Clinical similarity of biosimilar ABP 501 to adalimumab in the treatment of patients with moderate to severe plaque psoriasis: A randomized, double-blind, multicenter, phase III study

Kim Papp, MD, PhD,[a,b] Herve Bachelez, MD, PhD,[f] Antonio Costanzo, MD,[g] Peter Foley, MD,[c,h] Melinda Gooderham, MD,[b,i] Primal Kaur, MD,[j] Joanna Narbutt, MD, PhD,[k] Sandra Philipp, MD, PhD,[l] Lynda Spelman, MD,[d,m] Jolanta Weglowska, MD,[n] Nan Zhang, PhD,[j] and Bruce Strober, MD, PhD[e,o]

Waterloo and Peterborough, Ontario, Canada; Carlton, Woolloongabba, and Melbourne, Australia; Farmington, Connecticut; Paris, France; Rome, Italy; Thousand Oaks, California; Lodz and Wroclaw, Poland; and Berlin, Germany

From K Papp Clinical Research, Waterloo[a]; Probity Medical Research in Waterloo,[b] Carlton,[c] Woolloongabba,[d] and Farmington[e]; Sorbonne Paris Cité Université Paris Diderot, Department of Dermatology, Assistance Publique-Hopitaux de Paris Saint-Louis Hospital[f]; Dermatology Unit, Department of Neuroscience, Mental Health and Sensory Systems (NeSMOS) Department, Sapienza University of Rome[g]; Department of Medicine (Dermatology), University of Melbourne, St Vincent's Hospital Melbourne, Skin and Cancer Foundation Inc[h]; SKiN Centre for Dermatology, Peterborough[i]; Amgen Inc, Thousand Oaks[j]; Dermoklinika Medical Centre, Lodz[k]; Psoriasis Research and Treatment Center, University Hospital Charité, Berlin[l]; Veracity Clinical Research, Woolloongabba[m]; Regional Hospital, Department of Dermatology, Wroclaw[n]; and University of Connecticut Health Center.[o]

Amgen Inc funded this study and participated in the design and conduct of the study; collection, management, analysis, and interpretation of data; and preparation, review, and approval of the manuscript. All authors were involved in the decision to submit the manuscript for publication, and had the right to accept or reject comments or suggestions. A medical writer employed by MedVal Scientific Information Services LLC and funded by Amgen Inc participated in the writing of this manuscript and is acknowledged.

Disclosures: Dr Papp has served as a consultant, speaker, scientific officer, steering committee member, investigator, or advisory board member for 3M, Abbott, Akesis, Akros, Alza, Amgen, Astellas, Baxter, BMS, Boehringer Ingelheim, CanFite, Celgene, Cipher, Dermira, Eli Lilly, Forward Pharma, Funxional Therapeutics, Galderma, GSK, Isotechnika, Janssen, Johnson & Johnson, Kirin, Kyowa, Lypanosys, MedImmune, Merck-Serono, Mitsubishi Pharma, MSD, Novartis, Pfizer, Roche, Takeda, UCB, Valeant, and Vertex. Dr Bachelez has served as a consultant, speaker, steering committee member, investigator, or advisory board member for AbbVie, Amgen, Baxalta, Boehringer-Ingelheim, Celgene, Janssen, LEO Pharma, Lilly, MSD, Novartis, Pfizer, and Takeda, and received grant support from Pfizer. Dr Costanzo has been an investigator/consultant and speaker for AbbVie, Amgen, Celgene, Janssen, Lilly, Novartis, and Pfizer. Dr Foley has served as a consultant, investigator, speaker, and/or advisor for, and/or received travel grants from Galderma, LEO Pharma/Peplin, Ascent, Clinuvel, Janssen-Cilag, Eli Lilly, Australian Ultraviolet Services, Roche, CSL, 3M/iNova/Valeant, GSK/Stiefel, Abbott/AbbVie, Biogen Idec, Merck Serono, Schering-Plough/MSD, Wyeth/Pfizer, Amgen, Novartis, Celgene, Aspen, Boehringer Ingelheim, and BMS. Dr Gooderham has been an investigator, consultant, and/or speaker for AbbVie, Amgen, Boehringer Ingelheim, Celgene, Coherus, Dermira, Galderma, Janssen, LEO Pharma, Lilly, Medimmune, Merck Serono, Novartis, Regeneron, Roche, Sanofi Genzyme, Takeda, and Pfizer. Dr Kaur is an Amgen employee and stockholder. Dr Narbutt is an investigator for Amgen. Dr Philipp has been investigator, consultant, and/or speaker for AbbVie, Amgen, Almirall, Biogen, Boehringer-Ingelheim, BMS, Celgene, Janssen, LEO Pharma, Lilly, MSD, Novartis, Pfizer, and UCB. Dr Spelman has served on advisory boards for Galderma, Novartis, and AbbVie; undertakes sponsored clinical research for AbbVie, Amgen, Anacor, Ascend Biopharmaceuticals, Astellas, Australian Wool Innovation Limited, Blaze Bioscience, Celgene, Dermira, Eli Lilly, Galderma, Genentech, GlaxoSmith Kline, Kythera, LEO Pharma, Merck, Novartis, Phosphagenics, Regeneron, and Trius; and has received sponsored travel from Abbott, Novartis, and Janssen-Cilag. Dr Weglowska has been an investigator for Amgen, Pfizer, Novartis, Galderma, Eli Lilly, Dermira, Roche, Janssen-Cilag, Coherus, Genentech, LEO Pharma, Merck, Mylan, and Regeneron. Dr Zhang is an Amgen employee and stockholder. Dr Strober has served on a speakers bureau for AbbVie, receiving honoraria; is a consultant and advisory board member for AbbVie, Amgen, Astra Zeneca, Celgene, Dermira, Forward Pharma, Janssen, LEO Pharma, Eli Lilly, Cutanea-Maruho, Medac, Novartis, Pfizer, Sun, Stiefel/GlaxoSmithKline, UCB, and Boehringer Ingelheim, receiving honoraria for all; is an investigator for AbbVie, Amgen, GlaxoSmithKline, Novartis, Lilly, Janssen, Merck, XenoPort, Xoma, Celgene (payments to the University of Connecticut); is scientific director for Corrona Psoriasis Registry, receiving a consulting fee; received grant support to the University of Connecticut for a fellowship program from AbbVie and Janssen.

