BMJ TAG

Abrocitinib, tralokinumab and upadacitinib for treating moderate-to-severe atopic dermatitis

Supplementary material

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Note

This monograph is based on the Multiple Technology Assessment Report produced for NICE. The full report contained a considerable amount of data that were deemed confidential and were used by the Advisory Committee at NICE in their deliberations. The full version of the report with the confidential information removed is available on the NICE website: www.nice.org.uk.

The present monograph presents as full a version of the report as is possible while retaining readability, but some sections, sentences, tables and figures have been removed. Readers should bear in mind that the discussion, conclusions and implications for practice and research are based on all the data considered in the original full NICE report.

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1.1 Randomised controlled trials to inform clinical effectiveness

1.1.1 MEDLINE (via OVID)

MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) (search date 1 August 2019 to 8 July 2021)

1. exp Eczema/ or eczema*.tw.

2. exp Dermatitis, Atopic/

3. exp Dermatitis/ or dermatitis.tw.

4. or/1-3

5. exp Cyclosporine/

6. (c?closporin* or 'Cy A' or CyA or Cy-A or 'Cs A' or CsA or Cs-A or csaneoral or neoral or sandimmun*).tw.

7. (dupilumab or dupixent or 'regn 668' or REGN-668 or regn668 or 'sar 231893' or sar-231893 or sar231893 or 420K487FSG or 1190264-60-8).tw.

8. (baricitinib or olumiant or 'ly 3009104' or ly3009104 or ly-3009104 or 'incb 028050' or incb-028050 or incb028050 or 'incb 28050' or incb-28050 or incb28050 or ISP4442I3Y or 1187594-09-7).tw.

9. (abrocitinib or 'pf 04965842' or pf04965842 or pf-04965842 or 'pf 4965842' or pf-4965842 or pf4965842 or 73SM5SF3OR or 1622902-68-4).tw.

10. (tralokinumab or 'cat 354' or cat354 or cat-354 or GK1LYB375A or 1044515-88-9).tw.

11. (upadacitinib* or rinvoq* or 'ABT 494' or ABT-494 or ABT494 or 4RA0KN46E0 or 1310726-60-3 or 1607431-21-9).tw.

12. exp Antibodies, Monoclonal/ or exp Antibodies, Monoclonal, Humanized/

13. ((humanized adj8 (monoclonal* or antibod* or MoAb* or mAb or mAbs or fab*1)) or rhuMAb*).tw.

14. (chim?eric adj3 (monoclonal* or antibod* or MoAb* or mAb or mAbs)).tw.

15. ((biological*1 or biologic*1) adj (treatment* or therap* or medicine* or drug* or agent* or product*)).tw.

16. (biologic* response modifier* or BRM*).tw.

17. targeted therap*.tw.

18. (systemic adj immunosuppressive treatment$).tw.

19. immuno-modulatory treatment$.tw.

20. anti inflammatory treatment$.tw.

21. exp Immunosuppressive Agents/

22. exp Anti-Inflammatory Agents/

23. exp Janus Kinase Inhibitors/

24. exp Interleukins/ or exp interleukin-4/ or exp interleukin-13/

25. or/5-24

26. randomized controlled trial.pt.

27. controlled clinical trial.pt.

28. randomized.ab.

29. placebo.ab.

30. clinical trials as topic.sh.

31. randomly.ab.

32. trial.ti.

33. or/26-32

34. exp animals/ not humans.sh.

35. 33 not 34

36. 4 and 25 and 35

37. limit 36 to ed=20190801-20210708

1.1.2 EMBASE (via EMBASE)

Search date from 1 August 2019 to 8 July 2021

1. 'atopic dermatitis'/exp OR 'atopic dermatitis'

2. 'dermatitis'/exp

3. #1 OR #2

4. 'cyclosporine'/exp

5. c?closporin*:ab,ti OR 'Cy A':ab,ti,tt OR CyA:ab,ti,tt OR Cy-A:ab,ti,tt OR 'Cs A':ab,ti,tt or CsA:ab,ti,tt or Cs-A:ab,ti,tt or csaneoral:ab,ti,tt or neoral:ab,ti,tt or sandimmun*:ab,ti,tt

6. dupilumab:ab,ti,tt OR dupixent:ab,ti,tt OR 'regn 668':ab,ti,tt OR REGN-668:ab,ti,tt OR regn668:ab,ti,tt OR 'sar 231893':ab,ti,tt OR sar-231893:ab,ti,tt OR sar231893:ab,ti,tt OR 420K487FSG:ab,ti,tt OR 1190264-60-8:ab,ti,tt

7. baricitinib:ab,ti,tt OR olumiant:ab,ti,tt OR 'ly 3009104':ab,ti,tt OR ly3009104:ab,ti,tt OR ly-3009104:ab,ti,tt OR 'incb 028050':ab,ti,tt OR incb-028050:ab,ti,tt OR incb028050:ab,ti,tt OR 'incb 28050':ab,ti,tt OR incb-28050:ab,ti,tt OR incb28050:ab,ti,tt OR ISP4442I3Y:ab,ti,tt OR 1187594-09-7:ab,ti,tt

8. abrocitinib:ab,ti,tt OR 'pf 04965842':ab,ti,tt OR pf04965842:ab,ti,tt OR pf-04965842:ab,ti,tt OR 'pf 4965842':ab,ti,tt OR pf-4965842:ab,ti,tt OR pf4965842:ab,ti,tt OR 73SM5SF3OR:ab,ti,tt OR 1622902-68-4:ab,ti,tt

9. tralokinumab:ab,ti,tt OR 'cat 354':ab,ti,tt OR cat354:ab,ti,tt OR cat-354:ab,ti,tt OR GK1LYB375A:ab,ti,tt OR 1044515-88-9:ab,ti,tt

10. upadacitinib*:ab,ti,tt OR rinvoq*:ab,ti,tt OR 'ABT 494':ab,ti,tt OR ABT-494:ab,ti,tt OR ABT494:ab,ti,tt OR 4RA0KN46E0:ab,ti,tt OR 1310726-60-3:ab,ti,tt OR 1607431-21-9:ab,ti,tt

11. 'monoclonal antibody'/exp OR 'monoclonal antibody'

12. ((humani?ed) NEAR/5 (monoclonal* OR antibod* OR MoAb* OR mAb OR mAbs OR fab*1)):ab,ti,tt OR rhuMAb*:ab,ti,tt

13. ((chim?eric) NEAR/3 (monoclonal* OR antibod* OR MoAb* OR mAb OR mAbs)):ab,ti,tt

14. ((biological OR biologic) NEAR/2 (treatment* OR therap* OR medicine* OR drug* or agent* or product*)):ab,ti,tt

15. biologic* response modifier* OR BRM:ab,ti,tt

16. targeted therap*:ab,ti,tt

17. systemic NEAR/2 immunosuppressive treatment*:ab,ti,tt

18. immuno-modulatory treatment*:ab,ti,tt

19. anti inflammatory treatment*:ab,ti,tt

20. 'immunosuppressive agent'/exp OR 'immunosuppressive agent'

21. 'antiinflammatory agent'/exp OR 'antiinflammatory agent'

22. 'janus kinase inhibitor'/exp OR 'janus kinase inhibitor'

23. 'cytokine'/exp or 'cytokine'

24. interleukin 4:ab,ti,tt or interleukin 13:ab,ti,tt

25. #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24

26. 'randomized controlled trial'/de

27. 'controlled clinical trial'/de

28. #26 OR #27

29. random*:ti,ab,tt

30. ‘randomization’/de

31. ‘intermethod comparison’/de

32. placebo:ti,ab,tt

33. (compare:ti,tt OR compared:ti,tt OR comparison:ti,tt)

34. ((evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab))

35. (open NEXT/1 label):ti,ab,tt

36. ((double OR single OR doubly OR singly) NEXT/1 (blind OR blinded OR blindly)):ti,ab,tt

37. ‘double blind procedure’/de

38. (parallel NEXT/1 group*):ti,ab,tt

39. (crossover:ti,ab,tt OR ‘cross over’:ti,ab,tt)

40. ((assign* OR match OR matched OR allocation) NEAR/6 (alternate OR group OR groups OR intervention OR interventions OR patient OR patients OR subject OR subjects OR participant OR participants)):ti,ab,tt

41. (assigned:ti,ab,tt OR allocated:ti,ab,tt)

42. (controlled NEAR/8 (study OR design OR trial)):ti,ab,tt

43. (volunteer:ti,ab,tt OR volunteers:ti,ab,tt)

44. ‘human experiment’/de

45. Trial:ti,tt

46. #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR#39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45

