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Aims: Single-dose pharmacokinetic (PK) studies in healthy subjects have been the design of choice for bioequivalence determination for decades. This preference has been recently extended to PK similarity studies of proposed biosimilars. However, PK similarity studies can be complicated by the effect of immunogenicity response on drug disposition. The impact is exacerbated when there is an imbalance in host-specific immunological characteristics of subjects between the test and reference groups. Such complications remain poorly understood. The purpose of this communication is to show that the impact of immunogenicity response on PK similarity determination can be critical, using adalimumab as an example.

Methods: Data for adalimumab concentrations and immunogenicity response over 10 weeks were obtained from 133 healthy subjects receiving a 40 mg dose of Humira® in a PK similarity study. Also, a population PK model with a mechanistic construct for delineating the interplay between adalimumab disposition and antidrug antibodies response was utilized to estimate via simulation the probability that a PK similarity study would fail in typical study settings.

Results: The simulations showed that the immunogenicity response can have a profound impact on the outcome of PK similarity determination. As such, the probability of failing to achieve the similarity conclusion increased to 51.9%, from 13.8% in the absence of immunogenicity response.

Conclusion: This study provides a model-based framework for better understanding of how a PK similarity study can be optimally designed and for interpretation of the outcome of PK similarity determination when the drug disposition is affected in the presence of immunogenicity response.

KEYWORDS

biosimilar, immunogenicity, pharmacokinetics

Principal Investigator: The authors confirm that the Principal Investigator for this paper is Constantino Kantaridis, MD and that he had direct clinical responsibility for the study participants.

[Correction added on 16 May 2020, after first online publication: Supporting Information Figures S1 and S2 were included as Figure 3 of the main manuscript in this current version.]

1 | INTRODUCTION

Therapeutic biologics are increasingly important in treating many diseases due to their success in addressing previously unmet medical needs.[1] Biosimilars are expected to play an essential role in enhancing patient access to these important, often lifesaving, medications.[2] Biosimilars are biological products that are highly similar to and have no clinically meaningful differences from their respective reference products in terms of the safety, purity and potency of the product.[3] Pharmacokinetic (PK) similarity studies are generally regarded as a critical part of the overall biosimilarity assessments by providing the data that describe the degree of similarity in PK properties of the proposed biosimilar to the reference product based on prespecified bioequivalence (BE) criteria within which the 90% confidence intervals (CIs) of the test-to-reference ratios for predefined parameters are required to fall. The FDA Guidance[4] outlines specific recommendations on various study design elements to ensure that the study is designed optimally such that it is sensitive to the potential differences in PK properties between the proposed biosimilar and reference products, which include considerations of dosage, single dose versus multiple dose and healthy volunteers versus patients. Healthy volunteers are recommended as a preferred study population for PK similarity studies if the product can be safely administered to this population. The underlying assumption is that healthy subjects are likely to have less PK variability than patients with potentially confounding factors such as concomitant disease and medications. As a result, PK similarity studies are expected to be conducted in healthy subjects whenever appropriate for the given product safety profile, in conjunction with a single dose design.

While PK similarity determination with such a study design has been mostly shown to be highly efficient and informative in our experience,[5–8] there have been some complications associated with PK alterations caused by extensive immunogenicity response, especially when there was an imbalance in immunogenicity potential in terms of host-specific immunological characteristics between the test and reference groups. The impact of these complications on PK similarity determination remains poorly understood. The purpose of this communication is to show, in a quantitative way, the impact of immunogenicity response on the PK similarity determination using adalimumab as an example, which has an extensive immunogenicity response in healthy subjects in a single-dose setting.[9,10] This work utilized the adalimumab PK and immunogenicity response data from 133 healthy subjects receiving a single 40 mg dose of Humira in a PK similarity study, and a population PK model with a mechanistic construct for delineating the interplay between adalimumab disposition and antidrug antibody (ADA) response. The impact of the immunogenicity response on PK similarity determination was assessed, in a quantitative way, by increased probabilities of failing to achieve the similarity conclusion via trial simulations.

What is already known about this subject

- Pharmacokinetic studies in healthy subjects have been the preferred choice for bioequivalence determination for generics. This has recently been extended to pharmacokinetic similarity assessments for biosimilars.
- However, such a pharmacokinetic similarity assessment can be complicated by the immunogenicity response when the drug disposition is altered. The complications remain poorly understood.

What this study adds

- A mechanistic model is proposed to delineate the interplay between drug disposition and antidrug antibodies kinetics
- A model-based framework is provided for better understanding of the impact of immunogenicity response on the pharmacokinetic similarity determination to ensure appropriate interpretation of the study outcome as well as achieving an optimal design.

