Safety and Efficacy of Upadacitinib in Patients With Rheumatoid Arthritis Refractory to Biologic DMARDs: Results Through Week 204 From the SELECT-CHOICE Study

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Andrea Rubbert-Roth,[1] Koji Kato,[2] Boulos Haraoui,[3] Maureen Rischmueller,[4] Yanxi Liu,[2] Nasser Khan,[2] Heidi S. Camp,[2] Ricardo Xavier[5]

[1]Division of Rheumatology, Cantonal Clinic St Gallen, St Gallen, Switzerland; [2]AbbVie Inc., North Chicago, IL, USA; [3]Institut de Rhumatologie de Montréal, Montreal, QC, Canada; [4]The Queen Elizabeth Hospital and Basil Hetzel Institute, Woodville South, SA, Australia and Adelaide Medical School, University of Adelaide, Adelaide, SA, Australia; [5]Universidade Federal do Rio Grande do Sul, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil

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OBJECTIVE

- To evaluate the long-term safety and efficacy of upadacitinib (UPA) through week 204 in patients with RA from the long-term extension of the SELECT-CHOICE study

INTRODUCTION

- In SELECT-CHOICE, UPA 15 mg, a JAK inhibitor, resulted in significant improvements in clinical, functional, and patient-reported outcomes vs abatacept (ABA) through week 24 in patients with RA refractory to biologic (b)DMARDs[1]

METHODS

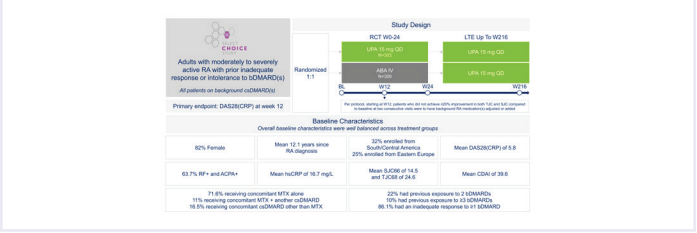
STUDY DESIGN

- RA patients were randomized 1:1 to receive oral UPA 15 mg once daily or intravenous ABA, each with stable conventional synthetic (cs) DMARDs for 24 weeks[1] **(Figure 1)**
- All patients who completed week 24 of the study could then enter the open-label long-term extension (LTE); those initially randomized to ABA were switched to UPA 15 mg, while patients initially randomized to UPA 15 mg continued treatment for up to 4 years

ASSESSMENTS AND STATISTICAL ANALYSIS

- Treatment-emergent adverse events (TEAEs) with UPA 15 mg exposure (any UPA 15 mg exposure, continuous UPA 15 mg, and UPA 15 mg exposure in patients initially randomized to ABA) are summarized through week 204 and are reported as exposure-adjusted event rates (events per 100 patient-years [E/100 PY])
- Efficacy endpoints in the overall patient population are shown through week 204
  - Efficacy outcomes were also examined in patients with a prior inadequate response or intolerance to ≥ 1 prior TNF inhibitor (TNF-IR)
- Efficacy data were analyzed using as observed (AO) and non-responder imputation (NRI) for binary endpoints or descriptive statistics based on AO and mixed-effect model repeated measures (MMRM) for continuous endpoints

Figure 1. Study Design and Baseline Patient Characteristics



ABA, abatacept; ACPA, anti-citrullinated protein antibodies; bDMARD, biologic DMARD; BL, baseline; csDMARD, conventional synthetic DMARD; IV, intravenous; LTE, long-term extension; RCT, randomized controlled trial; RF, rheumatoid factor; UPA, upadacitinib; QD, once daily; W, week.

