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A Randomized, Double-Blind Study Comparing Pharmacokinetics and Pharmacodynamics of Proposed Biosimilar ABP 798 With Rituximab Reference Product in Subjects With Moderate to Severe Rheumatoid Arthritis

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Abstract

ABP 798 is a proposed biosimilar to rituximab reference product (RP), an anti-CD20 monoclonal antibody. Pharmacokinetics (PK), pharmacodynamics (PD), and safety results from the comparative clinical study that evaluated the PK, PD, safety, efficacy, and immunogenicity of ABP 798 versus rituximab RP are presented here. Subjects with moderate to severe rheumatoid arthritis (RA) received 2 doses of ABP 798, United States-sourced RP (rituximab US) or European Union-sourced RP (rituximab EU), each consisting of two 1000-mg infusions 2 weeks apart. For the second dose (week 24), ABP 798- and rituximab EU-treated subjects received the same treatment; rituximab US-treated subjects transitioned to ABP 798. End points included area under the serum concentration-time curve from time 0 extrapolated to infinity and maximum observed serum concentration following the second infusion of the first dose (PK) and percentage of subjects with complete CD19+ cell depletion days 1-33 (PD). Primary analysis established PK similarity between ABP 798 and rituximab RP based on 90% confidence intervals of the adjusted geometric mean ratios being within a prespecified equivalence margin of 0.8 and 1.25. Complete CD19+ B-cell depletion on day 3 among groups confirmed PD similarity. These findings demonstrated PK/PD similarity between ABP 798 and rituximab RP in subjects with moderate to severe RA.

Keywords

ABP 798, biosimilar, rheumatoid arthritis, rituximab, pharmacokinetics

ABP 798 is being developed as a biosimilar to rituximab (Rituxan, MabThera),[1] a chimeric murine/human monoclonal immunoglobulin G1 kappa antibody directed against CD20 antigen expressed on B cells.[2] Rituximab reference product (RP) is approved for several indications, including moderate to severe rheumatoid arthritis (RA), non-Hodgkin's lymphoma, chronic lymphocytic leukemia, granulomatosis with

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[Correction added on 22 August 2020, after first online publication: the figures 1 and 2 are updated. The values of N is updated in the header of Table 7.]

polyangiitis and microscopic polyangiitis, and moderate to severe pemphigus vulgaris.[3,4] Rituximab has been used to treat rheumatologic diseases and hematologic malignancies for more than 20 years.[2] In moderately to severely active RA, rituximab RP is indicated in combination with methotrexate (MTX) for the treatment of adult patients who have had an inadequate response to 1 or more tumor necrosis factor (TNF) antagonist therapies.[3]

Rituximab RP primarily mediates B-cell lysis following binding to CD20; complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity are other potential mechanisms of action.[5] In RA, B cells are implicated in the pathogenesis of RA via production of rheumatoid factor (RF) and other autoantibodies, antigen presentation, T-cell activation, and/or proinflammatory cytokine production.[6] In the clinical setting, treatment with rituximab has been shown to induce depletion of peripheral B lymphocytes, with the majority of patients demonstrating near-complete depletion (as demonstrated by CD19 counts below the lower limit of quantification, 20 cells/μL) within 2 weeks after receiving the first dose, which lasted for at least 24 weeks or more than 3 years in rare instances.[7-9]

A biosimilar is a highly similar entity to a licensed biologic that shows no clinically meaningful differences compared with the originator RP in structure, purity, pharmacokinetics (PK), pharmacodynamics (PD), mechanism of action, potency, safety, and immunogenicity, notwithstanding any minor differences in some attributes.[10,11] Because of the complexity of biosimilar development and the potential clinical impact of any structural variations or other uncertainties, the regulatory pathway for approval is rigorous and systematic.[12] The European Medicines Agency (EMA) and Food and Drug Administration (FDA) guidelines recommend a comparative step-wise totality of evidence approach for the development of biosimilars. The first step is the comprehensive comparative analytical (structural and functional) characterization that forms the foundation for biosimilar development. This is followed by preclinical assessments, PK and PD evaluations, and finally a confirmatory clinical evaluation of efficacy, safety, and immunogenicity in a representative indication using sensitive population and sensitive end points.[10-12] Using this regulatory pathway, 2 rituximab biosimilars have been approved in the United States and European Union: Truxima (Celltrion) and Ruxience (Pfizer Inc.).[13-15] At the time of this publication, ABP 798 has not been approved by the FDA or other relevant regulatory agency, and the indications are as yet undetermined. Please consult ABP 798's later approved label in the relevant country for information regarding the approved uses for ABP 798 in your country.

The proposed biosimilar ABP 798 has the same amino acid sequence as rituximab RP and binds to CD20 like the RP, resulting in B-cell lysis. It is being developed with the same pharmaceutical form (except subcutaneous) and dosage strength as the FDA United States-licensed rituximab RP (rituximab US, Rituxan) and EMA EU-authorized rituximab RP (rituximab EU, MabThera). Analytical assessment has shown that ABP 798 is similar to rituximab RP.[16] Functional similarity of ABP 798 to rituximab RP was also demonstrated for binding properties (CD20, C1q, and Fcγ receptors), ADCC, and CDC.[16]

This comparative clinical study was conducted to evaluate the PK, PD, efficacy, safety, and immunogenicity of ABP 798 compared with rituximab RP in subjects with moderate to severe RA. Here we report the PK/PD and top-line safety and immunogenicity results.

The rituximab RP used in the study was sourced from the United States and the European Union to comply with regulatory requirements that mandate comparing the proposed biosimilar with a locally sourced RP. Pursuant to this requirement, the proposed biosimilar must be shown to be similar to the RP approved in the United States (for approval in the United States) or RP approved in the European Economic Area (for approval in the European Union). These comparisons along with the analytical assessments using the RP sourced from the United States and European Union complete the scientific bridge and provide the rationale for using a single-sourced comparator RP in future studies.[12]

Here, we report the results of PK, PD, overall safety, and immunogenicity of ABP 798 versus rituximab RP during dose period 1 (day 1 through first infusion of second dose); detailed efficacy, safety, and immunogenicity results over the entire study including dose period 2 have been reported elsewhere.

