Rheumatol Ther (2023) 10:901–915
https://doi.org/10.1007/s40744-023-00557-x

ORIGINAL RESEARCH

Long-Term Efficacy and Safety of Upadacitinib in Patients with Rheumatoid Arthritis: Final Results from the BALANCE-EXTEND Open-Label Extension Study

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Received: January 4, 2023 / Accepted: April 25, 2023 / Published online: May 18, 2023

ABSTRACT

Introduction: Upadacitinib (UPA) is an oral, selective Janus kinase inhibitor that has demonstrated favorable efficacy with an acceptable safety profile across a global, phase 3 program in rheumatoid arthritis (RA). This phase 2 open-label extension investigated the efficacy and safety of UPA through 6 years of treatment.

Methods: Patients from two phase 2b trials (BALANCE-1 and -2) enrolled in BALANCE-EXTEND (NCT02049138) and received open-label UPA 6 mg twice daily (BID). Dose increases to 12 mg BID were required for patients with < 20% improvement in swollen or tender joint counts at weeks 6 or 12 and permitted for those not achieving Clinical Disease Activity Index (CDAI) low disease activity (LDA; CDAI 2.8 to ≤ 10). Dose reduction to UPA 6 mg BID was permitted only for safety or tolerability reasons. After January 2017, the 6/12 mg BID doses were replaced by 15/30 mg once-daily extended-release equivalents. Efficacy and safety were monitored up to 6 years of UPA treatment; outcomes included rates of achievement of LDA or remission. Data were analyzed for patients who received the lower UPA dose

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40744-023-00557-x.

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throughout; titrated up to the higher UPA dose from weeks 6 or 12; or titrated to the higher UPA dose and back down.
Results: Overall, 493 patients entered BALANCE-EXTEND ('Never titrated', $n = 306$; 'Titrated up', $n = 149$; 'Titrated up and down', $n = 38$), and 223 patients (45%) completed the 6-year study. Total cumulative exposure was 1863 patient-years. Rates of LDA and remission were maintained through 6 years. Overall, 87%/70%/73% of patients in the 'Never titrated'/'Titrated up'/'Titrated up and down' groups achieved CDAI LDA at week 312, while the respective rates of Disease Activity Score 28 with C-reactive protein meeting LDA and remission criteria were 85%/69%/70% and 72%/46%/63%. Improvements in patient-reported outcomes were similar among the three groups. No new safety signals were identified.
Conclusions: In this open-label extension of two phase 2 studies, UPA demonstrated sustained efficacy and an acceptable safety profile through 6 years of treatment in patients who completed the study. These data support a favorable long-term benefit–risk profile of UPA in patients with RA.
Trial Registration: Trial registration number: NCT02049138.

Keywords: Extension; Janus kinase inhibitor; Phase 3; Rheumatoid arthritis; Treatment; Upadacitinib

Key Summary Points

Why carry out this study?

Many patients with rheumatoid arthritis (RA) receiving treatment with tumor necrosis factor inhibitors fail to achieve a satisfactory long-term clinical response; therefore, alternative advanced therapeutic options are needed.

Upadacitinib (UPA) is an oral, selective Janus kinase inhibitor that is approved for the treatment of moderately to severely active RA in Europe and the United States, among other regions worldwide.

This study investigated the long-term efficacy and safety of UPA in patients with moderately to severely active RA who received up to 6 years of treatment, by dose titration ('Never titrated'/'Titrated up'/'Titrated up and down').

What was learned from the study?

In patients who completed the study, UPA demonstrated sustained long-term efficacy, with an acceptable safety profile, regardless of titration.

UPA has a favorable long-term benefit–risk profile in patients with moderately to severely active RA.

INTRODUCTION

In patients with rheumatoid arthritis (RA), the ultimate goal of treatment is to achieve sustained remission. However, low disease activity (LDA) may be an alternative target for patients in which remission is not possible [1, 2]. A treat-to-target strategy is recommended for patients to achieve such goals, with methotrexate (MTX) as an initial disease-modifying antirheumatic drug (DMARD) treatment option [2]. For patients who do not respond to MTX, several biologic and targeted synthetic DMARDs, such as tumor necrosis factor inhibitors (TNFis) and Janus kinase (JAK) inhibitors, are now available [2].

Although treatment with TNFis is considered effective for many patients with RA, approximately 30% fail to achieve an improvement of 20% or more after 24 weeks, using the American College of Rheumatology (ACR) response criteria [3, 4]. For those who are refractory to initial TNFi treatment, switching to further TNFis results in a decline in response proportional to the number of therapies prescribed [5]. Other treatment options are needed for patients with RA with an inadequate response to TNFis and DMARDs. Our analysis of data from three phase 3 clinical trials shows that patients treated with

the JAK inhibitor upadacitinib (UPA), were found to have significant improvements in RA symptoms [6].

UPA is an oral, selective JAK inhibitor that has been evaluated in a global phase 3 program that included six randomized trials in patients with moderately to severely active RA [7–12] and is approved in this indication in Europe and the United States [13, 14]. Two earlier phase 2, randomized, controlled BALANCE trials evaluated UPA in patients with RA who had an inadequate response/intolerance to one or more TNFis (TNFi-IR; BALANCE-1 [15]) or an inadequate response to MTX (MTX-IR; BALANCE-2 [16]). Treatment with UPA led to rapid, dose-dependent improvements in RA signs and symptoms in both trials, with an acceptable safety profile. Long-term efficacy and safety data are essential to support the use of therapies in chronic, lifelong conditions such as RA. Here, we present data from the longest continuous exposure to UPA published to date, reporting an open-label extension (OLE) of the BALANCE clinical trials (BALANCE-EXTEND), in which patients received up to 6 years of treatment (NCT02049138).

METHODS

Study Design

BALANCE-1 and BALANCE-2 were international, 12-week, double-blind, placebo-controlled, phase 2b dose-ranging studies of UPA. Full details of both studies have been published previously. In summary, BALANCE-1 enrolled adults with active RA who were TNFi-IR [15], and BALANCE-2 enrolled adults with active RA who were MTX-IR [16]. Patients in both studies were randomized to receive UPA from 3 mg up to 18 mg twice daily (BID), matching placebo or, in the case of BALANCE-2, UPA 24 mg once daily (QD), for 12 weeks. The primary endpoint for both studies was the proportion of patients achieving 20% improvement in ACR response criteria (ACR20) at week 12. Following the 12-week BALANCE-1 and BALANCE-2 studies, patients entered the 312-week OLE, BALANCE-EXTEND. A schematic summary of the study design is provided in Supplementary Material Fig. 1.

