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ORIGINAL ARTICLE

Pharmacokinetic equivalence, comparable safety, and immunogenicity of an adalimumab biosimilar product (M923) to Humira in healthy subjects

Jan Hillson[1,a] | Tim Mant[2] | Molly Rosano[3,a] | Carolyn Huntenburg[4] | Mehrshid Alai-Safar[5] | Siddhesh Darne[5] | Donna Palmer[5] | Borislava G. Pavlova[6] | Jennifer Doralt[6] | Russell Reeve[7] | Niti Goel[7] | Doris Weilert[8] | Paul W. Rhyne[9,b] | Kamali Chance[7] | John Caminis[5] | James Roach[4,c] | Tanmoy Ganguly[4]

[1]ChemoCentryx, Mountain View, CA, USA

[2]QuintilesIMS, Reading, UK

[3]NuCana plc, Newton, MA, USA

[4]Momenta Pharmaceuticals, Inc., Cambridge, MA, USA

[5]Shire, Cambridge, MA, USA

[6]Shire, Vienna, Austria

[7]QuintilesIMS, Durham, NC, USA

[8]QuintilesIMS, Overland Park, KS, USA

[9]Biologics Development Services, Tampa, FL, USA

Correspondence
Tanmoy Ganguly, Momenta Pharmaceuticals, Inc., Cambridge, MA, USA.
Email: tganguly@momentapharma.com

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Abstract

The aims of this randomized, double-blind, three-arm, single-dose study were to demonstrate pharmacokinetic (PK) equivalence of the adalimumab biosimilar M923 (hereafter referred to as "M923") to each of 2 reference products, and to assess M923's safety and immunogenicity. Primary PK endpoints were maximum observed concentration (C_{max}), area under the curve (AUC) from time 0 extrapolated to infinity ($AUC_{0\text{-}inf}$), and AUC from time 0 to 336 hours ($AUC_{0\text{-}336}$). Secondary endpoints included safety and immunogenicity assessments. Healthy subjects were randomized 1:1:1 to receive a 40-mg dose of M923 (n = 107); adalimumab US Humira (n = 105), hereafter referred to as "US Humira"; or adalimumab EU Humira (n = 103), hereafter referred to as "EU Humira." PK equivalence was demonstrated for all primary PK endpoints. Geometric least squares means ratios (GMRs) for C_{max}, $AUC_{0\text{-}inf}$, and $AUC_{0\text{-}336}$ were 99.4, 100.9, and 100.5, respectively, between the M923 and EU Humira arms and 102.6, 104.2, and 102.9 between the M923 and US Humira arms. The 90% confidence intervals of the GMRs for all PK endpoints were within prespecified confidence bounds of 80%-125%. Adverse event rates were similar across the M923 (47.7%), US Humira (50.9%), and EU Humira (53.3%) arms and were generally mild (73.7%) or moderate (22.0%). The proportion of subjects with a confirmed antidrug antibody (ADA) response was similar across study arms. This study demonstrated bioequivalent PK among M923, US Humira, and EU Humira and demonstrated that the PK parameters were consistent with similar safety and tolerability profile and ADA response rates.

Abbreviations: ADA, antidrug antibody; BMI, body mass index; ECG, electrocardiogram; Ig, immunoglobulin; LS, least squares; nADA, neutralizing antidrug antibody; PK, pharmacokinetic; RA, rheumatoid arthritis; TNF-α, tumor necrosis factor – alpha.

[a]At the time of this study Jan Hillson and Molly Rosano were employees of Momenta Pharmaceuticals, Inc., Cambridge, MA, USA.
[b]At the time of this study Paul Rhyne was an employee of QuintilesIMS, Durham, NC, USA.
[c]At the time of this study James Roach was SVP, Development, and Chief Medical Officer, Momenta Pharmaceuticals, Inc., Cambridge, MA, USA.

KEYWORDS
biologicals, monoclonal antibodies, pharmacokinetics

1 | INTRODUCTION

Humira (adalimumab) is a fully human recombinant immunoglobulin (Ig) G1 monoclonal antibody that binds to the soluble form of human tumor necrosis factor (TNF)-α, thereby blocking interaction with its receptors, p55 (TNFR I) and p75 (TNFR II), and inhibiting the TNF-α–dependent proinflammatory cascade.[1] Humira also binds to the transmembrane form of TNF-α, which transmits strong inhibitory signals through transmembrane TNF-α.[2]

The clinical efficacy and safety of Humira for the treatment of chronic inflammatory disorders, such as rheumatoid arthritis (RA), Crohn's disease, ankylosing spondylitis, and psoriasis, have been demonstrated in several large clinical studies.[3–8] The findings of these studies led to the approval of Humira by both the US Food and Drug Administration and the European Medicines Agency for these indications.[9,10]

The high costs of biologic therapies (e.g., Humira) for the treatment of chronic inflammatory disorders, such as RA, can limit patient access to these treatments.[11] The development and incorporation of biosimilars into clinical practice has the potential to lower costs and increase access via affordability of these much-needed treatment options.[11] The availability of multiple biosimilars to a single agent has the potential to further increase options for access and lower costs by ensuring a more competitive marketplace. The marketing approval of biosimilar drug products requires assessment of risk and benefit based on equivalence studies, including clinical studies, to address any clinically significant differences in drug product that may arise due to a biological manufacturing process that differs from that used in the manufacture of the original drug product.[12]

Adalimumab biosimilar M923 (hereafter referred to as "M923") is a proposed biosimilar to Humira (adalimumab [AbbVie Inc., North Chicago, IL]; chemical formula: $C_{6428}H_{9912}N_{1694}O_{1987}S_{46}$). This first-in-human study, the first step in the clinical development process of M923, compared the pharmacokinetic (PK), safety, tolerability, and immunogenicity profiles of a single 40-mg subcutaneous injection of M923, adalimumab US Humira (hereafter referred to as "US Humira"), and adalimumab EU Humira (hereafter referred to as "EU Humira") in healthy subjects, with the objective of demonstrating PK equivalence and similarity with respect to short-term safety and immunogenicity.

