Abrocitinib (CIBINQO) in Atopic Dermatitis
National Drug Monograph
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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

- Abrocitinib is a Janus kinase inhibitor (JAKI) selective for JAK1.[1]
- It is one of the first two JAKIs approved for the systemic treatment of atopic dermatitis.

Indication Under Review in This Document

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

Dosage and Administration

Pretreatment Tests

- Tuberculosis, viral hepatitis screening, complete blood count (CBC). Obtaining a baseline lipid panel is not a recommendation in the US Prescribing Information but may be considered.
- Use of abrocitinib is not recommended in patients with platelet count < 150,000/mm^3, absolute lymphocyte count < 500/mm^3, absolute neutrophil count < 1,000/mm^3, or hemoglobin < 8 g/dL.

Immunizations

- Guideline-recommended immunizations including herpes zoster vaccination should be completed before initiating abrocitinib therapy.

Recommended Dosage

- 100 mg orally once daily with or without food. If there is an inadequate response after 12 weeks, the dose can be increased to 200 mg once daily. Discontinue therapy if there is an inadequate response to 200 mg once daily.

Concomitant Therapy

- **Contraindications**: Antiplatelet therapy except for low-dose aspirin (≤ 81 mg daily) during the first 3 months of treatment.
- Can be used with or without topical corticosteroids.
- See Drug Interactions.

Dosage Adjustments

- Dose should be reduced in patients with renal impairment according to the US Prescribing Information. Not recommended in severe renal impairment (estimated glomerular filtration rate [eGFR] 15–29 mL/min) and end-stage renal disease (eGFR < 15 mL/min).

- Not recommended in patients with severe (Child-Pugh C) hepatic impairment. No dosage adjustment is recommended in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment.
- Dose should be reduced in patients who are known or suspected CYP2C19 poor metabolizers based on genotype or previous history or experience with other CYP2C19 substrates.
- Dose should be reduced in patients who are taking strong inhibitors of CYP2C19.
- Discontinuation or dosage adjustment of abrocitinib is recommended for hematologic abnormalities (refer to US Prescribing Information).

Tests During Treatment

- CBC 4 weeks after starting therapy and after dose increases to monitor for hematocytopenias, especially thrombocytopenia and lymphopenia.
- Lipids approximately 4 weeks after starting therapy then as per clinical guidelines for hyperlipidemia.
- HBV DNA, ALT, AST as per guideline recommendations to monitor for HBV reactivation.
- Screening for TB every year should be considered for patients in highly endemic areas for TB.

Dosage Forms Under Review

- Tablets: 50, 100, and 200 mg

Clinical Evidence Summary

Efficacy Considerations

- This review focuses on two phase 3 randomized clinical trials (RCTs, JADE COMPARE[2,3,4,5] and JADE DARE[6]) that compared abrocitinib with dupilumab, each in combination with topical therapy, in the treatment of adults with moderate to severe atopic dermatitis. One of these trials (JADE COMPARE) also included a placebo group. JADE EXTEND evaluated the efficacy and safety of abrocitinib in dupilumab responders and nonresponders from JADE COMPARE.[7]
- Abrocitinib monotherapy (200 mg or 100 mg) was shown to be superior to placebo in achieving Investigator's Global Assessment response (defined as a score of 0 / Clear or 1 / Almost Clear and ≥ 2-point improvement from baseline; IGA-0/1) and Eczema Area and Severity Index-75 (EASI-75) response at Week 12 in two phase 3 RCTs (JADE MONO-1 and JADE MONO-2). These studies involved adults and adolescents with moderate to severe AD who had an inadequate response to topical corticosteroids or topical calcineurin inhibitors[8,9] or needed systemic therapies for disease control[8] or had a history of receiving systemic therapies for AD or for whom topical therapies were inadvisable.[9] In pooled analyses that included JADE MONO-1 and JADE MONO-2 as well as a phase 2b trial, abrocitinib achieved rapid itch relief by Day 2 that was associated with improved quality of life and sleep and occurred partly independently of overall disease improvement.[10] In addition, clinically meaningful improvements in skin clearance, itch, and quality of life were achieved with abrocitinib vs placebo in both abrocitinib IGA-0/1 nonresponders and responders.[11]
- A phase 3, responder-enriched, induction, randomized withdrawal, and retreatment trial (JADE REGIMEN) showed that abrocitinib monotherapy (200 mg or 100 mg) significantly reduced the probability of flare relative to placebo during maintenance therapy with a dose-related effect.[12] The cumulative probability of flare was 18.9%, 42.6%, and 80.9% with abrocitinib 200 mg, 100 mg, and placebo, respectively. In patients who flared, rescue with abrocitinib 200 mg plus topical therapy recaptured EASI-75 response in each treatment group at 12 weeks: 55% in the abrocitinib 200 mg group, 74.5% in the 100-mg group, and 91.8% in the placebo group.
- A phase 2b RCT[13] and a phase 3 trial in adolescents aged 12 to 17 years (JADE TEEN)[14] supported the efficacy of abrocitinib in moderate to severe AD.