2 | METHODS

2.1 | Study and data descriptions

The adalimumab concentration and immunogenicity response data used to construct a population PK model for describing the interplay between adalimumab concentration and ADA binding capacity measurements were obtained from a PK similarity study (ClinicalTrials.gov Identifier: NCT01870986). This was a Phase 1, three-arm, double-blind, randomized, parallel-group, single 40 mg dose, clinical trial comparing the PK of Humira sourced from the European Union, adalimumab-EU, Humira sourced from the United States, adalimumab-US, and a proposed adalimumab biosimilar, as well as assessing the safety and immunogenicity of these study drugs, in healthy subjects. The protocol and informed consent documentation were reviewed and approved by an institutional review board. A signed informed consent was required from each subject before any screening procedures, and this study was conducted in accordance with the Declaration of Helsinki and with all International Conference on Harmonization Good Clinical Practice guidelines. Only the adalimumab concentration and immunogenicity response data from the two Humira groups (n = 66 for one and n = 67 for the other) are included in this communication to allow the assumption that there was no contribution from possible differences in manufacture processes or product characteristics to the model parameter estimation,

and to outcomes of BE testing performed in the analysis. The study duration included an immunogenicity assessment with prespecified sample collections at 0 (predose), 336, 672, 1008 and 1680 hours post dose, and a PK evaluation with prespecified sample collections at 0 (predose), 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 264, 336, 504, 672, 840 and 1008 hours post dose, and an additional sample collection at 1680 hours post dose for facilitating the immunogenicity assessment at that time point. Both PK and immunogenicity samples were analysed at QPS, LLC (Newark, DE, USA) using validated bioanalytical procedures. The PK bioanalytical method (an enzyme-linked immunosorbent assay) had a lower limit of quantitation of 250 ng/mL. The inter-run assay accuracy, expressed as relative error for quality control (QC) samples, ranged from 0.0% to 3.9%. The assay precision, expressed as the inter-run coefficients of variation for QC samples, ranged from 3.2% to 4.3%. A validated cell-based assay which evaluates TNFα-induced cell cytotoxicity was utilized for detecting the ADA response (with an assay sensitivity of 251 ng/mL against a positive control, a monoclonal anti-adalimumab antibody). In the assay, adalimumab was used to block the TNFα-induced cell cytotoxicity and ADA present in the samples neutralized the blocking effect of adalimumab. For convenience, the terms of ADA positive and negative subjects are used in this communication as defined in Supporting Information Methods.

2.2 | Noncompartmental analysis and BE testing

In addition to the use of adalimumab concentration (along with immunogenicity response data) from the two Humira groups to construct a population PK model, as noted above, the data were also compared, using the conventional PK analysis procedures, including the standard BE testing, to show the influence of immunogenicity response on the comparison between the two groups and guide the model-based simulations (see Trial Simulation). To this end, noncompartmental analysis (NCA) was conducted to characterize the observed drug concentration-time profiles using Phoenix WinNonlin (Certara, Princeton, NJ, USA). The estimates of PK parameters including the peak concentration (C_{max}), the areas under the curve to the end of the first 2 weeks (AUC_{2wk}), to the last measurable concentration at T (AUC_T) and to infinity (AUC_∞), as well as the time to C_{max} (t_{max}), terminal disposition half-life ($t_{1/2}$) and clearance (CL/F), were obtained. The actual sample collection times were used in the PK parameter calculations. The BE testing on selected PK parameters, C_{max}, AUC_{2wk}, AUC_T and AUC_∞, was performed using the standard two one-sided tests procedure.

2.3 | PK structural model

To better understand the underlying relationship between adalimumab disposition and ADA kinetics following a single subcutaneous (SC) dose of Humira, a population PK model was constructed. As shown in Figure 1, the model is centred at the interaction between two state variables, adalimumab concentrations and ADA titers expressed in an equivalent molar unit (nM) established for the ADA positive control (PC), a monoclonal anti-adalimumab antibody utilized in the assay validation, based on a relationship of titre readouts to the concurrent adalimumab and ADA concentrations, as well as the dissociation constant for the adalimumab/ADA complex (see Supporting Information Methods). The drug is cleared in the central compartment following SC absorption via a first-order drug elimination process and an ADA-mediated drug elimination process. The postulated mechanism of drug disposition was motivated by the observed PK profiles in ADA negative subjects that tended to exhibit a mono-phasic terminal disposition phase and those in ADA positive subjects that tended to exhibit a downward-curved (accelerated) terminal disposition phase (Figure 2 and Supporting Information Figures S1 and S2). The ADA kinetics involves the delayed appearance of ADA in the central compartment, described in the model by a sequence of transit compartments, and removal of ADA via two parallel pathways (Figure 1). The mathematical representation of the model is provided in Supporting Information Table S1 and additional annotations in Supporting Information Methods.

