



Routine Assessment of Patient Index Data 3 (RAPID3) in Patients with Rheumatoid Arthritis Treated with Long-Term Upadacitinib Therapy in Five Randomized Controlled Trials

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ABSTRACT

Introduction: The Routine Assessment of Patient Index Data 3 (RAPID3) is a patient-reported outcome tool recommended for the assessment of disease activity in patients with rheumatoid arthritis (RA) in clinical practice. This analysis evaluated the long-term effect of

upadacitinib vs. comparators on RAPID3 scores in patients with RA in the phase 3 SELECT clinical trial program.

Methods: This post hoc analysis included data from five randomized controlled trials (RCTs) in patients receiving upadacitinib 15 mg or 30 mg once daily (QD) as monotherapy or in combination with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs). The proportions of patients reporting RAPID3 remission (scores ≤ 3) were assessed at week 60. Correlations between absolute scores for RAPID3 and Clinical Disease Activity Index

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(CDAI), Simplified Disease Activity Index (SDAI), and 28-joint Disease Activity Score with C-reactive protein (DAS28[CRP]) at week 60 were assessed using Spearman correlation coefficients.

Results: A total of 3117 patients were included from the SELECT-NEXT, -BEYOND, -MONOTHERAPY, -COMPARE, and -EARLY trials. By week 60, 32–52% of methotrexate-naïve and csDMARD inadequate responder (IR) patients treated with either upadacitinib 15 mg QD or upadacitinib 30 mg QD reported RAPID3 scores consistent with remission. The proportions were slightly lower in the biologic DMARD-IR SELECT-BEYOND population (19–28%). RAPID3 scores highly correlated (Spearman correlation values ≥ 0.58) with CDAI, SDAI, and DAS28(CRP) scores through week 60 (all $p < 0.001$).

Conclusions: Upadacitinib, as monotherapy or in combination with csDMARDs, was associated with patient-reported remission assessed by RAPID3 over 60 weeks across the SELECT RCTs in patients with RA.

Trial registration: SELECT-BEYOND (NCT02706847); SELECT-NEXT (NCT02675426); SELECT-MONOTHERAPY (NCT02706951); SELECT-EARLY (NCT02706873); SELECT-COMPARE (NCT02629159).

PLAIN LANGUAGE SUMMARY

Rheumatoid arthritis (RA) is a disease that causes inflammation of the joints. Doctors have several ways of assessing how bad a patient's disease is, and these often use a combination of signs and symptoms to develop a 'score'. One method is called RAPID3, which is a score based on an overall assessment of the disease by the patient, the level of pain, and the amount of physical disability. An advantage of RAPID3 is that it is quick and easy to use, and since it uses only patient-reported symptoms, it can be measured easily via telemedicine, without the need for an in-person consultation. In this study, we decided to look into the effect of upadacitinib, a drug used for the treatment of RA, on RAPID3 score in patients with RA. We

also investigated whether RAPID3 correlates with other ways of measuring RA severity, including scores that use physician-measured factors such as number of affected joints, as this can help show whether RAPID3 is a valid and useful tool. We found that upadacitinib led to long-term improvements in RAPID3 score, and that results were the same in different studies and patient groups, including patients who had not responded well to other treatments. We also found that RAPID3 correlated well with other measures, i.e., improvements in RAPID3 happened in parallel with improvements in other scores. Overall, these results suggest that RAPID3 can be a useful tool in patients with RA.

Keywords: RAPID3; Upadacitinib; Rheumatoid arthritis

Key Summary Points

Why carry out this study?

RAPID3 is a patient-reported outcome tool that assesses burden of disease in RA; the effect of upadacitinib treatment on RAPID3 has not yet been evaluated.

The aim of this study was to assess the effect of upadacitinib on RAPID3 scores in patients with RA and to determine the correlation between RAPID3 and other disease activity measures.

What was learned from the study?

Upadacitinib, as monotherapy or in combination with csDMARDs, was associated with long-term improvements in RAPID3; results were consistent over different studies and patient populations, including patients more refractory to treatment.

RAPID3 showed good correlation with other disease activity measures, supporting its use to assess disease activity and treatment responses across RA patient populations in clinical practice.

