Janus Kinase Inhibitors

e-Table 11. Upadacitinib Monotherapy (15 mg) GRADE Summary of Findings (Short-term)

Upadacitinib 15mg daily monotherapy compared to Placebo short-term

Patient or population: Adolescents and adults aged 12+ with moderate to severe atopic dermatitis short-term
Intervention: Upadacitinib 15mg daily monotherapy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo	**Risk with Upadacitinib 15mg daily monotherapy**				
IGA (0,1) follow-up: 16 weeks CRITICAL	63 per 1,000	**415 per 1,000** (301 to 571)	**RR 6.55** (4.75 to 9.02)	1199 (3 RCTs)[1, 2]	⨁⨁⨁⨁ High	
EASI75 follow-up: 16 weeks CRITICAL	145 per 1,000	**639 per 1,000** (522 to 783)	**RR 4.41** (3.60 to 5.40)	1199 (3 RCTs)[1, 2]	⨁⨁⨁⨁ High	
Pruritus improvement assessed with: ≥ 4-point improvement in patients with baseline NRS score of 4+ follow-up: 16 weeks	102 per 1,000	**470 per 1,000** (365 to 608)	**RR 4.63** (3.59 to 5.99)	1157 (3 RCTs)[1, 2]	⨁⨁⨁⨁ High	
Discontinuation due to AEs follow-up: 16 weeks CRITICAL	45 per 1,000	**29 per 1,000** (15 to 55)	**RR 0.64** (0.34 to 1.22)	1198 (3 RCTs)[1, 2]	⨁⨁⨁⨁ High	
POEM assessed with: 4-point or more improvement in POEM total score, assessed in patients with a POEM total score of ≥4 at baseline follow-up: 16 weeks CRITICAL	257 per 1,000	**731 per 1,000** (551 to 970)	**RR 2.84** (2.14 to 3.77)	1090 (2 RCTs)[1]	⨁⨁⨁⨁ High	

Serious Adverse Events follow-up: 16 weeks CRITICAL	28 per 1,000	**20 per 1,000** (10 to 42)	**RR 0.71** (0.34 to 1.47)	1198 (3 RCTs)[1, 2]	⊕⊕⊕⊕ High
Flares assessed with: patients who initiated rescue medication follow-up: 16 weeks CRITICAL	453 per 1,000	**104 per 1,000** (77 to 131)	**RR 0.23** (0.17 to 0.29)	1116 (2 RCTs)[1]	⊕⊕⊕⊕ High
Quality of life assessed with: 4-point or more improvement in DLQI, assessed in patients aged ≥16 years with a DLQI score of ≥4 at baseline follow-up: 16 weeks CRITICAL	288 per 1,000	**737 per 1,000** (636 to 852)	**RR 2.56** (2.21 to 2.96)	1005 (2 RCTs)[1]	⊕⊕⊕⊕ High
EASI100 follow-up: 16 weeks INFORMATIVE	12 per 1,000	**134 per 1,000** (64 to 279)	**RR 11.45** (5.47 to 23.94)	1199 (3 RCTs)[1, 2]	⊕⊕⊕⊕ High
EASI90 follow-up: 16 weeks INFORMATIVE	65 per 1,000	**459 per 1,000** (335 to 628)	**RR 7.06** (5.15 to 9.66)	1199 (3 RCTs)[1, 2]	⊕⊕⊕⊕ High
Treatment-emergent AEs follow-up: 16 weeks INFORMATIVE	558 per 1,000	**614 per 1,000** (553 to 675)	**RR 1.10** (0.99 to 1.21)	1116 (2 RCTs)[1]	⊕⊕⊕◯ Moderate[a]
Serious Infections follow-up: 16 weeks INFORMATIVE	4 per 1,000	**5 per 1,000** (1 to 44)	**RR 1.31** (0.14 to 12.24)	1116 (2 RCTs)[1]	⊕⊕⊕⊕ High[b]
Upper Respiratory Tract Infection follow-up: 16 weeks INFORMATIVE	60 per 1,000	**81 per 1,000** (53 to 123)	**RR 1.35** (0.89 to 2.05)	1198 (3 RCTs)[1, 2]	⊕⊕⊕⊕ High
Any infection follow-up: 16 weeks INFORMATIVE	200 per 1,000	**428 per 1,000** (210 to 872)	**RR 2.14** (1.05 to 4.36)	82 (1 RCT)[2]	⊕⊕⊕◯ Moderate[c]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI). **CI:** confidence interval; **RR:** risk ratio

Explanations:

a. Wide CI consistent with no difference and meaningful harm (based on MID 10%).

b. Low equitable event rates in a robust sample.

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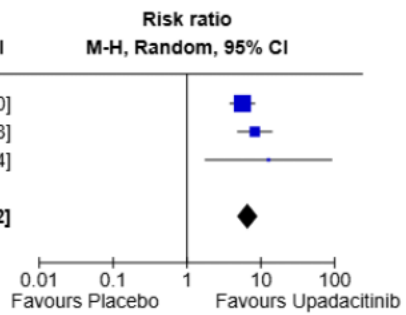
c. Very small sample leading to wide CI.

Analysis. IGA (0,1)

Study or Subgroup	Upadacitinib Events	Upadacitinib Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Random, 95% CI
Measure Up 1	135	281	24	281	63.6%	5.63 [3.77 , 8.40]
Measure Up 2	107	276	13	278	33.8%	8.29 [4.78 , 14.38]
NCT02925117	13	42	1	41	2.6%	12.69 [1.74 , 92.64]
Total (Wald[a])		**599**		**600**	**100.0%**	**6.55 [4.75 , 9.02]**
Total events:	255		38			

Test for overall effect: Z = 11.50 (P < 0.00001)



Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 1.71, df = 2 (P = 0.43); I² = 0%

Footnotes

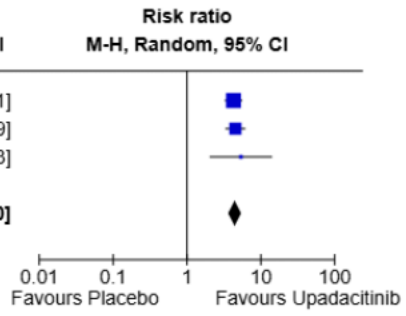
[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Analysis. EASI75

Study or Subgroup	Upadacitinib Events	Upadacitinib Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Random, 95% CI
Measure Up 1	196	281	46	281	54.2%	4.26 [3.24 , 5.61]
Measure Up 2	166	276	37	278	41.4%	4.52 [3.30 , 6.19]
NCT02925117	22	42	4	41	4.3%	5.37 [2.03 , 14.23]
Total (Wald[a])		**599**		**600**	**100.0%**	**4.41 [3.60 , 5.40]**
Total events:	384		87			

Test for overall effect: Z = 14.34 (P < 0.00001)



Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.24, df = 2 (P = 0.89); I² = 0%

Footnotes

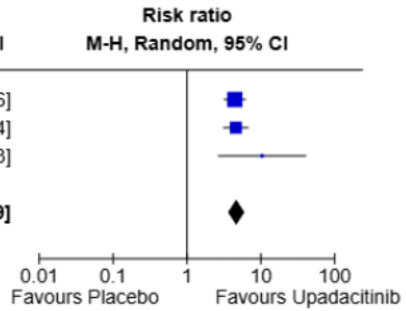
[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

13 *Analysis. Pruritus improvement*

Study or Subgroup	Upadacitinib Events	Upadacitinib Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Random, 95% CI
Measure Up 1	143	274	32	272	55.3%	4.44 [3.14 , 6.26]
Measure Up 2	113	270	25	274	41.2%	4.59 [3.08 , 6.84]
NCT02925117	19	32	2	35	3.5%	10.39 [2.62 , 41.13]
Total (Wald[a])		**576**		**581**	**100.0%**	**4.63 [3.59 , 5.99]**
Total events:	275		59			

Test for overall effect: Z = 11.72 (P < 0.00001)



Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 1.40, df = 2 (P = 0.50); I² = 0%

Footnotes

[a]CI calculated by Wald-type method.

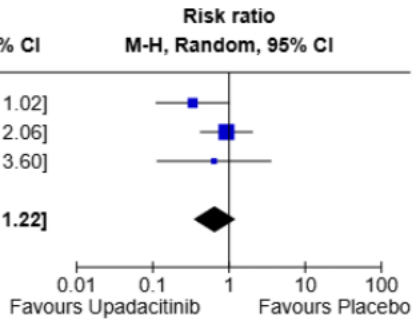
[b]Tau² calculated by DerSimonian and Laird method.

14

15 *Analysis. Discontinuations*

Study or Subgroup	Upadacitinib Events	Upadacitinib Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Random, 95% CI
Measure Up 1	4	281	12	281	30.5%	0.33 [0.11 , 1.02]
Measure Up 2	11	276	12	278	56.4%	0.92 [0.41 , 2.06]
NCT02925117	2	42	3	40	13.1%	0.63 [0.11 , 3.60]
Total (Wald[a])		**599**		**599**	**100.0%**	**0.64 [0.34 , 1.22]**
Total events:	17		27			

Test for overall effect: Z = 1.35 (P = 0.18)



Heterogeneity: Tau² (DL[b]) = 0.02; Chi² = 2.12, df = 2 (P = 0.35); I² = 6%

Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

16

17 *Analysis. POEM*

Study or Subgroup	Upadacitinib Events	Upadacitinib Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Random, 95% CI
Measure Up 1	209	278	63	276	48.4%	3.29 [2.62 , 4.13]
Measure Up 2	190	268	77	268	51.6%	2.47 [2.01 , 3.02]
Total (Wald[a])		**546**		**544**	**100.0%**	**2.84 [2.14 , 3.77]**
Total events:	399		140			

Test for overall effect: Z = 7.20 (P < 0.00001)

Heterogeneity: Tau² (DL[b]) = 0.03; Chi² = 3.47, df = 1 (P = 0.06); I² = 71%

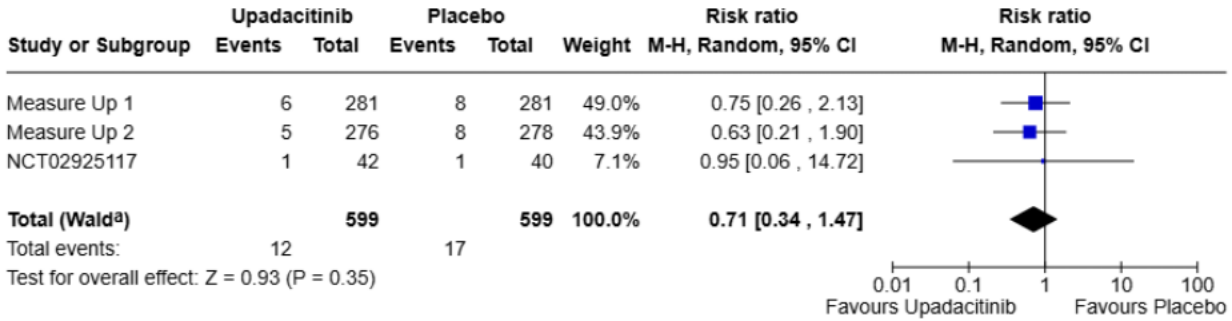
Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

18

19 *Analysis. Serious adverse events*



Study or Subgroup	Upadacitinib Events	Upadacitinib Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Random, 95% CI
Measure Up 1	6	281	8	281	49.0%	0.75 [0.26 , 2.13]
Measure Up 2	5	276	8	278	43.9%	0.63 [0.21 , 1.90]
NCT02925117	1	42	1	40	7.1%	0.95 [0.06 , 14.72]
Total (Wald[a])		**599**		**599**	**100.0%**	**0.71 [0.34 , 1.47]**
Total events:	12		17			

Test for overall effect: Z = 0.93 (P = 0.35)

Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.10, df = 2 (P = 0.95); I² = 0%

Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

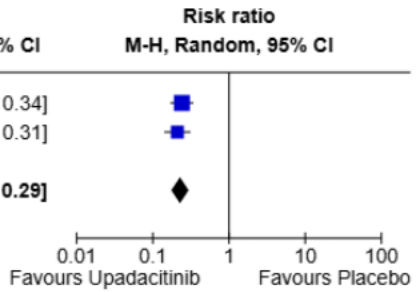
20

21

Analysis. Flare prevention

Study or Subgroup	Upadacitinib Events	Total	Placebo Events	Total	Weight	Risk ratio M-H, Random, 95% CI
Measure Up 1	32	281	133	281	56.5%	0.24 [0.17 , 0.34]
Measure Up 2	25	276	120	278	43.5%	0.21 [0.14 , 0.31]
Total (Wald[a])		**557**		**559**	**100.0%**	**0.23 [0.17 , 0.29]**
Total events:	57		253			

Test for overall effect: Z = 11.10 (P < 0.00001)



Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.26, df = 1 (P = 0.61); I² = 0%

Footnotes

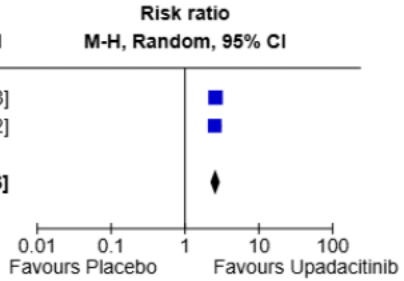
[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Analysis. Quality of life

Study or Subgroup	Upadacitinib Events	Total	Placebo Events	Total	Weight	Risk ratio M-H, Random, 95% CI
Measure Up 1	192	254	73	250	51.5%	2.59 [2.11 , 3.18]
Measure Up 2	180	251	71	250	48.5%	2.53 [2.04 , 3.12]
Total (Wald[a])		**505**		**500**	**100.0%**	**2.56 [2.21 , 2.96]**
Total events:	372		144			

Test for overall effect: Z = 12.49 (P < 0.00001)



Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.03, df = 1 (P = 0.87); I² = 0%

Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

References

1. Guttman-Yassky E, Teixeira HD, Simpson EL, Papp KA, Pangan AL, Blauvelt A et al. Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (Measure Up 1 and Measure Up 2): results from two replicate double-blind, randomised controlled phase 3 trials. Lancet 2021;397:2151-68.
2. Guttman-Yassky E, Thaçi D, Pangan AL, Hong HC, Papp KA, Reich K et al. Upadacitinib in adults with moderate to severe atopic dermatitis: 16-week results from a randomized, placebo-controlled trial. J Allergy Clin Immunol 2020;145:877-84.

e-Table 12. Upadacitinib Monotherapy (30 mg) GRADE Summary of Findings (Short-term)