Active-controlled Randomized Clinical Trials

Table 1 Methods of Active-controlled Phase 3 RCT Evaluating Abrocitinib Combination Therapy

Topic	JADE COMPARE		JADE DARE	
Study Design	16-week phase 3 MN DB DD PC RCT Controlled for multiplicity using a sequential Bonferroni-based procedure Not powered for abrocitinib–dupilumab comparison		26-week phase 3 MN DB DD RCT Controlled for multiplicity using a sequential approach	
Major Entry Criteria	≥ 18 yo ≥ 1-y history of AD that was moderate to severe at baseline (IGA ≥ 3 on 0–4 scale; EASI ≥ 16 on 0–72 scale; ≥ 10% BSA; PPNRS ≥ 4 on 0–10 scale) Unresponsive to topical agents (≥ 4-wk trial) or needed systemic therapy		≥ 18 yo ≥ 6 mo diagnosis of chronic AD that was moderate to severe at baseline (same definition as in JADE COMPARE) Required systemic therapies for AD in the past year or had an inadequate response to topical therapies (≥ 4 wks) Excluded patients with prior JAKI, IL-4, or IL-13 antagonists including dupilumab	
Interventions	• Abrocitinib 100 mg PO QD • Abrocitinib 200 mg PO QD • Dupilumab 600 mg then 300 mg SC Q2W • Placebo All patients received ≥ 1 topical therapy (low- or medium-potency TCS, TCNI, TPDE4I)		• Abrocitinib 200 mg PO QD + dummy dupilumab SC • Dupilumab 600 mg SC then 300 mg Q2W + dummy abrocitinib PO Required standardized background TCS, TCNI, or PDE4I therapy and nonmedicated emollients. Continuation of low- or medium-potency TCSs were allowed. High-potency TCSs (for up to 2 wks) or systemic CSs (for up to 10 d) were allowed after Wk 4	
Maintenance Phase or Long-term Extension	12-week phase 3 extension RCT (JADE EXTEND) to evaluate abrocitinib 200 mg and 100 mg in dupilumab responders and nonresponders		—	
Primary Efficacy Measures	Week 12 IGA-0/1 response		Week-2 PPNRS-4 Week-4 EASI-90	
Baseline Patient Characteristics	N = 837 Age 37.7 y Male 48.9% White 72.4% Moderate / Severe 64.6% / 35.4% Asthma 33.9%	Food Allergy 14.9% Prior topical agents only 56.5% Prior systemic agents 43.2% Prior nonbiologic 41.0% Prior biologic 2.3% Used topical agents during study 94.0%	N = 727 Age 36.0 y Male 54% White / Asian / Black 71% / 19% / 7% Moderate / Severe 60% / 40%	Used topical agents during study 98%: TCS 95%, TCNI 20%, PDE4I 1.1%

EASI-75, ≥ 75% improvement from baseline on the Eczema Area and Severity Index (scale, 0–72); **IGA-0/1**, Investigator's Global Assessment score of 0 / Clear or 1 / Almost Clear (scale, 0–4) with change from baseline of ≥ 2 points; **PDE4I**, Phosphodiesterase-4 inhibitor; **TCNI**, Topical calcineurin inhibitor; PPNRS, Peak pruritus numerical rating scale; **TCS**, Topical corticosteroid

JADE COMPARE

- Selected efficacy data for JADE COMPARE are summarized in Table 2.