RESULTS

PATIENTS

- Of the patients who entered the LTE on UPA 15 mg (n = 547), 151 (27.6%) patients discontinued treatment, with the most common reasons being adverse events (9.1%), withdrawal of consent (5.9%), and other reasons (7.3%); reasons for discontinuation were not mutually exclusive and patients may have listed more than 1 reason

SAFETY IN THE OVERALL POPULATION

- In RA patients, no new safety risks were identified with long-term exposure to UPA 15 mg (any UPA 15 mg exposure, continuous UPA 15 mg exposure, or UPA 15 mg exposure in patients initially randomized to ABA) through week 204 **(Table 1)**
- A total of 24 deaths occurred; 18 deaths were treatment-emergent (9 related to COVID-19) and 6 deaths were non-treatment-emergent (1 related to COVID-19)
  - For COVID-19-related deaths, patients were on average 65 years old and nearly all (excluding 1 patient) had no record of previous vaccination

Table 1. Summary of TEAEs and AEs of Special Interest With UPA 15 mg Exposure Through Week 204[a]

E/100 PY (95% CI)	Any UPA 15 mg QD[b] n = 579; PY = 1833.3	UPA 15 mg QD n = 303; PY = 978.3	UPA 15 mg QD Switched from ABA n = 276; PY = 855.0
Overall TEAEs			
Any AE	226.1 (219.3, 233.1)	241.4 (231.8, 251.4)	208.5 (199.0, 218.4)
Any serious AE	12.8 (11.2, 14.5)	13.3 (11.1, 15.8)	12.2 (9.9, 14.7)
Any AE leading to discontinuation of study drug	4.2 (3.3, 5.2)	5.7 (4.3, 7.4)	2.5 (1.5, 3.8)
All deaths[c]	1.3 (0.8, 1.9)	1.8 (1.1, 2.9)	0.7 (0.3, 1.5)
≤30 days after last dose of study drug	1.0 (0.6, 1.6)	1.4 (0.8, 2.4)	0.5 (0.1, 1.2)
>30 days after last dose of study drug	0.3 (0.1, 0.7)	0.4 (0.1, 1.0)	0.2 (0.0, 0.8)
TEAEs and AEs of Special Interest			
Any infection	72.7 (68.9, 76.7)	76.8 (71.4, 82.5)	68.1 (62.7, 73.8)
Serious infection	3.5 (2.7, 4.5)	3.4 (2.3, 4.7)	3.7 (2.6, 5.3)
Opportunistic infection[d]	0.2 (0.0, 0.5)	0.2 (0.0, 0.7)	0.1 (0.0, 0.7)
Herpes zoster	4.0 (3.2, 5.1)	3.5 (2.4, 4.9)	4.7 (3.3, 6.4)
COVID-19	8.8 (7.5, 10.3)	9.5 (7.7, 11.6)	8.1 (6.3, 10.2)
COVID-19 related AE	9.7 (8.3, 11.2)	10.7 (8.8, 13.0)	8.4 (6.6, 10.6)
GI perforation (adjudicated)	<0.1 (0.0, 0.3)	0.1 (0.0, 0.6)	0
CPK elevation	4.3 (3.4, 5.4)	3.4 (2.3, 4.7)	5.4 (3.9, 7.2)
Malignancies (excluding NMSC)	0.8 (0.5, 1.3)	1.1 (0.6, 2.0)	0.5 (0.1, 1.2)
NMSC	0.4 (0.2, 0.8)	0.5 (0.2, 1.2)	0.2 (0.0, 0.8)
MACE (adjudicated)[e]	0.3 (0.1, 0.6)	0.5 (0.2, 1.2)	0
VTE (adjudicated)[f]	0.4 (0.2, 0.8)	0.5 (0.2, 1.2)	0.2 (0.0, 0.8)

ABA, abatacept; AE, adverse event; CI, confidence interval; CPK, creatine phosphokinase; E, event; GI, gastrointestinal; LTE, long-term extension; NMSC, nonmelanoma skin cancer; PY, patient-year; QD, once daily; TEAE, treatment-emergent adverse event; UPA, upadacitinib.

[a]TEAEs are defined as any AE with onset on or after the first dose of study drug and ≤ 30 days after the last dose of study drug.