Upadacitinib 30mg daily monotherapy compared to Placebo short-term

Patient or population: Adolescents and adults aged 12+ with moderate to severe atopic dermatitis short-term
Intervention: Upadacitinib 30mg daily monotherapy
Comparison: Placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo	**Risk with Upadacitinib 30mg daily monotherapy**				
IGA (0,1) follow-up: 16 weeks CRITICAL	63 per 1,000	**560 per 1,000** (386 to 813)	**RR 8.84** (6.09 to 12.84)	1209 (3 RCTs)[1,2]	⊕⊕⊕⊕ High	
EASI75 follow-up: 16 weeks CRITICAL	145 per 1,000	**754 per 1,000** (618 to 919)	**RR 5.20** (4.26 to 6.34)	1209 (3 RCTs)[1,2]	⊕⊕⊕⊕ High	
Pruritus improvement assessed with: ≥ 4-point improvement in patients with baseline NRS score of 4+ follow-up: 16 weeks CRITICAL	102 per 1,000	**690 per 1,000** (538 to 883)	**RR 6.79** (5.30 to 8.70)	1105 (3 RCTs)[1,2]	⊕⊕⊕⊕ High	
Discontinuation due to AEs follow-up: 16 weeks CRITICAL	45 per 1,000	**37 per 1,000** (21 to 64)	**RR 0.81** (0.46 to 1.41)	1208 (3 RCTs)[1,2]	⊕⊕⊕⊕ High	
POEM assessed with: ≥ 4-point improvement in patients with a POEM total score of ≥4 at	257 per 1,000	**824 per 1,000** (674 to 1,000)	**RR 3.20** (2.62 to 3.90)	1093 (2 RCTs)[1]	⊕⊕⊕⊕ High	

baseline follow-up: 16 weeks CRITICAL					
Serious Adverse Events follow-up: 16 weeks CRITICAL	28 per 1,000	**25 per 1,000** (13 to 49)	**RR 0.88** (0.45 to 1.74)	1208 (3 RCTs)[1, 2]	⨁⨁⨁⨁ High[a]
Flares assessed with: patients who initiated rescue medication follow-up: 16 weeks CRITICAL	453 per 1,000	**63 per 1,000** (45 to 86)	**RR 0.14** (0.10 to 0.19)	1126 (2 RCTs)[1]	⨁⨁⨁⨁ High
Quality of life assessed with: ≥ 4-point improvement in patients aged ≥16 years with a DLQI score of ≥4 at baseline follow-up: 16 weeks CRITICAL	288 per 1,000	**801 per 1,000** (694 to 924)	**RR 2.78** (2.41 to 3.21)	1007 (2 RCTs)[1]	⨁⨁⨁⨁ High
EASI100 follow-up: 16 weeks INFORMATIVE	12 per 1,000	**209 per 1,000** (101 to 432)	**RR 17.91** (8.67 to 37.01)	1209 (3 RCTs)[1, 2]	⨁⨁⨁⨁ High
EASI90 follow-up: 16 weeks INFORMATIVE	65 per 1,000	**598 per 1,000** (439 to 815)	**RR 9.20** (6.76 to 12.54)	1209 (3 RCTs)[1, 2]	⨁⨁⨁⨁ High
Treatment-emergent AEs follow-up: 16 weeks INFORMATIVE	558 per 1,000	**675 per 1,000** (614 to 742)	**RR 1.21** (1.10 to 1.33)	1126 (2 RCTs)[1]	⨁⨁⨁◯ Moderate[b]
Serious Infections follow-up: 16 weeks INFORMATIVE	4 per 1,000	**6 per 1,000** (1 to 29)	**RR 1.58** (0.31 to 8.16)	1126 (2 RCTs)[1]	⨁⨁⨁◯ Moderate[c]
Upper Respiratory Tract Infection follow-up: 16 weeks INFORMATIVE	60 per 1,000	**99 per 1,000** (66 to 146)	**RR 1.64** (1.10 to 2.43)	1208 (3 RCTs)[1, 2]	⨁⨁⨁⨁ High
Any infection follow-up: 16 weeks INFORMATIVE	200 per 1,000	**404 per 1,000** (196 to 832)	**RR 2.02** (0.98 to 4.16)	82 (1 RCT)[2]	⨁⨁⨁◯ Moderate[d]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI). **CI:** confidence interval; **RR:** risk ratio

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Explanations

a. Marginal imprecision (based on MID of 2%) with equitable event rates.

b. Wide CI consistent with no difference and meaningful harm (based on MID of 10%).

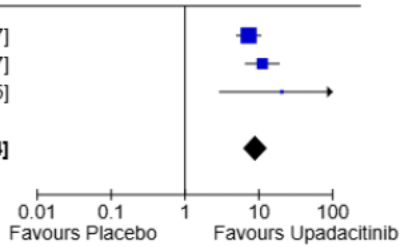
c. CI consistent with no difference and meaningful harm (based on MID of 2%).

d. Very small sample leading to wide CI.

Analysis. IGA (0,1)

Study or Subgroup	Upadacitinib Events	Upadacitinib Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Random, 95% CI
Measure Up 1	177	285	24	281	59.3%	7.27 [4.91 , 10.77]
Measure Up 2	147	282	13	278	37.2%	11.15 [6.48 , 19.17]
NCT02925117	21	42	1	41	3.5%	20.50 [2.89 , 145.45]
Total (Wald[a])		**609**		**600**	**100.0%**	**8.84 [6.09 , 12.84]**
Total events:	345		38			

Test for overall effect: Z = 11.46 (P < 0.00001)



Heterogeneity: Tau² (DL[b]) = 0.02; Chi² = 2.39, df = 2 (P = 0.30); I² = 16%

Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

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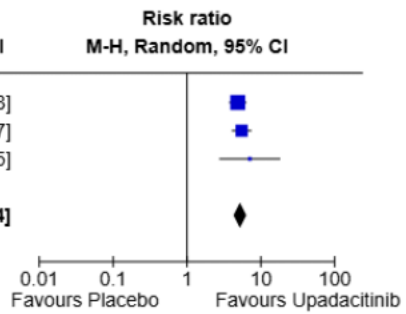
47 *Analysis. EASI75*

Study or Subgroup	Upadacitinib Events	Upadacitinib Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Random, 95% CI
Measure Up 1	227	285	46	281	54.0%	4.87 [3.71 , 6.38]
Measure Up 2	206	282	37	278	41.6%	5.49 [4.03 , 7.47]
NCT02925117	29	42	4	41	4.4%	7.08 [2.73 , 18.35]
Total (Wald[a])		**609**		**600**	**100.0%**	**5.20 [4.26 , 6.34]**
Total events:	462		87			

Test for overall effect: Z = 16.24 (P < 0.00001)



Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.76, df = 2 (P = 0.69); I² = 0%

Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

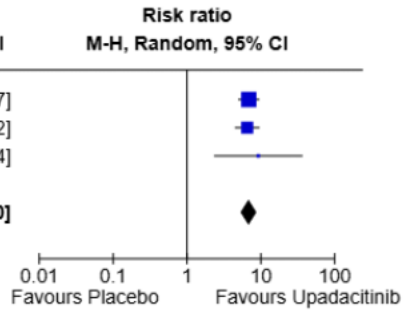
48

49

50 *Analysis. Pruritus improvement*

Study or Subgroup	Upadacitinib Events	Upadacitinib Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Random, 95% CI
Measure Up 1	168	208	32	272	55.6%	6.87 [4.93 , 9.57]
Measure Up 2	167	280	25	274	41.2%	6.54 [4.44 , 9.62]
NCT02925117	19	36	2	35	3.2%	9.24 [2.32 , 36.74]
Total (Wald[a])		**524**		**581**	**100.0%**	**6.79 [5.30 , 8.70]**
Total events:	354		59			

Test for overall effect: Z = 15.16 (P < 0.00001)



Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.23, df = 2 (P = 0.89); I² = 0%

Footnotes

[a]CI calculated by Wald-type method.

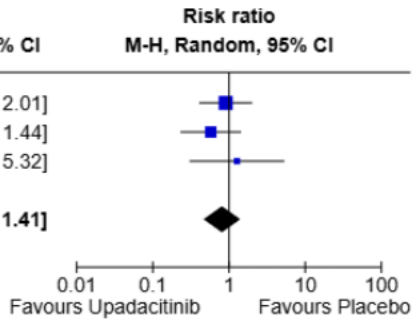
[b]Tau² calculated by DerSimonian and Laird method.

51

52 *Analysis. Discontinuations*

Study or Subgroup	Upadacitinib Events	Upadacitinib Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Random, 95% CI
Measure Up 1	11	285	12	281	48.2%	0.90 [0.41 , 2.01]
Measure Up 2	7	282	12	278	36.8%	0.58 [0.23 , 1.44]
NCT02925117	4	42	3	40	15.1%	1.27 [0.30 , 5.32]
Total (Wald[a])		**609**		**599**	**100.0%**	**0.81 [0.46 , 1.41]**
Total events:	22		27			

Test for overall effect: Z = 0.76 (P = 0.45)



Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.99, df = 2 (P = 0.61); I² = 0%

Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

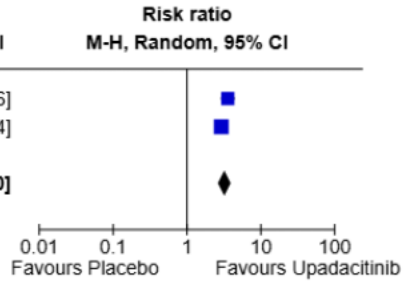
53

54

55 *Analysis. POEM*

Study or Subgroup	Upadacitinib Events	Upadacitinib Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Random, 95% CI
Measure Up 1	228	280	63	276	46.3%	3.57 [2.85 , 4.46]
Measure Up 2	225	269	77	268	53.7%	2.91 [2.39 , 3.54]
Total (Wald[a])		**549**		**544**	**100.0%**	**3.20 [2.62 , 3.90]**
Total events:	453		140			

Test for overall effect: Z = 11.43 (P < 0.00001)



Heterogeneity: Tau² (DL[b]) = 0.01; Chi² = 1.81, df = 1 (P = 0.18); I² = 45%

Footnotes

[a]CI calculated by Wald-type method.

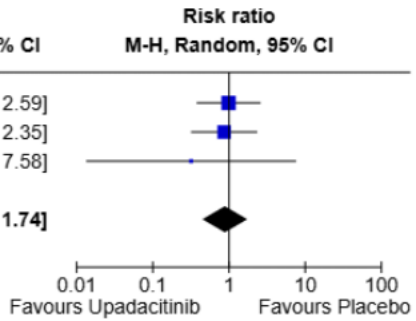
[b]Tau² calculated by DerSimonian and Laird method.

56

57 *Analysis. Serious adverse events*

Study or Subgroup	Upadacitinib Events	Upadacitinib Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Random, 95% CI
Measure Up 1	8	285	8	281	49.4%	0.99 [0.38 , 2.59]
Measure Up 2	7	282	8	278	46.0%	0.86 [0.32 , 2.35]
NCT02925117	0	42	1	40	4.6%	0.32 [0.01 , 7.58]
Total (Wald[a])		**609**		**599**	**100.0%**	**0.88 [0.45 , 1.74]**
Total events:	15		17			

Test for overall effect: Z = 0.37 (P = 0.71)



Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.45, df = 2 (P = 0.80); I² = 0%

Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

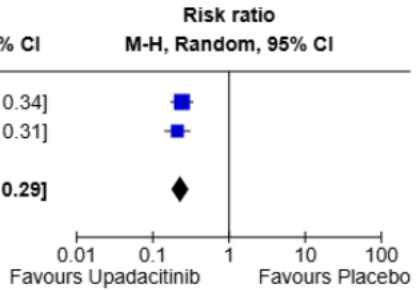
58

59

60 *Analysis. Flare prevention*

Study or Subgroup	Upadacitinib Events	Upadacitinib Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Random, 95% CI
Measure Up 1	32	281	133	281	56.5%	0.24 [0.17 , 0.34]
Measure Up 2	25	276	120	278	43.5%	0.21 [0.14 , 0.31]
Total (Wald[a])		**557**		**559**	**100.0%**	**0.23 [0.17 , 0.29]**
Total events:	57		253			

Test for overall effect: Z = 11.10 (P < 0.00001)



Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.26, df = 1 (P = 0.61); I² = 0%

Footnotes

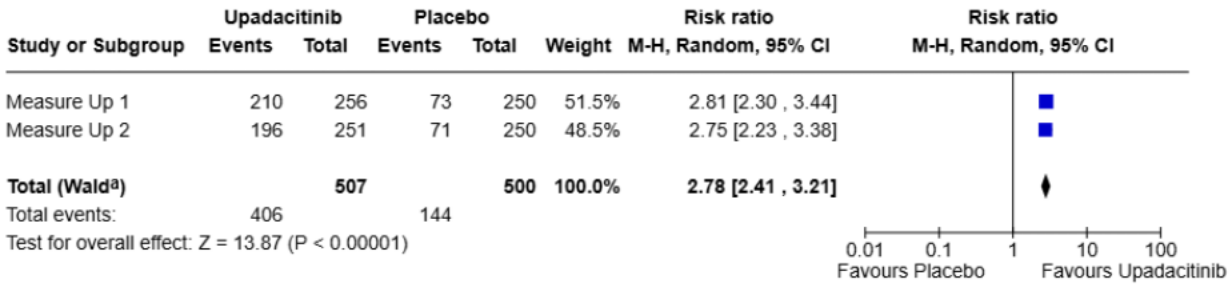
[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

61

62

Analysis. Quality of life



References

1. Guttman-Yassky E, Teixeira HD, Simpson EL, Papp KA, Pangan AL, Blauvelt A et al. Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (Measure Up 1 and Measure Up 2): results from two replicate double-blind, randomised controlled phase 3 trials. Lancet 2021;397:2151-68.
2. Guttman-Yassky E, Thaçi D, Pangan AL, Hong HC, Papp KA, Reich K et al. Upadacitinib in adults with moderate to severe atopic dermatitis: 16-week results from a randomized, placebo-controlled trial. J Allergy Clin Immunol 2020;145:877-84.

e-Table 13. Upadacitinib Combination Therapy (15 mg) GRADE Summary of Findings (Short-term)

Upadacitinib 15mg daily + TCS compared to Placebo + TCS short-term

Patient or population: Adolescents and adults aged 12+ with moderate to severe atopic dermatitis short-term
Intervention: Upadacitinib 15mg daily + TCS
Comparison: Placebo + TCS

Outcomes	**Anticipated absolute effects*** (95% CI)				Comments

	Risk with Placebo + TCS	Risk with Upadacitinib 15mg daily + TCS	Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	
IGA (0,1) follow-up: 16 weeks CRITICAL	99 per 1,000	**409 per 1,000** (266 to 627)	**RR 4.13** (2.69 to 6.33)	785 (2 RCTs)[1,2]	⊕⊕⊕⊕ High	
EASI75 follow-up: 16 weeks CRITICAL	246 per 1,000	**679 per 1,000** (490 to 940)	**RR 2.76** (1.99 to 3.82)	785 (2 RCTs)[1,2]	⊕⊕⊕⊕ High	
Pruritus improvement assessed with: ≥ 4-point improvement in patients with baseline NRS score of 4+ follow-up: 16 weeks CRITICAL	150 per 1,000	**518 per 1,000** (399 to 670)	**RR 3.46** (2.67 to 4.48)	758 (2 RCTs)[1,2]	⊕⊕⊕⊕ High	
Discontinuations due to AEs follow-up: 16 weeks CRITICAL	20 per 1,000	**15 per 1,000** (5 to 45)	**RR 0.74** (0.25 to 2.20)	784 (2 RCTs)[1,2]	⊕⊕⊕⊕ High	
Serious Adverse Events follow-up: 16 weeks CRITICAL	25 per 1,000	**21 per 1,000** (8 to 51)	**RR 0.81** (0.32 to 2.02)	784 (2 RCTs)[1,2]	⊕⊕⊕⊕ High[a]	
EASI90 follow-up: 16 weeks INFORMATIVE	117 per 1,000	**472 per 1,000** (256 to 873)	**RR 4.04** (2.19 to 7.48)	785 (2 RCTs)[1,2]	⊕⊕⊕⊕ High	
Treatment-emergent AEs follow-up: 16 weeks INFORMATIVE	511 per 1,000	**542 per 1,000** (486 to 614)	**RR 1.06** (0.95 to 1.20)	784 (2 RCTs)[1,2]	⊕⊕⊕⊕ High	
Serious Infections follow-up: 16 weeks INFORMATIVE	8 per 1,000	**8 per 1,000** (2 to 38)	**RR 1.01** (0.21 to 4.96)	784 (2 RCTs)[1,2]	⊕⊕⊕⊕ High[b]	
Upper respiratory tract infection follow-up: 16 weeks INFORMATIVE	73 per 1,000	**70 per 1,000** (39 to 125)	**RR 0.96** (0.54 to 1.72)	603 (1 RCT)[2]	⊕⊕⊕⊕ High	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI). **CI:** confidence interval; **RR:** risk ratio

Explanations

a. Equitable rates in moderate sample suggests safety.

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b. Results from a single trial are slightly imprecise, but a second trial reported no events in either arm; The totality of the evidence suggests no meaningful difference in rates.

