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A Phase 3 Randomised, Placebo-controlled, Double-Blind Study of Upadacitinib as Monotherapy in Patients with Active Rheumatoid Arthritis and Inadequate Response to Methotrexate: SELECT-MONOTHERAPY

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Running title: Upadacitinib monotherapy in patients with rheumatoid arthritis and inadequate response to MTX

ABSTRACT:

Background: Upadacitinib, an oral JAK1-selective inhibitor, demonstrated efficacy in combination with stable background csDMARDs in rheumatoid arthritis (RA) patients with inadequate response to DMARDs. We evaluated the safety and efficacy of upadacitinib monotherapy after switching from MTX versus continuing methotrexate (MTX) in patients with inadequate response to methotrexate (MTX-IR).

Methods: Patients with active RA despite stable MTX were randomised 2:2:1:1 to switch to once-daily upadacitinib 15mg or 30mg or to continue MTX (cMTX) at their prior dose as blinded study drug; Starting from Week14, patients randomised to cMTX were switched to UPA15 or 30mg per pre-specified assignment at baseline. The primary endpoints at Week14 were the proportion of patients achieving ACR20, and the proportion achieving low disease activity as DAS28(CRP)≤3.2 (NRI). Registration: www.clinicaltrials.gov;NCT02706951

Findings:

Of 648 randomised patients, 216 received cMTX, 217 received upadacitinib 15mg, and 215 received upadacitinib 30mg. 598 (92.3%) completed Week14. At Week14, ACR 20 was achieved by 89/216 patients (41%) receiving MTX, 147/217 (68%) receiving upadacitinib 15mg (MTX-adjusted difference 27, 95%CI 18-36, p<0.0001) and 153/215 (71%) receiving upadacitinib 30mg (MTX-adjusted difference 30, 95%CI 21-39, p<0.0001). DAS28(CRP) ≤3.2 was met by 42/216 (19%) receiving MTX, 97/217 (45%) receiving upadacitinib 15mg (MTX-adjusted difference 25, 17-34, p<0.0001) and 114/215 (53%) receiving upadacitinib 30mg (MTX-adjusted difference 34, 25-42, p<0.0001).

Adverse events were reported in 102 patients (47%) on cMTX, 103 (48%) on upadacitinib 15mg, and 105 (49%) on upadacitinib 30mg. Herpes zoster was reported by one (0.5%) on

cMTX, three (1.4%) on upadacitinib 15mg, and six (2.8%) on upadacitinib 30mg. Three malignancies [cMTX:1 (0.5%); upadacitinib 15mg:2 (0.9%)], three adjudicated MACE [upadacitinib 15mg:1(0.5%); upadacitinib 30mg:2 (0.9%)], one adjudicated pulmonary embolism (0.5%, upadacitinib 15mg) and one death [0.5%, upadacitinib 15mg, hemorrhagic stroke (ruptured aneurysm)] were reported in the study.

Interpretation: Upadacitinib monotherapy showed significant improvements in clinical and functional outcomes versus continuing MTX in this MTX-IR population. Safety observations were similar to those in prior upadacitinib RA studies.

RESEARCH IN CONTEXT

Evidence before the study

We performed a PubMed search using the terms “rheumatoid arthritis”, “Janus Kinase” and “clinical trial” (article type) on Nov 28th 2018 to identify reports of phase 3 efficacy and safety trials of JAK inhibitors in RA, and obtained 44 articles. Of these, one reported a phase 3 randomised controlled trial (RCT) of a JAK inhibitor as monotherapy in patients with inadequate response to csDMARDs (ORAL SOLO), and one a phase 3 RCT in patients with inadequate response to MTX (ORAL STRATEGY). ORAL SOLO compared 5 mg or 10 mg of tofacitinib twice-daily with placebo, assessing ACR20, HAQ-DI and 28-joint disease activity score using erythrocyte sedimentation rate (DAS28[ESR]) at 3 months, demonstrating significantly better responses on tofacitinib versus placebo for ACR20 and HAQ-DI, but not DAS28(ESR). ORAL STRATEGY assessed non-inferiority of tofacitinib 5 mg twice-daily monotherapy to tofacitinib 5 mg plus MTX or adalimumab plus MTX, for ACR50 at 6 months.

Added value

ORAL SOLO and SELECT-MONOTHERAPY were conducted in similar patient populations with established disease (approximately 6-8 years of RA disease duration), and moderately-to-severely active disease as evidenced by mean DAS28(CRP), and swollen and tender joint counts. ORAL SOLO compared tofacitinib versus placebo upon discontinuation of MTX and other csDMARDs in all three study groups with a washout before receiving study drug or placebo, whereas in SELECT-MONOTHERAPY, no washout was permitted; at baseline, patients who were assigned to receive upadacitinib monotherapy switched from their prior stable MTX to upadacitinib, while others continued with prior dose of MTX as a blinded study drug.

The efficacy of once-daily upadacitinib 15 and 30 mg in combination with background csDMARDs in patients with inadequate response to csDMARDs was assessed in the SELECT-NEXT study. SELECT-MONOTHERAPY is the first study to assess upadacitinib as

monotherapy. The responses with upadacitinib in both studies at 12/14 weeks were consistent, and upadacitinib monotherapy was significantly better than continuing MTX for clinical and functional improvements. In alignment with the goals of the treat-to-target strategy, the achievement of more stringent efficacy endpoints, such as remission and low disease activity by CDAI and SDAI, were assessed. Upadacitinib monotherapy resulted in 40-50% of these patients with inadequate response to MTX achieving low disease activity, and almost 20% achieving stringent remission by Week 14.

Implications

The data from SELECT-MONOTHERAPY are supportive of monotherapy with JAK inhibitors as a potential treatment option enabling disease control in patients with inadequate response to MTX, for whom combination treatment might be difficult for various reasons.

INTRODUCTION

The treatment goal for patients with rheumatoid arthritis (RA) is control of inflammation with subsequent preservation of joint structure and function. Methotrexate (MTX), a conventional synthetic disease modifying anti-rheumatic drug (csDMARD), is recommended as a first-line therapy for patients with RA. (1, 2) However, about one-half to two-thirds of patients receiving MTX monotherapy do not achieve satisfactory disease control. (3, 4) In these patients, the addition of a second csDMARD, a biological DMARD (bDMARD) or a targeted synthetic DMARD (tsDMARD) is recommended. (1, 2) Despite its proven effectiveness and safety, many patients are unable to tolerate MTX due to its side-effects (5, 6) (7) which may affect adherence and treatment outcomes. (8) Moreover, monotherapy with advanced treatments is frequently used even in the case of bDMARDs, where optimal outcomes require concomitant MTX.(9, 10) Therefore, therapies which can be used without concomitant MTX have an important place in the management of RA.

The Janus Kinase (JAK) family of enzymes is involved in intracellular signaling of diverse cellular processes, such as cellular proliferation, apoptosis, migration, hematopoiesis, and induction of cytokines, and thus in the pathogenesis of inflammation and immune-mediated inflammatory diseases, like RA. (11, 12)

Upadacitinib, an oral, reversible, JAK1-selective inhibitor has demonstrated efficacy with rapid onset of action in patients with an inadequate response to csDMARDs or bDMARDs when given with stable background csDMARDs. (13, 14) In this study, the safety and efficacy of upadacitinib monotherapy versus continuing MTX treatment in patients with an inadequate response to MTX were assessed.

PATIENTS AND METHODS

SELECT-MONOTHERAPY was conducted at 138 sites in 24 countries. The study enrolled patients with RA, at least 18 years of age, who fulfilled the 2010 ACR/European League Against Rheumatism (EULAR) classification criteria for RA (15). Eligible patients must have demonstrated active disease despite treatment with MTX, defined as at least 6 swollen joints out of 66, at least 6 tender joints out of 68, and C-reactive protein > 3 mg/L [upper limit of normal (ULN) 2.87 mg/L, hsCRP test]. Patients had been receiving MTX for at least 3 months, and on a stable dose for at least 4 weeks prior to entry (15-25 mg/week or at least 10 mg/week in patients intolerant to higher MTX doses after titration; patients in Japan should have been on 7.5-16 mg/week MTX). Key exclusion criteria included prior exposure to a bDMARD or JAK inhibitor, and a history of inflammatory joint disease other than RA.

The study was conducted per the International Conference on Harmonization (ICH) guidelines, applicable regulations and guidelines governing clinical study conduct, and the Declaration of Helsinki. Study-related documents were reviewed and approved by independent ethics committees and institutional review boards, and all patients provided written informed consent before participating in study-related procedures.

RANDOMISATION AND MASKING

SELECT-MONOTHERAPY is a double-blind, double-dummy phase 3 study. For ethical considerations, to ensure that patients were not untreated for any length of time, a MTX washout period was not required prior to randomisation. Patients were randomised 2:2:1:1 to either once-daily (QD) extended-release upadacitinib at 15 mg or 30 mg or to continue prior dose of MTX (cMTX) as a blinded study drug, which was administered for 14 weeks, followed by upadacitinib 15 mg, or 30 mg per pre-specified randomisation assignment **(Supplementary Figure 1)**. All patients who complete Week 14 are eligible to remain in an ongoing blinded extension period for up to 5 years to evaluate long-term safety, tolerability and efficacy of

upadacitinib. The primary analysis for the cMTX-controlled period was at Week 14, and the results are reported here; comparisons with cMTX were performed with combined data from the two cMTX groups.

Randomisation was stratified by geographical region. A randomisation schedule was generated by the AbbVie Statistics department, based on which patients were randomised using Interactive Response Technology (IRT). The study is registered as NCT02706951.

PROCEDURES

All csDMARDs other than MTX must have been discontinued with the protocol-specified washout period (≥4 weeks, ≥8 weeks for leflunomide). Patients were allowed to continue non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen and glucocorticoids (≤10 mg prednisone/day, or equivalent) at stable doses (for at least 1 week prior to study entry) and were required to take a dietary supplement of folic acid or an equivalent. Concomitant treatments contraindicated in the MTX label, and strong cytochrome P450 3A4 (CYP 3) inhibitors and inducers were not allowed throughout the study. No bDMARDs were allowed during the study.