INTRODUCTION

A treat-to-target approach aiming for remission or low disease activity (LDA) is advocated in the management of rheumatoid arthritis (RA) by both the American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology (EULAR) [1, 2]. Regular assessment of disease activity during routine care is required when aiming for such targets [1, 2]. There are several disease activity assessments recommended by the ACR, such as the 28-joint Disease Activity Score (DAS28), Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI), and Routine Assessment of Patient Index Data 3 (RAPID3) [3]. Most assessments include a mixture of physician evaluations, objective markers of inflammation, and patient-reported outcomes (PROs) [3]. However, RAPID3 is based solely on PROs, being a pooled index of Patient's Global Assessment of Disease Activity (PtGA), pain and physical function (Functional Component of the Health Assessment Questionnaire Disability Index [HAQ-DI]), and multidimensional HAQ (MDHAQ) [4]. Each measure is scored from 0 to 10, providing a total score out of 30: scores > 12 indicate high disease activity (HDA), > 6–12 moderate disease activity (MDA), > 3–6 LDA, and ≤ 3 remission [5].

RAPID3 is simple and quick to complete by patients and can be performed easily via telemedicine without requiring an in-person consultation with a rheumatologist. It is used alongside other clinical assessments by healthcare providers to evaluate overall disease activity and has shown good-to-excellent correlations with DAS28 using C-reactive protein (DAS28[CRP]) and CDAI/SDAI, with similar sensitivity for distinguishing active and control treatments in randomized controlled trials (RCTs) [5].

Upadacitinib is an oral selective Janus kinase-1 inhibitor indicated for use in moderately to severely active RA [6, 7]. Its efficacy and safety in RA, as monotherapy or in combination with methotrexate or other conventional syn-

thetic disease-modifying antirheumatic drugs (csDMARDs), has been demonstrated in the comprehensive phase 3 program of 'SELECT' RCTs across diverse patient populations, including csDMARD-naïve patients, csDMARD inadequate responder (IR) patients, and biologic DMARD (bDMARD) IR patients [8–14]. Integrated safety analyses and long-term extension data of these trials support the durability of upadacitinib efficacy and tolerability over a prolonged period [13, 14]. The objective of the current analysis was to evaluate the impact of upadacitinib vs. comparators using RAPID3 over 60 weeks, as well as to further explore the correlation of RAPID3 scores with other disease measures in the upadacitinib phase 3 SELECT clinical program in RA.

METHODS

Study Design and Patients

This post hoc analysis included data from five randomized controlled phase 3 trials from the upadacitinib RA clinical trial program: SELECT-NEXT [8] and SELECT-BEYOND [9] were placebo controlled, and SELECT-EARLY [10], SELECT-MONOTHERAPY [11], and SELECT-COMPARE [12] all had active comparators (methotrexate, methotrexate, and adalimumab, respectively). Only treatment groups evaluated at 60 weeks with no treatment crossover and reporting RAPID3 data from the trials were included in the analysis. Patient inclusion and exclusion criteria have been published previously [8–12]. In summary, all patients were adults aged > 18 years with moderately to severely active RA and were a mixture of methotrexate-naïve, methotrexate-IR, csDMARD-IR, or bDMARD-IR patients. Patients received upadacitinib (15 mg or 30 mg once daily [QD]) as monotherapy or in combination with csDMARDs. A summary of the study designs and patient populations of the SELECT trials is shown in Table S1 in the Supplementary Material.

Ethics Declaration

All SELECT trials were conducted according to the International Conference on Harmonization guidelines and the principles of the Declaration of Helsinki of 1964 and its later amendments. All patients provided written informed consent. The trial protocols were approved by the relevant independent ethics committees and institutional review boards of all participating institutions, and were sponsored by AbbVie. All authors have provided their approval for this version to be published.

Assessments

RAPID3 scores (consisting of PtGA scores of 0–10 and pain scores of 0–10 [assessed using visual analog scales], plus HAQ-DI scores multiplied by 3.3 [as a substitute for the functional component of the MDHAQ]) [15] were calculated at weeks 12, 24, and 60. The proportions of patients reporting RAPID3 remission, LDA, MDA, and HDA were assessed at week 60, as were the mean changes from baseline in RAPID3 scores. A 3.8-point decrease (improvement) in the RAPID3 score represents the minimal clinically important difference (MCID) [16].