2 | MATERIALS AND METHODS

This phase 1, randomized, double-blind, three-arm, single-dose study was conducted at 3 study sites in the United Kingdom. The study was registered with ClinicalTrials.gov on 22 January 2016 (identifier: NCT02675023) and conducted in accordance with the International Conference on Harmonisation, Guideline for Good Clinical Practice E6 (April 1996; Title 21 of the United States Code of Federal Regulations; the European Clinical Trial Directive [2001/20/EC and 2005/28/EC]); and applicable national and local regulatory requirements. The aspects of the study concerned with the investigational medicinal product met the requirements of EU Good Manufacturing Practice. The study protocol and informed consent form were reviewed and approved by the relevant ethics committees prior to implementation. Written informed consent was obtained from all subjects prior to screening.

2.1 | Eligibility criteria

Healthy men and women aged 18-55 years (inclusive) and with a body mass index (BMI) between 18.5 and 29.9 kg/m^2 (inclusive) were eligible to be included in this study as determined by medical history, physical examination, vital signs, and 12-lead electrocardiogram (ECG) at screening and admission. All subjects were to comply with the contraception requirements as specified in the study protocol or be of non-childbearing potential. Inclusion criteria are described in full in the Appendix S1.

Subjects were excluded from the study if they were previously treated with Humira or another recombinant human monoclonal antibody and/or had antidrug antibodies (ADAs) to Humira at screening. Exclusion criteria (described in full in Appendix S1) assisted selection of a homogeneous study population and minimized the risk of serious adverse drug reactions.

2.2 | Study design

The sample size (N = 324) was determined based on previously published estimates of variability in the primary PK parameters.[13,14] More specifically, Kaur et al. reported data from a study comparing ABP 501 to EU Humira, specifically a coefficient of variation (CV) of 41.7% for $AUC_{0\text{-inf}}$, 38.3% for $AUC_{0\text{-last}}$, and 30.5% for C_{max}. Assuming the equivalence bounds of 80% to 125% for the relative bioavailability, a true ratio of 1.00, 90% joint power (Bonferroni adjustment for multiplicity) for the 3 comparisons (M923 vs EU Humira, M923 vs US Humira, EU Humira vs US Humira), and a population CV of 41.7% (for $AUC_{0\text{-inf}}$), a sample size of 86 completers per arm (258 total) was required. Joint power was computed as 100% – (100% – single comparison power) × 3, using a Bonferroni correction for multiplicity. Assuming a loss of 20% of the data (15% for loss due to extrapolation to infinity, and 5% for dropouts), 108 subjects per arm (324 total) were needed to be randomized to achieve 90% power.

Subjects were screened between 45 days and 2 days prior to administration of study drug, and eligibility and baseline assessments

were conducted 1 day before drug administration. The route of administration for M923 was chosen to be similar to those of approved reference products as recommended by regulators.[15] Regulators also recommend that the dose should be in the ascending part of the dose-response curve; this criterion was used to select the appropriate dose. Following confirmation of eligibility, subjects were randomized in an approximate 1:1:1 ratio to a single 40-mg subcutaneous injection via SC injection to the lower abdomen of either M923 (Momenta Pharmaceuticals, Inc., Cambridge, MA, USA: 48.0 mg/mL; Batch number(s): Bulk Lot #925195, Manufacturing Lot #47371.1), or to 1 of 2 reference products: US Humira (Fisher Clinical Services, Inc., Allentown, PA, USA: 51.0 mg/mL; Bulk lot #1024659, Manufacturing lot # 47371.2, Expiry date: 30/Apr/16) or EU Humira (Fisher Clinical Services, Inc., Allentown, PA, USA: 50.0 mg/mL; Bulk lot #38466XD03, Manufacturing lot #17327.1, Expiry date: 31/Jan/16). Subjects received their assigned administration of study drug on day 1 and were followed for 71 days. Blood samples were taken predose and at the following postdose time points (in hours) for PK analysis: 8, 24 (day 2), 48 (day 3), 72 (day 4), 96 (day 5), 120 (day 6), 144 (day 7), 168 (day 8), 192 (day 9), 240 (day 11), 336 (day 15), 504 (day 22), 672 (day 29), 840 (day 36), 1008 (day 43), 1344 (day 57), and 1680 (day 71). Safety, tolerability, and immunogenicity were assessed periodically throughout the study. A final follow-up visit was scheduled on day 71 (Figure 1). Subjects who withdrew prior to the last planned observation in the study period were included in the analyses up to the time of discontinuation. Subjects were analyzed according to the treatment they actually received.

2.3 | Endpoints

The primary endpoints were maximum observed adalimumab concentration (C_{max}), area under the concentration vs time curve (AUC) from time 0 (predose) extrapolated to infinity ($AUC_{0\text{-}inf}$), and AUC from time 0 (predose) to 336 hours ($AUC_{0\text{-}336}$). $AUC_{0\text{-}336}$ was selected as an additional primary parameter for this study, since it is within 24 hours of the sampling time (360 hours) used for total exposure comparisons in the original US and EU Humira submissions and reported to be free of ADA formation. Secondary PK endpoints included time to maximum concentration (t_{max}), AUC from predose to last dose ($AUC_{0\text{-}last}$), AUC from predose to 1344 hours (day 57) ($AUC_{0\text{-}1344}$), apparent systemic clearance after extravascular dosing (CL/F), apparent volume of distribution (V_z/F), and terminal half-life ($t_{1/2}$). Safety variables included incidence of adverse events (including injection site reaction), vital signs, 12-lead ECGs, routine laboratory tests, and immunogenicity assessments.