Treatment

All patients in BALANCE-EXTEND initially received UPA 6 mg BID (pharmacologically equivalent to 15 mg QD) immediately after or up to 30 days following week 12 of BALANCE-1 or BALANCE-2. A dose increase to UPA 12 mg BID (pharmacologically equivalent to 30 mg QD) was required for patients with $< 20\%$ improvement in swollen joint count in 66 joints (SJC66) or tender joint count in 68 joints (TJC68) at week 6 or 12 versus baseline and was permitted for those not achieving Clinical Disease Activity Index (CDAI) LDA (disease activity score < 2.8 to ≤ 10) at week 6 or during any visits thereafter (subject to no safety concerns per the investigator's judgment). Study discontinuation was required for all patients who had $< 20\%$ improvement in SJC66 or TJC68 at 6 weeks after dose escalation or at any two consecutive scheduled study visits versus baseline. Dose reduction back to UPA 6 mg BID was permitted only for safety or tolerability reasons. Dose increases back to UPA 12 mg BID, after a prior dose reduction, were not permitted. From January 2017, patients receiving UPA 6 mg BID capsule doses were transitioned to UPA 15 mg QD extended-release tablets, and those receiving UPA 12 mg BID capsule doses were transitioned to UPA 30 mg QD extended-release tablets. In addition to study treatment, patients continued treatment with stable doses of MTX, non-steroidal anti-inflammatory drugs, and acetaminophen; corticosteroids were also permitted throughout the study. Oral DMARDs (except MTX) were prohibited up to week 24, then allowed thereafter per the investigator's clinical judgment.

Patients

Patients who completed BALANCE-1 or BALANCE-2 without safety concerns (i.e., clinically significant abnormal laboratory results or adverse events [AEs], or reaching one of the protocol-specific toxicity management

thresholds), or patients who did not fail to comply with the previous study protocols, were eligible to enter the BALANCE-EXTEND OLE study. Patients were excluded from BALANCE-EXTEND if they had ongoing infections that had not been successfully treated; anticipated requirement or receipt of any live vaccine during the study period, including up to 30 days after the last day of study drug; had abnormal laboratory values relating to liver or kidney function, hemoglobin, or blood cell counts; or were pregnant or breastfeeding.

Ethics

The BALANCE-EXTEND study was conducted in accordance with the International Conference on Harmonization guidelines, applicable regulations governing clinical trial conduct, and the Declaration of Helsinki 1964 and its later amendments. As per Good Clinical Practice (GCP), the study protocols were approved by an independent ethics committee (IEC)/institutional review board (IRB) at each site (Supplementary Material Table 1). All patients provided written informed consent.

Efficacy Endpoints

Study visits took place at baseline, week 6, week 12, and every 12 weeks thereafter until the end of the study, with an optional visit at week 18. Clinical efficacy endpoints included the proportion of patients achieving LDA based on the CDAI or Disease Activity Score 28 with C-reactive protein (DAS28-CRP), the proportion of patients achieving clinical remission based on the CDAI or DAS28-CRP, change from baseline in DAS28-CRP and CDAI, the proportion of patients achieving ACR20/50/70, and change from baseline in Physician's Global Assessment of disease activity (PhGA). LDA was defined as DAS28-CRP $\leq$ 3.2 or CDAI $\leq$ 10. Clinical remission was defined as DAS28-CRP $<$ 2.6 or CDAI $\leq$ 2.8. Patient-reported outcomes included change from baseline in the Health Assessment Questionnaire-Disability Index (HAQ-DI), the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Patient's Global Assessment of disease activity (PtGA), and patient's assessment of pain. Efficacy endpoints were assessed at weeks 6, 12, and every 12 weeks thereafter.

Patients were divided into three categories for efficacy analysis: (1) patients who received UPA 6 mg BID/15 mg QD for the duration of BALANCE-EXTEND (the 'Never titrated' group); (2) patients whose dose was titrated up to 12 mg BID/30 mg QD because of lack of efficacy, and who remained on that dose thereafter (the 'Titrated up' group); and (3) patients whose dose was titrated up to 12 mg BID/30 mg QD and later back down to 6 mg BID/15 mg QD owing to intolerance of the higher dose (the 'Titrated up and down' group).

Safety Assessments

Incidence of AEs, serious AEs, AEs leading to premature discontinuation, changes from baseline in vital signs, and clinical laboratory values (hematology, chemistry, and urinalysis) were analyzed. AEs of special interest included serious infections, opportunistic infections, herpes zoster, adjudicated gastrointestinal perforations, malignancies, adjudicated major adverse cardiovascular events (MACE), adjudicated venous thromboembolic events (VTE), and hepatic disorders. Mean changes from baseline in all continuous laboratory parameters and vital sign variables at each visit were summarized by treatment group.

Statistical Analyses

Efficacy data are reported as observed by the three treatment groups ('Never titrated', 'Titrated up', and 'Titrated up and down'). Changes from baseline were assessed using baseline data from the phase 2b studies. Descriptive statistics were generated for the following efficacy data: TJC68, SJC66, patient's assessment of pain, PtGA, PhGA, HAQ-DI, high-sensitivity CRP, DAS28-CRP, CDAI, FACIT-F, Rheumatoid Arthritis-Work Instability Scale (RA-WIS), and EuroQol 5-Dimension 5-Level (EQ-5D-5L) Index. The proportions of patients achieving LDA and remission thresholds, and the response

