

Subcutaneous Abatacept for the Treatment of Rheumatoid Arthritis: Longterm Data from the ACQUIRE Trial

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ABSTRACT. Objective. Assess longterm tolerability, safety, and efficacy of subcutaneous (SC) abatacept (ABA) in methotrexate-refractory patients with rheumatoid arthritis (RA).

Methods. The phase III, multinational Abatacept Comparison of Sub[QU]cutaneous Versus Intravenous in Inadequate Responders to Methotrexate (ACQUIRE) trial comprised a 6-month, randomized, double-blind (DB) period, in which patients received intravenous (IV) or SC ABA, plus MTX, followed by an open-label, longterm extension (LTE), in which patients received SC ABA, 125 mg/week. Safety and efficacy from the LTE (~3.5 yrs of exposure) are reported.

Results. Patients who completed the DB period (1372/1385, 99.1%) entered the LTE; 1134 patients (82.7%) kept taking the treatment at time of reporting. Mean (SD) was 31.9 months (6.8); median (range) exposure was 33.0 (8–44) months. Patients entering the LTE had longstanding, moderate-to-severe disease [mean 7.6 (7.9) yrs and DAS28 (C-reactive protein) 6.2 (0.9)]. Incidence rates (events/100 patient-yrs) were reported for serious adverse events (8.76, 95% CI 7.71, 9.95), infections (44.80, 95% CI 41.76, 48.01), serious infections (1.72, 95% CI 1.30, 2.27), malignancies (1.19, 95% CI 0.86, 1.66), and autoimmune events (1.31, 95% CI 0.95, 1.79). Twenty-seven patients (2%) experienced injection-site reactions; all except 1 were mild. American College of Rheumatology 20, 50, and 70 responses achieved during the DB period were maintained through the LTE, and on Day 981 were 80.2% (95% CI 77.2, 83.2), 63.5% (95% CI 58.2, 68.9), and 39.5% (95% CI 34.0, 44.9) for patients who kept taking SC ABA, and 80.0% (95% CI 77.0, 83.0), 63.2% (95% CI 57.8, 68.7), and 39.2% (95% CI 33.7, 44.7) for those who switched from IV to SC ABA.

Conclusion. These findings support SC ABA as a well-tolerated and efficacious longterm treatment for patients with RA and inadequate response to MTX (ClinicalTrials.gov identifier NCT00559585). (J Rheumatol First Release March 1 2014; doi:10.3899/jrheum.130112)

Key Indexing Terms:

ABATACEPT ACQUIRE RHEUMATOID ARTHRITIS LONGTERM SAFETY

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The longterm safety and efficacy profile of intravenous (IV) abatacept (ABA), a selective T cell costimulation modulator, is well established in patients with rheumatoid arthritis (RA), including methotrexate (MTX)-naive patients¹ and those with an inadequate response to MTX^{2,3,4,5} or anti-tumor necrosis factor (TNF) therapy⁶. A subcutaneous (SC) formulation of ABA is also available. Four phase II or III trials have investigated the tolerability and clinical effectiveness of a weekly fixed dose of 125 mg SC ABA, demonstrating low immunogenicity with safety and efficacy similar to that of the IV formulation^{7,8,9,10,11}.

The Abatacept Comparison of sub(QU)cutaneous versus intravenous in Inadequate Responders to methotrexate (ACQUIRE) trial was a multinational, phase IIIb, randomized, double-blind (DB) study that evaluated the comparable efficacy and safety of SC and IV ABA over 6 months¹². At Month 6, similar proportions of SC and IV ABA-treated patients achieved an American College of Rheumatology (ACR) 20 response (estimated difference: 0.3%, 95% CI -4.2, 4.8), confirming noninferiority of SC to IV ABA. The onset and magnitude of efficacy responses were equal for both formulations, and similar patient retention was also reported (94.2% for SC ABA vs 93.8% for IV ABA at Month 6). Overall safety was also similar between groups, including discontinuations due to adverse events (AE) and serious AE (SAE), serious infections, malignancies, and autoimmune events.

Here we describe the results from the open-label, longterm extension (LTE) of the ACQUIRE trial, in which all patients who completed the 6-month DB period received SC ABA 125 mg weekly for up to ~3.5 years of exposure, to assess the longterm safety, efficacy, and tolerability of SC ABA.

MATERIALS AND METHODS

Study design and patient population. Patients eligible for inclusion in the open-label LTE of the ACQUIRE trial (ClinicalTrials.gov identifier NCT00559585) were required to have met the inclusion criteria for, and to have completed, the 6-month, randomized, DB period¹². Patients included in the DB trial were ≥ 18 years of age with active RA that had responded inadequately to ≥ 3 months of treatment with MTX. Disease activity requirements at randomization were ≥ 10 swollen and ≥ 12 tender joints, and C-reactive protein (CRP) levels were ≥ 0.8 mg/dl. Patients were screened for tuberculosis (TB) and excluded if there was current clinical/radiographic/laboratory evidence of active TB or a history of active TB in the previous 3 years. Patients with a history of active TB ≥ 3 years ago were included if appropriately treated.

In the DB period, patients were randomized (1:1), with stratification by body weight (< 60 kg, 60–100 kg, > 100 kg), to receive ABA through one of 2 different routes: either SC injection (125 mg) on Day 1 and weekly thereafter, including an IV ABA infusion (~10 mg/kg based on weight range) on Day 1 only (the SC injection was administered ~30 min after the end of the IV infusion); or IV infusion (~10 mg/kg based on weight range) on Days 1, 15, and 29, and every 4 weeks thereafter (up to Day 162 for the SC ABA group, and up to Day 141 for the IV ABA group). During the open-label LTE, all eligible patients received SC ABA 125 mg weekly (from Day 169 of the DB period/Day 1 of the LTE).

During the DB period, MTX was maintained at the same dose as at trial

entry (≥ 15 mg/week); low-dose stable oral corticosteroids (≤ 10 mg/day, prednisone equivalent) and stable-dose nonsteroidal antiinflammatory drugs (NSAID) were also permitted. Adjustments to MTX, corticosteroids, and NSAID were permitted during the LTE at the discretion of the investigator, based on the clinical status of the patient. During the LTE period, sites were allowed to add traditional disease-modifying antirheumatic drugs (DMARD) at the discretion of the investigator. The addition of other biologic agents was not permitted.

