Upadacitinib (RINVOQ) in Atopic Dermatitis National Drug Monograph Addendum June 2022

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description / Mechanism of Action

- Upadacitinib is one of the first two JAKIs approved for the treatment of atopic dermatitis.
- Lower activity at JAK2 receptors, which are thought to play a key role in hematopoietic signaling, theoretically might reduce the risk of myelosuppression.

Indication Under Review in This Document

- Treatment of adults with refractory, moderate to severe atopic dermatitis not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable.[1]
    - *Limitations of Use*: Upadacitinib is not recommended in combination with other JAKIs, biologic immunomodulators, or with other immunosuppressants.

Dosage Regimen and Dosage Forms Under Review

Pre-treatment Assessments

- Refer to the prescribing information for important pre-treatment assessments.

Dosage for Atopic Dermatitis

- *Adults < 65 Years*: Initiate therapy with 15 mg once daily. If response is inadequate, consider increasing to 30 mg once daily. Discontinue therapy if response to 30 mg is inadequate. Use the lowest effective dose to maintain response.
- *Adults ≥ 65 Years*: 15 mg once daily.
- *Renal Impairment*: For severe renal impairment (CrCL < 30 mL/min), the recommended dosage is 15 mg once daily. For mild or moderate renal impairment (CrCL > 30 mL/min), no dosage adjustment is needed.

Dosage Forms

- Extended-release tablets, 15 and 30 mg

Clinical Evidence Summary

Efficacy Considerations

- Four phase 3 trials consistently showed marked, rapid benefits in improving or clearing AD symptoms including itch.
- The phase 3 Heads Up RCT showed that oral upadacitinib 30 mg was better than subcutaneous dupilumab in skin and pruritus outcomes.[2] This section focuses on the results of this head-to-head trial.

- Two identically designed, 16-week, phase 3, placebo-controlled RCTs (Measure Up 1 and Measure Up 2,[3] established the efficacy of upadacitinib (15 and 30 mg) monotherapy in the treatment of adults (85%) and adolescents (15%) with moderate to severe atopic dermatitis who were candidates for systemic therapy. Blinded extension studies up to Week 260 are ongoing, and results for up to Week 52 have been published.[4]
    - The Week-16 results for the co-primary outcomes of EASI75 response and validated Investigator Global Assessment for AD score of 0 (clear) or 1 (almost clear) with improvement by ≥ 2 grades from baseline (vIGA-AD 0/1 response) showed significant treatment benefits that were consistent between the two trials.
    - Onset of significant treatment differences in EASI75 response was achieved as early as Week 2 and in Worst Pruritus NRS-4 response as early as Week 1.
    - The percentages of patients who achieved EASI90 and EASI100 responses at Week 16 showed consistent treatment effects between the two trials. Significant treatment differences (upadacitinib 15 or 30 mg vs placebo) occurred rapidly, as early as Week 1 for EASI90 and Week 2 for EASI100 in both trials.
    - The two trials also consistently showed significant treatment differences in reductions in AD flares, skin pain, impact on sleep, impact on daily activities, anxiety or depression, and impact on quality of life.
    - The long-term extensions showed that 82.0% and 79.1% of patients who achieved EASI75 response at Week 16 maintained response on upadacitinib 15 mg through Week 52 of the Measure Up 1 and Measure Up 2 trials, respectively.[4] The corresponding response rates on upadacitinib 30 mg were 84.9% and 84.3%, respectively. IGA0/1 responses were lower: 59.2% and 52.6% on 15 mg, and 62.5% and 65.1% on 30 mg, in Measure Up 1 and Measure Up 2, respectively.
- One 52-week, phase 3, placebo-controlled RCT (AD Up) showed that upadacitinib plus topical corticosteroids (TCS) was superior to placebo plus TCS in achieving the co-primary outcomes of Week-16 EASI75 response and the percentage of patients achieving vIGA-AD 0/1 response in adults (87%) and adolescents (13%) with chronic moderate to severe AD.[5,6]
    - With both doses of upadacitinib vs placebo, onset of significant treatment differences were observed as early as Week 2 for EASI75 and vIGA-AD responses and Week 1 for Worst Pruritus Numerical Rating Scale score improvement of ≥ 4 points (NRS-4 response).
    - Upadacitinib 15 and 30 mg also reduced the median number of days to discontinuation of TCS therapy (where the protocol required every-3-week attempts to step down and discontinue TCS) vs placebo: 88 (95% CI 73 to not estimable) and 57 (41, 59) vs not estimable (120 to not estimable), respectively.
    - A TCS-sparing effect was observed, with upadacitinib 15 mg and 30 mg significantly increasing the mean number of TCS-free days with EASI75 response at Week 16 vs placebo: 33.5 and 47.5 days vs 7.9 days, respectively.
    - The EASI75 and Worst Pruritus NRS-4 response rates with combination therapy (upadacitinib plus TCS) were similar to those observed with monotherapy in the Measure Up 1 and 2 trials, suggesting that TCS therapy added little benefit to upadacitinib therapy.[5] However, this requires confirmation; there was no study comparing upadacitinib monotherapy with upadacitinib plus TCS.
- The 24-week interim results of a phase 3 safety RCT provided exploratory efficacy data for upadacitinib in combination with TCS in patients with moderate to severe AD in Japan (Rising Up).[7] Response rates were numerically better with upadacitinib 15 and 30 mg vs placebo, and with upadacitinib 30 mg vs 15 mg, at Week 16.[7]
- An 88-week phase 2b RCT provided supportive evidence with Week-16 dose-ranging data[8] and exposure-response subgroup analyses.[9]