Materials and Methods

Subjects

Men or women $\geq$18 and $\leq$80 years old with an RA diagnosis, as determined by meeting 2010 American College of Rheumatology (ACR)/European League Against Rheumatism classification criteria for RA for a duration of at least 6 months, were eligible. Subjects must have had active RA, defined as $\geq$6 swollen joints and $\geq$6 tender joints (based on a 66/68 joint count excluding distal interphalangeal joints) at screening and baseline; and erythrocyte sedimentation ratio $\geq$ 28 mm/h and/or serum C-reactive protein (CRP) > 1.0 mg/dL at screening. Subjects must also have had inadequate response or intolerance to other disease-modifying antirheumatic drugs (which must include intolerance or

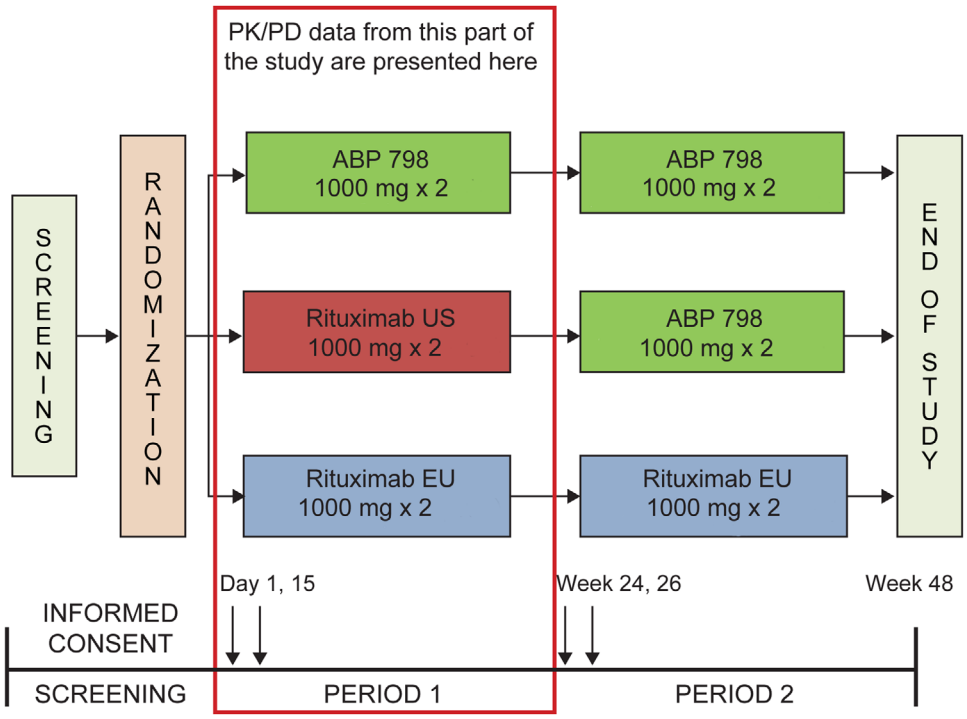

Figure 1. Study design.

inadequate response to 1 or more TNF inhibitor therapies).

Subjects were excluded if they had class IV RA (according to ACR-revised response criteria), Felty's syndrome (RA, splenomegaly, and granulocytopenia), history of prosthetic or native joint infection, active infection for which systemic anti-infectives were used ≤4 weeks or serious infection ≤8 weeks prior to first dose of the investigational product (IP) administration or malignancy ≤ 5 years (with the exception of treated and considered cured cutaneous squamous or basal cell carcinoma, in situ cervical cancer, or in situ breast ductal carcinoma).

Study Design

This was a randomized, double-blind, active-controlled study conducted in 57 centers in Bulgaria, Estonia, Germany, Hungary, Poland, and the United States (ClinicalTrials.gov NCT02792699). The study started on May 17, 2016; the last subject visit was on October 8, 2018. The study design is shown in Figure 1. This study was done in accordance with the terms of the Declaration of Helsinki, Good Clinical Practice guidelines, and all applicable regulatory requirements. The protocol was reviewed and approved by the relevant independent ethics committees for each center.

Study doses were based on approved doses in the United States and European Union for treating RA. A total of 2 doses were administered during the study; each dose consisted of 2 infusions of 1000 mg IP, 2 weeks apart (dose periods 1 and 2). In dose period 1, subjects were randomized (1:1:1) to receive 2 intravenous infusions of the first dose of either ABP 798, rituximab US (Rituxan; Genentech, Inc., South San Francisco, California), or rituximab EU (MabThera; Roche Pharma AG, Grenzach-Wyhlen, Germany) in a double-blinded fashion. In dose period 2 in week 24, subjects initially randomized to receive ABP 798 or rituximab EU arms received the second dose of the same treatment, and subjects initially randomized to receive rituximab US transitioned to receive ABP 798 for their second dose. The second dose may have been administered prior to week 24 in individual subjects (ie, any time from week 16 to week 24), as deemed necessary by the investigator.

Subject randomization was stratified by geographic region, seropositivity (RF positive and/or cyclic citrullinated peptide [CCP] positive vs RF negative, and CCP negative), and number of prior biologic therapies used for RA (1 vs >1).

Study duration was a total of up to 52 weeks, with the first dose administered on days 1 (week 0) and 15 (week 2), followed by the second dose in week 24 and week 26 and end-of-study (EOS) assessment in week 48 (or 24 weeks after the first infusion of the second dose for subjects retreated before week 24), plus a screening period of up to 4 weeks. The second dose may have been administered prior to week 24 in individual subjects, that is, anytime from week 16 to week 24 in

individual subjects if necessary in the opinion of the investigator.

All subjects on a stable dose of MTX (7.5-25 mg/week; oral or subcutaneous) for at least 8 weeks prior to receiving IP continued MTX for the duration of their participation in the study; dose reduction or change of route was allowed based on investigator discretion. Concomitant oral corticosteroids were permitted (≤10 mg prednisone or equivalent per day), if on a stable dose for at least 4 weeks before initiation of IP. Subjects receiving nonsteroidal anti-inflammatory drugs or low-potency analgesics could continue them in the study but must have been on a stable dose for ≥2 weeks prior to screening; dose reduction or discontinuation was allowed for safety reasons or standard of care, and temporary dose increases were permitted in case of flare.

An independent data-monitoring committee evaluated the safety data throughout the study, including an initial safety analysis after the first 18 subjects had received the first dose (1000 mg x 2 infusions of either ABP 798 or rituximab EU or rituximab US).