Assessments. Safety assessments were performed at each study visit during the DB period, and at 12-week intervals and yearly visits during the LTE. All AE, SAE, AE of interest, vital signs, and laboratory test abnormalities were recorded. AE of interest included infections, malignancies, autoimmune disorders, and injection-site reactions. Immunogenicity was evaluated by ELISA during the DB period of this study¹². During the LTE, however, a different assay was used to assess immunogenicity — electrochemiluminescence (ECL), based on the proportion of patients with a seropositive response defined as a titer value of ≥ 10 . The ECL immunoassay detected antibodies to CTLA-4 and possibly immunoglobulin (Ig), or the IgG and/or junction region. Persistent immunogenicity was defined as detection of at least 2 consecutive positive on-treatment serum samples within the same antibody reactivity. Efficacy assessments were performed at baseline and at each study visit during the DB period, at 12-week intervals and yearly visits during the LTE, and 7 days after the last SC injection for patients who discontinued the study prematurely. Improvement in signs and symptoms of RA was evaluated by ACR 20, 50, and 70 responses. Disease activity was evaluated by 28-joint Disease Activity Score (DAS28) based on CRP, Clinical Disease Activity Index (CDAI), and Simplified Disease Activity Index (SDAI) scores. The Health Assessment Questionnaire-Disability Index (HAQ-DI) was used to assess physical function, with a HAQ-DI response defined as an improvement from baseline of ≥ 0.3 units.

Statistical analyses. Safety assessments are presented for all patients who received at least 1 dose of SC ABA during the LTE; data are presented up to a maximum of 44 months of exposure following study initiation (which corresponds to the database cutoff date), and include events that occurred up to Day 56 (greater than 4 times the half-life of ABA in patients with RA) after the last dose of study drug for patients who discontinued the LTE. Safety data from the DB period are described according to original DB treatment group, to evaluate whether there is an increase in the incidence of safety events over time; DB data are presented up to the first dose of study drug in the LTE, or up to 56 days after the last dose of study drug for patients who discontinued the DB period or did not enter the LTE. Results from the safety assessments are presented as frequencies and incidence rates (IR). IR were calculated as events per 100 patient-years of exposure, with a patient's contribution to exposure ending at the time of the first occurrence of an AE.

Efficacy data are based on as-observed analyses, including all patients who entered the LTE and received at least 1 dose of ABA, and are presented according to patients' original DB treatment group (SC or IV ABA). Data are presented up to ~33 months (Day 981) of the study. Although the maximum time of exposure to ABA during the trial was 44 months, most patients had not reached this timepoint at time of analysis because of differential enrollment dates. Most patients had, however, reached Day 981 at the time of reporting, and we report efficacy up to this timepoint. No formal statistics were performed during the LTE, but descriptive statistics are provided for all assessments, including point estimates and 95% CI for the proportions of patients achieving each clinical efficacy outcome.

RESULTS

Patient disposition and baseline clinical characteristics. A total of 1372 patients continued into the LTE, accounting for 99.1% of patients who completed the 6-month DB period (Figure 1). At the time of reporting (as of October 3, 2011,

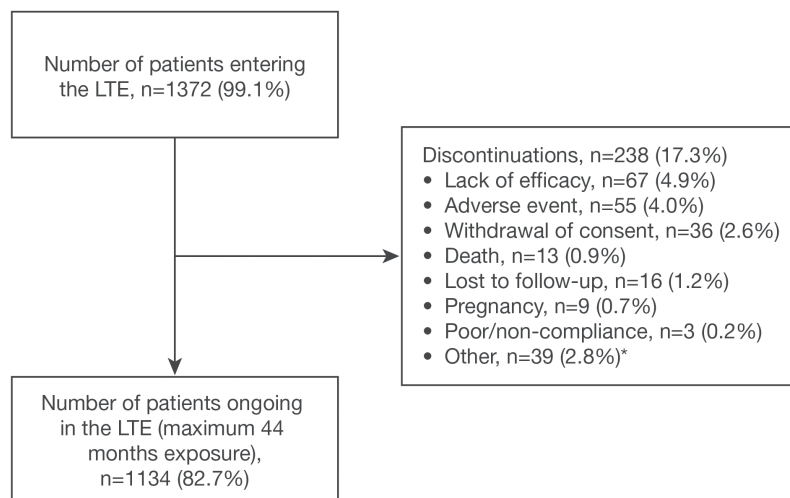


Figure 1. Patient disposition in the longterm extension (LTE). *Includes “Other”, “Administrative reason by sponsor”, and “Subject no longer meets study criteria” discontinuation categories. Last timepoint for the LTE is October 3, 2011, at which point mean (range) cumulative duration of abatacept exposure was 31.9 (8–44) months.

database lock, which corresponds to a maximum possible exposure time of 44 months), 1134 (82.7%) patients remained in the study and continued to receive SC ABA. During the LTE, 4.9% (n = 67) of patients discontinued owing to lack of efficacy, and 4.0% (n = 55) discontinued because of an AE. Mean (SD) duration of ABA exposure during the cumulative study period (DB plus LTE periods) was 31.9 (6.8) months; the median exposure was 33.0 (range 8–44) months. As the wide range of exposure indicates, some patients had not yet reached the later assessment

timepoints at the time of the efficacy analysis presented here because of differential enrollment dates; this is reflected in decreased patient numbers at these later timepoints.

Demographic and clinical characteristics at baseline for patients treated in the LTE were similar to those observed for the intent-to-treat population of patients treated in the DB period (Table 1)¹². Patients had longstanding [mean 7.6 (7.9) yrs], moderate-to-severe disease, as evidenced by tender and swollen joint counts of 29.6 (13.8) and 19.9 (9.2), respectively, and a mean DAS28-CRP of 6.2 (0.9).

Table 1. Baseline demographic and clinical characteristics for patients treated in the double-blind (DB) period and longterm extension (LTE). Data are mean (SD), unless otherwise stated.

Characteristics	DB Population		LTE Population
	SC ABA + MTX, n = 736	IV ABA + MTX, n = 721	SC ABA + MTX, n = 1372
Age, yrs	49.9 (13.2)	50.1 (12.6)	49.7 (12.8)
Sex, female %	84.4	80.4	82.4
Race, white %	74.7	74.5	74.5
Disease duration, yrs	7.6 (8.1)	7.7 (7.8)	7.6 (7.9)
Tender joint count	30.1 (14.1)*	29.1 (13.3)	29.6 (13.8) [¶]
Swollen joint count	20.4 (9.6) [†]	19.4 (8.6)	19.9 (9.2) [¶]
DAS28-CRP	6.2 (0.9) [§]	6.2 (0.8)	6.2 (0.9)**
CRP, mg/dl	2.6 (2.9) [‡]	2.7 (2.9)	2.7 (3.0) [¶]
HAQ-DI score	1.7 (0.7)	1.7 (0.7)	1.7 (0.7)
Pain, 100 mm VAS	67.8 (20.1)	66.8 (20.5)	67.2 (20.3)
Patient global assessment, 100 mm VAS	66.8 (20.4)	64.9 (20.0)	65.9 (20.2)
Physician global assessment, 100 mm VAS	64.3 (16.5)	63.1 (16.6)	63.6 (16.4)
RF-positive %	84.8 [‡]	85.9 ^{¶¶}	86.1 ^{¶¶}

*n = 736. †n = 735. ‡n = 734. §n = 733. ¶n = 711. ¶¶n = 1371. **n = 1370. ¶¶n = 1350. CRP: C-reactive protein; DAS28: 28-joint Disease Activity Score; HAQ-DI: Health Assessment Questionnaire-Disability Index; IV: intravenous; RF: rheumatoid factor; SC: subcutaneous; VAS: visual analog scale; ABA: abatacept; MTX: methotrexate.