Heads Up RCT – AD

Methods

- Selected study characteristics are summarized in Table 1.

Table 1 Heads Up Trial Methods

Topic	Heads Up RCT
Study Design	• Multinational, double-blind, double-dummy active-controlled RCT comparing in adults with moderate to severe AD • 24-week double-blind phase with 12-week follow-up or option to enter an open-label extension study • Randomization was stratified by baseline disease severity of moderate (validated Investigator Global Assessment–Atopic Dermatitis [vIGA-AD] of 3) vs severe (vIGA-AD of 4) and age (< 40, ≥ 40 to 65, ≥ 65 years). • Hierarchical multiplicity control.
Major Entry Criteria	• Adults (18–75 years) who had a diagnosis of AD with chronic symptoms (≥ 3 years) • Moderate to severe AD, defined as affected body surface area of ≥ 10%, EASI ≥ 16, validated Investigator's Global Assessment ≥ 3 (moderate), and weekly average Worst Pruritus Numerical Rating Scale (NRS) score ≥ 4. • Candidates for systemic therapy defined as inadequate response to TCS or TCI therapies OR use of systemic therapy within the 6 months prior OR topical therapies were medically inadvisable (because of important adverse effects or safety risks). • Topical emollient use twice daily for ≥ 7 days • No prior JAKI (including but not limited to ruxolitinib) • No prior dupilumab
Interventions	• Upadacitinib (30 mg once daily to Week 24) • Dupilumab (600 mg loading dose then 300 mg SC every 2 weeks from Week 2 to Week 22) • Rescue Therapy: Any topical or systemic immunomodulatory therapy could be initiated at any time based on investigator discretion. Patients who received rescue therapy were counted as nonresponders for binary outcome measures.
Primary Efficacy Measure	• EASI75 at Week 16
Baseline Patient Characteristics	• Mean age 37 y, male 54%, vIGA-AD of 4 (severe) 50%

EASI75, Eczema Area and Severity Index improvement from baseline by ≥ 75%; **vIGA**, Validated Investigator's Global Assessment

Results

Primary and Secondary Outcome Measures

- Efficacy data for the Heads Up active-controlled trial are summarized in Table 2.

