Collaborations in Rheumatology

Upadacitinib clinical data across RA, UC, and CD

US Medical Affairs Rheumatology

INDICATIONS[1]

Upadacitinib is a Janus kinase (JAK) inhibitor indicated for the treatment of:

Adults with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to one or more tumor necrosis factor (TNF) blockers.

> **Limitations of Use for RA:** Upadacitinib is not recommended for use in combination with other JAK inhibitors, biologic disease-modifying antirheumatic drugs (bDMARDs), or with potent immunosuppressants such as azathioprine and cyclosporine.

Adults with moderately to severely active ulcerative colitis (UC) who have had an inadequate response or intolerance to one or more TNF blockers.

Adults with moderately to severely active Crohn's disease (CD) who have had an inadequate response or intolerance to one or more TNF blockers.

> **Limitations of Use for UC and CD:** Upadacitinib is not recommended for use in combination with other JAK inhibitors, biological therapies for UC or CD, respectively, or with potent immunosuppressants such as azathioprine and cyclosporine.

As discussed in the podcast, upadacitinib has been studied in clinical trials across RA, UC, and CD.

This infographic presents important study information, including key study details, efficacy endpoints, and safety data.

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Upadacitinib 15 mg QD was shown to be effective at improving disease activity in patients with moderately to severely active RA in five studies, including patients who were bDMARD-IR in the SELECT-BEYOND study.

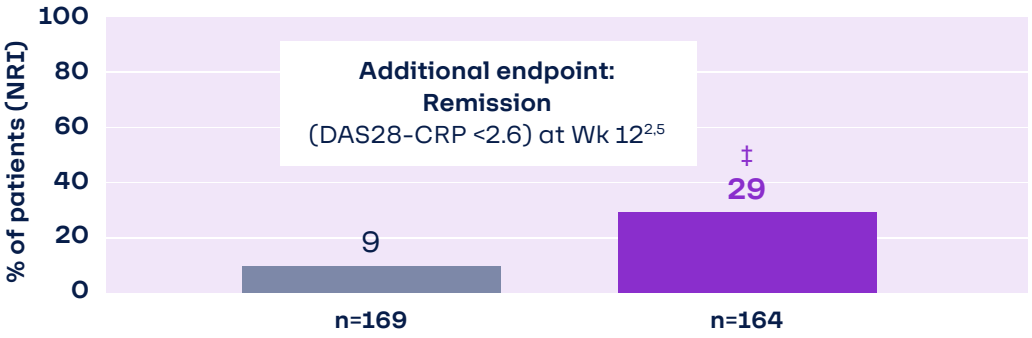
SELECT-BEYOND Study Design[2–4]

Adults with moderately to severely active RA who had an inadequate response or intolerance to ≥1 bDMARD were enrolled; 90% were TNFi-IR. Patients were randomized (2:2:1:1) to UPA15 or UPA30* or PBO for 12 wks. All patients were on background csDMARD therapy. From Wk 12, patients received UPA15 or UPA30. At Wk 24,†patients continued on UPA15 and UPA30 in the LTE. Following a protocol amendment, all patients on UPA30 in the LTE were switched to open-label UPA15.

***UPA30 is not an approved dosing regimen.** †Starting at Wk 24, initiation of, or change in, csDMARDs was permitted.

SELECT-BEYOND at Wk 12[2,5]: Key Endpoints

Primary Endpoint: 65% of patients in the UPA15 group achieved ACR20 at Wk 12, vs 28% in the PBO group (*P*<0.001)[1,2,5]



‡Comparisons not adjusted for multiplicity: nominal *P*<0.001 for UPA vs PBO.

Integrated RA Phase 3 Program Short-term Safety[1,6]:
PBO-controlled Studies (BEYOND, NEXT, and COMPARE [Wk 12])

TEAEs[§] of Special Interest n/100 PY[¶]	PBO + csDMARDs (n=1,042)	UPA15 + csDMARDs (n=1,035)
Serious infection	2.3	4.6
Active TB	0	0
HZ	1.2	2.7
Opportunistic infection (excluding TB/HZ/oral candidiasis)	1.2	1.9
Malignancy (excluding NMSC)	0.4	0.4
NMSC	0.4	0
Lymphoma	0	0
GI perforations	0	0
Adjudicated MACE[#]	1.2	0.4
Adjudicated VTE[‖]	0.4	0.8

Adverse reactions reported in ≥1% of RA patients treated with upadacitinib 15 mg in PBO-controlled trials are URTI, nausea, cough, and pyrexia.