Concomitant medications. Nearly all patients (99.6%) continued to receive MTX, and mean MTX dose remained consistent throughout the LTE of the ACQUIRE study, during which time adjustments were permitted. Weekly MTX doses were 16.2 (4.8), 15.9 (6.0), 15.8 (6.7), 15.7 (7.4), and 15.5 (8.4) at Days 169, 365, 533, 729, and 897, respectively. At randomization, 69.2% of patients were receiving oral steroids, at a mean (SD) dose of 4.6 mg (3.7); the proportions of patients receiving oral steroid remained relatively consistent throughout the trial, with 72.7% of patients receiving oral steroids at some point during the LTE, at a dose of 5.1 mg (5.4). During the LTE, 41 patients (3.0%) added hydroxychloroquine, 36 (2.6%) added sulfasalazine, and < 1% added leflunomide, chloroquine, cyclosporine, azathioprine, or gold sodium.

Safety. The overall safety experience, assessed by the IR of events, in the LTE (maximum of ~3 yrs' exposure) was similar to the experience reported in the 6-month DB period with both SC and IV ABA (Table 2). The IR of SAE was 8.76 (events per 100 patient-yrs; 95% CI 7.71, 9.95) during the LTE, which is comparable to that observed among patients receiving SC ABA in the DB period (9.02, 95% CI 6.31, 12.90). SAE resulted in discontinuation in 42 patients (3.1%) during the LTE, with the most common events (occurring in more than 1 patient) being breast cancer (5 patients, 0.4%), malignant lung neoplasm (3 patients, 0.2%), pneumonia, pulmonary tuberculosis and myocardial infarction (MI; 2 patients each, 0.1%). Twenty-one deaths (1.5%) were reported during the LTE, at an IR of 0.71 (95% CI 0.44, 1.09). These included sudden death, death with cause not specified, asthma attack, car accident, cardiac arrest, acute gastrointestinal infection, peritoneal carcinomatosis, multiple organ failure, secondary pneumonia and pulmonary TB, lung cancer, C1 fracture, primary lung cancer, pneumonia, acute MI, anal cancer, bronchopneumonia and coronary heart failure, sudden circulatory arrest, sudden cardiac death, metastatic cholangiocarcinoma, and MI.

Infections occurred at an IR of 44.80 (95% CI 41.81, 48.01) and serious infections occurred at an IR of 1.72 (95% CI 1.30, 2.27) during the LTE period, and were not increased compared with the 6-month DB period (Table 3). Serious infections occurring in more than 1 patient each during the LTE included pneumonia (10 patients, 0.7%, IR 0.34, 95% CI 0.18, 0.63); bronchitis and urinary tract infection (4 patients each, 0.3%, IR 0.14, 95% CI 0.05, 0.36); appendicitis and herpes zoster (3 patients each: 0.2%, IR 0.10, 95% CI 0.03, 0.31; and 0.10, 95% CI 0.03, 0.32, respectively); and gastroenteritis, lobar pneumonia, pulmonary TB, acute pyelonephritis, respiratory tract infection and sinusitis (2 patients each, 0.1%, IR 0.07, 95% CI 0.02, 0.27). Seven opportunistic infections occurred during the study, all during the LTE, including TB in 4 patients (IR 0.14, 95% CI 0.05, 0.36) and candidiasis in 3 patients (IR 0.10, 95% CI 0.03, 0.31). The patients with TB were a 35-year-old woman from South America with normal chest radiograph and negative purified protein derivative (PPD) at baseline, who had a positive culture on Day 349, was diagnosed with Grade II TB and discontinued study drug; a 56-year-old woman from Asia who had a normal chest radiograph and negative PPD test at baseline, developed pulmonary TB on the left lung based on PPD, quantiferon, chest radiograph, and computed tomography scan results at Day 317 and dropped out of the study; a 55-year-old man from South America who had a history of TB in childhood (treated with unknown antituberculous therapy for 1 yr), diagnosed with peritoneal TB on Day 537 of the study and subsequently discontinued; a 64-year-old woman from South America with no history of TB who developed secondary pneumonia and pulmonary TB on Day 791 of treatment and discontinued the study drug.

The IR of malignancies did not increase during the LTE period (1.19; 95% CI 0.86, 1.66) compared with the DB period (Table 2). Events that occurred in more than 1 patient included basal cell carcinoma (9 patients, 0.7%, IR 0.31;

Table 2. Summary of adverse events reported in the double-blind (DB) period and longterm extension (LTE). Table includes data from patients included in the anti-tumor necrosis factor failure substudy. Safety data are based on all patients who received at least 1 dose of abatacept (ABA) in the intent-to-treat population.

	DB Period SC ABA + MTX, n = 744		DB Period IV ABA + MTX, n = 731		LTE SC ABA + MTX, n = 1372	
	Patients with Event, n (%)	IR (95% CI)	Patients with Event, n (%)	IR (95% CI)	Patients with Event, n (%)	IR (95% CI)
Deaths	1 (0.1)	0.29 (0.01, 1.64)	5 (0.7)	1.51 (0.49, 3.53)	21 (1.5)	0.71 (0.44, 1.09)
SAE	31 (4.2)	9.02 (6.31, 12.90)	36 (4.9)	11.14 (8.04, 15.44)	238 (17.3)	8.76 (7.71, 9.95)
Discontinued owing to SAE	9 (1.2)	2.66 (1.22, 5.06)	14 (1.9)	4.25 (2.32, 7.13)	42 (3.1)	1.42 (1.03, 1.92)
AE	503 (67.6)	279.35 (255.46, 304.86)	478 (65.4)	265.67 (242.38, 290.59)	1147 (83.6)	107.73 (101.59, 114.15)
Discontinued owing to AE	16 (2.2)	4.75 (2.72, 7.72)	25 (3.4)	7.62 (4.93, 11.26)	56 (4.1)	1.90 (1.43, 2.47)
Infections	237 (31.9)	84.54 (74.12, 96.01)	227 (31.1)	82.92 (72.48, 94.44)	803 (58.5)	44.80 (41.76, 48.01)
Serious infections	5 (0.7)	1.48 (0.62, 3.56)	10 (1.4)	3.05 (1.64, 5.67)	50 (3.6)	1.72 (1.30, 2.27)
Malignancies	2 (0.3)	0.59 (0.15, 2.36)	5 (0.7)	1.52 (0.63, 3.65)	35 (2.6)	1.19 (0.86, 1.66)
Autoimmune events	6 (0.8)	1.78 (0.80, 3.96)	6 (0.8)	1.83 (0.82, 4.07)	38 (2.8)	1.31 (0.95, 1.79)

AE: adverse event; IV: intravenous; MTX: methotrexate; SAE: serious adverse event; SC: subcutaneous; IR: incidence rates.