2.4 | Stochastic model components

For each type of measurements (ie, adalimumab concentration and ADA titre), the observed value Y_{ij}, in a particular subject i at a particular timepoint j, was expressed as

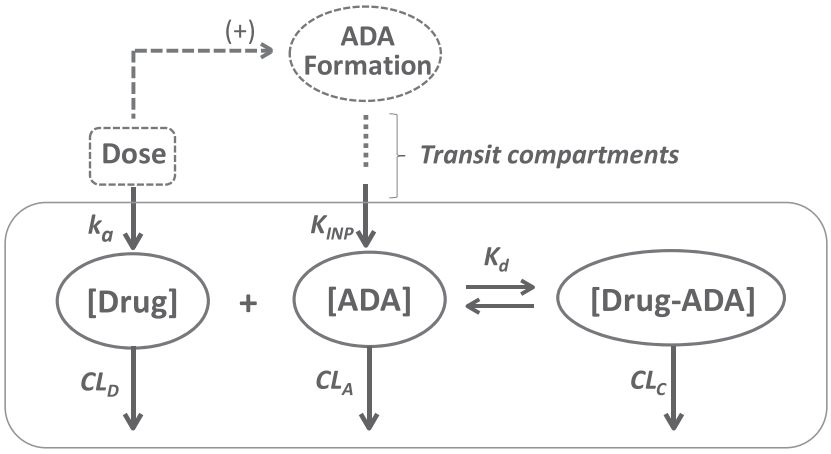

FIGURE 1 Adalimumab disposition interplaying with ADA formation and elimination, where the drug and ADA concentrations in the respective distribution volumes (V_D and V_A) are informed by drug level and ADA response measurements from commonly used bioanalytical procedures (Supporting Information Table S1 and Equation S6)

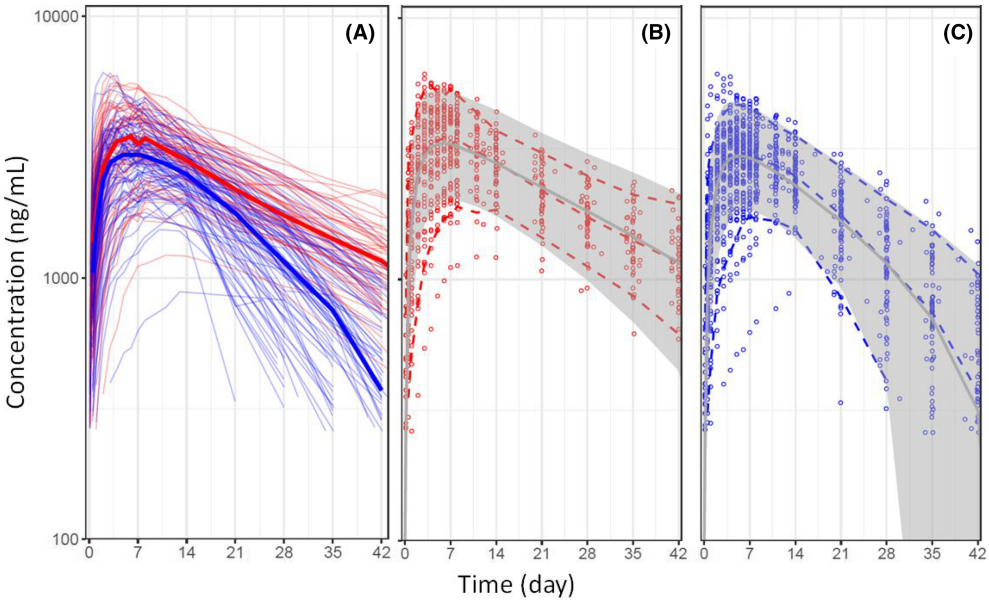

FIGURE 2 (A) Individual (thin lines) adalimumab PK profiles observed and the medians (thick lines) in ADA negative (red) and positive (blue) subjects following a single SC dose administration of Humira at 40 mg. (B) and (C) VPC plots for adalimumab PK profiles in ADA negative and positive subjects, respectively, where the dashed lines represent the 5th percentile, median and 95th percentile for the observed concentrations, the solid lines represent the medians of the simulated concentrations and the shaded areas indicate the 5th and 95th percentiles of the simulated concentrations

$$Y_{ij} = F_{ij} \times \exp(\varepsilon_{ij})$$

where F_{ij} is the corresponding value predicted by the model and ε_{ij} is a random, independent, normally distributed variable with a mean of 0 and variance of σ^2, which was estimated separately for each type of measurements. Samples with adalimumab concentrations below the quantification limit were handled using the Beal M3 method.[11]

The population model also included random effects for selected parameters to recognize differences between subjects, as well as similarities across observations within the same subject:

$$P = TVP \times \exp(\eta)$$

where *TVP* is the typical (population median) value for a given parameter, *P* is the corresponding parameter for an individual subject and η denotes a random variable, normally distributed with mean 0 and variance ω^2, representing the deviation of the *P* of an individual subject from the *TVP* on the natural logarithm scale.

The effects of continuous covariates were modelled using normalized power models:

$$TVP_j = P_{pop} \times \left(\frac{COV_j}{COV_{median}}\right)^{\theta}$$

where TVP_j represents the model predicted parameter for the *j*th individual with normalized covariate value (COV_j/COV_{median}), P_{pop} represents the population central tendency for the parameter at the median covariate value and θ represents the estimated scale factor.