Sample Collection

Blood sampling for PK analysis was done on day 1 (predose, end of infusion [EOI], and 3 and 6 hours postdose), day 2 (24 hours postdose), day 3 (48 hours postdose), day 15 (predose, EOI, and 3, 6 hours postdose), day 16, and day 17. In addition, samples were collected in week 4 (day 29), week 8 (day 57), week 12 (day 85), and predose week 24, week 26, week 30, and week 48 (EOS).

Blood samples for CD19+ B-cell counts were collected predose (day 1), day 2 (24 hours postdose), day 3 (48 hours postdose), and then week 4, week 24, and week 48 (EOS).

Subjects were monitored throughout the study for adverse events (AEs), clinical laboratory results, concomitant medication use, and vital signs. Blood samples for antidrug antibody (ADA) assessments were collected at baseline, week 2, week 24, week 30, and EOS.

Serum Rituximab Measurement

Avidin Gold Multi-Array 96-well microwell plates were blocked with Blocker BLOTTO in Tris-buffered saline (TBS) buffer. After a wash step, the microplate was coated with Mu anti-ABP 798 1.51.1 Mab capture reagent solution prepared in Blocker BLOTTO in TBS. The calibration standards, matrix blank, quality controls, and test samples were diluted in sample diluent for the MRD100 and, after a wash step, were loaded into the microplate wells. The ABP 798 or rituximab RP in the samples was captured by the immobilized Mu anti-ABP 798 1.15.1 Mab coated on the microplate wells. Unbound ABP 798 or rituximab RP was removed by washing. Ruthenium-conjugated Mu anti-ABP 798 1.26.2 Mab detection reagent was added to the microplate wells to bind the captured ABP 798 or rituximab RP. Unbound detection reagent was removed by washing. Following the final wash, read buffer T was added to the microplate wells for detection of bound ruthenium-conjugated Mu anti-ABP 798 1.26.2 Mab. When the Avidin Gold Multi-Array 96-well microplate was electrically stimulated, the ruthenium label, in the presence of the coreactant tripropylamine in the read buffer, emitted light at 620 nm, which is measured using the MSD SECTOR Imager 6000 and was proportional to the amount of ABP 798 or rituximab RP bound by the capture reagent. The response-versus-concentration relationship was regressed. The assay dynamic range is 250 to 16 000 ng/mL, with 250 ng/mL as the lower limit of quantification.

CD19+ Cell Counting

Samples were sent for PD assessment (CD19+ cell counts) at a central laboratory (Q2 Solutions/Quest, Valencia, California; San Juan Capistrano, California; Heston, Middlesex, UK; West Lothian, Scotland, UK).

ADA Quantification

ADA quantification was performed by PPD, Richmond, Virginia. All available protocol-specified samples were evaluated for binding ADA using a 2-tiered validated electrochemiluminescent-based bridging immunoassay, consisting of a screening assay and a confirmatory (specificity) assay, capable of detecting antibodies binding to ABP 798, rituximab US, and rituximab EU. Samples with a signal-to-noise (S/N) ratio greater than the assay cut point (1.38 S/N) were analyzed to confirm the specificity of the response. Samples demonstrating signal depletion greater than the depletion cut point in the confirmatory assay (18.7%) were reported as binding antibody positive. The screening assay sensitivity is 5.99 ng/mL, and the confirmatory assay sensitivity is 4.67 ng/mL.

Samples confirmed to be positive for binding antibodies were subsequently tested in a cell-based assay, also consisting of screening and confirmatory assays to determine neutralizing activity against ABP 798, rituximab US, or rituximab EU. The screening assay cut point is 0.722, the confirmatory assay cut point is 1.22, and the sensitivity is 48.6 ng/mL.

PK and PD End Points

The PK end points included area under the serum concentration-time curve (AUC) from time 0 (on day 1 before the first infusion of the first dose) extrapolated to infinity (AUC_{inf}), maximum observed serum concentration (C_{max2}) following the second infusion of the first

dose, AUC from time 0 to 14 days postdose ($AUC_{0\text{-}14\ d}$), AUC from time 0 to week 12 ($AUC_{0\text{-}12\ wk}$), and C_{max1} following the first infusion of the first dose. Additional PK end points were time of C_{max} (t_{max}), last measurable serum concentration after the second infusion up to week 12 (C_{last}), terminal elimination half-life ($t_{1/2}$), the terminal elimination rate constant (λ_z), clearance (CL), mean residence time, percent of AUC extrapolation ($\%AUC_{extrap}$), and $AUC_{0\text{-}12\ wk}/AUC_{inf}$.

The PD end point was the percentage of subjects with complete depletion in CD19+ cell count from day 1 to day 3.

Safety End Points

Safety end points included treatment-emergent AEs, serious AEs (SAEs), clinically significant changes in laboratory values and vital signs, and incidence of ADAs. Samples testing positive for binding antibodies were also tested for neutralizing antibodies.

Protocol Amendments

The original protocol date was March 14, 2014. Protocol changes regarding enrollment criteria and PK/PD assessment were as follows. Inclusion criteria were amended to specify that subjects must have had intolerance or an inadequate response to 1 or more TNF inhibitor therapies and that subjects must have completed at least 4 weeks of a tuberculosis prophylaxis regimen prior to enrollment (December 1, 2016). Exclusion criteria were modified to allow subjects with a positive hepatitis B surface antigen or hepatitis B core antibody result to enroll if documentation of hepatitis B virus immunization was provided, to add adalimumab to the list of biologic therapies not allowed within 3 months prior to first dose of IP and to add ocrelizumab to the list of prohibited prior treatments (December 1, 2016). Revisions to the multiplicity adjustments and error rates for statistical analysis of PK variables were made (October 16, 2017). A secondary objective was added for demonstration of PK similarity of rituximab US and rituximab EU (March 20, 2018).