Table 2 Heads Up: Primary and Ranked Secondary Outcome Results

Outcome Measure	Time Point (Wk)	UPA30	DUP	Relative Risk (95% CI)	Absolute Difference (95% CI)	Q
EASI75 response, n/N (%)	16	247/348 (71.0)	210/344 (61.1)	1.2 (1.0, 1.3)	10.0 (2.9, 16.9)	M[α]
% CFB in Worst Pruritus NRS, LSM (SD) (N)	16	–66.9 (1.9) (258)	–49.0 (2.0) (251)	—	–17.9 (–17.6, –18.2)	H
EASI100 response, n/N (%)	16	97/348 (27.9)	26/344 (7.6)	3.7 (2.5, 5.5)	20.3 (14.8, 25.8)	H
EASI90 response, n/N (%)	16	211/348 (60.6)	133/344 (38.7)	1.6 (1.3, 1.8)	21.9 (14.5, 29.0)	H
% CFB in Worst Pruritus NRS, LSM (SD) (N)	4	–59.5 (2.2) (333)	–31.7 (2.2) (310)	—	–27.8 (–27.5, –28.1)	H
EASI75 response, n/N (%)	2	152/348 (43.7)	60/344 (17.5)	2.5 (1.9, 3.2)	26.3 (19.6, 32.7)	H
% CFB in Worst Pruritus NRS, LSM (SD) (N)	1	–31.4 (1.7) (337)	–8.8 (1.8) (327)	—	–22.6 (–22.3, –22.9)	H
Worst Pruritus NRS-4	16	188/340 (55.3)	120/336 (35.7)	1.5 (1.3, 1.8)	19.6 (12.2, 26.7)	M[α]

Source: 2. Outcomes are ordered by ranking used for multiplicity adjustments. All p-values ≤ 0.006
NRS, Numerical rating scale; NRS-4, NRS improvement of ≥ 4 points; Q, GRADE quality of evidence (H = High)
[α] Downgraded for imprecision (the relative risk CI includes the value 1.0 / No Effect and the absolute difference CI is wide).

- The anticipated absolute effect for achieving EASI75 at 16 weeks was 122 more with a 95% CI of 0 fewer to 183 more per 1000 patients (Table 3). The 95% CI includes a worst case of no incremental skin benefit with upadacitinib over dupilumab.

Table 3 Absolute Effect for Achieving Skin and Itch Outcomes for Upadacitinib 30 mg vs Dupilumab at Week 16

Outcome Measure	AAE, per 1000 pts (95% CI)	NNT (95% CI)
EASI75 response	122 more (0 fewer to 183 more)	10 (6, 35)
EASI100 response	204 more (113 to 340 more)	5 (4, 7)
EASI90 response	232 more (116 to 309 more)	5 (4, 7)
Worst Pruritus NRS-4 response	179 more (107 to 286 more)	6 (4, 9)

AAE, Anticipated absolute effect for achieving the outcome in the given time period; **NNT**, Number needed to treat for one additional patient to benefit

- For Worst Pruritus NRS-4 response at Week 16, the anticipated absolute effect with upadacitinib vs dupilumab was 179 (107, 286) more per 1000 patients (Table 3).
- Unranked secondary efficacy outcomes at Week 24 showed numerically higher response rates with upadacitinib than dupilumab, respectively, for EASI75 (64.2% vs 59.5%), EASI90 (55.6% vs 47.6%), EASI100 (27.3% vs 13.1%), and Worst Pruritus NRS-4 (50.2% vs 41.9%).
- Most study patients did not receive rescue therapy. Before Week 16, 17.5% of upadacitinib patients vs 20.3% of dupilumab patients received rescue therapy consisting of TCS or TCI. Overall through Week 24, 25.3% vs 24.7%, respectively, received rescue therapy, mainly TCS or TCI, and 1.4% vs 0.6%, respectively, of upadacitinib vs dupilumab patients received systemic rescue therapy (biologic, nonbiologic immunomodulator, or phototherapy).[2]

Subgroup Analyses

- None.

Onset of Treatment Benefit (Earliest Significant Treatment Difference)

- By Week 2 for EASI75 response.
- By Week 1 for mean change from baseline in Worst Pruritus NRS.

Duration of an Adequate Therapeutic Trial

- Overall, an adequate trial duration in patients with AD seems to be 8 weeks for upadacitinib 15 and 30 mg. The adequate trial duration is the time by which responders would be expected to show benefit and

the earliest time at which treatment modification should be considered if there is no or inadequate response.