Table 2 Selected efficacy results for JADE COMPARE

Outcome	ABRO200	ABRO100	DUP	PBO
Primary Outcomes				
IGA-0/1 Response at Week 12, n/N (%)	106/219 (48.4)	86/235 (36.6)	88/241 (36.5)	18/129 (14.0)
Difference vs PBO (95% CI)	34.8 (26.1, 43.5)	23.1 (14.7, 31.4)	22.5 (14.2, 30.9)	REF
RR (95% CI) vs DUP	1.3 (1.1, 1.6)	1.0 (0.8, 1.3)	REF	NA
Difference vs DUP (95% CI)	11.9 (2.9, 20.7)	0.1 (–8.5, 8.7)	REF	NA
EASI-75 at Week 12, n/N (%)	154/219 (70.3)	138/235 (58.7)	140/241 (58.1)	35/129 (27.1)
Difference vs PBO (95% CI)	43.2 (33.7, 52.7)	31.9 (22.2, 41.6)	30.9 (21.2, 40.6)	REF
RR (95% CI) vs DUP	1.2 (1.1, 1.4)	1.0 (0.9, 1.2)	REF	NA
Difference vs DUP (95% CI)	12.2 (3.4, 20.7)	0.6 (–8.2, 9.4)	REF	NA
Secondary Outcomes				
PPNRS-4 Response at Week 2, n/N (%)	111/226 (49.1)	75/236 (31.8)	63/239 (26.4)	18/130 (13.8)
Difference vs PBO (95% CI)	34.9 (26.0, 43.7)	17.9 (9.5, 26.3)	12.5 (4.4, 20.7	REF
RR (95% CI) vs DUP	1.9 (1.5, 2.4)	1.2 (0.9, 1.6)	REF	NA
Difference vs DUP (95% CI)	22.1 (13.5, 30.7)	5.2 (–2.9, 13.4)	REF	NA
IGA-0/1 Response at Week 16, n/N (%)	105/221 (47.5)	80/230 (34.8)	90/232 (38.8)	16/124 (12.9)
Difference vs PBO (95% CI)	35.0 (26.3, 43.7)	22.1 (13.7, 30.5)	25.6 (17.1, 34.1)	REF
RR (95% CI) vs DUP	1.2 (1.0, 1.5)	0.9 (0.7, 1.1)	REF	NA
Difference vs DUP (95% CI)	9.4 (0.4, 18.5)	–3.5 (–12.2, 5.2)	REF	NA
EASI-75 Response at Week 16, n/N (%)	157/221 (71.0)	138/229 (60.3)	152/232 (65.5)	38/124 (30.6)
Difference vs PBO (95% CI)	40.4 (30.4, 50.4)	29.7 (19.5, 39.9)	34.7 (24.6, 44.8)	REF
RR (95% CI) vs DUP	1.1 (1.0, 1.2)	0.9 (0.8, 1.1)	REF	NA
Difference vs DUP (95% CI)	5.5 (–3.1, 14.1)	–5.1 (–13.9, 3.7)	REF	NA

Sources: 2, FDA Multi-discipline Review[15]
Bold blue values indicate significant treatment differences between abrocitinib and dupilumab.
ABRO, Abrocitinib; **CFB**, Change from baseline; **DUP**, Dupilumab 600 mg then 300 mg Q2W; **EASI-75**, ≥ 75% improvement on the Eczema Area and Severity Index; **IGA-0/1**, Investigator's Global Assessment of 0/Clear or 1/Almost Clear with change from baseline of ≥ 2 points; **PPNRS**-4 response, improvement of at least 4 points from baseline on the Peak Pruritus Numerical Rating Scale (range, 0–10)

Table 3 Absolute Effects for Achieving Selected Efficacy Outcomes for Abrocitinib 200 mg vs Dupilumab at Week 16, JADE COMPARE

Outcome Measure	AAE, per 1000 pts (95% CI)	NNT (95% CI)	Q
EASI-75 response	66 more (0 fewer, 131 more)	19 (NSD)	L[α]
PPNRS-4 response	237 more (132 more, 369 more)	5 (4, 7)	H

AAE, Anticipated absolute effect for achieving the outcome; **NNT**, Number needed to treat for one additional patient to benefit; **Q**, GRADE quality of evidence (H = High, L = Low)
[α] Downgraded for inconsistency (across timepoints at Week 12 and Week 16 and across similar outcome measures [EASI-75 and IGA-0/1]) and for imprecision (wide CIs, optimal information size not met)

  - The 95% CIs for the anticipated absolute effects include a worst case of no incremental EASI-75 benefit with abrocitinib 200 mg versus dupilumab.

- Other secondary efficacy results:
  - The median time to PPNRS-4 response was about 12 days, 29 days, and 30 days for abrocitinib 200 mg, 100 mg, and dupilumab, respectively, and not reached for placebo.
  - At Week 12, the probability of achieving PPNRS-4 response was about 75%, 65%, 62%, and 35% for abrocitinib 200 mg, dupilumab, abrocitinib 100, and placebo, respectively.