CDAI, SDAI, and DAS28(CRP), swollen and tender joint counts for 28 joints (SJC/TJC28), and high-sensitivity CRP (hsCRP) were also assessed at week 60. CDAI remission was defined as ≤ 2.8 ; DAS28(CRP) remission as < 2.6 ; and Boolean remission as $TJC \leq 1$, $SJC \leq 1$, $CRP \leq 1$ mg/dl, and $PtGA \leq 1$.

Statistical Analyses

Mean change from baseline in RAPID3 scores and the proportion of patients reporting RAPID3 remission (≤ 3), LDA (> 3 to ≤ 6), MDA (> 6 to ≤ 12), HDA (> 12), and improvements that exceeded the MCID were assessed. Correlations between RAPID3 and CDAI, SDAI, and DAS28(CRP) scores were assessed using Spearman correlation. Correlation coefficients < 0.3 were considered low correlation, 0.3–0.6 moderate correlation, and > 0.6 high correlation. A

Fig. 1 Percentage of patients in RAPID3 remission, LDA, MDA, and HDA across the SELECT trials at baseline and weeks 12/14, 24/26, and 60. Data are AO for SELECT-NEXT, -BEYOND, and -MONOTHERAPY, and LOCF for rescue patients then AO for SELECT-EARLY and -COMPARE. ADA adalimumab, AO as observed, bDMARD biologic disease-modifying antirheumatic drug, csDMARD conventional synthetic disease-modifying antirheumatic drug, EOW every other week, HDA high disease activity, IR inadequate response, LDA low disease activity, LOCF last observation carried forward, MDA moderate disease activity, MTX methotrexate, QD once daily, RAPID3 Routine Assessment of Patient Index Data 3, UPA upadacitinib

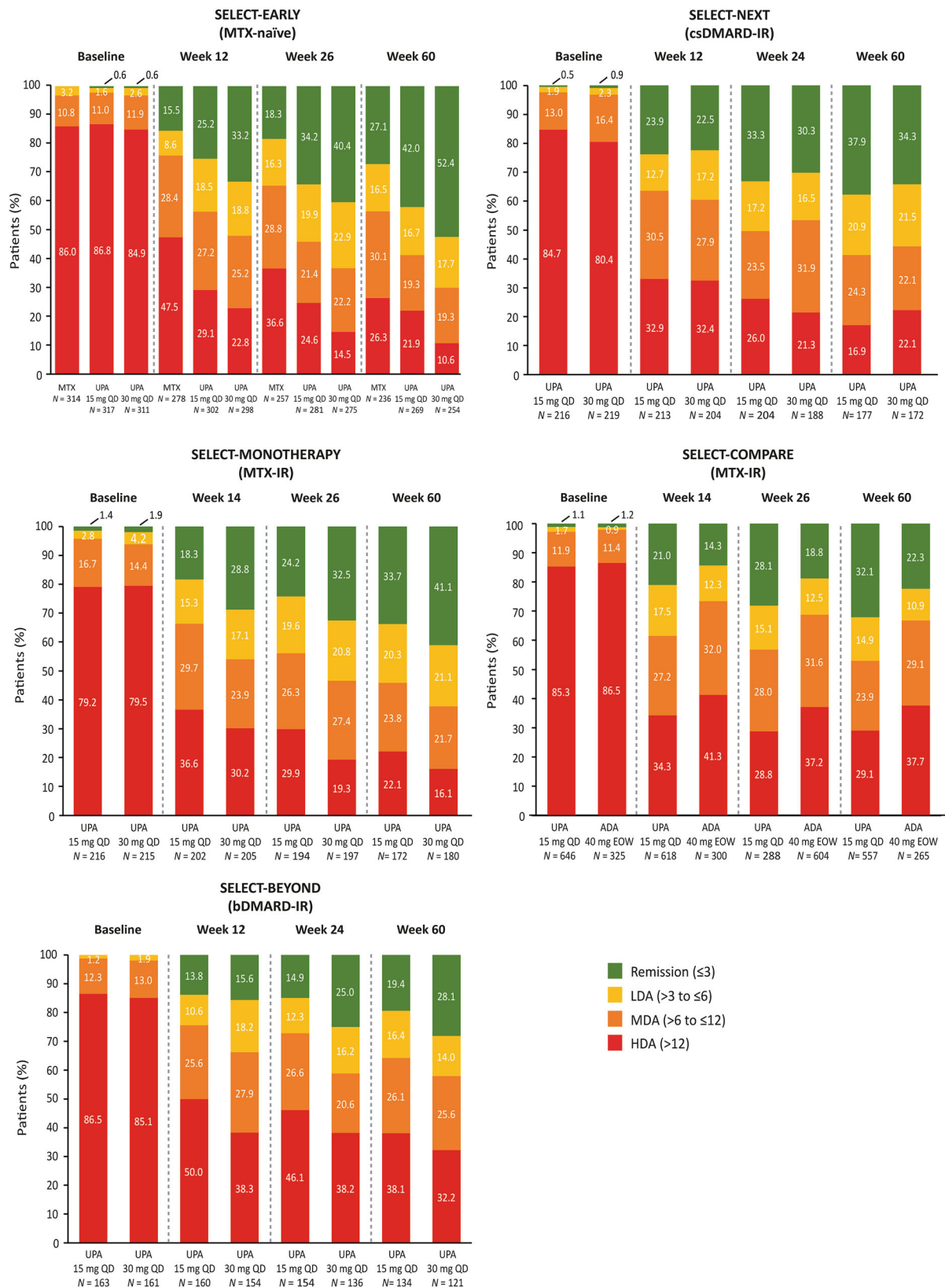
univariate logistic regression model with CDAI or Boolean remission at week 60 as the dependent variable, and early RAPID3 response as the independent variable, was used to assess the association between clinical remission and early RAPID3 response. Spearman correlations were also calculated between the individual components of RAPID3 and disease outcomes (CDAI, SDAI, DAS28[CRP], TJC28, and SJC28).