Presented as an abstract by Dr Papp et al at the 24th Annual Congress of the European Academy of Dermatology and Venereology, Copenhagen, Denmark, October 7-11, 2015; in Strober B, et al. Evaluation of efficacy and safety of ABP 501 in a phase 3 study in subjects with moderate to severe plaque psoriasis: 52-week results. J Am Acad Dermatol 2016;74(Suppl):AB249; and in Gooderham M, et al. Single transition from adalimumab to ABP 501: evaluation of immunogenicity in a phase 3 study in subjects with moderate to severe plaque psoriasis. J Am Acad Dermatol 2016;74(Suppl 1):AB275.

Accepted for publication December 8, 2016.

Reprint requests: Kim Papp, MD, PhD, K Papp Clinical Research, 135 Union St E, Waterloo, Ontario, Canada N2J 1C4. E-mail: kapapp@probitymedical.com.

Published online March 10, 2017.

0190-9622

© 2016 by the American Academy of Dermatology, Inc. Published by Elsevier, Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

http://dx.doi.org/10.1016/j.jaad.2016.12.014

Background: ABP 501 is a biosimilar of adalimumab.

Objective: We sought to compare the efficacy and safety of ABP 501 with adalimumab.

Methods: This 52-week, double-blind study randomized patients with moderate to severe psoriasis to ABP 501 or adalimumab. At week 16, those with 50% or more improvement in Psoriasis Area and Severity Index score from baseline on ABP 501 continued the same treatment, whereas adalimumab-treated patients were rerandomized to adalimumab or ABP 501. Clinical similarity in Psoriasis Area and Severity Index percent improvement from baseline to week 16 (primary end point) was established if the point estimate of treatment difference and its 2-sided 95% confidence interval between groups was within equivalence margin of ±15. Patients, including those undergoing a single transition at week 16, were evaluated for safety and immunogenicity.

Results: Psoriasis Area and Severity Index percent improvement at week 16 was 80.9 for ABP 501 and 83.1 for adalimumab (least-square mean difference −2.18 [95% confidence interval −7.39 to 3.02]). Adverse events (67.2% [117/174] vs 63.6% [110/173]) and antidrug antibody incidence (55.2% [96/174] vs 63.6% [110/173]) for ABP 501 vs adalimumab were similar. Safety, including immunogenicity, was similar among groups after single transition (week 20).

Limitations: The 52-week data are not reported here.

Conclusions: ABP 501 was shown to be clinically similar to adalimumab. Safety and immunogenicity were not impacted immediately after single transition (adalimumab to ABP 501). (J Am Acad Dermatol 2017;76:1093-102.)

Key words: ABP 501; adalimumab; biosimilar; efficacy; equivalence; psoriasis; safety.

CAPSULE SUMMARY

- ABP 501 is a biosimilar of adalimumab.
- Phase III clinical trial results demonstrated clinical equivalence between ABP 501 and adalimumab at week 16, and similarity in safety and immunogenicity 4 weeks after single transition.
- These findings support clinical similarity between ABP 501 and adalimumab.

Biologic treatments are highly effective for moderate to severe psoriasis[1-3]; however, the increasingly high costs associated with their use may be a treatment barrier for some patients.[4] Biosimilars are biologic drugs being developed as similar therapeutic and potentially lower-cost alternatives to already approved biologic treatments.[5] Biosimilars are not the same as generic, chemically derived drugs because of the complexities and proprietary processes involved in developing biological proteins, which can result in structural and functional differences between the biosimilar and its reference drug. As a result, regulatory agencies require that biosimilars demonstrate similarity based on a stepwise totality of evidence approach in structure, function, and clinical efficacy and safety to the reference drug.[5-7] For clinical trials, regulatory guidance recommends the inclusion of sensitive populations to detect any clinically meaningful differences between the proposed biosimilar and reference product.[6,8]

ABP 501 (AMJEVITA [adalimumab-atto], Amgen Inc, Thousand Oaks, CA) is a biosimilar of adalimumab (Humira, AbbVie Inc, North Chicago, IL),[9] a human IgG1 monoclonal antibody that binds to soluble and membrane-bound tumor necrosis factor (TNF)-alfa (anti—TNF-alfa). Both ABP 501 and adalimumab are indicated to treat several chronic inflammatory diseases including psoriasis.[9,10] Analytical assessment and human pharmacokinetic evaluation demonstrated similarity between ABP 501 and adalimumab.[11-13] To establish clinical similarity, 2 phase III studies were conducted to compare efficacy, safety, and immunogenicity of ABP 501 with adalimumab: 1 in patients with moderate to severe plaque psoriasis (NCT01970488) and 1 in patients with moderate to severe rheumatoid arthritis (NCT01970475).[14] Conducting 2 studies provided an opportunity to evaluate clinical similarity in different sensitive populations: immunocompromised patients with rheumatoid arthritis and immunocompetent patients with psoriasis.