The effects of categorical covariates were modelled similarly using the following expression:

$$TVP_j = P_{pop}\theta^{COV_j}$$

where COV_j is either 0 (eg, ADA negative) or 1 (eg, ADA positive), P_{pop} represents the typical value for the parameter when COV_j is 0 and θ represents the estimated parameters that describe the magnitude of the covariate-parameter relationships.

A chi-square test was used for the comparison of nested models, where a decrease in the objective function value of at least 6.63 units was defined as statistically significant ($P < 0.01$).

2.5 | Model evaluation

Uncertainty in parameter estimates was assessed by CIs obtained from bootstrap resampling, which was performed by repeatedly fitting the model to bootstrap replicates of 500 datasets. Parameter estimates were obtained for each of the replicate datasets and summarized to determine the CIs. A visual predicted check (VPC) was performed as part of the model evaluation. The adalimumab concentration-time profiles were simulated for 19 950 virtual subjects. Specific covariates for virtual subjects were generated by randomly sampling from the original datasets. The 90% prediction interval and the median of the simulated values were superimposed on the scatter plot of the observed values. An assessment of model adequacy was then made from this evaluation.

2.6 | Trial simulation

Trial simulation was carried out to assess the impact of immunogenicity response on the probability that one or more 90% CIs for the test-to-reference AUC_∞ ratios fall outside of the 80-125% BE criteria for a three-arm (Reference-1, Reference-2 and Test groups) PK similarity study. The choice of AUC_∞ here was based on the results from the NCA and BE testing (Table 2) showing that this full-PK-profile-derived BE endpoint was impacted the most in the presence of

immunogenicity response. For this purpose, three hypothetical cases were created in terms of incidences of immunogenicity responses. In Cases 1 and 2 where immunogenicity responses were assumed to be identical among the three groups, 0 and 39 ADA positive subjects were assigned to each group for Cases 1 and 2, respectively. Case 3 was the case where a small imbalance in immunogenicity response existed with 39, 43 and 35 ADA positive subjects assigned to the Reference-1, Reference-2, and Test groups, respectively, which were the incidences of ADA observed in the present study. Furthermore, in each case there were two scenarios: one where all three groups had an identical drug content and the other in which Test had a 5% higher drug content than the reference groups, since such a small difference in drug content often exists in a BE study.[12] For each scenario, 1000 PK similarity trials were simulated using the same single-dose, three-arm, parallel-group design as the present study. As such, in each trial there were three groups of subjects, randomly drawn from the same pools of simulated ADA positive and ADA negative subjects as identified by their individual Humira PK profiles (see details below), with 66, 67 and 66 subjects assigned to the Reference-1, Reference-2 and Test groups, respectively, of which each contained the case-specified number of ADA positive subjects. In doing this, it is implied that all subjects had received a single 40 mg dose of Humira, and as a result a failure to reach the BE conclusion can only be attributed to non-treatment effects. A total of 19 950 individual Humira concentration-time curves were simulated in NONMEM based on the proposed population PK model using the above-specified PK sampling time points over 10 weeks, resulting in a pool of Humira individual PK profiles for 7650 ADA negative subjects and another pool of Humira individual PK profiles for 12 300 ADA positive subjects.

For each of trial replicates, individual AUC_{∞} were calculated for the three groups of simulated PK profiles using the standard NCA approach and then the BE testing was performed comparing Test *vs* Reference-1, Test *vs* Reference-2 and Reference-1 *vs* Reference-2, using the two one-sided test procedures. This process was repeated until a set of 1000 trials was completed for a given scenario. A trial was considered successful if the 90% CIs for test-to-reference AUC_{∞} ratios fell within the 80-125% acceptance criteria for all three pairwise tests (Test *vs* Reference-1, Test *vs* Reference-2 and Reference-1 *vs* Reference-2), and otherwise counted as a failed trial.

2.7 | Software used for modelling and simulation

Nonlinear mixed effect modelling for the population PK model was performed using NONMEM version 7.1.2 (Ellicott City, MD, USA). The ADVAN6 subroutine and first-order conditional estimation method with interaction were used for the analysis. Bootstrap runs were performed using the software package Perl-speaks-NONMEM (Version 3.5.4, Uppsala Pharmacometrics, Uppsala, Sweden). R (version 3.0.2) was used to visualize the output and to perform trial simulations including the standard AUC_{∞} calculation and BE testing.

3 | RESULTS

3.1 | Immunogenicity response, and PK data and characterization

There were no apparent imbalances in demographic characteristics between the adalimumab-EU and adalimumab-US groups from which the adalimumab PK and immunogenicity response data were obtained. The mean (±SD) body weights of the subjects in the adalimumab-EU (n = 66) and adalimumab-US (n = 67) groups were 82.3 ± 11.6 and 80.2 ± 10.4 kg, respectively. The mean (±SD) ages were 35.1 ± 9.1 and 35.3 ± 9.3 for the adalimumab-EU and adalimumab-US groups, respectively. Of the 66 subjects in the adalimumab-EU group, 65 were male and 1 was female, and all 67 subjects in the adalimumab-US group were male.