Table 1 Demographics and baseline disease characteristics

Mean (SD) unless otherwise stated	Never titrated (*n* = 306)	Titrated up (*n* = 149)	Titrated up and down (*n* = 38)	Total (*N* = 493)
Age (years)	55.8 (12.6)	56.0 (12.6)	53.7 (8.5)	55.7 (12.3)
Sex, *n* (%)				
Male	60 (19.6)	32 (21.5)	9 (23.7)	101 (20.5)
Female	246 (80.4)	117 (78.5)	29 (76.3)	392 (79.5)
Race, *n* (%)				
White	293 (95.8)	132 (88.6)	37 (97.4)	462 (93.7)
Black/African American	9 (2.9)	12 (8.1)	1 (2.6)	22 (4.5)
Asian	1 (0.3)	2 (1.3)	0 (0.0)	3 (0.6)
Native Hawaiian/Pacific Islander	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)
Multiple	2 (0.7)	3 (2.0)	0 (0.0)	5 (1.0)
BMI (kg/m^2)	28.2 (5.4)	28.5 (5.1)	27.9 (4.7)	28.3 (5.3)
Duration of RA (years)	9.3 (8.7)	9.6 (8.4)	7.7 (6.5)	9.3 (8.5)
hsCRP	12.9 (17.8)	14.9 (20.2)	17.1 (28.1)	13.8 (19.5)
DAS28-CRP	5.6 (1.0)[a]	5.9 (1.0)[b]	5.8 (0.9)[c]	5.7 (1.0)[d]
CDAI	39.7 (12.7)[e]	42.5 (13.3)[f]	41.5 (12.3)[c]	40.7 (12.9)[g]
SDAI	40.9 (13.3)[e]	44.0 (13.7)[f]	43.2 (12.6)[c]	42.0 (13.4)[g]
ACPA (U/ml)	194.4 (91.3)	184.3 (97.9)	193.9 (93.2)	191.3 (93.4)
RF (KU/l)	191.6 (207.9)	162.0 (217.1)	128.9 (140.5)	177.8 (207.0)
TJC68	25.8 (14.5)	30.4 (15.9)	31.3 (15.7)	27.6 (15.2)
SJC66	16.7 (10.5)	18.8 (12.0)	19.3 (9.5)	17.5 (10.9)
PhGA (0–100 mm VAS)	64.4 (15.8)[h]	65.6 (15.4)[i]	65.0 (15.4)[j]	64.8 (15.6)[k]
PtGA (0–100 mm VAS)	62.4 (20.8)[a]	67.4 (20.5)[b]	66.5 (16.5)[c]	64.2 (20.5)[d]
Patient's assessment of pain (0–100 mm VAS)	63.8 (19.7)[a]	67.2 (19.6)[b]	66.5 (13.1)[c]	65.0 (19.3)[d]
HAQ-DI	1.5 (0.7)[l]	1.6 (0.6)[b]	1.5 (0.5)[c]	1.5 (0.7)[m]

Table 1 continued

Mean (SD) unless otherwise stated	Never titrated (n = 306)	Titrated up (n = 149)	Titrated up and down (n = 38)	Total (N = 493)
FACIT-F	29.6 (10.6)[l]	25.7 (10.2)[b]	28.3 (10.6)[c]	28.3 (10.6)[m]

Baseline disease characteristics at the time of preceding randomized controlled trial baseline are summarized
ACPA anti-cyclic citrullinated peptide antibodies, *BMI* body mass index, *CDAI* Clinical Disease Activity Index, *DAS28-CRP* Disease Activity Score 28 with C-reactive protein, *FACIT-F* Functional Assessment of Chronic Illness Therapy-Fatigue, *HAQ-DI* Health Assessment Questionnaire-Disability Index, *hsCRP* high-sensitivity C-reactive protein, *KU* kilounits, *PhGA* Physician's Global Assessment of disease activity, *PtGA* Patient's Global Assessment of disease activity, *RA* rheumatoid arthritis, *RF* rheumatoid factor, *SD* standard deviation, *SDAI* Simplified Disease Activity Index, *SJC66* swollen joint count in 66 joints, *TJC68* tender joint count in 68 joints, *U* units, *VAS* visual analog scale
[a]n = 305
[b]n = 146
[c]n = 37
[d]n = 488
[e]n = 297
[f]n = 144
[g]n = 478
[h]n = 298
[i]n = 147
[j]n = 38
[k]n = 483
[l]n = 304
[m]n = 487

rates of ACR20/50/70 were summarized with 95% confidence intervals.

Exposure-adjusted AE rates per 100 patient-years (PY) were summarized for exposure to UPA 6 mg BID/15 mg QD (prior to dose titration) and exposure to upadacitinib 12 mg BID/30 mg QD, respectively.

RESULTS

Patient Population

A total of 493 patients were enrolled into BALANCE-EXTEND from BALANCE-1 and BALANCE-2 and were treated with open-label UPA ('Never titrated', n = 306; 'Titrated up', n = 149; 'Titrated up and down', n = 38). Demographics and baseline disease characteristics are summarized in Table 1. Of the 493 subjects, 45.2% (223/493) completed 312 weeks of treatment ('Never titrated', n = 142; 'Titrated up', n = 51; 'Titrated up and down', n = 30). The most common reasons for study withdrawal included withdrawal of consent (n = 83; 16.8%) and AEs (n = 72; 14.6%), as displayed in Fig. 1. The mean (standard deviation [SD]) duration of UPA exposure was 3.8 (2.4) years (range < 1 to 6.2 years), with a total cumulative exposure of 1863 PY.

Efficacy

Rates of achievement of remission and LDA (Fig. 2), and of ACR responses (Fig. 3), were maintained through week 312. For all efficacy endpoints at week 312, the highest rates were observed in the 'Never titrated' group. Overall, 84% (n/N = 98/116), 87% (n/N = 110/127), and 72% (n/N = 80/111) of patients in the 'Never titrated' group achieved DAS28-CRP $\leq$ 3.2, CDAI LDA, and Simplified Disease Activity Index (SDAI) LDA at week 312, respectively, and 92% (n/N = 119/129) of patients in the 'Never