- Based on maximal EASI75 response rates and maximal change from baseline in Worst Pruritus NRS scores, the duration of an adequate therapeutic trial seemed to be 8 weeks for upadacitinib 30 mg and 16 weeks for dupilumab.[2]
- The adequate trial duration for upadacitinib 30 mg in Heads Up was consistent with those (8 weeks) for upadacitinib 15 and 30 mg using EASI75 response and Worst Pruritus NRS-4 response in the placebo-controlled Measure Up 1 and 2 trials.[3]
- In the AD Up trial, adequate trial durations seemed to be Week 8 for upadacitinib 30 mg and Week 12 for upadacitinib 15 mg for both EASI75 response and Worst Pruritus NRS-4 response.[6]

Durability of Response

- Treatments were not evaluated beyond Week 24.
- Although significant treatment differences in EASI75 response persisted to Week 16 (primary outcome), response rates for upadacitinib seemed to decrease somewhat from Week 8 to Week 16, while the rates for dupilumab continued to increase.[2]
- The EASI75 response rates decreased somewhat from Week 16 to Week 24 with both upadacitinib (from 71.0% to 64.2%) and dupilumab (61.1% to 59.5%).[2]

Evidence Gaps

- Hospitalization or readmission
- Health-related Quality of Life, especially sleep quality.
- Functional ability / Disability
- Patient Satisfaction, especially preference for oral upadacitinib vs injectable adalimumab therapy.
- Long-term efficacy with or without TCS.

Network Meta-analyses

- Three network meta-analyses reviewed studies of upadacitinib in patients with moderate to severe AD, none of which included the Heads Up trial (which directly compared upadacitinib and dupilumab).[10,11,12]
- The assessment time period was 8–16 weeks for the meta-analysis by Drucker (2022) and 12–16 weeks for the Pereyra-Rodriguez (2021) and Silverberg (2021) meta-analyses.
- Selected findings of the network meta-analyses are presented in Table 4 to Table 6.

Table 4 Summary of Network Meta-analyses Comparing Upadacitinib with Other Targeted AD Therapies