OUTCOMES

There were two independent primary endpoints comparing the efficacy of upadacitinib monotherapy at 15 mg and 30 mg with cMTX at Week 14: the percentage of patients who achieved a 20% improvement in the American College of Rheumatology criteria (an ACR20 response) (16) was required by the US Food and Drug Administration (FDA), and the percentage of patients who achieved a score of ≤3.2 in the 28- joint disease activity score (DAS28(CRP) (17) was required by the European Medicines Agency (EMA). Key secondary endpoints at Week 14 included the changes from baseline in DAS28(CRP) and health assessment questionnaire-disability index (HAQ-DI), the proportions of patients who achieved 50% or 70% improvement in the ACR criteria (ACR50 or ACR70 responses), DAS28(CRP)

<2.6, changes from baseline in short form 36 (SF36) - physical component score (PCS) and morning stiffness duration. Additional efficacy endpoints included the proportions of patients who achieved low disease activity (LDA) or clinical remission based on clinical disease activity index (CDAI; LDA ≤10 and remission ≤2.8) or simplified disease activity index (SDAI; LDA ≤11 and remission ≤3.3) and ACR-EULAR Boolean remission.(18)

The incidence and severity of treatment-emergent adverse events (AEs) was monitored throughout the study; adverse event coding was performed according to the Medical Dictionary for Regulatory Activities (MedDRA), version 19.1. Vital signs and laboratory tests were performed at every study visit. The Rheumatology Common Toxicity Criteria v.2.0 developed by the Outcome Measures in Rheumatology Drug Safety Working Group (OMERACT) (19) were used to grade the severity of AEs and the majority of abnormal laboratory changes, except for grading the severity of changes in creatine phosphokinase and serum creatinine for which the Common Toxicity Criteria developed by the National Cancer Institute (NCI) were used. (20) An independent, external Cardiovascular Adjudication Committee blindly adjudicated all suspected cardiovascular events including venous thromboembolic events.

STATISTICAL ANALYSIS

Efficacy analyses were conducted on the full analysis set which included all randomised patients who had received at least one dose of study drug. For binary endpoints, pairwise comparisons between upadacitinib and cMTX arms were performed using the Cochran-Mantel-Haenszel test adjusting for geographic region as a stratification factor. The primary and other categorical secondary endpoints were assessed using non-responder imputation (NRI); Patients with missing data at Week 14 or those who prematurely discontinue study drug were considered non responders. For continuous endpoints, statistical inference for each visit was done using mixed-effect model repeat measurement (MMRM) with observed data through Week

14, which included the categorical fixed effects of treatment, visit, and treatment-by-visit interaction, the stratification factor of geographic region, and the continuous fixed covariates of baseline measurement. The overall type I error rate of the primary and ranked key secondary endpoints for the two doses of upadacitinib were strongly controlled using a graphical multiple testing procedure.

Per-protocol analyses were conducted, excluding patients with major protocol deviations.

A sample size of 600 patients was planned to provide a 90% power for a 21% and 22% difference between upadacitinib monotherapy and cMTX treatment for achievement of ACR20 and DAS28(CRP)≤3.2, respectively, assuming cMTX responses of 37% and 15% for ACR20 and DAS28(CRP)≤3.2, respectively, at two-sided alpha =0.025 level of significance, accounting for a 10% dropout rate.

ROLE OF THE FUNDING SOURCE

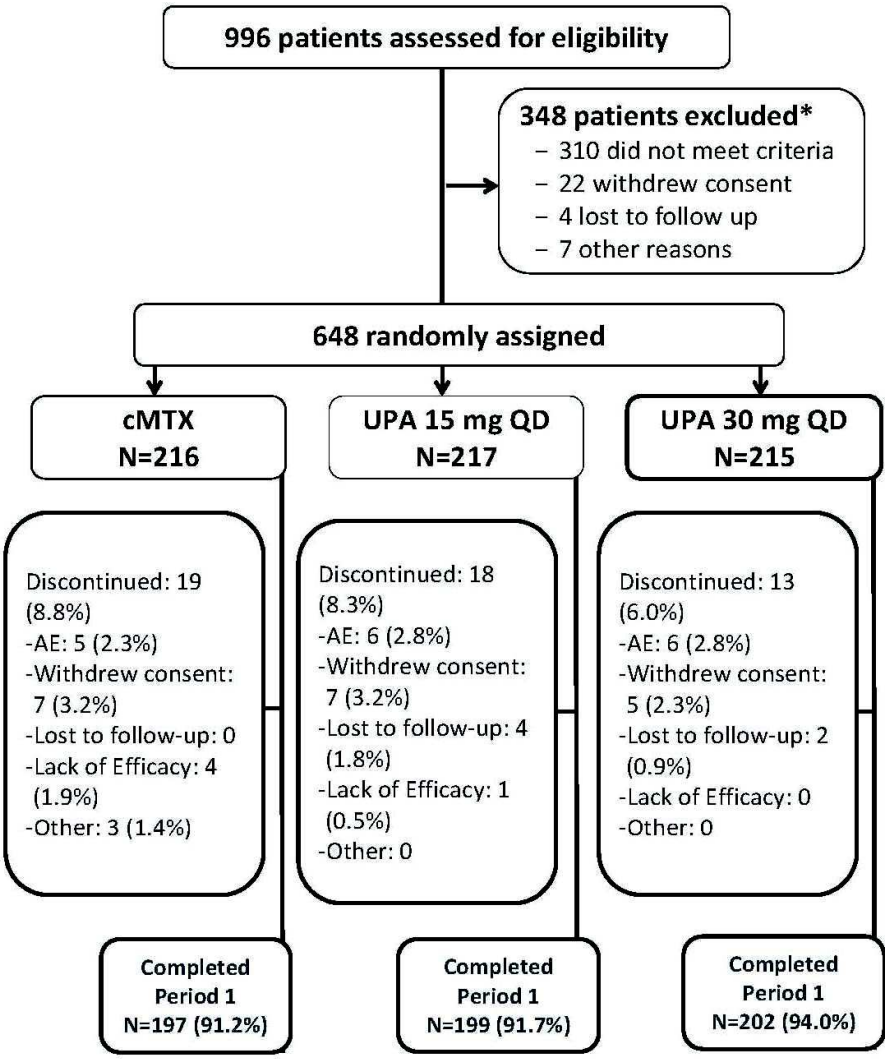
AbbVie was the study sponsor, and the study was designed by AbbVie, the authors and investigators. Clinical data were collected by the investigators, their teams, and AbbVie. AbbVie was involved in data analysis, the interpretation of results and the preparation, review and approval of the final version of this report. All the authors had access to the data, reviewed and approved the final version, made the decision to submit the manuscript for publication, and attest to the accuracy and completeness of the data. The corresponding author had full access to all the data and the final responsibility to submit for publication. A medical writer, employed by AbbVie, assisted with preparing an initial draft under the direction of the authors.

RESULTS

Between 23 Feb 2016 and 19 May 2017, 996 patients were screened, of which 310 did not meet the entry criteria, 22 withdrew consent, four were lost to follow-up, seven were not enrolled due to other reasons, and data for five patients were missing) **(Figure 1)**. A total of 648 patients underwent randomisation and all received at least one dose of study drug [cMTX (n=216), upadacitinib 15 mg QD (n=217) and upadacitinib 30 mg QD (n=215)]. The majority of patients were recruited from Eastern Europe (37%), North America (30%), and South and Central America (14%). Of the 648 patients enrolled, 598 (92.3%) completed study drug treatment through Week 14. Rates and reasons for discontinuation are in Figure 1.Overall, patient demographics and disease activity were similar across the treatment arms at baseline **(Table 1)**. The majority of patients were female (81%), with an overall mean age of 54.3 years and duration since RA diagnosis of 6.6 years. Five hundred and twelve patients (80%) were seropositive for either anti-citrullinated protein antibody (ACPA) or rheumatoid factor (RF). Patients had high disease activity, despite having an average duration of prior MTX therapy of more than 3 years. This may reflect management before entering the study that may not have fully adhered to current recommendations for some of these patients (1, 2). The mean MTX dose at baseline was 16.7 mg/week.

Figure 1. Patient disposition.

All randomised patients received study drug. The full analysis set included all randomised patients who received at least one dose of study drug. Only primary reasons for discontinuation are listed.



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224 * data for five patients is missing

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Table 1. Demographics and Characteristics at Baseline

	cMTX N=216	UPA 15 mg Mono N=217	UPA 30 mg Mono N=215
Female, n (%)	179 (83%)	174 (80%)	170 (79%)
Age, years	55.3 (11.1)	54.5 (12.2)	53.1 (12.7)
Geographical distribution of patients, n (%)			
North America	64 (30%)	64 (30%)	64 (30%)
South/Central America	31 (14%)	30 (14%)	30 (14%)
Western Europe	8 (4%)	8 (4%)	8 (4%)
Eastern Europe	79 (37%)	80 (37%)	80 (37%)
Asia[†]	22 (10%)	22 (10%)	21 (10%)
Other*	12 (6%)	13 (6%)	12 (6%)
Duration since RA Diagnosis (years)	5.8 (6.6)	7.5 (8.9)	6.5 (7.0)
RF and/or ACPA positive	169 (78%)	172 (79%)	171 (80%) [#]
Oral Glucocorticoid Use, n (%)	115 (53%)	114 (53%)	98 (46%)
-Oral Glucocorticoid Dose* (mg)	6.2 (2.6)	6.1(2.5)	5.9 (2.5)
Prior MTX Dose (mg/week)	16.7 (4.4)	16.8 (4.2)	16.5 (4.6)
Duration of prior MTX (years)[§]	3.3 (3.9)	3.8 (4.8)	3.8 (4.3)
TJC68	25.2 (16.0)	24.5 (15.1)	24.8 (15.2)
SJC66	16.9 (11.5)	16.4 (10.9)	16.9 (10.2)
PtGA (100 mm VAS)	59.6 (21.8)	62.2 (22.3)	59.4 (22.8)
Pain (100 mm VAS)	62.5 (21.3)	62.3 (22.5)	61.9 (22.1)
PhGA (100 mm VAS)	62.1 (17.5)	65.7 (18.5)	62.6 (17.8)
hsCRP (mg/L)	14.5 (17.3)	14.0 (16.5)	16.3 (20.8)
HAQ-DI	1.5 (0.7)	1.5 (0.7)	1.5 (0.7)
DAS28(CRP)	5.6 (1.0)	5.6 (0.9)	5.6 (1.1)
CDAI	37.8 (14.4)	38.0 (13.1)	38.4 (13.8)
SDAI	39.2 (14.6)	39.4 (13.4)	40.0 (14.3)

Data are n (%) or mean (SD). * Prednisone equivalent; # one patient with missing value
*Other includes South Africa, Turkey and Israel
[†]Japan only
[§]Data on prior use of other conventional synthetic disease modifying antirheumatic drugs are provided in Supplemental Table S5
MTX, methotrexate; TJC68, tender joint count of 68 joints; SJC66, swollen joint count of 66 joints; PtGA, patient's global assessment of disease activity; PhGA, physician's global assessment of disease activity; hsCRP, high sensitivity C-reactive protein; DAS28(CRP), 28-joint disease activity score based on CRP; HAQ-DI, health assessment questionnaire disability index; CDAI, clinical disease activity index; SDAI, simplified disease activity index