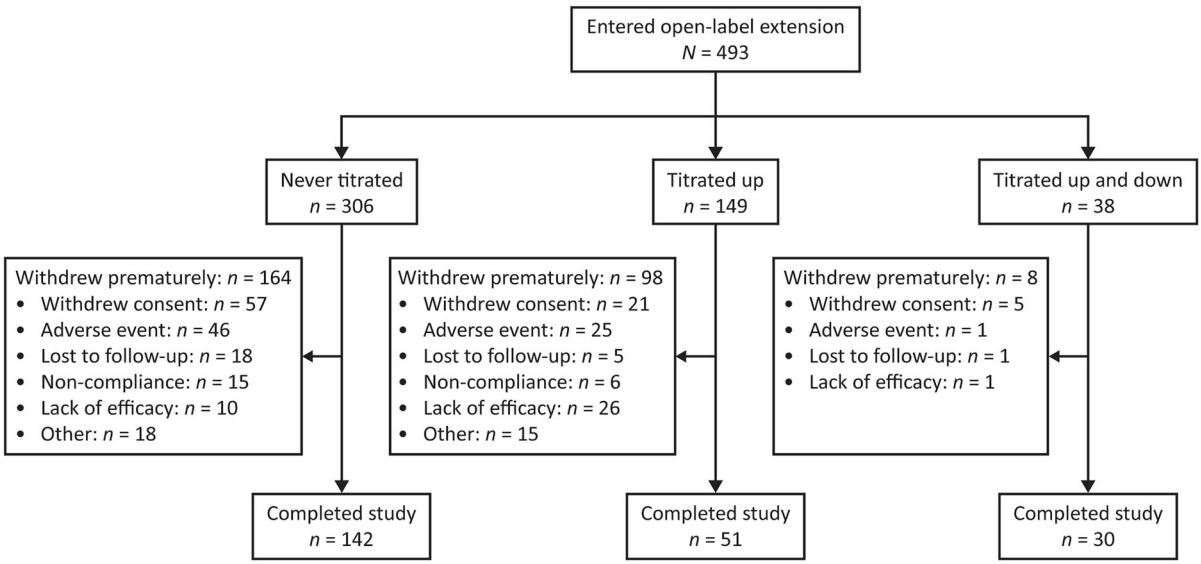

Fig. 1 Patient disposition. Never titrated: patients who received upadacitinib 6 mg BID/15 mg QD for the duration of BALANCE-EXTEND. Titrated up: patients who were titrated up from 6 mg BID/15 mg QD to 12 mg BID/30 mg QD because of lack of efficacy and remained on that dose thereafter. Titrated up and down: patients who were titrated up from 6 mg BID/15 mg QD to 12 mg BID/30 mg QD and were later titrated back down to 6 mg BID/15 mg QD because of intolerance. *BID* twice daily, *QD* once daily

titrated' group achieved ACR20 response rate. Mean (SD) change from baseline in PhGA at week 312 was similar across the three treatment groups: 'Never titrated', − 58.7 (16.1); 'Titrated up', − 55.2 (17.2); and 'Titrated up and down', − 49.4 (18.0) (data not shown).

Mean (SD) changes from baseline in HAQ-DI score at week 312 were similar across the three treatment groups: 'Never titrated', − 0.8 (0.7); 'Titrated up', − 0.8 (0.7); and 'Titrated up and down', − 0.7 (0.7) (Fig. 4a). A similar trend was observed for PtGA (Fig. 4b). Mean (SD) change from baseline in FACIT-F at week 312 was similar in the 'Never titrated' and 'Titrated up' groups (+ 10.7 [11.2] and + 11.6 [12.7], respectively), but less pronounced in the 'Titrated up and down' group (+ 8.6 [14.4]) (Fig. 4c). Mean (SD) change from baseline in the EQ-5D-5L Index at week 312 was similar across the three treatment groups: + 0.2 (0.3), + 0.2 (0.3), and + 0.1 (0.3) for the 'Never titrated', 'Titrated up', and 'Titrated up and down' groups, respectively, while the mean (SD) change from baseline in RA-WIS was slightly more pronounced in the 'Never titrated' and 'Titrated up' groups (− 4.2 [7.0] and − 3.9 [8.4], respectively) versus the 'Titrated up and down' group (− 2.9 [4.5]; data not shown). Lastly, mean (SD) change from baseline in patient's assessment of pain was slightly more pronounced in the 'Never titrated' group (− 44.1 [25.9]) compared with the 'Titrated up' and 'Titrated up and down' groups (− 40.3 [27.4] and − 33.4 [30.1], respectively) (Fig. 4d).

Safety

AEs, serious AEs, and AEs leading to discontinuation were more common on UPA 12 mg BID/30 mg QD exposure than on 6 mg BID/15 mg QD exposure (Table 2). Rates of infection (including serious and opportunistic infections and herpes zoster), anemia, and creatine phosphokinase elevation were higher on UPA 12 mg BID/30 mg QD versus on 6 mg BID/15 mg QD. Rates of malignancy were increased while receiving the higher versus the lower UPA dose, which was driven by the higher rate of non-melanoma skin cancer on UPA 12 mg BID/30 mg QD. Rates of hepatic disorder were slightly