[b]Includes patients who started on UPA 15 mg and patients who switched from ABA to UPA 15 mg at week 24.

[c]Deaths occurring ≤ 30 days after last dose of study drug were considered treatment-emergent; deaths > 30 days after last dose of study drug were considered non-treatment emergent.

[d]Excludes tuberculous and herpes zoster infections; no cases of tuberculosis were reported.

[e]MACE is defined as non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death.

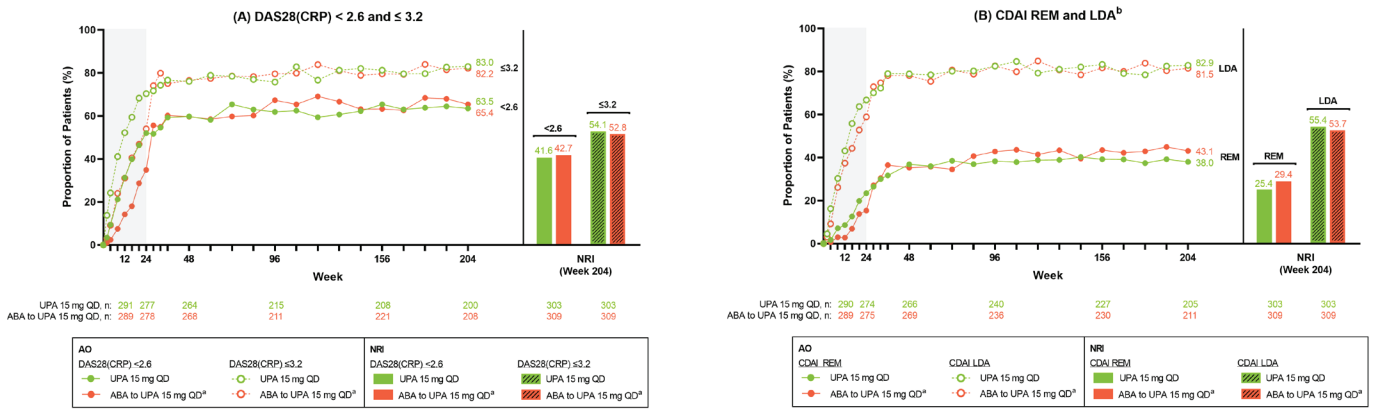
[f]VTE includes deep vein thrombosis (DVT) and pulmonary embolism (PE).

RESULTS (CONTINUED)

EFFICACY IN THE OVERALL POPULATION

- Of patients treated with continuous UPA 15 mg, a high proportion achieved DAS28(CRP) <2.6 or ≤3.2, which was maintained or further improved through week 204 **(Figure 2A)**
  - Approximately 40% of patients achieved CDAI remission and over 80% achieved LDA at week 204 (AO) **(Figure 2B)**; similar results were observed for SDAI **(Table 2)**
  - At week 204, 90%/75%/58% of patients achieved ACR20/50/70 (AO) **(Figure 3)**
  - Boolean remission was achieved at week 204 by 26.7% (95% CI: 20.7, 32.7) of patients (AO); conservative estimates using NRI showed similar results (19.1% [95% CI: 14.7, 23.6])
  - Improvements in HAQ-DI and pain were observed at week 204 **(Table 2)**
- Across all efficacy endpoints, similar results were observed in patients who switched from ABA to UPA 15 mg compared to those on continuous UPA 15 mg

Figure 2. Proportion of Patients Achieving DAS28(CRP) or CDAI Disease Activity States Through Week 204