Adverse reaction rates observed in clinical trials may not fully characterize the risks of UPA. Certain adverse events may require longer observation periods and longer-term patient exposure to ascertain risk.

Hypersensitive reactions (e.g., anaphylaxis and angioedema) have been reported. Discontinue if a serious hypersensitivity reaction occurs.[1]

[§]Defined as an adverse event with an onset date on or after the first dose of study drug in a controlled short-term period and prior to treatment switching and no more than 30 days after the last dose of study drug if subject discontinued study drug prematurely from controlled short-term period prior to treatment switching. [¶]Study size-adjusted number of subjects with at least 1 event per 100 PY. [#]MACE defined as cardiovascular death, nonfatal MI, and nonfatal stroke. [‖]VTE includes DVT and PE.

Want to learn more about the long-term efficacy and safety data for upadacitinib? Check out this video with Dr. Stan Cohen: https://rheumnow.com/therapeutic-update/long-term-efficacy-and-safety-jaki-ra

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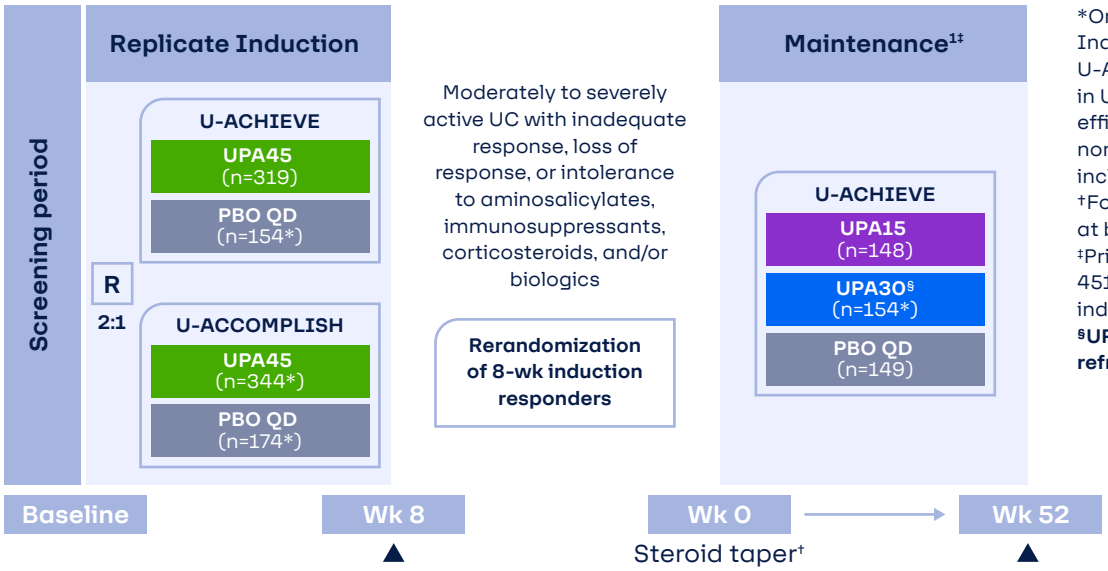
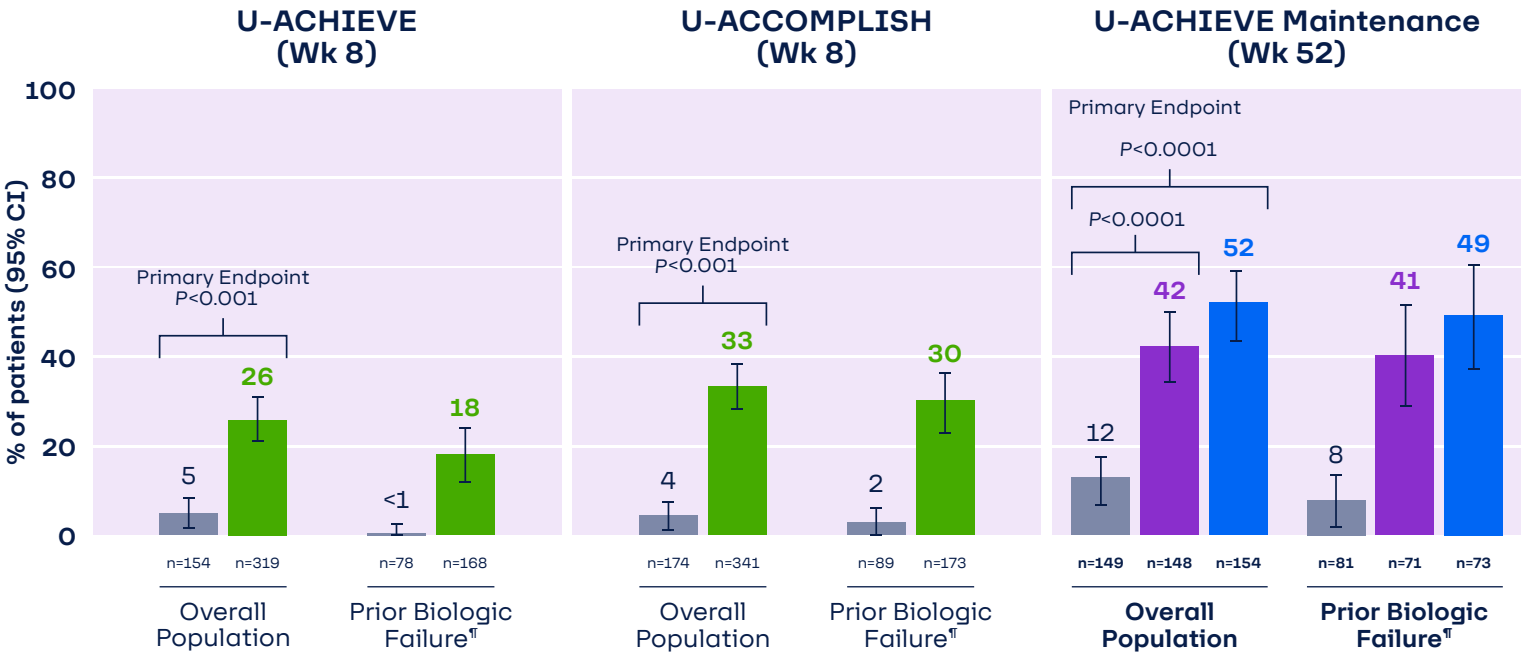
U-ACHIEVE and U-ACCOMPLISH Study Design[6]