Herein we report the results of a randomized, double-blind, multicenter phase III study designed to demonstrate clinical similarity in the efficacy,

Abbreviations used:

ADA:	antidrug antibody
CI:	confidence interval
PASI:	Psoriasis Area and Severity Index
PASI 50:	50% or more improvement in Psoriasis Area and Severity Index score from baseline
PASI 75:	75% or more improvement in Psoriasis Area and Severity Index score from baseline
PASI 90:	90% or more improvement in Psoriasis Area and Severity Index score from baseline
PASI 100:	100% improvement in Psoriasis Area and Severity Index score from baseline
SAE:	serious adverse event
TEAE:	treatment-emergent adverse event
TNF:	tumor necrosis factor

safety, and immunogenicity of biosimilar ABP 501 compared with adalimumab in the treatment of patients with moderate to severe plaque psoriasis.

METHODS

Study population

Patients 18 to 75 years of age who had stable moderate to severe plaque psoriasis for at least 6 months and were candidates for phototherapy or systemic therapy and who had inadequately responded to or were unable to tolerate or receive at least 1 conventional systemic therapy were eligible for enrollment. Patients were required to have disease involvement of 10% or more of the body surface area, a Psoriasis Area and Severity Index (PASI) score of 12 or more (scores range from 0-72, with higher scores indicating more severe disease),[15] and a static Physician Global Assessment of at least moderate severity (6-point scale, assessment ranges from clear to very severe).[16] Patients must have had no evidence of active tuberculosis according to local guidelines; women of childbearing potential were required to use contraception. Patients with nonplaque psoriasis, drug-induced psoriasis, or any other skin condition that might interfere with evaluation of efficacy were excluded. Patients who previously used adalimumab or a biosimilar of adalimumab, or any 2 or more biologics for psoriasis were also excluded. Other therapies not permitted during the study included ultraviolet B light and most topical therapies, except upper midstrength to least potent topical steroids and bland emollients, within 14 days of first study treatment dose; ultraviolet A light (with or without psoralen), excimer laser, and nonbiologic systemic therapies within 28 days of first study treatment dose; etanercept within 1 month before screening; and any other anti−TNF agent or ustekinumab within 3 months before screening.

This study was conducted in accordance with the current International Conference on Harmonization Good Clinical Practice Guidelines and the Declaration of Helsinki. The study protocol was approved by the institutional review board or independent ethics committee at each participating site and adhered to all local regulatory requirements including data protection requirements. Written informed consent was obtained from each patient before study enrollment.

Study design

This randomized, double-blind, multicenter, active-controlled phase III trial consisted of a 4-week screening period, after which eligible patients were randomized 1:1 to receive treatment with ABP 501 or adalimumab (Fig 1). Randomization was carried out by a computer-generated randomization schedule with stratification by prior biologic use and geographic region. Patients were allocated by an interactive voice and web response system. During the study, the patients, investigators, study center personnel, and sponsor remained blinded to the patient's randomized treatment assignment. ABP 501 and adalimumab were administered in identical syringes at an initial loading dose of 80 mg subcutaneously on week 1/day 1, followed by 40 mg subcutaneously every other week (starting at week 2) for 16 weeks. At week 16, patients with 50% or more improvement in PASI score from baseline (PASI 50) were eligible to continue in the study; patients initially randomized to receive ABP 501 continued treatment, and patients initially randomized to receive adalimumab were rerandomized in a 1:1 ratio to either continue adalimumab or switch to ABP 501. Rerandomization ensured that the blind was maintained. This report includes efficacy data through the initial treatment phase (week 16) and safety and immunogenicity data through week 20 after single transition from adalimumab to ABP 501 after rerandomization.

Assessments

The primary efficacy end point was the percent improvement in PASI score from baseline to week 16. Other key efficacy assessments included PASI 50 and 75% or more improvement in PASI score from baseline (PASI 75) responses, static Physician Global Assessment response of clear (0) or almost clear (1), and mean change in affected body surface area from baseline. Safety was assessed by

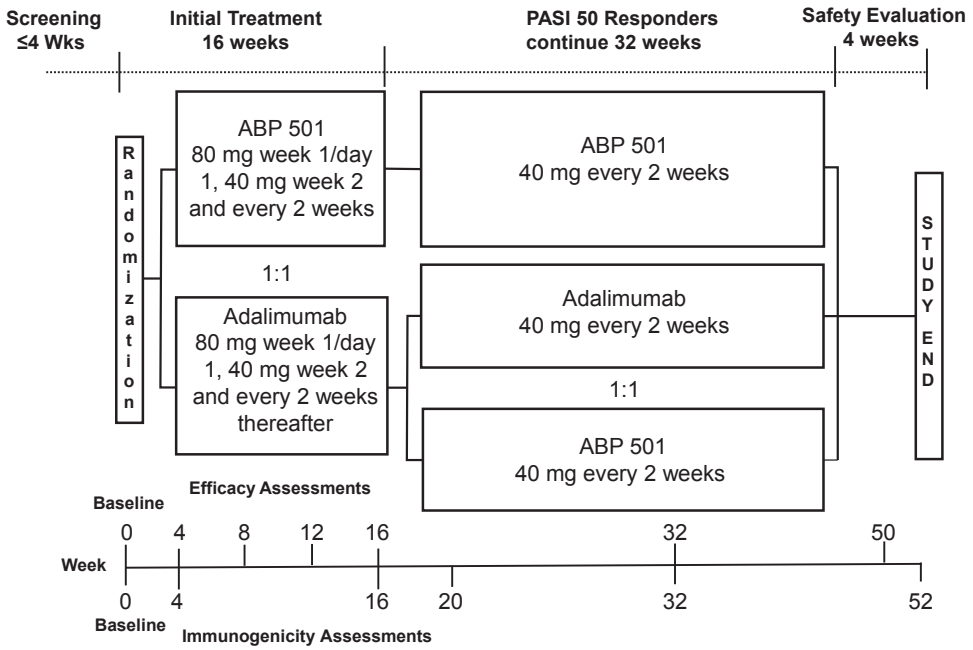

Fig 1. Study diagram. *PASI 50*, ≥50% Improvement in Psoriasis Area and Severity Index score from baseline.

monitoring for treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs), laboratory data, vital signs, and immunogenicity. Adverse events of interest (eg, infections, malignancies, hypersensitivity, demyelinating diseases) were also assessed based on *standard Medical Dictionary for Regulatory Activities* queries.