47. #46 NOT #28

48. (((random* NEXT/1 sampl* NEAR/8 (‘cross section*’ OR questionnaire* OR survey OR surveys OR database or databases)):ti,ab,tt) NOT (‘comparativestudy’/de OR ‘controlled study’/de OR ‘randomised controlled’:ti,ab,tt OR ‘randomized controlled’:ti,ab,tt OR ‘randomly assigned’:ti,ab,tt))

49. (‘cross-sectional study’/de NOT (‘randomized controlled trial’/de OR ‘controlled clinical study’/de OR ‘controlled study’/de OR ‘randomisedcontrolled’:ti,ab,tt OR ‘randomized controlled’:ti,ab,tt OR ‘control group’:ti,ab,tt OR ‘control groups’:ti,ab,tt))

50. (‘case control*’:ti,ab,tt AND random*:ti,ab,tt NOT (‘randomised controlled’:ti,ab,tt OR ‘randomized controlled’:ti,ab,tt))

51. (‘systematic review’:ti,tt NOT (trial:ti,tt OR study:ti,tt))

52. (nonrandom*:ti,ab,tt NOT random*:ti,ab,tt)

53. ‘random field*’:ti,ab,tt

54. (‘random cluster’ NEAR/4 sampl*):ti,ab,tt

55. (review:ab AND review:it NOT trial:ti,tt)

56. (‘we searched’:ab AND (review:ti,tt OR review:it))

57. ‘update review’:ab

58. (databases NEAR/5 searched):ab

59. ((rat:ti,tt OR rats:ti,tt OR mouse:ti,tt OR mice:ti,tt OR swine:ti,tt OR porcine:ti,tt OR murine:ti,tt OR sheep:ti,tt OR lambs:ti,tt OR pigs:ti,tt OR piglets:ti,tt OR rabbit:ti,tt OR rabbits:ti,tt OR cat:ti,tt OR cats:ti,tt OR dog:ti,tt OR dogs:ti,tt OR cattle:ti,tt OR bovine:ti,tt OR monkey:ti,tt OR monkeys:ti,tt OR trout:ti,tt OR marmoset*:ti,tt) AND ‘animal experiment’/de)

60. (‘animal experiment’/de NOT (‘human experiment’/de OR ‘human’/de))

61. #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR#57 OR #58 OR #59 OR #60

62. #47 NOT #61

63. #3 AND #25 AND #62

64. #63 AND [08/01/2019]/sd

1.1.3 CENTRAL (via CENTRAL)

Search date from 1 August 2019 to 8 July 2021

1. MeSH descriptor: [Dermatitis, Atopic] explode all trees

2. (atopic eczem*):ab,ti OR (atopic dermatit*):ab,ti

3. #1 OR #2

4. MeSH descriptor: [Cyclosporine] explode all trees

5. c?closporin*:ab,ti OR ‘Cy A’:ab,ti OR CyA:ab,ti OR Cy-A:ab,ti OR ‘Cs A’:ab,ti or CsA:ab,ti or Cs-A:ab,ti or csaneoral:ab,ti or neoral:ab,ti or sandimmun*:ab,ti

6. dupilumab:ab,ti OR dupixent:ab,ti OR ‘regn 668’:ab,ti OR REGN-668:ab,ti OR regn668:ab,ti OR ‘sar 231893’:ab,ti OR sar-231893:ab,ti OR sar231893:ab,ti OR 420K487FSG:ab,ti

7. baricitinib:ab,ti OR olumiant:ab,ti OR ‘ly 3009104’:ab,ti OR ly3009104:ab,ti OR ly-3009104:ab,ti OR ‘incb 028050’:ab,ti OR incb-028050:ab,ti OR incb028050:ab,ti OR ‘incb 28050’:ab,ti OR incb-28050:ab,ti OR incb28050:ab,ti OR ISP4442I3Y:ab,ti

8. abrocitinib:ab,ti OR 'pf 04965842':ab,ti OR pf04965842:ab,ti OR pf-04965842:ab,ti OR 'pf 4965842':ab,ti OR pf-4965842:ab,ti OR pf4965842:ab,ti OR 73SM5SF3OR:ab,ti

9. tralokinumab:ab,ti OR 'cat 354':ab,ti OR cat354:ab,ti OR cat-354:ab,ti OR GK1LYB375A:ab,ti

10. upadacitinib*:ab,ti OR rinvoq*:ab,ti OR 'ABT 494':ab,ti OR ABT-494:ab,ti OR ABT494:ab,ti OR 4RA0KN46E0:ab,ti

11. MeSH descriptor: [Antibodies, Monoclonal] explode all trees

12. ((humani?ed) NEAR/5 (monoclonal* OR antibod* OR MoAb* OR mAb OR mAbs OR fab*1)):ab,ti OR rhuMAb*:ab,ti

13. ((chim?eric) NEAR/3 (monoclonal* OR antibod* OR MoAb* OR mAb OR mAbs)):ab,ti

14. ((biological OR biologic) NEAR/2 (treatment* OR therap* OR medicine* OR drug* or agent* or product*)):ab,ti

15. biologic* response modifier* OR BRM:ab,ti

16. targeted therap*:ab,ti

17. systemic NEAR/2 immunosuppressive treatment*:ab,ti

18. immuno-modulatory treatment*:ab,ti

19. anti inflammatory treatment*:ab,ti

20. MeSH descriptor: [Immunosuppressive Agents] explode all trees

21. MeSH descriptor: [Anti-Inflammatory Agents] explode all trees

22. MeSH descriptor: [Janus Kinase Inhibitors] explode all trees

23. MeSH descriptor: [Cytokines] explode all trees

24. interleukin-4:ab,ti or interleukin-13:ab,ti

25. #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24

26. #3 AND #25

Line 26 limited to "Trials" and Cochrane Publication Date from Aug 2019 to Jul 2021.

1.2 Observational studies to inform clinical effectiveness

1.2.1 MEDLINE (via OVID)

MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) (search date 1 January 2019 to 30 July 2021)

1. exp Eczema/ or eczema*.tw. (23947)

2 exp Dermatitis, Atopic/ (21311)

3 exp Dermatitis/ or dermatitis.tw. (127608)

4 1 or 2 or 3 (132745)

5 exp Cyclosporine/ (29766)

6 (c?closporin* or 'Cy A' or CyA or Cy-A or 'Cs A' or CsA or Cs-A or csaneoral or neoral or sandimmun*).tw. (66284)

7 5 or 6 (71828)

8 Epidemiologic studies/ (8749)

9 exp case control studies/ (1205579)

10 exp cohort studies/ (2182735)

11 Case control.tw. (135536)

12 (cohort adj (study or studies)).tw. (242326)

13 Cohort analy$.tw. (9285)

14 (Follow up adj (study or studies)).tw. (51599)

15 (observational adj (study or studies)).tw. (125356)

16 Longitudinal.tw. (270907)

17 Retrospective.tw. (604313)

18 Cross sectional.tw. (406301)

19 Cross-sectional studies/ (379528)

20 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (3295061)

21 4 and 7 and 20 (182)

22 limit 21 to ed=20190101-20210730 (39)

1.2.2 EMBASE (via EMBASE)

Search date from 1 January 2019 to 30 July 2021

1. 'atopic dermatitis'/exp OR 'atopic dermatitis'

2. 'dermatitis'/exp

3. #1 OR #2

4. ‘cyclosporine’/exp

5. c?closporin*:ab,ti OR ‘Cy A’:ab,ti,tt OR CyA:ab,ti,tt OR Cy-A:ab,ti,tt OR ‘Cs A’:ab,ti,tt or CsA:ab,ti,tt or Cs-A:ab,ti,tt or csaneoral:ab,ti,tt or neoral:ab,ti,tt or sandimmun*:ab,ti,tt

6. #4 OR #5

7. ‘Clinical study’/exp

8. ‘Case control study’/exp

9. ‘Family study’/exp

10. ‘Longitudinal study’/exp

11. ‘Retrospective study’/exp

12. ‘Prospective study’/exp

13. ‘Randomized controlled trial (topic)’/exp

14. 12 not 13

15. ‘Cohort analysis’/exp

16. (Cohort adj (study or studies)):ab,ti,tt

17. (Case control adj (study or studies)):ab,ti,tt

18. (follow up adj (study or studies)):ab,ti,tt

19. (observational adj (study or studies)):ab,ti,tt

20. (epidemiologic* adj (study or studies)):ab,ti,tt

21. (cross sectional adj (study or studies)):ab,ti,tt

22. #7 OR #8 OR #9 OR #10 OR #11 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21

