Efficacy and safety of elsubrutinib or upadacitinib alone or in combination in patients with rheumatoid arthritis and inadequate response or intolerance to biologic therapies: a phase 2, multicentre, randomised controlled trial

Prof Roy Fleischmann, MD; Alan Friedman, MD; Edit Drescher, MD; Atul Singhal, MD; Gregorio Cortes-Maisonet, MD; Thao Doan, MD; Wenjing Lu, PhD; Zailong Wang, PhD; Ahmed Nader, PhD; William Housley, PhD; Prof Stanley Cohen, MD; Prof Peter C Taylor, PhD; Ricardo Blanco, MD

Metroplex Clinical Research Center, University of Texas Southwestern Medical Center at Dallas, Dallas, TX, USA (R Fleischmann, MD); **AbbVie, Inc., North Chicago, IL, USA** (A Friedman MD, T Doan MD, W Lu, PhD, Z Wang PhD, A Nader PhD, W Housley PhD); **Veszprém Csolnoky Ferenc County Hospital and Vital Medical Centre Private Clinic, Veszprém, Hungary** (E Drescher MD); **Southwest Rheumatology, Dallas, TX, USA** (A Singhal MD); **GCM Medical Group, San Juan, Puerto Rico** (G Cortes-Maisonet MD); **Metroplex Clinical Research Center, Dallas, TX, USA** (S Cohen MD); **Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK** (P C Taylor PhD); **Division of Rheumatology, Hospital Universitario Marqués de Valdecilla, Santander, Spain** (R Blanco MD)

Target Journal: *Lancet Rheumatology*

Word Count: 4146 (maximum 4500 words)

Correspondence to:
Dr Roy Fleischmann
8144 Walnut Hill Lane, Suite 810
Dallas, TX 75231, USA

rfleischmann@arthdocs.com

SUMMARY

Background ABBV-599 is a novel fixed-dose combination of the Bruton's tyrosine kinase inhibitor elsubrutinib (60 mg) and Janus kinase (JAK) inhibitor upadacitinib (15 mg) under investigation for the treatment of autoimmune diseases.

Methods In this randomised, double-blind, phase 2 trial (NCT03682705), adults with rheumatoid arthritis (RA) and inadequate response or intolerance to biologic disease-modifying antirheumatic drugs at 75 community sites in 8 countries were randomised 3:2:2:2:2:1 via interactive response technology to daily, orally administered ABBV-599; elsubrutinib 60, 20, or 5 mg; upadacitinib 15 mg; or placebo. The primary endpoint was change from baseline in disease activity score-28 using C-reactive protein (DAS28 [CRP]) at week 12 for all patients who received study drug. Pharmacokinetics and safety were also assessed.

Findings Between October 8, 2018, and March 26, 2020, 242 patients were randomised to ABBV-599 (n=62); elsubrutinib 60 mg (n=41), 20 mg (n=39), 5 mg (n=41); upadacitinib 15 mg (n=40); and placebo (n=19). Most patients were female (204/242; 84%), with a mean (SD) age of 58·0 (11·3) years. Compared with placebo, least squares mean (90% CI) changes from baseline in DAS28 (CRP) were –1·44 (–2·03 to –0·85; p<0·0001) for ABBV-599, –0·40 (–1·03 to 0·23; p=0·29) for elsubrutinib 60 mg, –0·20 (–0·85 to 0·44; p=0·61) for elsubrutinib 20 mg, –0·21 (–0·84 to 0·41; p=0·57) for elsubrutinib 5 mg, and –1·75 (–2·38 to –1·13; p<0·0001) for upadacitinib. No significant improvements in efficacy measures for elsubrutinib alone (any dose) versus placebo were detected, despite adequate plasma exposure and target engagement. Treatment-emergent adverse events were observed in 113 (47%) patients, with similar rates for all treatment groups and placebo.

Interpretation Significant improvements in RA disease activity metrics with ABBV-599 were driven by JAK inhibition by upadacitinib with no discernible effect by elsubrutinib.

Funding AbbVie, Inc.

Abstract Word Count: 295 (maximum 300 words)

Key Words: Antirheumatic agents; BTK inhibitor; clinical trial; elsubrutinib; human; Janus kinase inhibitor; rheumatology; rheumatoid arthritis; upadacitinib

RESEARCH IN CONTEXT

Evidence before this study

Biologic agents and Janus kinase inhibitors (JAKi) are used to treat patients with rheumatoid arthritis (RA). Bruton's tyrosine kinase (BTK) recently emerged as a potential therapeutic target in the treatment of autoimmune conditions. We searched PubMed for research articles and clinical guidelines from the last 10 years using the terms "rheumatoid arthritis", "biologics", "JAK", and "BTK." Prior clinical trial data revealed that biologics and JAKi can achieve meaningful clinical responses and are generally well-tolerated for patients with RA, resulting in these agents being currently recommended by most rheumatology societies, including the American College of Rheumatology and European Alliance of Associations for Rheumatology, as the preferred agents to be employed in combination with methotrexate (MTX) for patients with inadequate response to MTX alone. Yet not all patients achieve adequate or sustained disease control with biologics or JAKi; therefore, the need remains for other effective treatments. Based on a potential role of BTK in the aetiology of autoimmune diseases, BTK inhibitors (BTKi) recently entered clinical trials for patients with these conditions.

Added value of this study

To address the hypothesis that adding a BTKi to a JAKi-based regimen would provide clinical benefits beyond the JAKi alone, we initiated a clinical trial investigating the efficacy and safety of ABBV-599, the novel, orally administered, fixed-dose combination of a JAKi (upadacitinib 15 mg) and a BTKi (elsubrutinib 60 mg). Our results show that ABBV-599 was well-tolerated and resulted in significant improvements over placebo on composite measures of RA disease activity. However, despite elsubrutinib achieving expected levels of BTK receptor target

engagement, no significant improvements were detected when comparing ABBV-599 to upadacitinib alone.

Implications of the available evidence

Although these results provide additional support for the clinical benefits of JAK inhibition by upadacitinib in patients with RA, they do not support the addition of a BTKi to this regimen for this indication.

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease characterised by chronic inflammation; progressive, irreversible joint damage; pain; disability; loss of function; and reduced health-related quality of life.[1,2] The recommended first-line therapy for patients with active RA is methotrexate (MTX), intended to achieve disease remission or at least low-disease activity.[3,4] Recent recommendations from the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR) suggest adding biologic disease-modifying antirheumatic drugs (bDMARDs) or Janus kinase inhibitors (JAKi) to ongoing MTX administration for patients who do not experience an adequate response with MTX alone.[3,4]

Despite the availability of bDMARD and JAKi treatment options, some patients with RA do not achieve adequate disease control after their addition to MTX, let alone sustained remission.[5,6] Considering the ongoing symptoms and irreversible damage that can occur with continued active RA, effective management of patients with inadequate response to currently available treatments is needed.[7]

The first approved orally administered JAKi, tofacitinib, provides rapid onset of efficacy at least comparable to that of TNFi.[8-11] The presumed role of Bruton's tyrosine kinase (BTK) in propagating complex proinflammatory signals in immune cells that may contribute to autoimmune disease suggests that BTK inhibitors (BTKi) may be effective in treating RA.[12] Initial BTKi had significant off-target effects and were susceptible to treatment resistance, prompting the development of compounds with enhanced target selectivity and binding properties.[13] However, to date, fenebrutinib is the only compound that met a primary endpoint in

a clinical trial on autoimmune disease by demonstrating clinical efficacy and safety comparable to adalimumab in treating RA in a phase 2 study.[14]

Elsubrutinib is a novel BTKi in development for treatment of autoimmune inflammatory diseases that demonstrated potential disease-modifying effects in animal models of arthritis and lupus.[15] Here, we performed a proof-of-concept and dose-exploratory study to evaluate safety and efficacy of elsubrutinib and upadacitinib individually and in a fixed-dose combination (ABBV-599) versus placebo as a novel treatment for active RA in patients with inadequate response or intolerance to bDMARDs. The objective was to determine whether concurrent BTK and JAK inhibition may increase the treatment response compared with inhibiting either pathway alone, while maintaining an acceptable safety profile.

METHODS

Study design

This was a 12-week, randomised, double-blind, parallel-group, phase 2, dose-exploratory, multicentre study (NCT03682705) performed at 75 community sites in 8 countries in Europe and North America. The study was conducted in accordance with International Council for Harmonisation guidelines and ethical principles that have their origin in the Declaration of Helsinki, and the protocol was approved by Quorum Review IRB U.S. Board (now Advarra) (Quorum review file # 33488).