- At Week 16, the corresponding probability of achieving PPNRS-4 response was about 75%, 75%, 70%, and 48%, respectively, showing similar probabilities between abrocitinib and dupilumab at the later time point (Week 16).
- Abrocitinib was numerically better than dupilumab (and significantly better than placebo) in terms of achieving clinically meaningful patient-reported outcomes. At Week 16, the rates of achieving Patient-Oriented Eczema Measure scores < 3 (POEM-3) were 21.3% and 11.7% vs 12.4% and 4.8% for abrocitinib 200 mg and 100 mg vs dupilumab and placebo.[3] The corresponding percentages of patients that achieved ≥ 4-point improvement from baseline in the Dermatology Life Quality Index (DLQI-4) were 85.0% and 74.4% vs 83.4% and 59.7%, respectively.[3]

JADE DARE

- Selected efficacy outcomes for JADE DARE are shown in Table 4.

Table 4 Summary of Selected Efficacy Measures in JADE DARE

Outcome	ABRO200	DUP
Primary Outcomes		
PPNRS-4 at Week 2, n/N (%)	172/357 (48)	93/364 (26)
RR (95% CI) vs DUP	1.9 (1.5, 2.3)	REF
Difference vs DUP (95% CI)	22.6 (15.8, 29.5)	REF
EASI-90 at Week 4, n/N (%)	101/354 (29)	53/364 (15)
RR (95% CI) vs DUP	2.0 (1.5, 2.6)	REF
Difference vs DUP (95% CI)	14.1 (8.2, 20.0)	REF
Selected Secondary Outcome		
EASI-90 at Week 16	194/357 (54)	151/360 (42)
RR (95% CI) vs DUP	1.9 (1.6, 2.2)	REF
Difference vs DUP (95% CI)	12.5 (5.3, 19.7)	REF

Table 5 Absolute Effects for Achieving EASI-90 for Abrocitinib 200 mg vs Dupilumab at Week 16, JADE DARE

Outcome Measure	AAE, per 1000 pts (95% CI)	NNT (95% CI)	Q
EASI-90 response	377 (252, 503) more	4 (4, 6)	H

For abbreviations, see Table 3 footnotes.

- For the key secondary outcome of EASI-90 at Week 16, abrocitinib was both noninferior and significantly superior to dupilumab.
- Among patients who achieved EASI-90 for two consecutive visits, topical medications could be discontinued for a mean of 51 days (95% CI 46, 57) with abrocitinib 200 mg vs 33 days (28, 39) with dupilumab without losing EASI-90 response.
- Changes from baseline in Dermatology Life Quality Index (DLQI) scores were nominally better with abrocitinib than dupilumab at certain time points (Weeks 2, 12, 16, and 20) but the treatment differences decreased over time.
- Patient-Oriented Eczema Measure (POEM) scores showed a similar pattern to those seen with DLQI scores.

Onset of Treatment Benefit and Duration of an Adequate Therapeutic Trial

JADE COMPARE

- The onset of IGA-0/1 response and EASI-75 response effects (earliest significant treatment difference) between abrocitinib 200 mg or 100 mg and dupilumab could not be determined because statistical tests for significance were first performed only on multiplicity-adjusted results at Week 12.

- The duration of an adequate therapeutic trial (time to peak plateau) was 8 weeks for both IGA-0/1 response and EASI-75 response with both abrocitinib doses.[2] For dupilumab, the duration of an adequate trial was 16 weeks for IGA-0/1 response and ≥ 16 weeks for EASI-75 response.[2]
- In Kaplan-Meier analyses, abrocitinib 200 mg achieved complete or near complete control of signs and symptoms earlier than dupilumab.[4]
    - The median time to EASI-90 response was shortest for abrocitinib 200 mg: 59, 113, and 114 days for 200 mg, 100mg, and dupilumab, respectively.[4] The median time to EASI-90 response was not reached for placebo.
    - The median time to 0/No or 1/Very Minimal Itch on the PPNRS (PPNRS-0/1) was 86 and 116 days for abrocitinib 200 mg and dupilumab, respectively.[4] The median times were not reached for abrocitinib 100 mg and placebo.

JADE DARE

- A significant treatment difference in PPNRS-4 response occurred as early as Day 1.
- The duration of an adequate therapeutic trial was 8 weeks for PPNRS-4 response and 20 weeks for EASI-90 with abrocitinib 200 mg. The corresponding times for dupilumab were 16 weeks and ≥ 26 weeks, respectively.

Efficacy and Safety of Abrocitinib Based on Dupilumab Response: JADE EXTEND

- Of 223 patients randomized to dupilumab and switched to placebo for a 4-week washout (from Week 16 to Week 20) in JADE COMPARE, 203 (91.0%) entered JADE EXTEND and were rerandomized to abrocitinib 200 mg or abrocitinib 100 mg, each given once daily for 12 weeks to Week 32.
- As summarized below, abrocitinib at the higher and lower doses was able to achieve responses in substantial percentages of patients in dupilumab-exposed patients. Prior dupilumab nonresponders achieved lower response rates on abrocitinib than prior dupilumab responders.