2.4 | Quantification of serum drug concentrations

Serum M923 and adalimumab concentrations were determined using a validated, enzyme-linked immunosorbent assay that employed a TNF-coated plate (R&D Systems, Minneapolis, MN, USA) and horseradish peroxidase-conjugated mouse anti-human IgG antibody (Jackson ImmunoResearch Laboratories, Inc., West Grove, PA, USA) to detect bound analyte. M923 (48.0 mg/mL) and EU Humira (50.0 mg/mL) were used to develop a standard curve, and human IgG1 antibody (100 μg/mL; Enzo Life Sciences, Inc., Farmingdale, NY, USA) was used as an isotype control. Colorimetric intensity was determined using a SpectraMax Plus 384 spectrophotometer (Molecular Devices, LLC, Sunnyvale, CA, USA) reading at 450 nm with a correction of 650 nm. The lower limit of quantification was 300 ng/mL and the upper limit of quantification was 4800 ng/mL. Interassay precision and accuracy were calculated from quality control samples. The CV for M923 and EU Humira was ≤10.2% and ≤8.8%, respectively.

2.5 | Immunogenicity

Analysis of ADAs was conducted using a screening assay based on M923 to identify samples with potentially positive binding ADA. Samples positive in the screening assay were confirmed in a tiered manner based on assays to EU Humira, US Humira, and M923. For samples that were confirmed positive, a third assay was used to determine the relative ADA titer; further assays were used to determine the presence of neutralizing ADAs (nADAs) and human IgE ADA.

ADAs were measured using an electrochemiluminescence assay validated to detect anti-adalimumab antibodies in human serum.

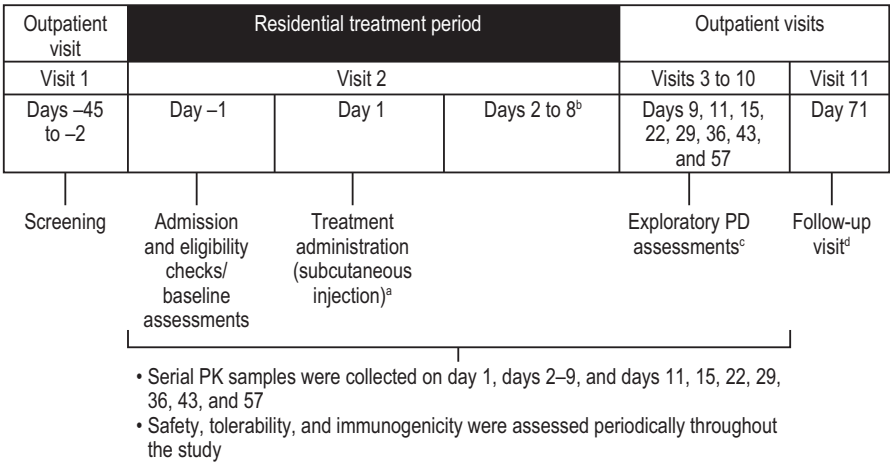

FIGURE 1 Study design. [a]Subjects were randomized to 1 of 3 administrations: adalimumab biosimilar M923, adalimumab US Humira, or adalimumab EU Humira; [b]Subjects could be discharged from the clinical unit on day 5, at the discretion of the investigator. [c]Data not available. [d]Includes safety/tolerability/PK/immunogenicity/exploratory PD assessments. PD, pharmacodynamics; PK, pharmacokinetics

Electrochemiluminescence was measured in relative light units using the MSD SECTOR Imager 2400 (Meso Scale Diagnostics, Rockville, MD, USA). The mean assay sensitivity was 1.96 ng/mL, and drug tolerances of 0.500 μg/mL, 2.00 μg/mL, and 0.417 μg/mL were observed for M923, US Humira, and EU Humira, respectively, at the low-positive control (15.0 ng/mL). Inter-run assay precision for the quality control samples and negative control was 6.2% to 7.1%.

Serum neutralizing anti-adalimumab antibodies were measured using a validated fluorescence assay using a SpectraMax i3x Multi-Mode Detection Platform (Molecular Devices, LLC). The low-positive control was 920 ng/mL and the high-positive control was 3000 ng/mL. The CV for high- and low-positive controls was 1.0% and 8.5%, respectively. Following a positive ADA result, samples were further evaluated for the presence of IgE (a specific isotype of ADA).

2.6 | Statistical analysis

The PK analysis set included all evaluable subjects in the safety analysis set with sufficient data to calculate at least 1 primary PK endpoint. Subjects with protocol deviations or events thought to affect PK were excluded. PK parameters were derived from the collected serum using noncompartmental methods with Phoenix® WinNonlin® version 6.4 (Certara, LP, Princeton, NJ, USA). The statistical analysis of the log-transformed primary endpoint and the select secondary PK endpoints ($AUC_{0\text{-last}}$ and $AUC_{0\text{-}1344}$) was based on an analysis of covariance model with a fixed effect for administration arm, baseline age, and baseline body weight as continuous covariates.

PK equivalence across the 3 administration arms was established if the 90% confidence intervals (CIs) for the geometric least squares (LS) means of the primary PK parameters for each comparison (M923 vs US Humira, M923 vs EU Humira, and US Humira vs EU Humira) fell within the predefined equivalence boundaries of 80% to 125%.