Comparison	NMA Estimate			
	Efficacy Outcomes		Safety Outcomes	
Drucker (2022)	**CFB in EASI,† MD (95% CrI) Q**	**CFB in Signs,† SMD (95% CrI) Q**	**SAE,† OR (95% CrI) Q**	**DAE,† OR (95% CrI) Q**
ABR100 vs UPA15, ± TAI	2.3 (0.1, 4.7) H	0.4 (0.2, 0.6) H	1.8 (0.7, 4.8) VL$^{\gamma}$	1.3 (0.6, 3.0) VL$^{\gamma}$
ABR200 vs UPA15, ± TAI	–2.0 (–4.3, 0.3) H	0.0 (–0.2, 0.2) H	0.9 (0.3, 2.7) VL$^{\gamma}$	1.2 (0.5, 2.9) VL$^{\gamma}$
BAR2 vs UPA15, ± TAI	5.4 (2.9, 7.9) H	0.8 (0.6, 1.0) H	0.7 (0.2, 1.8) L$^{\delta}$	1.4 (0.5, 3.9) VL$^{\gamma}$
BAR4 vs UPA15, ± TAI	3.4 (0.8, 6.0) H	0.6 (0.4, 0.8) H	1.0 (0.4, 2.6) VL$^{\gamma}$	2.7 (1.0, 7.4) VL$^{\gamma}$
DUP300 vs UPA15, ± TAI	0.2 (–1.9, 2.2) H	0.5 (0.3, 0.7) H	0.7 (0.3, 1.6) VL$^{\gamma}$	1.7 (0.7, 4.0) VL$^{\gamma}$
TRA300 vs UPA15, ± TAI	3.7 (1.4, 6.1) H	0.6 (0.4, 0.7) H	1.0 (0.4, 2.5) VL$^{\gamma}$	1.6 (0.7, 3.9) VL$^{\gamma}$
AZP vs UPA15, ± TAI	NE	0.5 (0.1, 0.9) M	NE	NE
CSAhd vs UPA15, ± TAI	NE	0.1 (–0.5, 0.7) M	NE	NE
CSAld vs UPA15, ± TAI	NE	0.4 (–0.2, 1.0) L$^{\alpha\ddagger}$	NE	NE
MTX vs UPA15, ± TAI	NE	0.2 (0.1, 0.4) L$^{\alpha\ddagger}$	NE	NE
ABR100 vs UPA30, ± TAI	4.9 (2.6, 7.2) H	0.6 (0.4, 0.8) H	1.8 (0.7, 5.0) VL$^{\gamma}$	1.0 (0.5, 2.3) VL$^{\gamma}$
ABR200 vs UPA30, ± TAI	0.6 (–1.7, 2.9) H	0.2 (0.0, 0.4) H	1.0 (0.3, 2.8) VL$^{\gamma}$	1.0 (0.4, 2.2) VL$^{\gamma}$
BAR2 vs UPA30, ± TAI	**7.9 (5.5, 10.4) H**	**1.0 (0.8, 1.2) H**	0.7 (0.2, 1.8) L$^{\delta}$	1.1 (0.4, 3.1) VL$^{\gamma}$
BAR4 vs UPA30, ± TAI	5.9 (3.4, 8.5) H	0.9 (0.7, 1.1) H	1.1 (0.4, 2.8) VL$^{\gamma}$	2.1 (0.8, 5.7) VL$^{\gamma}$
DUP300 vs UPA30, ± TAI	2.7 (0.6, 4.7) H	0.2 (0.1, 0.4) H	0.7 (0.3, 1.7) VL$^{\gamma}$	1.3 (0.6, 3.1) VL$^{\gamma}$
TRA300 vs UPA30, ± TAI	6.3 (3.9, 8.6) H	0.8 (0.6, 1.0) H	1.0 (0.4, 2.6) VL$^{\gamma}$	1.2 (0.5, 3.0) VL$^{\gamma}$
AZP vs UPA30, ± TAI	NE	0.8 (0.3, 1.2) M	NE	NE
CSAhd vs UPA30, ± TAI	NE	0.4 (–0.3, 1.0) L$^{\alpha\ddagger}$	NE	NE
CSAld vs UPA30, ± TAI	NE	0.7 (0.0, 1.3) L$^{\alpha\ddagger}$	NE	NE
MTX vs UPA30, ± TAI	NE	0.8 (0.1, 1.4) M$^{\beta}$	NE	NE
Pereyra-Rodriguez (2021)	**EASI75, OR (CI NR) Q**	**IGA0/1, OR (CI NR) Q**	**Severe AE**	**Any AE**
ABR100 vs UPA15, + TCS / – TCS	0.74 / **0.47** NE	0.66 / **0.39** NE	NR	NR
ABR200 vs UPA15, + TCS / – TCS	1.18 / 1.03 NE	1.11 / 0.73 NE	NR	NR
BAR2 vs UPA15, + TCS / – TCS	**0.41** / **0.25** NE	**0.34** / **0.23** NE	NR	NR
BAR4 vs UPA15, + TCS / – TCS	**0.49** / **0.34** NE	**0.48** / **0.34** NE	NR	NR
DUP300 vs UPA15, + TCS / – TCS	0.98 / 0.57 NE	0.79 / 0.54 NE	NR	NR
TRA300 vs UPA15, + TCS / – TCS	**0.44** / **0.27** NE	**0.34** / **0.22** NE	NR	NR
ABR100 vs UPA30, + TCS / – TCS	**0.41** / **0.27** NE	**0.31** / **0.22** NE	NR	NR
ABR200 vs UPA30, + TCS / – TCS	0.65 / 0.60 NE	0.52 / **0.42** NE	NR	NR
BAR2 vs UPA30, + TCS / – TCS	**0.22 / 0.15 NE**	**0.16 / 0.13 NE**	NR	NR
BAR4 vs UPA30, + TCS / – TCS	**0.27 / 0.19 NE**	**0.22 / 0.19 NE**	NR	NR
DUP300 vs UPA30, + TCS / – TCS	0.54 / **0.33** NE	**0.37** / **0.31** NE	NR	NR
TRA300 vs UPA30, + TCS / – TCS	**0.24 / 0.16 NE**	**0.16 / 0.12 NE**	NR	NR