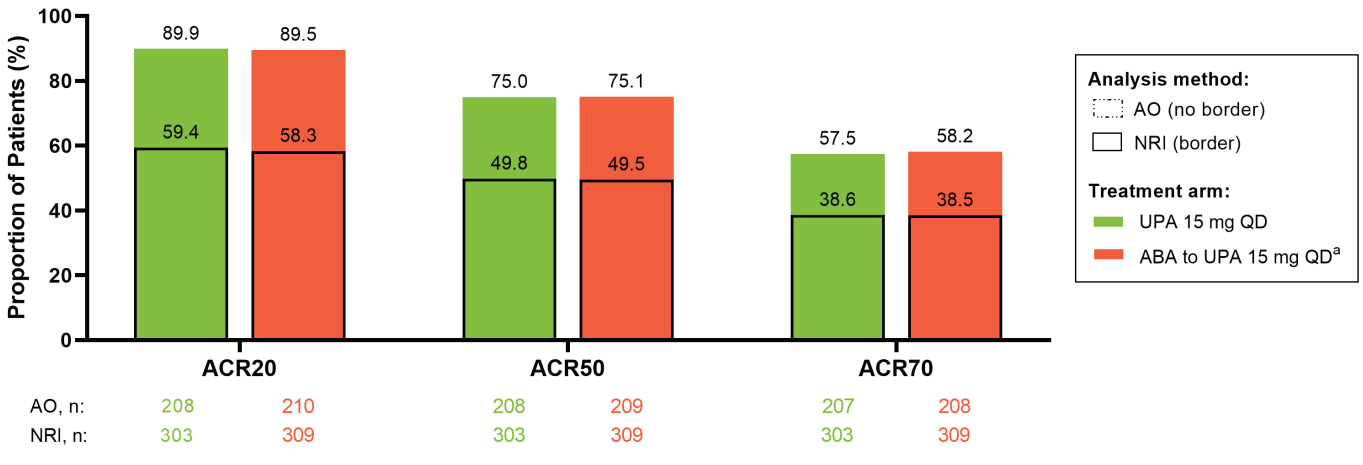
ABA, abatacept; AO, as observed; LDA, low disease activity; NRI, non-responder imputation; QD, once daily; REM, remission; UPA, upadacitinib.
[a]Patients randomized to ABA were switched to UPA 15 mg QD at week 24; shading indicates treatment with ABA. [b]CDAI REM is defined as ≤2.8; CDAI LDA is defined as ≤10.

Table 2. Efficacy Endpoints in Patients Treated With UPA 15 mg or ABA Switched to UPA 15 mg at Week 204[a]

Endpoint	UPA 15 mg QD		ABA to UPA 15 mg QD	
Proportion of patients, % (95% CI)	**AO**	**NRI**	**AO**	**NRI**
SDAI LDA (≤11), n	197, 82.2 (76.9, 87.6)	303, 53.1 (47.5, 58.8)	208, 82.2 (77.0, 87.4)	309, 53.4 (47.8, 59.0)
SDAI remission (≤3.3), n	197, 36.5 (29.8, 43.3)	303, 23.4 (18.7, 28.2)	208, 38.9 (32.3, 45.6)	309, 26.2 (21.3, 31.1)
Change from baseline, mean (95% CI)	**Descriptive (AO)**	**MMRM (AO)**	**Descriptive (AO)**	**MMRM (AO)**
HAQ-DI, n	207, -0.84 (-0.94, -0.74)	303, -0.76 (-0.84, -0.67)	210, -0.91 (-1.02, -0.81)	306, -0.78 (-0.86, -0.70)
Patient's assessment of pain, n	208, -44.7 (-48.7, -40.6)	303, -42.5 (-45.4, -39.5)	210, -50.3 (-54.3, -46.2)	306, -45.6 (-48.5, -42.6)

ABA, abatacept; AO, as observed; LDA, low disease activity; MMRM, mixed-effect model repeated measurement; QD, once daily; UPA, upadacitinib.
[a]Patients randomized to ABA were switched to UPA 15 mg QD at week 24.