Table 3. Subcutaneous injection-site reactions reported in the double-blind (DB) period and longterm extension (LTE). Data are n (%) patients with event.

Reaction Type	DB Period SC ABA + MTX, n = 736	DB Period IV ABA + MTX, n = 721	LTE SC ABA + MTX, n = 1372
Subcutaneous injection-site reaction	19 (2.6)	19 (2.6)	27 (2.0)
Erythema	5 (0.7)	1 (0.1)	6 (0.4)
Hematoma	4 (0.5)	5 (0.7)	6 (0.4)
Pain	1 (0.1)	4 (0.5)	6 (0.4)
Unspecified reaction	1 (0.1)	3 (0.4)	4 (0.3)
Pruritus	6 (0.8)	1 (0.1)	3 (0.2)
Hemorrhage	0	0	2 (0.1)
Papule	1 (0.1)	3 (0.4)	2 (0.1)
Rash	2 (0.3)	1 (0.1)	1 (<0.1)
Other*	4 (0.5)	0	4 (0.3)

*Other injection-site reactions reported in only 1 patient each included inflammation, nodule, paresthesia, and swelling. Safety data are based on all patients who received at least 1 dose of abatacept in the intent-to-treat population. IV: intravenous; ABA: abatacept; MTX: methotrexate; SC: subcutaneous.

95% CI 0.16, 0.59), breast cancer (5 patients, 0.4%, IR 0.17; 95% CI 0.07, 0.41), malignant lung neoplasm (3 patients, 0.2%, IR 0.10; 95% CI 0.03, 0.31), squamous cell carcinoma of skin (3 patients, 0.2%, IR 0.10; 95% CI 0.03, 0.31), and prostate cancer (2 patients, 0.1%, IR 0.07; 95% CI 0.02, 0.27).

Autoimmune events were reported at an IR of 1.31 (95% CI 0.95, 1.79) during the LTE, and were not increased relative to the DB period (Table 2). The most frequently reported events were psoriasis (9 patients, 0.7%, IR 0.31; 95% CI 0.16, 0.59), of which 2 events were exacerbations in patients previously diagnosed, and Sjögren syndrome (7 patients, 0.5%, IR 0.24; 95% CI 0.11, 0.50), one of which was classified as secondary, followed by episcleritis, vasculitis, erythema nodosum, and ulcerative colitis, which occurred in 3 patients each (0.2%, IR 0.10; 95% CI 0.03, 0.31). Autoimmune events in the LTE required interruption of treatment in 3 cases (Crohn disease, erythema nodosum, and psoriasis, 1 patient each) and discontinuation of treatment in 2 patients (leukocytoclastic vasculitis and multiple sclerosis).

During the LTE, 27 patients (2.0%) experienced a local injection-site reaction. All events were mild, except for a single event of moderate intensity (injection-site nodule). Other events included 6 erythema (0.4%), 6 hematoma (0.4%), 6 pain (0.4%), 4 unspecified reaction (0.3%), 3 pruritus (0.2%), 2 hemorrhage (0.1%), 2 papule (0.1%), and 1 rash (< 0.1%). The frequency of injection-site reactions with SC ABA during the LTE was comparable with the frequency reported for SC ABA and IV ABA (SC placebo) in the DB period [19 (2.6%) and 19 (2.6%), respectively].

Safety over time. The IR of SAE at 6-month intervals did not increase over time compared with that during the DB period (Figure 2). Similarly, over time, the IR by 6-month intervals for serious infections, malignancies, and autoimmune disorders did not increase with increasing ABA exposure (Figure 2). Note that at the final timepoint, 95% CI for SAE

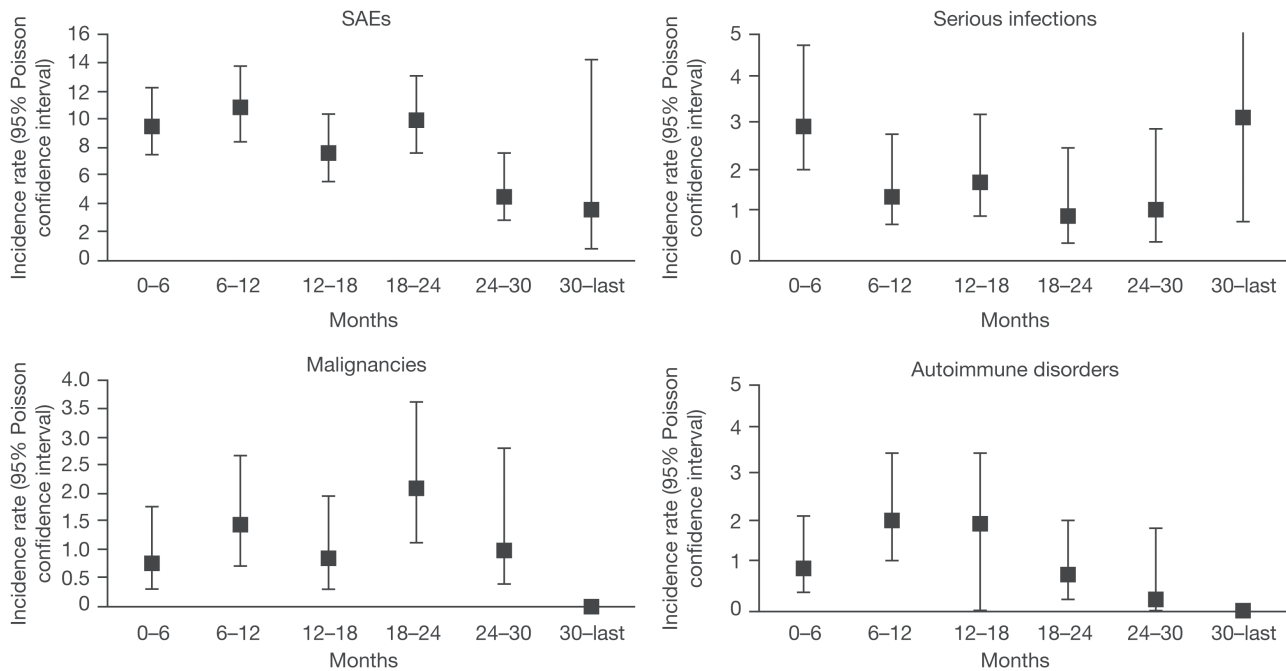
and serious infections are wide owing to diminishing patient numbers.