23. 3 AND 6 AND 23

24. #23 AND [01/01/2019]/sd

1.3 PRISMA flow diagrams - clinical effectiveness

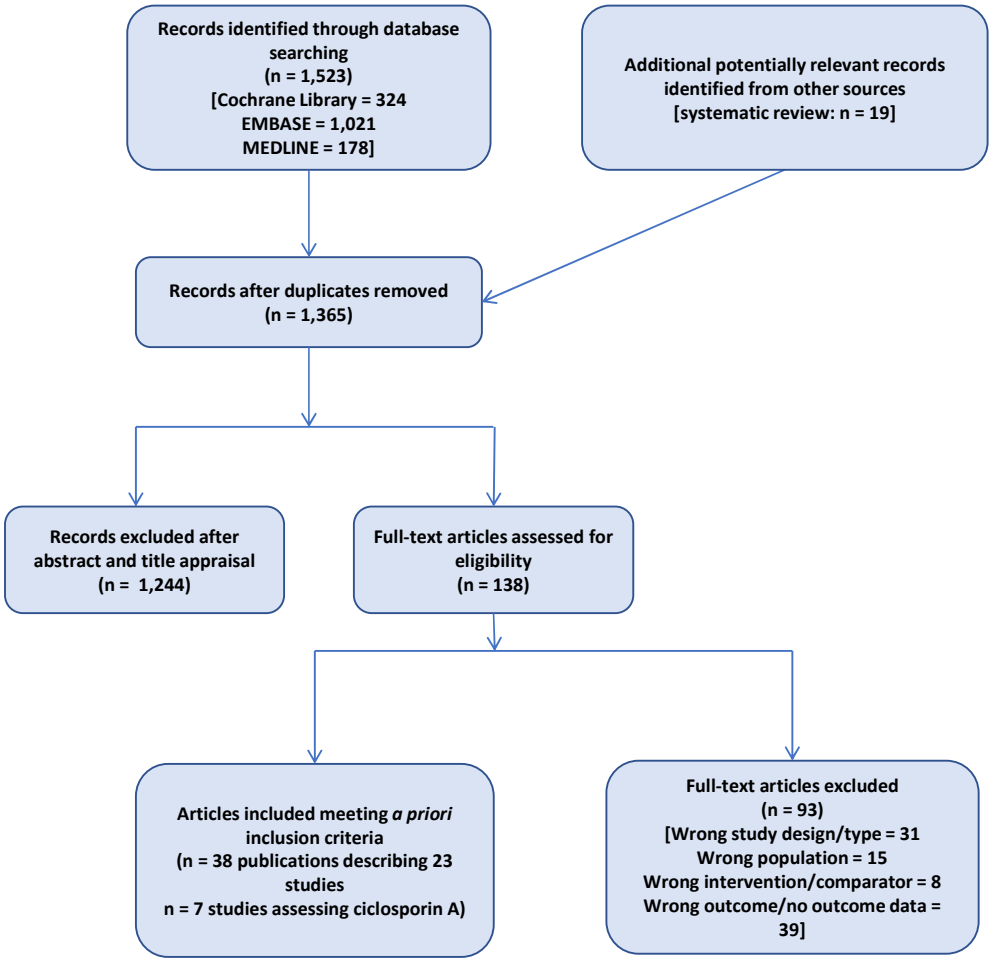

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for the literature review of RCTs[1]

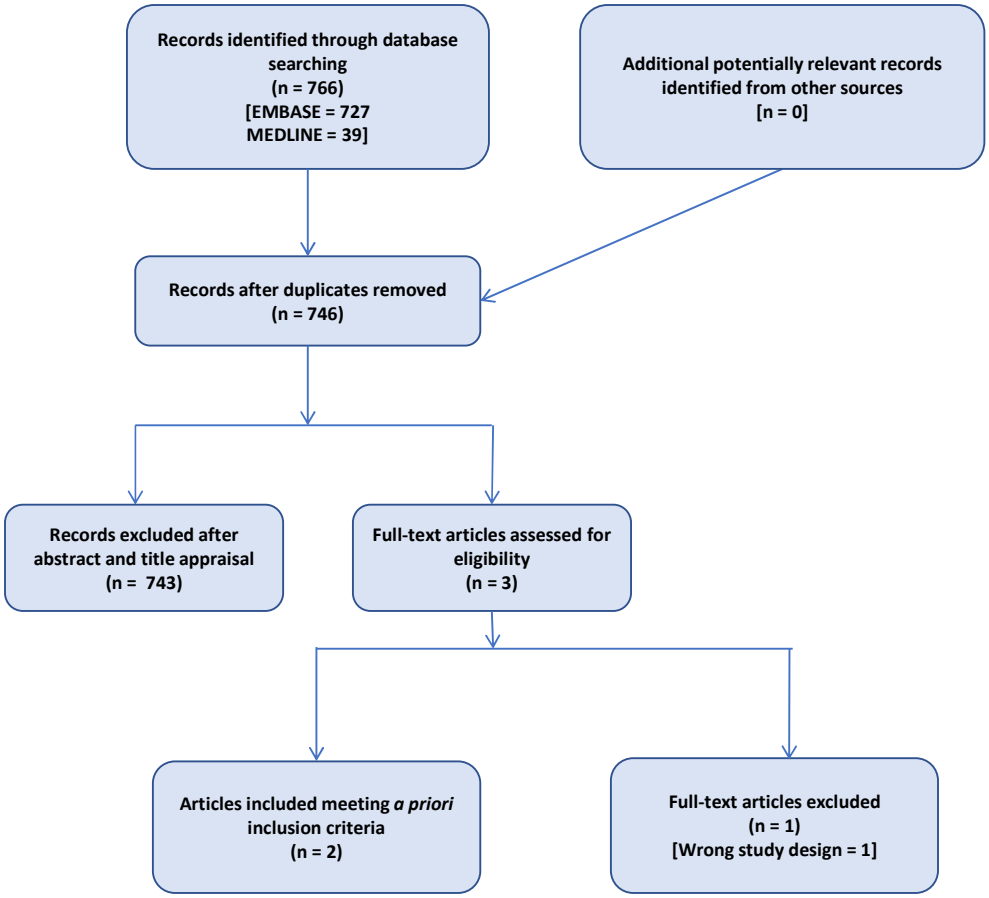

Figure 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for the literature review of observational studies of ciclosporin A[1]

1.4 Economic evaluations

1.4.1 MEDLINE (via OVID)

MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) (search date 1946 to July 07, 2021)

1 exp Eczema/ or eczema*.tw. (23877)

2 exp Dermatitis, Atopic/ (21241)

3 exp Dermatitis/ or dermatitis.tw. (127289)

4 or/1-3 (132406)

5 exp Cyclosporine/ (29732)

6 (c?closporin* or 'Cy A' or CyA or Cy-A or 'Cs A' or CsA or Cs-A or csaneoral or neoral or sandimmun*).tw. (66176)

7 (dupilumab or dupixent or 'regn 668' or REGN-668 or regn668 or 'sar 231893' or sar-231893 or sar231893 or 420K487FSG or 1190264-60-8).tw. (1031)

8 (baricitinib or olumiant or 'ly 3009104' or ly3009104 or ly-3009104 or 'incb 028050' or incb-028050 or incb028050 or 'incb 28050' or incb-28050 or incb28050 or ISP4442I3Y or 1187594-09-7).tw. (481)

9 (abrocitinib or 'pf 04965842' or pf04965842 or pf-04965842 or 'pf 4965842' or pf-4965842 or pf4965842 or 73SM5SF3OR or 1622902-68-4).tw. (32)

10 (tralokinumab or 'cat 354' or cat354 or cat-354 or GK1LYB375A or 1044515-88-9).tw. (79)

11 (upadacitinib* or rinvoq* or 'ABT 494' or ABT-494 or ABT494 or 4RA0KN46E0 or 1310726-60-3 or 1607431-21-9).tw. (165)

12 exp Antibodies, Monoclonal/ or exp Antibodies, Monoclonal, Humanized/ (249671)

13 ((humanized adj8 (monoclonal* or antibod* or MoAb* or mAb or mAbs or fab*1)) or rhuMAb*).tw. (7692)

14 (chim?eric adj3 (monoclonal* or antibod* or MoAb* or mAb or mAbs)).tw. (3898)

15 ((biological*1 or biologic*1) adj (treatment* or therap* or medicine* or drug* or agent* or product*)).tw. (27994)

16 (biologic* response modifier* or BRM*).tw. (3933)

17 targeted therap*.tw. (50825)

18 (systemic adj immunosuppressive treatment$).tw. (103)

19 immuno-modulatory treatment$.tw. (15)

20 anti inflammatory treatment$.tw. (2490)

21 exp Immunosuppressive Agents/ (325642)

22 exp Anti-Inflammatory Agents/ (528635)

23 exp Janus Kinase Inhibitors/ (635)

24 exp Interleukins/ or exp interleukin-4/ or exp interleukin-13/ (249951)

25 or/5-24 (1329133)

26 Economics/ (27346)

27 exp "Costs and Cost Analysis"/ (247076)

