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Pharmacokinetic Similarity of ABP 710, a Proposed Biosimilar to Infliximab: Results From a Randomized, Single-Blind, Single-Dose, Parallel-Group Study in Healthy Subjects

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Abstract

This was a randomized, single-blind, single-dose, 3-arm parallel-group study. Healthy subjects were randomized to receive ABP 710 (n = 50) or infliximab reference product (RP) sourced from the United States (infliximab US; n = 50) or the European Union (infliximab EU; n = 50) 5 mg/kg intravenously over 2 hours. The primary endpoint was area under the serum concentration–time curve from time 0 extrapolated to infinity (AUC_{inf}) for the comparison of ABP 710 to infliximab US and infliximab EU. Secondary endpoints included safety, tolerability, and immunogenicity. AUC_{inf} was similar across the 3 groups, showing similarity of ABP 710 to infliximab RP as well as similarity of infliximab US with infliximab EU. Geometric mean ratio of AUC_{inf} was 0.89 between ABP 710 and infliximab US, 1.00 between ABP 710 and infliximab EU, and 1.11 between infliximab US and infliximab EU. All 90% confidence intervals of the geometric mean ratios were fully contained within the prespecified standard pharmacokinetic equivalence criteria range of 0.80 to 1.25. Treatment-related adverse events were mild to moderate and reported for 83.7%, 86.0%, and 83.7% of subjects in the ABP 710, infliximab US, and infliximab EU treatment groups, respectively; incidence of antidrug antibody rates observed across the 3 groups were similar. Results of this study demonstrated pharmacokinetic similarity of ABP 710 with infliximab RP following a single 5-mg/kg intravenous injection. The safety and tolerability of ABP 710 and infliximab RP were comparable. These results add to the totality of evidence providing further support that the proposed biosimilar ABP 710 is similar to infliximab RP. (Trial ID: ACTRN12614000903684.)

Keywords

ABP 710, biosimilar, infliximab, pharmacokinetics, mAb

ABP 710 is being developed as a biosimilar to infliximab (Remicade®). Infliximab is a chimeric immunoglobulin G monoclonal antibody (mAb) produced in murine hybridoma cells by recombinant DNA technology. It neutralizes the biological activity of tumor necrosis factor-alpha (TNF-α) by binding with high affinity to the soluble and transmembrane forms of TNF-α and inhibits binding of TNF-α with its receptors. TNF-α blockade downregulates most other proinflammatory cytokines and therapeutics that block TNF-α and are used in a variety of TNF-α–dependent inflammatory diseases such as Crohn disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis.[1]

In general, the pharmacokinetics (PK) of infliximab are best described by a 1-compartment model with lin-

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[Correction added on 29 November 2019, after first online publication: the value of 141.42 is updated in pharmacokinetics section.]

ear elimination.[2] As circulating levels of TNF-α can vary based on active disease-related inflammation, the amount of inflammation in patients could impact clearance of TNF-α–mediated mAbs. Cross-study comparisons have shown that patients with the inflammatory disease ulcerative colitis had a 45.8% faster clearance of infliximab than healthy volunteers.[3] It has also been shown that C-reactive protein (CRP), a marker of inflammation, is positively correlated with clearance of infliximab. When CRP was used as a time-varying covariate in a PK model in a population of patients with inflammatory bowel disease, results indicated that a CRP of 100 mg/L increased infliximab clearance by 21.6%.[2] Combination therapy of infliximab with drugs with immunosuppressive effects can reduce disease-related inflammation and TNF-α as was suggested to be a factor in the case of patients receiving azathioprine who had a 15.1% decrease in infliximab clearance.[2,4,5] Infliximab is not known to have any direct drug-drug interactions, and serum concentrations have been shown to be unaffected by corticosteroids, mesalamine, or sulfasalazine or anti-infectives such as ciprofloxacin and metronidazole.[6] These drugs are commonly concomitant in clinical trials of patients with rheumatoid arthritis, although concomitant dosing is contraindicated with other biological disease-modifying antirheumatic drugs and immune suppressants such as abatacept and tocilizumab or atlizumab largely because of the possibility of an increased risk of infections.

A biosimilar is a biologic that is highly similar to an approved, branded biologic reference product (RP).[7,8] Biologics have revolutionized the treatment of autoimmune disorders; however, they are expensive options, leading to limited access to treatment. To expand access, regulatory agencies have established guidelines to provide an abbreviated development and approval pathway for biosimilars.[9–12] Due to the complex nature of manufacturing biologics, biosimilars, unlike generics, are not expected to be identical to the RP. Therefore, development typically includes a stepwise approach based on the concept of totality of evidence to demonstrate similarity between the proposed biosimilar and the RP. This approach is expected to incrementally reduce the residual uncertainty with respect to biosimilarity between the proposed biosimilar and the RP. The evaluation of biosimilarity begins with demonstration of analytical (structural, functional, and physiochemical) similarity, which forms the foundation of biosimilarity. This is then followed by preclinical and clinical pharmacology evaluations, including human PK and pharmacodynamics (PD), if relevant, and finally at least 1 confirmatory comparative clinical study to evaluate efficacy, safety, and immunogenicity in a representative indication using a sensitive patient population and end points to complete the totality of evidence.