Bold blue text indicates at least a moderate effect based on point estimates of the MD or SMD (see cutoffs under abbreviations below) or RR or OR of < 0.50 or > 2.0 (commonly considered to be clinically important).[13]

There were no reported direct comparisons between upadacitinib and active comparators and therefore no direct estimates. The network meta-analysis estimates (which combine direct estimates and indirect estimates) are the same as the indirect estimates except that GRADE quality of evidence could be lower for the NMA than the indirect estimate. Silverberg (2021) reported no indirect comparisons involving upadacitinib.

AZP, Azathioprine 1–2.5 mg/kg/d; **CFB**, Change from baseline; **CrI**, Credible interval; **CSAhd**, Cyclosporine higher dose (300 mg/d, 4–5 mg/kg/d); **CSAld**, Cyclosporine lower dose (150 mg/d, ≤ 3 mg/kg/d); **EASI**, Eczema Area and Severity Index (minimal clinically important change, 6.6)[10]; **MD**, Mean difference (definitions of the effect size of the MD: < 1, little or no difference; > 1 but < MCIC, small effect of uncertain importance / "reduces slightly"; > MCIC, moderate effect; > 2x MCIC, large effect[10]); **MTX**, Methotrexate 10–22.5 mg/week; **NE**, Not evaluated; **NMA**, Network meta-analysis; **Q**, GRADE quality of evidence as reported by the authors (H = High, M = Moderate, L = Low, VL = Very low); **SMD**, Standardized mean difference (Drucker, et al. [2022] definitions of the effect size of the SMD: < 0.2, little or no difference; 0.2–0.8, small effect of uncertain importance; and > 0.8 moderate effect / "reduces"; no SMD equivalent for large effect[10])

† Negative effect estimates favor the intervention (drug listed first). Positive effect estimates favor the comparator (drug listed second).

‡ Rated moderate in indirect estimate (different rating from that in the NMA estimate) with no change in the estimate size (downgraded to moderate for significant risk of bias).

α Downgraded for imprecision.

β Downgraded for significant risk of bias.

γ Double downgraded for imprecision (the upper and lower ends 95% CrI for the estimate would suggest different conclusions and CrIs very wide).

δ Downgraded for imprecision (the upper and lower ends 95% CrI for the estimate would suggest different conclusions).

Table 5 SUCRA cluster rank plot for combined efficacy and safety outcomes (EASI75 and Any Adverse Event) in

Plot Position†	Intervention
Upper rank efficacy / Upper rank safety	DUP300 +/– TCS
	UPA15 + TCS
	ABR100 + TCS
Upper rank efficacy / Lower rank safety	**UPA30 +/– TCS**
	ABR200 +/– TCS
	UPA15
	ABR100
Lower rank efficacy / Upper rank safety	BAR4
	TRA300 +/– TCS
	BAR2
Lower rank efficacy / Lower rank safety	BAR4 + TCS
	BAR2 + TCS

Source: Pereyra-Rodriguez (2021).[11] Drucker (2022) and Silverberg (2021) did not provider SUCRA cluster rank plots.

† SUCRA values typically range from 0.0 to 1.0, with higher numbers denoting better efficacy or safety, although for safety, higher values can sometimes denote worse safety. For monograph purposes, upper- / lower-rank efficacy and upper- / lower-rank safety were arbitrarily described using SUCRA rank cutoffs of ≥ / < 0.50 and as defined in the network meta-analysis based on cluster rank plots. For the Pereyra-Rodriguez (2021) review, upper / lower rank efficacy corresponded to efficacy SUCRA rank ≥ / < 0.50, respectively; upper / lower rank safety corresponded to safety SUCRA rank < / ≥ 0.50, respectively.