Prior Dupilumab Responders

- Among 82 prior dupilumab IGA-0/1 responders, 25 (83.3%) of 30 patients on abrocitinib 200 mg and 40 (76.9%) of 52 patients on abrocitinib 100 mg achieved IGA-0/1 at Week 12 of JADE EXTEND.
- Among 115 prior dupilumab PPNRS-4 responders, 35 (89.7%) of 39 abrocitinib 200 mg patients and 62 (81.6%) of 76 abrocitinib 100 mg patients achieved PPNRS-4 response at Week 12.

Prior Dupilumab Nonresponders

- Among 107 prior dupilumab IGA-0/1 nonresponders, 17 (47.2%) of 36 abrocitinib 200 mg patients and 25 (35.2%) of 71 abrocitinib 100 mg patients achieved IGA-0/1 response at Week 12.
- Among 67 prior dupilumab PPNRS-4 nonresponders, 17 (77.3%) of 22 abrocitinib 200 mg patients and 17 (37.8%) of 45 abrocitinib 100 mg patients achieved PPNRS-4 at Week 12.

Durability of Response

- Long-term efficacy (> 1 year) was not assessed.

Safety Considerations

Safety Profile in US Prescribing Information

- **Boxed Warnings**: Serious infections, mortality, malignancy, major adverse cardiovascular events (MACE), and thrombosis. Current or past smokers are at additional increased risk of malignancies and MACE.
- **Contraindications**: Antiplatelet therapy except for low-dose aspirin (≤ 81 mg daily) during the first 3 months of treatment.
- **Other Warnings / Precautions**
    - *Serious infections*: Include tuberculosis and viral reactivation including herpes and hepatitis B. Not recommended in patients with active hepatitis B virus (HBV) or hepatitis C virus (HCV). Monitor patients with inactive HBV for expression of HBV DNa during therapy and consult a liver specialist if HBV DNA is detected.

- *Hematologic abnormalities*: Increased risks of thrombocytopenia and lymphopenia. Check CBC at baseline and at 4 weeks, and 4 weeks after dose increases.
- *Lipid elevations*: LDL, total cholesterol, and HDL. Hyperlipidemia-related adverse events occurred in 3 patients on abrocitinib 200 mg (2.0 per 100 patient-years) and in 1 patient on abrocitinib 100 mg (0.6 per 100 patient years). The effect of the lipid elevations on cardiovascular morbidity and mortality is unknown.[1]
- *Immunizations*: Avoid live vaccines immediately prior to, during, and immediately after abrocitinib therapy.

- **Most Common Adverse Events (≥ 5%)**: Nasopharyngitis, nausea, headache.
- **Other Adverse Events of Interest**: Acne, retinal detachment, creatine phosphokinase (CPK) elevations

Safety Results from JADE COMPARE

- **Deaths and Serious Adverse Events**: No deaths occurred. Serious adverse events occurred at similar rates across treatment groups: 0.9% (2/226), 2.5% (6/238), 0.8% (2/242), and 3.8% (5/131) for abrocitinib 200 mg, abrocitinib 100 mg, dupilumab, and placebo, respectively.
- **Serious Infections**: Three serious infections occurred in 2 patients (0.8%) in the abrocitinib 100-mg group. They were pneumonia (which led to treatment discontinuation) and oral herpes in one patient and infectious diarrhea in the second patient.
- **Discontinuations Due to Adverse Events**: The rates of discontinuations due to adverse events were similar across treatment groups.
- **Selected and Common Adverse Events (≥ 5% of Patients)**
  - The higher dose of abrocitinib (200 mg) tended to be associated with higher rates of adverse events, and abrocitinib tended to have higher rates of selected and common adverse events, with the exception that dupilumab had higher rates of conjunctivitis vs abrocitinib (Table 6).