Statistical Analysis

Approximately 300 subjects were to be enrolled in this study. The sample size provided > 90% power to demonstrate similarity of the PK end points of AUC_{inf} and C_{max2} following the second infusion of the first dose. The majority of PK data were well above the lower limit of quantification (0.25 μg/mL), so assigning zero to values below the limit of quantification would have no impact on calculation of the means. PK similarity was assessed by comparing the 90% confidence interval (CI) for the geometric mean ratio (GMR) of the test (ABP 798) to reference (rituximab US or rituximab EU) and rituximab US to rituximab EU for AUC_{inf} and for C_{max2} following the second infusion of the first dose (dose period 1) with the bounds of 0.8 to 1.25, where $\alpha = 0.05$. The point estimates and CIs for the GMR were estimated from an analysis of the covariance model, using the PK parameter analysis set and adjusted for weight and geographic region. The PK analysis set consisted of all randomized subjects who received the full protocol-specified dose on day 1 and had an evaluable rituximab or ABP 798 serum concentration-time profile. The GMRs were obtained by exponentiating the difference of the means on the natural log scale. The CIs were obtained by exponentiating the CI for the difference between the means on the log scale. PK parameters were calculated using standard noncompartmental PK data analysis (Phoenix WinNonlin, version 6.3; Pharsight Corp., St. Louis, Missouri). Other PK end points, $AUC_{0\text{-}14\ d}$ after first infusion, $AUC_{0\text{-}12\ wk}$ after the first and second infusions of the first dose, and C_{max} after the first infusion of the first dose, were analyzed using the same methods as for AUC_{inf} and C_{max2}. In addition, sensitivity analyses were performed on the PK parameter analysis set, which included estimating the point estimates and CIs for the GMR using the primary statistical analysis model for the subgroups of subjects with negative-binding ADA status and negative neutralizing ADA status during the first dose period.

The PD similarity was evaluated descriptively by calculating the 90%CI of complete CD19+ cell depletion risk difference on day 3 between test and reference. Subjects with baseline values < 20 cells/μL or missing values were not evaluable for CD19+ depletion analyses. The point estimate and 90%CI were provided for rate difference and estimated using a generalized linear model with stratification factors as covariates. Descriptive statistics for CD19+ counts and the change from baseline were provided on day 3.

Subject incidences of AEs, grade ≥ 3 AEs, fatal AEs, SAEs, AEs leading to discontinuation from IP or discontinuation from study, and incidence of ADAs were summarized using descriptive statistics. Safety laboratory parameters and vital sign measurements were summarized using descriptive statistics at each scheduled visit.

Results

Subject Disposition and Characterization

A total of 436 subjects were screened, and 125 were screen failures. The top 3 reasons for screen failures were hepatitis B or C seropositivity (n = 38), failure to meet criteria for active RA (n = 27), and failure to meet negative tuberculosis criteria (n = 17). A total of 311 subjects were randomized (ABP 798, n = 104; rituximab EU, n = 104; rituximab US, n = 103); all

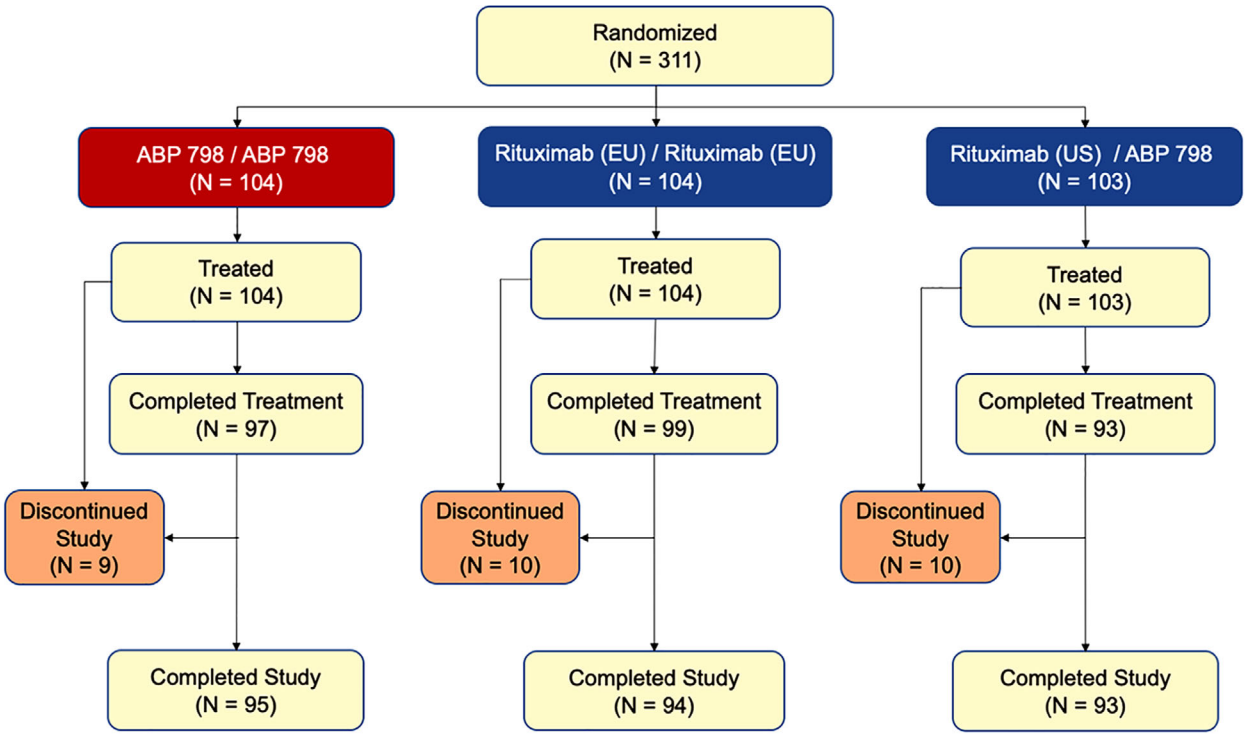

Figure 2. Subject disposition.

subjects were treated with at least 1 infusion of IP (Figure 2). Twenty-two subjects (7.1%) discontinued IP early, and the primary reason for discontinuation from IP was an AE (3.2%). Twenty-nine subjects (9.3%) discontinued the study, and the primary reason for study discontinuation was consent withdrawn (3.5%). No major imbalance as to subject counts was observed among treatment groups.

Key demographics and baseline characteristics were generally well-balanced among the 3 treatment groups, as summarized in Table 1. In the total population, 84.9% were female, 92.3% were Caucasian, and 90.7% were not Hispanic or Latino. The mean age ± standard deviation (SD) was 55.9 ± 10.91 years; 23.2% were 65 years of age or older. Overall, 246 subjects (79.1%) had a duration of RA of 5 years or more, with a mean duration of RA of 11.84 ± 8.194 years range, 0.6-44.0 years). The mean ± SD Disease Activity Score 28 joints C-reactive protein at study entry was 5.99 ± 1.015, indicative of active RA disease activity. The overall mean baseline weekly MTX dose was 16.4 ± 5.04 mg, with a minimum dose of 8 mg and a maximum dose of 25 mg weekly. Exposure to IP was comparable in both arms.