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At Week 14, significantly higher proportions of patients receiving upadacitinib 15 mg and 30 mg versus cMTX achieved the primary endpoints: An ACR20 response was achieved by 89 of 216 patients (41%; 95%CI, 35-48) receiving cMTX, 147 of 217 patients (68%; 62-74) receiving upadacitinib 15mg, and 153 of 215 patients (71%; 65-77) receiving upadacitinib 30mg ($p<0.0001$ for both doses versus cMTX). DAS28(CRP) ≤3.2 was met by 42 (19%; 14-25) receiving MTX, 97 (45%; 38-51) receiving upadacitinib 15mg, and 114 (53%; 46-60) receiving upadacitinib 30 mg ($p<0.0001$ for both doses versus cMTX) (**Figure 2**). Per-protocol analyses showed consistent results **(Supp Figure 2)**. Significantly higher proportions of patients achieved ACR 20/50/70 on upadacitinib 15 mg and 30 mg versus cMTX by the first follow-up visit at Week 2 and thereafter. At Week 14, 91 patients (42%; 35-49)] receiving upadacitinib 15mg and 112 patients (52%; 45-59) receiving upadacitinib 30mg versus 33 patients (15%; 11-20) receiving cMTX achieved ACR50 responses ($p<0.0001$ for both doses versus cMTX), and 49 (23%; 17-28) receiving upadacitinib 15mg, and 71 (33%; 27-39) receiving upadacitinib 30mg versus 6 (3%; 1-5) receiving cMTX achieved ACR70 responses ($p<0.0001$ for both doses versus cMTX) (**Figure 2 C, D and E**). From Week 2 through Week 14, mean improvements from baseline in all ACR core components, including pain, were significantly greater for patients on upadacitinib 15 and 30 mg versus cMTX **(Supp Figure 3).**

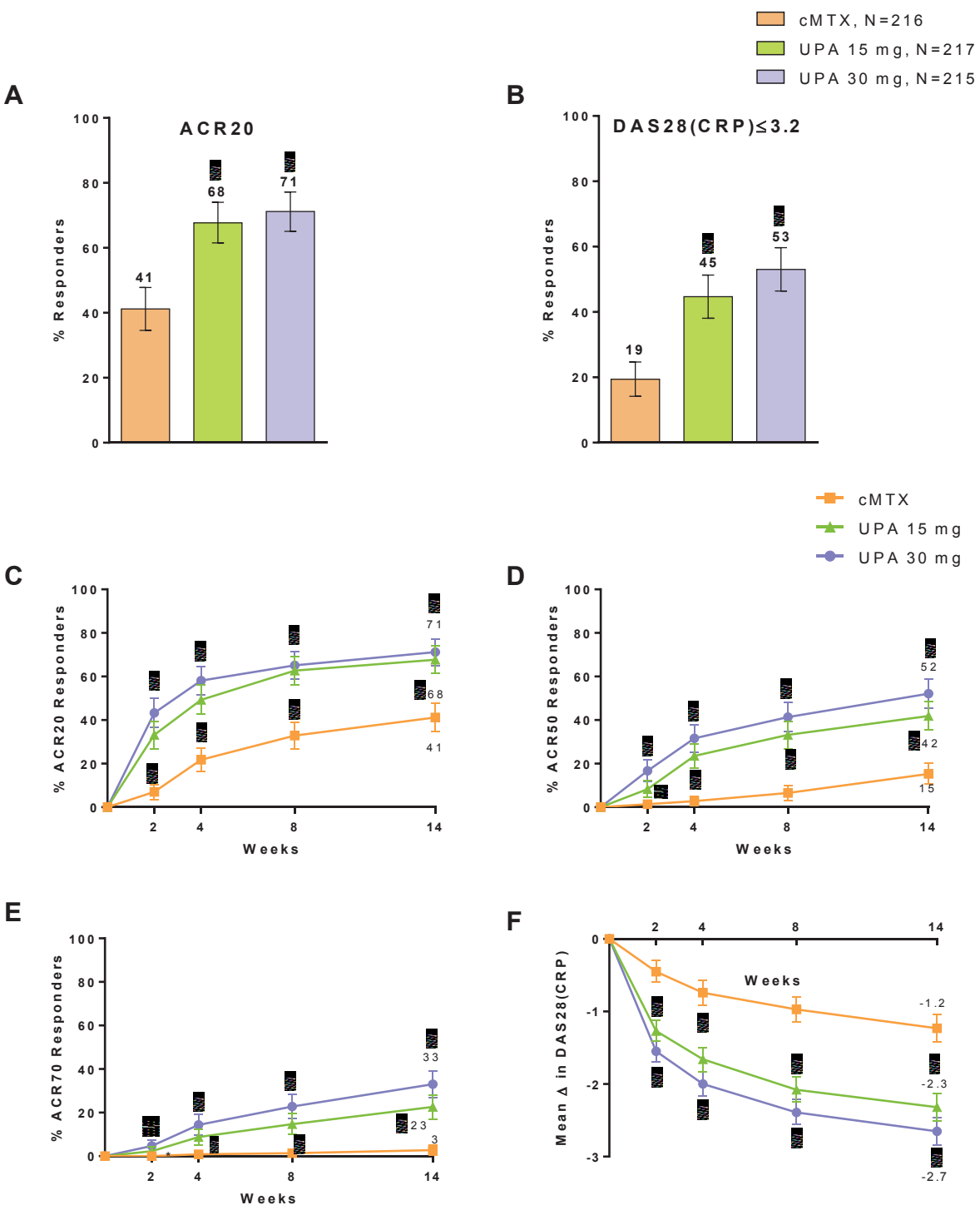
Significantly greater improvements from baseline in DAS28(CRP) were observed for both doses of upadacitinib versus cMTX from Week 2 onwards. A similar result was observed for decreases from baseline in CDAI (**Figure 2 F and Supp Fig 4 A).**

Figure 2. Patients achieving the primary endpoints (A) ACR20 and (B) DAS28(CRP) ≤3.2 at Week 14 (NRI) (C) ACR20 (D) ACR50 (E) ACR70 responses over 14 weeks (NRI analysis). Mean changes from baseline in (F) DAS28(CRP) (MMRM).

ACR, American College of Rheumatology; ACR20/50/70, 20%/50%/70% improvement in ACR score; DAS28(CRP), 28-joint Disease Activity Score using C-reactive protein; CDAI, clinical disease activity

index; HAQ-DI, health assessment questionnaire-disability index (HAQ-DI); NRI, nonresponder imputation; MMRM, Mixed Effect Model Repeat Measurement.

* P≤0.05, † P≤0.01, ‡ P≤, 0.001, § P≤0.0001 versus cMTX. Bars are 95% CI



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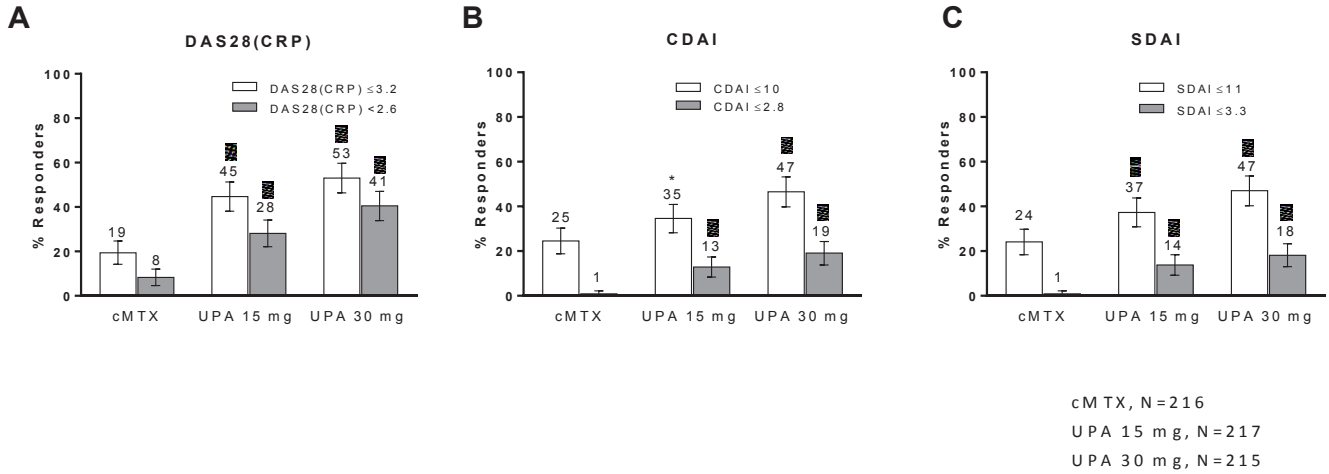
At Week 14, significantly higher proportions of patients receiving upadacitinib 15 mg and 30 mg versus cMTX achieved DAS28(CRP) <2.6, DAS28(CRP) ≤3.2, low disease or remission based on CDAI and SDAI, and Boolean remission **(Figure 3 and Supp Figure 5)**.

Figure 3. (A) Patients achieving DAS28(CRP) ≤3.2) or <2.6. (B) Patients achieving CDAI LDA (≤10) or clinical remission (≤2.8). (C) Patients achieving SDAI LDA (≤11) or clinical remission (≤3.3) at Week 14 (NRI analysis).

CDAI, Clinical Disease Activity Index; SDAI, Simplified Disease Activity Index.

* *P*≤0.05, † P≤0.01, ‡ P≤, 0.001, § P≤0.0001 versus cMTX. Bars are 95% CI



Significant improvements from baseline in physical function based on HAQ-DI were observed with upadacitinib versus cMTX; at Week 14, patients receiving upadacitinib 15 mg and 30 mg versus cMTX had a least square mean change from baseline in HAQ-DI of -0.65 (95%CI: -0.73 to -0.57) and -0.73 (-0.81 to-0.64) versus -0.32 (-0.41 to -0.24), respectively (p<0.001 for both doses versus cMTX). The minimum clinically important difference (MCID; ≥0.22) was achieved by 140 of 213 patients (66%; 95%CI 59-72) on upadacitinib 15 mg, and 148 of 204 patients

(73%; 66-79) on upadacitinib 30 mg versus 98 0f 205 patients (48%; 41-55) on cMTX (p<0.0001 for both doses versus cMTX) **(Supplemental Figure 3 A)**. Patients reported an improved health-related quality of life as indicated by significant improvements for upadacitinib at 15 mg (8.3; 95%CI: 7.2-9.4) and 30 mg (10.2; 9.1-11.3) versus cMTX (4.3; 3.2-5.4) at Week 14 in the SF-36 PCS (p<0.001 for both doses versus cMTX). The mean change in the duration (minutes) of morning stiffness was -53.0 minutes (95%CI: -72.2 to -33.9) for patients receiving cMTX; -94.6 minutes (95%CI: -113.6 to -75.5); and -102.3 minutes (95%CI: -121.2 to-83.5) for patients receiving upadacitinib with 15 mg and 30 mg, respectively (p=0.0012 and p=0.0001 versus cMTX) **(Supplemental Figure 3 B)**.