*One patient receiving PBO in U-ACHIEVE Induction, 3 receiving PBO in U-ACCOMPLISH, and 3 receiving UPA 45 mg in U-ACCOMPLISH were excluded from efficacy analyses because of site noncompliance; these patients were included in the safety analysis.
†For subjects taking corticosteroid therapy at baseline of induction studies (~40%).
‡Primary efficacy analysis was evaluated in 451 clinical responders to 8-wk UPA45 induction (per protocol).
§UPA30 may be considered for patients with refractory, severe, or extensive disease.

▲ **Primary endpoints:** Clinical remission per modified Mayo score at Wk 8 (U-ACHIEVE, U-ACCOMPLISH) and Wk 52 (U-ACHIEVE)

Clinical Remission per Modified Mayo Score: Induction and Maintenance (Primary Endpoint & Subgroup Analysis)[1,7,8]



Clinical remission per modified Mayo score: modified Mayo score ≤2, with SFS ≤1 and not greater than baseline, RBS 0, and endoscopic subscore ≤1 without friability.[1]
§UPA30 may be considered for patients with refractory, severe, or extensive disease. ¶No statistical inferences of data by treatment experience (prior biologic failure or no biologic failure) can be made.

Modified Mayo score = RBS + SFS + endoscopy[1]
PBO · UPA15 · UPA30§ · UPA45

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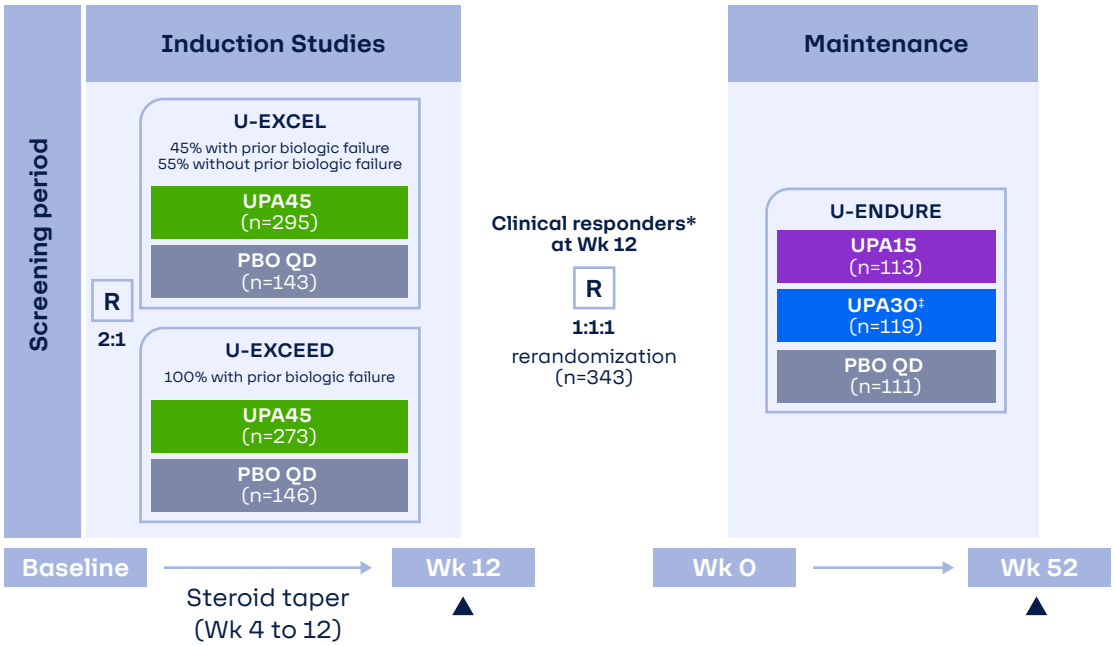
U-EXCEL, U-EXCEED, and U-ENDURE Study Design[9–12]



