Safety and Efficacy of Upadacitinib in Patients With Rheumatoid Arthritis and Inadequate Response or Intolerance to Biologic DMARDs: Results Through 5 Years From the SELECT-BEYOND Study

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OBJECTIVE

- To evaluate the efficacy and safety of upadacitinib over 5 years among patients with rheumatoid arthritis and prior inadequate response or intolerance to biologic DMARDs in a long-term extension of the SELECT-BEYOND study

INTRODUCTION

- The SELECT phase 3 upadacitinib (UPA) clinical program comprised six trials of approximately 4800 patients with rheumatoid arthritis (RA) targeting different patient populations, including inadequate responders to conventional synthetic (cs)DMARDs or biologic (b)DMARDs
- In SELECT-BEYOND, which was conducted in patients with active RA and inadequate response or intolerance to bDMARDs, treatment with UPA at 15 or 30 mg once daily led to significant improvements in clinical, functional, and patient-reported outcomes over 24 weeks[1]

METHODS

Study Design

- In SELECT-BEYOND, patients with an inadequate response or intolerance to ≥1 bDMARD(s) received UPA 15/30 mg once daily or placebo (PBO) for 12 weeks, each with background csDMARD(s) (**Figure 1**)
- From week 12 onwards, patients randomized to PBO switched to UPA 15 mg or 30 mg in a prespecified manner
- All patients who completed the week 24 visit could enter a blinded (to sites and patients) long-term extension (LTE) for an overall total of 5 years of treatment
- Per protocol amendment, patients receiving UPA 30 mg were switched to the approved 15 mg dose, with the earliest switch occurring at week 180

Assessments & Statistical Analysis

- Efficacy data up to week 260 are shown for patients randomized to UPA 15 mg or 30 mg, with efficacy analyses conducted based on the original treatment sequence
  - Efficacy outcomes were also examined in patients who failed ≥1 prior TNF inhibitor (TNF-IR)
- Data are reported as observed (AO); additionally, missing data for categorical endpoints were imputed using NRI and change from baseline data calculated by mixed effect model repeated measurement (MMRM) analysis
- Treatment-emergent adverse events (TEAEs) per 100 patient-years (PY) were summarized over 5 years for UPA 15 mg and 30 mg groups, which includes patients randomized to UPA as well as those who switched from PBO to UPA at week 12; TEAEs are also shown separately for those who switched from UPA 30 mg to 15 mg

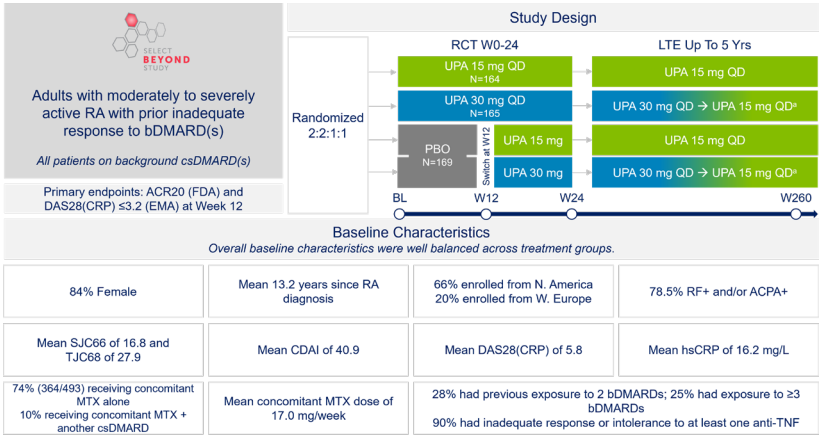
RESULTS

Patients

- Baseline characteristics were generally balanced across all treatment groups (**Figure 1**), and 90% of patients previously failed ≥1 TNF inhibitor prior to enrollment
- Of the 498 patients randomized, 418 (84%) completed week 24 and entered the LTE
- During the LTE, 197 (40%) patients discontinued study drug due to the following: TEAEs (13%), withdrawal of consent (7%), lack of efficacy (6%), lost to follow-up (4%), or other reasons (11%)
- Of the patients receiving concomitant corticosteroid or csDMARDs at baseline, approximately 20% and 10%, respectively, discontinued their use during the study