Patients

Eligible patients were ≥18 years of age, with a diagnosis of RA for ≥3 months based on the 2010 ACR/European League Against Rheumatism classification criteria for RA,[16] with active disease defined by ≥6 (of 66) swollen joints and ≥6 (of 68) tender joints at screening and baseline and high-sensitivity C-reactive protein (hsCRP) ≥3 mg/L at screening. Patients were required to have active disease despite treatment with no more than two background conventional synthetic (cs)DMARD therapies approved for RA (MTX [oral or parenteral], sulfasalazine, hydroxychloroquine, chloroquine, or leflunomide; combination of leflunomide with MTX was prohibited) for ≥3 months and at a stable dose for ≥4 weeks preceding the first dose of study treatment. Patients were also required to have had prior treatment with one or more bDMARDs for ≥3 months with continued evidence of active RA, or discontinuation for intolerability or toxicity, irrespective of treatment duration. All bDMARDs were discontinued for ≥5 times the mean terminal elimination half-life prior to initiation of the study treatment. All patient eligibility criteria are listed in the **appendix (p 1)**.

All patients provided written, informed consent.

Randomisation and masking

Eligible patients were randomised in a 3:2:2:2:2:1 ratio to receive ABBV-599 (upadacitinib 15 mg/elsubrutinib 60 mg); elsubrutinib 60 mg, 20 mg, or 5 mg; upadacitinib 15 mg; or placebo. At screening, patients were assigned a unique randomization number via interactive response technology (IRT). To achieve blinding, each patient received a treatment kit, also assigned via IRT, containing a combination of three physically identical capsules (elsubrutinib 5 mg, 20 mg, and/or matching placebo) plus one tablet (upadacitinib 15 mg or matching placebo), combined as needed to achieve the assigned dose in each treatment group (eg, ABBV-599: elsubrutinib 20 mg × 3, plus upadacitinib 15 mg). Randomisation was stratified by number of prior bDMARDs (failure of one or two vs more than two with the same mechanism of action [MOA] and/or two or more with different MOAs). The investigator, study site personnel, and patients were to remain blinded throughout the study, unless unblinding was necessary to address an urgent medical need.

Procedures

Dosing for elsubrutinib was based on pharmacokinetic (PK), pharmacodynamic, and safety results in healthy volunteers (unpublished), and dosing for upadacitinib was based on the phase 3 clinical program.[17,18] Following a 35-day screening period, patients received study treatment once daily via oral administration during the 12-week double-blind period, and visited the study centre at baseline, and weeks 2, 4, 8, and 12 for assessments. Follow up was conducted by phone 30 days after the week 12 visit (**appendix p 16**).

After completion of the primary study, participants in Europe and Canada could enrol in a 48-week, long-term extension (LTE) study (NCT03823378), during which patients continued the active double-blind treatment for up to 60 total weeks of treatment or were switched in a blinded manner from placebo to ABBV-599. (Patients in the US were not authorised by the FDA to participate in the LTE study.)

For safety outcomes, an independent internal data monitoring committee performed unblinded interim analyses at prespecified time points to review safety data. Physical examinations, vital sign measurements, and clinical laboratory testing were performed at each visit; electrocardiograms were done at screening and weeks 2, 4, 8, and 12.

Blood was collected at baseline and weeks 4, 8, and 12 to assess PK and potential interactions between upadacitinib and elsubrutinib. Plasma drug concentrations were also compared with those previously observed in healthy volunteers or in patients with RA (for upadacitinib).

Target engagement by elsubrutinib was assessed through measurement of BTK occupancy in peripheral blood mononuclear cells at Cambridge Biomedical Inc. (Boston, MA) from venous blood collected at baseline and weeks 4 and 12. Peripheral blood mononuclear cells were isolated by centrifugation, lysed, and prepared to a concentration of 30 µg total protein/100 µL and divided, and equal volumes of lysate were incubated with biotinylated rabbit anti-BTK monoclonal antibody (Rabbit mAb D9T6H-biotin, Cat. No.: 16135BC; Cell Signaling Technology, Danvers, MA) to detect total BTK, or biotinylated BTK probe PCI-41025 to detect free BTK. Each sample was incubated on streptavidin plates then probed with mouse anti-BTK monoclonal antibodies (clone 53/BTK, Cat. No.: 611117; BD Biosciences, San Jose, CA) and

goat anti-mouse SULFO TAG antibodies (Cat. No.: R32AC-1; Meso Scale Discovery, Rockville, MA) and quantified via relative luminescence to determine BTK occupancy rate.

Outcomes

The primary endpoint was change from baseline in disease activity score-28 using C-reactive protein (DAS28 [CRP]) at week 12. Pre-specified sensitivity analyses for this endpoint included a series of dose-response models and reassessment using historical placebo data to increase statistical power while minimizing the number of patients with active RA taking placebo (detailed below).

Secondary endpoints were proportions of patients who achieved ACR 20%, 50%, and 70% response criteria (ACR20/50/70); DAS28 (CRP) <2·6, ≤ 3·2, and ≤ 3·2 but ≥ 2·6; clinical disease activity index (CDAI) ≤2·8, ≤ 10, and ≤ 10 but > 2·8; and minimal clinically important difference (MCID; defined as a decrease ≥0·22) in change from baseline in Health Assessment Questionnaire Disability Index (HAQ-DI). Additional secondary endpoints were changes from baseline in DAS28 (CRP), DAS28 based on erythrocyte sedimentation rate (ESR), CDAI, HAQ-DI, simplified disease activity index (SDAI), morning stiffness severity and duration, and individual components of ACR response.

Pre-specified exploratory endpoints included exposure-response relationships between elsubrutinib and/or upadacitinib exposures and key efficacy endpoints (change from baseline in DAS28 (CRP) at week 12 and proportion of patients achieving ACR20/50/70 at week 12) to assess contributions of each compound to clinical efficacy as well as any exposure-dependent increases in response rates.

Routine safety evaluations included monitoring of treatment-emergent adverse events (TEAEs), defined as events with onset or worsening after the first study dose of study drug and within 30 days after the last study drug administration. Selected TEAEs of special interest included serious infections, serious gastrointestinal events, malignancies, electrocardiogram abnormalities, and selected laboratory abnormalities. Major adverse cardiovascular events (MACE) and venous thromboembolic events (VTE) were adjudicated by an independent, blinded cardiovascular adjudication committee.

Efficacy analyses during the LTE study included the mean change from baseline over time for DAS28 (CRP); routine safety evaluations were also performed.

Statistical analysis

Sample size determination

Statistical comparisons using a placebo group of 20 patients were estimated to provide 68% power for a pairwise comparison of elsubrutinib versus placebo or 70% power in detecting a dose-response model for elsubrutinib and placebo. To improve statistical power, a sample size of 240 was planned based on 40 patients per elsubrutinib arm plus 20 borrowed historical placebo patients, providing approximately 83% power to detect a –0·88 difference in DAS28 (CRP) change from baseline for elsubrutinib versus placebo (assuming a mean change from baseline of –0·77 with placebo and –1·65 for elsubrutinib, with common SD=1·5) using two-group *t* test with one-sided significant level α=0·05. A total of 60 patients treated with ABBV-599 was predicted to provide approximately 94% power to detect a –1·0 difference in DAS28 (CRP) least-squares mean (LSM) change from baseline for ABBV 599 versus the 40 patients treated with elsubrutinib (assuming a –1·65 mean change from baseline for elsubrutinib and –2·65 for

ABBV-599) using a two-group *t* test with one-sided significance level α=0·05 (common SD=1·5). Sample sizes of 60 and 40 for ABBV-599 and placebo, respectively, were over-powered because of the necessary power for elsubrutinib over placebo.

Analysis populations

Efficacy was assessed in all randomised patients who received at least one dose of study drug, and were grouped according to randomised treatment (full analysis set). Safety was assessed in all randomised patients who received one or more doses of study drug and were grouped according to actual treatment received (safety set).

Efficacy analyses

Primary and secondary efficacy endpoints were tested at significance level α=0·1 (two-sided). For continuous efficacy outcomes, least-squares (LS) mean changes from baseline at week 12 were compared between treatment groups and analysed using mixed-effect model for repeated measurements that included categorical fixed effects of treatment, visit, and treatment-by-visit interaction, prior bDMARD use, and the continuous fixed covariate of baseline measurement. Missing data, which included data collected after premature discontinuation from study treatment, were addressed via parameter estimation based on the assumption of data missing at random.

Categorical outcomes are presented as n (%) and were analysed using the Cochran-Mantel-Haenszel test, stratified by prior bDMARD use. Patients with missing evaluation or after premature discontinuation from study treatment were imputed as non-responders (non-responder imputation).

Dose-response relationships in elsubrutinib and placebo groups were characterised for DAS28 (CRP) using the multiple comparison procedures - modelling procedure based on a series of prespecified dose-response models. A significant dose-response relationship was defined as one or more model identified as statistically significant at α=0·1 (two-sided).