Adverse events were reported in 102 patients (47%) on cMTX, 103 (48%) on upadacitinib 15 mg, and 105 (49%) on upadacitinib 30 mg. Serious AEs were reported in 11 patients (5.1%) in the upadacitinib 15 mg arm, 6 patients (2.8%) in the cMTX arm and 6 patients (2.8%) in the upadacitinib 30 mg arm **(Table 2)**. Infections were reported in 57 patients (26.4%) in the cMTX arm, 42 patients (19.4%) in the upadacitinib 15 mg and 54 (25.1) in the upadacitinib 30 mg arm. There were two serious infections, one case of limb abscess in the upadacitinib 15 mg arm, and one case of urosepsis in the cMTX arm. There were four opportunistic infections reported, one in the cMTX arm (fungal oesophagitis) and three in the upadacitinib 30 mg arm (two cases of oral candidiasis and one of oropharyngeal candidiasis). Herpes zoster was more frequently reported in the upadacitinib 30 mg arm versus the upadacitinib 15 mg or cMTX arms; all were reported as non-serious and mild to moderate in severity by the investigators; of the 10 cases, eight involved one or two dermatomes and two cases in the upadacitinib 30 mg arm involved three or more dermatomes..

There were three malignancies, all in patients older than 60 years of age. One was reported in the cMTX arm (basal cell carcinoma) and two in the upadacitinib 15 mg arm (one patient with non-Hodgkin's lymphoma and one with breast cancer). Three major adverse cardiovascular

events (MACE) were confirmed by an independent Cardiovascular Adjudication Committee, all in patients with known cardiovascular (CV) risk factors; there was one event of hemorrhagic stroke due to a ruptured aneurysm (fatal) in a 68-year old male patient with CV risk factors (smoking for 46 years and hypertension) in the upadacitinib 15 mg arm, and two events reported in the upadacitinib 30 mg arm (one non-fatal myocardial infarction and one non-fatal stroke). One adjudicated pulmonary embolism was reported in the upadacitinib 15 mg arm in a patient with known risk factors (hypertension, BMI of 44.9 on estrogen therapy at the time of event), and with normal platelet counts throughout the treatment period. Besides the fatal case of hemorrhagic stroke due to ruptured aneurysm, described above, there were no other deaths reported. There were no reported cases of active tuberculosis, renal dysfunction or gastrointestinal perforation.

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Table 2. Adverse Events Summary

n (%) Patients	cMTX N=216	UPA 15 mg Mono N=217	UPA 30 mg Mono N=215
Any Adverse Event (AE)	102 (47.2)	103 (47.5)	105 (48.8)
Serious AE	6 (2.8)	11 (5.1)	6 (2.8)
AE Leading To Discontinuation Of Study Drug	6 (2.8)	8 (3.7)	6 (2.8)
Infection	57 (26.4)	42 (19.4)	54 (25.1)
-Serious Infection[†]	1 (0.5)	1 (0.5)	0
-Opportunistic Infection[‡]	1 (0.5)	0	3 (1.4)
-Herpes Zoster	1 (0.5)	3 (1.4)	6 (2.8)
-Tuberculosis	0	0	0
Hepatic disorder[¥]	4 (1.9)	4 (1.8)	5 (2.3)
Gastrointestinal perforation	0	0	0
Malignancy[γ]	1 (0.5)	2 (0.9)	0
-NMSC	1 (0.5)	0	0
-Lymphoma	0	1 (0.5)	0
VTE (adjudicated)	0	1 (0.5)[§]	0
MACE (adjudicated)[δ]	0	1 (0.5)	2 (0.9)
Death	0	1 (0.5)[Φ]	0

AE, adverse event; NMSC, non-melanoma skin cancer; VTE, venous thromboembolism (DVT and PE); MACE, major adverse cardiovascular event (CV death, nonfatal MI and nonfatal stroke)

[†]Serious Infection events: cMTX: urosepsis; UPA 15: abcess limb

[‡]Opportunistic infection events: cMTX: fungal oesophagitis; UPA 30: 2 oral candidiasis, 1 oropharyngeal candidiasis

[¥]Hepatic disorders: Except for 1 case of mild hepatic cyst, all due to liver enzyme elevation

[γ]Malignancies: cMTX: basal cell carcinoma; UPA 15: 1 non-Hodgkins' lymphoma, 1 breast cancer

[δ]MACE (adjudicated): UPA 15: 1 hemorrhagic stroke due to ruptured aneurysm (fatal), investigator deemed as unrelated to study drug; UPA 30: 1 myocardial infarction, 1 stroke; investigators reported both events as unrelated to study drug

[§]VTE: Pulmonary embolism (BMI 36, estrogen hormone therapy); investigator deemed as unrelated to study drug

[Φ]Death: Hemorrhagic stroke due to ruptured aneurysm

327

328 Mean hemoglobin levels remained within the normal ranges through Week 14 across the

329 treatment arms **(Supplemental Figure 6)** with smaller percentage decreases from baseline

noted for upadacitinib 15 mg (-0.3%) compared to cMTX (-0.8%) and upadacitinib 30 mg (-1.9%). The number of patients with Grade 3 hemoglobin decrease at any time during the study, including patients with a single isolated event, was higher in the upadacitinib 30 mg arm than in the cMTX and upadacitinib 15 mg arms **(Supplemental Table 1)**. One patient with Grade 4 hemoglobin decrease was reported in the upadacitinib 30 mg arm at a single time point during the study. No patient discontinued study drug due to abnormal hemoglobin values.

Although mean levels of neutrophils, lymphocytes and platelets remained within the normal ranges over 14 weeks, there were three patients with Grade 3 decreases in neutrophils (two in the upadacitinib 30 mg, and one in the cMTX arms), and none with Grade 4 decreases. Of note, approximately 30% of patients had Grade 2 lymphopenia at Baseline (1.0-1.5 x 10^9/L). There were comparable numbers of patients with Grade 3 decreases in lymphocytes in the cMTX and upadacitinib 30 mg arms, and fewer in the upadacitinib 15 mg arm. One patient (upadacitinib 30 mg group) had a Grade 4 decrease in lymphocyte values, which occurred at a single time point during the treatment period; no treatment-emergent infectious events were reported for this patient. A decrease in the mean level of platelets (-46.4 x 10^9/L) was observed in the upadacitinib 30 mg arm at Week 4, although levels returned to near Baseline levels by Week 14 **(Supplemental Figure 4 B, C and D);** there were no Grade 3 or 4 decreases. Increases in mean LDL-C (0.001, 0.352 and 0.439 mMol/L for cMTX, upadacitinib 15 and 30 mg, respectively) and HDL-C (0.003, 0.280 and 0.266 mMol/L) with upadacitinib treatment were observed, although the ratio of LDL-C:HDL-C (and TC:HDL-C) remained unchanged over the 14 week period **(Supplemental Figure 4 E and F, Supplemental Table 2)**.

Of five patients with Grade 3 alanine aminotransferase (ALT) elevations, two patients (one each in the cMTX and upadacitinib 30 mg arms) discontinued study drug due to elevations in ALT. Both patients experienced ALT elevations accompanied with fatigue and abdominal pain; the patient who was on upadacitinib 30 mg experienced cholelithiasis after 12 days of symptomatic ALT elevation. There were no Hy's law cases identified. There were two Grade 3 CPK

elevations each in upadacitinib 15 mg and upadacitinib 30 mg arms and none in the cMTX arm; none of the patients had rhabdomyolysis or discontinued the study drug due to an increased CPK value.

DISCUSSION

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The combination of bDMARDs and tsDMARDs with csDMARDs, in particular MTX is recommended for the management of RA. (1, 2) However, intolerance or contraindications to MTX may present an obstacle to effective treatment for some patients and information from registries suggests that about 40% of patients in clinical practice have stopped MTX (or other csDMARDs) after receiving a new therapy (21-23). The parenteral administration of bDMARDs is another potential hurdle for many patients. SELECT-MONOTHERAPY is the first trial comparing a JAK inhibitor to continued MTX in patients with an inadequate response to MTX. Previous trials have compared monotherapy with other JAK inhibitors versus placebo after complete washout of MTX in patients with inadequate response to MTX or cs/bDMARDs. (24, 25) The SELECT-MONOTHERAPY trial demonstrated that in patients with an inadequate response to MTX, who were switched to oral upadacitinib QD 15 or 30 mg monotherapy, there was a significant improvement in clinical signs and symptoms, physical function and quality of life measures compared to patients who continued on their prior MTX dose.

The efficacy of upadacitinib monotherapy was robust, with significant improvement across a range of clinical endpoints including responses considered to reflect low disease activity or clinical remission. Indeed, one third of the patients achieved an ACR70 response at 3 months; other agents, such as bDMARDs, usually lead to ACR70 rates of 20-25% at 6 months, when these responses tend to have peaked. (26) Moreover, up to 40% patients achieved DAS28(CRP)<2.6, and almost 20% of patients receiving upadacitinib 30 mg experienced remission according to the stringent CDAI, SDAI and ACR-EULAR Boolean definitions. While both doses of upadacitinib were associated with significant improvements, numerically higher responses were observed with upadacitinib 30 mg compared to 15 mg through Week 14 for some of the efficacy outcomes. This incremental efficacy benefit with 30 mg was not previously observed on a background of treatment with csDMARDs in the SELECT-NEXT and SELECT-

BEYOND studies in RA patients with inadequate response or intolerance to csDMARDs or bDMARDs, respectively, (27, 28) and was not apparent in the SELECT-EARLY study, which evaluated upadacitinib 15 mg and 30 mg monotherapy in a MTX-naïve population. (29) However, whether the 15mg or the 30mg dose is the more appropriate one for patients who switch from MTX to upadacitinib will have to be determined in conjunction with data from the other phase 3 upadacitinib trials.