The totality of evidence for ABP 710, a proposed biosimilar to infliximab, thus far includes analytical comparisons (structural and functional) that suggest that ABP 710 is similar to the infliximab RP. ABP 710 is an anti-TNF-α mAb, which has the same amino acid sequence as infliximab RP as well as the same pharmaceutical form and dosage strength. ABP 710 is similar in secondary and tertiary structure as well as overall conformational stability.[13] The similarity of ABP 710 with infliximab RP in in vitro binding to TNF-α, neonatal Fc receptor, and Fc gamma receptor Type IIIa and in vitro effector function activity of antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity has been demonstrated through multiple sensitive biological characterization assays.[13]

For approval in either the United States or the European Union, the proposed biosimilar must be shown to be similar to the RP approved in the respective region. To minimize the additional development costs, regulatory agencies allow the use of foreign-sourced comparators in clinical studies based on a scientific rationale to bridge the foreign product to the one approved in the local jurisdiction. In this case, the development of this bridge requires the evaluation of the proposed biosimilar ABP 710 with RP sourced from the 2 regions for analytical (structural and functional) comparison as well phase 1 PK. This phase 1 clinical study was performed to evaluate the PK similarity of ABP 710 with infliximab RP. The primary objective of this study was to demonstrate that the PK of ABP 710 is similar to that of infliximab RP as assessed by the area under the serum concentration–time curve from time 0 extrapolated to infinity (AUC_{inf}); the infliximab RP was sourced from the United States (infliximab US) and the European Union (infliximab EU). The secondary objectives were to determine the safety, tolerability, and immunogenicity of ABP 710 in healthy adult subjects compared with infliximab US and infliximab EU. In addition, PK similarity was also determined between infliximab US and infliximab EU as assessed by AUC_{inf}.

Methods

Subjects

Healthy adults 18 to 45 years of age with a body mass index of 18 to 30 kg/m^2 at screening were eligible for the study. Exclusion criteria included, but were not limited to, those with a history or evidence of a clinically significant disorder that could pose a risk to subject safety or interfere with the study; history or presence of conditions known to interfere with the distribution, metabolism, or excretion of drugs; evidence of any infection (bacterial, viral, parasitic, or systemic fungal) $\leq$30 days of investigational product (IP) administration; evidence of infection requiring inpatient

hospitalization or intravenous (IV) antibiotics ≤6 months, had tuberculosis (latent or active) ≤6 months of screening, or tuberculosis or fungal infection seen on chest x-ray ≤6 months; history of surgery or major trauma ≤12 weeks of screening or surgery planned during the study; reported a current malignancy or a malignancy ≤5 years (with the exception of surgically excised nonmelanoma skin cancer); were receiving or had received any investigational drug or device ≤30 days (or 5 half-lives, whichever is longer); use of any over-the-counter or prescription medications (other than vitamins, acetaminophen, and hormonal contraceptives) ≤14 days or 5 half-lives (whichever was longer) prior to receiving IP; all herbal medicines and supplements consumed ≤30 days prior to IP were reviewed; received live vaccines ≤1 month prior to IP or were planning to receive a vaccine during the study; had previously received infliximab or any product considered to be a biosimilar to infliximab; known or suspected sensitivity to products derived from mammalian cell lines; known or suspected sensitivity to premedication; donated blood or experienced loss of blood ≥500 mL during ≤2 months of screening; positive screen for alcohol and/or potential drugs of abuse at screening or before randomization; positive screen for HIV, hepatitis B virus surface antigen, hepatitis B core antibody, or hepatitis C virus; history of alcohol and/or substance abuse ≤12 months prior to screening; subjects who used >10 cigarettes per day ≤3 months or were not able to abide by the smoking policy of the site; inability or unwillingness to reside at the clinical pharmacology unit (CPU) for 3 consecutive days (2 nights); or inability to be available for follow-up assessments or protocol-required procedures.

This study was conducted in accordance with the International Conference on Harmonisation E6 Guidelines on Good Clinical Practice (CPMP/ICH/135/95). The investigators obtained Human Research Ethics Committee approval for the protocol, all protocol amendments, and the written informed consent prior to study initiation, in conformance with National Statement on Ethical Conduct in Human Research; National Health and Medical Research Council, 2007; and the Therapeutic Goods Administration publication "HRECs and the Therapeutic Goods Legislation." All subjects provided informed consent before the study. This study was conducted at 2 clinical research units in Australia (Nucleus Network Limited [The Centre for Clinical Studies], Melbourne and CMAX [A Division of IDT Australia Limited], Victoria) and approved by 2 Institutional Review Boards in Australia (Alfred Hospital Ethics Committee, Victoria, Australia; and Bellberry Human Research Ethics Committee, Eastwood, South Australia).