Prespecified historical data borrowing

A prespecified sensitivity analysis of the primary endpoint integrated historical placebo data from previous clinical trials with similar patient populations and eligibility criteria. A meta-analysis of 349 placebo patients from the RA-BEACON,[19] ORAL Step,[20] and BALANCE-I[21] clinical trials was performed to obtain the distribution of the control group mean for the historical data, which yielded a predicted change in DAS28 (CRP) mean (SD) of –0·80 (1·5) (95% CI –1·06 to –0·54) at week 12. In comparing elsubrutinib versus placebo in the sensitivity analysis, 20 historical placebo patients were expected to provide a Bayesian type I error rate/false positive rate <10%, and increase statistical power to approximately 83% for the comparison (and ≥85% for the dose-response model), while not exceeding the planned placebo group size for the current trial.[22] Another prespecified sensitivity analysis using historical data from patients treated with upadacitinib 15 mg (n=40), based on a meta-analysis of 206 patients from the phase 2 BALANCE-I[21] and phase 3 SELECT BEYOND[23] clinical trials, yielded a predicted change in DAS28 (CRP) mean (SD) of –2·32 (1·57) (95% CI –2·54 to –2·11) at week 12.

Historical control information was summarised as the prior distribution for the control group. With the control data from the study, the posterior distribution for the control group was used to compare with the treatment group**.** Success criteria in the sensitivity analyses using historical data were defined as the posterior probability of (treatment mean – control mean <0) >0·95 (equivalent to one-sided α=0·05 significant level).

Safety analyses

The number and percentage of patients who experienced TEAEs were tabulated using the Medical Dictionary for Drug Regulatory Activities (MedDRA) version 22·1.

Role of the funding source

The funder of the study (AbbVie, Inc.) participated in the study design, data collection, analysis, and interpretation; and writing, reviewing, and approving the report. All authors had full access to the study data, and the sponsor and investigators share responsibility for the decision to submit for publication.

RESULTS

Between October 8, 2018, and March 26, 2020, patients on eligible background csDMARDs (N=242) were randomised to ABBV-599 (n=62), elsubrutinib 60 mg (n=41), elsubrutinib 20 mg (n=39), elsubrutinib 5 mg (n=41), upadacitinib 15 mg (n=40), and placebo (n=19), and received one or more doses of the assigned study treatment. Overall, 215/242 (89%) patients completed the study drug (**Figure 1**). Demographics, baseline characteristics, and disease activity were similar across treatment groups (**Table 1**). Most patients were female (204/242 [84%]) and White (220/242 [91%]); the mean (SD) age at baseline was 58·0 (11·3) years. The majority of patients had failed treatment with one or two bDMARDs with the same MOA (**Table 1**).

For the primary endpoint, the LS mean (90% CI) changes from baseline in DAS28 (CRP) among patients treated with ABBV-599 and placebo at week 12 were –2·56 (–2·86, –2·26) and –1·12 (–1·64, –0·60), respectively, representing an LS mean difference of –1·44 (–2·03, –0·85; p<0·0001) (**Table 2**). Elsubrutinib alone did not demonstrate superiority to placebo, and there was no statistically significant difference between ABBV-599 and upadacitinib (**Table 2**). Changes in DAS28 (CRP) over time are shown in **Figure 2A**, and DAS28 (CRP) data at week 12 by body mass index subgroup are shown in the **appendix (p 6).**

Results for selected secondary efficacy endpoints are summarised in **Table 2** and **Table 3**. A significantly greater ACR20 response was observed with ABBV-599 at week 12 (40/62 [65%]) compared with elsubrutinib 60 mg (17/41 [41%], p=0·018), 20 mg (12/39 [31%], p=0·00039), and 5 mg (14/41 [34%], p=0·0012, but not upadacitinib or placebo (**Table 3**). ACR50 response was significantly improved with ABBV-599 (28/62 [45%]) vs elsubrutinib 60 mg (12/41 [29%], p=0·089), 20 mg (5/39 [13%], p<0·0001), 5 mg (7/41 [17%], p=0·00089), and placebo (4/19

[21%], p=0·027), but not upadacitinib. Similar results were observed for ACR70 response except no significant difference occurred between ABBV-599 and elsubrutinib 60 mg (**Table 3**).

Significantly greater proportions of patients in both the ABBV-599 (20/62 [32%], p=0·020) and upadacitinib (17/40 [43%], p=0·0020) groups achieved DAS28 (CRP) <2·6 at week 12 compared with placebo (2/19 [11%]) but not elsubrutinib (**Table 3**). The LSM (SE) change from baseline in CDAI score was also significantly increased in the ABBV-599 group (–27·0 [1·85]) compared with placebo (–14·6 [3·15], p=0·00066) and all elsubrutinib groups (all p<0·001), but not upadacitinib. The only significant difference in CDAI ≤2·8 occurred between ABBV-599 versus elsubrutinib 5 mg (9/62 [15%] *vs* 0 patients, respectively; p=0·0012), while a similar response rate to that of ABBV-599 occurred with upadacitinib (6/40 [15%]). The LSM (SE) change from baseline to week 12 in HAQ-DI score was significantly greater for the ABBV-599 group (–0·52 [0·08]) compared with elsubrutinib 60 mg (–0·31 [0·09], p=0·071), 20 mg (–0·12 [0·1], p=0·0013), and 5 mg (–0·18 [0·09], p=0·0041), but not upadacitinib (–0·54 [0·09], p=0·85) (**Table 2**). No significant between-group differences occurred in proportions of patients achieving a >0·22-point decrease from baseline in HAQ-DI. Results for additional secondary endpoints are summarized in the **appendix (pp 7–9)**.

TEAE frequency was generally balanced across treatment groups and similar to placebo (**Table 4**). Upper respiratory tract infection was the only TEAE that exceeded 5% frequency in the ABBV-599 group (4/62 [6%]), which had a similar rate in the placebo group (1/19 [5%]). No serious TEAEs were reported in the ABBV-599, elsubrutinib 60 mg, or upadacitinib groups. One patient in the elsubrutinib 20-mg group with a history of hypertension and a family history of cardiovascular disease experienced a serious adverse event of non-obstructive coronary artery

disease that resolved with concomitant therapy and no interruption of study drug. Other serious TEAEs are detailed in the footnote of **Table 4**.

A summary of TEAEs of special interest is provided in the **appendix (p 11)**. One patient in the ABBV-599 group who was not vaccinated against herpes zoster experienced a non-serious herpes zoster outbreak involving unilateral L3 and L4 dermatomes, which resolved with concomitant treatment and without interruption of study drug administration. One patient in the elsubrutinib 5-mg group with multiple comorbidities and cardiovascular risk factors died on study day 69 from cardiac arrest (adjudicated as a MACE). One malignancy (endometrial adenocarcinoma) was detected in a patient in the placebo group, which resulted in withdrawal from the study in accordance with the trial protocol. No active tuberculosis or adjudicated VTE were reported in the study.

Key laboratory values are summarized in the **appendix (pp 12–13)**. No patients developed rhabdomyolysis or myositis during the study.

Over 24 hours from dosing, plasma upadacitinib concentrations ranged from 10·1 to 36·0 ng/mL when administered alone and 5·8 to 33·6 ng/mL when administered with elsubrutinib 60 mg. Following dosing of 60 mg elsubrutinib, plasma concentrations ranged from 2·4 to 193 ng/mL when administered alone and 3·3 to 136 ng/mL when administered with upadacitinib.

Elsubrutinib exposures were two- to three-fold higher in patients with RA compared with healthy volunteers in previous studies (unpublished data), and elsubrutinib or upadacitinib exposures were not affected when coadministered as ABBV-599. BTK engagement was observed at all elsubrutinib doses, with more consistent BTK occupancy (>90%) at 20 and 60 mg (**Figure 2B**).

No exposure-response relationships occurred between elsubrutinib and any efficacy endpoint (**appendix p 17**). Following ABBV-599 administration, elsubrutinib exposure quartiles showed generally lower response rates versus upadacitinib alone across all evaluated efficacy endpoints, with no trends for exposure-response relationships detected within elsubrutinib exposure quartiles (**appendix p 18**).

In the sensitivity analysis using historical placebo data to assess change in DAS28 (CRP) from baseline to week 12, only elsubrutinib 60 mg met the prespecified success criterion versus placebo (mean [SE] –1·52 [0·23] *vs* –0·97 [0·23]; posterior probability >0·95), and the probability that elsubrutinib 60 mg was better than placebo was 0.96 (**appendix p 14**). When incorporating historical data from patients treated with upadacitinib, the prespecified success criterion for ABBV-599 versus upadacitinib (p>0·95) was not met. No statistically significant dose-response relationships for elsubrutinib occurred in dose-response models (not shown).

The LTE study was terminated prematurely when a lack of additional efficacy benefit for ABBV-599 versus upadacitinib alone became apparent. The limited data revealed that trends in DAS28 (CRP) (**appendix p 19**) and safety data (**appendix p 15**) observed in the initial 12-week treatment period were generally sustained.

Discussion

Results from this study in patients with active RA and a history of inadequate response or intolerance to bDMARDs on continued background csDMARDs indicate that the novel, orally administered JAKi/BTKi formulation ABBV-599 provides statistically significant and clinically meaningful improvements in RA disease activity compared with placebo after 12 weeks of treatment based on changes in DAS28(CRP), CDAI, and most ACR responses. ABBV-599 was generally well-tolerated, with TEAE rates similar to those in the placebo group, no incidence of serious TEAEs, and low rates of TEAEs of special interest.