Overall treatment-emergent AEs were reported at similar frequencies across the arms with a similar incidence of patients withdrawing due to adverse events observed across all treatment arms. Adverse events of interest for which a potential dose-relationship was observed include herpes zoster. Herpes zoster has been reported in other studies of JAK inhibitors, including upadacitinib. (27, 28, 30) In this study, all of the cases were considered non-serious, with most involving 1 or 2 dermatomes. Vaccination was not required prior to study participation but investigators were asked to consider local guidelines. Less than 5% of patients had prior herpes zoster vaccination. The MACE events in patients receiving upadacitinib occurred in patients with known risk factors including pre-existing CV conditions or a history of diabetes or a history of tobacco use. One VTE was reported in this study, also in a patient with risk factors. Long-term safety assessments across the phase 3 studies of upadacitinib in RA are needed to fully characterize rare events such as MACE and VTE. Laboratory abnormalities were consistent with observations in the upadacitinib RA studies and with other JAK inhibitors thus far. (13, 14, 30) A reduction in inflammation might be expected to result in an increase in hemoglobin. A potentially clinically significant decrease in hemoglobin was observed in a few patients in the upadacitinib 30 mg arm, although mean levels of hemoglobin remained within the normal range during the study, as did neutrophils, lymphocytes and platelets. As in other studies with upadacitinib and other JAK inhibitors, elevations in the levels of LDL-C and HDL-C were observed, while the ratio of LDL-C:HDL-C, an atherogenic indicator, remained unchanged.

Although an increase in lipids was not found to be associated with an increase in CV events including MACE, observations over a longer period are required.(31)

One limitation of the study was a relatively short cMTX-controlled period (14 weeks); however, this was done to avoid undertreating patients in the cMTX arm for an extended period (average prior duration of 3.6 years). The trial design did not include radiographic assessments; however, radiographic evaluation is usually at 6 or 12 months, whereas here we focused on clinical outcomes at 14 weeks. However, other trials in the SELECT program include radiographic assessments of upadacitinib in monotherapy and combination therapy. Another limitation was that the trial did not include an arm to assess combination therapy with upadacitinib and MTX compared to monotherapy.

In summary, the results of SELECT-MONOTHERAPY demonstrated that upadacitinib monotherapy was associated with significant improvement in multiple measures of disease outcomes, while having a safety profile consistent with previously reported findings. This favorable benefit-risk profile of upadacitinib monotherapy has the potential to provide a treatment option for patients who are intolerant to MTX or who prefer a treatment without the need for concomitant csDMARDs.

Contributors:

J Smolen, P Emery, S Cohen, AL Pangan, Y Zhang, A Friedman, A Othman and H Camp participated in the design of the study. W Rigby, Y Tanaka, JI Vargas, N Damjanov participated in data collection. Y Zhang, AL Pangan, A Friedman, A Othman and H Camp participated in data analyses. All the authors interpreted the data and participated in writing and critical review of the manuscript and approved the final version.

Declaration of interests:

JS Smolen: Research grants and/or consulting fees from AbbVie, BMS, Celgene, Chugai, Gilead, Janssen, Lilly, MSD, Novartis-Sandoz, Pfizer, Roche, Samsung, Sanofi, UCB.

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JI Vargas: fees from Abbvie during the conduct of the study

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W Rigby: Consulting fees from AbbVie, BMS, Genentech and Pfizer

Y Tanaka: Speaking fees and/or honoraria from Daiichi-Sankyo, Astellas, Eli Lilly, Chugai, Sanofi, Abbvie, Pfizer, YL Biologics, Bristol-Myers, Glaxo-Smithkline, UCB, Mitsubishi-Tanabe, Novartis, Eisai, Takeda, Janssen, Asahi-kasei. Research grants from Mitsubishi-Tanabe, Bristol-Myers

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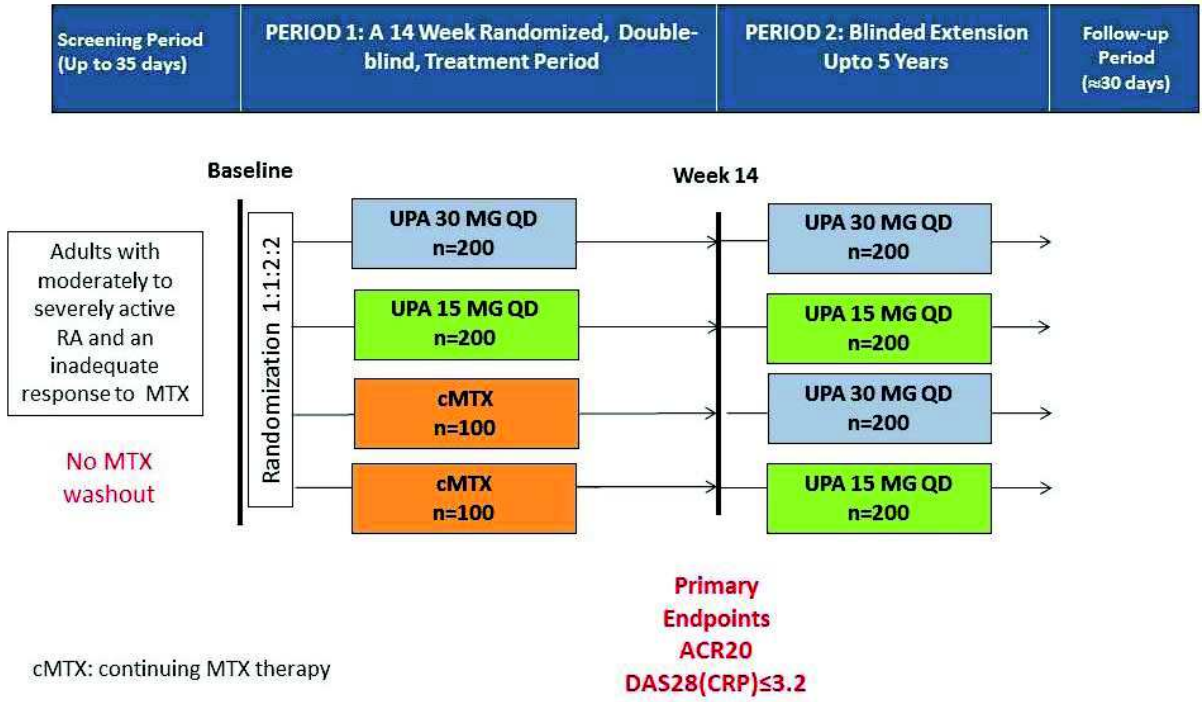
466 AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This
467 includes access to anonymized, individual and trial-level data (analysis data sets), as well as
468 other information (e.g., protocols and Clinical Study Reports), as long as the trials are not part of
469 an ongoing or planned regulatory submission. This includes requests for clinical trial data for
470 unlicensed products and indications.
471 These clinical trial data can be requested by any qualified researchers who engage in rigorous,
472 independent scientific research, and will be provided following review and approval of a
473 research proposal and statistical analysis plan, and execution of a Data Sharing Agreement.
474 Data requests can be submitted at any time and the data will be accessible for we months, with
475 possible extensions considered. For more information on the process , or to submit a request,
476 visit https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-
477 sharing/data-and-information-sharing-with-qualified-researchers.html.
478

SUPPLEMENT

Table of Contents:

500 **Supplemental Figure 1. Study design**

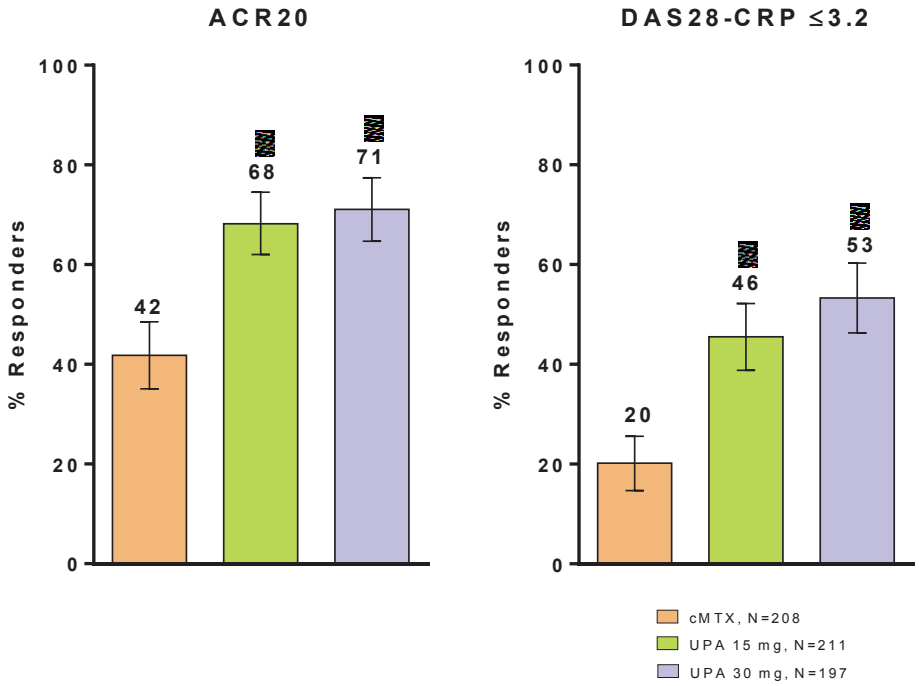
501



502

Supplemental Figure 2. Patients achieving the primary endpoints (A) ACR20 and (B) DAS28(CRP) ≤3.2 at Week 14 in the per-protocol set (NRI)