RESULTS (CONTINUED)

Figure 1. Overview of Study Design and Baseline Characteristics of SELECT-BEYOND



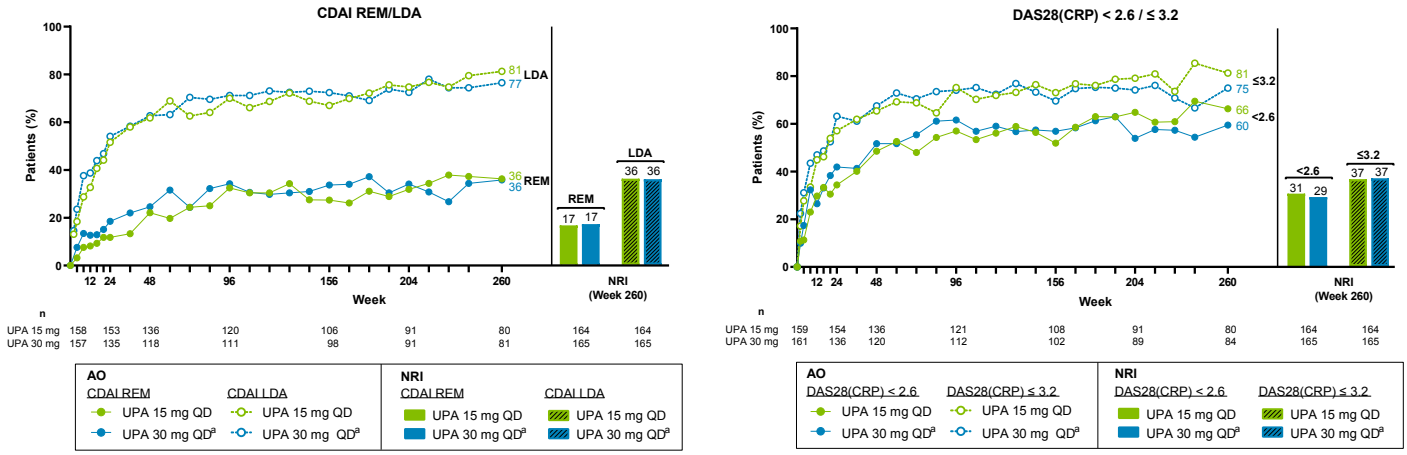
ACPA, anti-citrullinated peptide antibody; bDMARD, biologic DMARD; BL, baseline; csDMARD, conventional synthetic DMARD; LTE, long-term extension; PBO, placebo; QD, once daily; RCT, randomized controlled trial; RF, rheumatoid factor; UPA, upadacitinib; W, week.

[a]Per protocol ammendment, patients receiving UPA 30 mg were switched to UPA 15 mg, with the earliest switch beginning at week 180.

Efficacy in the Overall Population

- Achievement of CDAI and DAS28(CRP) disease activity targets over 5 years was similar in patients receiving either UPA 15 mg or 30 mg (**Figure 2**)
- Consistent results with UPA 15 mg and 30 mg for CDAI and DAS28(CRP) were also observed based on more conservative estimates using NRI
- By week 260, 88%/68%/51% of patients achieved ACR20/50/70 responses on UPA 15 mg and 88%/67%/46% on UPA 30 mg (AO) (**Figure 3**)

Figure 2. Proportions of Patients Achieving CDAI or DAS28(CRP) Disease Activity States Through 5 Years (AO, NRI)