Immunogenicity. During the LTE, a total of 142/1372 patients (10.3%) had a laboratory-reported positive antibody response to ABA. Only 29/1350 patients (2.1%) experienced persistent immunogenicity (defined as at least 2 consecutive positive samples); 23 patients (1.7%) had a persistent response while taking treatment; and 7 patients (0.5%) had a persistent response while not taking treatment. Among those patients who had a persistent response while taking treatment, 11 (0.8%) patients had a response to CTLA-4 and possibly Ig, and 12 patients (0.9%) had a response to Ig and/or the junction region. The majority of patients had low titers; 7/142 patients (4.9%) had at least 1 titer sample ≥ 100 and 0/142 patients (0%) experienced persistent high titers (defined as at least 2 consecutive samples ≥ 100).

No associations between immunogenicity and safety were observed. Among patients who experienced a positive antibody response to ABA, SAE were reported in 19/142 patients (13.4%), which was consistent with the incidence in the overall population (Table 2). The percentage of patients with a positive immunogenicity response and infections [88/142 (62.0%)], serious infections [3/142 (2.1%)], malignancies [2/142 (1.4%)], autoimmune events [4/142 (2.8%)], and local injection-site reactions [1/142 (0.7%)] was also consistent with the overall LTE population (Table 2).

The efficacy of SC ABA in patients with positive antibody responses was consistent with the results of the overall population reported below. Among patients who experienced a positive immunogenicity response and were taking treatment on Day 981 (n = 53), ACR 20, 50, and 70 response rates were 86.8% (95% CI 77.7, 95.9), 67.9% (95% CI 55.4, 80.5), and 34.0% (95% CI 21.2, 46.7), respectively.

Efficacy. During the original DB period, comparable clinical and functional efficacy was observed through Day 169 (end



Months (days)		0-6 (1-180)	6-12 (181-360)	12-18 (361-540)	18-24 (541-720)	24-30 (721-900)	30-Last (901-Last)
Total exposure (person years)	SAEs/serious infections	658.57	603.74	552.13	514.86	331.36	56.45
	Malignancies	668.90	638.77	604.21	579.03	379.11	63.81
	Autoimmune events	668.36	636.21	597.13	569.46	374.58	64.30

Figure 2. Incidence rates of adverse events (AE) by 6-month intervals for patients treated in the longterm extension. Includes data up to 56 days after the last dose of study drug. For patient-year calculation, patients who reported an AE in a previous 6-month interval did not contribute to total exposure in the next 6-month interval (even when those patients had exposure information in the next 6-month interval). SAE: serious adverse event; py: patient-year.

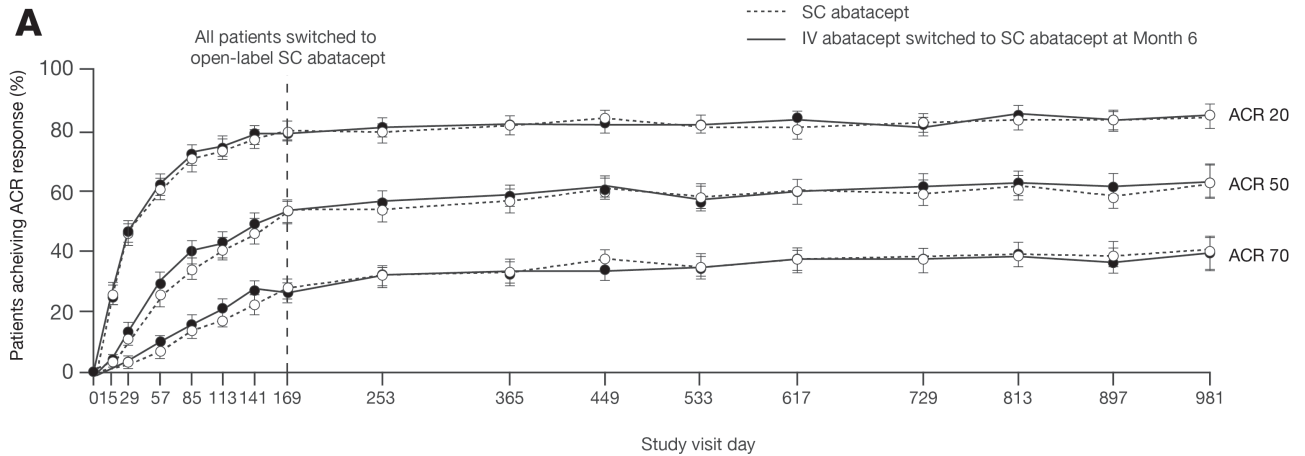
of DB period) for the original SC and IV ABA treatment groups. During the LTE, the original IV ABA arm demonstrated continuous clinical and functional improvement following the switch to SC ABA, comparable to the continuous clinical and functional improvement seen in patients from the original SC ABA arm (Figures 3 and 4). Although most patients reached Day 981 by the time of this analysis, not all patients had reached this point as a result of different enrollment dates in the trial. This resulted in lower patient numbers at the later time points of the efficacy analyses.

For the original SC ABA and IV ABA groups, respectively, ACR responses were maintained from Day 169 through Day 981 (Figure 3A). On Day 169, ACR 20 response rates were 80.2% (95% CI 77.2, 83.2) and 80.0% (95% CI 77.0, 83.0); ACR 50 response rates were 53.4% (95% CI 49.7, 57.1) and 52.8% (95% CI 49.1, 56.6); and ACR 70 response rates were 27.7% (95% CI 24.3, 31.0) and 26.7% (95% CI 23.3, 30.0). On Day 981, ACR 20 response rates were 84.8% (95% CI 80.8, 88.8) and 84.7% (95% CI 80.7, 88.8); ACR 50 response rates were 63.5% (95% CI 58.2, 68.9) and 63.2% (95% CI 57.8, 68.7); and ACR 70