The incidences of ADA response increased with time throughout the 10-week assessment period for both groups (see Table 1), with 12.1% and 57.6% for the adalimumab-EU group, respectively, and 23.9% and 64.2% for the adalimumab-US group, respectively, at 42 and 70 days. In addition to somewhat greater proportions of individuals who tested positive for ADA, the adalimumab-US group also had a trend toward more subjects with higher ADA titres, compared to the adalimumab-EU group (Table 1).

The mean (±SD) PK parameters for the adalimumab-EU and adalimumab-US groups are provided in Supporting Information Table S2. Table 2 summarizes the ratio of adjusted geometric means and the 90% CIs of the adalimumab-EU to adalimumab-US ratios for C_{max}, AUC_{2wk}, AUC_T and AUC_{∞}. While all the 90% CIs fell within the standard 80-125% BE acceptance window, the adalimumab-EU to adalimumab-US ratios had an upward trend from 98.6% or 96.8% (corresponding to little or no difference between the two groups) for C_{max} or AUC_{2wk}, to 105.6% or 109.7% (indicating some numerical separation between the two groups) for AUC_T or AUC_{∞}. The ADA

TABLE 1 Summary of ADA response by incidence and titre quartile[a]

	Adalimumab-EU, n = 66	Adalimumab-US, n = 67
Number (%) of ADA positive subjects		
At 14 days	0 (0%)	0 (0%)
At 28 days	0 (0%)	2 (3.0%)
At 42 days	8 (12.1%)	16 (23.9%)
At 70 days (end of study)	38 (57.6%)	43 (64.2%)
Number of subjects in each ADA titre quartile		
Lower 25% (≤1.1775)	8	12
25% to 50% (1.1775-1.4500)	14	7
50% - 75% (1.4500-1.8175)	12	9
Upper 25% (>1.8175)	5	15

[a]The ADA titre quartile was based upon the range of maximum ADA titres of all ADA positive subjects.

TABLE 2 The test-to-reference ratios and their 90% CIs for C_{max}, AUC_{2wk}, AUC_T and AUC_∞

Parameter	Test	Reference	Ratio ($Ratio_{WA}$[a])	90% CI
C_{max}	Adalimumab-EU	Adalimumab-US	98.6% (101.0%)	89.6-108.5
AUC_{2wk}	Adalimumab-EU	Adalimumab-US	96.8% (99.2%)	87.4-107.3
AUC_T	Adalimumab-EU	Adalimumab-US	105.6% (108.2%)	95.8-116.3
AUC_∞	Adalimumab-EU	Adalimumab-US	109.7% (112.4%)	97.4-123.5

[a]$Ratio_{WA}$ is the test-to-reference ratio which accounts for differences in body weight. For this purpose, each subject's body weight was multiplied by 0.494 mg/kg (equivalent to 40 mg dose based on the mean body weight [81.0 kg]).

positive subjects tended to have lower exposures with accelerated terminal disposition phases (see Figure 2A) compared to the ADA negative subjects.

3.2 | Model development and evaluation

A population PK model was developed which includes a mechanistic construct for the interplay between drug disposition and ADA response (see Supporting Information Table S1). This mechanistic model construct was based on a derived relationship of titre readouts by a common assay procedure versus the ADA concentrations in samples containing the drug at various concentrations (see Supporting Information Methods).

A total of 2784 samples (2255 for adalimumab concentrations and 529 for ADA titres) from 133 subjects were used for model development. The resultant model parameter estimates, including 90% CIs from bootstrap procedures, are shown in Table 3. The main application of this model in this communication was to generate replicates of the given PK similarity study via simulation, which called for appropriate representation of the immunogenicity influences, in addition to the typical PK variabilities (eg, between- and within-subject variability) and covariate effects, and construction of the distribution of BE determination outcomes from the study replicates. As a result, some covariates (eg, body weight and ADA status) were included with the emphasis on improving the model fit in terms of its ability to track the distribution of individual adalimumab concentrations, as well as the central tendency. The covariate-parameter effects of body weight on adalimumab clearance (CL_D) and distribution volume (V_D) were statistically significant ($P < 0.01$). In addition, there appeared to be a higher tendency for subjects with lower C_{max} to test positive for ADA during the study, and for ADA positive subjects to have higher ADA