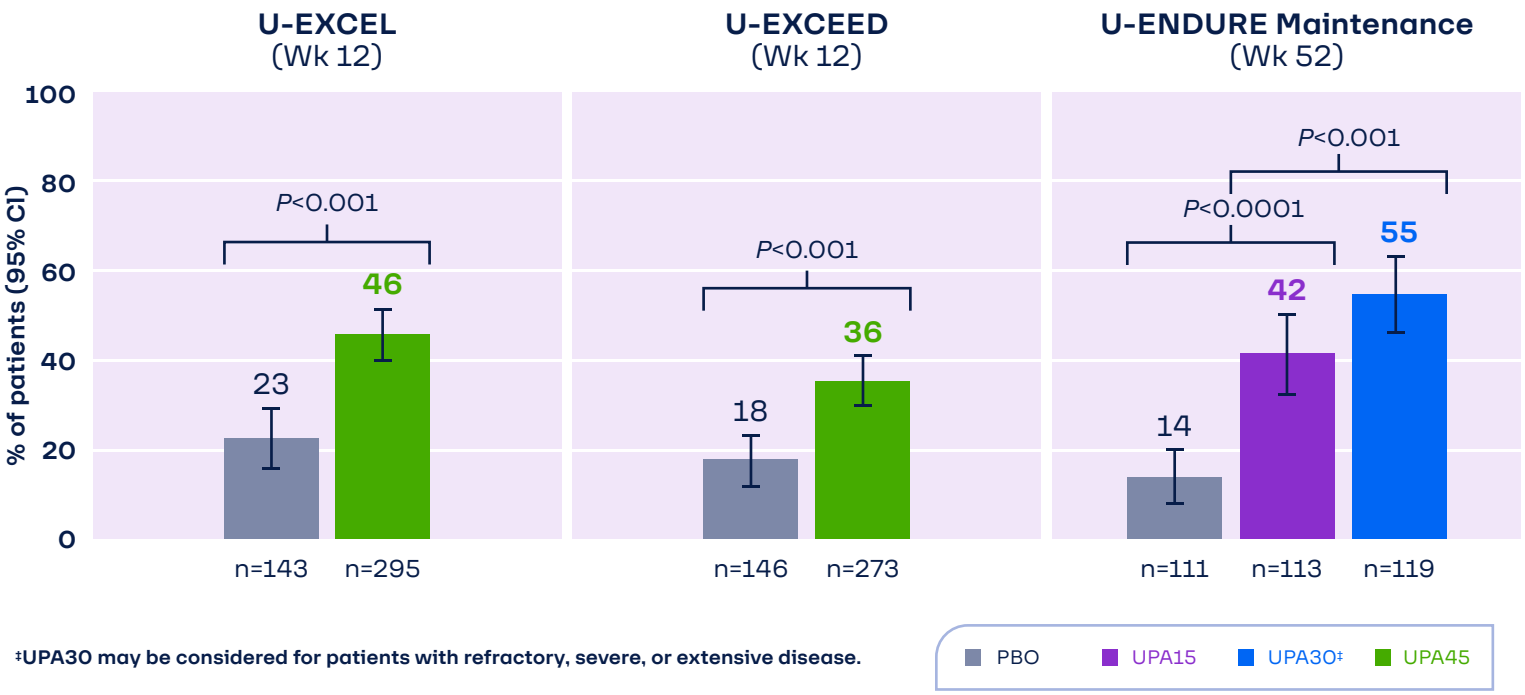
*CDAI clinical response was defined as a reduction of ≥100 points in CDAI score from baseline of induction. †Decrease in SES-CD >50% from baseline (or for patients with isolated ileal disease and a baseline SES-CD of 4, at least a 2-point reduction from baseline), scored by central reader. **‡UPA30 may be considered for patients with refractory, severe, or extensive disease.**