Data are presented as observed unless otherwise indicated. For SELECT-EARLY and SELECT-COMPARE, data are last observation carried forward for rescue patients then as observed. Non-responder imputations (NRIs) were used for RAPID3 remission agreement (assessed using kappa scores) with CDAI, SDAI, DAS28(CRP), and Boolean remission. Kappa scores of 0.21–0.40 show weak correlation, scores of 0.41–0.60 show moderate correlation, and scores ≥ 0.61 show strong correlation [17].

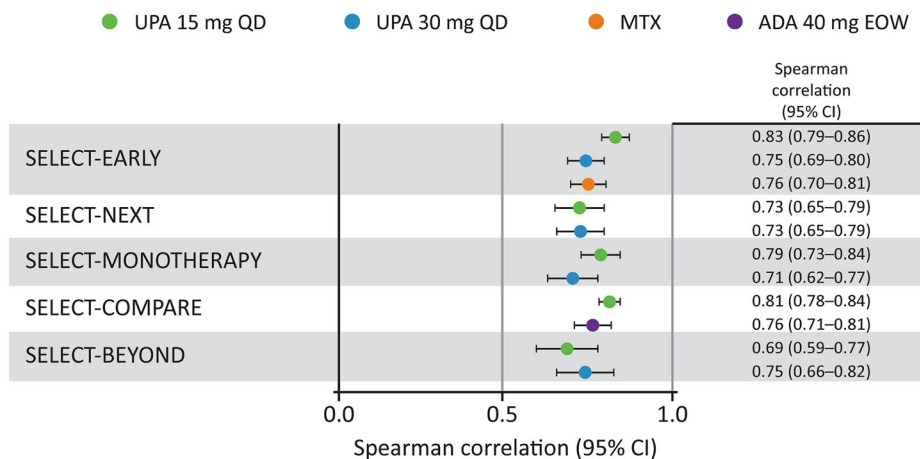
RESULTS

Patient Disposition and Baseline Disease Activity

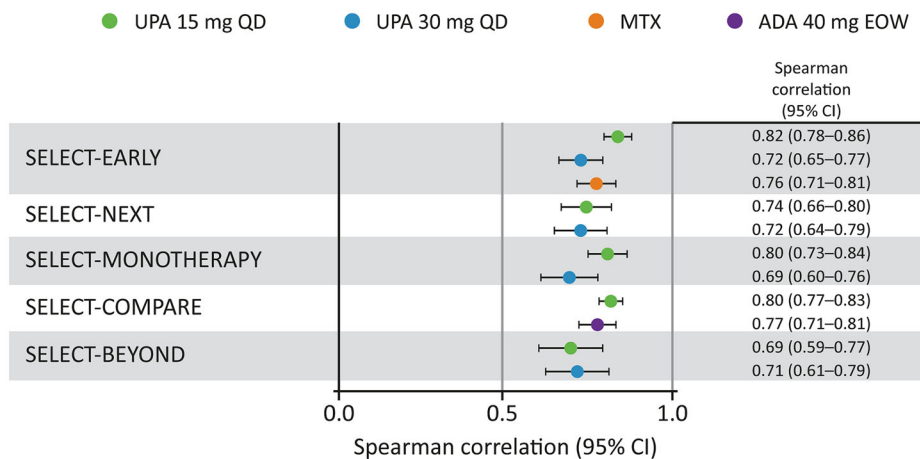
A total of 3117 patients who received active treatment (i.e., excluding placebo-treated patients) were included in the analysis across the five RCTs (440, 324, 431, 978, and 944 patients from SELECT-NEXT, -BEYOND, -MONOTHERAPY, -COMPARE, and -EARLY trials, respectively); 2477 patients received either upadacitinib 15 mg or 30 mg QD



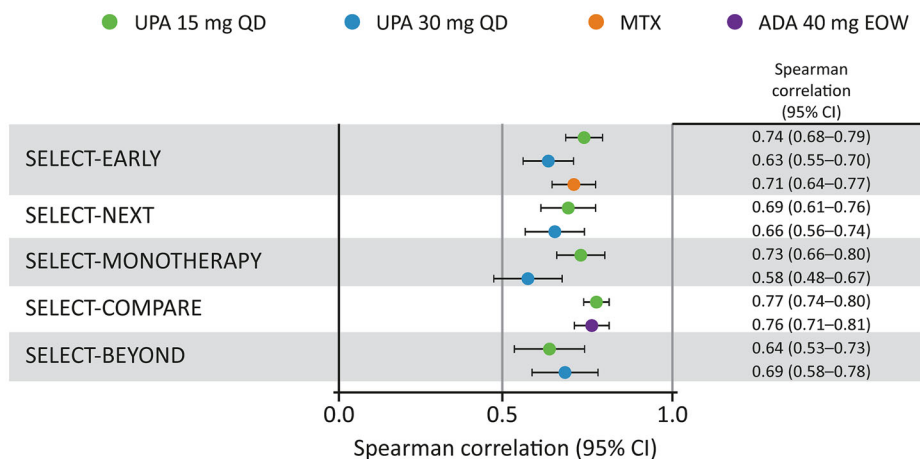
(A) CDAI



(B) SDAI



(C) DAS28(CRP)



◀ **Fig. 2** Correlation between RAPID3 scores and **A** CDAI, **B** SDAI, and **C** DAS28(CRP) scores across the SELECT trials at week 60. Correlation coefficients of < 0.3 considered low correlation, 0.3–0.6 moderate, and > 0.6 high. Data are AO for SELECT-NEXT, -BEYOND, and -MONOTHERAPY, and LOCF for rescue patients then AO for SELECT-EARLY and -COMPARE. *ADA* adalimumab, *AO* as observed, *CDAI* Clinical Disease Activity Index, *CI* confidence interval, *DAS28(CRP)* 28-joint Disease Activity Score using C-reactive protein, *EOW* every other week, *LOCF* last observation carried forward, *MTX* methotrexate, *QD* once daily, *RAPID3* Routine Assessment of Patient Index Data 3, *SDAI* Simplified Disease Activity Index, *UPA* upadacitinib