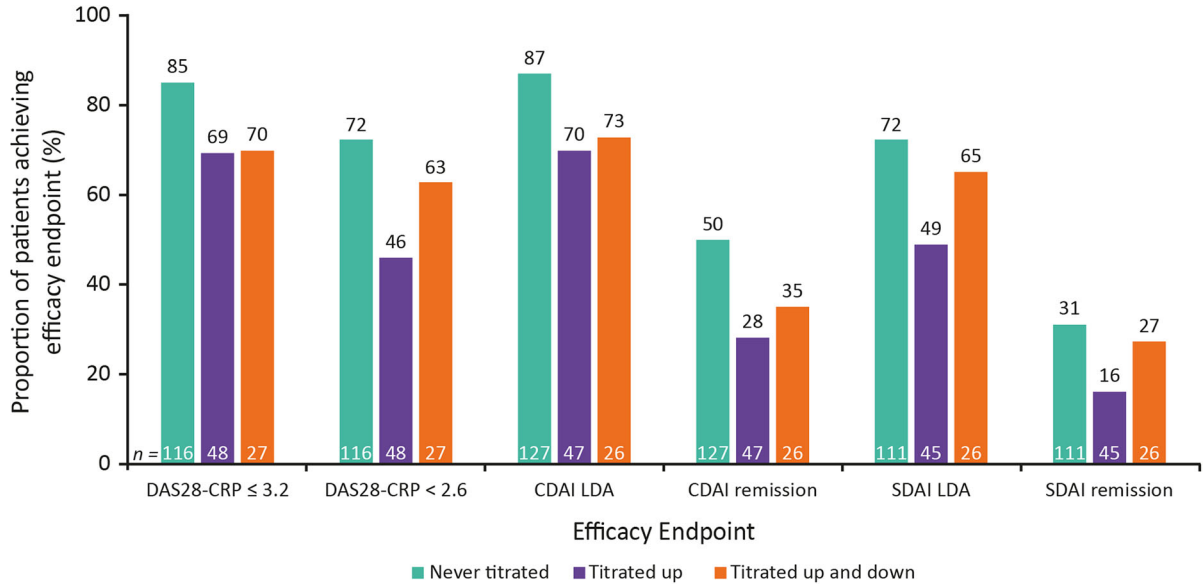

Fig. 2 DAS28-CRP $\leq$ 3.2/ $<$ 2.6, CDAI LDA/remission, and SDAI LDA/remission rates in BALANCE-EXTEND at week 312 (as-observed data). Never titrated: patients who received upadacitinib 6 mg BID/15 mg QD for the duration of BALANCE-EXTEND. Titrated up: patients who were titrated up from 6 mg BID/15 mg QD to 12 mg BID/30 mg QD because of lack of efficacy and remained on that dose thereafter. Titrated up and down: patients who were titrated up from 6 mg BID/15 mg QD to 12 mg BID/30 mg QD and were later titrated back down to 6 mg BID/15 mg QD because of intolerance. *BID* twice daily, *CDAI* Clinical Disease Activity Index, *DAS28-CRP* Disease Activity Score 28 with C-reactive protein, *LDA* low disease activity, *QD* once daily, *SDAI* Simplified Disease Activity Index

higher with UPA 6 mg BID/15 mg QD than with 12 mg BID/30 mg QD dosing. Frequencies of adjudicated MACE and adjudicated VTE were low with both UPA doses. The adjudicated MACE reported with UPA 6 mg BID/15 mg QD were non-fatal myocardial infarction (n = 4 events) and non-fatal stroke (n = 2 events), while the adjudicated VTE reported were deep-vein thrombosis (n = 5 events) and pulmonary embolism (n = 2 events), with one patient reporting concurrent deep-vein thrombosis and pulmonary embolism. The types and frequencies of AEs were consistent with those reported in the phase 3 program of UPA in RA populations.

Four treatment-emergent deaths occurred during the study: two deaths were of unknown cause in patients receiving UPA 6 mg BID/15 mg QD, one death resulted from Hodgkin's lymphoma in a patient receiving UPA 6 mg BID/15 mg QD, and one death resulted from COVID-19 infection in a patient receiving UPA 12 mg/30 mg QD. The most frequent AEs reported with UPA 6 mg BID/15 mg QD were urinary tract infection and nasopharyngitis (Table 3). The most frequent AEs reported with UPA 12 mg BID/30 mg QD were infections of the urinary tract and upper respiratory tract.

DISCUSSION

In this open-label extension of two phase 2 studies in patients with RA, UPA demonstrated sustained efficacy and an acceptable safety profile when administered for up to 6.2 years in patients who completed the study (223/493; 45%). The highest efficacy rates, including achievement of LDA and remission, were observed in patients who received UPA 6 mg BID/15 mg QD for the duration of the study with no change in dosage owing to efficacy or tolerability concerns. In contrast, efficacy of UPA treatment was generally lower among

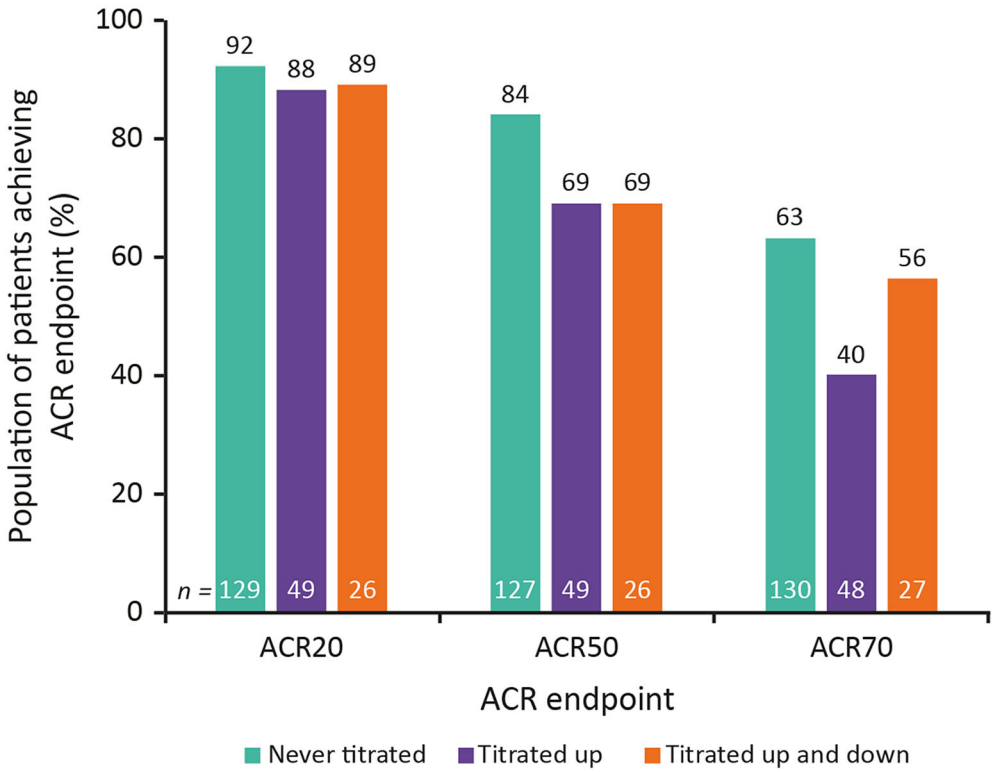

Fig. 3 ACR response rates in BALANCE-EXTEND at week 312 (as-observed data). Never titrated: patients who received upadacitinib 6 mg BID/15 mg QD for the duration of BALANCE-EXTEND. Titrated up: patients who were titrated up from 6 mg BID/15 mg QD to 12 mg BID/30 mg QD because of lack of efficacy and remained on that dose thereafter. Titrated up and down: patients who were titrated up from 6 mg BID/15 mg QD to 12 mg BID/30 mg QD and were later titrated back down to 6 mg BID/15 mg QD because of intolerance. *ACR* American College of Rheumatology, *ACR20/50/70* 20%/50%/70% improvement in ACR response criteria, *BID* twice daily, *QD* once daily

patients who required dose escalation to UPA 12 mg BID/30 mg QD and remained on the higher dose of UPA for the remainder of the study, suggestive of a more difficult-to-treat patient subpopulation. Overall, efficacy continued to improve or was maintained from week 6 through week 312 across all UPA treatment groups.