The safety analysis set included all subjects who received study drug. Safety assessments were summarized using descriptive statistics, as appropriate. For immunogenicity, the number and percentage of subjects testing positive for ADAs or nADAs before the dose of M923, EU Humira, or US Humira (day 1) and at scheduled postdose assessments were summarized by administration arm and sampling time. Time to seroconversion was calculated for subjects with confirmed postdose ADA response only. All statistical programming was performed utilizing SAS® version 9.4 (SAS Institute Inc., Cary, NC, USA). The data and statistical analysis comply with the recommendations on experimental design and analysis in pharmacology.[16]

3 | RESULTS

3.1 | Baseline characteristics and demographics

A total of 324 subjects were enrolled (109 in the M923 arm, 108 in the US Humira arm, and 107 in the EU Humira arm). The majority of subjects were male (315/324). Demographic and baseline characteristics, including age, sex, race, ethnicity, height, weight, and BMI, were similar across administration arms (Table 1). There were no premature withdrawals.

TABLE 1 Demographics and baseline characteristics

Parameter	M923 (N = 109)	US Humira (N = 108)	EU Humira (N = 107)
Age, years, mean (range)	32.2 (18-51)	32.9 (18-53)	32.1 (18-54)
Sex, n (%)			
Male	106 (97.2)	106 (98.1)	103 (96.3)
Female	3 (2.8)	2 (1.9)	4 (3.7)
Race, n (%)			
White	89 (81.7)	93 (86.1)	93 (86.9)
Black or African-American	7 (6.4)	8 (7.4)	6 (5.6)
Asian	5 (4.6)	4 (3.7)	4 (3.7)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
Other	8 (7.3)	3 (2.8)	4 (3.7)
Ethnicity, n (%)			
Hispanic or Latino	1 (0.9)	3 (2.8)	0 (0.0)
Not Hispanic or Latino	107 (98.2)	105 (97.2)	107 (100.0)
Not reported	1 (0.9)	0 (0.0)	0 (0.0)
Weight, kg, mean (range)	79.0 (61.7-99.2)	78.5 (60.1-98.7)	77.9 (61.7-99.0)
Height, cm, mean (range)	176.5 (153.0-194.0)	177.4 (161.0-202.0)	176.5 (152.0-194.0)
BMI, kg/m^2, mean (range)	25.4 (19.65-29.67)	24.9 (19.2-29.9)	25.0 (19.8-29.9)

BMI, body mass index; EU Humira, adalimumab EU Humira; M923, adalimumab biosimilar M923; US Humira, adalimumab US Humira.

3.2 | Pharmacokinetics

Of the 324 subjects who received study drug, 9 subjects were excluded from the PK analysis set; 5 failed to receive a complete dose and 4 had quantifiable predose concentrations greater than 5% of C_{max}. A total of 315 subjects were included in the PK analysis set (107 in the M923 arm, 105 in the US Humira arm, and 103 in the EU Humira arm). Twenty-seven of the 315 subjects in the PK analysis set had individual parameters which were excluded from the PK analysis set due to protocol deviations or failure to meet acceptability criteria. Half-life and related PK parameters could not be calculated in 6 subjects due to lack of defined terminal elimination phase (Table S1). Following administration of a single 40-mg subcutaneous dose, PK profiles of M923, US Humira, and EU Humira were similar (Figure 2).

The geometric LS means ratio (GMR) of the primary endpoints C_{max}, $AUC_{0\text{-inf}}$, and $AUC_{0\text{-}336}$ for the comparisons of M923 with either EU Humira or US Humira and between EU Humira and US Humira were fully contained within the 80% to 125% equivalence bounds (Table 2). Individual and geometric mean results by study arm for the primary parameters (C_{max}, $AUC_{0\text{-}336,}$ and $AUC_{0\text{-inf}}$) are illustrated in Figure 3. GMRs for the secondary endpoints $AUC_{0\text{-last}}$ and $AUC_{0\text{-}1344}$ for all study arm comparisons were also close to unity and fully contained within the equivalence bounds. There were no relevant differences in median time to C_{max} (144 hours for both M923 and EU Humira; 142 hours for US Humira) or geometric mean and range of the calculated $t_{1/2}$, CL/F, and V_z/F values (Table 3).

3.3 | Safety

All subjects dosed were included in the safety analysis. The percentage of subjects with at least 1 adverse event was comparable among the 3 administration arms, ranging from 47.7% to 53.3% (Table 4). The majority (73.7%) of adverse events were considered by the investigators to be mild in severity and unrelated to administration of M923, US Humira, or EU Humira. There were no deaths. One subject from the EU Humira arm reported 3 serious adverse events: foot fracture, laceration, and wound infection; the first 2 events were considered severe while the third was moderate; all were considered unrelated to EU Humira. The types of adverse events were similar across study arms. The most common (≥2%) adverse event across all study arms was headache (11.4%) (see Table 4). Infections, which are considered adverse events of special interest, included 15 events of nasopharyngitis (4 in the M923 arm, 8 in the US Humira arm, and 3 in the EU Humira arm), 11 upper respiratory tract infections (4 in the M923 arm, 4 in the US Humira arm, and 3 in the EU Humira arm) and 3 events of oral herpes (0 in the M923 arm, 2 in the US Humira arm, and 1 in the EU Humira arm. Injection site reactions (bruising, erythema, hematoma, and pain) were also considered events of special interest and were reported in 24 subjects (11 in the M923 arm, 9 in the US Humira arm, and 4 in the EU Humira arm). No meaningful differences over time among the 3 administration arms were observed in any safety assessments, including laboratory, ECG, or vital signs (data not shown).