(Supplementary Table S2). Detailed baseline characteristics of patients in each trial have been published previously [8–12] but, in summary, the majority of patients across all studies had RAPID3 HDA at baseline (mean scores: 17.2–19.2) (Supplementary Table S2).

RAPID3 Scores with Upadacitinib Treatment

By week 60, 32–52% of methotrexate-naïve and csDMARD-IR patients treated with either upadacitinib 15 mg QD or upadacitinib 30 mg QD were in RAPID3 remission, with slightly lower proportions among bDMARD-IR patients in SELECT-BEYOND (19.4 and 28.1%, respectively) (Fig. 1). When including LDA, this figure increased to 47–70% in methotrexate-naïve and csDMARD-IR patients treated with upadacitinib, with again a lower proportion of the more refractory SELECT-BEYOND population reporting remission or LDA (35.8–42.1%) (Fig. 1). In patients receiving methotrexate in SELECT-EARLY, 27.1% reported remission and 43.6% reported remission or LDA at week 60. In patients receiving adalimumab (SELECT-COMPARE), 22.3% of patients reported remission and 33.2% reported remission or LDA (Fig. 1). The percentages of upadacitinib-treated patients reporting RAPID3 remission at weeks 12/14 and weeks 24/26 were 14–33% and 15–40%, respectively, across trials (Fig. 1). With methotrexate (SELECT-EARLY), the percentages were 15.5 and 18.3% at weeks 12 and 26,