References

1. Katoh N, Ohya Y, Murota H, Ikeda M, Hu X, Ikeda K et al. A phase 3 randomized, multicenter, double-blind study to evaluate the safety of upadacitinib in combination with topical corticosteroids in adolescent and adult patients with moderate-to-severe atopic dermatitis in Japan (Rising Up): An interim 24-week analysis. JAAD Int 2022;6:27-36.
2. Reich K, Teixeira HD, de Bruin-Weller M, Bieber T, Soong W, Kabashima K et al. Safety and efficacy of upadacitinib in combination with topical corticosteroids in adolescents and adults with moderate-to-severe atopic dermatitis (AD Up): results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2021;397:2169-81.

e-Table 14. Upadacitinib Combination Therapy (30 mg) GRADE Summary of Findings (Short-term)

Upadacitinib 30mg daily + TCS compared to Placebo + TCS short-term

Patient or population: Adolescents and adults aged 12+ with moderate to severe atopic dermatitis short-term
Intervention: Upadacitinib 30mg daily + TCS
Comparison: Placebo + TCS

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo + TCS	**Risk with Upadacitinib 30mg daily + TCS**				
IGA (0,1) follow-up: 16 weeks CRITICAL	99 per 1,000	**556 per 1,000** (408 to 758)	**RR 5.62** (4.12 to 7.66)	782 (2 RCTs)[1,2]	⊕⊕⊕⊕ High	
EASI75 follow-up: 16 weeks CRITICAL	246 per 1,000	**808 per 1,000** (588 to 1,000)	**RR 3.28** (2.39 to 4.51)	782 (2 RCTs)[1,2]	⊕⊕⊕⊕ High	
Pruritus improvement assessed with: ≥ 4-point improvement in patients with baseline NRS score of 4+ follow-up: 16 weeks CRITICAL	150 per 1,000	**601 per 1,000** (467 to 775)	**RR 4.02** (3.12 to 5.18)	757 (2 RCTs)[1,2]	⊕⊕⊕⊕ High	

Discontinuations due to AEs follow-up: 16 weeks CRITICAL	20 per 1,000	**13 per 1,000** (4 to 39)	**RR 0.64** (0.21 to 1.94)	781 (2 RCTs)[1,2]	⊕⊕⊕⊕ High
Serious Adverse Events follow-up: 16 weeks CRITICAL	25 per 1,000	**13 per 1,000** (4 to 38)	**RR 0.51** (0.17 to 1.50)	781 (2 RCTs)[1,2]	⊕⊕⊕⊕ High
EASI100 follow-up: 16 weeks INFORMATIVE	13 per 1,000	**226 per 1,000** (83 to 611)	**RR 17.14** (6.33 to 46.42)	601 (1 RCT)[2]	⊕⊕⊕⊕ High
EASI90 follow-up: 16 weeks INFORMATIVE	117 per 1,000	**591 per 1,000** (432 to 809)	**RR 5.06** (3.70 to 6.93)	785 (2 RCTs)[1,2]	⊕⊕⊕⊕ High
Treatment-emergent AEs follow-up: 16 weeks INFORMATIVE	511 per 1,000	**747 per 1,000** (404 to 1,000)	**RR 1.46** (0.79 to 2.70)	781 (2 RCTs)[1,2]	⊕⊕⊕◯ Moderate[a]
Serious Infections follow-up: 16 weeks INFORMATIVE	8 per 1,000	**5 per 1,000** (0 to 92)	**RR 0.62** (0.03 to 12.03)	781 (2 RCTs)[1,2]	⊕⊕⊕◯ Moderate[b]
Upper respiratory tract infections follow-up: 16 weeks INFORMATIVE	73 per 1,000	**78 per 1,000** (44 to 136)	**RR 1.07** (0.61 to 1.87)	600 (1 RCT)[2]	⊕⊕⊕⊕ High

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI). **CI:** confidence interval; **RR:** risk ratio

Explanations

a. CI consistent with meaningful benefit and harm (based on MID of 10%).

b. CI consistent with no difference and meaningful harm (based on MID of 2%).

References

1. Katoh N, Ohya Y, Murota H, Ikeda M, Hu X, Ikeda K et al. A phase 3 randomized, multicenter, double-blind study to evaluate the safety of upadacitinib in combination with topical corticosteroids in adolescent and adult patients with moderate-to-severe atopic dermatitis in Japan (Rising Up): An interim 24-week analysis. JAAD Int 2022;6:27-36.

2. Reich K, Teixeira HD, de Bruin-Weller M, Bieber T, Soong W, Kabashima K et al. Safety and efficacy of upadacitinib in combination with topical corticosteroids in adolescents and adults with moderate-to-severe atopic dermatitis (AD Up): results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2021;397:2169-81.

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e-Table 15. Abrocitinib Monotherapy (100 mg) GRADE Summary of Findings (Short-term)

Abrocitinib 100mg daily monotherapy compared to Placebo short-term

Patient or population: Adolescents and adults aged 12+ with moderate to severe atopic dermatitis short-term
Intervention: Abrocitinib 100mg daily monotherapy
Comparison: Placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo	**Risk with Abrocitinib 100mg daily monotherapy**				
IGA (0,1) follow-up: 12 weeks CRITICAL	78 per 1,000	**263 per 1,000** (159 to 433)	**RR 3.37** (2.04 to 5.55)	570 (3 RCTs)[1-3]	⨁⨁⨁◯ Moderate[a]	
EASI75 follow-up: 12 weeks CRITICAL	122 per 1,000	**413 per 1,000** (279 to 611)	**RR 3.39** (2.29 to 5.01)	570 (3 RCTs)[1-3]	⨁⨁⨁⨁ High	
Pruritus improvement Assessed with: ≥4-point improvement from baseline in PP-NRS score follow-up: 12 weeks CRITICAL	163 per 1,000	**416 per 1,000** (273 to 634)	**RR 2.56** (1.68 to 3.90)	559 (3 RCTs)[1-3]	⨁⨁⨁⨁ High	
Discontinuation due to Adverse Event follow-up: 12 weeks CRITICAL	123 per 1,000	**81 per 1,000** (33 to 193)	**RR 0.66** (0.27 to 1.57)	581 (3 RCTs)[1-3]	⨁⨁⨁◯ Moderate[b]	
POEM Assessed with: change from baseline follow-up: 12 weeks CRITICAL	MD **4.12 lower** (6.08 lower to 2.16 lower)		-	445 (2 RCTs)[2, 3]	⨁⨁⨁◯ Moderate[c]	
Serious Adverse Events follow-up: 12 weeks	26 per 1,000	**30 per 1,000** (9 to 96)	**RR 1.15** (0.36 to 3.71)	469 (2 RCTs)[2, 3]	⨁⨁⨁⨁ High	

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CRITICAL					
Quality of life Assessed with: DLQI mean score change from baseline follow-up: 12 weeks CRITICAL	MD **3.69 lower** (5.24 lower to 2.13 lower)		-	391 (2 RCTs)[2, 3]	⊕⊕⊕◯ Moderate[d]
EASI90 follow-up: 12 weeks INFORMATIVE	59 per 1,000	**215 per 1,000** (119 to 389)	**RR 3.68** (2.04 to 6.65)	570 (3 RCTs)[1-3]	⊕⊕⊕◯ Moderate[e]
Treatment-emergent Adverse Events follow-up: 12 weeks INFORMATIVE	555 per 1,000	**660 per 1,000** (560 to 777)	**RR 1.19** (1.01 to 1.40)	469 (2 RCTs)[2, 3]	⊕⊕⊕◯ Moderate[e]
Conjunctivitis Assessed with: participants with conjunctivitis follow-up: 12 weeks INFORMATIVE	0 per 1,000	**-- per 1,000** (0 to 0)	**RR 4.47** (0.24 to 82.01)	233 (1 RCT)[3]	⊕⊕⊕⊕ High
Nasopharyngitis Assessed with: participants with nasopharyngitis follow-up: 12 weeks INFORMATIVE	84 per 1,000	**136 per 1,000** (75 to 244)	**RR 1.62** (0.90 to 2.91)	469 (2 RCTs)[2, 3]	⊕⊕⊕◯ Moderate[b]
Upper respiratory tract infection Assessed with: participants with URTI follow-up: 12 weeks INFORMATIVE	62 per 1,000	**73 per 1,000** (37 to 145)	**RR 1.19** (0.60 to 2.35)	581 (3 RCTs)[1-3]	⊕⊕⊕⊕ High
Herpes Viral Infection Assessed with: participants with a herpes viral infection follow-up: 12 weeks INFORMATIVE	0 per 1,000	**-- per 1,000** (0 to 0)	**RR 5.46** (0.31 to 97.58)	233 (1 RCT)[3]	⊕⊕⊕⊕ High
Infections Assessed with: participants with any infection follow-up: 12 weeks	263 per 1,000	**411 per 1,000** (297 to 568)	**RR 1.56** (1.13 to 2.16)	345 (2 RCTs)[2, 3]	⊕⊕⊕◯ Moderate[b]

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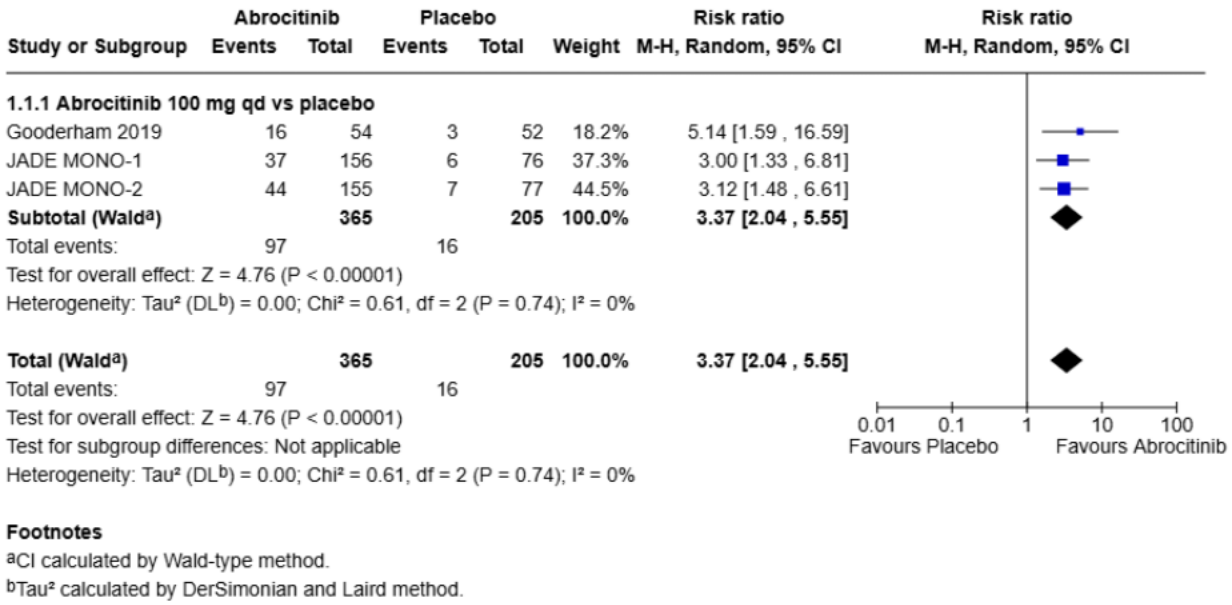
INFORMATIVE					
Folliculitis Assessed with: participants with folliculitis follow-up: 12 weeks INFORMATIVE	26 per 1,000	**3 per 1,000** (53 to --)	**RR 0.10** (0.00 to 2.05)	236 (1 RCT)[2]	⊕⊕⊕⊕ High

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

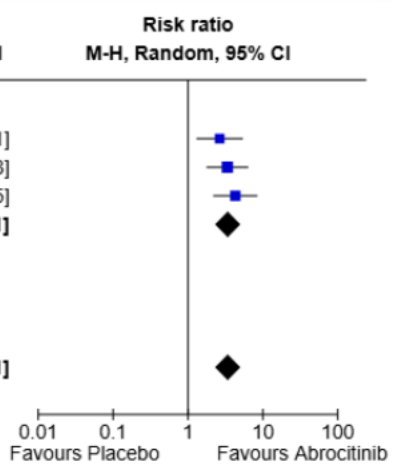
a Imprecision: Downgraded one level because the 95% CI for the absolute effect includes benefits smaller than the prespecified MCID (12%)
b Imprecision: Downgraded one level because the 95% CI includes effects both greater than and smaller than the prespecified MCID (10%)
c Imprecision: Downgraded one level because the 95% CI includes effects both greater than and smaller than the prespecified MCID (3.4 points)
d Imprecision: Downgraded one level because the 95% CI includes effects both greater than and smaller than the prespecified MCID (3.3 points)
e Imprecision: Downgraded one level because the 95% CI for the absolute effect includes benefits smaller than the prespecified MCID (10%)

Analysis. IGA (0,1)



Analysis. EASI75

Study or Subgroup	Abrocitinib Events	Abrocitinib Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Random, 95% CI
1.3.1 Abrocitinib 100 mg qd vs placebo						
Gooderham 2019	22	54	8	52	30.0%	2.65 [1.30 , 5.41]
JADE MONO-1	62	156	9	76	36.9%	3.36 [1.76 , 6.38]
JADE MONO-2	69	155	8	77	33.1%	4.28 [2.17 , 8.45]
Subtotal (Wald[a])		**365**		**205**	**100.0%**	**3.39 [2.29 , 5.01]**
Total events:	153		25			
Test for overall effect: Z = 6.12 (P < 0.00001)						
Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.94, df = 2 (P = 0.63); I² = 0%						
Total (Wald[a])		**365**		**205**	**100.0%**	**3.39 [2.29 , 5.01]**
Total events:	153		25			
Test for overall effect: Z = 6.12 (P < 0.00001)						
Test for subgroup differences: Not applicable						
Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.94, df = 2 (P = 0.63); I² = 0%						



Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

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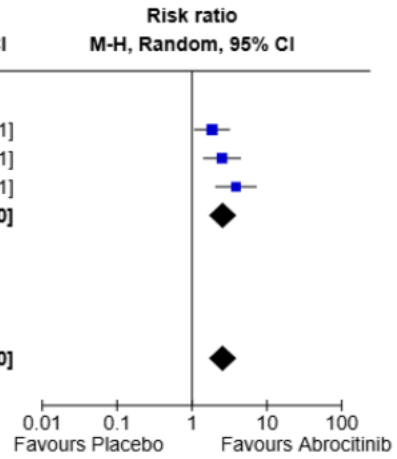
116 *Analysis. Pruritus improvement*

Study or Subgroup	Abrocitinib Events	Abrocitinib Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Random, 95% CI
1.4.1 Abrocitinib 100 mg qd vs placebo						
Gooderham 2019	25	54	13	52	36.3%	1.85 [1.07 , 3.21]
JADE MONO-1	55	147	11	74	33.7%	2.52 [1.40 , 4.51]
JADE MONO-2	70	155	9	77	30.0%	3.86 [2.04 , 7.31]
Subtotal (Wald[a])		**356**		**203**	**100.0%**	**2.56 [1.68 , 3.90]**
Total events:	150		33			
Test for overall effect: Z = 4.37 (P < 0.0001)						
Heterogeneity: Tau² (DL[b]) = 0.05; Chi² = 3.07, df = 2 (P = 0.22); I² = 35%						
Total (Wald[a])		**356**		**203**	**100.0%**	**2.56 [1.68 , 3.90]**
Total events:	150		33			
Test for overall effect: Z = 4.37 (P < 0.0001)						
Test for subgroup differences: Not applicable						
Heterogeneity: Tau² (DL[b]) = 0.05; Chi² = 3.07, df = 2 (P = 0.22); I² = 35%						



Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

117

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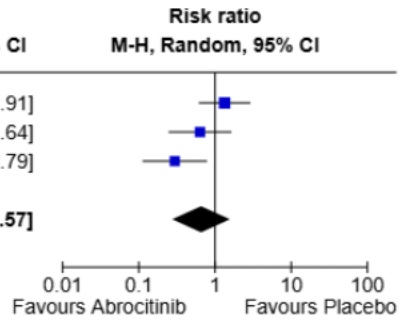
118 *Analysis. Discontinuations*

Study or Subgroup	Abrocitinib Events	Abrocitinib Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Random, 95% CI
Gooderham 2019	12	56	9	56	36.5%	1.33 [0.61 , 2.91]
JADE MONO-1	9	156	7	77	32.1%	0.63 [0.25 , 1.64]
JADE MONO-2	6	158	10	78	31.4%	0.30 [0.11 , 0.79]
Total (Wald[a])		**370**		**211**	**100.0%**	**0.66 [0.27 , 1.57]**
Total events:	27		26			