The incidence of antidrug antibodies (ADAs) was assessed using a validated electrochemiluminescent bridging immunoassay. A 2-tiered approach was conducted simultaneously to detect all ADAs that bind to the biologic drug (binding antibodies) and confirm the specificity of the binding antibodies.[17] The assay sensitivity for ADAs was approximately 0.02 μg/mL in the presence of 25 μg/mL drug using an affinity purified rabbit positive control antibody diluted in pooled human serum. For the specificity assay, samples that showed a signal-to-noise ratio reduction in the presence of excess soluble drug[18] were reported as positive. Samples positive for binding ADAs were tested for neutralizing antibodies, which interfere with the therapeutic activity of the biologic drug. All samples were tested against ABP 501 and adalimumab.

Statistical analysis

Efficacy data were analyzed using the full analysis set, which included all patients initially randomized in the study with missing values imputed using the last observation carried forward method. The safety analysis included all randomized patients who received at least 1 dose of study drug, and the immunogenicity analysis included patients in the safety analysis who had at least 1 evaluable antibody test result. Clinical equivalence for the primary end point was evaluated by comparing the 2-sided 95% confidence interval (CI) of the difference in PASI percent improvement from baseline to week 16 between treatment groups with the equivalence margin of ±15. A sample size of 340 patients was calculated to provide greater than 90% power to demonstrate clinical equivalence at a .025 significance level. The 2-sided 95% CI of the group difference was estimated using an analysis of covariance with baseline PASI score and stratification factors of geographic region and prior biologic use as covariates. Descriptive statistics were provided for secondary efficacy assessments. Safety and immunogenicity data were summarized descriptively through week 16 and post-week 16 (after rerandomization) through week 20, which included data for the patients transitioned from adalimumab to ABP 501 (adalimumab/ABP 501).

RESULTS

Patient characteristics

In total, 350 patients (175 per treatment group) were enrolled and randomized and included in the full analysis set for efficacy evaluation; 347 patients (ABP 501, n = 174; adalimumab, n = 173) received at least 1 dose of study drug and included in the safety analysis (Fig 2). A total of 164 of 175 (94%) patients in

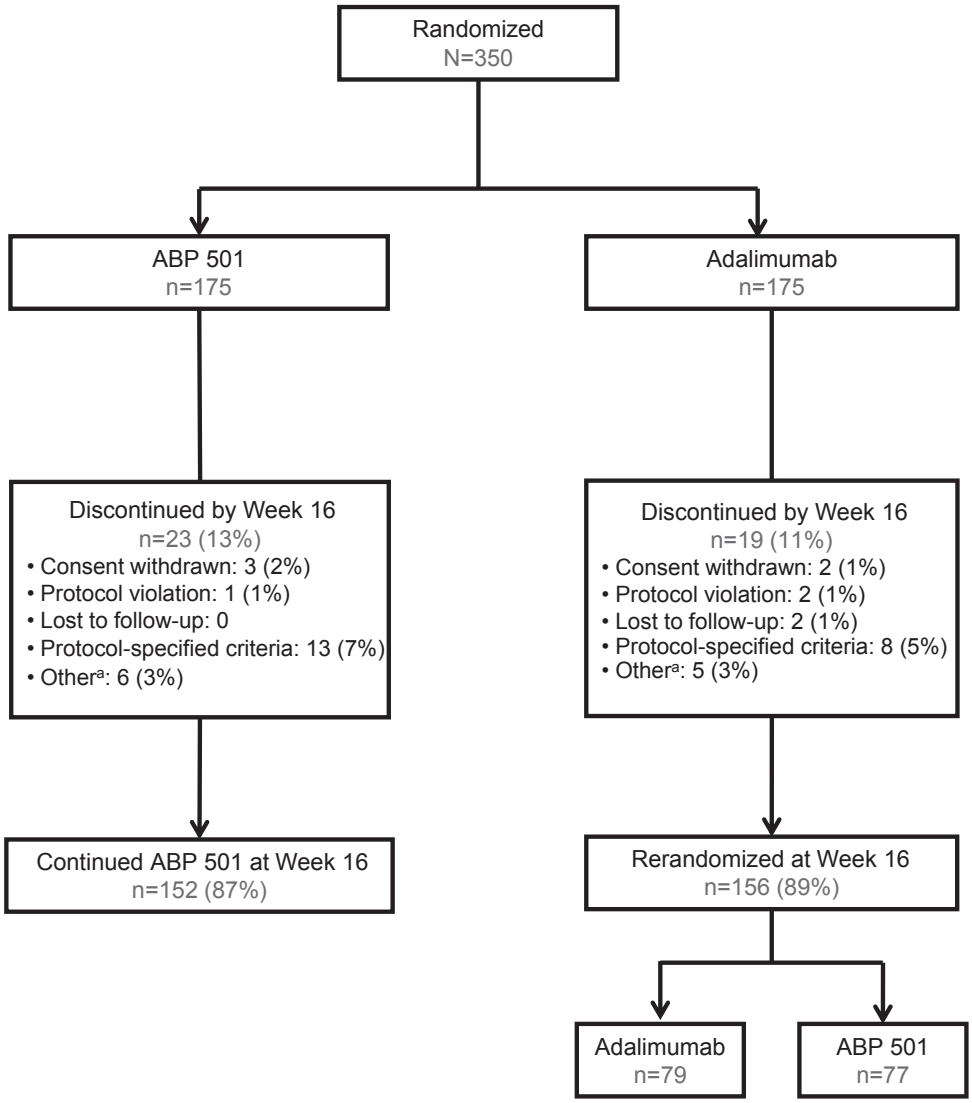

Fig 2. Patient disposition. [a]Patients discontinued because of adverse events.

the ABP 501 group and 162 of 175 (93%) in the adalimumab group completed the study through week 16. Of those, 152 (87%) patients from the ABP 501 group continued receiving ABP 501 and 156 (89%) patients from the adalimumab group were rerandomized to either continue receiving adalimumab (n = 79) or transition to ABP 501 (n = 77). The most common reason patients were not rerandomized at week 16 was failure to achieve PASI 50. Patient demographics and baseline characteristics were generally well balanced between treatment groups (Table I).