Pharmacokinetics

As presented in Figure 3, the mean concentration-time profiles through week 12 show a high degree of similarity among the 3 treatments.

The results of the PK end points for dose period 1 are presented in Table 2 and Figure 4. For AUC_{inf} and C_{max2}, PK similarity was established between ABP 798 and rituximab US and between ABP 798 and rituximab EU because the 90%CIs of the adjusted GMRs for both comparisons were within the prespecified equivalence margin of 0.8 and 1.25. PK similarity was also established between rituximab US and rituximab EU for AUC_{inf} and C_{max2}. In addition, 90%CIs for the GMRs for $AUC_{0\text{-}14\,d}$, $AUC_{0\text{-}12\,wk}$, and C_{max1} were also within the (0.8-1.25) margin for bioequivalence, thus, supporting PK similarity between ABP 798 and rituximab (Table 3 and Figure 4). The $t_{1/2}$ and CL were also similar across the 3 groups and are listed in Table 4.

Pharmacodynamics

The percentage of subjects showing complete CD19+ B-cell depletion from day 1 to day 3 was similar in ABP 798 and rituximab RP based on subjects with a baseline CD19 count ≥ 20 cell/μL (ABP 798, 92 of 97 [94.8%]; rituximab EU, 93 of 96 [96.9%]; and rituximab US, 90 of 97 [92.8%]; Table 5). CD19+ B-cell counts dropped rapidly following the first infusion of the first dose for ABP 798, rituximab RP sourced from the United States, and rituximab RP sourced from the European Union; counts for day 1, and day 2 are shown in Figure 5. These results indicate that the PD effects, as assessed by CD19+ B-cell depletion, were similar among the 3

Table 1. Demographics and Baseline Characteristics

	ABP 798 (n = 104)	Rituximab EU (n = 104)	Rituximab US (n = 103)
Age, years			
Mean (SD)	54.6 (10.70)	56.8 (11.34)	56.4 (10.66)
Race, n (%)			
American Indian or Alaska Native	2 (1.9)	0 (0.0)	0 (0.0)
Asian (other)	0 (0.0)	2 (1.9)	1 (1.0)
Black or African American	5 (4.8)	3 (2.9)	10 (9.7)
White	97 (93.3)	99 (95.2)	91 (88.3)
Other	0 (0.0)	0 (0.0)	1 (1.0)
Sex, n (%)			
Female	90 (80.5)	91 (87.5)	83 (80.6)
Weight (kg), mean (SD)	79.14 (17.039)	75.89 (18.047)	77.49 (17.907)
Height (cm), mean (SD)	164.41 (9.400)	163.51 (7.872)	165.22 (8.975)
Body mass index (kg/m^2), mean (SD)	29.39 (6.421)	28.50 (7.143)	28.38 (6.286)
Prior biologic use for RA, n (%)			
0	0 (0.0)	0 (0.0)	1 (1.0)
1	54 (51.9)	58 (55.8)	55 (53.4)
>1	50 (48.1)	46 (44.2)	47 (45.6)
Duration of RA (y), mean (SD)	11.37 (7.400)	11.69 (7.945)	12.48 (9.186)
Seropositivity, n (%)			
RF positive and/or CCP positive	85 (81.7)	91 (87.5)	88 (85.4)
RF negative and CCP negative	19 (18.3)	13 (12.5)	15 (14.6)
DAS28-CRP, mean (SD)	6.09 (1.035)	5.84 (1.006)	6.03 (0.997)
Baseline MTX dose (mg/week), mean (SD)	15.8 (5.29)	16.6 (5.11)	16.8 (4.68)
Geographic region, n (%)			
Eastern Europe	59 (56.7)	58 (55.8)	59 (57.3)
North Europe	38 (36.5)	40 (38.5)	39 (37.9)
Western Europe	7 (6.7)	6 (5.8)	5 (4.9)

DAS28-CRP, Disease Activity Score 28 joints-C-reactive protein; MTX, methotrexate; RA, rheumatoid arthritis; RF, rheumatoid factor; SD, standard deviation.

Table 2. Ratio of Adjusted Least-Squares Geometric Means for AUC_{inf} and C_{max2} of ABP 798, Rituximab US, and Rituximab EU

Treatment and Comparison	AUC_{inf}	C_{max2} (following second infusion of first dose)
Ratio of least-squares GM (90%CI)		
ABP 798 versus rituximab US	0.96 (0.89-1.03)	0.98 (0.94-1.03)
ABP 798 versus rituximab EU	0.88 (0.82-0.95)	0.94 (0.89-0.98)
Rituximab US versus rituximab EU	0.92 (0.86-1.00)	0.95 (0.91-1.00)

AUC_{inf}, area under the serum concentration-time curve from time 0 extrapolated to infinity; CI, confidence interval; C_{max2}, maximum observed serum concentration following the second infusion of first dose; GM, geometric mean.

arms, confirming PD similarity in ABP 798 and rituximab RP.

Safety

The safety analysis was conducted in all 311 subjects who received IP (Table 6). During dose period 1 (from day 1 until the first infusion of the second dose), the frequency, type, and severity of AEs were similar in the treatment groups. A total of 15 subjects experienced ≥ grade 3 AEs (ABP 798, 4 [3.8%]; rituximab EU, 6 [5.8%]; rituximab US, 4 [3.9%]). None were considered related to treatment, and all resolved. AEs led to IP or study discontinuation in 8 subjects (ABP 798, 3 [2.9%], rituximab EU, 1 [1.0%]; rituximab US, 4 [3.9%]). There were no trends indicative of clinically important abnormalities in laboratory assessments or vital signs. Additional safety data will be presented elsewhere.