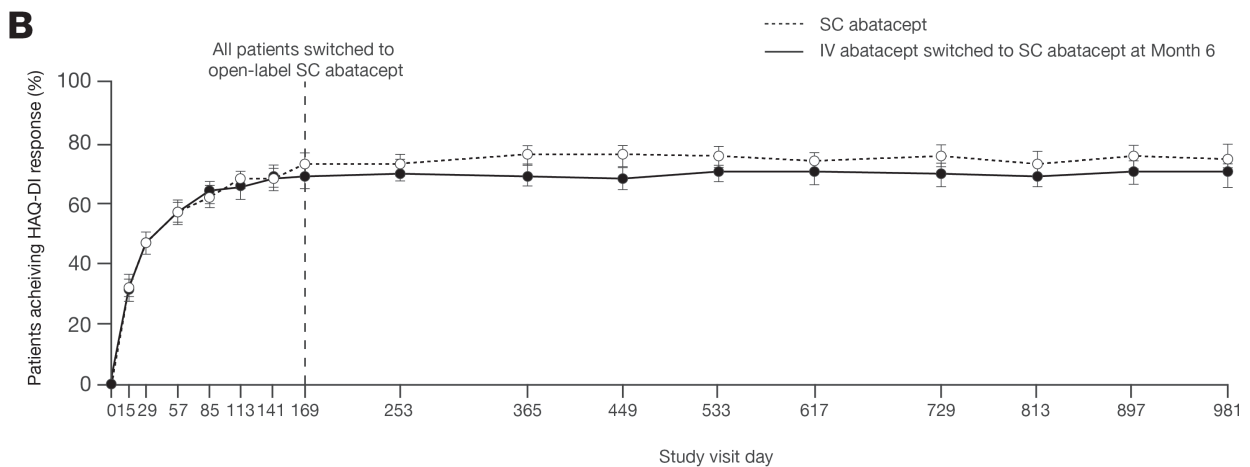
response rates were 39.5% (95% CI 34.0, 44.9) and 39.2% (95% CI 33.7, 44.7).

Improvements in physical function outcomes seen during the DB period were also maintained throughout the LTE for both the original SC and IV ABA groups, respectively (Figure 3B). On Day 169, 72.6% (95% CI 69.3, 76.0) and 68.3% (95% CI 64.8, 71.8); and on Day 981, 73.8% (95% CI 68.9, 78.7) and 70.0% (95% CI 64.8, 75.1) had achieved a HAQ-DI response.

Disease activity outcomes achieved in the DB period were maintained for patients who remained on treatment, for both original DB treatment groups (Figure 4). The proportions of patients achieving a DAS28-CRP ≤ 3.2 were 39.9% (95% CI 36.2, 43.5) and 41.7% (95% CI 37.9, 45.4) on Day 169 for the original SC and IV treatment groups, respectively; and were 55.2% (95% CI 49.5, 61.0) and 57.1% (95% CI 51.2, 62.9) on Day 981 (Figure 4A). The proportions of patients achieving DAS28-CRP < 2.6 were 24.2% (95% CI 21.0, 27.4) and 25.0% (95% CI 21.7, 28.3) on Day 169 for the original SC and IV ABA treatment groups, respectively, and were 38.5% (95% CI 32.9, 44.2) and 34.5% (95% CI 28.9,



		Patients with available data at each visit day*, according to the original treatment group															
		15	29	57	85	113	141	169	253	365	449	533	617	729	813	897	981
ACR 20	SC abatacept	685	687	684	685	687	685	686	685	661	648	627	611	600	585	525	310
	IV switched to SC abatacept	665	668	668	669	670	671	670	667	652	635	620	606	587	573	515	301
ACR 50	SC abatacept	688	690	687	686	686	684	689	683	663	648	628	613	598	585	529	310
	IV switched to SC abatacept	669	673	671	672	670	671	672	668	653	635	620	606	587	573	517	302
ACR 70	SC abatacept	689	689	688	686	689	690	690	685	666	650	626	616	600	584	530	309
	IV switched to SC abatacept	669	673	670	672	669	671	671	666	655	637	619	606	586	574	516	301

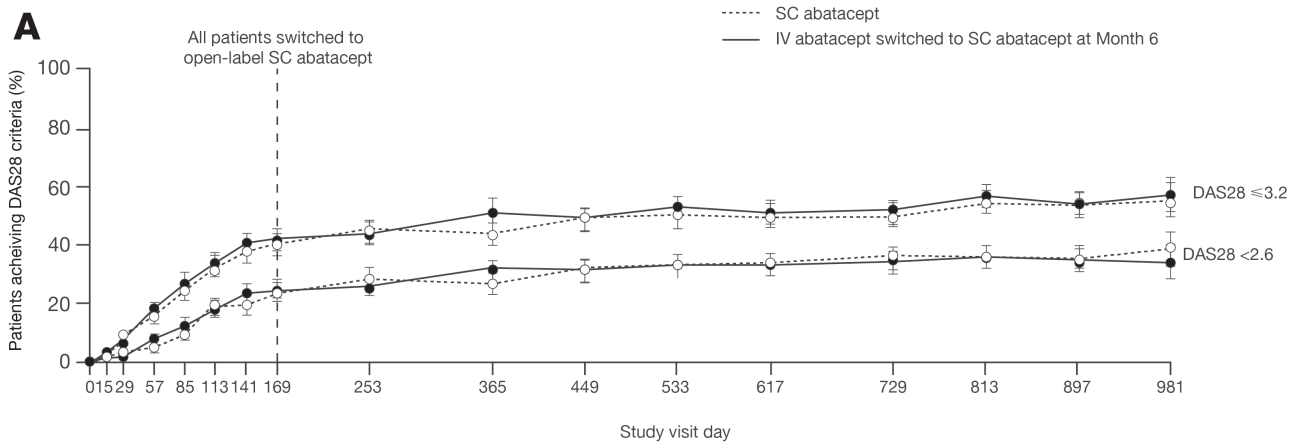


		Patients with available data at each visit day*, according to the original treatment group															
		15	29	57	85	113	141	169	253	365	449	533	617	729	813	897	981
SC abatacept		689	690	688	687	691	690	691	685	666	652	629	617	602	588	530	313
IV switched to SC abatacept		669	673	671	673	673	672	672	668	656	637	623	607	588	575	516	303

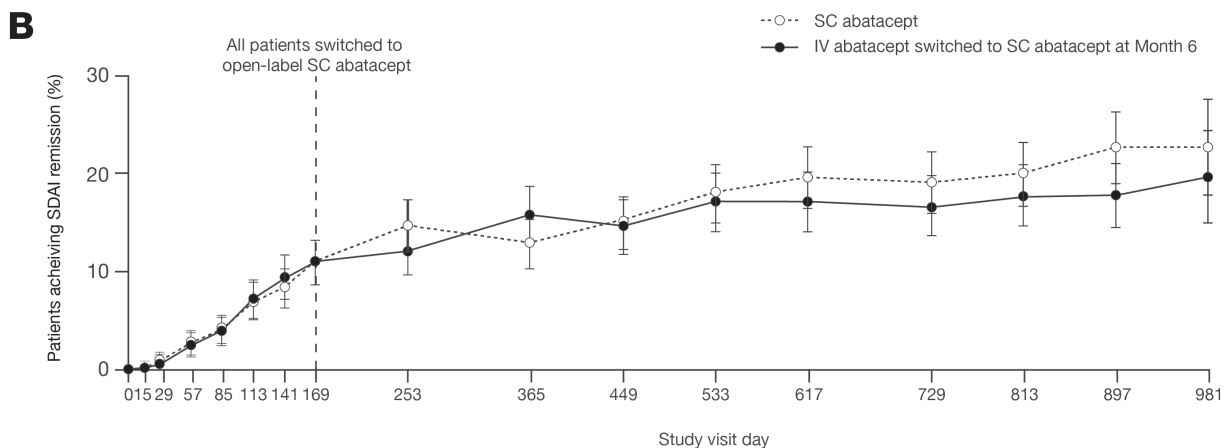
Figure 3. Clinical and functional efficacy according to American College of Rheumatology responses over time (A) and HAQ-DI response rates over time (B). HAQ response is defined as an improvement of at least 0.3 units from baseline. As-observed analysis, based on patients entering the longterm extension who received at least 1 dose of abatacept. *Not all patients reached later timepoints at time of data analysis. ACR: American College of Rheumatology; IV: intravenous; SC: subcutaneous; HAQ-DI: Health Assessment Questionnaire-Disability Index.