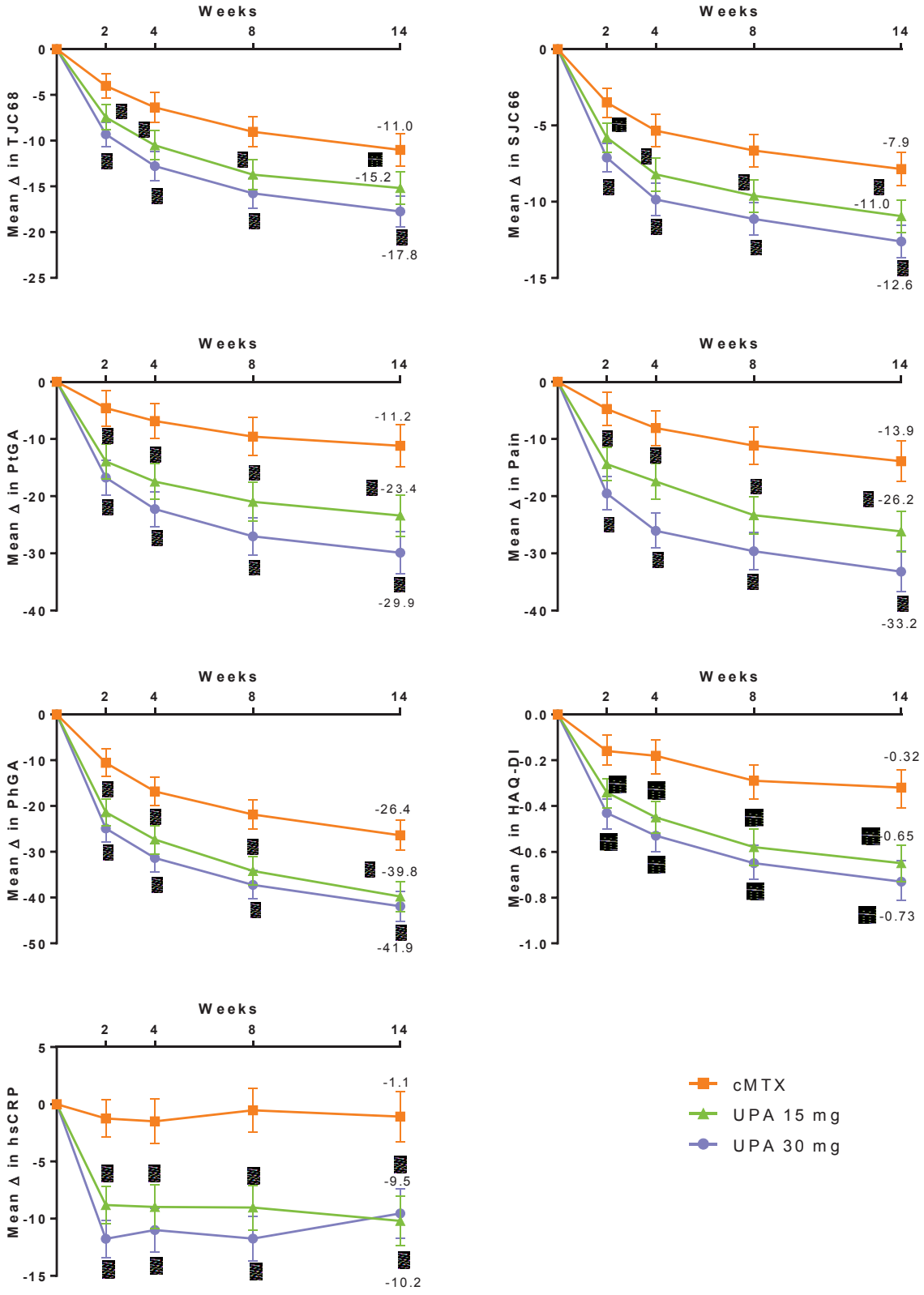
§ P≤0.0001 versus cMTX. Bars are 95% CI



Supplemental Figure 3. Mean change from Baseline in individual core components of the ACR score (A) TJC68 (B) SJC66 (C) PtGA (D) Pain (E) PhGA (F) HAQ-DI (G) hsCRP (MMRM)

TJC68, tender joint count in 68 joints; SJC66, swollen joint ocunt in 66 joints; PtGA, patient's global assessment of disease activity; PhGA, physician's global assessment of disease activity; HAQ-DI, health assessment questionnaire-disability index; hsCRP, high-sensitivity C-reactive protein; MMRM, Mixed Effect Model Repeat Measurement.

* P≤0.05, † P≤0.01, ‡ P≤, 0.001, § P≤0.0001 versus cMTX. Bars are 95% CI


Weeks
2
4
8
14
Mean Δ in TJC68
0
-5
-10
-15
-20
-25
-11.0
-15.2
-17.8
Mean Δ in SJC66
-7.9
-11.0
-12.6
Mean Δ in PtGA
-11.2
-23.4
-29.9
Mean Δ in Pain
-13.9
-26.2
-33.2
Mean Δ in PhGA
-26.4
-39.8
-41.9
Mean Δ in HAQ-DI
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
-0.32
-0.65
-0.73
Mean Δ in hsCRP
5
-1.1
-9.5
-10.2
cMTX
UPA 15 mg
UPA 30 mg

521

522 Mean change from baseline at each time point

Change from BL in HAQ-DI			
Week	**cMTX**	**UPA 15 mg**	**UPA 30 mg**
2	-0.16	-0.34	-0.43
4	-0.18	-0.45	-0.53
8	-0.29	-0.58	-0.65
14	-0.32	-0.65	-0.73
Mean absolute value at BL			
BL	1.5	1.5	1.5

Change from BL in PhGA			
Week	**cMTX**	**UPA 15 mg**	**UPA 30 mg**
2	-10.57	-21.35	-24.91
4	-16.81	-27.33	-31.37
8	-21.86	-34.17	-37.21
14	-26.38	-39.79	-41.91
Mean absolute value at BL			
BL	62.1	65.7	62.6

Change from BL in hsCRP			
Week	**cMTX**	**UPA 15 mg**	**UPA 30 mg**
2	-1.25	-8.8	-11.76
4	-1.49	-8.97	-11
8	-0.52	-9.03	-11.75
14	-1.07	-10.2	-9.54
Mean absolute value at BL			
BL	14.5	14.0	16.3

Change from BL in SJC66			
Week	**cMTX**	**UPA 15 mg**	**UPA 30 mg**
2	-3.5	-5.79	-7.11
4	-5.34	-8.21	-9.85
8	-6.65	-9.61	-11.13
14	-7.86	-10.95	-12.6
Mean absolute value at BL			
BL	16.9	16.4	16.9

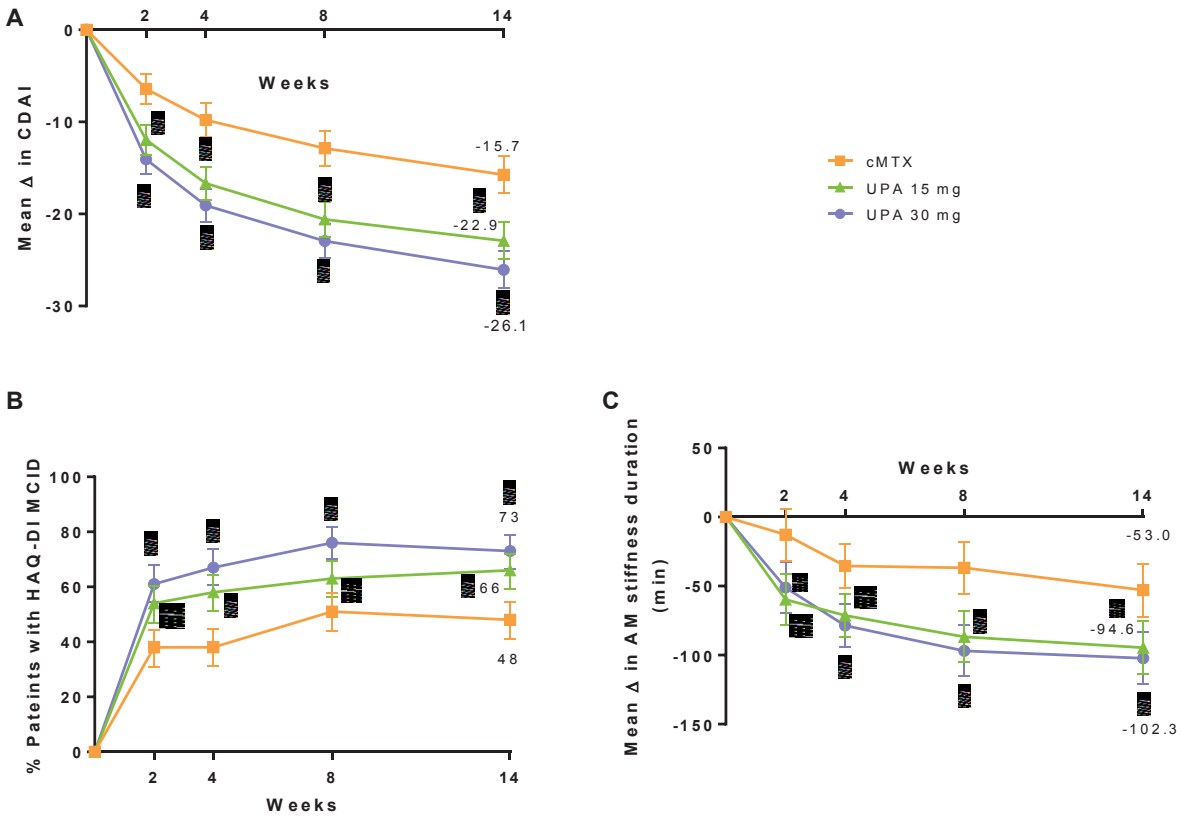
Change from BL in Pain			
Week	**cMTX**	**UPA 15 mg**	**UPA 30 mg**
2	-4.74	-14.37	-19.52
4	-8.08	-17.41	-26.04
8	-11.14	-23.32	-29.61
14	-13.88	-26.15	-33.18
Mean absolute value at BL			
BL	62.5	62.3	61.9

Change from BL in TJC68			
Week	**cMTX**	**UPA 15 mg**	**UPA 30 mg**
2	-4.02	-7.45	-9.31
4	-6.37	-10.51	-12.79
8	-9.03	-13.71	-15.76
14	-11.02	-15.17	-17.75
Mean absolute value at BL			
BL	25.2	24.5	24.8

Change from BL in PtGA			
Week	**cMTX**	**UPA 15 mg**	**UPA 30 mg**
2	-4.6	-13.93	-16.76
4	-6.85	-17.44	-22.26
8	-9.59	-20.98	-27.03
14	-11.18	-23.4	-29.89
Mean absolute value at BL			
BL	59.6	62.2	59.4

Supplemental Figure 4. (A) Mean change from Baseline in CDAI (MMRM) (B) Change from Baseline in HAQ-DI ≤0.22 (NRI analysis). (C) Least Square Mean Change from Baseline in Morning Stiffness Duration (minutes).

* *P*≤0.05, † P≤0.01, ‡ P≤, 0.001, § P≤0.0001 versus cMTX. Bars are 95% CI
CDAI, clinical disease activity index; HAQ-DI, health assessment questionnaire-disability index



537

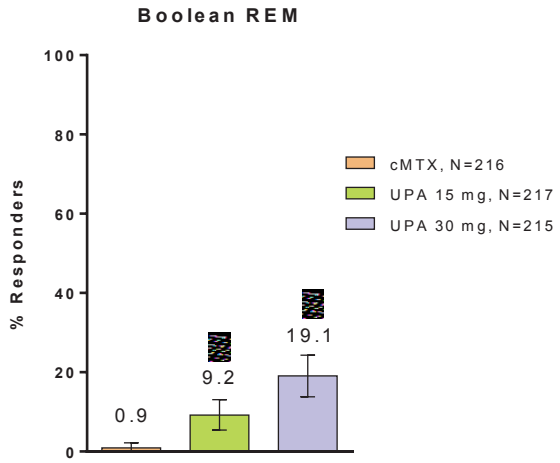
538 Values at each time point

Change from BL in CDAI			
Week	**cMTX**	**UPA 15 mg**	**UPA 30 mg**
2	-6.41	-11.94	-14.06
4	-9.79	-16.67	-19.07
8	-12.85	-20.59	-22.93
14	-15.73	-22.91	-26.06
Patients achieving HAQ-DI MCID			
Week	**cMTX**	**UPA 15 mg**	**UPA 30 mg**
2	38	54	61
4	38	58	67
8	51	63	76
14	48	66	73
Change from BL in Morning Stiffness Duration (mins)			
Week	**cMTX**	**UPA 15 mg**	**UPA 30 mg**
2	-12.8	-59.8	-51.1
4	-35.5	-71.2	-78.6
8	-36.8	-86.7	-96.9
14	-53	-94.6	-102.3

539

Supplemental Figure 5. Patients achieving Boolean Remission at Week 14 (NRI analysis).