Table 6 Selected and Common Adverse Events in Dupilumab-controlled Trials

	JADE COMPARE				JADE DARE	
Adverse Event	ABRO200 N = 226	ABRO100 N = 238	DUP N = 242	PBO N = 131	ABRO200 N = 362	DUP N = 365
Deaths, %	0.0	0.0	0.0	0.0	0.6	0.0
Serious Adverse Events, %	0.9	2.5	0.8	3.8	1.6	1.6
Serious Infections, %	0.0	0.8	0.0	0.0	—	—
Discontinuations Due to Adverse Events, %	4.4	2.5	3.3	3.8	3.3	2.0
Selected and Common Adverse Events (≥ 5%)						
Nausea	11.1	4.2	2.9	1.5	19.3	2.1
Acne / Folliculitis	6.6	2.9	1.2	0.0	12.9	3.0
Headache	6.6	4.2	5.4	4.6	12.9	6.5
Herpes zoster	1.8	0.8	0.0	0.0	2.4	0.5
Thrombocytopenia	0.9	0.0	0.0	0.0	—	—
Conjunctivitis	1.3	0.8	6.2	2.3	2.7	10.7

ABRO, Abrocitinib; **AE**, Adverse event; **DUP**, Dupilumab 600 mg then 300 mg Q2W; **TEAE**, Treatment-emergent adverse event

Drug Interactions

Affect Abrocitinib

- *Strong CYP2C19 inhibitors*: Increased exposure to abrocitinib and its two active metabolites, M1 and M2. Abrocitinib dosage reduction is recommended.
- *Moderate to strong inhibitors of both CYP2C19 and CYP2C9*: Increased exposure to abrocitinib and its two active metabolites, M1 and M2. Avoid concomitant use.
- *Strong CYP2C19 or CYP2C9 inducers*: Decreased exposure to abrocitinib and its two active metabolites. Avoid concomitant use.

Affect Other Drugs

- P-gp substrate where small changes in concentration may lead to serious or life-threatening toxicities: Increased exposure to P-gp substrate. E.g., digoxin. Monitor or dose titrate P-gp substrate.
- *Antiplatelets*: May increase risk of bleeding with thrombocytopenia. Contraindicated except for low-dose aspirin (≤ 81 mg daily) during the first 3 months of abrocitinib therapy.

Evidence Gaps

- Hospitalization or readmission
- Patient Satisfaction (especially between oral abrocitinib and subcutaneously injected dupilumab)

Network Meta-analyses (NMAs)

- Three NMAs published in 2022 have included abrocitinib studies, including two that evaluated comparative efficacy and safety[16,17](Table 7) and one that evaluated only the comparative safety of abrocitinib.[18]
- Outcomes were measured at 12–16 weeks[16] and 8–16 weeks[17] in the efficacy-safety NMAs and 12–40 weeks in the safety NMA.[18]

Table 7 Summary of Efficacy and Safety Network Meta-analyses Comparing Abrocitinib with Other Targeted Therapies

Comparison	NMA Estimate			
	Efficacy Outcomes		Safety Outcomes	
Wan, et al. (2022)[16]	**EASI, OR (95% CI)**	**IGA, OR (95% CI)**	**TEAEs, OR (95% CI)**	
Abrocitinib vs baricitinib	**1.92 (1.03, 3.57)***	1.48 (0.79, 3.02)	**2.20 (1.37, 3.89)**	
Abrocitinib vs upadacitinib	**0.41 (0.23, 0.75)**	**0.32 (0.18, 0.67)**	1.51 (0.89, 2.65)	
Drucker, et al. (2022)[17]	**CFB in EASI, MD (95% CrI) Q**	**CFB in POEM, SMD (95% CrI) Q**	**SAE, OR (95% CI)**	**DAE, OR (95% CI)**
Abrocitinib 100 mg vs 200 mg	**–4.3 (–6.0, –2.7) H**	**–3.2 (–4.2, –2.2) H**	1.9 (0.9, 4.2) VL	1.1 (0.6, 1.8) L
Abrocitinib 100 mg vs baricitinib 2 mg	**3.1 (0.5, 5.6) H***	1.2 (–0.4, 2.7) M	2.7 (0.9, 8.3) VL	0.9 (0.3, 2.5) VL
Abrocitinib 100 mg vs baricitinib 4 mg	1.1 (–1.6, 3.7) M	–0.5 (–2.1, 1.1) H	1.7 (0.6, 5.1) VL	0.5 (0.2, 1.3) VL
Abrocitinib 100 mg vs dupilumab	**–2.1 (–4.1, –0.3) H**	**–2.3 (–3.5, –1.2) H**	2.6 (1.1, 6.4) L	0.8 (0.4, 1.7) L
Abrocitinib 100 mg vs tralokinumab	1.4 (–1.1, 3.9) M	0.4 (–1.1, 1.8) H	1.7 (0.7, 4.7) VL	0.8 (0.3, 2.0) VL
Abrocitinib 100 mg vs upadacitinib 15 mg	–2.3 (–4.7, 0.1) H	–2 (–6.3, 2.2) M	1.8 (0.7, 4.8) VL	1.3 (0.6, 3.0) VL
Abrocitinib 100 mg vs upadacitinib 30 mg	**–4.9 (–7.2, –2.6) H**	**–5.6 (–10.0, –1.5) H**	1.8 (0.7, 5.0) VL	1.0 (0.5, 2.3) VL
Abrocitinib 200 mg vs baricitinib 2 mg	**7.4 (4.8, 9.9) H***	**4.4 (2.9, 5.9) H***	1.4 (0.5, 4.6) VL	0.9 (0.3, 2.4) VL
Abrocitinib 200 mg vs baricitinib 4 mg	**5.4 (2.7, 8.0) H***	**2.7 (1.2, 4.3) H***	0.9 (0.3, 2.9) VL	0.5 (0.2, 1.3) VL
Abrocitinib 200 mg vs dupilumab	**2.2 (0.2, 4.0) H***	0.9 (–0.2, 2.0) H	1.4 (0.5, 3.6) VL	0.8 (0.3, 1.6) VL
Abrocitinib 200 mg vs tralokinumab	**5.7 (3.2, 8.2) H***	**3.6 (2.1, 5.0) H***	0.9 (0.3, 2.7) VL	0.8 (0.3, 1.9) VL
Abrocitinib 200 mg vs upadacitinib 15 mg	2.0 (–0.3, 4.3) M	1.2 (–3, 5.4) M	0.9 (0.3, 2.7) VL	1.2 (0.5, 2.9) VL
Abrocitinib 200 mg vs upadacitinib 30 mg	–0.6 (–2.9, 1.7) H	–2.4 (–6.7, 1.7) M	1.0 (0.3, 2.8) VL	1.0 (0.4, 2.2) VL