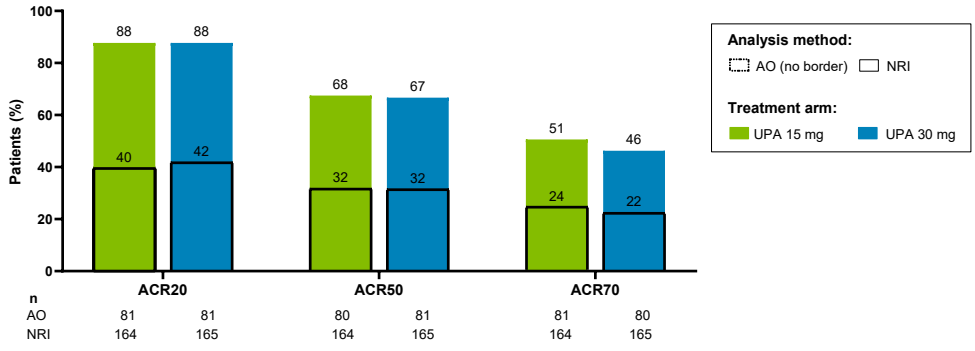


AO, as observed; LDA, low disease activity; QD, once daily; REM, remission; UPA, upadacitinib.

[a]Patients in the UPA 30 mg treatment group were switched to receiving UPA 15 mg per protocol amendment. The switch occurred at different visits across the patient population, with the earliest switch occurring at the week 180 visit.

Cutpoints for CDAI were ≤2.8 for REM and ≤10 for LDA. Data are from patients who were initially randomized to UPA 15 mg or 30 mg. The total numbers of patients (n) in each treatment group are shown at weeks 4, 24, 48, 96, 156, 204, and 260.

Figure 3. Proportions of Patients Achieving ACR20/50/70 Responses at Week 260 (AO, NRI)



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[a]Patients in the UPA 30 mg treatment group were switched to receiving UPA 15 mg per protocol amendment. The switch occurred at different visits across the patient population, with the earliest switch occurring at the week 180 visit.

Data are from patients who were initially randomized to UPA 15 mg or 30 mg; n indicates the total number of patients in each treatment group at week 260.

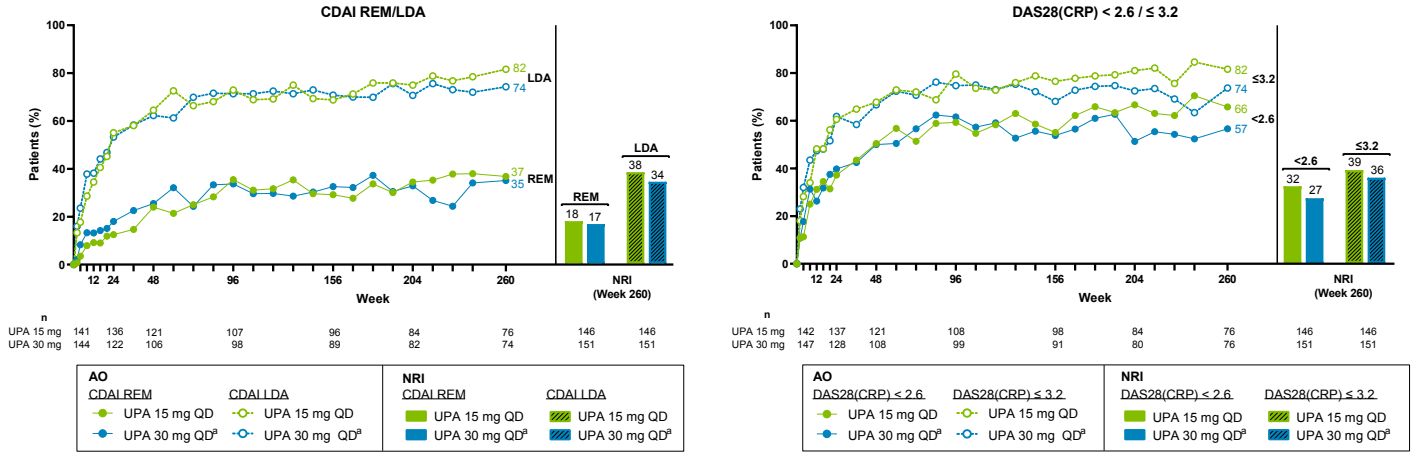
RESULTS (CONTINUED)