28 Economics, Nursing/ (4005)

29 Economics, Medical/ (9138)

30 Economics, Pharmaceutical/ (2998)

31 exp Economics, Hospital/ (25197)

32 Economics, Dental/ (1918)

33 exp "Fees and Charges"/ (30792)

34 exp Budgets/ (13849)

35 budget*.ti,ab,kf. (31686)

36 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf. (245409)

37 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2 (318761)

38 (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf. (177361)

39 (value adj2 (money or monetary)).ti,ab,kf. (2613)

40 exp models, economic/ (15703)

41 economic model*.ab,kf. (3592)

42 markov chains/ (15088)

43 markov.ti,ab,kf. (24570)

44 monte carlo method/ (29848)

45 monte carlo.ti,ab,kf. (52739)

46 exp Decision Theory/ (12508)

47 (decision* adj2 (tree* or analy* or model*)).ti,ab,kf. (27667)

48 or/26-47 (782831)

49 4 and 25 and 48 (146)

50 limit 49 to yr="2014 -Current" (59)

51 exp animals/ not humans.sh. (4857607)

52 50 not 51 (57)

1.4.2 EMBASE (via EMBASE)

Search date from 1974 to July 09, 2021

#37	#36 AND [2014-2021]/py	642
#36	#34 NOT #35	1771

#35 'animal experiment'/de NOT ('human experiment'/de OR 'human'/de) AND [embase]/lim 2321323

#34 #3 AND #25 AND #33 1779

#33 #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 3247837

#32 ('econometrics'/exp OR 'econometric':ti,ab) AND [embase]/lim 1368

#31 ('budget impact analysis'/exp OR 'budget impact':ti,ab) AND [embase]/lim 4338

#30 ('economic evaluation'/exp OR 'economic evaluation':ti,ab) AND [embase]/lim 266443

#29 ('economic model'/exp OR 'statistical model'/exp OR 'decision analysis'/exp OR 'discrete event simulation'/exp) AND [embase]/lim 147630

#28 ('economic model*':ti,ab OR 'decision tree':ti,ab OR 'markov':ti,ab OR 'decision analysis':ti,ab OR 'discrete event simulation':ti,ab) AND [embase]/lim 42539

#27 ('cost analysis':ti,ab OR 'cost-analysis':ti,ab OR 'cost effective*':ti,ab OR 'cost-effective*':ti,ab OR 'cost utility':ti,ab OR 'cost-utility':ti,ab OR 'costminimization':ti,ab OR 'costminimisation':ti,ab OR 'cost-minimisation':ti,ab OR 'cost-minimization':ti,ab OR 'cost minimization':ti,ab OR 'cost minimisation':ti,ab) AND [embase]/lim 175010

#26 ('health economics'/exp OR 'pharmacoeconomics'/exp OR 'cost'/exp OR 'cost effectiveness analysis'/exp OR 'cost benefit analysis'/exp OR 'cost utility analysis'/exp OR 'cost minimization analysis'/exp) AND [embase]/lim 708212

#25 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 4061307

#24 ('interleukin 4':ab,ti,tt OR 'interleukin 13':ab,ti,tt) AND [embase]/lim 13841

#23 ('cytokine'/exp OR 'cytokine') AND [embase]/lim1631402

#22 ('janus kinase inhibitor'/exp OR 'janus kinase inhibitor') AND [embase]/lim 18353

#21 ('antiinflammatory agent'/exp OR 'antiinflammatory agent') AND [embase]/lim 1991759

#20 ('immunosuppressive agent'/exp OR 'immunosuppressive agent') AND [embase]/lim 1079320

#19 anti AND inflammatory AND treatment*:ab,ti,tt AND [embase]/lim 132898

#18 'immuno modulatory' AND treatment*:ab,ti,tt AND [embase]/lim 519

#17 (systemic NEAR/2 immunosuppressive) AND treatment*:ab,ti,tt AND [embase]/lim 754

#16 targeted AND therap*:ab,ti,tt AND [embase]/lim 213262

#15 (biologic* AND response AND modifier* OR brm:ab,ti,tt) AND [embase]/lim 6359

#14 (((biological OR biologic) NEAR/2 (treatment* OR therap* OR medicine* OR drug* OR agent* OR product*)):ab,ti,tt) AND [embase]/lim 56354

#13 ((chim?eric NEAR/3 (monoclonal* OR antibod* OR moab* OR mab OR mabs)):ab,ti,tt) AND [embase]/lim 105

#12 (((humani?ed NEAR/5 (monoclonal* OR antibod* OR moab* OR mab OR mabs OR fab*1)):ab,ti,tt) OR rhumab*:ab,ti,tt) AND [embase]/lim 14200

#11 ('monoclonal antibody'/exp OR 'monoclonal antibody') AND [embase]/lim 625485

#10 (upadacitinib*:ab,ti,tt OR rinvoq*:ab,ti,tt OR 'abt 494':ab,ti,tt OR abt494:ab,ti,tt OR 4ra0kn46e0:ab,ti,tt OR '1310726 60 3':ab,ti,tt OR '1607431 21 9':ab,ti,tt) AND [embase]/lim 485

#9 (tralokinumab:ab,ti,tt OR cat354:ab,ti,tt OR 'cat 354':ab,ti,tt OR gk1lyb375a:ab,ti,tt OR '1044515 88 9':ab,ti,tt) AND [embase]/lim 137

#8 (abrocitinib:ab,ti,tt OR pf04965842:ab,ti,tt OR 'pf 04965842':ab,ti,tt OR 'pf 4965842':ab,ti,tt OR pf4965842:ab,ti,tt OR 73sm5sf3or:ab,ti,tt OR '1622902 68 4':ab,ti,tt) AND [embase]/lim 68

#7 (baricitinib:ab,ti,tt OR olumiant:ab,ti,tt OR ly3009104:ab,ti,tt OR 'ly 3009104':ab,ti,tt OR 'incb 028050':ab,ti,tt OR incb028050:ab,ti,tt OR 'incb 28050':ab,ti,tt OR incb28050:ab,ti,tt OR isp4442i3y:ab,ti,tt OR '1187594 09 7':ab,ti,tt) AND [embase]/lim 1041

#6 (dupilumab:ab,ti,tt OR dupixent:ab,ti,tt OR 'regn 668':ab,ti,tt OR regn668:ab,ti,tt OR 'sar 231893':ab,ti,tt OR sar231893:ab,ti,tt OR 420k487fsg:ab,ti,tt OR '1190264 60 8':ab,ti,tt) AND [embase]/lim 1771

#5 (c?closporin*:ab,ti OR cya:ab,ti,tt OR 'cy a':ab,ti,tt OR csa:ab,ti,tt OR 'cs a':ab,ti,tt OR csaneoral:ab,ti,tt OR neoral:ab,ti,tt OR sandimmun*:ab,ti,tt) AND [embase]/lim 84287

#4 'cyclosporine'/exp AND [embase]/lim 152680

#3 #1 OR #2 157924

#2 'dermatitis'/exp AND [embase]/lim 155248

#1 ('atopic dermatitis'/exp OR 'atopic dermatitis') AND [embase]/lim 47130

1.4.3 Cost-Effectiveness Analysis Registry

Date of searches: July 07, 2021

The search was conducted at the level of the condition using the basic search function and the term: “dermatitis”. Additionally, a publication date limit of 2014 was applied. The following number of records were retrieved:

- Methods: 9
- Ratios: 3

International Network of Agencies for Health Technology Assessment (INAHTA) database

Date of searches: July 07, 2021

The search was conducted at the level of the condition using the basic search function and the term: "dermatitis". Additionally, a publication date limit of 2014 was applied. The following number of records were retrieved: 4.

1.4.4 Eligibility criteria economic evaluations

Table 1. Eligibility criteria: economic evaluations

Criteria	Inclusion	Exclusion
Population	Patients with moderate-to-severe AD and aged ≥12 years.	• Patients with mild to moderate AD; • Paediatric patients (aged <12 years); • Patients suffering from other dermatological conditions; • AD affecting the hands.
Interventions	The interventions below will be considered as monotherapy or in combination with TCS: • Abrocitinib; • Baricitinib; • CsA; • Dupilumab; • Tralokinumab; • Upadacitinib.	None.
Comparators	Specified interventions versus each other or BSC. Where interventions are evaluated as a monotherapy, the intervention will be compared with other monotherapies and not in combination with TCS, and vice versa. BSC may include: emollients, low to mid potency topical corticosteroids, and rescue therapy including higher potency topical or oral corticosteroids or TCIs.	None.
Outcomes	• Costs per unit of outcome (e.g. ICERs) • QALYs; • LYG.	None.
Study design	Economic evaluations: • Cost-utility analyses • Cost-effectiveness analyses • Cost-minimisation analyses • Cost-benefit analyses • Cost-consequence analyses.	• Budget impact analysis; • Commentaries and letters; • Systematic and non-systematic reviews; • Study protocols with no results.
Limits	• Publications after January 1, 2014	• Publications prior to 1 January

	• Publications in English (numbers of relevant non-English studies will be reported).	2014; • Non-English studies (numbers of relevant non-English studies will be reported).