Study Design

This was a randomized, single-blind, single-dose, 3-arm, parallel-group study conducted at 2 CPUs in Australia using infliximab US and infliximab EU (Figure 1). Approval for this study was granted by the Human Research Ethics Committee and was conducted accordingly. The study protocol was approved by an independent ethics committee or institutional review board at each site before study initiation. A total of 150 subjects were enrolled in the study. Screening occurred ≤28 days before dosing. Eligible subjects were admitted to the CPU on day –1 and randomized in a ratio of 1:1:1 by the 2 regions such that the ratio of subjects to receive ABP 710 (Amgen Inc, Thousand Oaks, California), infliximab US (Remicade; Janssen Biotech, Horsham, Pennsylvania), or infliximab EU (Remicade; Janssen Biologics BV, Leiden, The Netherlands) was the same before dosing on day 1. Subjects were pretreated with an antihistamine (eg, diphenhydramine) and paracetamol 30 minutes before the start of the 5-mg/kg IV infusion over 2 hours of IP. Subjects were discharged from the CPU on study day 2 after the 24-hour postdose assessments were complete. Safety evaluations and blood sampling for PK and antidrug antibody (ADA) assessments were evaluated at postdose follow-ups. Subjects were monitored throughout the study for adverse events (AEs), clinical laboratory results, concomitant medication use, and vital signs. Samples for PK assessments were collected on day 1 (before dosing, end of infusion [approximately 2 hours]); 4, 8, 12, and 24 hours after the start of the infusion; at each return visit to the CPU (days 3, 8, 15, 22, 36, 50); and at the end of the study (day 57). Serum concentrations were determined using a validated electrochemiluminescent (ECL) assay that was fully validated for performance parameters consistent with those established for quantitative PK methods as described within the bioanalytical US Food and Drug Administration guidance document and industry literature.[14–16] This ECL assay was qualified and validated with resultant data demonstrating that it is sensitive, accurate, and robust in the quantification of all 3 test products in healthy human serum. The assay range was from 10 to 5000 ng/mL. The ECL assay method was based on the Meso Scale Discovery platform using an anti-idiotype mAb to capture ABP 710 and infliximab RP from test samples and a second ruthenium-labeled anti-idiotype to detect the bound test products.[16] Samples for ADA assessments were collected before dosing and at prespecified visits, including days 1, 15, 36, and 57. ADA status was assessed with a 2-tiered approach, including a screening assay and a confirmatory assay, using highly sensitive and drug-tolerant assays based on the Meso Scale Discovery ECL platform.[14,17] Assays were developed and validated for each IP—ABP 710,

SCREENING	SUBJECTS IN RESIDENCE				POST-DOSE FOLLOW UP	END OF STUDY
Day -28 to Day -2	Day -1	Randomization	Day 1 (Dosing)	Day 2	Day 3 through Day 50	Day 57
Informed Consent & Screening Informed Consent, medical history, screening procedures during the 28 days prior to dosing	**Study Day -1** Confirm eligibility and predose assessments	**Randomization** (1:1:1)	**Study Drug Administration** A: ABP 710 (n=50) B: Infliximab (US) (n=50) C: Infliximab (EU) (n=50)		**Out Patient** PK parameters and Safety Assessments on study days 3, 8, 15, 22, 36, 50	**Study Day 57 End of Study Visit** Clinically Significant, clinical, or laboratory abnormalities will be followed until resolution or until considered stable
	In Patient PK parameters and Safety Assessments Subjects discharged on study day 2 after 24-hour post dose assessments are complete					
Planned Treatments ABP 710: 5 mg/kg infusion Infliximab (US): 5 mg/kg infusion Infliximab (EU): 5 mg/kg infusion						

Figure 1. Study design.

infliximab US, and infliximab EU—and each serum sample was tested using each of these 3 assays. Samples positive for binding ADAs were subsequently tested in a corresponding ligand-binding bioassay to determine neutralizing activity against ABP 710, infliximab US, or infliximab EU. The sensitivity of the ADA detection assay was the same for both ABP 710 and infliximab. The assays were validated with a tolerance of 25 µg/mL of drug, and the highest observed maximum observed concentration (C_{max}) in this study was <6.0 mg/mL. Drug interference was thus not expected from the collected samples. The neutralizing antibody cell-based bioassay was expected to detect all classes of antibodies that inhibit the biological activity of the drug.[14,17]

Safety Evaluation

Safety and immunogenicity of ABP 710 compared with infliximab were evaluated through descriptive summaries of AEs, concomitant medications, and incidence of ADAs.

Statistical Methods

Approximately 150 healthy adult male and female subjects were planned to be enrolled in this study. The PK parameter population consisted of all subjects with an evaluable infliximab RP or ABP 710 serum concentration–time profile; this population was used for the primary analysis of PK equivalence. The safety analysis set consisted of all subjects who received any amount of IP.