- Boolean remission was achieved by 28% of patients on UPA 15 mg and 23% on UPA 30 mg at week 260 (AO)
- Functional and pain-related outcomes showed similar improvements with UPA 15/30 mg: the mean change from baseline was -0.6/-0.6 for HAQ-DI and -39/-37 mm for patient's assessment of pain at week 260 (AO)
  - Using MMRM, the mean change from baseline in HAQ-DI and pain with UPA 15/30 mg treatment was -0.5/-0.5 and -35/-32 mm
  - Additionally, 79% and 69% of patients receiving UPA 15 mg and 30 mg, respectively, achieved minimal clinically important difference (MCID) in HAQ-DI of ≤ -0.22 (AO)
- Overall, patients who switched from PBO showed similar efficacy at week 260 (data not shown); moreover, no apparent loss of benefit was observed with UPA 15 mg treatment in patients who switched from UPA 30 mg to UPA 15 mg

Efficacy in the TNF-IR Subgroup

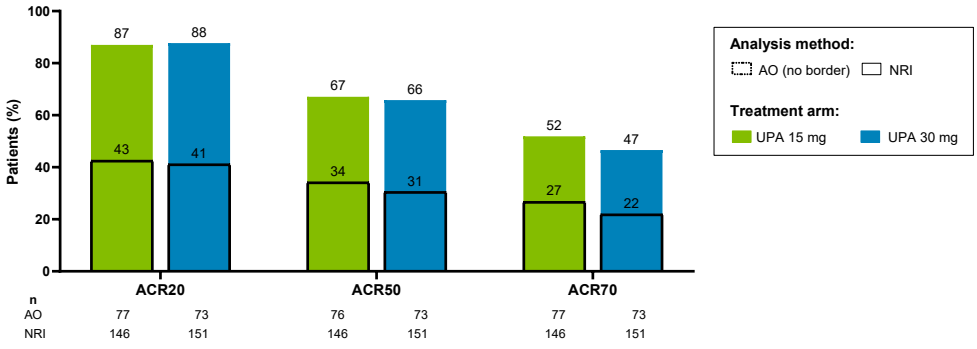
- Consistent efficacy results were observed in TNF-IR patients receiving either UPA 15 mg or 30 mg compared to the overall population (**Figures 4 and 5**)
- Functional and pain-related outcomes were also similar between the TNF-IR subgroup and the overall population and between those receiving UPA 15 mg or 30 mg
  - Among TNF-IR patients, the mean change from baseline in HAQ-DI and pain on UPA 15/30 mg was -0.5/-0.5 and -35/-32 at week 260 (MMRM)
  - In the TNF-IR subgroup, 78% and 67% of patients receiving UPA 15 mg and 30 mg, respectively, achieved MCID HAQ-DI of ≤ -0.22 at week 260 (AO)

Figure 4. Proportions of TNF-IR Patients Achieving CDAI or DAS28(CRP) Disease Activity States Through 5 Years (AO, NRI)



AO, as observed; IR, inadequate response; LDA, low disease activity; QD, once daily; REM, remission; UPA, upadacitinib.
[a]Patients in the UPA 30 mg treatment group were switched to receiving UPA 15 mg per protocol amendment. The switch occurred at different visits across the patient population, with the earliest switch occurring at the week 180 visit.
Cutpoints for CDAI were ≤2.8 for REM and ≤10 for LDA. Data are from TNF-IR patients who were initially randomized to UPA 15 mg or 30 mg. The total numbers of patients (n) in each treatment group are shown at weeks 4, 24, 48, 96, 156, 204, and 260.

Figure 5. Proportions of TNF-IR Patients Achieving ACR20/50/70 Responses at Week 260 (AO, NRI)



AO, as observed; IR, inadequate response; LDA, low disease activity; QD, once daily; REM, remission; UPA, upadacitinib.
[a]Patients in the UPA 30 mg treatment group were switched to receiving UPA 15 mg per protocol amendment, with the earliest switch occurring at the week 180 visit.
Data are from patients who were initially randomized to UPA 15 mg or 30 mg and failed ≥1 prior TNF inhibitor; n indicates the total number of patients in each treatment group at week 260.