Abbreviations: AD, atopic dermatitis; BSC, best supportive care; CsA, ciclosporin; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids

1.4.5 PRISMA flow diagram – economic evaluations

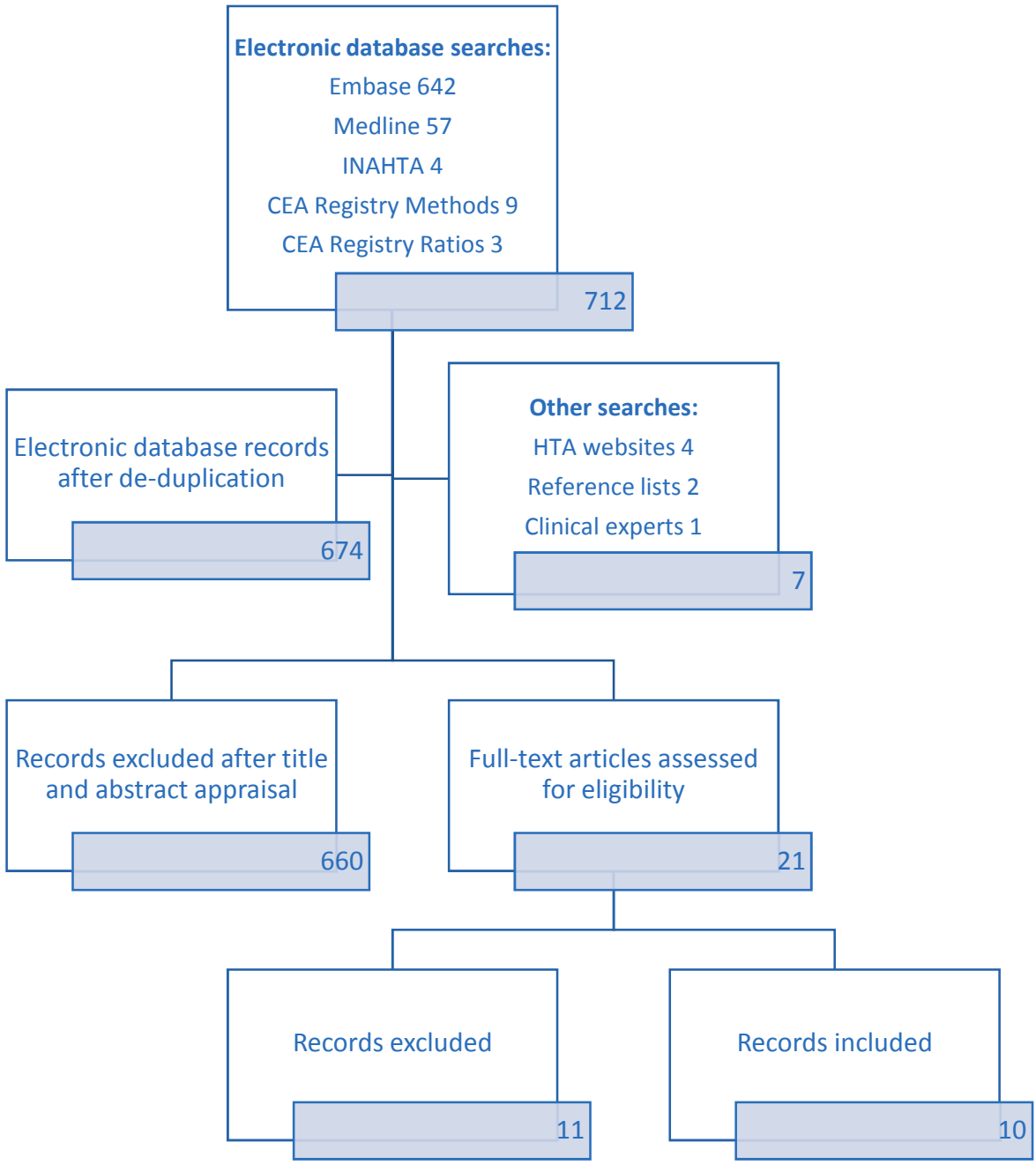

Figure 3. PRISMA diagram for economic evaluations

1.5 HRQoL

1.5.1 MEDLINE (via OVID)

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) <1946 to July 07, 2021>

1 exp Eczema/ or eczema*.tw. (23877)

2 exp Dermatitis, Atopic/ (21241)

3 exp Dermatitis/ or dermatitis.tw. (127289)

4 or/1-3 (132406)

5 Quality-Adjusted Life Years/ (13489)

6 Value of Life/ (5752)

7 (qaly$ or qald$ or qale$ or qtime$).ti,ab,kf. (12037)

8 (quality adjusted or adjusted life year$).ti,ab,kf. (18927)

9 disability adjusted life.ti,ab,kf. (3933)

10 daly$1.ti,ab,kf. (3457)

11 ((index adj3 wellbeing) or (quality adj3 wellbeing) or qwb).ti,ab,kf. (867)

12 (multiattribute$ or multi attribute$).ti,ab,kf. (1013)

13 (utility adj3 (score$1 or scoring or valu$ or measur$ or evaluat$ or scale$1 or instrument$1 or weight or weights or weighting or information or data or unit or units or health$ or life or estimat$ or elicit$ or disease$ or mean or cost$ or expenditure$1 or gain or gains or loss or losses or lost or analysis or index$ or indices or overall or reported or calculat$ or range$ or increment$ or state or states or status)).ti,ab,kf. (37025)

14 utility.ab. /freq=2 (19443)

15 utilities.ti,ab,kf. (7855)

16 disutili$.ti,ab,kf. (514)

17 (HSUV or HSUVs).ti,ab,kf. (84)

18 health$1 year$1 equivalent$1.ti,ab,kf. (40)

19 (hye or hyes).ti,ab,kf. (75)

20 (hui or hui1 or hui2 or hui3).ti,ab,kf. (1679)

21 (illness state$1 or health state$1).ti,ab,kf. (7132)

22 (euro qual or euro qual5d or euro qol5d or eq-5d or eq5-d or eq5d or euroqual or euroqol or euroqual5d or euroqol5d).ti,ab,kf. (12804)

23 (eq-sdq or eqsdq).ti,ab,kf. (1)

24 (short form$ or shortform$).ti,ab,kf. (37081)

25 (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf. (23691)

26 (sf6 or sf 6 or sf6d or sf 6d or sf six or sfsix or sf8 or sf 8 or sf eight or sfeight).ti,ab,kf. (3511)

27 (sf12 or sf 12 or sf twelve or sftwelve).ti,ab,kf. (5288)

28 (sf16 or sf 16 or sf sixteen or sfsixteen).ti,ab,kf. (30)

29 (sf20 or sf 20 or sf twenty or sftwenty).ti,ab,kf. (344)

30 (15D or 15-D or 15 dimension).ti,ab,kf. (5600)

31 (standard gamble$ or sg).ti,ab,kf. (11899)

32 (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf. (2041)

33 or/5-32 (159787)

34 4 and 33 (387)

35 limit 34 to yr="2014 -Current" (215)

36 exp animals/ not humans.sh. (4857607)

37 35 not 36 (206)

1.5.2 EMBASE (via EMBASE)

Elsevier Embase <1974 to July 09, 2021>

#16 #15 AND [2014-2021]/py 1527

#15 #13 NOT #14 2029

#14 'animal experiment'/de NOT ('human experiment'/de OR 'human'/de) AND [embase]/lim 2321323

#13 #3 AND #12 2045

#12 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 181954

#11 ('health years equivalent':ti,ab OR 'health-years equivalent':ti,ab OR 'hye':ti,ab OR 'hui':ti,ab OR 'hui1':ti,ab OR 'hui2':ti,ab OR 'hui3':ti,ab OR 'sf36':ti,ab OR 'sf 36':ti,ab OR 'thirtysix':ti,ab OR 'thirty six':ti,ab OR 'sf6':ti,ab OR 'sf 6':ti,ab OR 'sf6d':ti,ab OR 'sf 6d':ti,ab OR 'sf six':ti,ab OR 'sfsix':ti,ab OR 'sf8':ti,ab OR 'sf 8':ti,ab OR 'sf eight':ti,ab OR 'sfeight':ti,ab OR 'sf12':ti,ab OR 'sf 12':ti,ab OR 'sf twelve':ti,ab OR 'sftwelve':ti,ab OR 'sf16':ti,ab OR 'sf 16':ti,ab OR 'sf sixteen':ti,ab OR 'sfsixteen':ti,ab OR 'sf20':ti,ab OR 'sf 20':ti,ab OR 'sf twenty':ti,ab OR 'sftwenty':ti,ab OR '15d':ti,ab OR '15-d':ti,ab OR '15 dimension':ti,ab) AND [embase]/lim 82935