PK parameters were calculated using noncompartmental methods and actual sampling times (Phoenix WinNonlin Professional Network Edition, Version 6.3; Pharsight Corp, St Louis, Missouri) for all subjects with an evaluable infliximab RP or ABP 710 serum concentration–time profile. PK similarity was assessed by comparing the 90% confidence intervals (CIs) for the geometric mean (GM) test-to-reference ratios (GMR) for AUC_{inf}, maximum concentration (C_{max}), and AUC from time 0 to time of last measurable concentration (AUC_{last}) with the protocol-specified bioequivalence criteria of 0.80 and 1.25. Prior to statistical modeling, PK parameters were log-transformed. Point estimates and 90%CIs for the mean difference in logarithmic PK parameters were estimated using an analysis of variance model for comparisons of ABP 710 and infliximab US and infliximab EU. Point estimates and 90%CIs for GMRs were then calculated by transforming back to the original scale. Serum concentrations and PK parameters were also summarized using descriptive statistics by treatment group.

Subgroup/sensitivity statistical analyses were predetermined and performed on the PK parameter population. Serum ABP 710 and RP concentrations and PK parameters were summarized descriptively, with PK parameters derived using an analysis of variance model including treatment alone. Within the subgroup

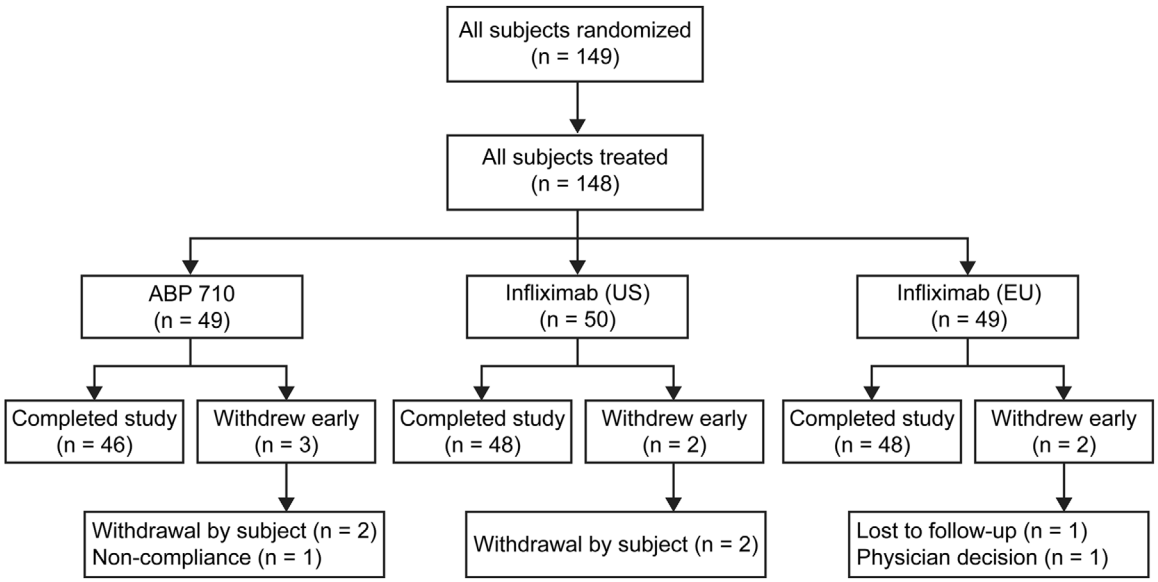


Figure 2. Subject disposition.

Table 1. Summary of Demographic Data and Baseline Characteristics

Parameter	ABP 710 (n = 49)	Infliximab US (n = 50)	Infliximab EU (n = 49)
Mean age, y (range)	27.4 (18-44)	25.8 (18-45)	26.3 (18-43)
Women, n (%)	25 (51.0)	25 (50.0)	32 (65.3)
Ethnicity, n (%)			
Hispanic or Latino	4 (8.2)	1 (2.0)	2 (4.1)
Not Hispanic or Latino	45 (91.8)	49 (98.0)	47 (95.9)
Race, n (%)			
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Asian—first-generation Japanese	7 (14.3)	7 (14.0)	8 (16.3)
Asian—second-generation Japanese	1 (2.0)	1 (2.0)	0 (0.0)
Asian—other	4 (8.2)	5 (10.0)	5 (10.2)
Black or African American	0 (0.0)	0 (0.0)	1 (2.0)
Native Hawaiian or other Pacific Islander	1 (2.0)	0 (0.0)	0 (0.0)
White	35 (71.4)	34 (68.0)	34 (69.4)
All other	1 (2.0)	3 (6.0)	1 (2.0)
Mean weight, kg (range)	69.03 (43.0-101.3)	71.15 (50.1-100.1)	64.57 (46.3-95.9)
Mean height, cm (range)	171.8 (150-192)	171.7 (151-190)	167.3 (150-192)
Mean BMI, kg/m^2 (range)	23.20 (18.8-29.6)	24.03 (18.3-29.4)	22.90 (18.6-29.0)

BMI, body mass index; EU, European Union; US, United States.

of binding ADA-negative subjects, AUC_{inf}, $C_{max,}$ and AUC_{last} were summarized and compared between groups.