Efficacy

At week 16, the PASI percent improvement from baseline (primary end point) was 80.9 in the ABP 501 group and 83.1 in the adalimumab group (Fig 3) (least-square mean difference −2.18 [95% CI −7.39 to 3.02]). The 95% CI fell within the prespecified margin (−15 to 15) demonstrating clinical similarity between ABP 501 and adalimumab. Additional analyses of patients with 90% or more improvement in PASI score from baseline (PASI 90) and 100% improvement in PASI score from baseline (complete response) at 16 weeks were undertaken and showed a similar response for both treatment groups (Fig 4). Results for other key efficacy assessments at week 16, reported in Table II, were similar between groups.

Safety

Through week 16. During the 16-week treatment period, 67.2% (117 of 174) and 63.6% (110 of 173) of patients in the ABP 501 and adalimumab groups had at least 1 TEAE (Table III). There were no imbalances of 5% or more observed in any TEAEs, by preferred term, between the ABP

Table I. Baseline demographics and psoriasis disease characteristics (randomized patients)

	ABP 501 n = 175	Adalimumab n = 175
Characteristics		
Age, median (Q1, Q3), y	46 (35, 54)	41 (33, 56)
Male, n (%)	112 (64.0)	116 (66.3)
Race, n (%)		
White	167 (95.4)	157 (89.7)
Asian	5 (2.9)	8 (4.6)
Other	1 (0.6)	6 (3.4)
BMI, median (Q1, Q3), kg/m^2	28.7 (24.8, 33.5)	28.53 (25.8, 33.2)
Region, n (%)		
Eastern Europe	71 (40.6)	70 (40)
Western Europe	43 (24.6)	43 (24.6)
Other	61 (34.9)	62 (35.4)
Duration of psoriasis, median (Q1, Q3), y	18.5 (11, 27)	18 (10, 28)
PASI score, median (Q1, Q3)	17.1 (13.8, 22.7)	18.3 (14.4, 24.7)
BSA affected, median (Q1, Q3)	20 (15, 32)	23 (15, 40)
sPGA, n (%)		
Clear/almost clear	0	0
Moderate	106 (60.6)	102 (58.3)
Severe	61 (34.9)	61 (34.9)
Very severe	7 (4)	10 (5.7)
Previous psoriasis treatment, n (%)		
Biological therapy	33 (18.9)	30 (17.1)
Systemic* or phototherapy	128 (73.1)	135 (77.1)
Concomitant topical steroid, n (%)	16 (9.1)	20 (11.4)

BMI, Body mass index; *BSA*, body surface area; *PASI*, Psoriasis Area and Severity Index; *Q1*, quartile 1; *Q3*, quartile 3; *sPGA*, static Physician Global Assessment.
*Excludes biologic therapy.

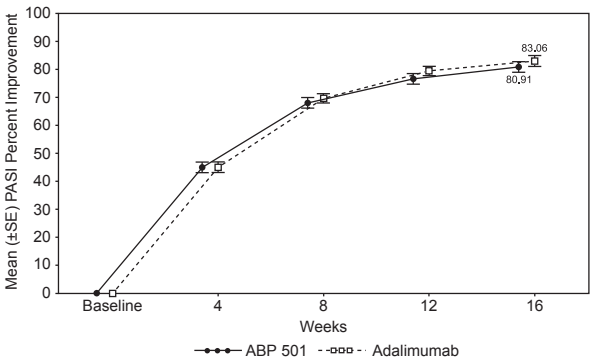

Fig 3. Percentage Improvement in Psoriasis Area and Severity Index (*PASI*) scores through week 16.

501 and adalimumab groups. The number of patients with TEAEs leading to withdrawal of active treatment was similar between groups (4% [7/174] ABP 501 vs 2.9% [5/173] adalimumab). There were 7 SAEs reported in 6 patients treated with ABP 501 (acute myocardial infarction, appendicitis, arrhythmia, chronic obstructive pulmonary disease, hypersensitivity, lentigo maligna, and postoperative abscess) and 5 SAEs reported in 5 patients treated with adalimumab (bronchitis, metrorrhagia, osteoarthritis, patellofemoral pain syndrome, and syncope) during the 16-week treatment period. Mean changes from baseline in laboratory values including hematology and serum chemistry were generally similar between groups. There were no clinically meaningful changes observed in vital signs from baseline to week 16.

Post-week 16 through week 20. TEAEs occurring after rerandomization (post-week 16) through week 20 were reported in 23% (35 of 152) of patients who continued on ABP 501 (ABP 501/ABP 501), 19% (15 of 79) of patients who continued on adalimumab (adalimumab/adalimumab), and 15.6% (12 of 77) of patients who switched from adalimumab to ABP 501 (adalimumab/ABP 501) (Table IV), with no imbalances 5% or more observed in any TEAEs among the 3 groups. During this time 2 SAEs were reported in the ABP 501/ABP 501 group (cerebral ischemia and drug-induced liver injury).