3.4 | ADA assessment and analysis

The overall incidence of binding ADA response and nADA response is represented in Figure 4 and Table S2, and the mean time to first seroconversion was 42 to 45 days across the 3 administration arms. Over time, the rates of ADA formation were similar across all study arms (Table 5). The proportion of confirmed ADA responses increased in all study groups to 78.0%, 73.1%, and 75.7% at day 71 in the M923, US Humira, and EU Humira arms, respectively. Similarly, the incidence of confirmed nADA response was reported in 18 (16.5%) subjects following M923 administration, 30 (27.8%) subjects following US Humira administration, and 22 (20.6%) subjects following EU Humira administration overall (Table 5). Of these, 1 subject (in the US Humira arm) had a confirmed positive nADA response at baseline prior to drug administration.

Time to development of ADA and titer of ADA varied among individuals within each cohort. Approximately, 15% to 18% of subjects had only a single incidence of a confirmed positive ADA response, which was most commonly associated with the final assessment on day 71; in these subjects ADA titer was low (ie, ≤1:8). Subjects with confirmed positive ADAs had maximum titers of

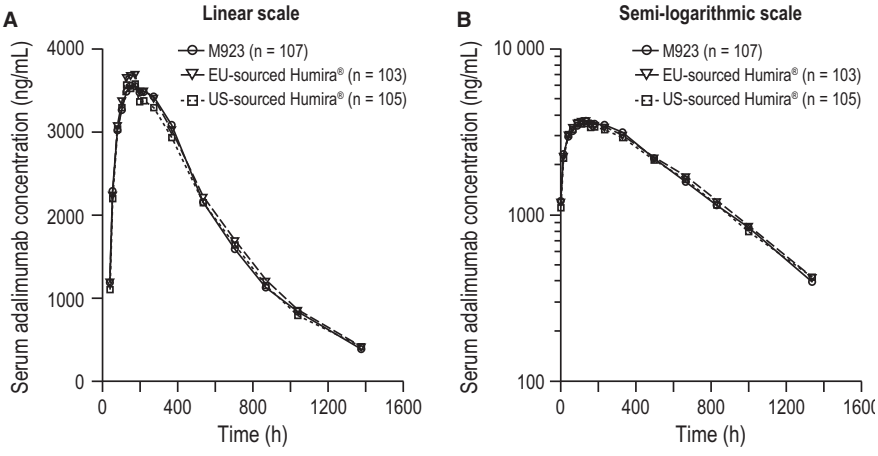

FIGURE 2 Mean serum concentration-time profiles, shown in both (A) linear and (B) semi-logarithmic scales

TABLE 2 Statistical comparison of primary and secondary PK parameters[a]

Parameter (unit)	Administration	n	Geometric LS means	95% CI	Pair	Administration comparison ratio (%)	90% CI
Primary PK							
C_{max}, ng/mL	M923	107	3907	3738-4084			
	EU Humira	103	3931	3758-4113	M923 vs EU Humira	99.39	94.25-104.81
	US Humira	105	3809	3643-3983	M923 vs US Humira	102.58	97.31-108.14
					US Humira vs EU Humira	103.21	97.85-108.86
$AUC_{0\text{-}inf}$, ng·hr/mL	M923	101	2 641 000	2 479 000-2 813 000			
	EU Humira	95	2 617 000	2 452 000-2 794 000	M923 vs EU Humira	100.90	93.48-108.90
	US Humira	91	2 534 000	2 371 000-2 709 000	M923 vs US Humira	104.20	96.47-112.54
					US Humira vs EU Humira	103.27	95.50-111.67
$AUC_{0\text{-}336}$, ng·hr/mL	M923	106	1 053 000	1 010 000-1 098 000			
	EU Humira	100	1 048 000	1 003 000-1 094 000	M923 vs EU Humira	100.51	95.55-105.73
	US Humira	101	1 023 000	979 700-1 068 000	M923 vs US Humira	102.94	97.88-108.27
					US Humira vs EU Humira	102.42	97.30-107.81
Secondary PK							
$AUC_{0\text{-}1344}$, ng·hr/mL	M923	61	2 759 000	2 650 000-2 873 000			
	EU Humira	55	2 737 000	2 622 000-2 856 000	M923 vs EU Humira	100.82	95.94-105.95
	US Humira	51	2 862 000	2 738 000-2 991 000	M923 vs US Humira	96.41	91.67-101.38
					US Humira vs EU Humira	95.62	90.81-100.68
$AUC_{0\text{-}last}$, ng·hr/mL	M923	107	2 310 000	2 137 000-2 498 000			
	EU Humira	103	2 341 000	2 162 000-2 535 000	M923 vs EU Humira	98.68	89.86-108.37
	US Humira	105	2 192 000	2 026 000-2 372 000	M923 vs US Humira	105.38	96.02-115.66
					US Humira vs EU Humira	106.79	97.21-117.31

$AUC_{0\text{-}1344}$, area under the curve from time 0 to 1344 hours; $AUC_{0\text{-}336}$, area under the curve from time 0 to 336 hours; $AUC_{0\text{-}inf}$, area under the curve from time 0 to infinity; $AUC_{0\text{-}last}$, area under the curve from time 0 to last dose; CI, confidence interval; C_{max}, maximum observed concentration; EU Humira, adalimumab EU Humira; LS, least squares; M923, adalimumab biosimilar M923; PK, pharmacokinetics; US Humira, adalimumab US Humira.
[a]Results based on an analysis of covariance model with a fixed effect for administration and baseline age and body weight as continuous covariates.

≤1:256, with the exception of 4 subjects (1 each in the M923 and EU Humira arms and 2 in the US Humira arm) who developed higher titers up to and or exceeding 1:32 800, all of which were associated with detectable nADAs.