Results

Subject Disposition and Characteristics

Subject disposition is summarized in Figure 2. A total of 149 subjects were enrolled and randomized; 49 subjects were dosed with ABP 710, 50 with infliximab US, and 49 with infliximab EU. There were 7 subjects who did not complete the study. Reasons for early discontinuation included withdrawal of consent, lost to follow-up, and 1 discontinuation at the request of the physician before the subject received any dosing. A summary of baseline characteristics is provided in Table 1. Baseline characteristics were comparable between treatment groups.

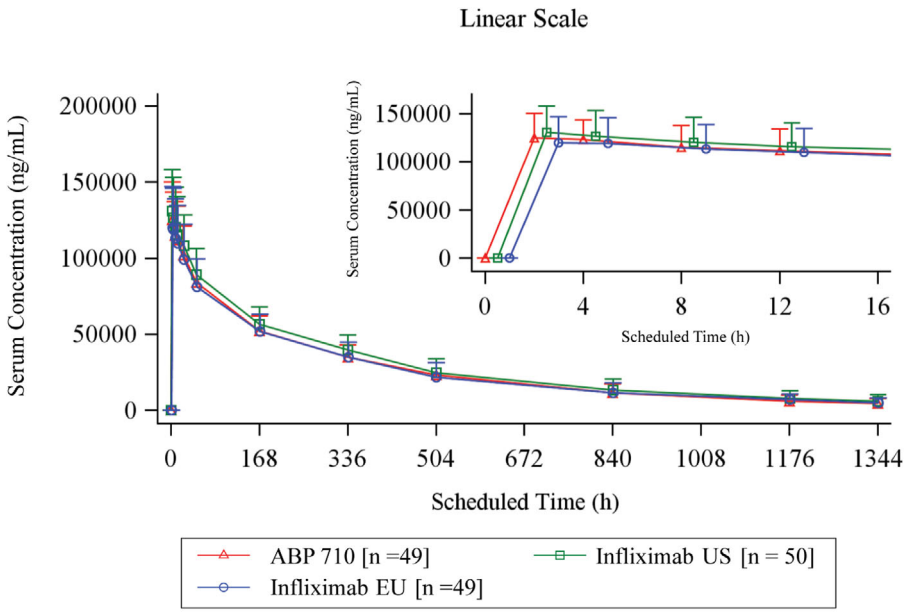
Pharmacokinetics

Pharmacokinetic results are shown in Table 2 and Figure 3. The mean serum concentration–time profiles after a single 5-mg/kg IV infusion over 2 hours of ABP 710, infliximab US, or infliximab EU were similar among the 3 groups. Peak concentrations were observed with a median of 2 to 3 hours following the end of infusion, after which concentrations declined in a monophasic manner with the half-life and standard

Table 2. Pharmacokinetic Results: Ratio of Least Squares Geometric Means (90%CI)

	AUC_{inf} µg • h/mL			AUC_{last} µg • h/mL			C_{max} µg/mL		
	AM (SD)	GM [n](%)	GMR (90%CI)	AM (SD)	GM [n](%)	GMR (90%CI)	AM (SD)	GM [n](%)	GMR (90%CI)
ABP 710 vs Infliximab US	36 819.4 (9920.93)	33 532.8 [46] (28)	0.89 (0.812-0.985)	34 449.8 (8126.00)	33 506.2 [46] (24)	0.91 (0.837-0.989)	130.17 (23.234)	128.14 [49] (18)	0.97 (0.917-1.030)
	41 623.7 (12 181.49)	39 756.2 [47] (32)		38 202.5 (9841.62)	36 896.1 [49] (28)		134.26 (26.642)	131.90 [50] (19)	
ABP 710 vs Infliximab EU	36 819.4 (9920.93)	33 532.8 [46] (28)	1.00 (0.904-1.096)	34 449.8 (8126.00)	33 506.2 [46] (24)	1.00 (0.918-1.086)	130.17 (23.234)	128.14 [49] (18)	1.02 (0.962-1.083)
	37 016.1 (10 016.01)	35 712.2 [47] (28)		34 528.3 (8313.62)	33 587.2 [47] (24)		127.30 (22.126)	125.48 [48] (17)	
Infliximab US vs Infliximab EU	41 623.7 (12 181.49)	39 756.2 [47] (32)	1.11 (1.011-1.225)	38 202.5 (9841.62)	36 896.1 [49] (28)	1.10 (1.010-1.192)	134.26 (26.642)	131.90 [50] (19)	1.05 (0.991-1.114)
	37 016.1 (10 016.01)	35 712.2 [47] (28)		34 528.3 (8313.62)	33 587.2 [47] (24)		127.30 (22.126)	125.48 [48] (17)	

AM, arithmetic mean; AUC_{inf}, area under the serum concentration–time curve from time 0 extrapolated to infinity; AUC_{last}, area under the serum concentration–time curve from time 0 to time of last measurable concentration; CI, confidence interval; C_{max}, maximum concentration; GM, geometric mean; GMR, geometric mean ratio; SD, standard deviation.