40.2) on Day 981 (Figure 4A). For patients entering the LTE, the mean baseline CDAI score was 43.86 (12.34), and the SDAI score was 46.54 (13.11). The proportions of patients achieving CDAI-defined remission (score \leq

2.8) and SDAI-defined remission (score \leq 3.3) were maintained from Day 169 through Day 981 among patients entering the LTE, for both DB treatment groups (Figures 4B and 4C).



	Patients with available data at each visit day*, according to the original treatment group															
	15	29	57	85	113	141	169	253	365	449	533	617	729	813	897	981
SC abatacept	685	685	680	679	680	678	685	684	657	646	627	613	598	578	519	288
IV switched to SC abatacept	659	668	666	657	663	662	667	660	651	631	616	601	584	566	507	275



	Patients with available data at each visit day*, according to the original treatment group															
	15	29	57	85	113	141	169	253	365	449	533	617	729	813	897	981
SC abatacept	684	683	679	678	679	677	684	681	656	646	626	613	598	577	518	287
IV switched to SC abatacept	656	665	665	656	662	662	665	659	651	630	615	601	583	566	506	275

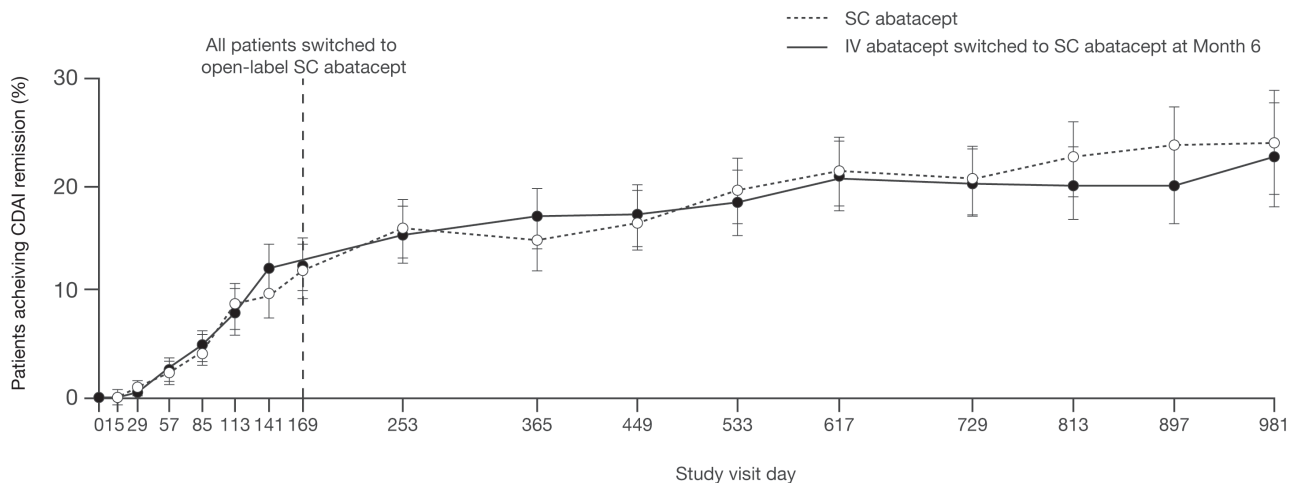
Figure 4. Disease activity outcomes according to DAS28-CRP outcomes over time (A), SDAI remission over time (B), and CDAI remission (C) over time. *Not all patients reached later timepoints at time of data analysis. CDAI remission is defined as ≤ 2.8 . SDAI remission is defined as ≤ 3.3 . As-observed analysis, based on patients entering the LTE who received at least 1 dose of abatacept. DAS28: 28-joint Disease Activity Score; IV: intravenous; SC: subcutaneous; CDAI: Clinical Disease Activity Index; SDAI: Simplified Disease Activity Index; CRP: C-reactive protein; LTE: longterm extension.

DISCUSSION

In the DB period of the ACQUIRE trial, SC and IV ABA demonstrated comparable efficacy and safety over 6 months of treatment in patients with RA and inadequate response to MTX. The LTE of the ACQUIRE study demonstrates consistent safety and maintained clinical efficacy for patients who received open-label SC ABA up to a maximum of 44 months.

The overall safety profile of SC ABA during the LTE was

consistent with the DB period; there were no new safety signals identified with increased exposure during the LTE. Results of our study support and extend findings from other phase II and III trials with SC ABA (125 mg/week) administered for up to 18 months^{8,9,11}. IR of SAE, serious infections, malignancies, and autoimmune events remained stable throughout the study when evaluated at 6-month intervals, and were not increased compared with the DB period. This is consistent with reports of safety events from



	Patients with available data at each visit day*, according to the original treatment group															
	15	29	57	85	113	141	169	253	365	449	533	617	729	813	897	981
SC abatacept	687	687	685	686	687	687	690	684	663	650	627	617	601	584	526	308
IV switched to SC abatacept	660	668	670	671	670	669	671	665	654	633	620	607	585	575	515	301

Figure 4. C.

the pooled SC ABA clinical trial experience of 1879 patients with 3086 patient-years of exposure, in which the IR of SAE evaluated at 6-month intervals did not increase with increasing ABA exposure (9.25, 95% CI 7.46, 11.48; 10.75, 95% CI 8.72, 13.24; 8.21, 95% CI 6.29, 10.72; 8.85, 95% CI 6.26, 12.51; and 12.06, 95% CI 7.49, 19.39)^{13,14}. Moreover, the longterm safety profile seen here with SC ABA is similar to the consistent longterm profile demonstrated for IV ABA, which was reported for 4419 patients with more than 12,000 cumulative patient-years of exposure¹⁵, and demonstrated that IR of hospitalized infections (3.35, 2.63, 2.31, 2.33, 1.55, 2.48, and 3.03 from years 1 to 7, respectively) and malignancies (0.62, 0.55, 0.81, 0.81, 0.99, 0.53, and 1.66 from years 1 to 7, respectively) evaluated at 12-month intervals remained relatively stable with increasing ABA exposure.