Test for overall effect: Z = 0.95 (P = 0.34)



Heterogeneity: Tau² (DL[b]) = 0.38; Chi² = 5.65, df = 2 (P = 0.06); I² = 65%

Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

119

120

121 *Analysis. POEM*

Study or Subgroup	Abrocitinib Mean	Abrocitinib SD	Abrocitinib Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean difference IV, Random, 95% CI
1.5.1 Abrocitinib 100 mg qd vs placebo								
JADE MONO-1	-6.8	7.512895	153	-3.7	7.877124	76	48.9%	-3.10 [-5.23 , -0.97]
JADE MONO-2	-8.7	7.181242	140	-3.6	7.439506	76	51.1%	-5.10 [-7.15 , -3.05]
Subtotal (Wald[a])			**293**			**152**	**100.0%**	**-4.12 [-6.08 , -2.16]**

Test for overall effect: Z = 4.12 (P < 0.0001)

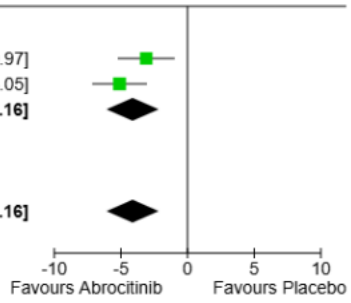
Heterogeneity: Tau² (REML[b]) = 0.86; Chi² = 1.75, df = 1 (P = 0.19); I² = 43%

Total (Wald[a])			**293**			**152**	**100.0%**	**-4.12 [-6.08 , -2.16]**

Test for overall effect: Z = 4.12 (P < 0.0001)

Test for subgroup differences: Not applicable

Heterogeneity: Tau² (REML[b]) = 0.86; Chi² = 1.75, df = 1 (P = 0.19); I² = 43%



Footnotes

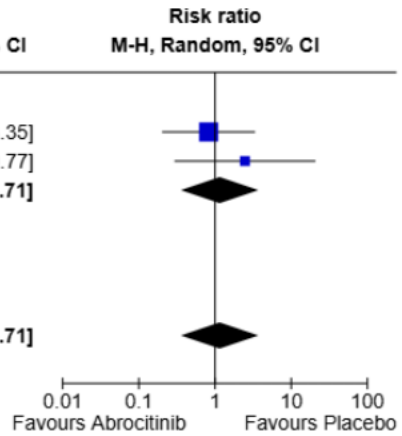
[a]CI calculated by Wald-type method.

[b]Tau² calculated by Restricted Maximum-Likelihood method.

122

123 *Analysis. Serious adverse events*

Study or Subgroup	Abrocitinib Events	Abrocitinib Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Random, 95% CI
1.7.1 Abrocitinib 100 mg qd vs placebo						
JADE MONO-1	5	156	3	77	69.7%	0.82 [0.20 , 3.35]
JADE MONO-2	5	158	1	78	30.3%	2.47 [0.29 , 20.77]
Subtotal (Wald[a])		**314**		**155**	**100.0%**	**1.15 [0.36 , 3.71]**
Total events:	10		4			
Test for overall effect: Z = 0.23 (P = 0.82)						
Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.73, df = 1 (P = 0.39); I² = 0%						
Total (Wald[a])		**314**		**155**	**100.0%**	**1.15 [0.36 , 3.71]**
Total events:	10		4			
Test for overall effect: Z = 0.23 (P = 0.82)						
Test for subgroup differences: Not applicable						
Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.73, df = 1 (P = 0.39); I² = 0%						



Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

124

125

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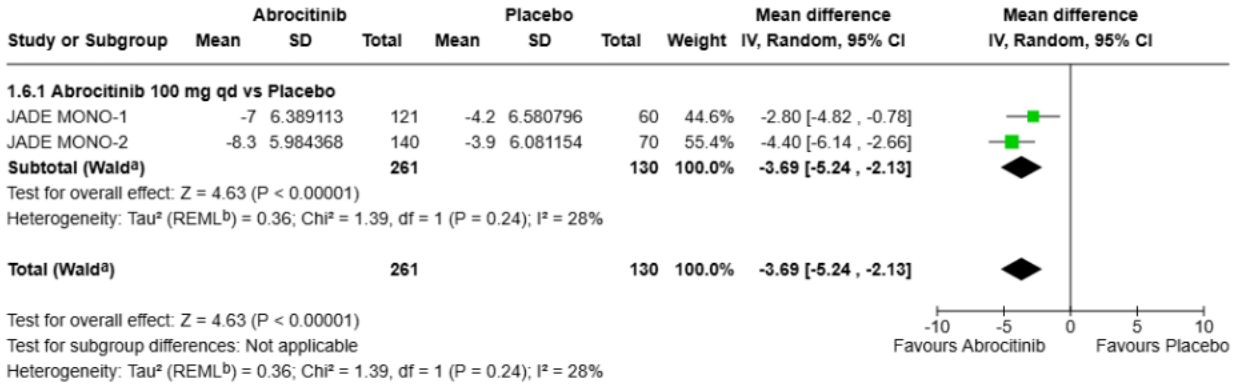
Analysis. Quality of life



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1. Gooderham MJ, Forman SB, Bissonnette R, Beebe JS, Zhang W, Banfield C et al. Efficacy and Safety of Oral Janus Kinase 1 Inhibitor Abrocitinib for Patients With Atopic Dermatitis: A Phase 2 Randomized Clinical Trial. JAMA Dermatol 2019;155:1371-9.
2. Silverberg JI, Simpson EL, Thyssen JP, Gooderham M, Chan G, Feeney C et al. Efficacy and Safety of Abrocitinib in Patients With Moderate-to-Severe Atopic Dermatitis: A Randomized Clinical Trial. JAMA Dermatol 2020;156:863-73.
3. Simpson EL, Sinclair R, Forman S, Wollenberg A, Aschoff R, Cork M et al. Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. Lancet 2020;396:255-66.

e-Table 16. Abrocitinib Monotherapy (200 mg) GRADE Summary of Findings (Short-term)

Abrocitinib 200mg daily monotherapy compared to Placebo short-term

Patient or population: Adolescents and adults aged 12+ with moderate to severe atopic dermatitis short-term
Intervention: Abrocitinib 200mg daily monotherapy
Comparison: Placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo	**Risk with Abrocitinib 200mg daily monotherapy**				
IGA (0,1) follow-up: 12 weeks CRITICAL	78 per 1,000	**405 per 1,000** (249 to 659)	**RR 5.19** (3.19 to 8.44)	561 (3 RCTs)[1-3]	⊕⊕⊕⊕ High	
EASI75 follow-up: 12 weeks CRITICAL	122 per 1,000	**621 per 1,000** (426 to 905)	**RR 5.09** (3.49 to 7.42)	560 (3 RCTs)[1-3]	⊕⊕⊕⊕ High	
Pruritus improvement Assessed with: PP-NRS, ≥4-point improvement from baseline in PP-NRS score follow-up: 12 weeks CRITICAL	163 per 1,000	**554 per 1,000** (359 to 852)	**RR 3.41** (2.21 to 5.24)	552 (3 RCTs)[1-3]	⊕⊕⊕⊕ High	
Discontinuation due to Adverse Event follow-up: 12 weeks CRITICAL	123 per 1,000	**68 per 1,000** (32 to 140)	**RR 0.55** (0.26 to 1.14)	575 (3 RCTs)[1-3]	⊕⊕⊕⊕ High	
POEM Assessed with: POEM, change from baseline follow-up: 12 weeks CRITICAL	MD **7.16 lower** (8.63 lower to 5.69 lower)		-	447 (2 RCTs)	⊕⊕⊕⊕ High	
Serious Adverse Events follow-up: 12 weeks	26 per 1,000	**22 per 1,000** (7 to 76)	**RR 0.87** (0.26 to 2.94)	464 (2 RCTs)	⊕⊕⊕⊕ High	

CRITICAL					
Quality of life Assessed with: DLQI, change from baseline follow-up: 12 weeks CRITICAL	MD **5.48 lower** (6.79 lower to 4.18 lower)		-	388 (2 RCTs)	⊕⊕⊕⊕ High
EASI90 follow-up: 12 weeks INFORMATIVE	59 per 1,000	**379 per 1,000** (215 to 670)	**RR 6.48** (3.67 to 11.44)	560 (3 RCTs)[1-3]	⊕⊕⊕⊕ High
Treatment-emergent Adverse Events follow-up: 12 weeks INFORMATIVE	555 per 1,000	**721 per 1,000** (616 to 843)	**RR 1.30** (1.11 to 1.52)	464 (2 RCTs)	⊕⊕⊕⊕ High
Conjunctivitis Assessed with: Participants with conjunctivitis follow-up: 12 weeks INFORMATIVE	0 per 1,000	**-- per 1,000** (0 to 0)	**RR 4.53** (0.25 to 83.06)	231 (1 RCT)	⊕⊕⊕⊕ High
Nasopharyngitis Assessed with: participants with nasopharyngitis follow-up: 12 weeks INFORMATIVE	84 per 1,000	**97 per 1,000** (52 to 180)	**RR 1.16** (0.62 to 2.15)	464 (2 RCTs)	⊕⊕⊕⊕ High
Upper respiratory tract infection Assessed with: participants with URTI follow-up: 12 weeks INFORMATIVE	62 per 1,000	**62 per 1,000** (31 to 122)	**RR 1.01** (0.51 to 1.98)	575 (3 RCTs)[1-3]	⊕⊕⊕⊕ High
Herpes Viral Infection Assessed with: participants with a herpes viral infection follow-up: 12 weeks INFORMATIVE	0 per 1,000	**-- per 1,000** (0 to 0)	**RR 4.53** (0.25 to 83.06)	231 (1 RCT)	⊕⊕⊕⊕ High
Infections	263 per 1,000	**389 per 1,000** (279 to 542)	**RR 1.48** (1.06 to 2.06)	342 (2 RCTs)	⊕⊕⊕⊕ High

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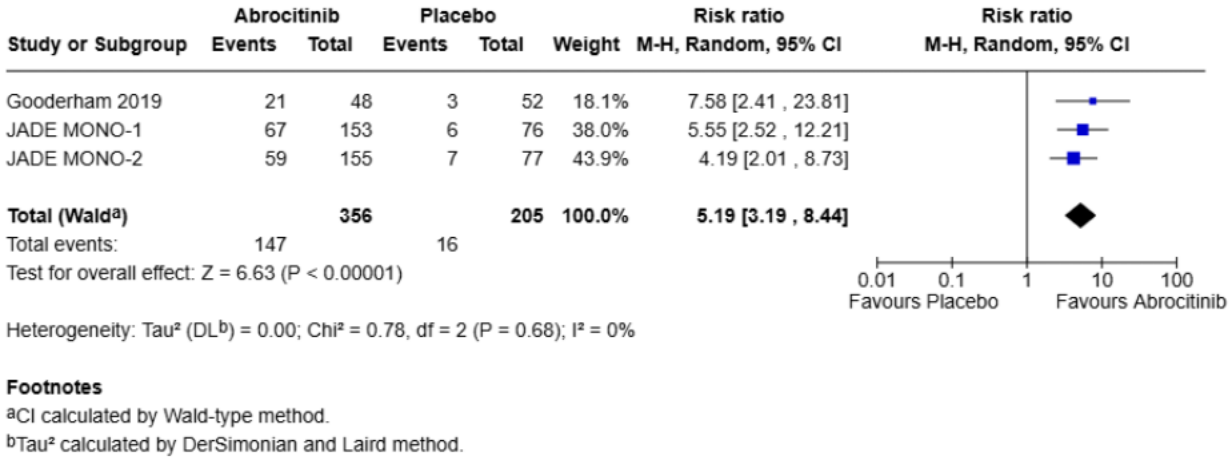
Assessed with: participants with any infection follow-up: 12 weeks INFORMATIVE					
Folliculitis Assessed with: participants with folliculitis follow-up: 12 weeks INFORMATIVE	26 per 1,000	**32 per 1,000** (6 to 163)	**RR 1.26** (0.25 to 6.34)	233 (1 RCT)	⨁⨁⨁⨁ High

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).**CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a.CI crosses the 10% MCID and includes both meaningful benefit and harm.

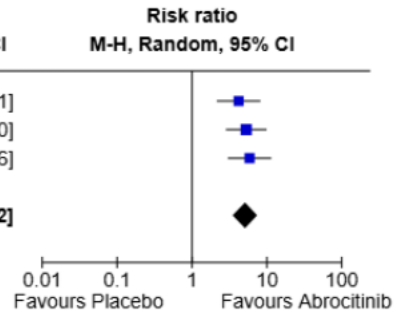
Analysis. IGA (0,1)



Analysis. EASI75

Study or Subgroup	Abrocitinib Events	Abrocitinib Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Random, 95% CI
Gooderham 2019	31	48	8	52	31.6%	4.20 [2.15 , 8.21]
JADE MONO-1	96	153	9	76	36.4%	5.30 [2.83 , 9.90]
JADE MONO-2	94	154	8	77	31.9%	5.88 [3.01 , 11.46]
Total (Wald[a])		**355**		**205**	**100.0%**	**5.09 [3.49 , 7.42]**
Total events:	221		25			

Test for overall effect: Z = 8.45 (P < 0.00001)



Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.53, df = 2 (P = 0.77); I² = 0%

Footnotes

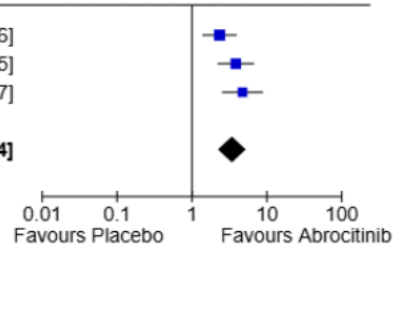
[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Analysis. Pruritus improvement

Study or Subgroup	Abrocitinib Events	Abrocitinib Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Random, 95% CI
Gooderham 2019	28	48	13	52	36.5%	2.33 [1.38 , 3.96]
JADE MONO-1	84	147	11	74	33.9%	3.84 [2.19 , 6.75]
JADE MONO-2	85	154	9	77	29.6%	4.72 [2.51 , 8.87]
Total (Wald[a])		**349**		**203**	**100.0%**	**3.41 [2.21 , 5.24]**
Total events:	197		33			

Test for overall effect: Z = 5.58 (P < 0.00001)



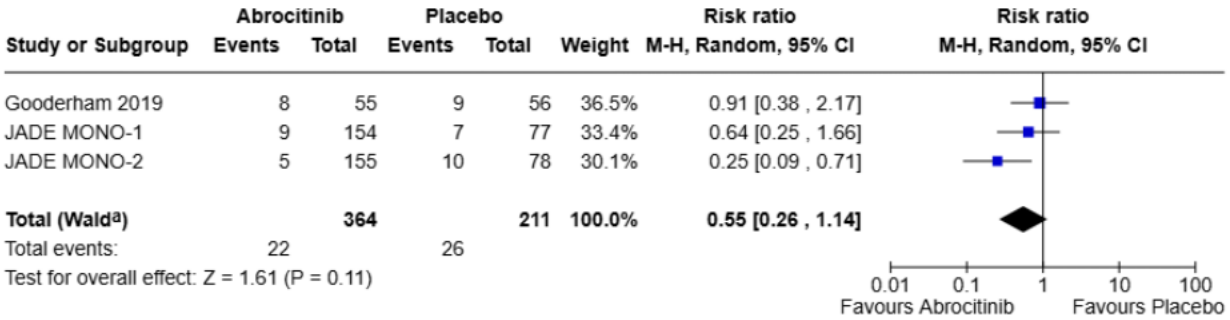
Heterogeneity: Tau² (DL[b]) = 0.06; Chi² = 3.40, df = 2 (P = 0.18); I² = 41%

Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

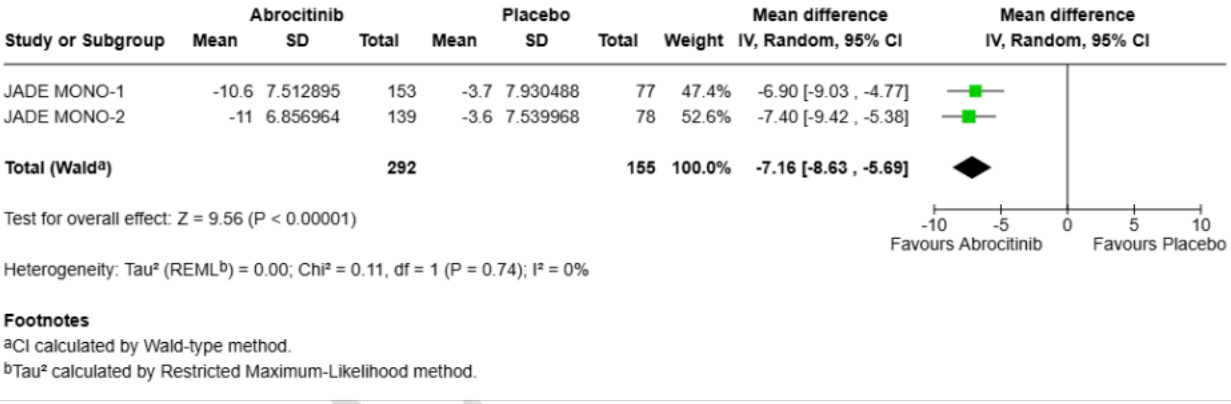
153 *Analysis. Discontinuations*



154

155

156 *Analysis. POEM*

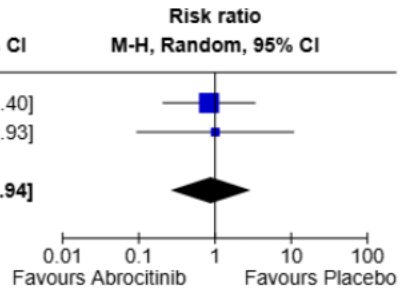


157

Analysis. Serious adverse events

Study or Subgroup	Abrocitinib Events	Abrocitinib Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Random, 95% CI
JADE MONO-1	5	154	3	77	74.2%	0.83 [0.20 , 3.40]
JADE MONO-2	2	155	1	78	25.8%	1.01 [0.09 , 10.93]
Total (Wald[a])		**309**		**155**	**100.0%**	**0.87 [0.26 , 2.94]**
Total events:	7		4			

Test for overall effect: Z = 0.22 (P = 0.83)



Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 0.02, df = 1 (P = 0.89); I² = 0%

Footnotes

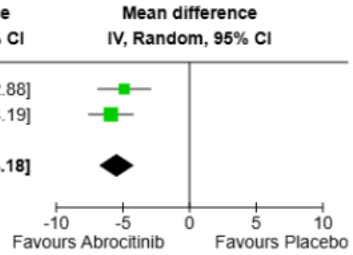
[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Analysis. Quality of life

Study or Subgroup	Abrocitinib Mean	Abrocitinib SD	Abrocitinib Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean difference IV, Random, 95% CI
JADE MONO-1	-9.1	6.334997	119	-4.2	6.580796	60	41.8%	-4.90 [-6.92 , -2.88]
JADE MONO-2	-9.8	5.664449	139	-3.9	6.081154	70	58.2%	-5.90 [-7.61 , -4.19]
Total (Wald[a])			**258**			**130**	**100.0%**	**-5.48 [-6.79 , -4.18]**

Test for overall effect: Z = 8.24 (P < 0.00001)



Heterogeneity: Tau² (REML[b]) = 0.00; Chi² = 0.55, df = 1 (P = 0.46); I² = 0%

Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by Restricted Maximum-Likelihood method.

References

1. Gooderham MJ, Forman SB, Bissonnette R, Beebe JS, Zhang W, Banfield C et al. Efficacy and Safety of Oral Janus Kinase 1 Inhibitor Abrocitinib for Patients With Atopic Dermatitis: A Phase 2 Randomized Clinical Trial. JAMA Dermatol 2019;155:1371-9.
2. Silverberg JI, Simpson EL, Thyssen JP, Gooderham M, Chan G, Feeney C et al. Efficacy and Safety of Abrocitinib in Patients With Moderate-to-Severe Atopic Dermatitis: A Randomized Clinical Trial. JAMA Dermatol 2020;156:863-73.
3. Simpson EL, Sinclair R, Forman S, Wollenberg A, Aschoff R, Cork M et al. Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. Lancet 2020;396:255-66.

e-Table 17. Abrocitinib Combination Therapy (100 mg) GRADE Summary of Findings (Short-term)

Abrocitinib 100mg daily + TCS compared to Placebo + TCS short-term[4]

Patient or population: Adolescents and adults aged 12+ with moderate to severe atopic dermatitis short-term
Intervention: Abrocitinib 100mg daily + TCS
Comparison: Placebo + TCS

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo + TCS	**Risk with Abrocitinib 100mg daily + TCS**				
IGA (0,1) follow-up: 16 weeks CRITICAL	129 per 1,000	**348 per 1,000** (213 to 568)	**RR 2.70** (1.65 to 4.40)	354 (1 RCT)	⨁⨁⨁⨁ High	
EASI75 follow-up: 16 weeks CRITICAL	306 per 1,000	**604 per 1,000** (454 to 800)	**RR 1.97** (1.48 to 2.61)	353 (1 RCT)	⨁⨁⨁⨁ High	

Pruritus improvement PP-NRS, ≥4-point improvement from baseline in PP-NRS score follow-up: 16 weeks CRITICAL	138 per 1,000	**318 per 1,000** (199 to 507)	**RR 2.30** (1.44 to 3.66)	366 (1 RCT)	⊕⊕⊕⊕ High
Discontinuation due to Adverse Event follow-up: 16 weeks CRITICAL	38 per 1,000	**25 per 1,000** (8 to 81)	**RR 0.66** (0.21 to 2.12)	369 (1 RCT)	⊕⊕⊕⊕ High
POEM Assessed with: POEM, change from baseline follow-up: 16 weeks CRITICAL	MD **4.2 lower** (5.76 lower to 2.64 lower)		-	366 (1 RCT)	⊕⊕⊕⊕ High
Serious Adverse Events follow-up: 16 weeks CRITICAL	23 per 1,000	**25 per 1,000** (6 to 99)	**RR 1.10** (0.28 to 4.33)	369 (1 RCT)	⊕⊕⊕⊕ High
Quality of life Assessed with: DLQI, change from baseline follow-up: 16 weeks CRITICAL	MD **2.8 lower** (3.9 lower to 1.7 lower)		-	369 (1 RCT)	⊕⊕⊕◯ Moderate[a]
EASI90 follow-up: 16 weeks INFORMATIVE	115 per 1,000	**378 per 1,000** (229 to 625)	**RR 3.30** (2.00 to 5.46)	369 (1 RCT)	⊕⊕⊕⊕ High
Treatment-emergent Adverse Events follow-up: 16 weeks INFORMATIVE	534 per 1,000	**508 per 1,000** (417 to 625)	**RR 0.95** (0.78 to 1.17)	369 (1 RCT)	⊕⊕⊕⊕ High
Conjunctivitis Assessed with: participants with conjunctivitis follow-up: 16 weeks INFORMATIVE	23 per 1,000	**8 per 1,000** (1 to 50)	**RR 0.37** (0.06 to 2.17)	369 (1 RCT)	⊕⊕⊕⊕ High
Nasopharyngitis	69 per 1,000	**93 per 1,000** (44 to 195)	**RR 1.35** (0.64 to 2.84)	369 (1 RCT)	⊕⊕⊕⊕ High

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Assessed with: participants with nasopharyngitis follow-up: 16 weeks INFORMATIVE					
Upper respiratory tract infection Assessed with: participants with URTI follow-up: 16 weeks INFORMATIVE	46 per 1,000	**50 per 1,000** (19 to 131)	**RR 1.10** (0.42 to 2.87)	369 (1 RCT)	⊕⊕⊕⊕ High
Herpes Viral Infection Assessed with: participants with a herpes viral infection follow-up: 16 weeks INFORMATIVE	0 per 1,000	**-- per 1,000** (0 to 0)	**RR 2.76** (0.13 to 57.09)	369 (1 RCT)	⊕⊕⊕⊕ High
Infections Assessed with: participants with any infection follow-up: 16 weeks INFORMATIVE	232 per 1,000	**429 per 1,000** (244 to 754)	**RR 1.85** (1.05 to 3.25)	112 (1 RCT)	⊕⊕⊕⊕ High

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Imprecision: The 95 % CI crosses the prespecified MCID (3.3 points)

e-Table 18. Abrocitinib Combination Therapy (200 mg) GRADE Summary of Findings (Short-term)

Abrocitinib 200mg daily + TCS compared to Placebo + TCS short-term[4]
Patient or population: Adolescents and adults aged 12+ with moderate to severe atopic dermatitis short-term **Intervention:** Abrocitinib 200mg daily + TCS **Comparison:** Placebo + TCS

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Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo + TCS	**Risk with Abrocitinib 200mg daily + TCS**				
IGA (0,1) follow-up: 16 weeks CRITICAL	129 per 1,000	**475 per 1,000** (294 to 766)	**RR 3.68** (2.28 to 5.94)	345 (1 RCT)	⨁⨁⨁⨁ High	
EASI75 follow-up: 16 weeks CRITICAL	306 per 1,000	**711 per 1,000** (539 to 938)	**RR 2.32** (1.76 to 3.06)	345 (1 RCT)	⨁⨁⨁⨁ High	
Pruritus improvement Assessed with: PP-NRS, ≥4-point improvement from baseline in PP-NRS score follow-up: 16 weeks CRITICAL	138 per 1,000	**492 per 1,000** (313 to 770)	**RR 3.55** (2.26 to 5.56)	356 (1 RCT)	⨁⨁⨁⨁ High	
Discontinuation due to Adverse Event follow-up: 16 weeks CRITICAL	38 per 1,000	**44 per 1,000** (15 to 127)	**RR 1.16** (0.40 to 3.32)	357 (1 RCT)	⨁⨁⨁⨁ High	
POEM Assessed with: POEM, change from baseline follow-up: 16 weeks CRITICAL	MD **7.5 lower** (9.03 lower to 5.97 lower)		-	357 (1 RCT)	⨁⨁⨁⨁ High	
Severe Adverse Event follow-up: 16 weeks CRITICAL	23 per 1,000	**18 per 1,000** (4 to 78)	**RR 0.77** (0.18 to 3.40)	357 (1 RCT)	⨁⨁⨁⨁ High	
Serious Adverse Events follow-up: 16 weeks CRITICAL	23 per 1,000	**9 per 1,000** (2 to 52)	**RR 0.39** (0.07 to 2.28)	357 (1 RCT)	⨁⨁⨁⨁ High	

Quality of life Assessed with: DLQI, change from baseline follow-up: 16 weeks CRITICAL	MD **5.5 lower** (6.6 lower to 4.4 lower)		-	357 (1 RCT)	⊕⊕⊕⊕ High
EASI90 follow-up: 16 weeks INFORMATIVE	115 per 1,000	**487 per 1,000** (297 to 798)	**RR 4.25** (2.59 to 6.97)	357 (1 RCT)	⊕⊕⊕⊕ High
Treatment-emergent Adverse Events follow-up: 16 weeks INFORMATIVE	534 per 1,000	**620 per 1,000** (513 to 748)	**RR 1.16** (0.96 to 1.40)	357 (1 RCT)	⊕⊕⊕⊕ High
Conjunctivitis Assessed with: Participants with conjunctivitis follow-up: 16 weeks INFORMATIVE	23 per 1,000	**13 per 1,000** (3 to 65)	**RR 0.58** (0.12 to 2.83)	357 (1 RCT)	⊕⊕⊕⊕ High
Nasopharyngitis Assessed with: participants with nasopharyngitis follow-up: 16 weeks INFORMATIVE	69 per 1,000	**67 per 1,000** (30 to 148)	**RR 0.97** (0.44 to 2.15)	357 (1 RCT)	⊕⊕⊕⊕ High
Upper respiratory tract infection Assessed with: participants with URTI follow-up: 16 weeks INFORMATIVE	56 per 1,000	**53 per 1,000** (31 to 94)	**RR 0.96** (0.55 to 1.69)	932 (4 RCTs)	⊕⊕⊕⊕ High
Herpes Viral Infection Assessed with: participants with a herpes viral infection follow-up: 16 weeks INFORMATIVE	0 per 1,000	**-- per 1,000** (0 to 0)	**RR 5.23** (0.28 to 96.44)	357 (1 RCT)	⊕⊕⊕⊕ High

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

184
185

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1. Gooderham MJ, Forman SB, Bissonnette R, Beebe JS, Zhang W, Banfield C et al. Efficacy and Safety of Oral Janus Kinase 1 Inhibitor Abrocitinib for Patients With Atopic Dermatitis: A Phase 2 Randomized Clinical Trial. JAMA Dermatol 2019;155:1371-9.
2. Silverberg JI, Simpson EL, Thyssen JP, Gooderham M, Chan G, Feeney C et al. Efficacy and Safety of Abrocitinib in Patients With Moderate-to-Severe Atopic Dermatitis: A Randomized Clinical Trial. JAMA Dermatol 2020;156:863-73.
3. Simpson EL, Sinclair R, Forman S, Wollenberg A, Aschoff R, Cork M et al. Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. Lancet 2020;396:255-66.
4. Bieber T, Simpson EL, Silverberg JI, Thaçi D, Paul C, Pink AE et al. Abrocitinib versus Placebo or Dupilumab for Atopic Dermatitis. N Engl J Med 2021;384:1101-12.