TABLE 3 Adalimumab PK model parameter estimates

Parameter[a]	Units	Estimate (90% CI)	IIV (90% CI)
CL_D (clearance of unbound drug)	L/h	0.0124 (0.0120, 0.0133)	33.2% (30.5%, 35.0%)
Exponent for body weight effect		0.701 (0.648, 0.730)	
Ratio: ADA positive to negative subjects		1.38 (1.25, 1.43)	
V_D (distribution volume of unbound drug)	L	10.3 (10.2, 11.0)	23.4% (21.5%, 25.0%)
Exponent for body weight effect		1 (FIX)	
Correlation between $\eta(CL_D)$ and $\eta(V_D)$		0.236 (0.129, 0.368)	
CL_C (clearance of drug-ADA complex)	L/h	0.111 (0.109, 0.139)	…
Exponent for body weight effect		Same as that for CL_D	
V_A and V_C (distribution volume for unbound ADA and complex)	L	1.86 (1.64, 2.02)	…
Exponent for body weight effect		1 (FIX)	
CL_A/V_A (ratio of clearance to distribution volume for unbound ADA)	1/h	0.00138 (FIX)	…
K_d (dissociation constant)	nM	3 (FIX)	…
K_a (absorption rate constant)	1/h	0.0221(0.0205, 0.0233)	45.9% (45.7%, 64.2%)
K_{tr} (rate constant of transit compartments)	1/h	0.000644 (0.000613, 0.000767)	56.7% (53.6%, 67.2%)
K_{INP} (ADA production rate)	1/h	0.132 (0.105, 0.136)	24.7% (22.9%, 26.5%)
Ratio: ADA positive to negative subjects		9.45 (7.34, 9.97)	
Correlation between $\eta(K_{INP})$ and $\eta(K_{tr})$		−0.149 (−0.326, −0.0662)	
Residual variability for drug concentration	%	12.3 (11.3, 12.7)	…
Residual variability for log10(ADA_{titer})	%	29.1 (26.2, 30.2)	…

[a]Clearance or distribution volume of drug-related speices should be interpreted as apparent clearance or distribution volume since the unknown subcutaneous bioavailability was part of the parameters.

production rate (K_{INP}). To account for these, the ADA status of a given subject was included as a categorical covariate on CL_D and K_{INP}, both of which were statistically significant ($P < 0.01$). Furthermore, the inclusion of covariance between ηs for CL_D and V_D was statistically significant ($P < 0.01$). The inclusion of covariance between ηs for the ADA production rate (K_{INP}) and the rate constant of transit compartments (K_{tr}), although it did not improve objective function value, led to an improvement in VPC in terms of the centre of distribution. VPC plots are provided in Figure 2B,C to compare the distribution of model-simulated prediction intervals (PI) versus observations from the ADA positive and negative subjects. Individual predictions of drug concentrations and concurrent ADA titres over time are shown in comparison with the respective observed data in Supporting Information Figures S1 and S2. The goodness-of-fit plots (Supporting Information Figure S3) also showed that the population and individual model predictions adequately described the observed data with no apparent trend in the individual weighted residuals over the concentration range and time points evaluated. Clearly, the model describes the adalimumab PK well for both ADA positive subjects whose profile exhibited a downward-curved terminal disposition phase (nonlinear) and ADA negative subjects whose profile exhibited a mono-phasic terminal disposition phase (linear), providing an insight into the underlying relationship between adalimumab disposition and ADA response kinetics.

3.3 | Trial simulation

The results of trial simulation for the six specified scenarios are summarized in Table 4. The impact of immunogenicity response was relatively limited when the immunogenicity response was balanced among the groups (Case 2). Conversely, an imbalanced immunogenicity response had a profound adverse impact on the outcome of BE testing, especially when it acted in concert with a small difference in drug content (Case 3). As such, the probability of failing to achieve the given BE conclusion increased to 51.9% from 13.8% in the absence of immunogenicity response (Case 1).

4 | DISCUSSION

A single-dose PK study in healthy subjects is generally the design of choice for BE determination whenever the product can be safely administered to this population. Such a design assumes that healthy subjects are likely to produce less PK variability compared to patients with potentially confounding factors (eg, underlying and/or concomitant disease and concomitant medications).[12] This preference has been recently extended to PK similarity assessments for biosimilars.[4] However, PK similarity determination in such a setting can be complicated by the immunogenicity response that alters the drug disposition (to a degree varying from subject to subject). Therefore, it is important to develop a framework for better understanding of the impact of immunogenicity response, not only as added sources of variability but also as a potential for introducing a bias, to ensure appropriate interpretation of the study outcome as well as achieving an optimal study design at the outset.

For this purpose, it is crucial to understand the dynamic relationship between the drug disposition and ADA response. A population PK model with a mechanistic construct for delineating this dynamic relationship was developed as the cornerstone of the present study, which consists of component 1 based on ADA mediated drug disposition (AMDD) and component 2 (Supporting Information Equation S6) defining the ADA binding capacity in a concentration term from concurrent drug concentration and ADA titre measurements. The utility of AMDD in describing the impact of immunogenicity on the pharmacokinetics of a biologic drug has been previously discussed (eg, Chen et al[13]). The modelling work by Chen et al was motivated in part by the limitation of commonly used bioanalytical procedures for ADA concentrations to being quasi-quantitative due to the heterogeneous nature of ADAs and based on the hypothesis that an ADA response can be inferred from the PK alteration. As a result, the model operated under some restrictive assumptions, including that only induction of ADA causes an alteration of the PK and no ADA is elicited during the PK characterization following the first dose. With the addition of component 2, the proposed model allows the dynamic relationship between the drug disposition and ADA response to be informed by drug concentration and ADA titre measurements obtained from commonly used bioanalytical procedures, without those restrictive assumptions. It was shown through the model evaluations that the proposed model tracked very well with the entire dataset (n = 133) of full adalimumab PK and ADA titre profiles at both population (Figure 2B,C) and individual (Supporting Information Figures S1 and S2) levels.