respectively, and for adalimumab (SELECT-COMPARE), 14.3 and 18.8%, respectively, at weeks 14 and 26 (Fig. 1). Overall, the percentages at weeks 12/14 and 24/26 were maintained or continued to improve through week 60.

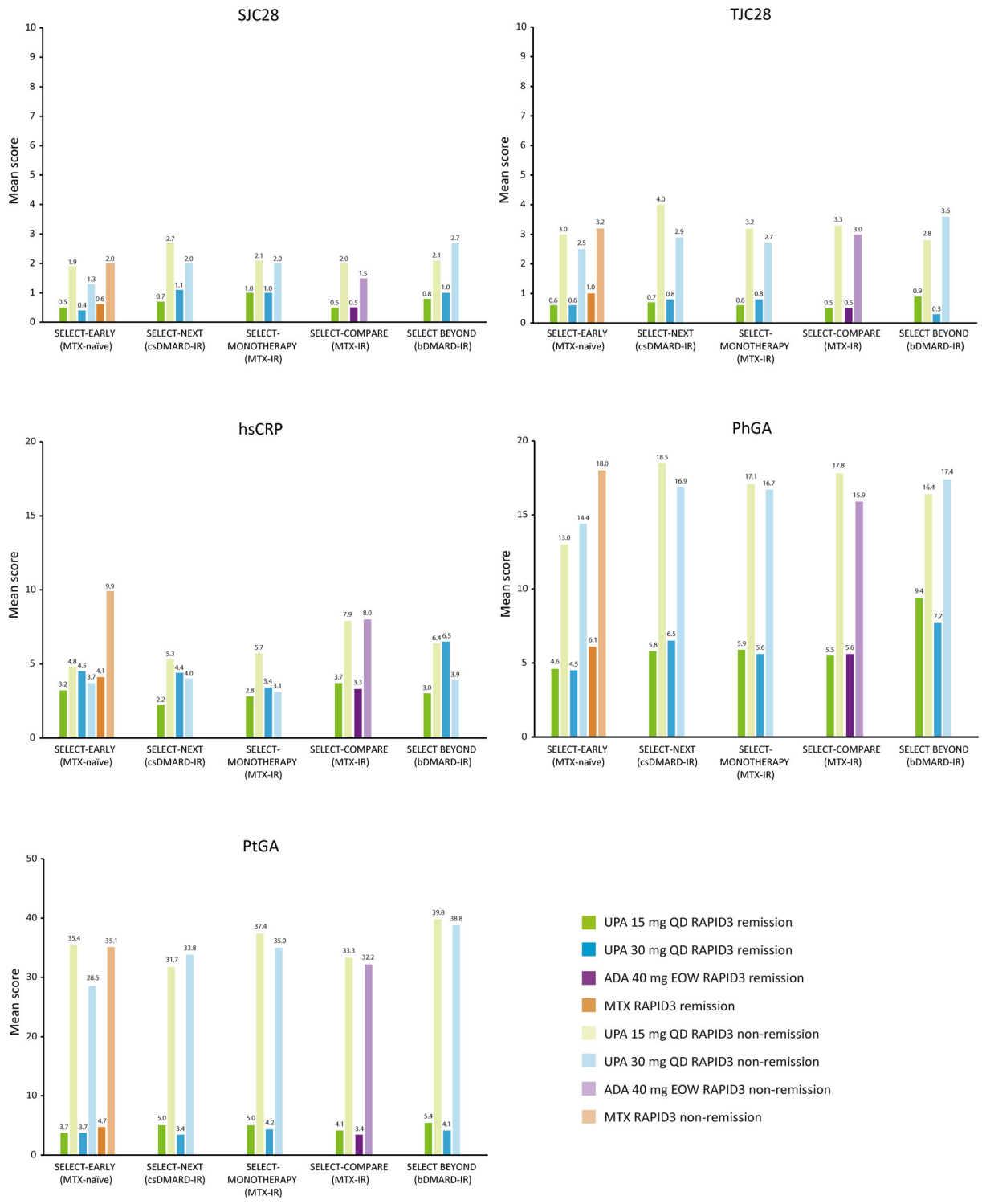
The smallest mean (standard deviation) changes from baseline at week 60 in RAPID3 scores were reported in bDMARD-IR patients from SELECT-BEYOND (upadacitinib 15 mg QD – 8.6 [6.8]; upadacitinib 30 mg QD – 9.3 [7.3]), while the largest were in methotrexate-naïve patients from SELECT-EARLY (– 12.0 [7.6] and – 13.4 [7.2], respectively). The majority of patients treated with upadacitinib 15 mg QD and upadacitinib 30 mg QD (74–92%) reported improvements from baseline in RAPID3 scores at week 60 that exceeded the MCID (Supplementary Fig. S1). The percentages of methotrexate-treated patients (SELECT-EARLY) and adalimumab-treated patients (SELECT-COMPARE) who reported improvements \geq MCID were 77 and 77%, respectively (Supplementary Fig. S1).