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e-Table 19. Abrocitinib Monotherapy (100 mg) GRADE Summary of Findings (Long-term)

Abrocitinib 100mg daily monotherapy compared to Placebo long-term[1]

Patient or population: Adolescents and adults aged 12+ with moderate to severe atopic dermatitis long-term
Intervention: Abrocitinib 100mg daily monotherapy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo	**Risk with Abrocitinib 100mg daily monotherapy**				
IGA (0,1) follow-up: 52 weeks CRITICAL	117 per 1,000	**369 per 1,000** (255 to 532)	**RR 3.14** (2.17 to 4.53)	522 (1 RCT)	⨁⨁⨁⨁ High	
EASI75 follow-up: 52 weeks CRITICAL	140 per 1,000	**465 per 1,000** (335 to 645)	**RR 3.32** (2.39 to 4.60)	522 (1 RCT)	⨁⨁⨁⨁ High	
Pruritus improvement PP-NRS, ≥4-point improvement from baseline in PP-NRS score follow-up: 52 weeks CRITICAL	83 per 1,000	**273 per 1,000** (172 to 434)	**RR 3.28** (2.06 to 5.21)	468 (1 RCT)	⨁⨁⨁⨁ High	
Discontinuation due to Adverse Events Follow-up: 40 weeks CRITICAL	15 per 1,000	**19 per 1,000** (5 to 70)	**RR 1.26** (0.34 to 4.64)	532 (1 RCT)	⨁⨁⨁⨁ High	
Serious Adverse Events Follow-up: 40 weeks CRITICAL	7 per 1,000	**8 per 1,000** (1 to 53)	**RR 1.01** (0.14 to 7.10)	532 (1 RCT)	⨁⨁⨁⨁ High	
Flares Assessed with: number of patients with loss of response requiring	809 per 1,000	**429 per 1,000** (364 to 493)	**RR 0.53** (0.45 to 0.61)	532 (1 RCT)	⨁⨁⨁⨁ High	

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rescue medication follow-up: 40 weeks CRITICAL					
EASI90 follow-up: 52 weeks INFORMATIVE	106 per 1,000	**375 per 1,000** (256 to 552)	**RR 3.54** (2.41 to 5.20)	522 (1 RCT)	⊕⊕⊕⊕ High
Treatment-emergent Adverse Events Follow-up: 40 weeks INFORMATIVE	453 per 1,000	**539 per 1,000** (453 to 639)	**RR 1.19** (1.00 to 1.41)	532 (1 RCT)	⊕⊕⊕⊕ High
Serious Infections Assessed with: patients with any serious infection Follow-up: 40 weeks INFORMATIVE	7 per 1,000	**8 per 1,000** (1 to 53)	**RR 1.01** (0.14 to 7.10)	532 (1 RCT)	⊕⊕⊕⊕ High
Any Infection Assessed with: patients with any infection Follow-up: 40 weeks INFORMATIVE	49 per 1,000	**117 per 1,000** (63 to 219)	**RR 2.40** (1.29 to 4.49)	532 (1 RCT)	⊕⊕⊕⊕ High
Herpes Viral Infection assessed with: participants with a herpes viral infection follow-up: 40 weeks INFORMATIVE	7 per 1,000	**8 per 1,000** (1 to 53)	**RR 1.01** (0.14 to 7.10)	532 (1 RCT)	⊕⊕⊕⊕ High
Nasopharyngitis Assessed with: participants with nasopharyngitis Follow-up: 40 weeks INFORMATIVE	19 per 1,000	**38 per 1,000** (13 to 109)	**RR 2.02** (0.70 to 5.82)	532 (1 RCT)	⊕⊕⊕⊕ High
Upper respiratory tract infection Assessed with: participants with URTI Follow-up: 40 weeks INFORMATIVE	22 per 1,000	**30 per 1,000** (11 to 86)	**RR 1.34** (0.47 to 3.82)	532 (1 RCT)	⊕⊕⊕⊕ High

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Severe adverse events follow-up: 40 weeks INFORMATIVE	56 per 1,000	**34 per 1,000** (15 to 76)	**RR 0.60** (0.27 to 1.36)	532 (1 RCT)	⨁⨁⨁⨁ High

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **RR:** risk ratio

References

1. Blauvelt A, Silverberg JI, Lynde CW, Bieber T, Eisman S, Zdybski J et al. Abrocitinib induction, randomized withdrawal, and retreatment in patients with moderate-to-severe atopic dermatitis: Results from the JAK1 Atopic Dermatitis Efficacy and Safety (JADE) REGIMEN phase 3 trial. J Am Acad Dermatol 2022;86:104-12.

e-Table 20. Abrocitinib Monotherapy (200 mg) GRADE Summary of Findings (Long-term)

Abrocitinib 200mg daily monotherapy compared to Placebo long-term[1]

Patient or population: Adolescents and adults aged 12+ with moderate to severe atopic dermatitis who responded to abrocitinib at 12 weeks
Intervention: Abrocitinib 200mg daily monotherapy
Comparison: Placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo	**Risk with Abrocitinib 200mg daily monotherapy**				
IGA (0,1) follow-up: 40 weeks CRITICAL	117 per 1,000	**541 per 1,000** (382 to 767)	**RR 4.61** (3.25 to 6.53)	521 (1 RCT)	⨁⨁⨁⨁ High	
EASI75 follow-up: 40 weeks CRITICAL	140 per 1,000	**657 per 1,000** (482 to 898)	**RR 4.69** (3.44 to 6.41)	521 (1 RCT)	⨁⨁⨁⨁ High	

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Pruritus improvement Assessed with: PP-NRS, ≥4-point improvement from baseline in PP-NRS score follow-up: 40 weeks CRITICAL	83 per 1,000	**490 per 1,000** (318 to 756)	**RR 5.88** (3.82 to 9.07)	456 (1 RCT)	⊕⊕⊕⊕ High
Discontinuation due to Adverse Events follow-up: 40 weeks CRITICAL	15 per 1,000	**60 per 1,000** (20 to 178)	**RR 4.02** (1.36 to 11.85)	533 (1 RCT)	⊕⊕⊕◯ Moderate[a]
Severe adverse events follow-up: 40 weeks CRITICAL	56 per 1,000	**56 per 1,000** (28 to 113)	**RR 1.00** (0.50 to 2.01)	533 (1 RCT)	⊕⊕⊕◯ Moderate[b]
Serious Adverse Events follow-up: 40 weeks CRITICAL	7 per 1,000	**49 per 1,000** (11 to 214)	**RR 6.52** (1.49 to 28.63)	533 (1 RCT)	⊕⊕⊕◯ Moderate[c]
Flares Assessed with: number of patients with loss of response requiring rescue medication follow-up: 40 weeks CRITICAL	809 per 1,000	**186 per 1,000** (146 to 243)	**RR 0.23** (0.18 to 0.30)	533 (1 RCT)	⊕⊕⊕⊕ High
EASI90 follow-up: 40 weeks INFORMATIVE	106 per 1,000	**545 per 1,000** (378 to 787)	**RR 5.14** (3.56 to 7.42)	521 (1 RCT)	⊕⊕⊕⊕ High
Treatment-emergent Adverse Events follow-up: 40 weeks INFORMATIVE	453 per 1,000	**630 per 1,000** (539 to 743)	**RR 1.39** (1.19 to 1.64)	533 (1 RCT)	⊕⊕⊕⊕ High
Serious Infections Assessed with: patients with any serious infection follow-up: 40 weeks INFORMATIVE	7 per 1,000	**19 per 1,000** (4 to 96)	**RR 2.51** (0.49 to 12.82)	533 (1 RCT)	⊕⊕⊕⊕ High

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Any Infection Assessed with: patients with any infection follow-up: 40 weeks INFORMATIVE	49 per 1,000	**166 per 1,000** (91 to 300)	**RR 3.40** (1.87 to 6.16)	533 (1 RCT)	⊕⊕⊕⊕ High
Herpes Viral Infection Assessed with: participants with a herpes viral infection follow-up: 40 weeks INFORMATIVE	7 per 1,000	**34 per 1,000** (7 to 155)	**RR 4.52** (0.99 to 20.71)	533 (1 RCT)	⊕⊕⊕◯ Moderate[d]
Nasopharyngitis Assessed with: participants with nasopharyngitis follow-up: 40 weeks INFORMATIVE	19 per 1,000	**68 per 1,000** (25 to 180)	**RR 3.61** (1.36 to 9.59)	533 (1 RCT)	⊕⊕⊕⊕ High
Upper respiratory tract infection Assessed with: participants with URTI follow-up: 40 weeks INFORMATIVE	22 per 1,000	**30 per 1,000** (11 to 85)	**RR 1.34** (0.47 to 3.80)	533 (1 RCT)	⊕⊕⊕⊕ High

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **RR:** risk ratio

Explanations

a. CI crosses the 10% MCID threshold and includes both clinically important harm and no important difference.

b. CI consistent with both meaningful benefit and harm (based on MID of 2%)

c. CI consistent with no difference and meaningful harm (based on MID of 2%)

d. CI crosses the 20% MCID threshold and includes no important difference and clinically important harm.

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References

1. Blauvelt A, Silverberg JI, Lynde CW, Bieber T, Eisman S, Zdybski J et al. Abrocitinib induction, randomized withdrawal, and retreatment in patients with moderate-to-severe atopic dermatitis: Results from the JAK1 Atopic Dermatitis Efficacy and Safety (JADE) REGIMEN phase 3 trial. J Am Acad Dermatol 2022;86:104-12.

e-Table 21. Baricitinib Monotherapy (2 mg) GRADE Summary of Findings (Short-term)

Baricitinib 2mg monotherapy daily for 16 weeks compared to Placebo

Patient or population: Adolescents and adults aged 12+ with moderate to severe atopic dermatitis
Intervention: Baricitinib 2mg monotherapy daily for 16 weeks
Comparison: Placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo	**Risk with Baricitinib 2mg monotherapy daily for 16 weeks**				
IGA (0,1) follow-up: 16 weeks CRITICAL	49 per 1,000	**147 per 1,000** (96 to 227)	**RR 3.04** (1.97 to 4.68)	1032 (3 RCTs)[1, 2]	⊕⊕⊕◯ Moderate[a]	
EASI75 follow-up: 16 weeks CRITICAL	77 per 1,000	**216 per 1,000** (154 to 302)	**RR 2.82** (2.01 to 3.95)	1032 (3 RCTs)	⊕⊕⊕◯ Moderate[b]	
Pruritus improvement Assessed with: PP-NRS ≥4-point improvement follow-up: 16 weeks CRITICAL	58 per 1,000	**179 per 1,000** (117 to 271)	**RR 3.06** (2.01 to 4.64)	934 (3 RCTs)	⊕⊕⊕◯ Moderate[c]	
Discontinuation due to Adverse Event follow-up: 16 weeks CRITICAL	16 per 1,000	**18 per 1,000** (7 to 46)	**RR 1.17** (0.47 to 2.95)	1030 (3 RCTs)	⊕⊕⊕⊕ High	
POEM Assessed with: POEM, mean change from baseline follow-up: 16 weeks CRITICAL	MD **4.57 lower** (6.04 lower to 3.11 lower)		-	509 (3 RCTs)	⊕⊕⊕◯ Moderate[d]	

Serious Adverse Events follow-up: 16 weeks CRITICAL	28 per 1,000	**14 per 1,000** (5 to 37)	**RR 0.50** (0.19 to 1.31)	1030 (3 RCTs)	⊕⊕⊕⊕ High
Flares assessed with: patients requiring rescue therapy follow-up: 16 weeks CRITICAL	702 per 1,000	**519 per 1,000** (463 to 575)	**RR 0.74** (0.66 to 0.82)	1032 (3 RCTs)	⊕⊕⊕⊕ High
Quality of life Assessed with: DLQI, mean change from baseline follow-up: 16 weeks CRITICAL	MD **3.03 lower** (4.14 lower to 1.92 lower)		-	508 (3 RCTs)	⊕⊕⊕◯ Moderate[e]
EASI90 follow-up: 16 weeks INFORMATIVE	36 per 1,000	**132 per 1,000** (80 to 217)	**RR 3.67** (2.23 to 6.03)	1032 (3 RCTs)	⊕⊕⊕◯ Moderate[c]
Treatment-emergent Adverse Events follow-up: 16 weeks INFORMATIVE	538 per 1,000	**560 per 1,000** (501 to 630)	**RR 1.04** (0.93 to 1.17)	1030 (3 RCTs)	⊕⊕⊕⊕ High
Serious Infections follow-up: 16 weeks INFORMATIVE	7 per 1,000	**7 per 1,000** (0 to 109)	**RR 1.01** (0.06 to 15.94)	291 (1 RCT)[1]	⊕⊕⊕◯ Moderate[f]
Herpes Simplex follow-up: 16 weeks INFORMATIVE	23 per 1,000	**38 per 1,000** (18 to 79)	**RR 1.61** (0.77 to 3.36)	1030 (3 RCTs)	⊕⊕⊕⊕ High
Upper respiratory tract infection follow-up: 16 weeks INFORMATIVE	31 per 1,000	**42 per 1,000** (23 to 77)	**RR 1.33** (0.72 to 2.47)	1030 (3 RCTs)	⊕⊕⊕⊕ High
Conjunctivitis follow-up: 16 weeks INFORMATIVE	12 per 1,000	**16 per 1,000** (5 to 57)	**RR 1.34** (0.38 to 4.71)	739 (2 RCTs)[2]	⊕⊕⊕⊕ High

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

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Explanations

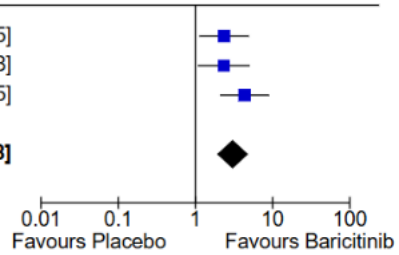
a. CI consistent with no meaningful difference and benefit (based on MID of 12%)
b. CI consistent with no meaningful difference and benefit (based on MID of 15%)
c. CI consistent with no meaningful difference and benefit (based on MID of 10%)
d. CI consistent with no meaningful difference and benefit (based on MID of 3.4 points)
e. CI consistent with no meaningful difference and benefit (based on MID of 3.3 points)
f. Low event rate in moderate sample leading to wide CI consistent with no meaningful difference and harm (based on MID of 2%)

Analysis. IGA (0,1)

Study or Subgroup	Baricitinib Events	Baricitinib Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Fixed, 95% CI
BREEZE-AD1	14	123	12	249	34.0%	2.36 [1.13 , 4.95]
BREEZE-AD2	13	123	11	244	31.6%	2.34 [1.08 , 5.08]
BREEZE-AD5	35	147	8	146	34.4%	4.35 [2.09 , 9.05]
Total		**393**		**639**	**100.0%**	**3.04 [1.97 , 4.68]**
Total events:	62		31			

Test for overall effect: Z = 5.05 (P < 0.00001)

Heterogeneity: Chi² = 1.79, df = 2 (P = 0.41); I² = 0%

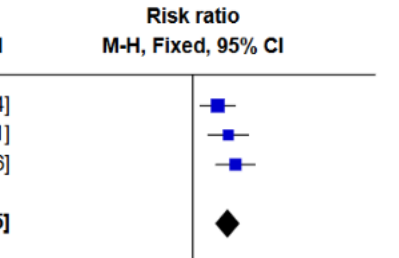


Analysis. EASI75

Study or Subgroup	Baricitinib Events	Baricitinib Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Fixed, 95% CI
BREEZE-AD1	23	123	22	249	39.8%	2.12 [1.23 , 3.64]
BREEZE-AD2	22	123	15	244	27.5%	2.91 [1.57 , 5.41]
BREEZE-AD5	43	146	12	147	32.7%	3.61 [1.98 , 6.56]
Total		**392**		**640**	**100.0%**	**2.82 [2.01 , 3.95]**
Total events:	88		49			

Test for overall effect: Z = 6.03 (P < 0.00001)

Heterogeneity: Chi² = 1.74, df = 2 (P = 0.42); I² = 0%

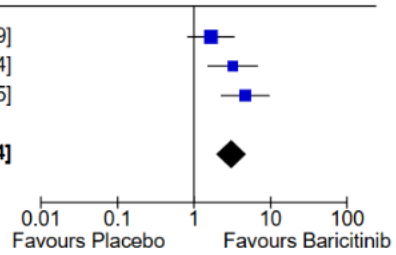


Analysis. Pruritus improvement

Study or Subgroup	Baricitinib Events	Baricitinib Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Fixed, 95% CI
BREEZE-AD1	12	100	16	222	40.5%	1.67 [0.82 , 3.39]
BREEZE-AD2	16	106	10	213	27.1%	3.22 [1.51 , 6.84]
BREEZE-AD5	37	146	8	147	32.5%	4.66 [2.25 , 9.65]
Total		**352**		**582**	**100.0%**	**3.06 [2.01 , 4.64]**
Total events:	65		34			

Test for overall effect: Z = 5.24 (P < 0.00001)

Heterogeneity: Chi² = 4.11, df = 2 (P = 0.13); I² = 51%

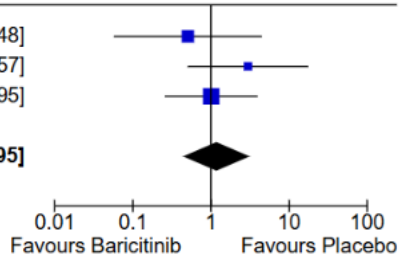


Analysis. Discontinuation due to adverse events

Study or Subgroup	Baricitinib Events	Baricitinib Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Fixed, 95% CI
BREEZE-AD1	1	123	4	249	33.2%	0.51 [0.06 , 4.48]
BREEZE-AD2	3	123	2	244	16.8%	2.98 [0.50 , 17.57]
BREEZE-AD5	4	145	4	146	50.0%	1.01 [0.26 , 3.95]
Total		**391**		**639**	**100.0%**	**1.17 [0.47 , 2.95]**
Total events:	8		10			

Test for overall effect: Z = 0.34 (P = 0.74)