The significant improvements with ABBV-599 compared with all doses of elsubrutinib alone on efficacy endpoints suggest that the effect is achieved exclusively through JAKi provided by upadacitinib, with no involvement of BTKi. First, the magnitude of changes from baseline in DAS28 (CRP) was similar for ABBV-599 and upadacitinib alone, both of which showed significant improvements versus elsubrutinib. Second, elsubrutinib alone did not lead to significant improvement versus placebo on any clinical endpoint, except for a ≥95% probability that the 60-mg dose was better than placebo on the primary endpoint when historical placebo data were included. Third, results with upadacitinib alone were similar to those of ABBV-599 on endpoints where ABBV-599 led to significant improvements versus placebo, except when upadacitinib but not ABBV-599 led to significant improvements in ACR20 response. These results may have been due to high variability associated with a small placebo group size, possibly combined with the low threshold required to achieve ACR20 response. Finally, maximal BTK occupancy by elsubrutinib is expected on peripheral B cells following doses of 20 mg to 60 mg with no additional effect expected at higher doses, and our PK results suggest that elsubrutinib achieved adequate target engagement with no exposure-dependent increases in

efficacy response rates. Therefore, the lack of clinical effects with elsubrutinib alone was likely not caused by inadequate exposure or BTK target engagement.

In general, data from clinical trials on BTKi to treat autoimmune conditions have not been encouraging. Only fenebrutinib has shown positive results in patients with RA, by leading to significant improvements versus placebo in ACR20 response, HAQ-DI score, and change from baseline in DAS28 (CRP) at week 12 in a phase 2 trial in patients with previous inadequate response to TNFi.[14] Similar trials with other BTKi including spebrutinib,[24] poseltinib,[25] tirabrutinib,[26] evobrutinib,[27] and BMS-986142,[28] were unsuccessful in meeting primary efficacy endpoints in patients with RA. In phase 2 trials on other autoimmune conditions, fenebrutinib[29] and evobrutinib[30] did not meet primary endpoints in patients with systemic lupus erythematosus, nor BMS-986142[31] and tirabrutinib[32] for Sjogren's syndrome.

Negative findings with multiple BTKi compounds may result, in part, from variability in BTKi-target interactions. Specifically, on target binding, BTKi can hold BTK in an active or inactive conformation, bind covalently or non-covalently, or inhibit one or both of the activating phosphotyrosines (pY223 and pY551) on BTK.[33,34] Elsubrutinib binds irreversibly to the BTK hinge region, holding BTK in an active conformation and covalently modifying the active site at cysteine 481, resulting in durable inhibition of pY223. By contrast, fenebrutinib irreversibly binds to the BTK H3 region to hold BTK in an inactive conformation, resulting in full inhibition of both pY223 and pY551.[35] Ibrutinib is a "back-pocket binder" that forces BTK into an inactive conformation in a manner similar to that of H3-region binders, but may not fully block pY551.[35] Future research should determine if and how different binding configurations could provide therapeutic value for BTKi to treat autoimmune diseases.

This study was limited by small sample sizes, a short assessment period, lack of long-term results, and a study population that may not have been fully representative of the general population with RA. The HAQ-DI secondary endpoint for change from baseline at week 12 did not reach statistical significance, likely attributable to an insufficient sample size carrying a low probability of detecting statistically significant difference between groups. The study may have also been limited by the use of historical placebo data borrowing in sensitivity analyses. This approach is sometimes used in trials for rare or aggressive conditions for which withholding active treatment could lead to irreversible harm, and statistical approaches can help integrate borrowed data while minimizing bias. As there are multiple effective medications available to treat RA, minimizing the number of patients on placebo is particularly important. Despite our efforts to seamlessly integrate the historical data, variables such as country of residence or treatment history can affect placebo responses,[35,36] and potential differences in placebo response between phase 2 and phase 3 studies must also be considered.[37] Although we limited historical data usage to the sensitivity analysis, these data should be interpreted with caution.

In conclusion, ABBV-599 led to significant improvements in important composite metrics of RA disease activity in patients with previous inadequate response or intolerance to bDMARDs; however, these effects are likely driven exclusively by the effect of the upadacitinib (JAKi) based on the lack of effect by elsubrutinib (BTKi) administered alone. The lack of significant improvements with ABBV-599 versus upadacitinib alone strongly suggests that the combination of this BTKi with a JAK inhibitor does not offer any advantage in clinical control of RA disease activity, and, as a result, ABBV-599 has been discontinued from further clinical development for the treatment of RA but remains under clinical investigation for other complex autoimmune diseases (Clinicaltrials.gov identifiers: NCT04451772 and NCT03978520).

Data Sharing Statement

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymised, individual and trial-level data (analysis data sets), as well as other information (e.g., 20-22s and clinical study reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and statistical analysis plan and execution of a data sharing agreement. Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

Contributors

AF, TD, ZW, and AN contributed to the study design. RF, AF, ED, AS, GC-M, ZW, AN, SC, and PCT contributed to data acquisition. RB contributed to data acquisition and interpretation. WL, and ZW performed the statistical analyses, and RF, AF, TD, WL, ZW, AN, SC, and PCT contributed to data interpretation. RF and RB were responsible for verifying the underlying data. All authors developed drafts of the manuscript and approved the final draft, and had full access to all study data and final responsibility for the decision to submit for publication.

Declaration of interests

RF reports funding/grant support from AbbVie, Amgen, Biogen, Bristol Myers Squibb, Gilead, GlaxoSmithKline, Janssen, Lilly, Novartis, Pfizer, Regeneron, Roche, Sanofi-Aventis, Samumed, Teva, UCB, Viela, and VORSO, and honorarium for consultancy from AbbVie, Amgen, Bristol Myers Squibb, Gilead, GlaxoSmithKline, Janssen, Lilly, Novartis, Pfizer, and UCB.

AF, TD, WL, ZW, and WH report that they are full-time employees of AbbVie and may hold AbbVie stock or stock options.

AN reports he was a full-time employee of AbbVie at the time of the investigation.

ED and AS report no conflicts to disclose.

GC-M reports he has received funding/grant support from AbbVie, Amgen, Bristol Myers Squibb, Lilly, Moderna, Pfizer, UCB, and Vertex.

SC reports he has received funding/grant support and/or honorarium for consultancy from AbbVie, Aclaris, Amgen, Genetech, Lilly, Pfizer, and Roche.

PCT reports he has received funding/grant support from Celgene, Galapagos, and Lilly, and honorarium for consultancy from AbbVie, Biogen, Bristol Myers Squibb, Fresenius, Galapagos, Gilead, GlaxoSmithKline, Janssen, Lilly, Nordic Pharma, Pfizer, Roche, Sanofi, and UCB.

RB reports he has received funding/grant support from AbbVie, Merck Sharp & Dohme, and Roche, and honorarium for consultancy from AbbVie, Bristol Myers Squibb, Galapagos, Janssen, Lilly, Merck Sharp & Dohme, Pfizer, and Roche.

Acknowledgments

AbbVie Inc. participated in the study design; study research; collection, analysis, and interpretation of data; and writing, reviewing, and approving this manuscript. All authors had access to the data, participated in the development and review of the document, and in the decision to submit this manuscript. AbbVie and the authors thank all study investigators for their contributions and the patients who participated in this study. AbbVie funded the research for this study and provided writing support for this manuscript. Medical writing support, funded by AbbVie, was provided by Nate Connors, PhD, ISMPP, CMPP™ and Kersten Reich, MPH, ISMPP, CMPP™ of JB Ashtin, who developed the first draft based on an author-approved outline and assisted in implementing author revisions. The authors would like to acknowledge Thierry R Sornasse (AbbVie) for their contributions during the development of this manuscript.

References

1. Smolen JS, Aletaha D, Barton A, Burmester GR, Emery P, Firestein GS, et al. Rheumatoid arthritis. *Nat Rev Dis Primers* 2018; **4:** 18001.

2. Aletaha D, Smolen JS. Diagnosis and management of rheumatoid Arthritis: A Review. *JAMA* 2018; **320:** 1360–72.

3. Fraenkel L, Bathon JM, England BR, St Clair EW, Arayssi T, Carandang K, et al. 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol* 2021; **73:** 1108–23.

4. Smolen JS, Landewe RBM, Bijlsma JWJ, Burmester GR, Dougados M, Kerschbaumer A, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis* 2020; **79:** 685–99.

5. Scott IC, Ibrahim F, Panayi G, Cope AP, Garrood T, Vincent A, et al. The frequency of remission and low disease activity in patients with rheumatoid arthritis, and their ability to identify people with low disability and normal quality of life. *Semin Arthritis Rheum* 2019; **49:** 20–26.

6. Yu C, Jin S, Wang Y, Jiang N, Wu C, Wang Q, et al. Remission rate and predictors of remission in patients with rheumatoid arthritis under treat-to-target strategy in real-world studies: a systematic review and meta-analysis. *Clin Rheumatol* 2019; **38:** 727–38.

7. Winthrop KL, Weinblatt ME, Bathon J, Burmester GR, Mease PJ, Crofford L, et al. Unmet need in rheumatology: reports from the Targeted Therapies meeting 2019. *Ann Rheum Dis* 2020; **79:** 88–93.