Table 6 Other Considerations About the Network Meta-analyses – AD

Consideration	Drucker (2022)	Pereyra-Rodriguez (2021)	Silverberg (2021)
Heterogeneity Among Trials	Evaluated but not reported	Substantial	Little evidence of detectable heterogeneity
Inconsistency Among Trials	Not mentioned	Significant disagreement between direct and indirect estimates	Could not be assessed
Evidence of Violation of Transitivity Assumptions	Not mentioned	Not mentioned	Not mentioned
Limitations	Included Measure Up 1 and 2 and AD Up but not Heads Up. Questionable GRADE quality assessments of evidence for indirect comparisons between two active therapies (e.g., rated as high in the absence of direct comparisons).	Included Measure Up 1 and 2, and AD Up but not Heads Up. No GRADE quality of evidence assessment; only assessed risk of bias. No long-term trials.	Included only the phase 2b trial. No GRADE quality of evidence assessment; only assessed risk of bias. No long-term trials.
Funding by mfr	No	No (Not funded)	Yes – Pfizer (abrocitinib)
Author(s) COI with AbbVie	Yes	Yes	Yes

- Overall, the results across the network meta-analyses suggested that upadacitinib 15 mg may be better in improving EASI or EASI75 response efficacy than baricitinib 2 mg and tralokinumab (with effect sizes that could be clinically important), and similar in efficacy to dupilumab, abrocitinib, and baricitinib 4 mg. The certainties of the differences in effects were rated high in one NMA (despite only indirect comparisons) but not assessed in another NMA.
- Based on SUCRA cluster rank plots combining efficacy and safety outcomes, upadacitinib 15 mg + TCS was among the drugs that might have the more desirable combination of upper rank efficacy and upper rank safety effects; the other interventions might be dupilumab +/– TCS and abrocitinib 100 mg + TCS.

- Upadacitinib 15 mg monotherapy and upadacitinib 30 mg (+/– TCS) might present a trade-off between upper rank efficacy and lower rank safety (i.e., higher risk of adverse events of uncertain effect size). Abrocitinib 100 mg monotherapy and abrocitinib 200 mg +/– TCS might also present a similar trade-off.
- However, only one NMA provided cluster rank plots and this NMA did not include the Heads Up trial or use GRADE to assess the quality of evidence for drug comparisons.[11] Taken together with the results of the Heads Up trial, it seems reasonable to conclude that in the short term upadacitinib has better efficacy and similar or worse safety (depending on the dose) than dupilumab. It may be premature to infer that upadacitinib would be a better choice than tralokinumab or baricitinib (off-label treatment).

Safety Considerations

- The safety profile of upadacitinib in patients with AD was generally consistent with that in patients with rheumatoid arthritis.[1]
- Eczema herpeticum / Kaposi's varicelliform eruption were among additional adverse events reported in patients with AD.[1]

Upadacitinib vs Dupilumab

- Compared with dupilumab, upadacitinib 30 mg had a
    - higher risk of acne (15.8% vs 2.6%, respectively; relative risk [RR] 6.0 [95% CI 3.0, 12.0]); NNT 8 [95% CI 6, 12])[2];
    - higher risk of increased CPK (6.6% vs 0.3%, respectively; RR 22.7 [3.1, 167.4]; NNT 16 [12, 28])[2] (possibly due to JAK1 inhibition, which might increase CPK by stimulating myoblast differentiation[5]);
    - lower risk of conjunctivitis (1.4% vs 8.4%, respectively; RR 0.2 [0.1, 0.4]; NNT 15 [10, 27])[2];
    - numerically higher risks of serious adverse events (2.9% vs 1.2%, respectively), withdrawals due to adverse events (2.0% vs 1.2%, respectively), serious infection (1.1% vs 0.6%, respectively), herpes zoster (2.0% vs 0.9%, respectively), hepatic disorders 2.9% vs 1.2%, respectively), anemia (2.0% vs 0.3%, respectively), neutropenia (1.7% vs 0.6%, respectively); lymphopenia (0% vs 0.6%); and adverse events leading to mortality (0.3% vs 0.0%); and
    - similar risks of malignancy (excluding nonmelanoma skin cancer), lymphoma, adjudicated MACE, and adjudicated venous thromboembolic events (0.0% vs 0.0% for each of these adverse events of special interest).