The incidences of ADA response were, by the cell-based assay used in this study, 57.6% and 64.2% at the end of the 10-week assessment in the adalimumab-EU and adalimumab-US groups, respectively. The same immunogenicity samples were also analysed by an electrochemiluminescence (ECL) ADA assay, with an acid dissociation sample preprocess step and a higher assay sensitivity (10.5 ng/mL). The incidences of ADA response by the ECL assay were 89.4% and 94.0% at the end of the 10-week assessment in the adalimumab-EU and adalimumab-US groups, respectively. It should be apparent from Supporting Information Equation S6 that the choice of an ADA assay format/procedure can be important. It is conceivable from the design of each assay that the ECL assay with an acid dissociation sample preprocess step could not differentiate between drug-bound and unbound forms of ADA, as the acid dissociation step converted all drug-bound ADA to its unbound form, whereas the cell-based assay preserved the equilibrium between the drug-bound and unbound forms of ADA, as well as the equilibrium between the ADA bound and unbound forms of the drug, in the samples. Therefore, only the ADA measurements by the cell-based assay were utilized in the analysis, which permitted a relationship between the titre readouts and ADA concentrations in samples containing the drug at various concentrations to be established. It is expected that, under similar conditions, the utility of the proposed model can be generalized for

TABLE 4 Probability of the 90% CIs for test-to-reference AUC_{∞} ratios falling outside of the 80-125% BE criteria[a]

	Number of ADA positive subjects			Drug content	
	Reference-1 (n = 66)	Test (n = 66)	Reference-2 (n = 67)	No difference	5% higher in Test
Case 1	0	0	0	4.8%	13.8%
Case 2	39	39	39	10.8%	22.7%
Case 3	39	35	43	20.5%	51.9%

[a]The probability that one or more 90% CIs for the test-to-reference AUC_{∞} ratios fell outside of the 80-125% BE criteria for the three pairwise comparisons (Test *vs* Reference-1, Test *vs* Reference-2 and Reference-1 *vs* Reference-2) in the hypothetical three-arm PK similarity study (see Methods).

other biologics (see Supporting Information Methods) for which the ADA response plays an appreciable role in drug disposition, with the disposition representation (eg, one-compartment *vs* two-compartment characteristics) appropriate for the given drug. Furthermore, it is expected that the proposed model can be applied for characterizing the biologics PK data from multiple dose settings, including those[14,15] in which the observed ADA response is time or dose dependent, with dosing and ADA input functions appropriate for the given setting. In these applications, the proposed model should have the advantage of being informed by both drug concentration and ADA titre measurements.

The adalimumab PK profile was altered considerably in the presence of immunogenicity response, resulting in an accelerated terminal phase (or clearance) with increased variability (Figure 2A). Table 1 shows that the vast majority of ADA detections occurred toward the later part of PK profiling (at 42 days or later). Besides the increased variability, the immunogenicity response could bring a bias into the BE determination if there were imbalances in incidence of ADA response and/or its drug binding capacity due to an imperfect randomization in host-specific immunological characteristics between the groups, which, as a nontreatment related event whose magnitude is study specific, often occurs when the sample size is relatively small. Table 1 shows some imbalance between the two groups in that the adalimumab-US group had more subjects who tested positive for ADA at 42 days (23.9% *vs* 12.1%) and 70 days (64.2% *vs* 57.6%) and belonged to the highest quartile of titres (n = 15 *vs* n = 5) than the adalimumab-EU group. This is consistent with a trend toward an increased adalimumab-EU to adalimumab-US ratio from C_{max} or AUC_{2wk} (resulting from the early part of the PK profile) to AUC_T or AUC_{∞} (resulting from both early and later parts of the PK profile) in Table 2. For example, for weight-adjusted PK parameters, the C_{max} and AUC_{2wk} estimates for the adalimumab-EU and adalimumab-US groups were essentially identical, with respective test-to-reference ratios of 101.0% and 99.2%. However, the AUC_T and AUC_{∞} estimates became separate between the adalimumab-EU and adalimumab-US groups, with respective test-to-reference ratios of 108.2% and 112.4%. This suggests that the impact of ADA response was more profound on the later part of the PK profile and was imbalanced, yielding a greater PK alteration (or a greater reduction in AUC_T and AUC_{∞}) in the adalimumab-US group than the adalimumab-EU group. These effects toward an increased ratio could complicate the BE determination on AUC_{∞} (Table 2) if the adalimumab-EU to adalimumab-US ratio for C_{max} (98.6%) or AUC_{2wk} (96.8%) were ever so slightly higher (say by 1.2%). To this end, for the weight-adjusted AUC_{∞}, the 90% CI was in fact outside of the BE acceptance criteria (data not shown). It should be pointed out that the adalimumab-EU to adalimumab-US ratios remained essentially unchanged from C_{max} to AUC_{∞} in other adalimumab PK similarity studies with a similar design, including the sample size.[9,16]