8. Combe B, Kivitz A, Tanaka Y, van der Heijde D, Simon JA, Baraf HSB, et al. Filgotinib versus placebo or adalimumab in patients with rheumatoid arthritis and inadequate response to methotrexate: a phase III randomised clinical trial. *Ann Rheum Dis* 2021; **80:** 848–58.

9. Fleischmann R, Mysler E, Hall S, Kivitz AJ, Moots RJ, Luo Z, et al. Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis (ORAL Strategy): a phase 3b/4, double-blind, head-to-head, randomised controlled trial. *Lancet* 2017; **390:** 457–68.

10. Fleischmann R, Pangan AL, Song I-H, Mysler E, Bessette L, Peterfy C, et al. Upadacitinib versus placebo or adalimumab in patients with rheumatoid arthritis and an inadequate response to methotrexate: results of a phase III, double-blind, randomized controlled trial. *Arthritis & Rheumatology* 2019; **71:** 1788–1800.

11. Taylor PC, Keystone EC, van der Heijde D, Weinblatt ME, Del Carmen Morales L, Reyes Gonzaga J, et al. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. *N Engl J Med* 2017; **376**: 652–662.

12. Chang BY, Huang MM, Francesco M, Chen J, Sokolove J, Magadala P, et al. The Bruton tyrosine kinase inhibitor PCI-32765 ameliorates autoimmune arthritis by inhibition of multiple effector cells. *Arthritis Res Ther* 2011; **13:** R115.

13. Bose P, Gandhi V. Managing chronic lymphocytic leukemia in 2020: an update on recent clinical advances with a focus on BTK and BCL-2 inhibitors. *Fac Rev* 2021; **10:** 22.

14. Cohen S, Tuckwell K, Katsumoto TR, Zhao R, Galanter J, Lee C, et al. Fenebrutinib versus placebo or adalimumab in rheumatoid arthritis: a randomized, double-blind, phase II trial (ANDES Study). *Arthritis Rheumatol* 2020; **72:** 1435–46.

15. Goess C, Harris CM, Murdock S, McCarthy RW, Sampson E, Twomey R, et al. ABBV-105, a selective and irreversible inhibitor of Bruton's tyrosine kinase, is efficacious in multiple preclinical models of inflammation. *Mod Rheumatol* 2019; **29:** 510–522.

16. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 2010; **62:** 2569–81.

17. Smolen JS, Pangan AL, Emery P, Rigby W, Tanaka Y, Vargas JI, et al. Upadacitinib as monotherapy in patients with active rheumatoid arthritis and inadequate response to methotrexate (SELECT-MONOTHERAPY): a randomised, placebo-controlled, double-blind phase 3 study. *Lancet* 2019; **393:** 2303–2311.

18. Conaghan PG, Mysler E, Tanaka Y, Da Silva-Tillmann B, Shaw T, Liu J, et al. Upadacitinib in rheumatoid arthritis: a benefit-risk assessment across a phase III program. *Drug Saf* 2021; **44:** 515–530.

19. Smolen JS, Kremer JM, Gaich CL, DeLozier AM, Schlichting DE, Xie L, et al. Patient-reported outcomes from a randomised phase III study of baricitinib in patients with rheumatoid arthritis and an inadequate response to biological agents (RA-BEACON). *Ann Rheum Dis* 2017; **76:** 694–700.

20. Burmester GR, Blanco R, Charles-Schoeman C, Wollenhaupt J, Zerbini C, Benda B, et al. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. *Lancet* 2013; **381:** 451–60.

21. Kremer JM, Emery P, Camp HS, Friedman A, Wang L, Othman AA, et al. A phase IIb study of ABT-494, a selective JAK-1 inhibitor, in patients with rheumatoid arthritis and an

518 inadequate response to anti-tumor necrosis factor therapy. *Arthritis Rheumatol* 2016; **68:**
519 2867–77.

520 22. Neuenschwander B, Capkun-Niggli G, Branson M, Spiegelhalter DJ. Summarizing
521 historical information on controls in clinical trials. *Clin Trials* 2010; **7:** 5–18.

522 23. Genovese MC, Fleischmann R, Combe B, Hall S, Rubbert-Roth A, Zhang Y, et al. Safety
523 and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to
524 biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): a double-blind,
525 randomised controlled phase 3 trial. *Lancet* 2018; **391:** 2513–24.

526 24. Schafer PH, Kivitz AJ, Ma J, Korish S, et al. Spebrutinib (CC-292) Affects Markers of B
527 cell activation, chemotaxis, and osteoclasts in patients with rheumatoid arthritis: results
528 from a mechanistic study. *Rheumatol Ther* 2020; **7**: 101–19.

529 25. Genovese MC, Spindler A, Sagawa A, Park W, Dudek A, Kivitz A, et al. Safety and
530 efficacy of poseltinib, Bruton's tyrosine kinase inhibitor, in patients with rheumatoid
531 arthritis: a randomized, double-blind, placebo-controlled, 2-part phase II study. *J*
532 *Rheumatol* 2021; **48**: 969–76.

533 26. Clinicaltrials.gov. Study to evaluate safety and pharmacokinetics of GS-4059
534 (tirabrutinib) in healthy volunteers and participants with rheumatoid arthritis (RA).
535 September 9, 2020. https://clinicaltrials.gov/ct2/show/NCT02626026 (Accessed
536 September 20, 2021).

537 27. Peterfy C, Buch M, Choy E, Schett G, Parsons-Rich D, Patel A, et al. A phase IIb,
538 randomized, double-blind study in patients with rheumatoid arthritis evaluating the safety
539 and efficacy of evobrutinib compared with placebo in patients with an inadequate
540 response to methotrexate. *Arthritis Rheumatol* 2020; **72**: 4032–35.

28. Clinicaltrials.gov. Efficacy and safety study of BMS-986142 in patients with moderate to severe rheumatoid arthritis. May 28, 2019. https://clinicaltrials.gov/ct2/show/NCT02638948 (accessed September 21, 2021).

29. Isenberg D, Furie R, Jones NS, Guibord P, Galanter J, Lee C, et al. Efficacy, safety, and pharmacodynamic effects of the Bruton's tyrosine kinase inhibitor fenebrutinib (GDC-0853) in systemic lupus erythematosus: results of a phase II, randomized, double-blind, placebo-controlled trial. *Arthritis Rheumatol* 2021. doi: 10.1002/art.41811.

30. ClinicalTrials.gov. A phase II study of M2951 in SLE. April 12, 2021. https://clinicaltrials.gov/ct2/show/results/NCT02975336 (accessed September 9, 2021).

31. ClinicalTrials.gov. Proof of concept study to evaluate the efficacy and safety of BMS-931699 (lulizumab) or BMS-986142 in primary Sjögren's syndrome. October 4, 2018. https://clinicaltrials.gov/ct2/show/NCT02843659 (accessed September 21, 2021).

32. Clinicaltrials.gov. Study to assess safety and efficacy of filgotinib, lanraplenib and tirabrutinib in adults with active Sjogren's syndrome. October 23, 2020. https://clinicaltrials.gov/ct2/show/NCT03100942 (accessed September 21, 2021).

33. von Hundelshausen P, Siess W. Bleeding by Bruton tyrosine kinase-inhibitors: dependency on drug type and disease. *Cancers (Basel)* 2021; **13:** 1103.

34. Joseph RE, Amatya N, Fulton DB, Engen JR, Wales TE, Andreotti A. Differential impact of BTK active site inhibitors on the conformational state of full-length BTK. *Elife* 2020; **9:** e60470.

35. Nagai K, Matsubayashi K, Ide K, Seto K, Kawasaki Y, Kawakami K. Factors influencing placebo responses in rheumatoid arthritis clinical trials: a meta-analysis of randomized, double-blind, placebo-controlled studies. *Clin Drug Investig* 2020; **40:** 197–209.

564 36. Collignon O, Schritz A, Spezia R, Senn SJ. Implementing historical controls in oncology
565 trials. *Oncologist* 2021; **26:** e859–e862.

566 37. Kerschbaumer A, Smolen JS, Herkner H, Stefanova T, Chwala E, Aletaha D. Efficacy
567 outcomes in phase 2 and phase 3 randomized controlled trials in rheumatology. *Nat*
568 *Med*. 2020;26(6):974-980.