Correlation Between RAPID3 and Other Disease Activity Measures

Mean RAPID3 scores were highly correlated with mean scores in other disease activity measures, with Spearman correlation values of > 0.6 (except for one value of 0.58) across all trials, patient populations, and treatment arms (upadacitinib and comparators) through week 60 (Fig. 2). Spearman correlation values ranged from 0.69 to 0.83 for CDAI, 0.69–0.82 for SDAI, and 0.58–0.77 for DAS28(CRP) ($p < 0.001$ for all correlations).

Scores for components of the composite measures of disease activity, including SJC28, TJC28, hsCRP, Physician's Global Assessment of Disease Activity, and PtGA, were consistently lower in patients who reported RAPID3 remission compared with those not in remission at week 60 (Fig. 3). Similar trends were evident when comparing components of disease activity in patients in RAPID3 LDA compared with those who were not (data not shown).

At week 60, there were moderate-to-high agreements between RAPID3 remission in the



◀**Fig. 3** Scores for components of composite measures of disease activity (CDAI, SDAI, and DAS28[CRP]) in patients with RAPID3 remission vs. patients not in RAPID3 remission at week 60. Remission/non-remission at week 60 determined through NRI. Component scores are AO for SELECT-NEXT, -BEYOND, and -MONOTHERAPY, and LOCF for rescue patients then AO for SELECT-EARLY and -COMPARE. *ADA* adalimumab, *AO* as observed, *bDMARD* biologic disease-modifying antirheumatic drug, *CDAI* Clinical Disease Activity Index, *csDMARD* conventional synthetic disease-modifying antirheumatic drug, *DAS28(CRP)* 28-joint Disease Activity Score using C-reactive protein, *EOW* every other week, *hsCRP* high-sensitivity C-reactive protein, *IR* inadequate response, *LOCF* last observation carried forward, *MTX* methotrexate, *NRI* non-responder imputation, *PbGA* Physician's Global Assessment of Disease Activity, *PtGA* Patient's Global Assessment of Disease Activity, *QD* once daily, *RAPID3* Routine Assessment of Patient Index Data 3, *SDAI* Simplified Disease Activity Index, *SJC28* swollen joint count for 28 joints, *TJC28* tender joint count for 28 joints, *UPA* upadacitinib

upadacitinib 15 mg QD and 30 mg QD treatment groups and remission defined by CDAI (range of kappa scores, 0.52–0.67), SDAI (0.51–0.68), DAS28(CRP) (0.35–0.60), and Boolean remission (0.53–0.72) using NRI ($p < 0.001$ for all correlations; Supplementary Table S3). Similar results were evident with as-observed data: CDAI kappa scores 0.47–0.62, SDAI kappa scores 0.47–0.61, DAS28(CRP) kappa scores 0.30–0.47, and Boolean remission kappa scores 0.53–0.72 ($p < 0.001$ for all kappa scores).

Univariate logistic regression analyses showed associations between early RAPID3 scores, including change from baseline and reporting of remission/LDA at weeks 12/14, and CDAI or Boolean remission at week 60, as demonstrated by both odds ratios (Supplementary Table S4A) and C-indices (Supplementary Table S4B).