▲ **Co-primary endpoints:** CDAI clinical remission and endoscopic response† at Wk 12 (U-EXCEL, U-EXCEED) and Wk 52 (U-ENDURE)

Endoscopic Response (Co-primary Endpoint)[1]: Induction and Maintenance

- U-EXCEL (Wk 12): 46% of UPA45 patients achieved endoscopic response vs 13% PBO (*P*<0.001)
- U-EXCEED (Wk 12): 34% of UPA45 patients achieved endoscopic response vs 3% PBO (*P*<0.001)
- U-ENDURE (Wk 52): Compared to 7% of PBO patients, 28% of UPA15 patients (*P*<0.001) and 41% of UPA30‡ patients achieved endoscopic response (*P*<0.001)

Clinical Remission (CDAI <150; Co-primary Endpoint)[1]: Induction and Maintenance



‡UPA30 may be considered for patients with refractory, severe, or extensive disease.

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Short-term Safety: Induction
UC and CD

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AESIs, n (%)	UC: Pooled induction through Wk 8[1,13]		CD: Pooled induction through Wk 12[14]		
	PBO n=378	UPA45 n=719	PBO n=347	UPA45 (PBO-controlled) n=674	All UPA45 (inclusive of PBO-controlled)* n=938
Serious infection	5 (1.3)	9 (1.3)	6 (1.7)	13 (1.9)	21 (2.2)
Opportunistic infection (excluding TB/HZ/ oral candidiasis)	1 (0.3)	3 (0.4)	0	2 (0.3)	3 (0.3)
Active TB	0	0	0	0	0
HZ	0	4 (0.8)	0	15 (2.2)	20 (2.1)
Malignancy excluding NMSC	0	0	0	0	0
NMSC	0	0	0	0	0
Renal dysfunction	0	0	0	2 (0.3)	2 (0.2)
Hepatic disorder	9 (9.4)	25 (3.5)	10 (2.9)†	18 (2.7)†	23 (2.5)†
Adjudicated GI perforation	1 (0.3)	0	0	1 (0.1)	4 (0.4)
Adjudicated MACE‡	0	0	0	0	0
Adjudicated VTE§	1 (0.3)	1 (0.1)	0	0	0
Anemia	21 (5.6)	25 (3.5)	19 (5.5)	50 (7.4)	64 (6.8)
Neutropenia	1 (0.3)	33 (4.6)	1 (0.3)	14 (2.1)	18 (1.9)
Lymphopenia	2 (0.5)	18 (2.5)	8 (2.3)	11 (1.6)	16 (1.7)
CPK elevation	5 (1.3)	37 (5.1)	4 (1.2)	20 (3.0)	26 (2.8)

Adverse reaction rates observed in clinical trials may not fully characterize the risks of UPA. Certain adverse events may require longer observation periods and longer-term patient exposure to ascertain risk.

UC Common AEs (≥2% of UPA45 patients): URTI, acne, increased blood CPK, neutropenia, rash, elevated liver enzymes, lymphopenia, folliculitis, and herpes simplex.

CD Common AEs (≥2% of UPA45 patients): URTI, anemia, acne, pyrexia, increased blood CPK, influenza, herpes simplex, leukopenia, neutropenia, and HZ.

*Includes all patients who received at least one dose of UPA 45 mg during any portion of induction or extended treatment period, regardless of blinding status. †For CD hepatic disorder, most events were reported as transaminase increase; none of the hepatic disorder events were serious. ‡MACE defined as cardiovascular death, nonfatal MI, and nonfatal stroke. §VTE defined as DVT and PE.