Following a positive ADA result, subjects were further evaluated for the presence of IgE (a specific isotype of ADA). The presence of IgE was confirmed in 13 subjects (2 in the M923 arm, 8 in the US Humira arm, and 3 in the EU Humira arm). The development of IgE was associated with nADA in 7 subjects (5 in the US Humira arm and 2 in the EU Humira arm). There was an association between higher titers and the formation of nADAs and between IgE and the development of nADAs.

4 | DISCUSSION

As part of the evaluation of biosimilarity, comparative PK studies in a homogenous and sensitive population of healthy volunteers are recommended to detect potential differences in the PK of test and reference products.[17] This randomized, double-blind study was the first time that M923 was administered to healthy human subjects. The primary aim of the study was to investigate and compare the PK profiles of M923, US Humira, and EU Humira after administration of a subcutaneous single dose of 40 mg. According to guideliness, PK equivalence would be demonstrated if the 90% GMR CIs for exposure endpoints C_{max} and various AUCs across study arms were within the predefined acceptance range of confidence bounds of 80% to 125%. For all primary endpoints (C_{max}, $AUC_{0\text{-}inf}$, and $AUC_{0\text{-}336}$) across each pairwise comparison (M923/US Humira, M923/EU Humira, and US Humira/EU Humira), PK equivalence was clearly demonstrated (CI range: 93%-113%). Secondary exposure PK parameters ($AUC_{0\text{-}1344}$ and $AUC_{0\text{-}last}$) were also fully contained within the 80% to 125% equivalence bounds for all study arm pairings. All LS means ratios for comparisons of study arms were close to unity for both the primary and secondary exposure PK endpoints. Other secondary PK endpoints, t_{max}, $t_{1/2}$, CL/F, and V_z/F were also similar between study arms. The PK parameters for M923 were also found to be concordant (considering intersubject variability) or within the range of those reported for US Humira and EU Humira in patients with RA.[4,5]

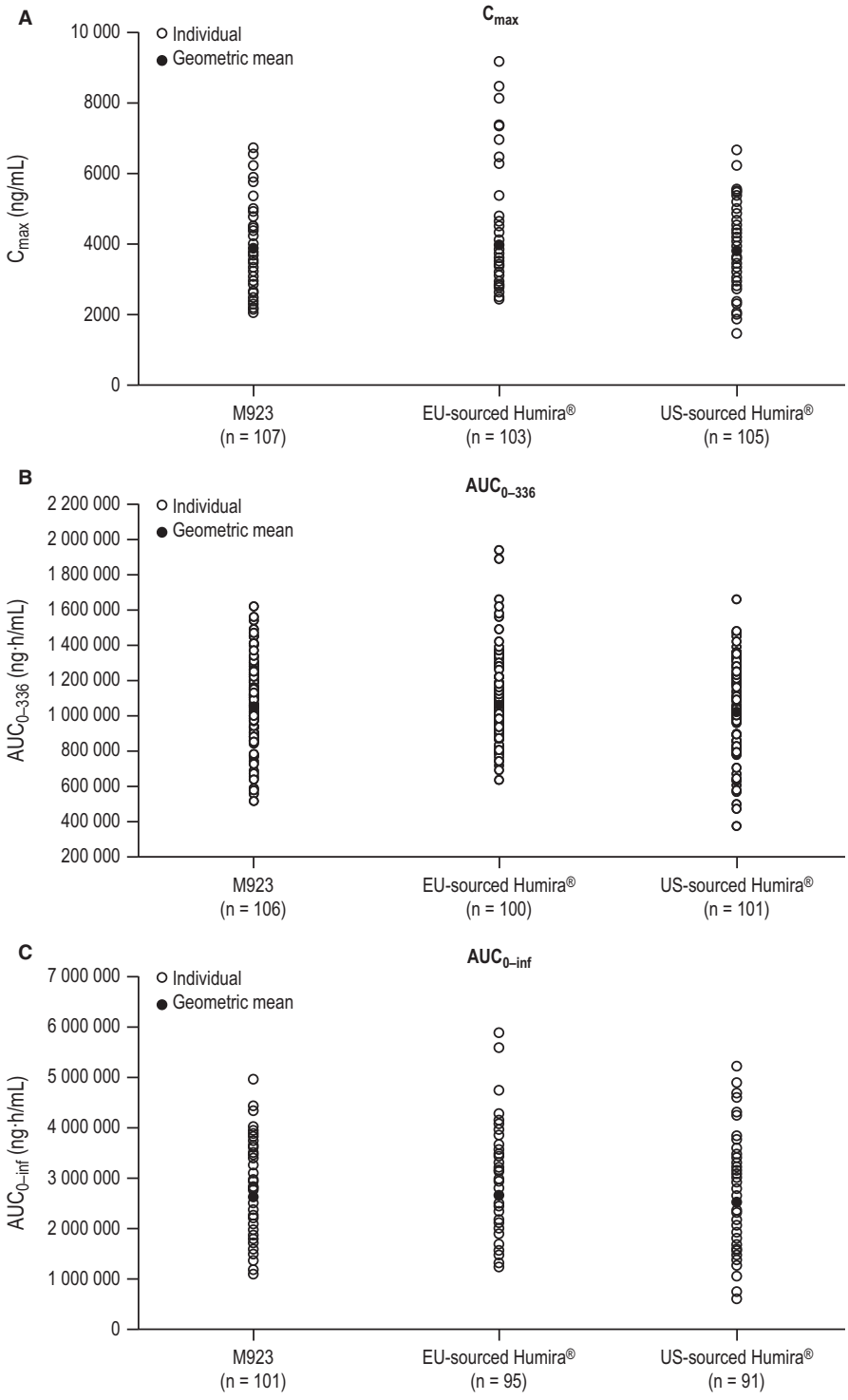

FIGURE 3 Primary PK parameters: individual and geometric mean (A) C_{max}, (B) $AUC_{0\text{-}336}$, and (C) $AUC_{0\text{-}inf}$. $AUC_{0\text{-}336}$, area under the curve from time 0-336 hours; $AUC_{0–inf}$, area under the curve from time 0 to infinity; C_{max}, maximum observed concentration