Bold blue text indicates significant treatment difference. **Bold blue asterisk (*)** indicates that the result favors abrocitinib.
Q, GRADE quality of evidence (H = High, M = Moderate, L = Low, VL = Very low)

Table 8 SUCRA rankings for Change from baseline in EASI

Rank	Intervention	SUCRA
1	Upadacitinib 30 mg	0.95
2	**Abrocitinib 200 mg**	0.94
3	Upadacitinib 15	0.87
4	Dupilumab	0.86
5	**Abrocitinib 100 mg**	0.76
6	Baricitinib 4 mg	0.70
7	Tralokinumab	0.68
8	Baricitinib 2 mg	0.55

Source: 17
SUCRA, Surface under the cumulative ranking curve (range, 0–100)

- The safety NMA included 18 RCTs that compared JAKIs with placebo (K = 17) or dupilumab (K = 2).
    - For both serious adverse events and discontinuations due to adverse events, no significant differences were shown between abrocitinib and each of baricitinib, upadacitinib, or dupilumab.
    - Relative to the US-approved JAKIs included in the NMA, dupilumab was the safest treatment, and upadacitinib second safest, in terms of serious adverse events, discontinuations due to adverse events, serious infections, and herpes zoster.
    - Upadacitinib was safest for *any infection*.
    - An NMA could not be performed for *any cardiac or vascular disorder* because of an insufficient number of events.

Table 9 Other Considerations About the Network Meta-analyses

Consideration	Wan, et al. (2022)	Drucker, et al. (2022)	Alves, et al. (2022)
Heterogeneity Among Trials	Unable to assess	Not reported	Identified except for *any adverse effects* data
Evidence of Violation of Transitivity Assumptions	Not mentioned	Not mentioned	Not mentioned
Limitations	Short-term data Included a SRMA[18] and 4 RCTs of abrocitinib[2,8,9,13] Only included placebo-controlled RCTs for oral JAKIs	Short-term data Included 3 abrocitinib RCTs[2,8,9]	Short-term data Included 1 abrocitinib RCT[12]
Funding by Mfr	No	No	Not reported
Author(s) COI with Pfizer	No	Yes	No

Other Therapeutic Options

- Systemic treatments for moderate to severe atopic dermatitis include phototherapy, conventional immunomodulators (e.g., cyclosporine, azathioprine, mycophenolate, and methotrexate), and targeted biologic immunomodulators such as dupilumab and tralokinumab-ldrm.
- For treatment of refractory moderate to severe atopic dermatitis, the only other option is upadacitinib, another JAKI with the same FDA approved indication as abrocitinib (Table 10).
- No evidence-based society guidelines include recommendations for abrocitinib in the management of atopic dermatitis.