Adverse events of interest. Adverse events of interest through week 16 are reported in Table III. Treatment-emergent infections that occurred in 3% or more of either treatment group (ABP 501, adalimumab) were nasopharyngitis (14.4% [25/174], 15.6% [27/173]), upper respiratory tract infection

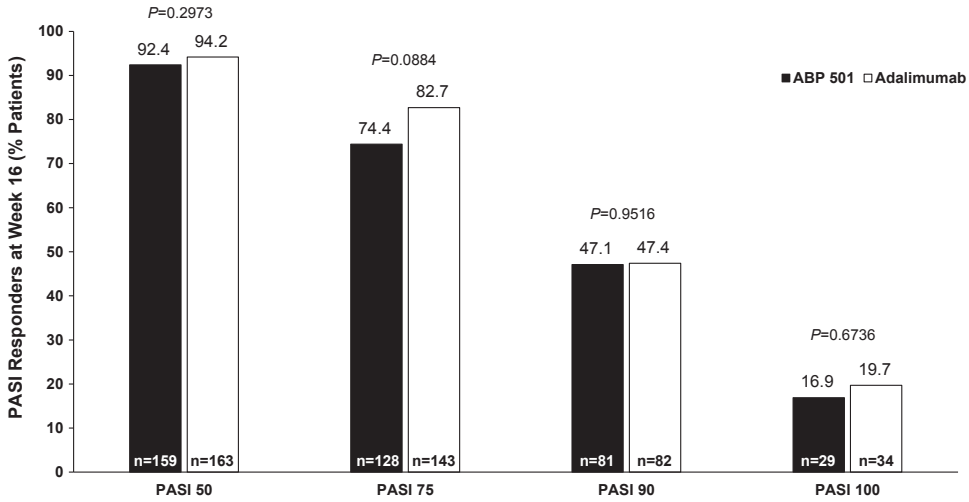

Fig 4. Psoriasis Area and Severity Index (*PASI*) responders at week 16.

Table II. Static Physician Global Assessment and body surface area clinical response at week 16 (full analysis set [last observation carried forward])

Assessment	ABP 501	Adalimumab	Treatment difference*	*P* value†
sPGA, clear/almost clear, n/total n (%)	101/172 (58.7)	113/173 (65.3)	−7.4	.1422
BSA affected, total, n	172	172		
Change from baseline, mean (SD)	−18.0 (13.57)	−22.1 (17.11)	1.93	.0809

BSA, Body surface area; *sPGA*, static Physician Global Assessment.
*Treatment difference for ABP 501−adalimumab for sPGA was estimated using a generalized linear model adjusted for prior biologic use, region, and baseline scores; treatment difference for BSA was estimated using analysis of covariance adjusted for prior biologic use, region, and baseline BSA score.
†*P* values for the treatment differences between ABP 501 and adalimumab were not statistically significant.

(5.2% [9/174], 5.2% [9/173]), and rhinitis (1.7% [3/174], 3.5% [6/173]). There were no deaths during the study period and no cases of demyelinating disease, heart failure, lupuslike syndromes, or reactivation of latent tuberculosis were reported.

Immunogenicity

During the initial 16-week treatment period, 55.2% (96 of 174) and 63.6% (110 of 173) of patients in the ABP 501 and adalimumab groups developed binding ADAs, and 9.8% (17 of 174) and 13.9% (24 of 173) developed neutralizing antibodies. Antibodies were also assessed through week 20 including patients who were rerandomized post-week 16. The frequency of developing binding ADAs and neutralizing antibodies was 54.6% (83/152) and 7.2% (11/152) for ABP 501/ABP 501, 59.5% (47/79) and 11.4% (9/79) for adalimumab/adalimumab, and 64.9% (50/77) and 13% (10/77) for adalimumab/ABP 501.

DISCUSSION

The development process for biosimilars is particularly challenging because of the complexities pertaining to cell line selection and the manufacturing processes of biologics. Therefore, a key consideration for regulatory approval is a thorough characterization that shows no clinically meaningful differences between the proposed biosimilar and its reference product.[6] Supporting evidence involves detailed comparative analytical (functional and biological) analysis, any relevant preclinical (toxicology) studies, and clinical studies (pharmacokinetics/pharmacodynamics, efficacy, safety, immunogenicity), including 1 or more phase III trials conducted in sensitive populations. The Food and Drug Administration recently approved the biosimilars ABP 501 (AMJEVITA [Amgen Inc]), Erelzi (etanercept-szzs, Novartis Pharma AG, Stein, Switzerland), and Inflectra (infliximab-dyyb, Hospira, Lake Forest, IL), for some or all the indications of their reference products, including psoriasis.[9,19-23] Biosimilars of infliximab (Remsima, Celltrion Healthcare, Budapest, Hungary) and etanercept (Benepali, Samsung Bioepis UK Limited, Chertsey, United Kingdom) are already approved in Europe for rheumatologic and dermatologic disease and, for the infliximab biosimilar, gastrointestinal diseases as well.[2,24,25] Biosimilars of

Table III. Treatment-emergent adverse events through week 16 (safety analysis)

AE, n (%)	ABP 501 n = 174	Adalimumab n = 173
Any TEAEs	117 (67.2)	110 (63.6)
Grade ≥3 AEs	8 (4.6)	5 (2.9)
Serious AEs	6 (3.4)	5 (2.9)
TEAEs leading to discontinuation of drug	7 (4.0)	5 (2.9)
Treatment-related AEs	43 (24.7)	43 (24.9)
AEs occurring in ≥5% of patients in any treatment group, preferred term		
Nasopharyngitis	25 (14.4)	27 (15.6)
Headache	13 (7.5)	18 (10.4)
Upper respiratory tract infection	9 (5.2)	9 (5.2)
Other TEAEs of interest		
Infections	59 (33.9)	58 (33.5)
Serious infections	2 (1.1)	1 (0.6)
Hypersensitivity	8 (4.6)	7 (4.0)
Injection-site reactions	3 (1.7)	9 (5.2)
Liver enzyme elevations	4 (2.3)	2 (1.2)
Hematologic reactions	0	3 (1.7)
Malignancies*	1 (0.6)	1 (0.6)
Demyelinating diseases	0	0
Any heart failure AE	0	0
Any lupus-like syndrome AE	0	0
Reactivation of tuberculosis	0	0

For each category or preferred term, patients are included only once, even if they experienced multiple events in that category.
AE, Adverse event; *TEAE*, treatment-emergent adverse event.
*Bowen disease occurred in an ABP 501—treated patient and lentigo maligna occurred in an adalimumab-treated patient.