Concentration values below BLQ presented as zero and included as such in the calculation of means.

Figure 3. Mean serum ABP 710, infliximab US, and infliximab EU concentration-time profiles. Concentration values below BLQ presented as 0 and included as such in the calculation of means (± SD). BLQ, below limit of quantification.

deviation of 304.92 hours (135.51), 331.76 hours (144.30), and 304.64 hours (141.42) for ABP 710, infliximab US, and infliximab EU, respectively. The GMs of PK parameters after a single dose were similar among the 3 groups. Likewise, both peak and overall exposures, as well as the time to reach maximum (peak) plasma concentration following drug administration were similar across the 3 treatment groups. Following a single dose, the GMs of AUC_{inf} and C_{max} for ABP 710 were 33 532.8 µg · h/mL and 128.14 µg/mL. The GMs of AUC_{inf} and C_{max} for infliximab US were 39 756.2 µg · h/mL and 131.90 µg/mL. The GMs of AUC_{inf} and C_{max} for infliximab EU were 35712.2 µg · h/mL and 125.48 µg/mL. Ratios of adjusted least-squares (LS) GMs (90%CIs) between ABP 710 and infliximab US for AUC_{inf} and C_{max} were 0.89 (0.812–0.985) and 0.97 (0.917–1.030). Ratios of adjusted LS GMs (90%CIs) between ABP 710 and infliximab EU for AUC_{inf} and C_{max} were 1.00 (0.904–1.096) and 1.02 (0.962–1.083). The 90%CIs for the ratios of

Table 3. Summary of Adverse Events

	ABP 710 (n = 49)	Infliximab US (n = 50)	Infliximab EU (n = 49)
Any treatment-emergent AE, n (%)	41 (83.7)	43 (86.0)	41 (83.7)
Any serious AE, n (%)	0 (0.0)	0 (0.0)	1 (2.0)
Treatment-emergent AEs reported in ≥5% of subjects in any treatment group, n (%)[a]			
Somnolence	28 (57.1)	30 (60.0)	21 (42.9)
Headache	15 (30.6)	16 (32.0)	16 (32.7)
Nasopharyngitis	0 (0.0)	7 (14.0)	6 (12.2)
Upper respiratory tract infection	3 (6.1)	3 (6.0)	1 (2.0)
Nausea	3 (6.1)	1 (2.0)	2 (4.1)
Lethargy	1 (2.0)	1 (2.0)	3 (6.1)

AE, adverse event; EU, European Union; US, United States.
[a]By preferred term.

Table 4. Immunogenicity

	ABP 710 (N = 49)	Infliximab US (N = 50)	Infliximab EU (N = 49)
Binding antibody assay positive (%)			
Day 1	0/49 (0.0)	0/50 (0.0)	0/49 (0.0)
Day 15	3/47 (6.4)	2/48 (4.2)	4/48 (8.3)
Day 36	16/47 (34.0)	11/49 (22.4)	13/48 (27.1)
End of study (day 57)	19/48 (39.6)	16/50 (32.0)	13/48 (27.1)
Anytime	21/49 (42.9)	18/50 (36.0)	16/49 (32.7)
Neutralizing antibody assay positive (%)			
Day 1	0/49 (0.0)	0/50 (0.0)	0/49 (0.0)
Day 15	0/47 (0.0)	0/48 (0.0)	0/48 (0.0)
Day 36	3/47 (6.4)	0/49 (0.0)	1/48 (2.1)
End of study (day 57)	6/48 (12.5)	5/50 (10.0)	9/48 (18.8)
Anytime	6/49 (12.2)	5/50 (10.0)	9/49 (18.4)
Neutralizing antibody assay positive as a percentage of positive (%)			
Day 1	0/0 (0.0)	0/0 (0.0)	0/0 (0.0)
Day 15	0/3 (0.0)	0/2 (0.0)	0/4 (0.0)
Day 36	3/16 (18.8)	0/11 (0.0)	1/13 (7.7)
End of study (day 57)	6/19 (31.6)	5/16 (31.3)	9/13(69.2)
Anytime	6/21 (28.6)	5/18 (27.8)	9/16 (56.3)

EU, European Union; US, United States.