* P≤0.05, † P≤0.01, ‡ P≤, 0.001, § P≤0.0001 versus cMTX. Bars are 95% CI



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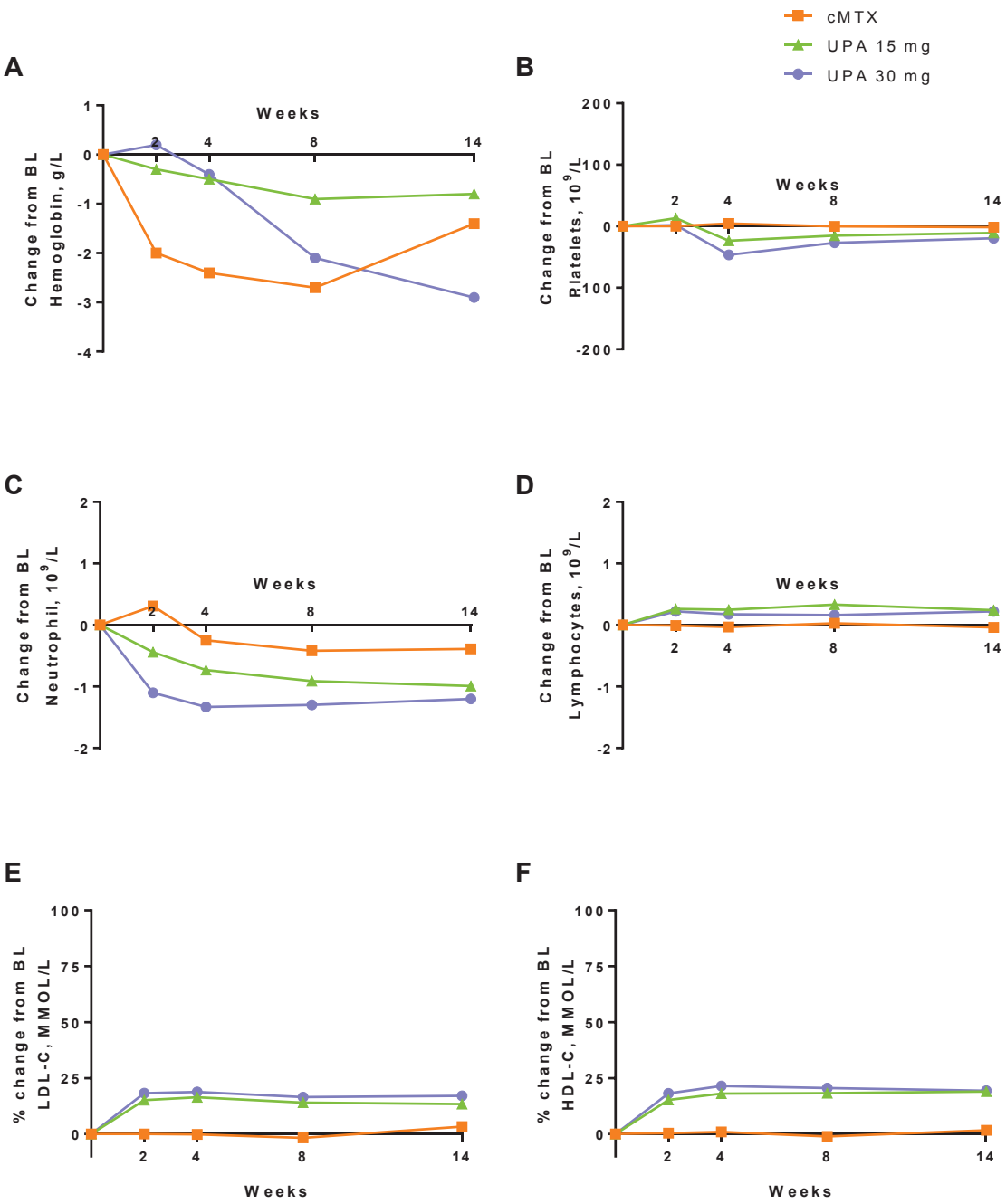
547 **Supplemental Figure 6. Changes from baseline in mean levels of (A) hemoglobin (B)**

548 **platelets (C) neutrophils (D) lymphocytes. Percent changes from Baseline in (E) LDL-**

549 **Cholesterol (F) HDL-Cholesterol.**



550
551

552 Values at each time point

Mean change in Hemoglobin, g/L			
week	**cMTX**	**UPA 15 mg**	**UPA 30 mg**
2	-2	-0.3	0.2
4	-2.4	-0.5	-0.4
8	-2.7	-0.9	-2.1
14	-1.4	-0.8	-2.9

Mean change in Platelets x 10^9			
week	**cMTX**	**UPA 15 mg**	**UPA 30 mg**
2	0	13.1	1.9
4	4.6	-23.5	-46.4
8	-0.2	-15.2	-26.8
14	-1.6	-10.8	-19.4

Mean change in Lymphocytes x 10^9			
week	**cMTX**	**UPA 15 mg**	**UPA 30 mg**
2	-0.01	0.26	0.22
4	-0.03	0.25	0.17
8	0.03	0.33	0.16
14	-0.04	0.24	0.22

Mean change in HDL-C, mMol/L			
week	**cMTX**	**UPA 15 mg**	**UPA 30 mg**
2	0.419	15.229	18.175
4	0.969	18.071	21.489
8	-1.085	18.24	20.588
14	1.722	19.028	19.42

Mean change in Neutrophils x 10^9			
week	**cMTX**	**UPA 15 mg**	**UPA 30 mg**
2	0.31	-0.44	-1.1
4	-0.25	-0.73	-1.33
8	-0.42	-0.91	-1.3
14	-0.39	-0.99	-1.2

Mean change in LDL-C, mMol/L			
week	**cMTX**	**UPA 15 mg**	**UPA 30 mg**
2	0.006	15.126	18.236
4	-0.137	16.466	18.835
8	-1.686	14.055	16.498
14	3.381	13.435	17.126

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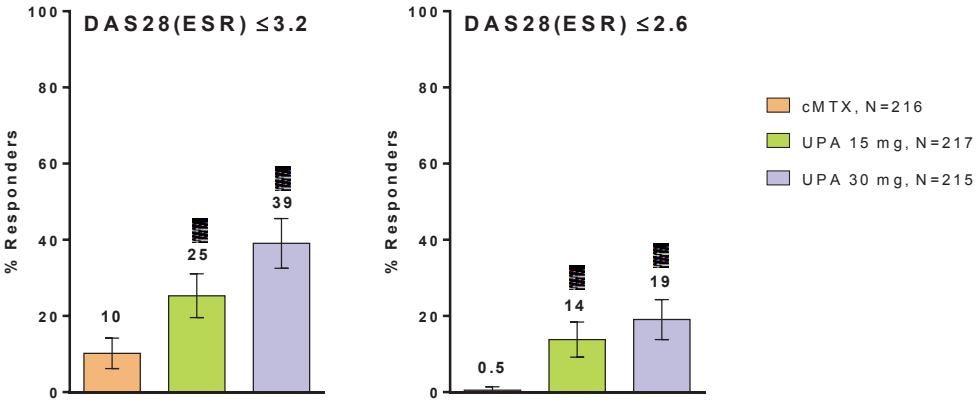
Supplemental Figure 7. Patients achieving DAS28(ESR)<2.6 or ≤3.2 at Week 14 (NRI analysis).

‡ P≤, 0.001, § P≤0.0001 versus cMTX. Bars are 95% CI



Supplemental Table 1. Patients with worsening in grade at any time during study including single isolated values, n (%)

		cMTX N=216†	UPA 15 mg QD N=217†	UPA 30 mg QD N=215†
Hemo-globin (g/dL)	Grade 3 (decr 2.1 - 2.9 or Hb >7.0-<8.0)	4 (1.9)	5 (2.3)	9 (4.2)
	Grade 4 (decr ≥3.0 or Hb <7.0)	0	0	1 (0.5)
Lympho-cytes (x10^9/L)	Grade 3 (0.5 - <1.0)	20 (9.3)	13 (6.0)	21 (9.9)
	Grade 4 (< 0.5)	0	0	1 (0.5)
Neutrophils (x10^9/L)	Grade 3 (0.5 - <1.0)	1 (0.5)	0	2 (0.9)
	Grade 4 (< 0.5)	0	0	0
ALT (U/L)	Grade 3 (3.0 - 8.0 x ULN)	4 (1.9)	1 (0.5)	4 (1.9)
	Grade 4 (> 8.0 x ULN)	0	0	0
AST (U/L)	Grade 3 (3.0 - 8.0 x ULN)	0	1 (0.5)	2 (0.9)
	Grade 4 (> 8.0 x ULN)	0	0	0
CPK	Grade 3 (>5.0 x ULN – 10.0 x ULN)	0	2 (0.9)	2 (0.9)
	Grade 4 (>10.0 x ULN)	0	0	0
Creatinine	Grade 3 (>3.0 - 6.0 x ULN)	0	0	0
	Grade 4 (>6.0 x ULN)	0	0	0

Grading is based OMERACT criteria; except CPK and Creatinine, where NCI CTC criteria are used.
†For hemoglobin, lymphocytes, neutrophils, N=214, 215 and 213 for cMTX, UPA 15mg and UPA 30mg respectively; For ALT/AST/CPK/creatinine, N=215, 215 and 214.