Figure 3. Proportion of TNF-IR Patients Achieving ACR20/50/70 Responses at Week 204



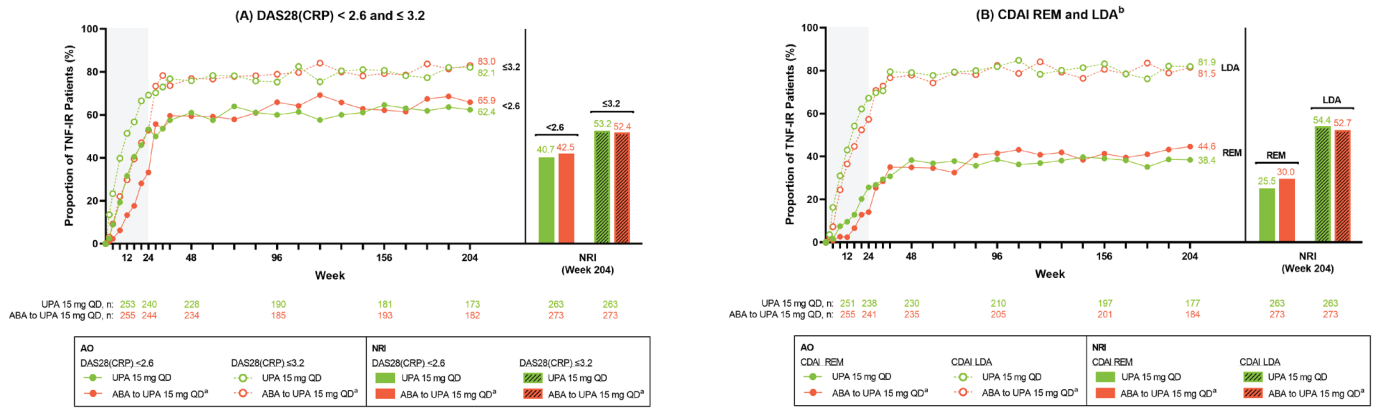
ABA, abatacept; AO, as observed; LDA, low disease activity; NRI, non-responder imputation; QD, once daily; REM, remission; UPA, upadacitinib.

RESULTS (CONTINUED)

EFFICACY IN THE TNF-IR SUBGROUP

- Similar to the overall patient population, a high proportion of TNF-IR patients treated with continuous UPA 15 mg achieved DAS28(CRP) <2.6 or ≤3.2 **(Figure 4)**, CDAI and SDAI remission and LDA **(Figure 4** and **Table 3)**, and ACR20/50/70 responses **(Figure 5)**
  - Boolean remission was achieved at week 204 by 26.6% (95% CI: 20.0, 33.1) of TNF-IR patients using AO and 19.0% (95% CI: 14.3, 23.8) using NRI
  - Improvements in HAQ-DI and pain were also observed at week 204 **(Table 3)**

Figure 4. Proportion of TNF-IR Patients Achieving DAS28(CRP) or CDAI Disease Activity States Through Week 204