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Short-term Safety: Maintenance
UC and CD

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AESIs, E (E/100 PY)	UC: U-ACHIEVE maintenance through Wk 52[1]			CD: U-ENDURE (overall population) maintence through Wk 52[12,14]		
	PBO n=378 PY=135.0	UPA15 n=250 PY=199.4	UPA30 n=251 PY=218.5	PBO n=223 PY=107.0	UPA15 n=221 PY=148.2	UPA30 n=229 PY=166.5
Serious infection	8 (5.9)	10 (5.0)	8 (3.7)	9 (8.4)	9 (6.1)	13 (7.8)
Opportunistic infection (excluding TB/HZ/ oral candidiasis)	2 (1.5)	2 (1.0)	2 (0.9)	0	1 (0.7)	1 (0.6)
Active TB	0	0	0	0	0	0
HZ	0	12 (6.0)	16 (7.3)	5 (4.7)	6 (4.0)	12 (7.2)
Malignancy excluding NMSC	1 (0.7)	1 (0.5)	2 (0.9)	0	1 (0.7)*	2 (1.2)*
NMSC	0	0	3	0	0	0
Lymphoma	0	0	0	NR	NR	NR
Renal dysfunction	1 (0.7)	1 (0.5)	1 (0.5)	2 (1.9)	0	0
Hepatic disorder	8 (5.9)	34 (17.0)	21 (9.6)	3 (2.8)†	11 (7.4)†	17 (10.2)†
Adjudicated GI perforation	2 (1.5)	0	0	1 (0.9)*	1 (0.7)*	1 (0.6)*
Adjudicated MACE‡	1 (0.7)	0	1 (0.5)	0	0	0
Adjudicated VTE§	0	2 (1.0)	2 (0.9)	0	0	0
Anemia	19 (14.1)	12 (6.0)	11 (5.0)	13 (12.2)	15 (10.1)	11 (6.6)
Neutropenia	7 (5.2)	12 (6.0)	19 (8.7)	1 (0.9)	3 (2.0)	5 (3.0)
Lymphopenia	5 (3.7)	9 (4.5)	7 (3.2)	10 (9.3)	4 (2.7)	10 (6.0)
CPK elevation	5 (3.7)	16 (8.0)	22 (10.1)	3 (2.8)	5 (3.4)	8 (4.8)

Adverse reaction rates observed in clinical trials may not fully characterize the risks of UPA. Certain adverse events may require longer observation periods and longer-term patient exposure to ascertain risk.

UC

Common AEs (≥2% of UPA15 or UPA30 patients)[1]: URTI, increased blood CPK, neutropenia, elevated liver enzymes, rash, HZ, folliculitis, hypercholesterolemia, influenza, herpes simplex, lymphopenia, and hyperlipidemia.

CD

Patients who received PBO or UPA15 during maintenance therapy and lost response were treated with rescue UPA30 (N=336). Among these patients, GI perforation was reported in three patients (1/100 PY) through long-term treatment.
Common AEs (≥2% of UPA15 or UPA30 patients): URTI, pyrexia, HZ, headache, acne, gastroenteritis, fatigue, increased blood CPK, elevated liver enzymes, leukopenia, neutropenia, bronchitis, pneumonia, and cough.

*n (n/100 PY). †Hepatic disorder included transaminase elevations that were mild or moderate, asymptomatic, nonserious and uncommonly led to treatment discontinuation. ‡MACE defined as cardiovascular death, nonfatal MI, and nonfatal stroke. §VTE defined as DVT and PE.

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Long-term Exposure Safety:
Across RA, UC, and CD[15–17]

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Long-term exposure AESIs E E/100 PY (95% CI) unless otherwise stated, 95% CIs have not been generated for CD data	RA (As of 8/2022) 6 Phase 3 Trials Any UPA15 n=3,209 PY=10,782.7	UC (As of 8/2022) 2 Phase 3 Trials Any UPA15 n=285 PY=504.1	 Any UPA30* n=291 PY=549.7	CD (As of 2/2023) 2 Phase 3 Trials Any UPA15 n=221 PY=295.8	 Any UPA30* n=739 PY=1179.2
INFECTIONS					
Serious infections	388 3.6 (3.2-4.0)	18 3.6 (2.1-5.6)	25 4.5 (2.9-6.7)	9 3.0	84 7.1
Active TB	6 <0.1 (0.0-0.1)	0	0	0	1 <0.1
Opportunistic infection (excluding TB/HZ/oral candidiasis)	30 0.3 (0.2-0.4)	2 0.4 (0.0-1.4)	3 0.5 (0.1-1.6)	2[#] 0.7	5[#] 0.4
HZ	350 3.2 (2.9-3.6)	24 4.8 (3.1-7.1)	35 6.4 (4.4-8.9)	9 3.0	57 4.8
MORTALITY					
Death	66[†] 0.6 (0.5-0.8)	1[‡] 0.2 (0.0-1.1)	1[§] 0.2 (0.0-1.0)	0	2[¶,‖] 0.2
MALIGNANCY					
Malignancy (excluding NMSC)	76[†] 0.7 (0.6-0.9)	2[‡] 0.4 (0.0-1.4)	3[§] 0.5 (0.1-1.6)	2 0.7	11 0.9
Lymphoma	4[†] <0.1 (0.0-0.1)	0	0[§]	0	2 0.2
NMSC	45[†] 0.4 (0.3-0.6)	0	6[§] 1.1 (0.4-2.4)	0	7 0.6
CARDIOVASCULAR EVENTS					
Adjudicated VTE**	41[†] 0.4 (0.3-0.5)	4[‡] 0.8 (0.2-2.0)	4[§] 0.7 (0.2-1.9)	0	3 0.3
Adjudicated MACE[††]	36[†] 0.3 (0.2-0.5)	0	2[§] 0.4 (0.0-1.3)	0	2 0.2
GASTROENTEROLOGICAL EVENTS					
Adjudicated GI perforations	4[†] <0.1 (0.0-0.1)	0	0	1 0.3	9 0.8