The results of this long-term analysis are consistent with those of the UPA phase 3 clinical trial program, including the findings from SELECT-COMPARE, a long-term extension where patients with RA and MTX-IR are treated with UPA 15 mg QD, adalimumab 40 mg every other week, or placebo [17]. After 156 weeks of treatment in SELECT-COMPARE, 93% (n/N = 260/281) and 57% (n/N = 159/281) of patients who received continuous UPA 15 mg QD achieved CDAI LDA and CDAI remission, respectively, and 93% (n/N = 243/261) and 81% (n/N = 212/261) achieved DAS28-CRP thresholds of ≤ 3.2 and < 2.6, respectively. Similarly, after 312 weeks of the BALANCE-EXTEND OLE, 87% and 50% of 'Never titrated' patients achieved CDAI LDA and remission, respectively, and 85% and 72% achieved DAS28-CRP thresholds of ≤ 3.2 and < 2.6, respectively. DAS28-CRP and CDAI response rates observed in patients originating from BALANCE-1 (TNFi-IR) versus BALANCE-2 (MTX-IR) were expected to be generally similar based on results from the double-blind period [15, 16], although the

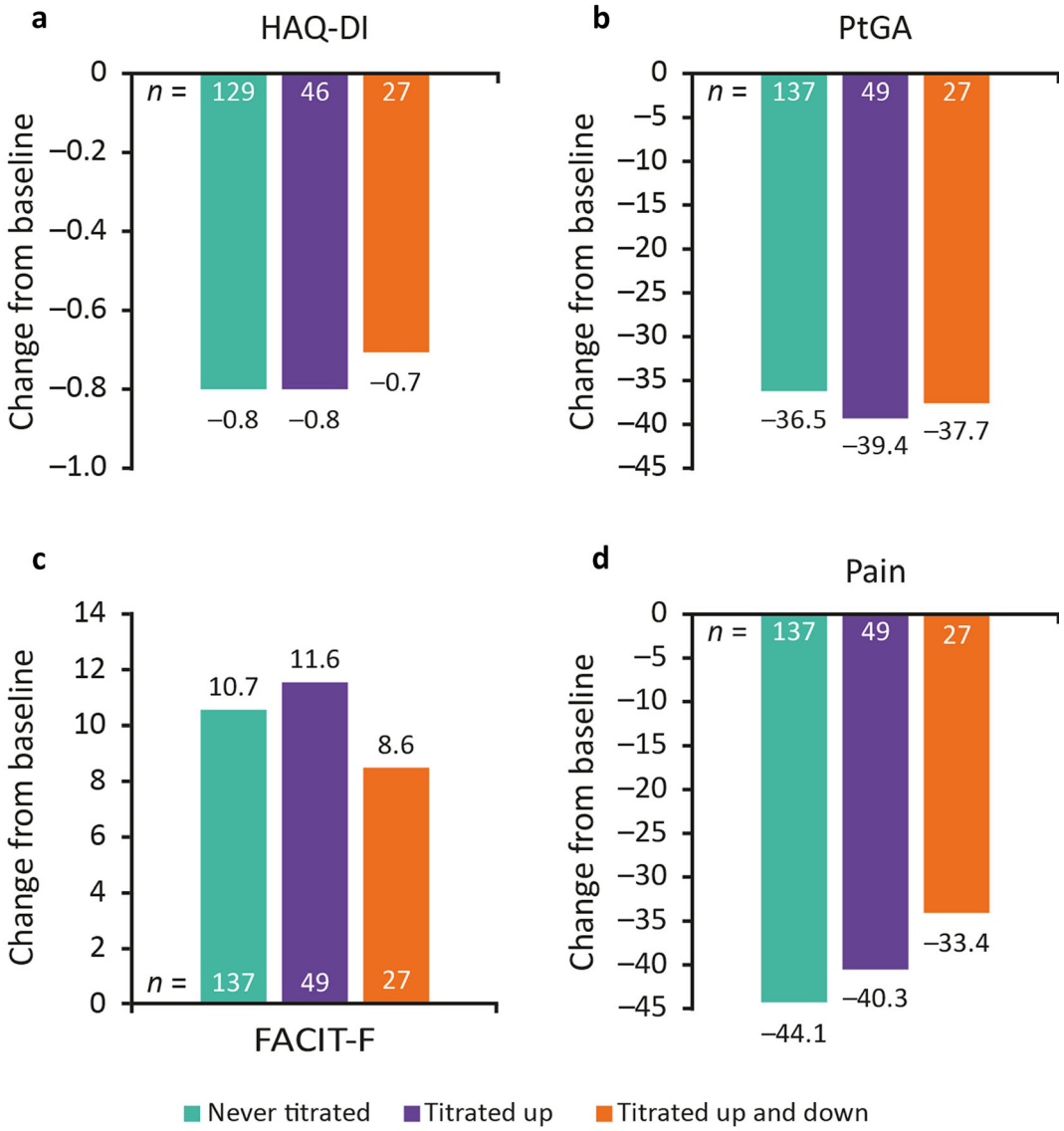

Fig. 4 Change from baseline in HAQ-DI (**a**), PtGA (**b**), FACIT-F (**c**), and patient's assessment of pain (**d**) in BALANCE-EXTEND at week 312 (as-observed data). Never titrated: patients who received upadacitinib 6 mg BID/15 mg QD for the duration of BALANCE-EXTEND. Titrated up: patients who were titrated up from 6 mg BID/15 mg QD to 12 mg BID/30 mg QD because of lack of efficacy and remained on that dose thereafter. Titrated up and down: patients who were titrated up from 6 mg BID/15 mg QD to 12 mg BID/30 mg QD and were later titrated back down to 6 mg BID/15 mg QD because of intolerance. *BID* twice daily, *FACIT-F* Functional Assessment of Chronic Illness Therapy-Fatigue, *HAQ-DI* Health Assessment Questionnaire-Disability Index, *PtGA* Patient's Global Assessment of disease activity, *QD* once daily

current OLE analysis did not directly compare these subgroups.