The occurrence of malignancies and autoimmune events is of interest for longterm biologic treatment. The IR of overall malignancy reported in the ACQUIRE LTE study (1.19) is within the range of IR reported for cohorts of DMARD-treated patients with RA (0.67–1.77)¹⁶. The IR reported here with SC ABA for breast and lung cancers (0.17 and 0.10, respectively) were also within the range of IR reported for cohorts of DMARD-treated patients with RA (0.14–0.34, 0.09–0.26, respectively)¹⁶. The IR of different malignancies that occurred in the ACQUIRE LTE are also consistent with the IR reported for the pooled SC ABA clinical trial experience (0.46 for basal cell carcinoma, 0.16 each for breast cancer and squamous cell carcinoma of skin)¹⁴ and the pooled IV ABA clinical trial experience

(0.15 and 0.12 for lung and breast cancers, respectively)¹⁵. The IR of overall autoimmune events in the ACQUIRE study (1.31) and specific autoimmune events, including psoriasis (0.31), were also consistent with IR reported for the pooled SC ABA clinical trial experience (1.28 and 0.29, respectively)¹⁴ and the pooled IV ABA clinical trial experience (1.99 and 0.57, respectively)¹⁵.

Four cases of TB (0.14, 95% CI 0.05, 0.36) were reported, all of them in endemic areas, one of which was a patient with a history of TB. Two patients were PPD-negative at entry, and all were diagnosed with TB more than a year after initiation of ABA treatment. This is consistent with reports from the pooled IV ABA clinical trial experience, in which 8 cases of TB were reported, with an IR of 0.07/100 patient-years¹⁵.

The frequency of injection-site reactions, including pain, was relatively low in the LTE and similar to that in the DB period, and events were generally mild. This is consistent with previous clinical trial reports of SC ABA use, and further demonstrates that the frequency of SC injection-site reactions is reduced with increasing treatment time^{8,9}.

During the LTE, 21 deaths were recorded (IR 0.71, 95% CI 0.44, 1.09), of which 7 were classified as being due to MI or sudden death. None of these events were classified as related to treatment by the investigators. This is consistent with the pooled IV ABA clinical trial experience, during which 73 deaths were reported at an IR of 0.60 (95% CI 0.47, 0.76), including 26 due to cardiac disorders^{15,17}. There are no available data to suggest an increased CV risk with ABA treatment of RA, with comparable proportions of

ABA- and placebo-treated patients experiencing serious cardiac disorders during the pooled IV ABA clinical trial experience (IR 1.42, 95% CI 0.98, 1.99 and 2.24, 95% CI 1.34, 3.50)¹⁵.

Immunogenicity to SC ABA reported in this LTE was based on ECL analysis, and ~10% of patients experienced an immunologic response either during treatment or following discontinuation. However, few patients (2.1%) experienced persistent immunogenicity, and titers were generally low and transient, and did not increase with continued dosing. Further, immunogenicity did not appear to affect the safety or efficacy of SC ABA. Comparisons of data from this study with other ABA studies are problematic given immunogenicity has previously been evaluated using ELISA, rather than ECL^{7,8,9,10,11,18}. There are a number of differences between the 2 assay types; notably, ECL has a greatly increased sensitivity compared to ELISA (12.2 ng/ml vs 275 µg/ml). However, the 6-month DB period of our study reported comparable rates of immunogenicity based on ELISA for SC and IV ABA-treated patients (1.1 vs 2.3%)¹².

Safety and efficacy benefits were supported by high patient retention, with ~83% of patients treated in the LTE remaining in the study at the time of assessment (up to a maximum of 3.5 yrs) and few discontinuations owing to lack of efficacy (4.9%) over ~33 months. This is comparable with longterm retention rates seen with IV ABA in similar patient populations; 82.3% and 90.9% of IV ABA-treated patients who continued treatment at Year 3 in the AIM study and at Year 2 of the ATTEST trial^{3,4}. Retention rates observed in randomized clinical trials with anti-TNF (plus background DMARD) have ranged from 62% to 82% after 2 years, with 4% to 8% discontinuing as a result of lack of efficacy^{19,20,21,22}.

The original DB period of ACQUIRE demonstrated comparable clinical and functional efficacy for SC and IV ABA over 6 months, with high proportions of patients achieving disease activity targets and clinically meaningful improvements in ACR and HAQ-DI scores. Longterm administration of SC ABA during the LTE, up to Day 981, was associated with maintained improvements in ACR and HAQ-DI responses for patients who continued taking treatment. In particular, the proportions of patients achieving disease activity targets of DAS28, SDAI, and CDAI remission were maintained through the LTE. Similar longterm outcomes have been reported for patients treated with IV ABA in a similar population of patients with RA and inadequate response to MTX^{3,5}. Clinical and functional benefits were maintained longterm during the ACQUIRE study, regardless of whether patients received SC ABA throughout, or switched from IV ABA to SC ABA at the start of the LTE. These observations support findings from the ATTUNE study, which evaluated safety and efficacy in patients who switched from IV to SC ABA⁹. Together these

observations suggest that patients can safely switch from a monthly ~10 mg/kg dose of IV ABA to a fixed weekly 125 mg dose of SC ABA with maintained clinical efficacy.

Nearly all patients continued to receive concomitant MTX, and the mean dose remained stable throughout the LTE of the ACQUIRE study. Mean steroid dose remained consistent with mean dose at entry into the LTE. Further, the proportions of patients receiving steroids throughout this LTE is consistent with other ABA reports, including a head-to-head trial of SC ABA and adalimumab, in which 65.1 and 64.0% of patients received concomitant corticosteroids at any time over 2 years²³. These proportions are consistent with reports of steroid use in clinical trials with other biologics, which have ranged from 67.9 to 50.4%, although it is generally acknowledged that concomitant steroid dosing is not widely reported²⁴.

There are limitations to our study and subsequent analysis that should be noted. In accordance with many other reports of LTE data, efficacy in our study is based on as-observed analyses, which include only patients with available data and can be vulnerable to discontinuations among those who do not respond as well to treatment. Further, the LTE was open-label in nature, which, although standard for longterm reporting, can result in bias of results toward improved efficacy outcomes (based on subjective reporting) and increased safety event reporting.

The findings from the LTE of the ACQUIRE study represent the largest and longest observation period for SC ABA treatment: up to 44 months for some patients. With continued longterm treatment, SC ABA was well tolerated with no increase in the incidence of safety events over time, consistent with previous findings^{13,14}. SC ABA was associated with high patient retention and demonstrated maintained improvements in clinical and functional efficacy outcomes and disease activity targets.

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