LS GMs of AUC_{inf}, C_{max}, and AUC_{last} were fully contained within the 0.80 to 1.25 interval for which bioequivalence was evaluated in this average bioequivalence approach, thus confirming PK similarity between ABP 710 and infliximab RP. Because this was not an average bioequivalence and not a typical approach, the interval does not need to include one. The 90%CIs for the ratios of LS GMs of AUC_{inf}, C_{max}, and AUC_{last} for infliximab US and infliximab EU were also fully contained within the 0.80 to 1.25 interval for which bioequivalence was evaluated, thus confirming PK similarity between infliximab US and infliximab EU.

Safety

A summary of AEs is shown in Table 3. The most frequent treatment-emergent AEs (TEAEs) included somnolence, headache, nasopharyngitis, upper respiratory tract infection, nausea, and lethargy. The majority of TEAEs were mild or moderate. There were no deaths, serious AEs, or TEAEs leading to discontinuation from the study. The incidence of TEAEs was similar in the 3 treatment groups (ABP 710, 83.7%; infliximab US, 86.0%; infliximab EU, 83.7%).

Immunogenicity

There were no preexisting binding or neutralizing ADAs at baseline. All samples were tested against ABP 710, infliximab US, and infliximab EU. The ECL assay sensitivity for binding ADAs was <100 ng/mL for ABP 710, infliximab EU, and infliximab US screening and specificity assays. ADAs developed by day 15 in some subjects and increased through day 57, reaching 19 of 48 (39.6%) for ABP 710, 16 of 50 (32.0%) for infliximab US, and 13 of 48 (27.1%) for infliximab EU (Table 4).

Table 5. Percent Change in Clearance and Half-Life Between ABP 710 and Infliximab by Binding ADA Status in Healthy Subjects

		ABP 710		Infliximab US		Infliximab EU	
Parameter	ADA subset	AM (SD)	GM (% CV) [n]	AM (SD)	GM (% CV) [n]	AM (SD)	GM (% CV) [n]
CL (L/h)	Negative	0.008611 (0.00239)	0.008312 (27.33) [28]	0.008163 (0.0024481)	0.007842 (28.82) [32]	0.008528 (0.0023132)	0.008235 (27.31) [33]
	Positive	0.011520 (0.0031642)	0.011126 (27.39) [21]	0.011270 (0.0027790)	0.010979 (23.46) [18]	0.010888 (0.0027785)	0.010575 (25.33) [15]
% Change in CL[a]			33.9		40.0		28.4
$t_{1/2}$ (hr)	Negative	382.0 (85.08)	373.2 (22.27) [26]	398.4 (105.27)	382.7 (31.12) [30]	372.9 (88.94)	362.1 (25.48) [33]
	Positive	204.7 (123.56)	166.1 (79.74) [20]	214.2 (129.5)	177.3 (73.05) [17]	143.7 (107.49)	114.5 (76.96) [14]
% Change in $t_{1/2}$[a]			–55.5		–53.7		–68.4

ADA, antidrug antibody; AM, arithmetic mean; CL, clearance; CV, percent coefficient of variation; EU, European Union; GM, geometric mean; n, number of subjects with nonmissing values; SD, standard deviation; $t_{1/2}$, half-life; US, United States.
[a]Geometric means used to calculate percent difference of binding ADA positive vs binding ADA negative.

Neutralizing ADAs developed by day 36 in some subjects and persisted through day 57, while 6 of 48 (12.5%) subjects dosed with ABP 710, 5 of 50 (10.0%) subjects dosed with infliximab US, and 9 of 48 (18.8%) subjects dosed with infliximab EU tested positive for the development of neutralizing ADA.

PK parameters were similarly affected by binding ADA status for the 3 treatments. Statistical analysis confirmed that there was no interaction of treatment and binding ADA status on infliximab clearance (CL) and half-life. The percent change in CL and half-life for ABP 710 (33.9% and –55.5%, respectively) compared with infliximab EU (28.4% and –68.4%, respectively) and infliximab US (40.0% and –53.7%, respectively) (Table 5) was not statistically significant. In addition, there was no interaction of treatment and neutralizing ADA status on infliximab US CL. The percent change in CL for infliximab US (68.0%) compared with ABP 710 (43.5%) and infliximab EU (42.2%) (Table 6) was not statistically significant.

Discussion

Analytical results indicate that ABP 710 is analytically similar to both infliximab US and infliximab EU. ABP 710, infliximab US, and infliximab EU have similar potency, in vitro binding to TNF–α, Fc neonatal receptor, and Fc gamma receptor Type III, and in vitro effector function activity of antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity.[13] This study was designed to evaluate the PK similarity of the proposed biosimilar ABP 710 with infliximab RP. The study also evaluated the safety, tolerability, and immunogenicity of ABP 710 compared with infliximab RP when given to healthy subjects. This study was conducted in healthy subjects to provide a homogenous population for sensitive PK comparisons. A dose of 5 mg/kg provided sufficient exposure to accurately evaluate the PK in healthy subjects within the dose range with linear kinetics (3-20 mg/kg). A dose of 5 mg/kg is the maximum dose for most indications of the RP.[9]

This study design met US Food and Drug Administration and European Medicines Agency guidelines contributing to the development and approval of biosimilar agents.[9,10,18] The stepwise developmental approach is designed to determine the similarity of the proposed biosimilar to the RP with respect to analytical (physicochemical, structural, and functional) characteristics, PK profile and clinical efficacy, safety, tolerability, and immunogenicity. The results of analytical and functional similarity evaluations of ABP 710 and infliximab have been reported previously.[13] The results of this study further support that ABP 710 is similar to infliximab by demonstrating equivalence of ABP 710 to infliximab with respect to the PK profile.