Long-term UPA treatment was associated with an acceptable safety profile in BALANCE-EXTEND, with a low incidence of malignancies, cardiovascular and hematologic AEs, and infections over 1863 PY of exposure. The types of serious infections reported with any UPA treatment were generally consistent with those expected in a population with moderately to

Table 2 Summary of exposure-adjusted AE rates in BALANCE-EXTEND and in the global phase 3 RA clinical trials program

E/100 PY (95% CI)[a]	BALANCE-EXTEND (phase 2)		Phase 3 RA program[b]
	UPA 6 mg BID/15 mg QD (*n* = 493; PY = 1277)	UPA 12 mg BID/30 mg QD (*n* = 187; PY = 498)	UPA 15 mg QD (*n* = 3209; PY = 9079)
Any AE	138.4 (132.0, 145.0)	238.0 (224.6, 252.0)	205.5 (202.5, 208.5)
Any SAE	7.9 (6.4, 9.6)	15.3 (12.0, 19.1)	12.4 (11.7, 13.2)
AE leading to discontinuation	4.2 (3.2, 5.5)	5.8 (3.9, 8.4)	4.9 (4.4, 5.3)
All deaths	0.4 (0.1, 0.9)	0.6 (0.1, 1.8)	0.5 (0.4, 0.7)[c]
Infection	49.2 (45.5, 53.2)	80.4 (72.7, 88.7)	63.9 (62.3, 65.6)
Serious infection	1.4 (0.8, 2.2)	4.0 (2.5, 6.2)	2.8 (2.4, 3.1)
Opportunistic infection[d]	0.2 (0.0, 0.6)	0.4 (0.0, 1.5)	0.3 (0.2, 0.4)
Herpes zoster	2.0 (1.3, 3.0)	6.4 (4.4, 9.1)	3.0 (2.6, 3.3)
Active tuberculosis	< 0.1 (0.0, 0.4)	0	< 0.1 (0.0, 0.1)
Anemia	1.1 (0.6, 1.8)	3.6 (2.1, 5.7)	3.0 (2.7, 3.4)
Neutropenia	1.3 (0.8, 2.1)	1.0 (0.3, 2.3)	2.1 (1.8, 2.5)
Lymphopenia	1.7 (1.1, 2.6)	1.6 (0.7, 3.2)	1.7 (1.4, 1.9)
Adjudicated GI perforation	0	0	< 0.1 (0.0, 0.1)
Any malignancy	1.2 (0.7, 1.9)	3.2 (1.8, 5.2)	1.1 (0.9, 1.4)
Excluding NMSC	0.8 (0.4, 1.4)	1.2 (0.4, 2.6)	0.7 (0.6, 0.9)
NMSC	0.4 (0.1, 0.9)	2.0 (1.0, 3.7)	0.4 (0.3, 0.5)
CPK elevation	3.4 (2.5, 4.6)	5.4 (3.6, 7.9)	4.4 (4.0, 4.9)
Hepatic disorder	4.1 (3.0, 5.3)	3.4 (2.0, 5.5)	10.2 (9.5, 10.8)
Adjudicated VTE[e]	0.5 (0.2, 1.0)	0.8 (0.2, 2.1)	0.4 (0.3, 0.6)
Adjudicated MACE[f]	0.5 (0.2, 1.0)	0.8 (0.2, 2.1)	0.4 (0.3, 0.5)
Lymphoma	0.2 (0.0, 0.6)	0	< 0.1 (0.0, 0.1)
Renal dysfunction	< 0.1 (0.0, 0.4)	0.2 (0.0, 1.1)	0.2 (0.1, 0.4)

AE adverse event, *BID* twice daily, *CI* confidence interval, *CPK* creatine phosphokinase, *E/100 PY* events per 100 PY, *GI* gastrointestinal, *MACE* major adverse cardiovascular events, *NMSC* non-melanoma skin cancer, *PY* patient-years, *QD* once daily, *RA* rheumatoid arthritis, *SAE* serious AE, *UPA* upadacitinib, *VTE* venous thromboembolic events

[a]Multiple events occurring in the same patients are counted in the calculation of E/100 PY

[b]Cut-off date: June 30, 2021 (data on file)

[c]Not including non-treatment-emergent deaths

[d]Excluding tuberculosis and herpes zoster

[e]VTE defined as deep vein thrombosis and pulmonary embolism

[f]MACE defined as cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke

Table 3 Most common AEs reported in BALANCE-EXTEND

Events (E/100 PY)[a]	UPA 6 mg BID/ 15 mg QD (n = 493; PY = 1277)	UPA 12 mg BID/ 30 mg QD (n = 187; PY = 498)	UPA 6 mg BID/15 mg QD post-down- titration (n = 38; PY = 89)
Urinary tract infection	84 (6.6)	54 (10.9)	6 (6.8)
Upper respiratory tract infection	71 (5.6)	63 (12.7)	8 (9.0)
Bronchitis	67 (5.2)	24 (4.8)	8 (9.0)
Nasopharyngitis	75 (5.9)	19 (3.8)	3 (3.4)
Blood CPK increased	44 (3.4)	27 (5.4)	4 (4.5)
Rheumatoid arthritis[b]	33 (2.6)	35 (7.0)	1 (1.1)
Hypercholesterolemia	35 (2.7)	18 (3.6)	3 (3.4)
Herpes zoster	24 (1.9)	25 (5.0)	3 (3.4)
Hypertension	23 (1.8)	19 (3.8)	1 (1.1)
Oral herpes	10 (0.8)	15 (3.0)	17 (19.2)
Sinusitis	15 (1.2)	24 (4.8)	0
Fall	9 (0.7)	23 (4.6)	1 (1.1)