Table IV. Treatment-emergent adverse events post-week 16 through week 20 (safety analysis)

AE, n (%)	ABP 501/ ABP 501 n = 152	Adalimumab/ adalimumab n = 173	Adalimumab/ ABP 501 n = 77
Any TEAEs	35 (23.0)	15 (19.0)	12 (15.6)
Serious AEs	2 (1.3)	0	0
AEs occurring in ≥2% of any treatment group, preferred term			
Back pain	3 (2.0)	2 (2.5)	2 (2.6)
Diarrhea	1 (0.7)	1 (1.3)	2 (2.6)
Headache	3 (2.0)	1 (1.3)	0
Alanine aminotransferase increased	3 (2.0)	0	0
Nasopharyngitis	0	2 (2.5)	1 (1.3)
Psoriasis	1 (0.7)	2 (2.5)	0

For each category or preferred term, patients are included only once, even if they experienced multiple events in that category.
AE, Adverse event; *TEAE*, treatment-emergent adverse event.

infliximab (Inflectra [Hospira], Remsima [Celltrion Healthcare]) are also approved in Canada for rheumatologic and dermatologic indications only.[26,27]

Results from this phase III trial demonstrated clinical similarity of biosimilar ABP 501 to adalimumab as measured by the percent improvement in PASI response (primary end point) from baseline to week 16 of treatment in patients with moderate to severe plaque psoriasis. This primary end point was selected over the commonly used PASI 75 (or PASI 50) response because it assesses PASI improvement as a continuous variable, which may provide more useful information in a comparative analysis, rather than a binary assessment of meeting a minimum response threshold.[28] Furthermore, similar proportions of patients achieved PASI 50, PASI 75, PASI 90, and 100% improvement in PASI score from baseline responses. Similar efficacy between ABP 501 and adalimumab was also shown using additional standard clinical measures for assessing improvement in patients with moderate to severe psoriasis, including the static Physician Global Assessment and body surface area affected, providing a robust assessment of clinical efficacy.

Adalimumab and other TNF-alfa inhibitors, although generally well tolerated, are associated with increased risk of infections, which can be serious.[2,29-31] In this study, no new safety signals were detected during the observation period. Adverse events in the study were similar to the known safety profile of adalimumab from clinical trials[32,33] and were balanced between treatment groups. The frequencies of developing ADAs for patients in each treatment group, including those patients who transitioned from adalimumab to ABP 501, were also balanced. Long-term surveillance, however, including data from larger treatment populations, will be needed to further assess the safety profile of the biosimilar, particularly for rare events, and this can be considered a limitation to the current study. The upcoming report of the 52-week data from this study and the results from the ongoing open-label extension study in patients with rheumatoid arthritis (NCT02114931) will provide additional insight into the long-term safety and immunogenicity profile of ABP 501.

Analytical comparison of ABP 501 with adalimumab (United States and European Union) has shown that the 2 molecules are highly similar with respect to physicochemical properties and biological activity. Pharmacokinetic equivalence of ABP 501 to adalimumab (United States and European Union) was demonstrated in a phase I single-dose study conducted in healthy adults.[11-13] Results from the current analysis provide comparative data on the clinical efficacy, safety, and immunogenicity profile

of ABP 501 with that of adalimumab, specifically in immunocompetent patients with psoriasis, providing a sensitive population to determine any clinically meaningful differences. Similar efficacy, safety, and immunogenicity between ABP 501 and adalimumab was also shown in a separate clinical trial that included 526 patients with moderate to severe rheumatoid arthritis.[34] Together, these data contribute to the confirmation of overall similarity between the proposed biosimilar and its originator.

In summary, this randomized, double-blind study demonstrated clinical similarity of ABP 501 to adalimumab in percent PASI improvement at week 16. Similar efficacy to the reference product was also shown in a variety of secondary assessments. The safety profiles of the treatment groups were comparable through 16 weeks, and there was no impact on safety and immunogenicity after a single transition from adalimumab to ABP 501.

The authors wish to thank all the investigators and patients involved in this study. The authors also thank Monica Ramchandani-Toddywala, PhD, of Amgen and Sarah Mizne, PharmD, of MedVal Scientific Information Services LLC, for providing medical writing and editorial assistance.