#10 ('qaly*':ti,ab OR 'quality adjusted':ti,ab OR 'quality-adjusted':ti,ab OR 'adjusted life year*':ti,ab OR 'disability adjusted':ti,ab OR 'disability-adjusted':ti,ab OR 'daly':ti,ab OR 'dalys':ti,ab) AND [embase]/lim 30513

#9 ('euroqol':ti,ab OR 'euro qol':ti,ab OR 'eq5d*':ti,ab OR 'eq 5d*':ti,ab OR 'eq-5d*':ti,ab) AND [embase]/lim 21463

#8 ('standard gamble':ti,ab OR 'time trade off':ti,ab OR 'time trade-off':ti,ab OR 'tto':ti,ab) AND [embase]/lim 3104

#7 ('utility value*':ti,ab OR 'health utility':ti,ab OR 'health utilities':ti,ab OR 'hsuv':ti,ab OR 'hsuvs':ti,ab OR 'disutilit*':ti,ab) AND [embase]/lim 6666

#6 'quality of life assessment'/exp AND [embase]/lim 77916

#5 'utility value'/exp AND [embase]/lim 178

#4 'quality adjusted life year'/exp AND [embase]/lim 26535

#3 #1 OR #2 157951

#2 'dermatitis'/exp AND [embase]/lim 155275

#1 ('atopic dermatitis'/exp OR 'atopic dermatitis') AND [embase]/lim 47139

1.5.3 Cost-Effectiveness Analysis Registry

Date of searches: July 07, 2021

The search was conducted at the level of the condition using the basic search function and the term "dermatitis". Additionally, a publication date limit of 2014 was applied. The following number of records were retrieved:

- Utility weights: 4

International Network of Agencies for Health Technology Assessment (INAHTA) database

Date of searches: July 07, 2021

The search was conducted at the level of the condition using the basic search function and the term "dermatitis". Additionally, a publication date limit of 2014 was applied. The following number of records were retrieved: 4.

1.5.4 Eligibility criteria HRQoL studies

Table 2. Eligibility criteria: studies reporting HRQoL data

Criteria	Inclusion	Exclusion
Population	Patients with moderate-to-severe AD and aged ≥12 years.	• Patients with mild to moderate AD; • Paediatric patients (aged <12 years); • Patients suffering from other dermatological conditions; • AD affecting the hands.
Interventions	None.	None.
Comparators	None.	None.

Outcomes	• Preference-based multi-attribute utility values (e.g. EQ-5D, HUI-3, SF-6D) • Direct utility elicitation tools (TTO, standard gamble, rating scale) • Generic health-related quality of life questionnaires (e.g. SF-36, SF-12).	Outcomes not listed.
Study design	Studies reporting original HRQoL data.	• Commentaries and letters; • Systematic and non-systematic reviews; • Study protocols with no results.
Limits	• Publications after January 1, 2014 • Publications in English (numbers of relevant non-English studies will be reported).	• Publications prior to 1 January 2014; • Non-English studies (numbers of relevant non-English studies will be reported).

Abbreviations: AD, atopic dermatitis; EQ-5D, EuroQol 5 Dimensions; HRQoL, health-related quality of life; HUI, health utilities index; SF-6D, short-form 6-dimension; SF-12, 12-item short-form health survey; TTO, time trade-off

1.5.5 PRISMA flow diagram - HRQoL

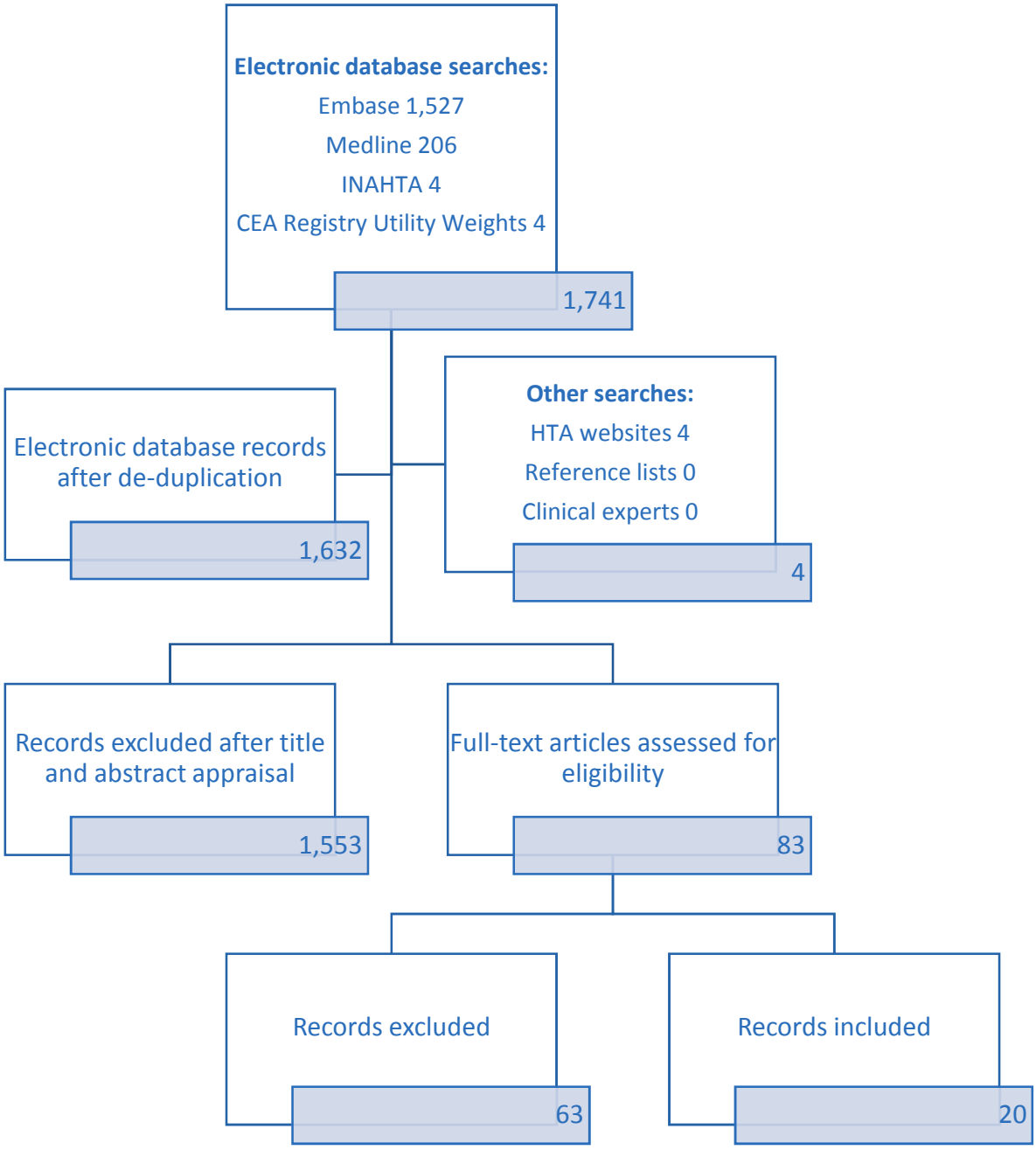

Figure 4. PRISMA diagram for studies reporting HRQoL data

2 Tables of excluded studies

2.1 Randomised controlled trials of clinical effectiveness

Table 3. Studies excluded from the systematic review of randomised controlled trials for clinical effectiveness with rationale

Study	Reason for exclusion

Correction[2]	Wrong population
Alexis 2020[3]	Wrong outcome
Andres 2020[4]	Wrong study type
Armstrong 2020[5]	Wrong study type
Armstrong 2021a[6]	Wrong study type
Armstrong 2021b[7]	Wrong study type
Beck 2014[8]	Wrong intervention
Beck 2019a[9]	Wrong outcome
Beck 2019b[10]	Wrong outcome
Beck 2019c[11]	Wrong outcome
Beck 2020a[12]	Wrong study type
Beck 2020b[13]	Wrong study type
Beck 2021a[14]	Wrong outcome
Beck 2021b[15]	Wrong study type
Bhutani 2020[16]	Wrong population
Bieber 2014[17]	Wrong intervention
Blake 2019[18]	Wrong outcome
Blauvelt 2019[19]	Wrong intervention
Blauvelt 2020a[20]	Wrong study type
Blauvelt 2020b[21]	Wrong study type
Blauvelt 2020c[22]	Wrong study type
Blauvelt 2020d[23]	Wrong study type
Blauvelt 2021a[24]	Wrong study type
Blauvelt 2021b[25]	Wrong study type
Blauvelt 2021c[26]	Wrong study type
Callewaert 2019[27]	Wrong outcome
Cork 2019[28]	Wrong study type
Cork 2020[29]	Wrong outcome
Cork 2021a[30]	Wrong outcome
Cork 2021b[31]	Wrong population
Cork 2021c[32]	Wrong study type
de Bruin-Weller 2020a[33]	Wrong outcome
de Bruin-Weller 2020b[34]	Wrong outcome
Deng 2019[35]	Wrong study type
Drucker 2018[36]	Wrong study type
Elewski 2021[37]	Wrong outcome
Gooderham 2020a[38]	Wrong population
Gooderham 2020b[39]	Wrong population
Gooderham 2021a[40]	Wrong population