AE adverse event, *BID* twice daily, *CPK* creatine phosphokinase, *E/100 PY* events per 100 PY, *PY* patient-years, *QD* once daily, *UPA* upadacitinib

[a]Includes events reported with a frequency $\geq$ 3 E/100 PY in either group. Multiple events occurring in the same patients are counted in the calculation of E/100 PY

[b]Medical Dictionary for Regulatory Activities preferred term for worsening of disease

severely active RA. Although the data were obtained in different trials, and are therefore not directly comparable, the overall rate of AEs with UPA 6 mg BID/15 mg QD in BALANCE-EXTEND (138.4 events/100 PY) was numerically lower than that reported with UPA 15 mg QD in the long-term extension of SELECT-COMPARE (214.9 events/100 PY); however, the types of AEs and overall tolerability were generally similar [17]. The types and frequencies of AEs with UPA were also similar to those reported in long-term studies of baricitinib [18], while the incidence rates of MACE were numerically lower than those reported for tofacitinib in the ORAL Surveillance population [19].

Limitations of this analysis include the study's open-label design and lack of a non-UPA comparator arm. In addition, assessments in long-term analyses may have been biased because of the premature withdrawal of patients in whom treatment was less effective or intolerable. Furthermore, as aforementioned, only patients without safety concerns in BALANCE-1 and -2 were eligible to enter BALANCE-EXTEND. Results should also be interpreted with caution due to the small patient population (particularly in the 'Titrated up' and 'Titrated up and down' groups), and the fact that the titration groups are 'self-selected' based on patient response to treatment, as opposed to being randomly assigned; it is due to this that data are reported as observed, without further statistical analyses. Despite these limitations, the findings of BALANCE-EXTEND strengthen the evidence for long-term efficacy and safety of UPA in patients with RA.

CONCLUSIONS

In BALANCE-EXTEND, UPA treatment for up to 312 weeks demonstrated sustained long-term efficacy in patients with RA who completed the study, with continued improvement in physical function over time. Long-term treatment with UPA was associated with an acceptable safety profile, with no new safety signals reported. The types and frequencies of AEs were consistent with those reported in the phase 3 program of UPA in RA populations and other studies of JAK inhibitors. Overall, the results remain favorable for the long-term benefit–risk profile of UPA in patients with RA.

ACKNOWLEDGMENTS

AbbVie and the authors thank the participants, study sites, and investigators who participated in this clinical trial.

Funding. AbbVie funded this trial and participated in the trial design, research, analysis, data collection, interpretation of data, and the review and approval of the publication. All authors had access to relevant data and participated in the drafting, review, and approval of this publication. No honoraria or payments were made for authorship. Publication for this study, including the journal's Rapid Service Fee, was covered by AbbVie.

Medical Writing and Editorial Assistance. Medical writing support was provided by Dan Booth, PhD, on behalf of 2 the Nth (Cheshire, UK), and was funded by AbbVie.

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.

Author Contributions. Alan Kivitz, Alvin F. Wells, Juan I. Vargas, Herbert S. B. Baraf, Maureen Rischmueller, Justin Klaff, Nasser Khan, Yihan Li, Kyle Carter, Alan Friedman, and Patrick Durez contributed to the study conception and design. Material preparation, data collection, and analyses were performed by Alan Kivitz, Herbert S. B. Baraf, and Juan I. Vargas. All authors had access to relevant data and participated in the drafting, review, and approval of this publication.

Prior Presentation. This study was previously included as a poster presentation at the European Congress of Rheumatology (EULAR), June 1–4, 2022, Copenhagen, Denmark (POS0685 poster session; Kivitz A, Wells AF, Ignacio Vargas J, et al. Long-term safety and efficacy of upadacitinib in patients with rheumatoid arthritis: final results from the BALANCE-EXTEND open-label extension study. Ann Rheum Dis. 2022;81:620–1. http://dx.doi.org/10.1136/annrheumdis-2022-eular.1819).

Disclosures. Alan Kivitz has received consulting fees and/or honoraria from AbbVie, Amgen, Boehringer Ingelheim, Celgene Corporation, EcoR1 Capital, Flexion Therapeutics, Genentech, Gilead, GlaxoSmithKline, Grünenthal, Horizon, Janssen, Lilly, Merck, Novartis, Orion, Pfizer, Regeneron Pharmaceuticals, SUN Pharma Advanced Research, and UCB; owns stocks or options in Amgen, Gilead, GlaxoSmithKline, Novartis, Pfizer, and Sanofi; has received fees from AbbVie for his role as a Principal Investigator in the study; and is a board and/or advisory board member for AbbVie, Bendcare LLC, Boehringer Ingelheim, ChemoCentryx, Flexion, Gilead, Grünenthal, Horizon, Janssen, Lilly, Novartis, Pfizer, Regeneron, and UCB. Alvin F. Wells has received consulting fees and research support from AbbVie. Juan I. Vargas has received honoraria and fees from AbbVie as a Principal Investigator in the study. Herbert S. B. Baraf has received grant/research support from AbbVie, Genentech, Gilead, Janssen, and Lilly; has acted as a consultant for Gilead and Janssen; and has received honoraria and fees from AbbVie as a Principal Investigator in the study. He has retired from the Center for Rheumatology and Bone Research since the completion of the study. Maureen Rischmueller has received

grant/research support from AbbVie, Amgen, BMS, Janssen Global Services, Lilly, Novartis, Pfizer, Sanofi Pasteur Biologics, and UCB Biosciences; and has acted as a consultant for AbbVie, BMS, CSL Behring, Gilead, Janssen Global Services, Lilly, Pfizer, Sanofi US Services, and UCB Biosciences. Justin Klaff, Nasser Khan, Yihan Li, Kyle Carter, and Alan Friedman are employees of AbbVie and may own stocks or options. Patrick Durez has received speaker fees from AbbVie, Galapagos, Lilly, Nordimed, and Thermo Fisher Scientific Inc.

Compliance with Ethics Guidelines. The BALANCE-EXTEND study was conducted in accordance with the International Conference on Harmonization guidelines, applicable regulations governing clinical trial conduct, and the Declaration of Helsinki 1964 and its later amendments. As per GCP, the study protocols were approved by an IEC/IRB at each site (Supplementary Material Table 1). All patients provided written informed consent.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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