PtGA, pain, and HAQ-DI individually correlated less closely with CDAI, SDAI, and DAS28(CRP) at week 60 than the composite RAPID3 score (Supplementary Table S5). Conversely, PtGA and pain showed a higher correlation with CDAI, SDAI, and DAS28(CRP) than RAPID3 score.

DISCUSSION

This analysis showed that upadacitinib, as monotherapy or in combination with csDMARDs, was associated with long-term improvements in physical function, PtGA, and pain, as measured by RAPID3, over 60 weeks in the phase 3 SELECT RA clinical program. The results were consistent over different studies and patient populations, even in those considered more refractory to treatment. Generally, greater proportions of patients treated with upadacitinib 30 mg QD reported RAPID3 remission compared with upadacitinib 15 mg QD, with maintained improvement in the percentages in remission in both treatment groups from week 12 through to week 60. Similar PRO improvements (at 12 or 14 weeks) with upadacitinib 15 mg or 30 mg QD across the individual trials of the SELECT clinical trial program were reported [18–21], and the present analysis extends these previous assessments of PROs with upadacitinib treatment.

Moderate-to-high correlations seen between RAPID3 scores and other disease activity measures in this analysis are in line with similar associations reported in other analyses from both RCTs and observational data [5, 22–25]. It should be noted that these correlations extended beyond the initial double-blind periods of the SELECT trials into the open-label phases up to 60 weeks. Composite RAPID3 scores correlated more closely with TJC28 and SJC28 than any of the individual components, suggesting that RAPID3 offers some advantages vs. its components in assessing joint symptoms. PtGA showed a higher correlation with CDAI, SDAI, and DAS28(CRP) than overall RAPID3 score; this is not unexpected, as PtGA is a component of CDAI/SDAI/DAS28(CRP) and therefore likely to show a strong correlation with the composite scores. These observations support the use of RAPID3 in clinical practice to assess disease activity in RA alongside other physician-reported and objective measures of disease.

RAPID3 can quickly and easily be calculated from the MDHAQ [26, 27]. In the present analyses we used HAQ-DI for the functional component, as in several previous studies

[28–30]. For example, a post hoc analysis was carried out of long-term (24-month) RAPID3 data in two phase 3 RCTs in methotrexate-naïve or methotrexate-IR patients with RA receiving the Janus kinase inhibitor tofacitinib as monotherapy or with background methotrexate [29]. Results were similar to the current analysis: most patients reported maintained RAPID3 responses from baseline to 24 months with tofacitinib treatment, and RAPID3 remission or LDA at 6 months was associated with better treatment outcomes at month 24.

This analysis has several limitations. It was conducted post hoc and the statistical assessment did not control for multiple comparisons. Furthermore, not all SELECT trials were included in the analysis; SELECT-CHOICE [31] was not included as it did not assess RAPID3 and there are no long-term data currently available. While one of the strengths of this analysis results from the data being collected in a rigorous manner as part of a series of RCTs, this also means that the outcomes may not be generalizable to a wider patient population. Consequently, future analyses from real-world studies or observational data may be valuable to confirm the performance of RAPID3 disease assessment for upadacitinib-treated patients in routine clinical practice.

CONCLUSIONS

This post hoc analysis has shown that treatment with upadacitinib, as monotherapy or in combination with csDMARDs, was associated with improvements in RAPID3 (PtGA, pain, and physical function) over 60 weeks across five RCTs in the SELECT phase 3 clinical program in patients with RA. RAPID3 correlated highly with other disease activity measures, supporting its use to assess disease activity and treatment responses across RA patient populations in clinical practice as a simple and quick PRO.

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Compliance with Ethics Guidelines. All SELECT trials were conducted according to the International Conference on Harmonization guidelines and the principles of the Declaration of Helsinki of 1964 and its later amendments. All patients provided written informed consent. The trial protocols were approved by the relevant independent ethics committees and institutional review boards of all participating institutions, and were sponsored by AbbVie. All authors have provided their approval for this version to be published. The study reports a post hoc analysis of data from five previously published clinical trials. Ethics approval was obtained for each of those trials, and is reported in the published papers.

Data Availability. AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis datasets), as well as other information (e.g., protocols and clinical study reports), provided 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 <https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html>.

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