Heterogeneity: Chi² = 1.67, df = 2 (P = 0.43); I² = 0%

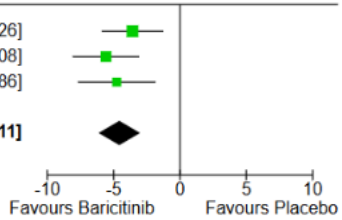


Analysis. POEM

Study or Subgroup	Baricitinib Mean	Baricitinib SD	Baricitinib Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean difference IV, Fixed, 95% CI
BREEZE-AD1	-6.26	6.562103	52	-2.68	6.448814	72	39.9%	-3.58 [-5.90 , -1.26]
BREEZE-AD2	-7.06	6.071573	40	-1.48	6.057326	52	34.5%	-5.58 [-8.08 , -3.08]
BREEZE-AD5	-7.44	10.246423	146	-2.67	14.743216	147	25.5%	-4.77 [-7.68 , -1.86]
Total			**238**			**271**	**100.0%**	**-4.57 [-6.04 , -3.11]**

Test for overall effect: Z = 6.10 (P < 0.00001)

Heterogeneity: Chi² = 1.34, df = 2 (P = 0.51); I² = 0%

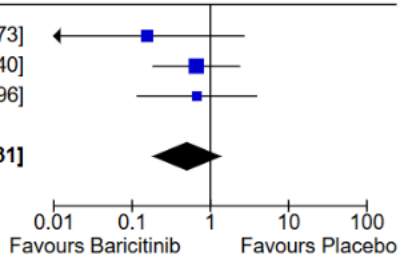


Analysis. Serious adverse events

Study or Subgroup	Baricitinib Events	Baricitinib Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Fixed, 95% CI
BREEZE-AD1	0	123	6	249	32.3%	0.16 [0.01 , 2.73]
BREEZE-AD2	3	123	9	244	45.2%	0.66 [0.18 , 2.40]
BREEZE-AD5	2	145	3	146	22.4%	0.67 [0.11 , 3.96]
Total		**391**		**639**	**100.0%**	**0.50 [0.19 , 1.31]**
Total events:	5		18			

Test for overall effect: Z = 1.41 (P = 0.16)

Heterogeneity: Chi² = 0.93, df = 2 (P = 0.63); I² = 0%



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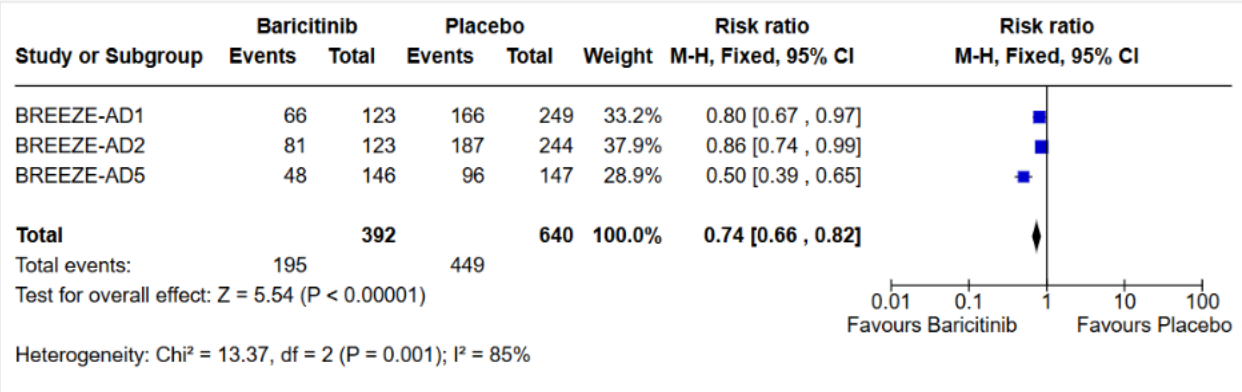
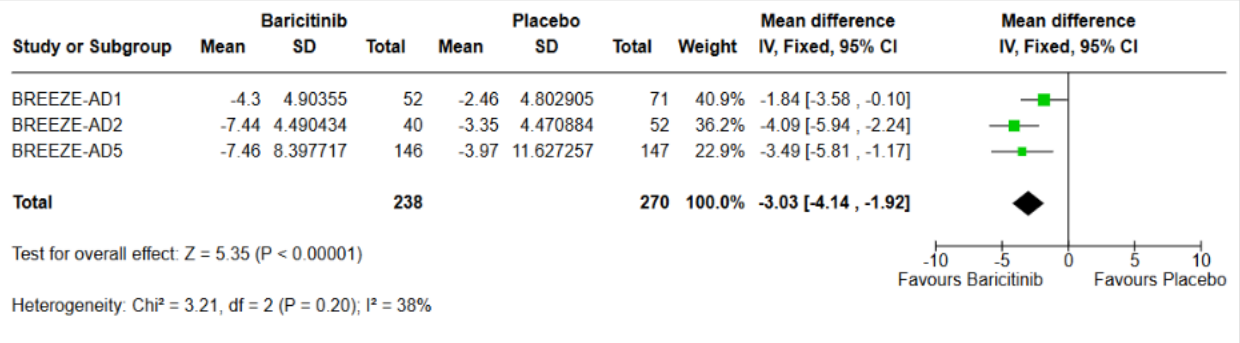
Analysis. Flare Prevention



Analysis. Quality of life



References

1. Simpson EL, Forman S, Silverberg JI, Zirwas M, Maverakis E, Han G et al. Baricitinib in patients with moderate-to-severe atopic dermatitis: Results from a randomized monotherapy phase 3 trial in the United States and Canada (BREEZE-AD5). J Am Acad Dermatol 2021;85:62-70.

2. Simpson EL, Lacour JP, Spelman L, Galimberti R, Eichenfield LF, Bissonnette R et al. Baricitinib in patients with moderate-to-severe atopic dermatitis and inadequate response to topical corticosteroids: results from two randomized monotherapy phase III trials. Br J Dermatol 2020;183:242-55.

e-Table 22. Baricitinib Monotherapy (4 mg) GRADE Summary of Findings (Short-term)

Baricitinib 4mg monotherapy daily for 16 weeks compared to Placebo

Patient or population: Adolescents and adults aged 12+ with moderate to severe atopic dermatitis
Intervention: Baricitinib 4mg monotherapy daily for 16 weeks
Comparison: Placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo	**Risk with Baricitinib 4mg monotherapy daily for 16 weeks**				
IGA (0,1) follow-up: 16 weeks CRITICAL	47 per 1,000	**153 per 1,000** (93 to 251)	**RR 3.28** (2.00 to 5.39)	741 (2 RCTs)[1]	⨁⨁⨁◯ Moderate[a]	
EASI75 follow-up: 16 weeks CRITICAL	75 per 1,000	**230 per 1,000** (157 to 338)	**RR 3.06** (2.09 to 4.50)	741 (2 RCTs)	⨁⨁⨁◯ Moderate[b]	
Pruritus improvement Assessed with: PP-NRS, ≥4-point improvement from baseline in PP-NRS score follow-up: 16 weeks CRITICAL	60 per 1,000	**204 per 1,000** (129 to 322)	**RR 3.41** (2.16 to 5.39)	647 (2 RCTs)	⨁⨁⨁◯ Moderate[c]	
Discontinuation due to Adverse Event follow-up: 16 weeks	12 per 1,000	**12 per 1,000** (3 to 48)	**RR 0.99** (0.25 to 3.95)	741 (2 RCTs)	⨁⨁⨁⨁ High	

CRITICAL					
POEM Assessed with: POEM, mean change from baseline follow-up: 16 weeks CRITICAL	The mean POEM, mean change from baseline was **0**	MD **5.58 lower** (7.18 lower to 3.97 lower)	-	242 (2 RCTs)	⊕⊕⊕⊕ High
Serious Adverse Events follow-up: 16 weeks CRITICAL	30 per 1,000	**12 per 1,000** (4 to 41)	**RR 0.40** (0.12 to 1.36)	741 (2 RCTs)	⊕⊕⊕⊕ High
Flares assessed with: patients requiring rescue therapy follow-up: 16 weeks CRITICAL	716 per 1,000	**494 per 1,000** (430 to 566)	**RR 0.69** (0.60 to 0.79)	741 (2 RCTs)	⊕⊕⊕⊕ High
Quality of life Assessed with: DLQI, mean change from baseline follow-up: 16 weeks CRITICAL	The mean DLQI, mean change from baseline was **0**	MD **4.26 lower** (5.46 lower to 3.06 lower)	-	241 (2 RCTs)	⊕⊕⊕◯ Moderate[d]
EASI90 follow-up: 16 weeks INFORMATIVE	37 per 1,000	**145 per 1,000** (84 to 250)	**RR 3.98** (2.31 to 6.85)	741 (2 RCTs)	⊕⊕⊕◯ Moderate[c]
Treatment-emergent Adverse Events follow-up: 16 weeks INFORMATIVE	552 per 1,000	**563 per 1,000** (491 to 640)	**RR 1.02** (0.89 to 1.16)	741 (2 RCTs)	⊕⊕⊕⊕ High
Herpes Simplex follow-up: 16 weeks INFORMATIVE	28 per 1,000	**57 per 1,000** (27 to 117)	**RR 1.99** (0.96 to 4.11)	741 (2 RCTs)	⊕⊕⊕⊕ High
Upper respiratory tract infection follow-up: 16 weeks INFORMATIVE	22 per 1,000	**32 per 1,000** (13 to 79)	**RR 1.45** (0.59 to 3.55)	741 (2 RCTs)	⊕⊕⊕⊕ High

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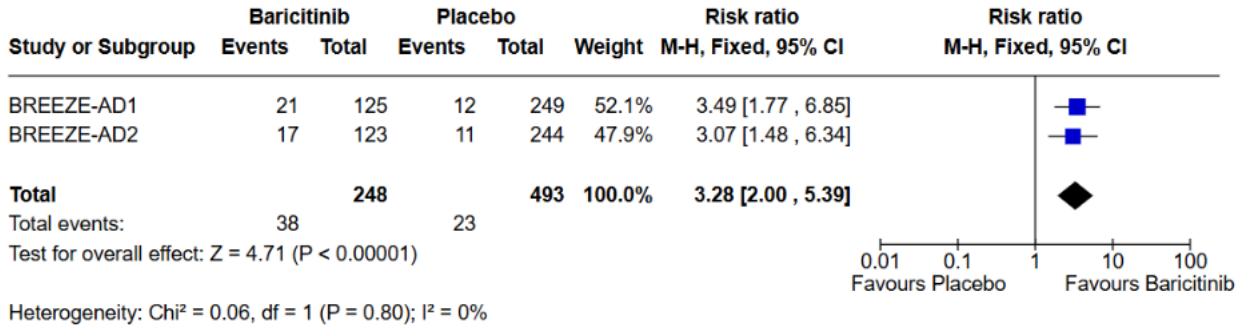
Conjunctivitis follow-up: 16 weeks INFORMATIVE	12 per 1,000	**6 per 1,000** (1 to 33)	**RR 0.46** (0.08 to 2.69)	741 (2 RCTs)	⨁⨁⨁⨁ High

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. CI consistent with no meaningful difference and benefit (based on MID of 12%)
b. CI consistent with no meaningful difference and benefit (based on MID of 15%)
c. CI consistent with no meaningful difference and benefit (based on MID of 10%)
d. CI consistent with no meaningful difference and benefit (based on MID of 3.3 points)

Analysis. IGA (0,1)



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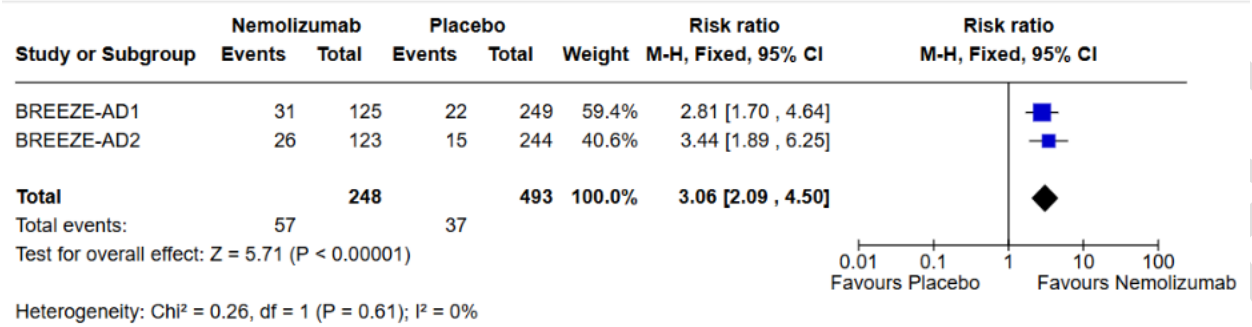
Analysis. EASI75

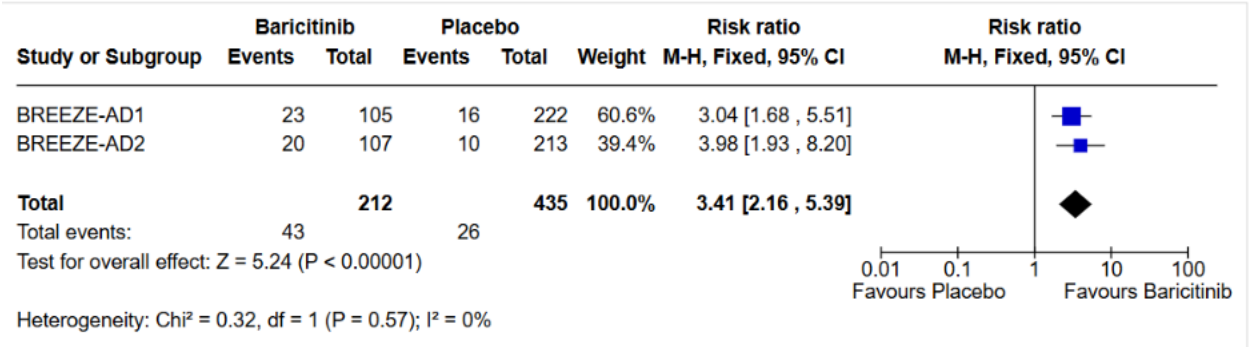


Study or Subgroup	Nemolizumab Events	Total	Placebo Events	Total	Weight	Risk ratio M-H, Fixed, 95% CI
BREEZE-AD1	31	125	22	249	59.4%	2.81 [1.70 , 4.64]
BREEZE-AD2	26	123	15	244	40.6%	3.44 [1.89 , 6.25]
Total		**248**		**493**	**100.0%**	**3.06 [2.09 , 4.50]**
Total events:	57		37			

Test for overall effect: Z = 5.71 (P < 0.00001)

Heterogeneity: Chi² = 0.26, df = 1 (P = 0.61); I² = 0%

Analysis. Pruritus improvement



Study or Subgroup	Baricitinib Events	Total	Placebo Events	Total	Weight	Risk ratio M-H, Fixed, 95% CI
BREEZE-AD1	23	105	16	222	60.6%	3.04 [1.68 , 5.51]
BREEZE-AD2	20	107	10	213	39.4%	3.98 [1.93 , 8.20]
Total		**212**		**435**	**100.0%**	**3.41 [2.16 , 5.39]**
Total events:	43		26			

Test for overall effect: Z = 5.24 (P < 0.00001)

Heterogeneity: Chi² = 0.32, df = 1 (P = 0.57); I² = 0%

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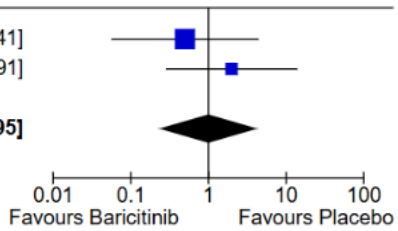
Analysis. Discontinuation due to adverse events

Study or Subgroup	Baricitinib Events	Baricitinib Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Fixed, 95% CI
BREEZE-AD1	1	125	4	249	66.6%	0.50 [0.06 , 4.41]
BREEZE-AD2	2	123	2	244	33.4%	1.98 [0.28 , 13.91]
Total		**248**		**493**	**100.0%**	**0.99 [0.25 , 3.95]**
Total events:	3		6			

Test for overall effect: Z = 0.01 (P = 0.99)