Adverse reaction rates observed in clinical trials and long-term extension studies may not predict rates observed in clinical practice.

***UPA30 may be considered for patients with refractory, severe, or extensive disease.** [†]Data shown are n, n/100 PY (95% CI) and have varied exposures (PY=10,700-10,800). [‡]Data shown are n, n/100 PY (95% CI) and have varied exposures (PY=500-505). [§]Data shown are n, n/100 PY (95% CI) and have varied exposures (PY=535-550). [#]For CD, data reported for any opportunistic infection excluding TB and HZ. [¶]Data shown are n, n/100 PY. [‖]Includes both treatment-emergent and non-treatment emergent deaths. **VTE defined as DVT and PE. [††]MACE defined as cardiovascular death, nonfatal MI, and nonfatal stroke.

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IMPORTANT SAFETY CONSIDERATIONS AND BOXED WARNING

Serious Infections: Patients treated with upadacitinib are at increased risk for developing serious infections that may lead to hospitalization or death. These infections include tuberculosis (TB), invasive fungal, bacterial, viral, and other infections due to opportunistic pathogens. Most patients who developed these infections were taking concomitant immunosuppressants, such as methotrexate or corticosteroids. Test for latent TB before and during therapy; treat latent TB prior to use. Consider the risks and benefits prior to initiating therapy in patients with chronic or recurrent infection. If a serious infection develops, interrupt upadacitinib until the infection is controlled.

Mortality: In a postmarketing safety study in RA patients ≥ 50 years of age with at least one cardiovascular (CV) risk factor comparing another JAK inhibitor to TNF blockers, a higher rate of all-cause mortality, including sudden CV death, was observed with the JAK inhibitor.

Malignancies: Malignancies have been observed in upadacitinib treated patients. In RA patients treated with another JAK inhibitor, a higher rate of lymphomas and lung cancers was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with upadacitinib, particularly in patients with a known malignancy (other than a successfully treated non-melanoma skin cancer [NMSC]), patients who develop a malignancy when on treatment, and patients who are current or past smokers. NMSCs have been reported in patients treated with upadacitinib. Periodic skin examination is recommended for patients who are at increased risk for skin cancer. Advise patients to limit sunlight exposure by wearing protective clothing and using sunscreen.

Major Adverse Cardiovascular Events (MACE): In RA patients who were ≥ 50 years of age with at least one CV risk factor treated with another JAK inhibitor, a higher rate of MACE (CV death, myocardial infarction, and stroke) was observed compared with TNF blockers. Patients who are current or past smokers are at additional increased risk. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with upadacitinib. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur. **Discontinue upadacitinib in patients that have experienced a myocardial infarction or stroke.**

Thrombosis: Thrombosis, including deep vein thrombosis, pulmonary embolism, and arterial thrombosis, have occurred in patients treated with JAK inhibitors, including upadacitinib. Many of these adverse events were serious and some resulted in death. In RA patients who were ≥ 50 years of age with at least one CV risk factor treated with another JAK inhibitor, a higher rate of thrombosis was observed when compared with TNF blockers. Avoid upadacitinib in patients at risk. Patients with symptoms of thrombosis should discontinue upadacitinib and be promptly evaluated.

Hypersensitivity Reactions: Upadacitinib is contraindicated in patients with known hypersensitivity to upadacitinib or any of its excipients. Serious hypersensitivity reactions such as anaphylaxis and angioedema were reported in patients receiving upadacitinib in clinical trials. If a clinically significant hypersensitivity reaction occurs, discontinue upadacitinib and institute appropriate therapy.

Other Serious Adverse Reactions: Patients treated with upadacitinib also may be at risk for other serious adverse reactions, including gastrointestinal perforations, neutropenia, lymphopenia, anemia, lipid elevations, liver enzyme elevations, and embryo-fetal toxicity.