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Supplemental Table 2. Ratio of LDL-C:HDL-C			
	cMTX	**Upadacitinib 15 mg QD**	**Upadacitinib 30 mg QD**
Baseline	2.085	1.955	2.097
Week 14	2.070	1.900	2.055
Mean LDL-C (MMOL/L)			
Baseline	3.057	2.850	2.906
Week 14	3.064	3.241	3.334

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567

568 **Supplemental Table 3. Values at each time point for Fig 2**

ACR20			
week	**cMTX**	**UPA 15 mg**	**UPA 30 mg**
2	7	33.2	43.3
4	21.8	49.3	58.1
8	32.9	62.7	65.1
14	41.2	67.7	71.2

ACR50			
week	**cMTX**	**UPA 15 mg**	**UPA 30 mg**
2	1.4	8.3	16.7
4	2.8	23.5	31.6
8	6.5	33.2	41.4
14	15.3	41.9	52.1

ACR70			
week	**cMTX**	**UPA 15 mg**	**UPA 30 mg**
2	0	2.3	4.7
4	0.9	8.8	14.4
8	1.4	14.7	22.8
14	2.8	22.6	33

Change from BL in DAS28(CRP)			
week	**cMTX**	**UPA 15 mg**	**UPA 30 mg**
2	-0.45	-1.27	-1.55
4	-0.74	-1.66	-2.00
8	-0.97	-2.08	-2.39
14	-1.23	-2.32	-2.65

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Supplemental Table 4. Primary, ranked secondary and additional endpoints at Week 14

	cMTX N=216	UPA 15 mg QD N=217	UPA 30 mg QD N=215	Difference between UPA 15 mg QD and cMTX (95% CI)	Difference between UPA 30 mg QD and cMTX (95% CI)
ACR20	41%	68%	71%	27% (18 to 36) §	30% (21 to 39) §
DAS28(CRP) ≤3.2	19%	45%	53%	25% (17 to 34) §	34% (25 to 42) §
ACR50	15%	42%	52%	27% (19-35) §	37% (29 to 45) §
ACR70	3%	23%	33%	20% (14 to 26) §	30% (24 to 37) §
DAS28(CRP) <2.6	8%	28%	41%	20% (13 to 27) §	32% (25 to 40) §
SDAI ≤11	24%	37%	47%	13% (5 to 22) †	23% (14 to 32) §
SDAI ≤3.3	1%	14%	18%	13% (8 to 18) §	17% (12 to 23) §
CDAI ≤10	25%	35%	47%	10% (2 to 19)*	22% (13 to 31) §
CDAI ≤2.8	1%	13%	19%	12% (7 to 17) §	18% (13-24) §
Boolean REM	1%	9%	19%	8% (4 to 12) §	18% (13 to 24) §
Change in DAS28(CRP)	-1.2	-2.3	-2.7	-1.1 (-1.3 to -0.8) §	-1.4 (-1.7 to -1.2) §
Change in HAQ-DI	-0.32	-0.65	-0.73	-0.33 (-0.44 to -0.22) ‡	-0.41 (-0.51 to -0.30) ‡
Change in SF-36 PCS	4.3	8.3	10.2	4.0 (2.5 to 5.4) ‡	5.9 (4.4 to 7.3) ‡
Change in morning stiffness duration (min)	-53.0	-94.6	-102.3	-41.5 (-66.6 to -16.5) †	-49.3 (-74.2 to -24.4) §

Data are percentage of patients with a response, or least squares mean. The treatment difference between the cMTX and upadacitinib arms is followed by 95% CI

* P≤0.05, † P≤0.01, ‡ P≤, 0.001, § P≤0.0001 versus cMTX

Missing data was handled using non-responder imputation for categorical endpoints and by

Mixed Effect Model Repeat Measurement for continuous endpoints.

571

572

Supplemental Table 5. Prior synthetic DMARDs per patient	
Number of prior synthetic DMARDs	n (%) of patients; N=648
0	0
1	429 (66.2)
2	153 (23.6)
3	48 (7.4)
≥4	18 (2.8)

List of Inclusion Criteria

1. Adult male or female, at least 18 years old.

2. Diagnosis of RA for ≥ 3 months who also fulfill the 2010 ACR/EULAR classification criteria for RA.

3. Subjects must have been on oral or parenteral MTX therapy ≥ 3 months and on a stable dose (15 to 25 mg/week; or ≥ 10 mg/week in subjects who are intolerant of MTX at doses ≥ 12.5 mg/week) for ≥ 4 weeks prior to first dose of study drug.

4. Must have discontinued all csDMARDs other than MTX (see Inclusion Criterion 3) ≥ 4 weeks prior to first dose of study drug. The washout period for specific csDMARDS prior to first dose of study drug is specified below or should be at least five times the mean terminal elimination half-life of a drug:

   - ≥ 4 weeks for minocycline, penicillamine, sulfasalazine, hydroxychloroquine, chloroquine, azathioprine, gold formulations, cyclophosphamide, tacrolimus, cyclosporine, mycophenolate;
   - ≥ 8 weeks for leflunomide if no elimination procedure was followed, or adhere to an elimination procedure (i.e., 11 days with colestyramine, or 30 days washout with activated charcoal or as per local label).

5. Subject meets both of the following disease activity criteria:

   a. ≥ 6 swollen joints (based on 66 joint counts) and ≥ 6 tender joints (based on 68 joint counts) at Screening and Baseline Visits; and

   b. hsCRP ≥ 3 mg/L (central lab) at Screening Visit.

6. Stable dose of non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, oral corticosteroids (equivalent to prednisone ≤ 10 mg), or inhaled corticosteroids for stable medical conditions are allowed but must have been at a stable dose ≥ 1 week prior to the first dose of study drug.

7. Subjects must have discontinued all high-potency opiates for at least 1 week and traditional Chinese medicines for at least 4 weeks prior to the first dose of study drug (refer to Section 5.2.3.2 for prohibited medications).

8. Women of childbearing potential (refer to Section 5.2.4) must not have a positive serum pregnancy test at the Screening Visit and must have a negative urine pregnancy test at baseline visit prior to study drug dosing.

9. If female, subject must be either postmenopausal, OR permanently surgically sterile OR for women of childbearing potential practicing at least one protocol specified method of birth control (refer to Section 5.2.4), that is effective from Study Day 1 through at least 180 days after the last dose of study drug.

10. Male subjects who are sexually active with female partner(s) of childbearing potential must agree from Study Day 1 through 180 days after the last dose of study drug to practice the protocol-specified contraception (refer to Section 5.2.4).

11. Subjects must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures.

List of Exclusion Criteria

1. Prior exposure to any JAK inhibitor (including but not limited to tofacitinib, baricitinib, and filgotinib).

2. Prior exposure to any bDMARDs.

3. History of any arthritis with onset prior to age 17 years or current diagnosis of inflammatory joint disease other than RA (including but not limited to gout, systemic lupus erythematosus, psoriatic arthritis, axial spondyloarthritis including ankylosing spondylitis and non-radiographic axial spondyloarthritis, reactive arthritis, overlap connective tissue diseases, scleroderma, polymyositis, dermatomyositis, fibromyalgia [currently with active symptoms]. Current diagnosis of secondary Sjogren's Syndrome is permitted.

4. Has been treated with intra-articular, intramuscular, intravenous, trigger point or tender point, intra-bursa, or intra-tendon sheath corticosteroids in the preceding 8 weeks prior to the first dose of study drug.

5. Has been treated with any investigational drug within 30 days or 5 half-lives of the drug (whichever is longer) prior to the first dose of study drug or is currently enrolled in another clinical study.

6. Female who is pregnant, breastfeeding, or considering becoming pregnant during the study or for approximately 180 days after the last dose of study drug.

7. Male who is considering fathering a child or donating sperm during the study or for approximately 180 days after the last dose of study drug.

8. Any active, chronic or recurrent viral infection that, based on the Investigator's clinical assessment, makes the subject an unsuitable candidate for the study, including hepatitis B virus (HBV) or hepatitis C virus (HCV), recurrent or disseminated (even a single episode) herpes zoster, disseminated (even a single episode) herpes simplex, or known history of human immunodeficiency virus (HIV). HBV, HCV and HIV infections are defined as:

- HBV: hepatitis B surface antigen (HBs Ag) positive (+) or detected sensitivity on the HBV deoxyribonucleic acid (DNA) polymerase chain reaction (PCR) qualitative test for Hepatitis B core antibody (HBc Ab) positive (+) subjects;

- HCV: HCV ribonucleic acid (RNA) detectable in any subject with anti-HCV antibody (HCV Ab).
- HIV: confirmed positive anti-HIV antibody (HIV Ab) test.

9. Subject has active TB or meets TB exclusionary parameters.

10. Systemic use of known strong cytochrome P450 3A (CYP3A) inhibitors or strong CYP3A inducers from Screening through the end of the study.

11. Receipt of any live vaccine within 4 weeks prior to the first dose of study drug, or expected need of live vaccination during study participation including at least 4 weeks after the last dose of study drug.

12. History of any malignancy except for successfully treated NMSC or localized carcinoma in situ of the cervix.

13. History of clinically significant (per Investigator's judgment) drug or alcohol abuse within the last 6 months.

14. History of gastrointestinal perforation (other than appendicitis or penetrating injury), diverticulitis or significantly increased risk for GI perforation per investigator judgment.

15. Conditions that could interfere with drug absorption including but not limited to short bowel syndrome.

16. Subject has been a previous recipient of an organ transplant.

17. History of clinically significant medical conditions or any other reason that in the opinion of the Investigator would interfere with the subject's participation in this study or would make the subject an unsuitable candidate to receive study drug.

18. Active infection(s) requiring treatment with parenteral anti-infectives within 30days, or oral anti-infectives within 14 days prior to the first dose of study drug.

19. History of an allergic reaction or significant sensitivity to constituents of the study drug(s) (and their excipients) and/or other products in the same class.

20. Laboratory values meeting the following criteria within the Screening period prior to the first dose of study drug:

- Serum aspartate transaminase (AST) > 2 × ULN;
- Serum alanine transaminase (ALT) > 2 × ULN;
- Estimated glomerular filtration rate (GFR) by simplified 4-variable Modification of Diet in Renal Disease (MDRD) formula < 40 mL/min/1.73m^2;

- Total white blood cell (WBC) count < 2,500/μL;
- Absolute neutrophil count (ANC) < 1,500/μL;
- Platelet count < 100,000/μL;
- Absolute lymphocyte count < 850/μL;
- Hemoglobin < 10 g/dL.

21. History of any of the following cardiovascular conditions:

- Moderate to severe congestive heart failure (New York Heart Association classIII or IV);
- Recent (within past 6 months) cerebrovascular accident, myocardial infarction, coronary stenting;
- Uncontrolled hypertension as defined by a confirmed systolic blood pressure >160 mmHg or diastolic blood pressure > 100 mmHg;
- Any other condition which, in the opinion of the Investigator, would put the subject at risk by participating in the protocol.

22. Clinically relevant or significant ECG abnormalities, including ECG with QT interval corrected for heart rate (QTc) using Fridericia's correction formula (QTcF) > 500 msec.

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DATA SHARING STATEMENT

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual and trial-level data (analysis data sets), as well as other information (e.g., protocols 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 we months, with possible extensions considered. For more information on the process , or to submit a request, visit https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.