Heterogeneity: Chi² = 0.87, df = 1 (P = 0.35); I² = 0%

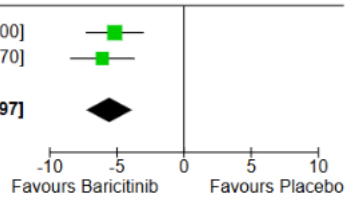


Analysis. POEM

Study or Subgroup	Baricitinib Mean	Baricitinib SD	Baricitinib Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean difference IV, Fixed, 95% CI
BREEZE-AD1	-7.84	6.69328	70	-2.68	6.448814	72	54.9%	-5.16 [-7.32 , -3.00]
BREEZE-AD2	-7.56	6.096819	48	-1.48	6.057326	52	45.1%	-6.08 [-8.46 , -3.70]
Total			**118**			**124**	**100.0%**	**-5.58 [-7.18 , -3.97]**

Test for overall effect: Z = 6.82 (P < 0.00001)

Heterogeneity: Chi² = 0.31, df = 1 (P = 0.58); I² = 0%



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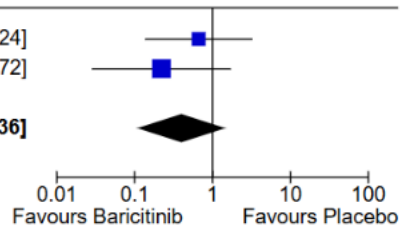
Analysis. Serious adverse events

Study or Subgroup	Baricitinib Events	Baricitinib Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Fixed, 95% CI
BREEZE-AD1	2	125	6	249	39.9%	0.66 [0.14 , 3.24]
BREEZE-AD2	1	123	9	244	60.1%	0.22 [0.03 , 1.72]
Total		**248**		**493**	**100.0%**	**0.40 [0.12 , 1.36]**
Total events:	3		15			

Test for overall effect: Z = 1.47 (P = 0.14)

Heterogeneity: Chi² = 0.72, df = 1 (P = 0.40); I² = 0%

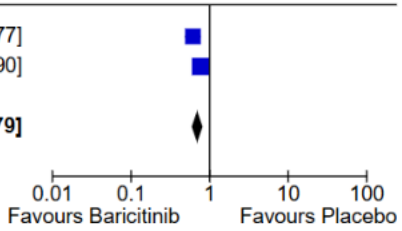


Analysis. Flare Prevention

Study or Subgroup	Baricitinib Events	Baricitinib Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Fixed, 95% CI
BREEZE-AD1	51	125	166	249	47.0%	0.61 [0.49 , 0.77]
BREEZE-AD2	72	123	187	244	53.0%	0.76 [0.65 , 0.90]
Total		**248**		**493**	**100.0%**	**0.69 [0.60 , 0.79]**
Total events:	123		353			

Test for overall effect: Z = 5.29 (P < 0.00001)

Heterogeneity: Chi² = 2.49, df = 1 (P = 0.11); I² = 60%



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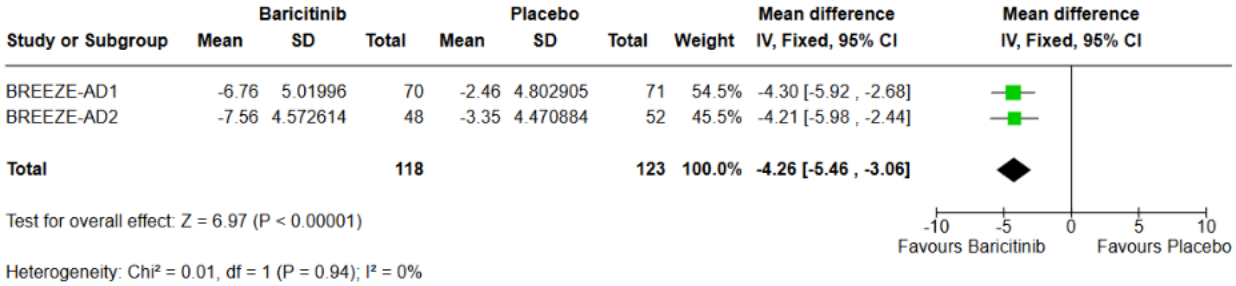
Analysis. Quality of life



References

1. Simpson EL, Lacour JP, Spelman L, Galimberti R, Eichenfield LF, Bissonnette R et al. Baricitinib in patients with moderate-to-severe atopic dermatitis and inadequate response to topical corticosteroids: results from two randomized monotherapy phase III trials. Br J Dermatol 2020;183:242-55.

e-Table 23. Baricitinib Combination Therapy (2 mg) GRADE Summary of Findings (Short-term)

Baricitinib 2mg daily + TCS for 16 weeks compared to Placebo + TCS

Patient or population: Adolescents and adults aged 12+ with moderate to severe atopic dermatitis
Intervention: Baricitinib 2mg daily + TCS for 16 weeks
Comparison: Placebo + TCS

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo + TCS	**Risk with Baricitinib 2mg**				

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		daily + TCS for 16 weeks				
IGA (0,1) follow-up: 16 weeks CRITICAL	116 per 1,000	**198 per 1,000** (132 to 298)	**RR 1.71** (1.14 to 2.58)	582 (3 RCTs)[1-3]	⊕⊕⊕◯ Moderate[a]	
EASI75 follow-up: 16 weeks CRITICAL	203 per 1,000	**347 per 1,000** (258 to 463)	**RR 1.71** (1.27 to 2.28)	582 (3 RCTs)[1-3]	⊕⊕⊕◯ Moderate[b]	
Pruritus improvement Assessed with: PP-NRS, ≥4-point improvement from baseline in PP-NRS score follow-up: 16 weeks CRITICAL	142 per 1,000	**306 per 1,000** (205 to 456)	**RR 2.15** (1.44 to 3.21)	479 (2 RCTs)[1,3]	⊕⊕⊕◯ Moderate[c]	
Discontinuation due to Adverse Event follow-up: 16 weeks CRITICAL	36 per 1,000	**10 per 1,000** (2 to 60)	**RR 0.29** (0.05 to 1.67)	313 (2 RCTs)[2,3]	⊕⊕⊕⊕ High	
POEM Assessed with: POEM, mean change from baseline follow-up: 16 weeks CRITICAL	The mean POEM, mean change from baseline was **0**	MD **2.99 lower** (4.48 lower to 1.5 lower)	-	466 (2 RCTs)[1,3]	⊕⊕⊕◯ Moderate[d]	
Serious Adverse Events follow-up: 16 weeks CRITICAL	25 per 1,000	**13 per 1,000** (2 to 68)	**RR 0.50** (0.09 to 2.65)	303 (2 RCTs)[2,3]	⊕⊕◯◯ Low[e]	
Flares assessed with: patients requiring rescue therapy follow-up: 16 weeks CRITICAL	92 per 1,000	**46 per 1,000** (17 to 129)	**RR 0.50** (0.18 to 1.41)	218 (1 RCT)[3]	⊕⊕⊕⊕ High	
Quality of life	MD **1.77 lower** (2.98 lower to 0.56 lower)		-	496 (2 RCTs)[1,3]	⊕⊕⊕⊕ High	

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Assessed with: DLQI, mean change from baseline follow-up: 16 weeks CRITICAL					
EASI90 follow-up: 16 weeks INFORMATIVE	96 per 1,000	**144 per 1,000** (90 to 232)	**RR 1.51** (0.94 to 2.43)	582 (3 RCTs) [1-3]	⊕⊕⊕◯ Moderate[c]
Upper Respiratory Tract Infection follow-up: 16 weeks INFORMATIVE	19 per 1,000	**49 per 1,000** (14 to 174)	**RR 2.58** (0.73 to 9.09)	303 (2 RCTs) [2,3]	⊕⊕⊕◯ Moderate[f]
Conjunctivitis follow-up: 16 weeks INFORMATIVE	20 per 1,000	**9 per 1,000** (0 to 214)	**RR 0.44** (0.02 to 10.47)	86 (1 RCT)[2]	⊕⊕◯◯ Low[f,g]
Herpes Simplex follow-up: 16 weeks INFORMATIVE	19 per 1,000	**6 per 1,000** (1 to 60)	**RR 0.33** (0.03 to 3.13)	303 (2 RCTs)[2,3]	⊕⊕⊕◯ Moderate[h]
Treatment-emergent Adverse Events follow-up: 16 weeks INFORMATIVE	512 per 1,000	**666 per 1,000** (574 to 769)	**RR 1.30** (1.12 to 1.50)	495 (2 RCTs)[1,3]	⊕⊕⊕◯ Moderate[f]
Serious Infections follow-up: 16 weeks INFORMATIVE	20 per 1,000	**15 per 1,000** (4 to 56)	**RR 0.74** (0.20 to 2.79)	495 (2 RCTs)[1,3]	⊕⊕⊕◯ Moderate[e]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. CI consistent with no meaningful difference and benefit (based on MID of 12%)
b. CI consistent with no meaningful difference and benefit (based on MID of 15%)
c. CI consistent with no meaningful difference and benefit (based on MID of 10%)
d. CI consistent with no meaningful difference and benefit (based on MID of 3.4 points)
e. CI consistent with benefit and harm (based on MID of 2%)
f. CI consistent with no meaningful difference and harm (based on MID of 10%)
g. Low event rate in a very small sample.
h. Small sample is concerning for precision.

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References

1. Bieber T, Reich K, Paul C, Tsunemi Y, Augustin M, Lacour JP et al. Efficacy and safety of baricitinib in combination with topical corticosteroids in patients with moderate-to-severe atopic dermatitis with inadequate response, intolerance or contraindication to ciclosporin: results from a randomized, placebo-controlled, phase III clinical trial (BREEZE-AD4). Br J Dermatol 2022;187:338-52.
2. Guttman-Yassky E, Silverberg JI, Nemoto O, Forman SB, Wilke A, Prescilla R et al. Baricitinib in adult patients with moderate-to-severe atopic dermatitis: A phase 2 parallel, double-blinded, randomized placebo-controlled multiple-dose study. Journal of the American Academy of Dermatology 2019;80:913-21.e9.
3. Reich K, Kabashima K, Peris K, Silverberg JI, Eichenfield LF, Bieber T et al. Efficacy and Safety of Baricitinib Combined With Topical Corticosteroids for Treatment of Moderate to Severe Atopic Dermatitis: A Randomized Clinical Trial. JAMA Dermatol 2020;156:1333-43.

e-Table 24. Baricitinib Combination Therapy (4 mg) GRADE Summary of Findings (Short-term)

Baricitinib 4mg daily + TCS for 16 weeks compared to Placebo + TCS

Patient or population: Adolescents and adults aged 12+ with moderate to severe atopic dermatitis
Intervention: Baricitinib 4mg daily + TCS for 16 weeks
Comparison: Placebo + TCS

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo + TCS	**Risk with Baricitinib 4mg daily + TCS for 16 weeks**				
IGA (0,1) follow-up: 16 weeks CRITICAL	116 per 1,000	**254 per 1,000** (170 to 379)	**RR 2.20** (1.47 to 3.28)	49201 (3 RCTs) [1-3]	⨁⨁⨁◯ Moderate[a]	

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EASI75 follow-up: 16 weeks CRITICAL	203 per 1,000	**392 per 1,000** (293 to 524)	**RR 1.93** (1.44 to 2.58)	492 (3 RCTs) [1-3]	⊕⊕⊕◯ Moderate[b]
Pruritus improvement Assessed with: PP-NRS, ≥4-point improvement from baseline in PP-NRS score follow-up: 16 weeks CRITICAL	142 per 1,000	**382 per 1,000** (260 to 561)	**RR 2.69** (1.83 to 3.95)	389 (2 RCTs) [1,3]	⊕⊕⊕⊕ High
Discontinuation due to Adverse Event follow-up: 16 weeks CRITICAL	36 per 1,000	**73 per 1,000** (27 to 195)	**RR 2.02** (0.75 to 5.42)	316 (2 RCTs) [2,3]	⊕⊕⊕◯ Moderate[c]
POEM Assessed with: POEM, mean change from baseline follow-up: 16 weeks CRITICAL	The mean POEM, mean change from baseline was **0**	MD **5.19 lower** (6.47 lower to 3.91 lower)	-	373 (2 RCTs) [1,3]	⊕⊕⊕⊕ High
Serious Adverse Events follow-up: 16 weeks CRITICAL	25 per 1,000	**32 per 1,000** (9 to 107)	**RR 1.25** (0.37 to 4.20)	306 (2 RCTs) [2,3]	⊕⊕⊕◯ Moderate[d]
Flares Assessed with: proportion of patients with AD flares assessed with: patients requiring rescue medication follow-up: 16 weeks CRITICAL	92 per 1,000	**54 per 1,000** (20 to 144)	**RR 0.59** (0.22 to 1.57)	220 (1 RCT) [3]	⊕⊕⊕⊕ High
Quality of life Assessed with: DLQI, mean change from baseline follow-up: 16 weeks CRITICAL	The mean DLQI, mean change from baseline was **0**	MD **3.18 lower** (4.46 lower to 1.89 lower)	-	405 (2 RCTs) [1,3]	⊕⊕⊕◯ Moderate[e]

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EASI90 follow-up: 16 weeks INFORMATIVE	96 per 1,000	**197 per 1,000** (125 to 310)	**RR 2.06** (1.31 to 3.24)	492 (3 RCTs) [1-3]	⊕⊕⊕◯ Moderate[f]
Upper Respiratory Tract Infection follow-up: 16 weeks INFORMATIVE	19 per 1,000	**34 per 1,000** (8 to 140)	**RR 1.80** (0.44 to 7.31)	306 (2 RCTs) [2,3]	⊕⊕⊕◯ Moderate[c]
Conjunctivitis follow-up: 16 weeks INFORMATIVE	20 per 1,000	**9 per 1,000** (0 to 208)	**RR 0.43** (0.02 to 10.21)	87 (1 RCT) [2]	⊕⊕◯◯ Low[c,g]
Herpes Simplex follow-up: 16 weeks INFORMATIVE	19 per 1,000	**25 per 1,000** (6 to 99)	**RR 1.33** (0.34 to 5.20)	306 (2 RCTs) [2,3]	⊕⊕⊕⊕ High
Treatment-emergent Adverse Events follow-up: 16 weeks INFORMATIVE	512 per 1,000	**723 per 1,000** (620 to 840)	**RR 1.41** (1.21 to 1.64)	404 (2 RCTs) [1,3]	⊕⊕⊕⊕ High
Serious Infections follow-up: 16 weeks INFORMATIVE	20 per 1,000	**20 per 1,000** (6 to 72)	**RR 1.00** (0.28 to 3.61)	404 (2 RCTs) [1,3]	⊕⊕⊕◯ Moderate[d]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI). **CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. CI consistent with no meaningful difference and benefit (based on MID of 12%)
b. CI consistent with no meaningful difference and benefit (based on MID of 15%)
c. CI consistent with no meaningful difference and harm (based on MID of 10%)
d. CI consistent with no meaningful difference and harm (based on MID of 2%)
e. CI consistent with no meaningful difference and benefit (based on MID of 3.3 points)
f. CI consistent with no meaningful difference and benefit (based on MID of 10%)
g. Very small sample is concerning for precision.

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References

1. Bieber T, Reich K, Paul C, Tsunemi Y, Augustin M, Lacour JP et al. Efficacy and safety of baricitinib in combination with topical corticosteroids in patients with moderate-to-severe atopic dermatitis with inadequate response, intolerance or contraindication to ciclosporin: results from a randomized, placebo-controlled, phase III clinical trial (BREEZE-AD4). Br J Dermatol 2022;187:338-52.
2. Guttman-Yassky E, Silverberg JI, Nemoto O, Forman SB, Wilke A, Prescilla R et al. Baricitinib in adult patients with moderate-to-severe atopic dermatitis: A phase 2 parallel, double-blinded, randomized placebo-controlled multiple-dose study. Journal of the American Academy of Dermatology 2019;80:913-21.e9.
3. Reich K, Kabashima K, Peris K, Silverberg JI, Eichenfield LF, Bieber T et al. Efficacy and Safety of Baricitinib Combined With Topical Corticosteroids for Treatment of Moderate to Severe Atopic Dermatitis: A Randomized Clinical Trial. JAMA Dermatol 2020;156:1333-43.

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