RESULTS (CONTINUED)

Safety

- Dose-dependent increases in the rates of herpes zoster and CPK elevation were observed with UPA 30 mg vs 15 mg (**Table 1**)
- Serious infectious events and treatment-emergent deaths were comparable between both UPA doses
- No new safety issues were identified from the long-term study, and results were consistent with the known safety profile of upadacitinib[3]

Table 1. Treatment-Emergent Adverse Event Summary Through 5 Years[a]

Event	UPA 15 mg QD (n = 236; PY = 759.5) Events (E/100 PY)	UPA 30 mg QD (n = 240; PY = 621.9) Events (E/100 PY)	UPA 30 mg QD Switched to UPA 15 mg QD (n = 138; PY = 155.5) Events (E/100 PY)
Any AE	2082 (274.1)	2202 (354.1)	269 (173.0)
Serious AEs	159 (20.9)	145 (23.3)	34 (21.9)
Any AE leading to discontinuation of study drug	66 (8.7)	61 (9.8)	14 (9.0)
Any Infection	656 (86.4)	725 (116.6)	63 (40.5)
Serious infection	38 (5.0)	39 (6.3)	7 (4.5)
Opportunistic infection[b]	4 (0.5)	0	1 (0.6)
Herpes zoster	29 (3.8)	46 (7.4)	9 (5.8)
COVID-19	18 (2.4)	4 (0.6)	13 (8.4)
Malignancies (excluding NMSC)	10 (1.3)	4 (0.6)	1 (0.6)
NMSC	8 (1.1)	5 (0.8)	3 (1.9)
CPK elevation[c]	21 (2.8)	33 (5.3)	4 (2.6)
MACE (adjudicated)	10 (1.3)	2 (0.3)	0
VTE (adjudicated)[d]	11 (1.4)	3 (0.5)	2 (1.3)
GI perforation (adjudicated)	0	2 (0.3)	0
All deaths[e]	9 (1.2)	5 (0.8)	2 (1.3)
Treatment-emergent deaths[f]	7 (0.9)	5 (0.8)	2 (1.3)
Non-treatment-emergent deaths[g]	2 (0.3)	0	0

AE, adverse event; CPK, creatine phosphokinase; GI, gastrointestinal; MACE, major adverse cardiovascular event; NMSC, non-melanoma skin cancer; PY, patient-years; QD, once daily; TEAE, treatment-emergent adverse event; UPA, upadacitinib; VTE, venous thromboembolism.

[a]Data include all patients receiving upadacitinib, with assignment based on drug dosage at the time of event. TEAEs are reported separately for patients who switched from UPA 30 mg to the approved 15 mg dosage, with the earliest switch occurring at week 180.

[b]Opportunistic infections exclude oral candidiasis and herpes zoster. No cases of TB were reported during the study.

[c]One case of rhabdomyolysis (with an alternative etiology of influenza) was reported on UPA 30 mg.

[d]VTE is defined as pulmonary embolism (PE) and deep vein thrombosis (DVT).

[e]A total of sixteen deaths and 17 TEAEs leading to death (two of which were related to COVID-19) were reported as follows. Eight events on UPA 15 mg: 2 cardiovascular (CV) deaths and one event each of PE, DVT, infection, injury due to a fall, acute respiratory failure (related to COVID-19), and a cardiac device pacing issue. Seven events on UPA 30 mg: 2 CV deaths, 2 injury, 1 PE, 1 malignancy, and 1 general disorder. Two events in patients who switched from UPA 30 mg to 15 mg: 1 multiple organ dysfunction syndrome (related to COVID-19) and 1 acute respiratory failure.

[f]Deaths ≤30 days after last dose.

[g]Deaths >30 days after last dose.

CONCLUSIONS

- Treatment with either upadacitinib 15 mg or 30 mg continued to be effective in improving clinical and functional outcomes in rheumatoid arthritis through 5 years
- At week 260, over three-quarters of patients attained CDAI low disease activity in this treatment-refractory population
- The safety profile observed over 5 years was consistent with earlier assessments of upadacitinib treatment in this population[1,2]

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