Immunogenicity

All 311 subjects had samples available for immunogenicity assessments (Table 7). Following administration of ABP 798 or rituximab RP, during dose period 1, 13 subjects (13.4%) in the ABP 798 group, 10 subjects (10.6%) in the rituximab EU group, and 19 subjects (19.6%) in the rituximab US group developed binding ADAs. During this dose period 1, eight subjects (8.2%)

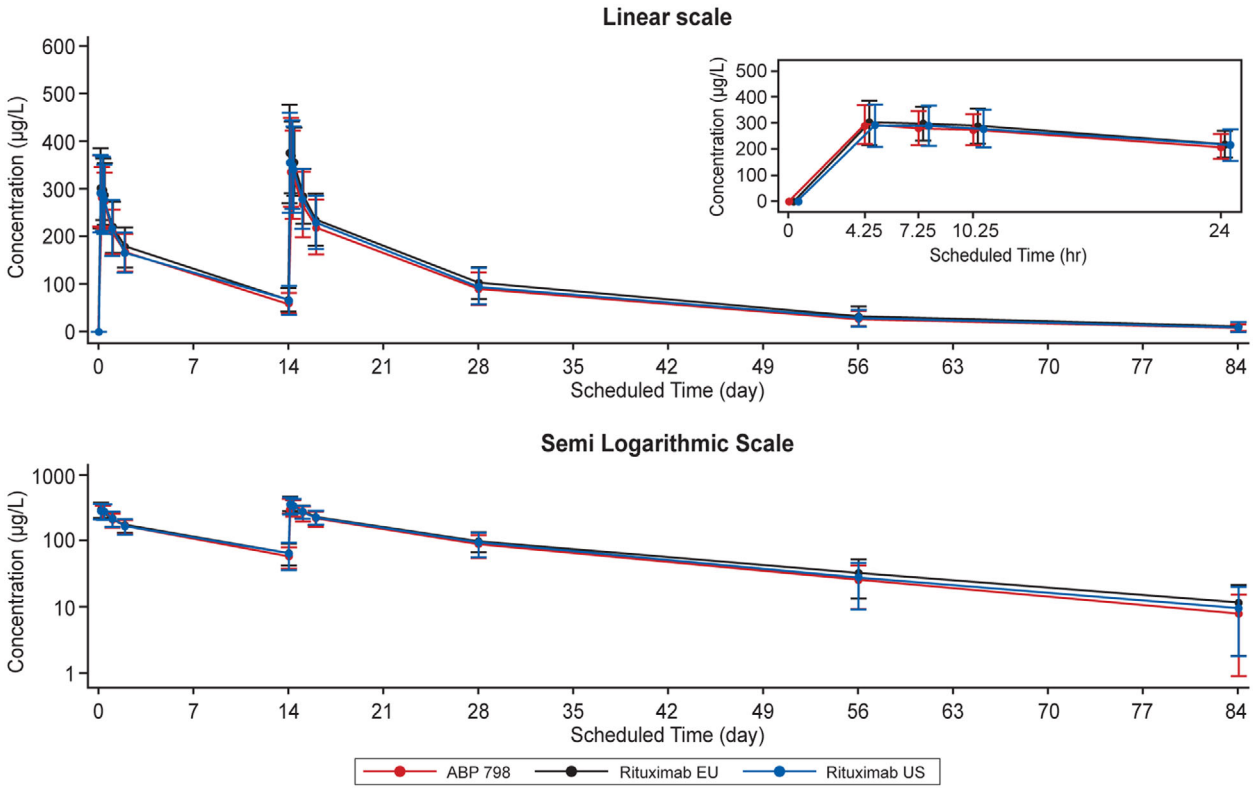

Figure 3. Mean ± SD serum concentrations over time by treatment through week 12.

Table 3. Comparison of Secondary PK End Points

Treatment and Comparison	$AUC_{0\text{-}12\ wk}$ (µg·h/mL)	$AUC_{0\text{-}14\ d}$ (µg·h/mL)	C_{max1} (µg/mL)
Ratio of least-squares GM (90%CI)			
ABP 798 versus rituximab US	0.96 (0.90-1.03)	0.97 (0.92-1.03)	0.99 (0.95-1.04)
ABP 798 versus rituximab EU	0.90 (0.84-0.96)	0.94 (0.89-1.00)	0.95 (0.90-1.00)
Rituximab US versus rituximab EU	0.94 (0.87-1.00)	0.97 (0.91-1.02)	0.95 (0.91-1.00)

$AUC_{0\text{-}12\ wk}$, area under the serum concentration-time curve from time 0 to week 12; $AUC_{0\text{-}14\ d}$, area under the serum concentration-time curve from time 0 to day 14; CI, confidence interval; C_{max1}, maximum observed serum concentration following the first infusion of the first dose; GM, geometric mean; PK, pharmacokinetic.

in the ABP 798 group, 2 subjects (2.1%) in the rituximab EU, and 8 subjects (8.2%) in the rituximab US group developed neutralizing ADAs (Table 6). The difference in the incidence of binding and neutralizing ADAs was not statistically significant between the 3 groups.

PK-ADA Relationship

Summary of PK parameters from sensitivity analyses performed in a subgroup of subjects with negative-binding ADA status in dose period 1 and those with negative neutralizing ADA status in dose period 1 are presented in Figure 4. PK parameters from these subgroups, without the interference of ADA, were similar between treatments; no significant differences were observed.

Discussion

The results presented here demonstrate that ABP 798 has PK/PD similar to rituximab RP. The PK similarity demonstration was based on 90%CI for AUC_{inf} and C_{max2} being within a prespecified equivalence margin of 0.8 and 1.25 for overall exposure, which is the standard for demonstrating PK bioequivalence. This was supported by results for the ratio of least-squares geometric means for ABP 798 and rituximab RP of the PK parameters $AUC_{0\text{-}12\ wk}$, $AUC_{0\text{-}14\ d}$, and C_{max1} and the similarity of the individual PK parameters for ABP 798 and rituximab RP of %AUC, $AUC_{0\text{-}12\ weeks}$, AUC_{inf}, CL, $t_{1/2}$, and $\%AUC_{extrap}$, $AUC_{0\text{-}14\ d}$, $AUC_{0\text{-}12\ wk}$, and C_{max1}. The PK characteristics for ABP 798 and rituximab RP here were shown to be consistent with those previously reported for rituximab in the RA patient population.[17]