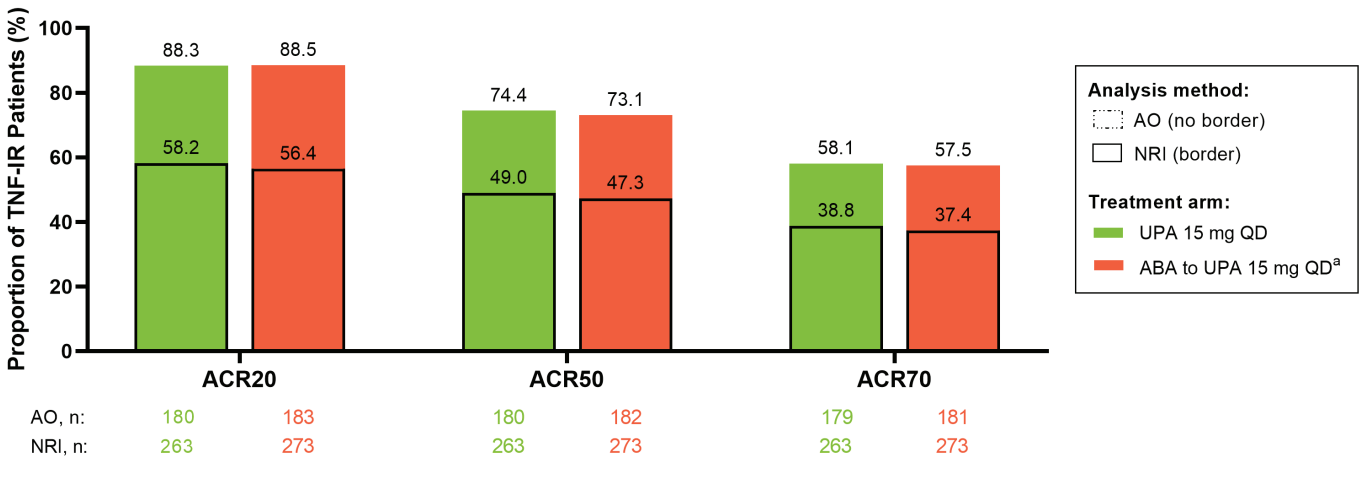
ABA, abatacept; AO, as observed; LDA, low disease activity; NRI, non-responder imputation; QD, once daily; REM, remission; TNF-IR; tumor necrosis factor inhibitor—inadequate response or intolerance; UPA, upadacitinib.
[a]Patients randomized to ABA were switched to UPA 15 mg QD at week 24; shading indicates treatment with ABA.
[b]CDAI REM is defined as ≤2.8; CDAI LDA is defined as ≤10.

Table 3. Efficacy Endpoints in TNF-IR Patients Treated With UPA 15 mg or ABA Switched to UPA 15 mg at Week 204[a]

Endpoint	UPA 15 mg QD		ABA to UPA 15 mg QD	
Proportion of patients, % (95% CI)	**AO**	**NRI**	**AO**	**NRI**
SDAI LDA (≤ 11), n	170, 81.2 (75.3, 87.1)	263, 52.1 (46.1, 58.1)	182, 83.0 (77.5, 88.4)	273, 53.1 (47.2, 59.0)
SDAI remission (≤ 3.3), n	170, 36.5 (29.2, 43.7)	263, 23.2 (18.1, 28.3)	182, 40.1 (33.0, 47.2)	273, 26.7 (21.5, 32.0)
Change from baseline, mean (95% CI)	**Descriptive (AO)**	**MMRM (AO)**	**Descriptive (AO)**	**MMRM (AO)**
HAQ-DI, n	179, -0.85 (-0.95, -0.74)	263, -0.76 (-0.84, -0.67)	183, -0.91 (-1.02, -0.79)	270, -0.77 (-0.86, -0.68)
Patient's assessment of pain, n	180, -43.7 (-48.1, -39.2)	263, -42.1 (-45.4, -38.9)	183, -50.2 (-54.6, -45.8)	270, -44.9 (-48.1, -41.7)

ABA, abatacept; AO, as observed; LDA, low disease activity; MMRM, mixed effect model repeated measurement; NRI, non-responder imputation; QD, once daily; UPA, upadacitinib.
[a]Patients randomized to ABA were switched to UPA 15 mg QD at week 24.

Figure 5. Proportion of TNF-IR Patients Achieving ACR20/50/70 Responses at Week 204



ABA, abatacept; AO, as observed; NRI, non-responder imputation; QD, once daily; tumor necrosis factor inhibitor—inadequate response or intolerance; UPA, upadacitinib.
[a]Patients randomized to ABA were switched to UPA 15 mg QD at week 24.

CONCLUSIONS

- The safety profile of UPA 15 mg through week 204 is consistent with previous findings[1] and the broader RA clinical program
- Efficacy responses with UPA 15 mg were maintained over time and across patient populations, including DAS28(CRP) <2.6 and ≤3.2, CDAI/SDAI remission and LDA, ACR20/50/70 responses, and patient-reported outcomes[1]
- These data further support the long-term safety and efficacy of UPA for the treatment of patients with RA

REFERENCES

1. Rubbert-Roth A, et al. *N Engl J Med*. 2020;383:1511–21.

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