Vaccinations: Avoid use of live vaccines during, or immediately prior to, upadacitinib therapy. Prior to initiating upadacitinib, it is recommended that patients be brought up to date with all immunizations, including varicella zoster or prophylactic herpes zoster vaccinations, in agreement with current immunization guidelines.

Medication Residue in Stool: Reports of medication residue in stool or ostomy output have occurred in patients taking upadacitinib. Most reports described patients with shortened gastrointestinal transit times. Instruct patients to contact their healthcare provider if medication residue is observed repeatedly.

Common Adverse Reactions in RA: The most common adverse reactions (≥1%) were upper respiratory tract infections, herpes zoster, herpes simplex, bronchitis, nausea, cough, pyrexia, acne, and headache.

Common Adverse Reactions in UC: The most common adverse reactions (≥5%) reported are upper respiratory tract infections, increased blood creatine phosphokinase, acne, neutropenia, elevated liver enzymes, and rash.

Common Adverse Reactions in CD: The most common adverse reactions (≥5%) reported are upper respiratory tract infections, anemia, pyrexia, acne, herpes zoster, and headache.

Review accompanying upadacitinib full Prescribing Information for additional information, visit www.rxabbvie.com or contact AbbVie Medical Information at 1-800-633-9110.

Abbreviations: ACR, American College of Rheumatology; ACR20, improvement of ≥20% in ACR core criteria; AE, adverse event; AESI, adverse event of special interest; AS, ankylosing spondylitis; bDMARD, biologic disease-modifying antirheumatic drug; CD, Crohn's disease; CDAI, Crohn's disease activity index; CI, confidence interval; CPK, creatine phosphokinase; csDMARD, conventional synthetic disease-modifying antirheumatic drug; CV, cardiovascular disease; DAS28-CRP, Disease Activity Score for rheumatoid arthritis with C-reactive protein; DVT, deep vein thrombosis; E, events; GI, gastrointestinal; HZ, herpes zoster; JAK, Janus kinase; LTE, long-term extension; MACE, major adverse cardiovascular events; MI, myocardial infarction; NMSC, nonmelanoma skin cancer; NR, not reported; nr-axSpA, nonradiographic axial spondyloarthritis; NRI, non-responder imputation; PBO, placebo; PE, pulmonary embolism; PsA, psoriatic arthritis; PY, patient-years; QD, once daily; R, randomization; RA, rheumatoid arthritis; RBS, rectal bleeding subscore; SES-CD, simple endoscopic activity score of Crohn's disease; SFS, stool frequency subscore; TB, tuberculosis; TEAE, treatment-emergent adverse event; TNF, tumor necrosis factor; TNFi-IR, inadequate responder to tumor necrosis factor inhibitor; UC, ulcerative colitis; UPA, upadacitinib; UPA15, upadacitinib 15 mg QD; UPA30, upadacitinib 30 mg QD; UPA45, upadacitinib 45 mg QD; URTI, upper respiratory tract infection; VTE, venous thromboembolism; Wk, week.

References: 1. RINVOQ® (upadacitinib) [package insert]. North Chicago, IL: AbbVie Inc. **2.** Genovese MC et al. *Lancet*. 2018;391(10139):2513–2524. **3.** Data on file, AbbVie Inc. ABVRRTI68669. **4.** ClinicalTrials.gov. Updated February 25, 2022. Accessed June 21, 2022. https://clinicaltrials.gov/ct2/show/NCT02706847. **5.** Data on file, AbbVie Inc. ABVRRTI72945. **6.** Data on file, AbbVie Inc. ABVRRTI71258. **7.** Data on file, AbbVie Inc. ABVRRTI73222. **8.** Danese S et al. *Lancet*. 2022;399(10341):2113–2128. **9.** Loftus EV Jr et al. UEGW 2022. Oral presentation OP129. **10.** Colombel JF et al. DDW 2022. Oral presentation 867f. **11.** ClinicalTrials.gov identifier: NCT03345823. Updated February 2, 2023. Accessed January 30, 2023. https://clinicaltrials.gov/ct2/show/NCT03345823. **12.** Panes J et al. ACG 2022. Oral presentation 44. **13.** Data on file, AbbVie Inc. ABVRRTI73268. **14.** Data on file. AbbVie, Inc. ABVRRTI75361. **15.** Data on file, AbbVie Inc. ABVRRTI74922. **16.** Data on file, AbbVie Inc. ABVRRTI75356; **17.** Data on file, AbbVie Inc. ABVRRTI75992.