REFERENCES

1. Menter A, Gottlieb A, Feldman SR, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. *J Am Acad Dermatol*. 2008;58:826-850.
2. Nast A, Gisondi P, Ormerod AD, et al. European S3-Guidelines on the systemic treatment of psoriasis vulgaris. Update 2015 EDF in cooperation with EADV and IPC. Available from: http://onlinelibrary.wiley.com/store/10.1111/jdv.13354/asset/supinfo/jdv13354-sup-0001-DataS1.pdf?v=1&s=b537740852c89200b2131f209dbd2a0af20ead88. Accessed February 15, 2017.
3. Papp K, Gulliver W, Lynde C, Poulin Y, Ashkenas J. Canadian guidelines for the management of plaque psoriasis: overview. *J Cutan Med Surg*. 2011;15:210-219.
4. Cheng J, Feldman SR. The cost of biologics for psoriasis is increasing. *Drugs Context*. 2014;3:212266.
5. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, and Center for Biologics Evaluation and Research. Quality considerations in demonstrating biosimilarity of a therapeutic protein product to a reference product. Guidance for industry. Available from: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm291134.pdf. Accessed November 18, 2016.
6. U.S. Department of Health and Human Services. Scientific considerations in demonstrating biosimilarity to a reference product. Guidance for industry. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf. Accessed November 18, 2016.
7. European Medicines Agency. Guideline on similar biological medicinal products. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf. Accessed November 18, 2016.
8. European Medicines Agency Committee for Medicinal Products for Human Use. Guideline on similar biological medicinal products containing monoclonal antibodies - non-clinical and clinical issues. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf. Accessed November 18, 2016.
9. AMJEVITA (adalimumab-atto) injection for subcutaneous use [prescribing information]. Thousand Oaks, CA: Amgen Inc; 2016.
10. Humira (adalimumab) injection [prescribing information]. North Chicago, IL: AbbVie Inc; 2015.
11. Kaur PP, Chow V, Zhang N, Moxness M, Markus R. Pharmacokinetic equivalence of ABP 501 relative to adalimumab: results from a randomized, single-blind, single-dose, parallel group study in healthy subjects. *Arthritis Rheum*. 2014;66(Suppl):S661-S662 (abstract 1504).
12. Kaur P, Chow V, Zhang N, Moxness M, Markus R. A randomized, single-blind, single-dose, three-arm, parallel group study in healthy subjects to demonstrate pharmacokinetic equivalence of ABP 501 and adalimumab: results of comparison with adalimumab (EU). *Ann Rheum Dis*. 2014;73(Suppl):479 (abstract FRI0264).
13. Kaur P, Chow V, Zhang N, Markus R. A randomized, single-blind, single-dose, three-arm, parallel group study in healthy subjects demonstrating pharmacokinetic equivalence of proposed biosimilar ABP 501 with adalimumab. *United European Gastroenterol J*. 2015;3(5S):A606 (abstract P1584).
14. Amgen Inc. Efficacy and safety study of ABP 501 compared to adalimumab in subjects with moderate to severe rheumatoid arthritis. Available from: https://clinicaltrials.gov/ct2/show/NCT01970475. Accessed February 16, 2017.
15. Fredriksson T, Pettersson U. Severe psoriasis—oral therapy with a new retinoid. *Dermatologica*. 1978;157:238-244.
16. Feldman SR, Krueger GG. Psoriasis assessment tools in clinical trials. *Ann Rheum Dis*. 2005;64(suppl 2):ii65-ii68.
17. U.S. Food and Drug Administration, Center for Drug Evaluation and Research. *Assay development and validation for immunogenicity testing of therapeutic protein products guidance for industry*. Silver Springs, MD: Food and Drug Administration, Center for Drug Evaluation and Research; 2016.
18. Menting SP, Coussens E, Pouw MF, et al. Developing a therapeutic range of adalimumab serum concentrations in management of psoriasis: a step toward personalized treatment. *JAMA Dermatol*. 2015;151:616-622.
19. U.S. Food and Drug Administration. FDA approves Inflectra, a biosimilar to Remicade. Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm494227.htm. Accessed November 18, 2016.
20. Inflectra (infliximab-dyyb) [prescribing information]. Lake Forest, IL: Hospira; 2016.
21. U.S. Food and Drug Administration. FDA approves AMJEVITA, a biosimilar to Humira [press release]. Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm522243.htm. Accessed November 18, 2016.
22. U.S. Food and Drug Administration. FDA approves Erelzi, a biosimilar to Enbrel [press release]. Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm518639.htm. Accessed November 18, 2016.
23. *Erelzi (etanercept-szzs) injection, for subcutaneous use [prescribing information]*. Stein, Switzerland: Novartis Pharma AG; 2016.
24. European Medicines Agency Committee for Medicinal Products for Human Use. Summary of opinion (initial

authorization). Benepali etanercept. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/004007/WC500196736.pdf. Accessed November 18, 2016.

25. European Medicines Agency. Remsima 100 mg powder for concentrate for solution for infusion [summary of product characteristics]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002576/WC500150871.pdf. Accessed February 16, 2017.
26. Health Canada. Remsima summary basis of decision. Available from: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd_smd_2014_remsima_160195-eng.php. Accessed November 18, 2016.
27. Health Canada. Summary basis of decision (SBD): ^{Pr} Inflectra. Available from: http://www.hcsc.gc.ca/dhpmps/prodpharma/sbdsmd/drugmed/sbd_smd_2014_inflectra_159493eng.php. Accessed November 18, 2016.
28. Kircik L, Zhang N, Kaur P. Statistical considerations for demonstrating similarity and interpretation of clinical results in trials evaluating biosimilars. *J Am Acad Dermatol*. 2016;75 (abstract 2625).
29. Menter A, Thaci D, Papp KA, et al. Five-year analysis from the ESPRIT 10-year postmarketing surveillance registry of adalimumab treatment for moderate to severe psoriasis. *J Am Acad Dermatol*. 2015;73:410-419.
30. Tracey D, Klareskog L, Sasso EH, Salfeld JG, Tak PP. Tumor necrosis factor antagonist mechanisms of action: a comprehensive review. *Pharmacol Ther*. 2008;117:244-279.
31. Mansouri Y, Goldenberg G. Biologic safety in psoriasis: review of long-term safety data. *J Clin Aesthet Derm*. 2015;8:30-42.
32. Saurat JH, Stingl G, Dubertret L, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). *Br J Dermatol*. 2008;158:558-566.
33. Menter A, Tyring SK, Gordon K, et al. Adalimumab therapy for moderate to severe psoriasis: a randomized, controlled phase III trial. *J Am Acad Dermatol*. 2008;58:106-115.
34. Cohen SB, Genovese MC, Choy EH, et al. Randomized, double-blind, phase 3 study of efficacy and safety of ABP 501 compared with adalimumab in subjects with moderate to severe rheumatoid arthritis. *Arthritis Rheumatol*. 2015;67(suppl 10) (abstract 2054).