Gooderham 2021b[41]	Wrong study type
Guttman-Yassky 2019a[42]	Wrong intervention
Guttman-Yassky 2019b[43]	Wrong outcome
Guttman-Yassky 2019c[44]	Wrong study type
Guttman-Yassky 2019d[45]	Wrong intervention
Guttman-Yassky 2020a[46]	Wrong outcome
Guttman-Yassky 2020b[47]	Wrong outcome
Guttman-Yassky 2021[48]	Wrong outcome
Hamilton 2014[49]	Wrong intervention
Lacour 2020a[50]	Wrong study type
Lacour 2020b[51]	Wrong study type
Lake 2019[52]	Wrong study type
Lebwohl 2021[53]	Wrong study type
Lio 2021[54]	Wrong outcome
Marcoux 2021[55]	Wrong population
McMichael 2021[56]	Wrong outcome
Merola 2020a[57]	Wrong outcome
Merola 2020b[58]	Wrong outcome
Paller 2020a[59]	Wrong population
Paller 2020b[60]	Wrong population
Paller 2020c[61]	Wrong population
Paller 2020d[62]	Wrong population
Paller 2021a[63]	Wrong population
Paller 2021b[64]	Wrong population
Papp 2020[65]	Wrong outcome
Peng 2019[66]	Wrong intervention
Raniga 2021[67]	Wrong outcome
Reich 2020a[68]	Wrong outcome
Reich 2020b[69]	Wrong outcome
Reich 2020d[70]	Wrong study type
Reich 2020e[71]	Wrong study type
Seigfried 2020[72]	Wrong outcome
Silverberg 2018a[73]	Wrong outcome
Silverberg 2018b[74]	Wrong outcome
Silverberg 2020[75]	Wrong outcome
Silverberg 2021a[76]	Wrong outcome
Silverberg 2021b[77]	Wrong outcome
Silverberg 2021c[78]	Wrong outcome
Silverberg 2021d[79]	Wrong population

Silverberg 2021e[80]	Wrong outcome
Simpson 2019[81]	Wrong outcome
Simpson 2020a[82]	Wrong outcome
Simpson 2020b[83]	Wrong outcome
Simpson 2020c[84]	Wrong outcome
Simpson 2020d[85]	Wrong outcome
Simpson 2021a[86]	Wrong study type
Simpson 2021b[87]	Wrong outcome
Simpson 2021c[88]	Wrong population
Thaci 2020a[89]	Wrong study type
Thaci 2020b[90]	Wrong study type
Tofte 2018[91]	Wrong study type
Tsianakas 2018[92]	Wrong intervention
Wu 2021[93]	Wrong outcome
Zheng 2020[94]	Wrong study type

2.2 Economic evaluations

Table 4. Excluded studies list: economic evaluations

#	Bibliographic reference	Reason for exclusion
1	Ariëns LFM, van Nimwegen KJM, Shams M, de Bruin DT, van der Schaft J, van Os-Medendorp H, De Bruin-Weller M. Economic Burden of Adult Patients with Moderate-to-severe Atopic Dermatitis Indicated for Systemic Treatment. Acta Derm Venereol. 2019 Jul; 99(9): 762-768.	Irrelevant study design
2	Ariëns LFM, van der Schaft J, van Os-Medendorp H, De Bruin-Weller M. The economic impact of patients with moderate-to-severe atopic dermatitis eligible for systemic treatment. Br. J. Dermatol. 2018; 179(1): e38.	Irrelevant study design
3	Cabout E, Eymere S, Launois R, Aslanian F, Taïeb C, Seité S. Cost Effectiveness of Emollients in the Prevention of Relapses in Atopic Dermatitis. Clin Cosmet Investig Dermatol. 2020; 13: 987-996	Irrelevant comparison
4	Costanzo A, Furneri G, Bitonti R, Pedone MP, Fanelli F, Di Turi R. Cost-effectiveness analysis of dupilumab for the treatment of severe atopic dermatitis in adults in Italy: Analisi costo-utilità di dupilumab per il trattamento della dermatite atopica grave negli adulti in Italia. Glob Reg Health Technol Assess. 2020; 7(1): 57-65	Non-English publication
5	Edwards HA, McMeniman EK. 12-month cost comparison of dupilumab treatment versus alternatives for severe atopic dermatitis. The Australasian College of Dermatologists. 2021	Irrelevant study design
6	Edwards HA, McMeniman EK. The cost of dupilumab treatment for severe atopic dermatitis is largely offset by broader health-care savings and improvement in quality of life. Australas J Dermatol. 2020 May; 61(2): e273-e275	Irrelevant study design
7	Freund D, Choi J. Is ICER NICEr?. PharmacoEconomics. 2018; 36: 385–386	Irrelevant study design

8*	Gutknecht M, Reinert R, Augustin M. Review of Health Economic Analysis in Atopic Dermatitis. 2019	Irrelevant study design
9	Sach TH, McManus E, Levell NJ. Understanding economic evidence for the prevention and treatment of atopic eczema. Br J Dermatol. 2019; 181(4): 707-716	Irrelevant study design
10	Takenaka M, Matsumoto M, Murota H, Inoue S, Shibahara H, Yoshida K, Takigawa S, Ishimoto A. Cost-effectiveness analysis of delgocitinib in adult patients with atopic dermatitis in Japan. J Cutan Immunol Allergy. 2021; 00: 1-9	Irrelevant comparison
11	Wu AC, Fuhlbrigge AL, Robayo MA, Shaker M. Cost-Effectiveness of Biologics for Allergic Diseases. J Allergy Clin Immunol Pract. 2021 Mar; 9(3): 1107-1117	Irrelevant study design Irrelevant comparison

*Exported reference from the electronic databases could not be identified (J. Dermatol. Nurses' Assoc. 2020; 12(2):1945-760X). As such, the abstract at the 24th World Congress of Dermatology Milan 2019 which included the same authors and title was considered for inclusion.

2.3 Health related quality of life

Table 5. Excluded studies list: economic evaluations

#	Bibliographic reference	Reason for exclusion
1	Alegre-Sanchez A, de Perosanz-Lobo D, Pascual-SÃ¡nchez A, Pindado-Ortega C, Fonda-Pascual P, Moreno-Arrones ÃM, JaÃon-Olasolo P. Impact on Quality of Life in Dermatology Patients Attending an Emergency Department, Actas Dermo-Sifiliográficas (English Edition). 2017; 108(10): 918-923	Irrelevant population
2	Ali FM, Kay R, Finlay AY, Piguet V, Kupfer J, Dalgard F, Salek MS. Mapping of the DLQI scores to EQ-5D utility values using ordinal logistic regression. Qual Life Res. 2017 Nov; 26(11): 3025-3034	Irrelevant population
3	Augustin M, Langenbruch A, Blome C, Gutknecht M, Werfel T, Ständer S, Steinke S, Kirsten N, Silva N, Sommer R. Characterizing treatment-related patient needs in atopic eczema: insights for personalized goal orientation. J Eur Acad Dermatol Venereol. 2020 Jan; 34(1): 142-152	Irrelevant outcome
4	Blauvelt A, Szepietowski JC, Papp K, Simpson, E, Silverberg JI, Kim, BS, Kwatra SG, Kuligowski ME, Venturanza ME, Sun K, Kircik L. 325 Ruxolitinib cream rapidly decreases skin pain in atopic dermatitis. Journal of Investigative Dermatology. 2021 May; 141(5): S57	Abstract with insufficient detail
5	Cabout E, Trouiller JB, Launois R, Taieb C,SEITE, S. PSY1 COST-EFFECTIVENESS OF EMOLLIENTS IN PATIENTS WITH ATOPIC DERMATITIS. Value in Health. 2019; 22: S901.	Original HRQoL data not reported
6	Cabout E, Eymere S, Launois R, Aslanian F, Taïeb C, Seité S. Cost Effectiveness of Emollients in the Prevention of Relapses in Atopic Dermatitis. Clin Cosmet Investig Dermatol. 2020 Dec 21; 13: 987-996	Original HRQoL data not reported Irrelevant population
7	Canadian Agency for Drugs and Technologies in Health (CADTH). Drug Reimbursement Review Dupilumab (Dupixent). 2018	Original HRQoL data not reported Utility data redacted
8	Carvalho D, Aguiar P, Mendes-Bastos P, Palma-Carlos A, Freitas J, Ferrinho P. Quality of Life and Characterization of Patients With Atopic Dermatitis in Portugal: The QUADEP Study. J Investig Allergol Clin Immunol. 2020; 30(6): 430-438	Irrelevant outcome Irrelevant population