Results of this phase 1 study demonstrate PK similarity between ABP 710 and both infliximab US and infliximab EU for the primary PK end point AUC_{inf} following a single 5-mg/kg IV infusion in healthy subjects. PK similarity was also demonstrated for the primary PK end point AUC_{inf} for the comparison of infliximab US to infliximab EU. In addition to the primary

Table 6. Percent Change in Clearance and Half-Life Between ABP 710 and Infliximab by Neutralizing ADA Status in Healthy Subjects

Parameter	ADA Subset	AM (SD)	ABP 710 GM (% CV) [n]	AM (SD)	Infliximab (US) GM (% CV) [n]	AM (SD)	Infliximab (EU) GM (% CV) [n]
CL (L/h)	Negative	0.008611 (0.00239)	0.008312 (27.33) [28]	0.008163 (0.0024481)	0.007842 (28.82) [32]	0.008528 (0.0023132)	0.008235 (27.31) [33]
	Positive	0.012213 (0.0028438)	0.011924 (24.75) [6]	0.013447 (0.0033394)	0.013171 (22.05) [5]	0.011943 (0.0027141)	0.011711 (20.66) [8]
% Change in CL[a]			43.5		68.0		42.2
$t_{1/2}$ (h)	Negative	382.0 (85.08)	373.2 (22.27) [26]	398.4 (105.27)	382.7 (31.12) [30]	372.9 (88.94)	362.1 (25.48) [33]
	Positive	81.29 (26.30)	77.0 (39.51) [6]	83.12 (10.72)	82.6 (13.09) [5]	76.92 (25.73)	73.1 (35.81) [8]
% Change in $t_{1/2}$[a]			–79.4		–78.4		–79.8

ADA, antidrug antibody; AM, arithmetic mean; CL, clearance; CV, percent coefficient of variation; EU, European Union; GM, geometric mean; n, number of subjects with nonmissing values; PK, pharmacokinetic; SD, standard deviation; $t_{1/2}$, half-life; US, United States.
[a]Geometric means used to calculate percent difference of neutralizing ADA positive vs neutralizing ADA negative.

end point, PK similarity was also demonstrated for the secondary PK end points (AUC_{last} and C_{max}) for the comparison of ABP 710 to both infliximab US and infliximab EU and for the comparison of infliximab US to infliximab EU. For all PK parameters, the 90%CIs of GMR were contained within the prespecified standard equivalence margin of 0.8 to 1.25. The safety and immunogenicity profiles were similar among the treatment groups. The safety profile is consistent with what is known about infliximab, and no new or unexpected safety signals were noted.

Conclusions

In conclusion, in this phase 1 study, after a single 5-mg/kg IV dose, the PK of ABP 710 was similar to that of infliximab US and infliximab EU. The safety, tolerability, and immunogenicity were also similar. In addition to the results of structural and functional characterization, these results provide further support that the proposed biosimilar ABP 710 is highly similar to infliximab RP.

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Conflicts of Interest

All authors are/were employees and stockholders of Amgen, Inc.

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Data-Sharing Statement

There is a plan to share data. This may include deidentified individual patient data for variables necessary to address the specific research question in an approved data-sharing request as well as related data dictionaries, study protocol, statistical analysis plan, informed consent form, and/or clinical study report. Data sharing requests relating to data in this paper will be considered after the publication date and (1) this product and indication (or other new use) have been granted marketing authorization in both the United States and Europe or (2) clinical development discontinues and the data will not be submitted to regulatory authorities. There is no end date for eligibility to submit a data-sharing request for these data. Qualified researchers may submit a request containing the research objectives, the Amgen product(s) and Amgen study/studies in scope, end points/outcomes of interest, statistical analysis plan, data requirements, publication plan, and qualifications of the researcher(s). In general, Amgen does not grant external requests for individual patient data for the purpose of reevaluating safety and efficacy issues already addressed in the product labeling. A committee of internal advisors reviews requests. If not approved, a Data Sharing Independent Review Panel may arbitrate and make the final decision. Requests that pose a potential conflict of interest or an actual or potential competitive risk may be declined at Amgen's sole discretion and without further

arbitration. Upon approval, information necessary to address the research question will be provided under the terms of a data-sharing agreement. This may include anonymized individual patient data and/or available supporting documents, containing fragments of analysis code where provided in analysis specifications. Further details are available at the following: http://www.amgen.com/datasharing

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