The time-varying effect of ADA response on the disposition of adalimumab was captured adequately by the proposed model, which operated as a function of adalimumab concentrations and concurrent ADA binding capacity measurements (see Supporting Information Table S1 and Figures S1 and S2). As shown in Supporting Information Figures S1 and S2, in ADA positive subjects, the ADA response developed gradually over time in terms of both incidence and titre, during which the adalimumab concentrations declined monotonically, at an accelerated rate, showing a more profound impact on the later part of the PK profile. Also, it is shown that the time courses of ADA development and its impact on adalimumab concentrations varied greatly from subject to subject. Conceivably, all subjects might have developed ADA with varying levels of drug-binding capacity whether or not they tested positive by the given assay at some point[9] following dose administration. For ADA positive subjects, accelerated adalimumab clearance was more apparent from the downward curved terminal disposition phases, particularly when the first ADA detection occurred at 42 days or earlier, compared to the ADA negative subjects (Figure 3).

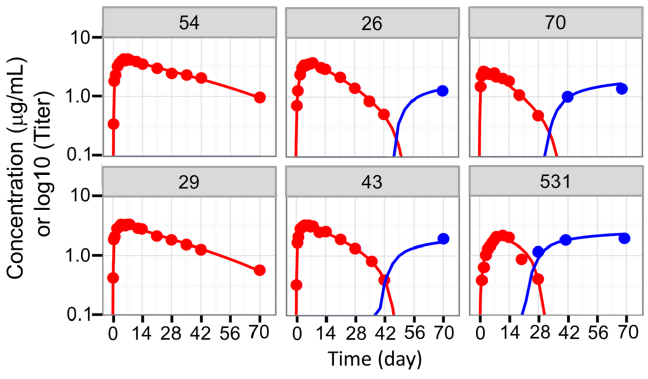

FIGURE 3 Representative individual predictions (lines) of adalimumab concentrations (red) and concurrent ADA titers (blue) over time, and the corresponding observations (dots), for those with no ADA detected during the study (subjects 29 and 54), ADA detected late (subjects 26 and 43), and ADA detected early (subjects 70 and 531) (Supporting Information Figures S1 and S2)

The impact of ADA response on the PK similarity determination was measured in a quantitative manner via simulation in terms of the probability that the study would fail to meet the 80-125% BE acceptance criteria for AUC_{∞}. The simulation results clearly showed that the ADA response reduced the probability of achieving the BE conclusion from the comparison of AUC_{∞} among the three groups (Table 4). More importantly, it was shown that a relatively minor imbalance in ADA response among the three groups imposed a profound adverse impact on the probability of achieving the BE conclusion. This impact was more dramatic when the minor imbalance in ADA response was combined with a small, otherwise acceptable, difference in drug content. Therefore, for highly immunogenic biologics like adalimumab, adequately managing the immunogenicity-related risk for failing to reach the study conclusion correctly may call for an increased emphasis on using the batches of test and reference products that differ minimally in drug content from each other whenever possible and/or adding a protection against a potential imbalance in ADA response in study design, such as an increased sample size. Also, it is prudent to exercise caution in study outcome interpretation, with a full understanding of whether there are imbalanced influences of ADA response on drug disposition among the groups, especially between the two reference groups in a typical three-arm PK similarly study.

In conclusion, we developed a population PK model with a mechanistic construct for delineating the dynamic relationship between drug disposition and ADA response which offers a better understanding of the PK behaviour of biologic products between individuals with and without the immunogenicity response that alters drug disposition. This population PK model was applied via simulation for estimating the probability that a PK similarity study would fail to reach the conclusion correctly under various influences of the immunogenicity response, as quantitative measures of these influences. As a result, the application provides a framework for deliberating how a PK similarity study can be optimally designed in cases where the immunogenicity response alters drug disposition, and for ensuring appropriate interpretation of the outcome of PK similarity determination in such cases.

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COMPETING INTERESTS

K.H.L., C.U., D.Y., C.K. and D.F.A. are full-time employees of and declare stock holdings and/or stock options from Pfizer Inc. K.L.S. and X.M. were employees of and declare stock holdings and/or stock options from Pfizer Inc. at the time of the study.

CONTRIBUTORS

K.H.L., D.Y., K.L.S., C.K., D.F.A. and X.M. were involved in the conception and trial design. D.Y., K.L.S., C.K. and X.M. were responsible for subject safety monitoring and data acquisition. K.H.L., C.U., D.Y. and X.M. performed data analysis and interpretation. K.H.L., C.U. and X.M. performed model and simulation analysis. K.H.L. and X.M. wrote the manuscript with input from all authors.

DATA AVAILABILITY STATEMENT

Upon request, and subject to certain criteria, conditions and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (1) for indications that have been approved in the US and/or EU or (2) in programs that have been terminated (ie, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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SUPPORTING INFORMATION

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

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