Although demographic and baseline characteristics were similar across administration arms, we cannot rule out potential gender differences that may exist or potential differences seen when a nonhealthy population is studied. It is noteworthy that no gender-related PK differences were observed after correction for a patient's body weight in RA patients and healthy volunteers.[18]

Furthermore, these PK findings are in line with similarly designed phase 1 studies that also demonstrated PK similarity between single 40-mg subcutaneous injections of the biosimilar ABP 501, FKB327, LBAL, and MSB11022 and either US Humira or EU Humira in healthy subjects.[13,19–21] Therefore, the PK profile for M923 observed in healthy subjects may be predictive of equivalent PK in patients with immune-mediated conditions for which Humira has been approved.

M923 was demonstrated to be well tolerated, with a safety profile that was comparable to that observed for EU Humira and US Humira. The incidence, severity, and type of adverse events

TABLE 3 Descriptive statistics for secondary PK parameters

Parameter (unit)	Administration	N[a]	Geometric LS means	Median (range)	CV%
V_z/F, L	M923	101	6.73	6.93 (2.59-16.6)	34.2
	US Humira	91	6.63	6.62 (2.52-13.8)	31.9
	EU Humira	95	6.62	6.71 (2.81-14.4)	30.8
$t_{1/2,}$ hr	M923	104	311	312 (99.9-923)	46.6
	US Humira	101	313	323 (42.4-955)	50.8
	EU Humira	102	319	324 (90.7-888)	49.5
CL/F, L/hr	M923	101	0.0153	0.0144 (0.00807-0.0368)	34.4
	US Humira	91	0.0158	0.0152 (0.00764-0.0649)	49.6
	EU Humira	95	0.0151	0.0143 (0.00680-0.0320)	33.8
T_{max}, hr	M923	107		144.00 (47.15-504.00)	
	US Humira	105		141.78 (48.00-336.40)	
	EU Humira	103		144.00 (48.00-339.83)	

CL/F, apparent systemic clearance after extravascular dosing; CV, coefficient of variation; EU Humira, adalimumab EU Humira; LS, least squares; M923, adalimumab biosimilar M923; PK, pharmacokinetics; $t_{1/2}$, terminal half-life; t_{max}, time to maximum concentration (median and range only); US Humira, adalimumab US Humira; V_z/F, apparent volume of distribution.

[a]Twenty-seven of the 315 subjects in the PK analysis set had individual parameters that were excluded from the PK analysis set due to protocol deviations or failure to meet acceptability criteria. Half-life and related PK parameters could not be calculated in 6 subjects due to lack of defined terminal elimination phase.

TABLE 4 Summary of safety results

AE type, n (%)	M923 N = 109	US Humira N = 108	EU Humira N = 107	Total N = 324
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious AEs	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.3)
AEs leading to early withdrawal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any AEs	52 (47.7)	55 (50.9)	57 (53.3)	164 (50.6)
AEs by severity				
Mild	39 (35.8)	44 (40.7)	41 (38.4)	124 (38.3)
Moderate	18 (16.5)	15 (13.9)	21 (19.6)	54 (16.7)
Severe	3 (2.7)	4 (3.8)	3 (2.8)	10 (3.1)
Most common (≥2%) AEs				
Headache	7 (6.4)	14 (13.0)	16 (15.0)	37 (11.4)
Nasopharyngitis	4 (3.7)	8 (7.4)	3 (2.8)	15 (4.6)
Oropharyngeal pain	4 (3.7)	4 (3.8)	3 (2.8)	12 (3.7)
Upper respiratory tract infection[a]	4 (3.7)	4 (3.7)	3 (2.8)	11 (3.4)
Seasonal allergy	2 (1.8)	4 (3.7)	4 (3.7)	10 (3.1)
Injection site bruising	5 (4.6)	4 (3.7)	0 (0.0)	9 (2.8)
Rhinitis	2 (1.8)	3 (2.8)	4 (3.7)	9 (2.8)
Influenza-like illness	4 (3.7)	2 (1.9)	2 (1.9)	8 (2.5)
Injection site erythema	3 (2.8)	4 (3.7)	1 (0.9)	8 (2.5)
Back pain	3 (2.8)	2 (1.9)	1 (0.9)	6 (1.9)

AE, adverse event; EU Humira, adalimumab EU Humira; M923, adalimumab biosimilar M923; US Humira, adalimumab US Humira.

[a]Includes 1 patient with a viral upper respiratory tract infection in the M923 arm.

were similar across study arms with no unexpected findings. Infection and injection site reactions, among the most frequently reported adverse events for M923, are consistent with those defined as adverse events of special interest for the drug class[9,22,23] and were similar in incidence across the 3 study arms. Furthermore, there were no differences seen in adverse events between treatment groups in those subjects who developed an ADA response.