Upadacitinib vs Placebo

- The safety profile of upadacitinib in patients with AD was generally consistent with that in patients with rheumatoid arthritis.

Gaps in Safety Data

- Long-term safety experience

Other Therapeutic Options

- The FDA approved upadacitinib for use after inadequate response of other systemic treatment alternatives, or when those therapies are medically inadvisable. Systemic treatment alternatives include phototherapy, conventional immunomodulators (e.g., cyclosporine, azathioprine, mycophenolate, and methotrexate) and targeted biologic immunomodulators such as dupilumab and tralokinumab.
- The approved place in therapy of upadacitinib is at the same level as abrocitinib, another JAKI approved for refractory moderate to severe AD (Table 7).
- No evidence-based society guidelines on the management of AD include recommendations for upadacitinib.

Table 7 Treatment Alternatives for Moderate to Severe AD Inadequately Responding to Other Systemic Drugs

Drug (Formulary Status)	Place in Therapy in PI	Safety Considerations	Other Considerations
Upadacitinib (NonF, CFU)	Refractory moderate to severe AD for which other systemic drugs are inadequate or inadvisable	• Serious infections, mortality, malignancy, MACE, thrombosis, GI perforation, decreased lymphocytes and neutrophils, increased liver enzymes and lipids. • High rate of acne in AD studies • In AD (but not in PsA), should reduce dosage in severe renal impairment. • Not recommended for use in severe hepatic impairment.	• Superior to dupilumab in improving skin and itch. • An incremental benefit from adding TCS to upadacitinib therapy has not been proven. • TCS-sparing effects. • Oral convenience. • Not recommended for co-use with strong CYP3A4 inhibitors or inducers.
Abrocitinib (TBD)	Same as upadacitinib	• Contraindicated in patients on antiplatelets, except for low-dose (≤ 81 mg/d) aspirin, in the first 3 months of therapy. • Similar to upadacitinib except lacks warnings about decreased hemoglobin, decreased neutrophils, and increased liver enzymes. • Unlike upadacitinib, has warning for decreased platelets, which recover ~40% by 12 weeks. • Not recommended for use in severe renal impairment or ESRD. Should reduce dosage in mild and moderate renal impairment. • Not recommended for use in severe hepatic impairment.	• Abrocitinib 200 mg was superior to dupilumab only in itch response at Week 2.[14] Similar to dupilumab for EASI75 and IGA responses, and numerically higher or similar itch response vs dupilumab at other time points. • Lacks evidence of TCS-sparing effects. • Oral convenience. • Co-use with moderate to strong inhibitors of both CYP2C19 and CYP2C9 should be avoided.

Projected Place in Therapy

Potential Place in Therapy in AD Based on the Evidence

- The approved labeling recommends the use of upadacitinib in adults with moderate to severe AD who are refractory or intolerant to other systemic drug products. It is notable that the efficacy and safety of upadacitinib in such patients are unknown since upadacitinib was evaluated in patients who did not necessarily have inadequate response to prior systemic therapies.
- For candidates for systemic therapy, moderate to high quality evidence suggested that upadacitinib (30 mg) was similar to or better than dupilumab in improving skin clearance and pruritus but was significantly or numerically worse in most safety measures. Effects were mostly small to negligible and some were potentially clinically important. The comparative efficacy and safety of the lower dose of upadacitinib (15 mg) vs dupilumab has not been evaluated directly.
- The comparative efficacy and safety between upadacitinib and systemic therapies other than dupilumab and comparative long-term safety with other AD therapies are unknown.

Potential Place in Therapy in AD in VHA

- Considering overall risks and benefits, upadacitinib may be used for the treatment of patients with moderate to severe AD who have an inadequate response or intolerance to other systemic therapies, including and not limited to **phototherapy**, short-term induction therapy with **cyclosporine** or a **systemic corticosteroid** (if induction is indicated), **two conventional maintenance therapies**, and **dupilumab,** unless these treatments are medically inadvisable.

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