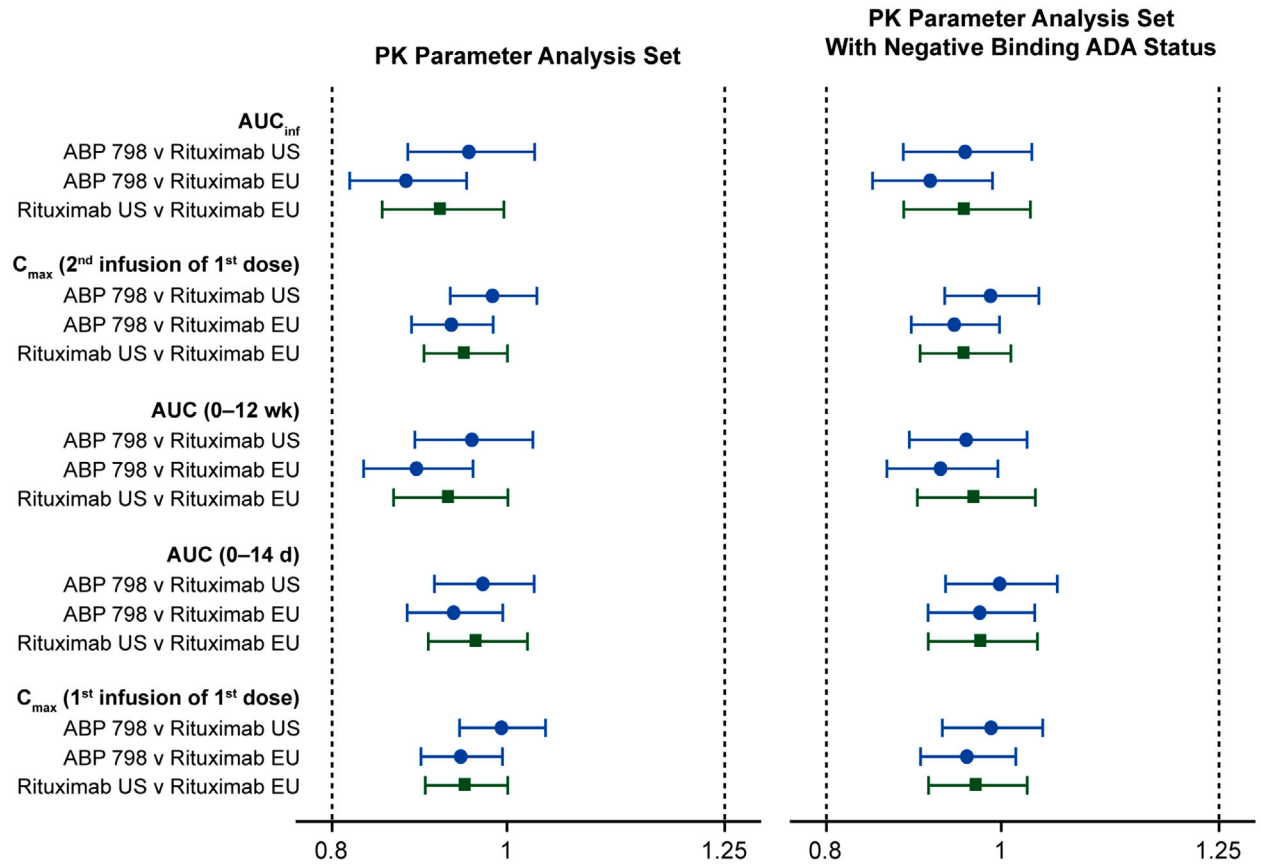

Figure 4. Ratio of geometric means and 90% confidence intervals for pharmacokinetic (PK) parameters in all subjects and negative binding antidrug antibody (ADA) subgroup. AUC_{inf}, area under the serum concentration-time curve from time 0 extrapolated to infinity; C_{max}, maximum observed serum concentration; $AUC_{0\text{-}12\ wk}$, area under the serum concentration-time curve from time 0 to week 12; $AUC_{0\text{-}14\ d}$, area under the serum concentration-time curve from time 0 to day 14.

Table 4. Descriptive Summary of Additional PK Parameters for ABP 798, Rituximab EU, and Rituximab US

PK Parameter, Mean (SD)	ABP 798	Rituximab US	Rituximab EU
n	96	96	98
$t_{1/2}$, h	355.30 (108.57)	355.42 (110.81)	393.68 (121.01)
n	94	94	96
CL, L/h	0.014 (0.076)	0.013 (0.01)	0.012 (0.00)
n	101	98	103
$\%AUC_{extrap}$, %	3.17 (3.17)	3.24 (2.96)	4.10 (3.46)
n	96	96	98
$AUC_{0\text{-}12\ wk}/AUC_{inf}$	0.97 (0.02)	0.97 (0.03)	0.96 (0.03)

AUC, area under the serum concentration-time curve; $\%AUC_{extrap}$, percent of AUC extrapolation; $AUC_{0\text{-}12\ wk}$, AUC from 0 to 12 weeks; AUC_{inf}, AUC from time 0 extrapolated to infinity; CL, clearance; PK, pharmacokinetic; SD, standard deviation; $t_{1/2}$, terminal elimination half-life.

The primary mechanism of action of rituximab involves depletion of B cells through multiple mechanisms. The present study also demonstrated similar PD effects of CD19+ B-cell complete depletion among subjects in the 3 study groups (ABP 798, rituximab US, rituximab EU) following administration of the same doses, thereby confirming that ABP 798 is similar to rituximab RP.

In addition to establishing PK/PD similarity in ABP 798 and rituximab RP, the present study also established PK/PD similarity in rituximab sourced from US and EU (rituximab US and rituximab EU) and allowed the establishment of a scientific bridge.

The safety analysis revealed that the frequency, type, and severity of AEs were similar between treatment groups during the dose period 1, with no clinically

Table 5. Statistical Comparison of CD19+ Complete Depletion on Day 3

	ABP 798 (n = 104)	Rituximab EU (n = 104)	Rituximab US (n = 103)
Percent of subjects with CD19+ cell complete depletion, n/N1 (%)	92/97 (94.8)	93/96 (96.9)	90/97 (92.8)
Risk difference[a] (ABP-rituximab)		−2.45	1.87
90%CI		−10.83-5.93	−6.10-9.84

CI, confidence interval.
Note: n is the number of subjects meeting the criteria at the visit; NI is the number of subjects who were randomized, had an assessment at the visit, and had a nonmissing baseline result ≥ 20 cells/μL.
[a]Based on a generalized linear model adjusted for geographic region, seropositivity, and prior biologic use as covariates in the model.