569

TABLES

Table 1: **Patient demographics and baseline characteristics**

	ABBV-599 (n=62)	ELS 60 mg (n=41)	ELS 20 mg (n=39)	ELS 5 mg (n=41)	UPA 15 mg (n=40)	Placebo (n=19)
Age, y, mean (SD)	56·2 (12·8)	59·2 (11·1)	59·7 (11·0)	58·1 (11·0)	57·7 (10·6)	57·6 (9·1)
Sex						
Female, n (%)	48 (77)	36 (88)	35 (90)	33 (80)	35 (88)	17 (89)
Male, n (%)	14 (23)	5 (12)	4 (10)	8 (20)	5 (12)	2 (11)
Race, n (%)						
White	58 (94)	36 (88)	35 (90)	35 (85)	37 (93)	19 (100)
Black or African American	3 (5)	4 (10)	4 (10)	3 (7)	3 (8)	0 (0)
Other	1 (2)	1 (2)	0 (0)	3 (7)	0 (0)	0 (0)
BMI, kg/m^2, mean (SD)	30·0 (5·7)	31·8 (8·7)	32·0 (5·6)	28·7 (6·1)	31·5 (9·8)	30·1 (5·5)
Duration of RA symptoms, y, mean (SD)	12·6 (8·3)	18·9 (10·2)	12·4 (7·4)	15·3 (9·4)	14·9 (8·7)	12·4 (6·5)
Time since RA diagnosis, y, mean (SD)	11·7 (8·1)	17·8 (10·5)	11·6 (7·6)	14·1 (9·6)	13·7 (8·9)	11·9 (6·9)
CRP, mg/L, mean (SD)	16·3 (21·9)	21·2 (25·4)	15·7 (20·4)	18·1 (24·0)	16·8 (17·8)	17·1 (14·1)
Anti-CCP status, n (%)						
Negative	20 (32)	7 (17)	7 (18)	11 (27)	10 (25)	3 (16)
Positive	42 (68)	34 (83)	32 (82)	30 (73)	30 (75)	16 (84)
Rheumatoid factor status, n (%)						
Negative	22 (35)	8 (20)	8 (21)	11 (27)	10 (25)	2 (11)
Positive	40 (65)	33 (80)	31 (79)	30 (73)	30 (75)	17 (89)
DAS28 (CRP), mean (SD)	5·6 (1·0)	6·0 (0·9)	5·6 (0·9)	6·0 (1·0)	5.9 (0·7)	5·9 (1·0)
(>5·1), n (%)*	41 (68)	35 (88)	22 (59)	32 (78)	32 (80)	14 (74)
CDAI, mean (SD)	37·8 (13·1)	40·7 (12·3)	37·4 (12·6)	42·0 (12·6)	40·1 (10·8)	40·7 (12·9)
High disease activity (>22), n (%)*	54 (92)	39 (98)	36 (97)	36 (95)	38 (97)	17 (94)
Missing	3	1	2	3	1	1
HAQ-DI, mean (SD)	1·4 (0·7)	1·7 (0·5)	1·7 (0·5)	1·7 (0·6)	1·6 (0·6)	1·6 (0·6)
Concomitant csDMARD, n (%)*						

MTX	32 (53)	24 (59)	19 (49)	31 (76)	20 (51)	8 (42)
Other csDMARD	21 (35)	11 (27)	16 (41)	8 (20)	14 (36)	8 (42)
MTX + other csDMARD	7 (12)	6 (15)	4 (10)	2 (5)	5 (13)	3 (16)
Missing	2	0	0	0	1	0
Prior exposure to bDMARDs, n (%)						
Failed ≤2 biologics with same MOA	51 (82)	34 (83)	28 (72)	31 (76)	30 (75)	15 (79)
Failed ≥3 biologics with same MOA and/or ≥2 with different MOA	11 (18)	7 (17)	11 (28)	10 (24)	10 (25)	4 (21)

bDMARD=biologic disease–modifying antirheumatic drug; BMI=body mass index; CCP=cyclic citrullinated peptide; CDAI=clinical disease activity index; CRP=C-reactive protein; csDMARD=conventional synthetic disease–modifying antirheumatic drug; DAS28=disease activity score (28 joints); ELS=elsubrutinib; HAQ-DI=Health Assessment Questionnaire Disability Index; MOA=mechanism of action; MTX=methotrexate; RA=rheumatoid arthritis; UPA=upadacitinib; Y=years.

*Percentages calculated on non-missing values.

Table 2: **Efficacy results for the primary endpoint and key secondary endpoints for changes from baseline at week 12**

Treatment	n	Change from baseline* LS mean (SE)	Between-group difference (LS mean [90% CI]) vs Placebo	p value†	vs ABBV-599	p value†
DAS28 (CRP) (primary endpoint)						
Placebo	18	–1·12 (0·31)	-	-	-	-
ABBV-599 (60 mg/15 mg)	54	–2·56 (0·18)	–1·44 (–2·03 to –0·85)	<0·0001	-	-
ELS 60 mg	35	–1·52 (0·23)	–0·40 (–1·03 to 0·23)	0·29	1·04 (0·58 to 1·51)	0·00029
ELS 20 mg	29	–1·32 (0·24)	–0·20 (–0·85 to 0·44)	0·61	1·24 (0·75 to 1·73)	<0·0001
ELS 5 mg	34	–1·33 (0·22)	–0·21 (–0·84 to 0·41)	0·57	1·23 (0·76 to 1·69)	<0·0001
UPA 15 mg	37	–2·87 (0·22)	–1·75 (–2·38 to –1·13)	<0·0001	–0·31 (–0·77 to 0·15)	0·27
HAQ-DI (secondary endpoint)						
Placebo	18	–0·30 (0·13)	-	-	-	-
ABBV-599 (60 mg/15 mg)	54	–0·52 (0·08)	–0·22 (–0·47 to 0·03)	0·14	-	-
ELS 60 mg	35	–0·31 (0·09)	0·00 (–0·27 to 0·26)	0·98	0·22 (0·02 to 0·41)	0·071
ELS 20 mg	29	–0·12 (0·10)	0·19 (–0·08 to 0·46)	0·26	0·41 (0·20 to 0·61)	0·0013
ELS 5 mg	35	–0·18 (0·09)	0·12 (–0·14 to 0·38)	0·45	0·34 (0·15 to 0·54)	0·0041
UPA 15 mg	36	–0·54 (0·09)	–0·24 (–0·51 to 0·02)	0·13	–0·02 (–0·22 to 0·17)	0·85
CDAI (secondary endpoint)						
Placebo	18	–14·57 (3·15)	-	-	-	-
ABBV-599 (60 mg/15 mg)	52	–27·00 (1·85)	–12·43 (–18·36 to –6·49)	0·00066	-	-
ELS 60 mg	35	–17·50 (2·25)	–2·93 (–9·23 to 3·36)	0·44	9·49 (4·83 to 14·16)	0·00092
ELS 20 mg	29	–16·70 (2·38)	–2·13 (–8·60 to 4·33)	0·59	10·30 (5·41 to 15·18)	0·00060
ELS 5 mg	33	–16·51 (2·27)	–1·94 (–8·28 to 4·39)	0·61	10·49 (5·76 to 15·21)	0·00031
UPA 15 mg	36	–28·85 (2·20)	–14·28 (–20·55 to –8·01)	0·00022	–1·85 (–6·48 to 2·78)	0·51

CDAI=clinical disease activity index; CRP=C-reactive protein; DAS28=disease activity score (28 joints); HAQ-DI=Health Assessment Questionnaire Disability Index; ELS=elsubrutinib; LS=least squares; UPA=upadacitinib.
*Baseline is defined as the last non-missing value prior to the first dose of study drug. †Based on a mixed-effect repeated-measurements model.

Table 3: **Results of selected secondary efficacy endpoints (response rates) at week 12**