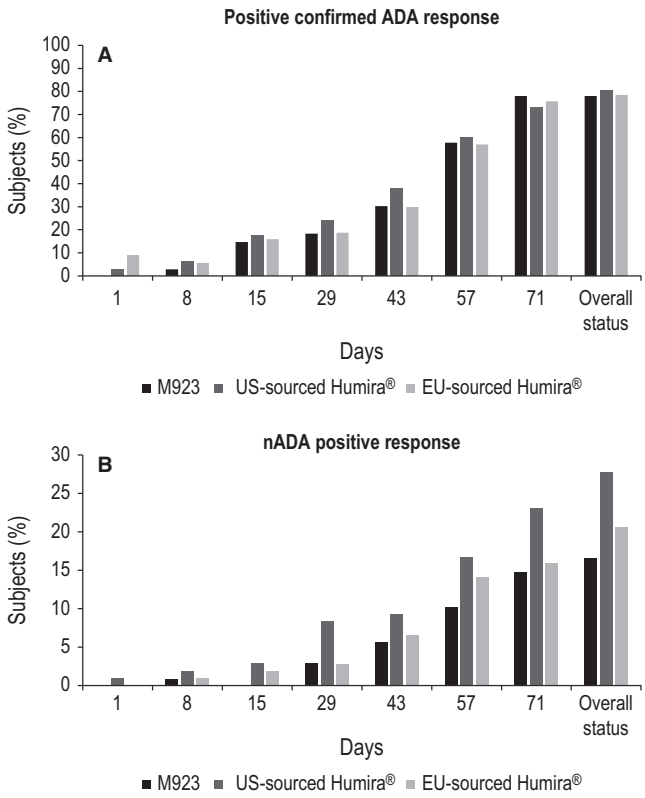

FIGURE 4 Antidrug antibodies across time and overall status (at any time): (A) Overall confirmed positive ADA response; (B) Neutralizing ADA-positive response. ADA, antidrug antibodies; nADA, neutralizing antidrug antibodies

As previously reported, and as illustrated in this study, adalimumab is highly immunogenic in healthy volunteers. Multiple factors contribute to ADA formation, including composition of the biological agent and route of administration.[24] In patients with RA, the concomitant use of methotrexate has been implicated in the lower proportion of ADA-positive patients observed.[25] The presence of ADAs can limit drug effectiveness or induce hypersensitivity and other adverse reactions.[24,26] The generation of ADAs is increasingly recognized as a mechanism that contributes to primary and secondary failure of biological drugs in chronic inflammatory diseases,[24,25,27] although variability has been reported.[7]

In this study, the percentages of subjects over time with binding ADA formation and nADA formation were similar among all study arms. The results were also consistent with other recent studies evaluating biosimilars of Humira.[13,19,21] In the M923 study, the proportion of subjects with a confirmed ADA response, the rate of ADA seroconversion over time, and the occurrence of nADAs were in line with that reported by Kaur et al.[13] A lower ADA response (44%) has been reported with LBAL, a Humira biosimilar that is currently in development.[20] The ADA responses with M923 and other Humira biosimilars[13,19,21] are higher (>70%) than historically reported for Humira registration trials[9,10] or in a real-world study in RA.[25] The lower ADA response may reflect the fact that in some of these studies, patients may have also been receiving agents that could suppress the immune system and thereby reduce the incidence of antibody formation.[25] Interestingly, in each biosimilar study, similar ADA responses have been reported between each biosimilar and Humira. The differences seen when comparing ADA responses between studies may reflect the use of different assay methods and/or methods with differing sensitivities for measurement of the ADA response.[28]

5 | CONCLUSION

This phase 1 PK study in healthy volunteers demonstrated similarity in PK between M923 and both US Humira and EU Humira following administration of a subcutaneous single dose of 40 mg, consistent with regulatory guidelines.[29,30] PK equivalence of M923 to US Humira and EU Humira was demonstrated, and no meaningful differences in the safety or immunogenicity profiles were observed. These results supported the initiation of confirmatory and supportive clinical studies for the development of M923, a proposed biosimilar to adalimumab.

TABLE 5 Incidence of ADA and nADA formation by study day and administration

	Overall positive confirmed ADA response			Neutralizing ADA positive response		
Study day/time point, n (%)	M923 N = 109	US Humira N = 108	EU Humira N = 107	M923 N = 109	US Humira N = 108	EU Humira N = 107
Day 1/predose	0 (0.0)	3 (2.8)	1 (0.9)	0 (0.0)	1 (0.9)	0 (0.0)
Day 8/168 hr	3 (2.8)	7 (6.5)	6 (5.6)	1 (0.9)	2 (1.9)	1 (0.9)
Day 15/336 hr	16 (14.7)	19 (17.6)	17 (15.9)	0 (0.0)	3 (2.8)	2 (1.9)
Day 29/672 hr	20 (18.3)	26 (24.1)	20 (18.7)	3 (2.8)	9 (8.3)	3 (2.8)
Day 43/1008 hr	33 (30.3)	41 (38.0)	32 (29.9)	6 (5.5)	10 (9.3)	7 (6.5)
Day 57/1344 hr	63 (57.8)	65 (60.2)	61 (57.0)	11 (10.1)	18 (16.7)	15 (14.0)
Day 71/follow-up	85 (78.0)	79 (73.1)	81 (75.7)	16 (14.7)	25 (23.1)	17 (15.9)
Overall status	85 (78.0)	87 (80.6)	84 (78.5)	18 (16.5)	30 (27.8)	22 (20.6)

ADA, antidrug antibody; EU Humira, adalimumab EU Humira; M923, adalimumab biosimilar M923; nADA, neutralizing antidrug antibody; US Humira, adalimumab US Humira.

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DISCLOSURE

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AUTHOR CONTRIBUTIONS

TG, RR, NG, TM, BP, JR, KC, and MR contributed to the conception and design of the study. TM and JC contributed to data acquisition. TG, RR, NG, TM, BP, JD, JC, and JR contributed to data analysis and interpretation. RR, BP, and JD contributed to the statistical analysis of the data. All authors contributed to drafting of the manuscript, revised the manuscript critically for important intellectual content, and approved the final submitted version.

ORCID

Tanmoy Ganguly http://orcid.org/0000-0003-0681-4737

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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