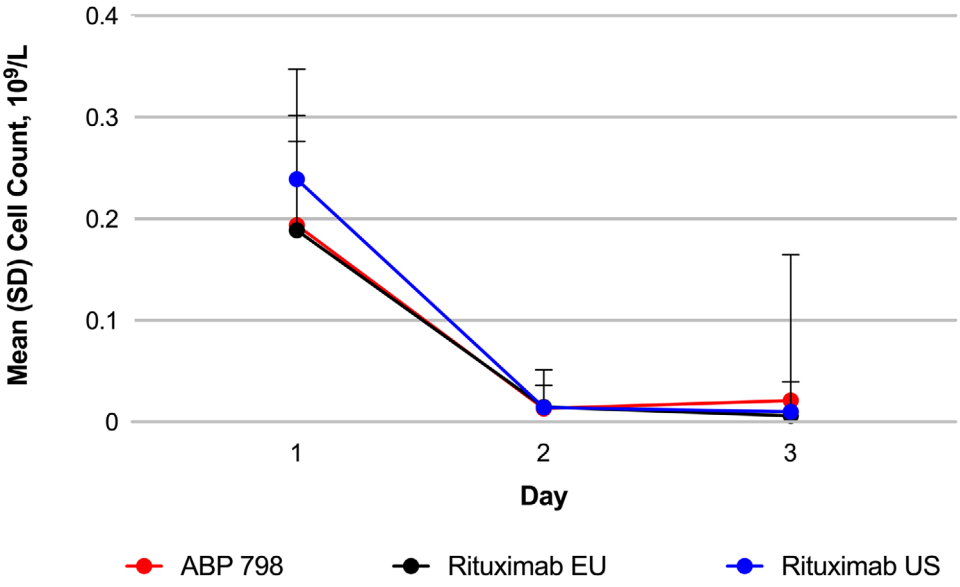

Figure 5. Mean + SD CD19+ B-cell counts from day 1 to day 3. SD, standard deviation.

meaningful differences discerned; these were consistent with the safety profile of rituximab RP. Although there appeared to be a trend for lower immunogenicity with rituximab EU, differences were not significant. A similar proportion of subjects developed binding and neutralizing ADAs over the course of the study; the development of ADAs was similar across treatment arms during dose period 1. PK parameters, without the interference of ADA, were similar between treatments.

The current study was conducted in an RA patient population since the profound and prolonged B-cell depletion mediated by rituximab precluded study conduct in healthy subjects. Even though regulatory guidelines for biosimilar development recommend that PK studies be generally conducted in healthy subjects, as this allows a sensitive PK comparison in a homogeneous population, it must be noted that the RA population provides stable concomitant treatment use and low flare rates in patients with controlled disease. In addition, rituximab RP has shown a linear PK in RA that is known to be stable over time with between-subject variability of about 40%, which allowed for sensitive PK comparisons in this study. Also, the RA population provides a homogenous CD19+ cell baseline that permits sensitive evaluation of potential PD differences.

Conclusions

The results presented here demonstrate that ABP 798 has PK/PD similar to rituximab RP in patients with active moderate to severe RA on a background of MTX who had an inadequate response or intolerance to 1 or more TNF antagonist therapies. Importantly, top-line safety, and immunogenicity were similar in ABP 798 and rituximab RP; detailed safety results are presented elsewhere.[18] Given that human PK/PD studies are fundamental components establishing similarity between a proposed biosimilar and the originator RP during biosimilar development, these results support the clinical development of ABP 798 as a proposed biosimilar to rituximab.

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Table 6. Overall Safety Results[a]

n (%)	ABP 798 (N = 104)	Rituximab EU (N = 104)	Rituximab US (N = 103)
Safety			
Any adverse event	52 (50.0)	44 (42.3)	44 (42.7)
Any ≥ grade 3 adverse event	4 (3.8)	6 (5.8)	4 (3.9)
Any fatal adverse event	0 (0.0)	0 (0.0)	0 (0.0)
Any serious adverse event	4 (3.8)	5 (4.8)	5 (4.9)
Any ≥ grade 3 adverse event	4 (3.8)	6 (5.8)	4 (3.9)
Pneumonia	0 (0.0)	1 (1.0)	0 (0.0)
Alanine aminotransferase increased	1 (1.0)	0 (0.0)	0 (0.0)
Capillary leak syndrome	1 (1.0)	0 (0.0)	0 (0.0)
Coronary artery disease	1 (1.0)	0 (0.0)	0 (0.0)
Diverticulitis	1 (1.0)	0 (0.0)	0 (0.0)
Essential hypertension	1 (1.0)	0 (0.0)	0 (0.0)
Acute myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)
Chronic cardiac failure	0 (0.0)	0 (0.0)	1 (1.0)
Dermatitis allergic	0 (0.0)	0 (0.0)	1 (1.0)
Erysipelas	0 (0.0)	0 (0.0)	1 (1.0)
Forearm fracture	0 (0.0)	1 (1.0)	0 (0.0)
Lymphopenia	0 (0.0)	1 (1.0)	0 (0.0)
Sepsis syndrome	0 (0.0)	1 (1.0)	0 (0.0)
Tubulointerstitial nephritis	0 (0.0)	0 (0.0)	1 (1.0)
Upper respiratory tract infection	0 (0.0)	1 (1.0)	0 (0.0)
Urinary tract infection	0 (0.0)	1 (1.0)	0 (0.0)
Any adverse event leading to discontinuation of IP/study	3 (2.9)	1 (1.0)	4 (3.9)

IP, investigational product; N, subjects with a binding negative or no result at baseline and at least a postbaseline result; n, number of subjects with event.
[a]Events occurring during the first study period (day 1 until the first infusion of the second dose).

Table 7. Immunogenicity Findings[a]

Finding, n (%)	ABP 798 (N = 97)	Rituximab EU (N = 94)	Rituximab US (N = 97)
Developing antibody incidence			
Binding antibody positive	13 (13.4%)	10 (10.6%)	19 (19.6%)
Neutralizing antibody positive	8 (8.2%)	2 (2.1%)	8 (8.2%)

N, subjects with a binding negative or no result at baseline and at least a postbaseline result; n, number of subjects with event; IP, investigational product.
[a]Day 1 until the first infusion of the second dose.

Conflicts of Interest

Gerd Burmester received consulting fees from Amgen, Sandoz, and Biogen and has received speaker honoraria from Biogen. David Chien, Vincent Chow, Melissa Gessner, and Jean Pan are employees and stockholders of Amgen. Stanley Cohen has received consulting fees as well as grant and research support from Amgen, AbbVie, Boehringer-Ingelheim, Genentech, Lilly, and Pfizer.

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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, also related data dictionaries, study protocol, statistical analysis plan, informed consent form, and/or clinical study report. Data-sharing requests relating to data in this article will be considereded 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

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Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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