			Between-group difference (90% CI)			
Treatment	**N**	**Response rate n (%)**	**vs Placebo**	**p value**	**vs ABBV-599**	**p value**
DAS28 (CRP) ≤2·6						
Placebo	19	2 (11)	-	-	21·2 [6·20, 36·19]	0·020
ABBV-599	62	20 (32)	21·2 (6·20 to 36·19)	0·020	-	-
ELS 60 mg	41	8 (20)	9·5 (–5·82 to 24·87)	0·31	–12·7 (–26·54 to 1·06)	0·13
ELS 20 mg	39	3 (8)	–2·0 (–15·35 to 11·33)	0·80	–23·1 (–35·15 to –11·03)	0·0016
ELS 5 mg	41	4 (10)	–0·6 (–14·24 to 12·95)	0·94	–21·9 (–34·14 to –9·65)	0·0033
UPA 15 mg	40	17 (43)	31·1 (14·52 to 47·71)	0·0020	9·7 (–5·81 to 25·24)	0·30
CDAI ≤2·8						
Placebo	19	1 (5)	-	-	9·0 (–2·12 to 20·19)	0·18
ABBV-599	62	9 (15)	9·0 (–2·12 to 20·19)	0·18	-	-
ELS 60 mg	41	3 (7)	2·2 (–8·74 to 13·09)	0·74	–7·2 (–17·12 to 2·71)	0·23
ELS 20 mg	39	2 (5)	0·4 (–9·85 to 10·58)	0·95	–8·7 (–18·16 to 0·81)	0·13
ELS 5 mg	41	0	–5·2 (–13·46 to 3·06)	0·30	–14·3 (–21·53 to –7·02)	0·0012
UPA 15 mg	40	6 (15)	9·3 (–2·78 to 21·30)	0·21	0·1 (–11·28 to 11·45)	0·99
HAQ-DI MCID						
Placebo	19	9 (47)	-	-	10·9 (–10·11 to 31·90)	0·39
ABBV-599	62	36 (58)	10·9 (–10·11 to 31·90)	0·39	-	-
ELS 60 mg	41	22 (54)	6·9 (–15·13 to 28·91)	0·61	–4·2 (–20·17 to 11·71)	0·66
ELS 20 mg	39	17 (44)	–2·7 (–25·17 to 19·80)	0·84	–15·0 (–31·59 to 1·63)	0·14
ELS 5 mg	41	18 (44)	–3·1 (–25·37 to 19·24)	0·82	–14·7 (–30·98 to 1·68)	0·14
UPA 15 mg	40	22 (55)	7·4 (–14·92 to 29·74)	0·59	–4·4 (–20·81 to 11·96)	0·66
ACR20						
Placebo	19	9 (47)	-	-	16·9 (–2·47 to 36·23)	0·15
ABBV-599	62	40 (65)	16·9 (–2·47 to 36·23)	0·15	-	-
ELS 60 mg	41	17 (42)	–6·3 (–27·17 to 14·65)	0·62	–23·0 (–38·97 to –6·95)	0·018
ELS 20 mg	39	12 (31)	–15·1 (–35·29 to 5·04)	0·22	–34·1 (–49·88 to –18·26)	0·00039
ELS 5 mg	41	14 (34)	–12·8 (–33·08 to 7·45)	0·30	–31·0 (–46·67 to –15·26)	0·0012
UPA 15 mg	40	29 (73)	25·9 (6·01 to 45·84)	0·032	7·7 (–7·60 to 22·99)	0·41
ACR50						
Placebo	19	4 (21)	-	-	24·4 (6·27 to 42·59)	0·027
ABBV-599	62	28 (45)	24·4 (6·27 to 42·59)	0·027	-	-
ELS 60 mg	41	12 (29)	8·7 (–10·18 to 27·59)	0·45	–15·7 (–30·92 to –0·51)	0·089
ELS 20 mg	39	5 (13)	–7·4 (–24·43 to 9·59)	0·47	–33·3 (–47·02 to –19·66)	<0·0001
ELS 5 mg	41	7 (17)	–3·5 (–21·08 to 14·08)	0·74	–28·6 (–42·79 to –14·45)	0·00089
UPA 15 mg	40	19 (48)	25·9 (6·63 to 45·22)	0·027	0·5 (–15·82 to 16·74)	0·96
ACR70						
Placebo	19	3 (16)	-	-	9·9 (–6·48 to 26·26)	0·32
ABBV-599	62	16 (26)	9·9 (–6·48 to 26·26)	0·32	-	-
ELS 60 mg	41	6 (15)	–0·1 (–15·97 to 15·74)	0·99	–11·0 (–22·95 to 0·89)	0·13
ELS 20 mg	39	2 (5)	–9·9 (–24·33 to 4·55)	0·26	–20·4 (–31·54 to –9·32)	0·0025
ELS 5 mg	41	4 (10)	–5·5 (–20·86 to 9·80)	0·55	–15·7 (–27·78 to –3·67)	0·032
UPA 15 mg	40	11 (28)	11·1 (–6·07 to 28·29)	0·29	0·6 (–13·68 to 14·96)	0·94

Based on Cochran-Mantel-Haenszel test stratified by number of prior bDMARD use (failed 1 or 2 biologics with the same mechanism of action; failed ≥3 biologics with the same mechanism of action and/or ≥2 biologics with multiple mechanisms of action). ACR=American College of Rheumatology; CDAI=clinical disease activity index; CRP=C-reactive protein; DAS28=disease activity score (28 joints); ELS=elsubrutinib; HAQ-DI=Health

Assessment Questionnaire Disability Index; MCID=minimal clinically important difference, defined as change from baseline ≤ –0·22; UPA=upadacitinib.

Table 4: **Safety summary**

	ABBV-599 (n=62)	ELS 60 mg (n=41)	ELS 20 mg (n=39)	ELS 5 mg (n=41)	UPA 15 mg (n=40)	Placebo (n=19)
Any TEAE, n (%)	27 (44)	23 (56)	20 (51)	19 (46)	14 (35)	10 (53)
TEAE with reasonable possibility of being drug related*	12 (19)	12 (29)	9 (23)	2 (5)	8 (20)	5 (26)
Serious TEAE[†]	0 (0)	0 (0)	2 (5)[‡]	3 (7)[§]	0 (0)	1 (5)
AE leading to study drug discontinuation	3 (5)	2 (5)	1 (3)	3 (7)	1 (3)	1 (5)
Deaths	0 (0)	0 (0)	0 (0)	1 (2)[¶]	0 (0)	0 (0)
AEs reported by ≥5% of patients in any group, n (%)						
Upper respiratory tract infection	4 (6)	2 (5)	3 (8)	2 (5)	2 (5)	1 (5)
Worsening RA	0 (0)	3 (7)	3 (8)	3 (7)	0 (0)	2 (11)
Urinary tract infection	0 (0)	4 (10)	2 (5)	2 (5)	3 (8)	0 (0)
Cough	1 (2)	2 (5)	0 (0)	0 (0)	2 (5)	0 (0)
Bronchitis	0 (0)	1 (2)	0 (0)	1 (2)	0 (0)	1 (5)
Tooth infection	0 (0)	0 (0)	1 (3)	0 (0)	1 (3)	1 (5)
ALT increased	0 (0)	0 (0)	0 (0)	0 (0)	2 (5)	0 (0)
Alopecia	0 (0)	0 (0)	2 (5)	0 (0)	0 (0)	0 (0)
Arthralgia	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5)
Arthritis	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (5)
Erythema	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5)
Peripheral swelling	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (5)
Sinusitis	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (5)
Animal bite	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5)
Endometrial adenocarcinoma	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5)
Blood glucose increased	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5)
Bone deformity	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5)
Pain in extremity	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5)
PSA increased	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5)
Vitamin D deficiency	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5)

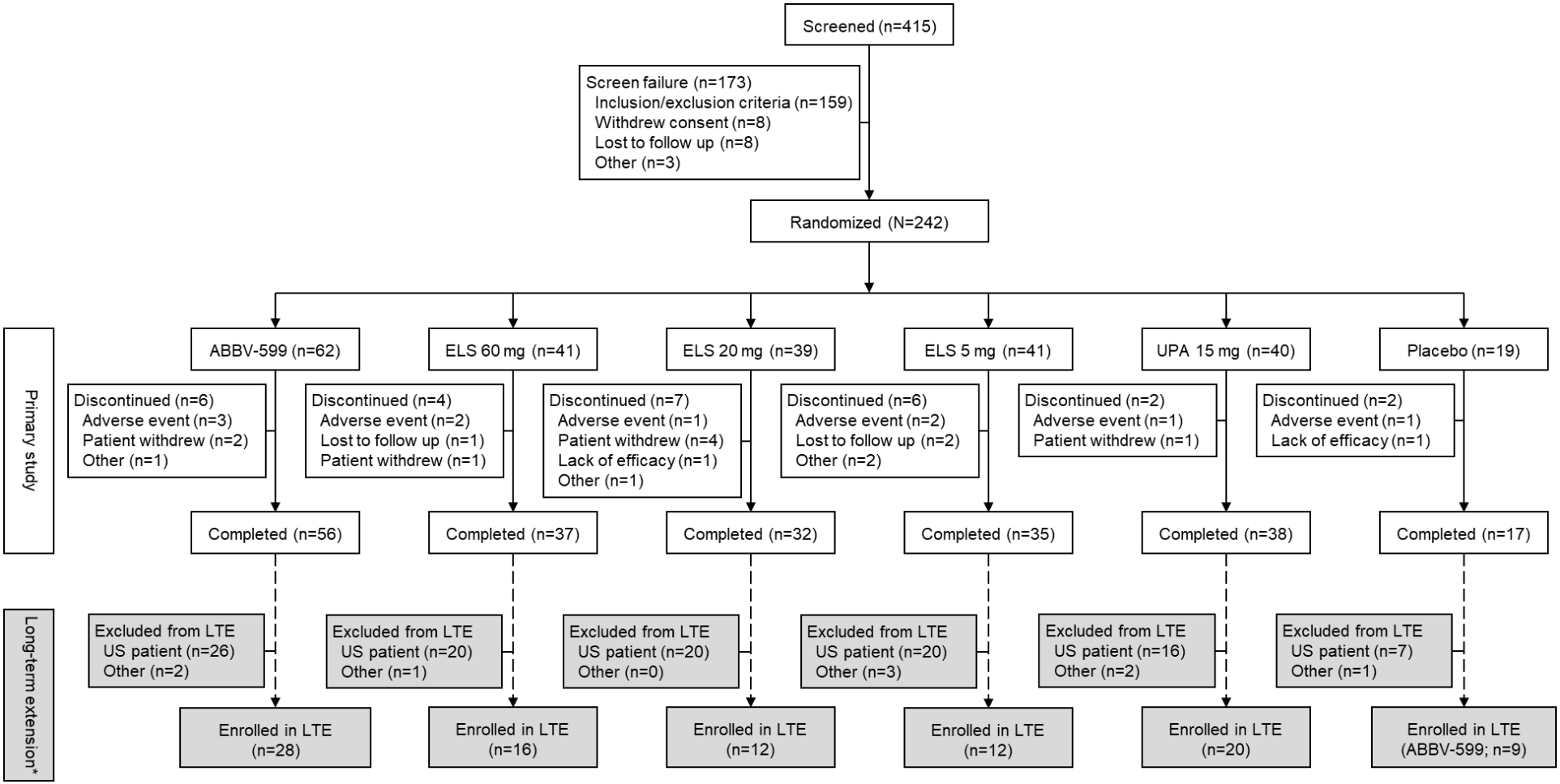
AE=adverse event; ALT=alanine aminotransferase; ELS=elsubrutinib; PSA=prostate specific antigen; RA=rheumatoid arthritis; TEAE=treatment-emergent adverse events; UPA=upadacitinib. *As assessed by investigator. [†]No serious TEAEs were considered related to study treatment by investigators. [‡]Coronary artery disease and lumbar radiculopathy were reported for one patient each. [§]Pyelonephritis, bone fractures from a traffic accident, and fatal cardiac arrest were reported for one patient each. [¶]Cardiac arrest that was not considered related to study treatment.