Table 10 Treatment Alternatives for Moderate to Severe Atopic Dermatitis Inadequately Responding to Other Systemic Drugs

Drug	Formulary Status / CFU Place in Therapy	Safety Considerations	Other Considerations
Abrocitinib	TBD / TBD	*Contraindications*: Antiplatelets except for low-dose aspirin (≤ 81 mg/d) during the first 3 months of therapy. *Pretreatment Evaluations:* Unlike upadacitinib, has no recommendations to perform baseline hepatic tests and to verify pregnancy status. *Renal Impairment:* Unlike upadacitinib, use in severe renal impairment is not recommended, and dosage adjustment is recommended for mild and moderate renal impairment. *Drug Interactions:* Greater number than and different from those for upadacitinib (see text). *Laboratory Monitoring During Therapy*: Unlike upadacitinib, abrocitinib has a recommendation to check **CBC** 4 weeks after treatment initiation and 4 weeks after dose increases. **Lipid panel** should be checked 4 weeks vs 12 weeks after starting therapy with abrocitinib vs upadacitinib, respectively, then as per clinical guidelines on hyperlipidemia.	*Head-to-head Trials*: Depending on the dose, abrocitinib may be better than or similar to dupilumab in improving itch and inconsistently better than or similar to dupilumab for skin outcomes.[19] *Other Indications*: None. *TCS-sparing Effects*: Lacks evidence.
Upadacitinib	NonF, CFU / After dupilumab OR tralokinumab-ldrm	*Contraindications*: Hypersensitivity. [Unlike with abrocitinib, antiplatelet therapies are allowable in the first 3 months.] *Pretreatment Evaluations:* Similar to those for abrocitinib except baseline hepatic tests and verification of pregnancy status are recommended. *Renal Impairment:* Can be used in severe renal impairment with dosage adjustment. Not recommended in end-stage renal disease. No dosage adjustments for mild and moderate renal impairment. *Warnings*: Similar to those for abrocitinib except upadacitinib has GI perforations and liver enzyme elevations. *Drug Interactions*: CYP3A4 inhibitors (adjust dose with upadacitinib 15 mg; avoid with 30 mg). CYP3A4 inducers (avoid co-use). *Laboratory Monitoring During Therapy*: CBC and liver enzymes as per routine patient management. Lipid panel 12 weeks after starting therapy then as per hyperlipidemia clinical guidelines.	*Head-to-head Trials*: Superior to dupilumab in improving skin and itch. *Other Indications*: Rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, ankylosing spondylitis, nonradiographic axial spondylo-arthritis. *TCS-sparing Effects*: Yes.

AD, Atopic dermatitis; **CFU**, Criteria for Use; **TBD**, To be decided; **TCS**, Topical corticosteroid

Projected Place in Therapy

- **Potential Place in Therapy Based on the Evidence**. Low- to high-quality evidence from two active-controlled trials showed that, in patients with moderate to severe atopic dermatitis who had an inadequate response to topical medications or needed systemic therapy for disease control, abrocitinib 200 mg was consistently better and faster-acting than dupilumab particularly in achieving PPNRS-4 (itch) responses, inconsistently better in achieving EASI-75 responses, but generally more likely to cause adverse events. Abrocitinib 100 mg was similar to dupilumab in IGA-0/1, EASI-75, and PPNRS-4 efficacy. The 200-mg dose of abrocitinib was numerically more effective than the 100-mg dose but more likely to cause safety issues; hence, the recommended dosage starts with the 100-mg dose. While a substantial percentage of dupilumab nonresponders will respond to abrocitinib 100 mg, higher response rates will likely to be achieved with the 200-mg dose. Notably, the majority of dupilumab PPNRS-4 (itch) nonresponders achieve response after switching to abrocitinib. Findings of network meta-analyses suggest that abrocitinib 200 mg may be similar in effectiveness to upadacitinib (15 and 30 mg; moderate to high certainty of evidence) and more effective than tralokinumab (high certainty evidence). In contrast,

abrocitinib 100 mg may be less effective than dupilumab (high certainty of evidence) and upadacitinib 30 mg (high certainty evidence) and similar in effectiveness to tralokinumab (moderate certainty evidence) and upadacitinib 15 mg (moderate to high certainty evidence).

- **Potential Place in Therapy in VHA**. Abrocitinib may be an alternative to (at the same level as) upadacitinib, another JAKI, in patients with refractory, moderate to severe atopic dermatitis who have an inadequate response to other systemic drug products, including biologics, or when they are medically inadvisable. Issues for consideration when choosing between abrocitinib and upadacitinib include a contraindication with antiplatelets other than low-dose aspirin in the first 3 months of therapy, more limitations for use in patients with renal impairment, additional CBC monitoring, and a greater number of drug interactions with abrocitinib. Furthermore, the lower dose of abrocitinib (100 mg) may be less effective than the higher dose of upadacitinib (300 mg).

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