FIGURE LEGENDS

Figure 1 : **Patient disposition.**

Figure 2: **(A) Change from baseline in DAS28 (CRP) through week 12 by treatment group.** Each point represents the least-squares mean (SE) change from baseline value. CRP=C-reactive protein; DAS28=disease activity score (28 joints); ELS=elsubrutinib; UPA=upadacitinib. **(B): BTK occupancy at week 4 and week 12 by treatment group.** Each circle represents one patient. ABBV-105=elsubrutinib; BTK=Bruton's tyrosine kinase; PD=premature discontinuation; QD=once daily.

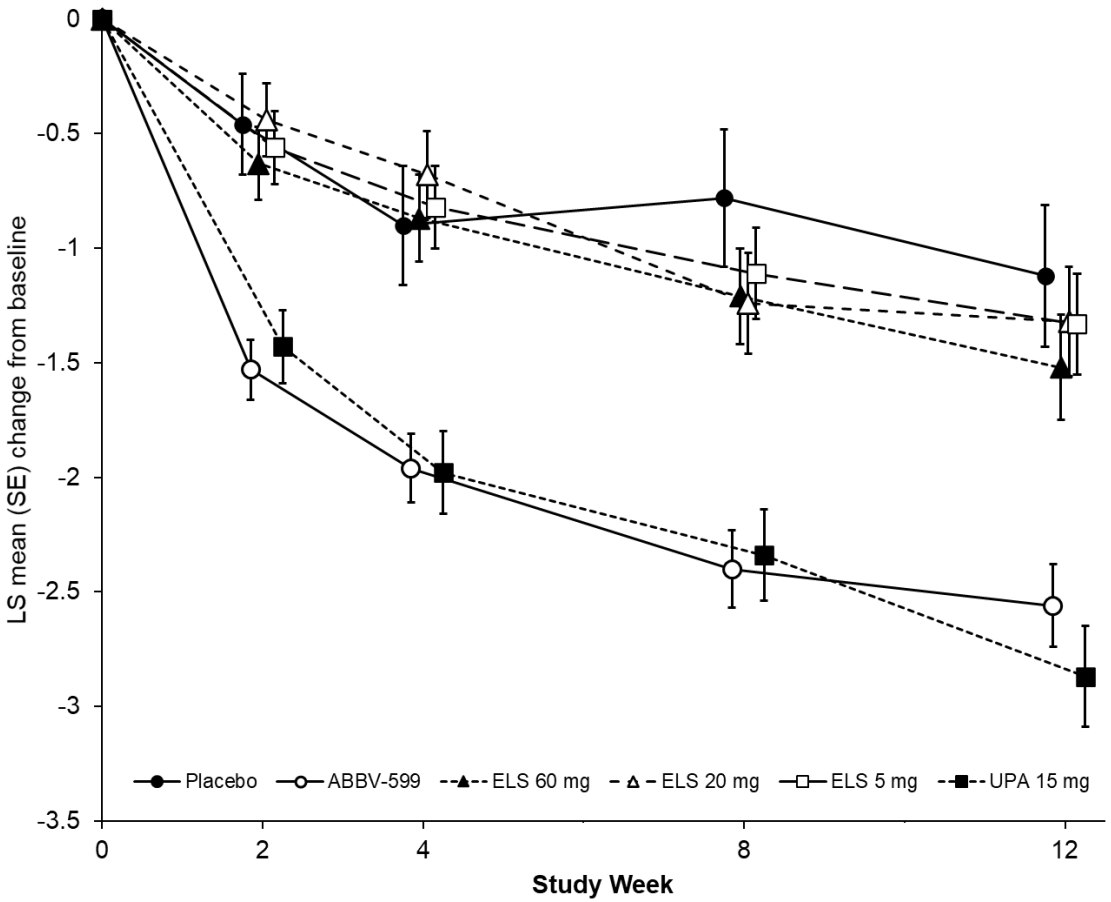
Figure 1. **Patient disposition**



All randomized patients received at least one dose of study drug, and "completed" is defined as having received all planned study treatments.
LTE=long-term extension. *Only patients outside the US were eligible for the LTE.

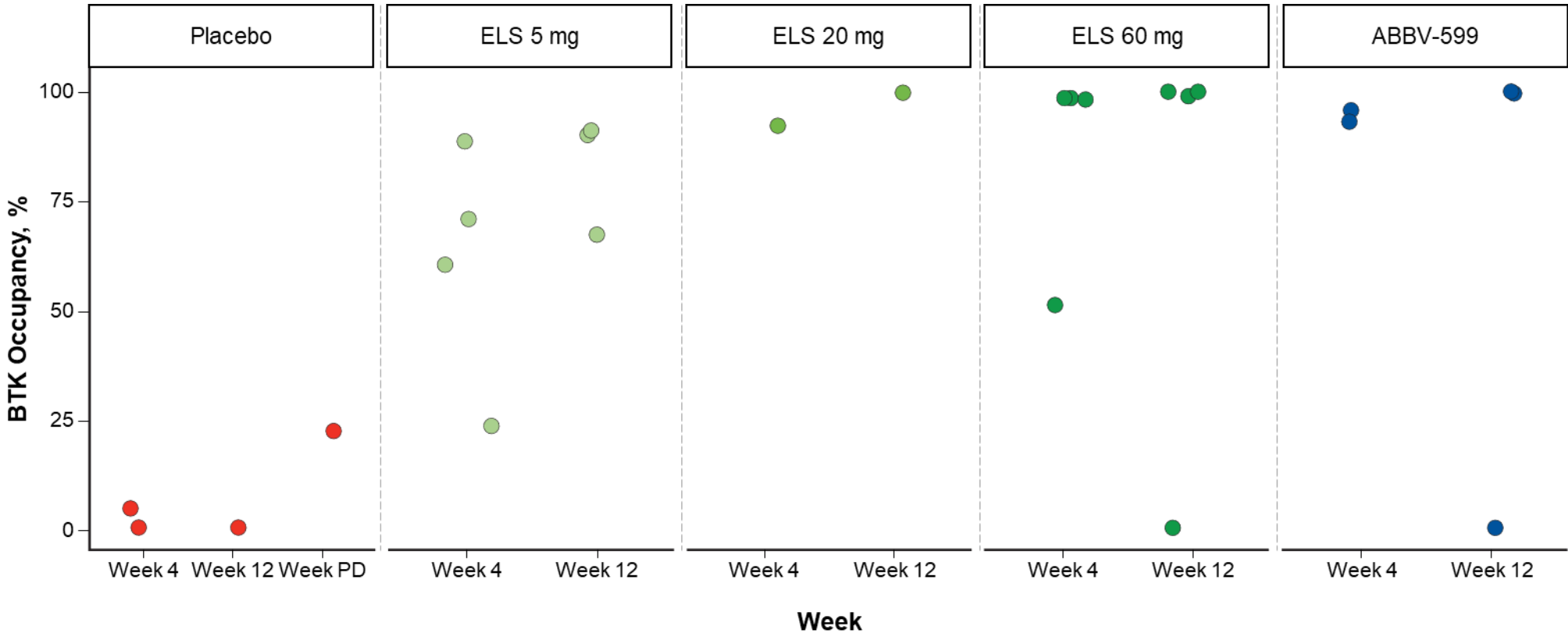
Figure 2. (A) Change from baseline in DAS28 (CRP) through week 12 by treatment group. (B) BTK occupancy at week 4 and week 12 by treatment group.

A



Each point represents the least-squares mean (SE) change from baseline value.
CRP=C-reactive protein; DAS28=disease activity score (28 joints); ELS=elsubrutinib; UPA=upadacitinib.

B



Each circle represents one patient.
ABBV-105=elsubrutinib; BTK=Bruton's tyrosine kinase; PD=premature discontinuation.