9	Cheng B, Silverberg J. 599 Impact of atopic dermatitis on overall health-related quality of life and health utility scores in US adult patients. Journal of Investigative Dermatology. 2019 May; 139(5): S103	Abstract with insufficient detail
10	Cheng BT, Silverberg JI. Association between atopic dermatitis and lower health utility scores in US adults. Ann Allergy Asthma Immunol. 2020 Jan; 124(1): 88-89	Abstract with insufficient detail
11	Cork MJ, Eckert L, Simpson EL, Armstrong A, Barbarot S, Puig L, Girolomoni G, de Bruin-Weller M, Wollenberg A, Kataoka Y, Remitz A, Beissert S, Mastey V, Ardeleanu M, Chen Z, Gadkari A, Chao J. Dupilumab improves patient-reported symptoms of atopic dermatitis, symptoms of anxiety and depression, and health-related quality of life in moderate-to-severe atopic dermatitis: analysis of pooled data from the randomized trials SOLO 1 and SOLO 2. J Dermatolog Treat. 2020 Sep; 31(6): 606-614	Irrelevant outcome
12	Costanzo A, Furneri G, Bitonti R, Pedone MP, Fanelli F, Di Turi R. Cost-effectiveness analysis of dupilumab for the treatment of severe atopic dermatitis in adults in Italy: Analisi costo-utilità di dupilumab per il trattamento della dermatite atopica grave negli adulti in Italia. Glob Reg Health Technol Assess. 2020; 7(1): 57-65	Non-English publication
13	Bruin-Weller M, Pink AE, Patrizi A, Giménez-Arnau AM, Agner T, Roquet-Gravy P-P, Jayawardena S, Ardeleanu M, Kerkmann U, Rizova E. 161 EUROSTAD Prospective Observational Study: Baseline Characteristics, Atopic Dermatitis Severity, and Patient-Reported Outcomes. Journal of Investigative Dermatology. 2019; 139(9): S241	Irrelevant outcome
14	Bruin-Weller M, Pink AE, Patrizi A, Giménez-Arnau AM, Agner T, Roquet-Gravy P-P, Jayawardena S, Ardeleanu M, Kerkmann U, Rizova E. EUROSTAD prospective observational study: Baseline characteristics, atopic dermatitis severity, and patient-reported outcomes. Journal of Investigative Dermatology. 2019; 81(4): AB58	Irrelevant outcome
15	Eckert L, Gupta S, Amand C, Gadkari A, Mahajan S. Impact of atopic dermatitis on patient self-reported quality of life, productivity loss, and activity impairment: An analysis using the National Health and Wellness survey. J. Am. Acad. Dermatol. 2016; 74(5): AB87	Abstract with insufficient detail
16	Eckert L, Gupta S, Amand C, Gadkari A, Mahajan S. Comparison of atopic dermatitis with psoriasis on patient self-reported quality of life and productivity loss: Analysis of the National Health and Wellness Survey. J. Am. Acad. Dermatol. 2016; 74(5): AB85	Abstract with insufficient detail
17	Eckert L, Gupta S, Amand C, Gadkari A, Mahajan P, Gelfand JM. Impact of atopic dermatitis on health-related quality of life and productivity in adults in the United States: An analysis using the National Health and Wellness Survey. J Am Acad Dermatol. 2017 Aug; 77(2) :274-279	AD severity unclear. Authors contacted with no response
18	Eckert L, Gupta S, Gadkari A, Mahajan P, Gelfand JM. Burden of illness in adults with atopic dermatitis: Analysis of National Health and Wellness Survey data from France, Germany, Italy, Spain, and the United Kingdom. J Am Acad Dermatol. 2019 Jul; 81(1): 187-195	Irrelevant outcome
19	Eckert L, Gupta S, Gadkari A, Mahajan P, Wei W, Gelfand JM. Burden of illness in atopic dermatitis (AD) patients by self-reported severity: Analysis of national health and wellness survey data from France, Germany, Italy, Spain, and the UK. Presented at European Academy of Allergy and Clinical Immunology (EAACI), June 17–21, 2017, Helsinki, Finland	Irrelevant outcome

20	Eckert L, Gupta S, Gadkari A, Mahajan P, Wei W, Gelfand JM. Burden of illness in adults with atopic dermatitis: Analysis of national health and wellness survey data from France, Germany, Italy, Spain, and the UK. Allergy Eur. J. Allergy Clin. Immunol. 2017; 72(0): 44	Abstract with insufficient detail
21	Fanelli F, Pedone MP, Serra A, Bitonti R, Furneri G. PBI11 Cost-Effectiveness Analysis of Dupilumab for the Treatment of Atopic Dermatitis in Adolescent Patients in Italy. Value in Health. 2020; 23: S412	Abstract with insufficient detail
22	Huet F, Shourick J, Séité S, Taïeb C, Misery L. Pain in Atopic Dermatitis: An Online Population-based Survey. Acta Derm Venereol. 2020 Jul; 100(14): adv00198.	Irrelevant outcome
23	Ikeda M, Uehara H, Tsuge M. Efficacy and safety of long-term treatment with dupilumab for moderate-to-severe atopic dermatitis. 2019	Unavailable
24	Kamei K, Horise T, Yoshii N, Tanaka A. Burden of illness, medication adherence, and unmet medical needs in Japanese patients with atopic dermatitis: A retrospective analysis of a cross-sectional questionnaire survey. J Dermatol. 2021; 00: 1–8	Irrelevant population (authors confirmed patients with mild AD included, proportion unknown)
25	Kornmehl H, Singh S, Johnson M, Armstrong A. Direct-access online care for the management of atopic dermatitis: A randomized controlled clinical trial examining patient quality of life. J. Invest. Dermatol. 2017; 137(5): S58	Irrelevant outcome
26	Kornmehl H, Singh S, Johnson MA, Armstrong AW. Direct-Access Online Care for the Management of Atopic Dermatitis: A Randomized Clinical Trial Examining Patient Quality of Life. Telemed J E Health. 2017 Sep; 23(9): 726-732	Irrelevant population
27	Kupfer J, Schut C, Gieler U, Tomas-aragones L, Lien L, Dalgard F. THE BURDEN OF ATOPIC DERMATITIS AND ACNE - A COMPARISON WITH A STRATIFIED CONTROL GROUP. Acta Dermato Venereologica. 2016; 96:123	Abstract with insufficient detail
28	Kuznik A, Bégo-Le-Bagousse G, Eckert L, Gadkari A, Simpson E, Graham CN, Miles L, Mastey V, Mahajan P, Sullivan SD. Economic Evaluation of Dupilumab for the Treatment of Moderate-to-Severe Atopic Dermatitis in Adults. Dermatol Ther (Heidelb). 2017 Dec; 7(4): 493-505	Original HRQoL data not reported
29	Kwatra SG, Huang AH, Jhaveri M, Gruben D, Fung S, DiBonaventura M. 16443 Prevalence and impact of psychosocial comorbidities on health status among patients with moderate-to-severe atopic dermatitis in the United States: Analysis of the 2017 US National Health and Wellness Survey. J. Am. Acad. Dermatol.2020; 83(6): AB179	Irrelevant outcome
30	Kwatra SG, Huang AH, Jhaveri M, Gruben D, Fung S, DiBonaventura M. 16434 Health status, work productivity, and health care resource utilization in patients with moderate-to-severe atopic dermatitis: Analysis of the 2017 United States National Health and Wellness Survey. J. Am. Acad. Dermatol. 2020; 83(6): AB63	Irrelevant outcome
31	Langenbruch A, Radtke M, Franzke N, Ring J, Foelster-Holst R, Augustin M. Quality of health care of atopic eczema in Germany: results of the national health care study AtopicHealth. J Eur Acad Dermatol Venereol. 2014 Jun; 28(6): 719-26	Irrelevant outcome
32	Le PH, Vo TQ, Nguyen NH. Quality of life measurement alteration among Vietnamese: Impact and treatment benefit related to eczema. J Pak Med Assoc. 2019 Jun;69(Suppl 2)(6):S49-S56	Abstract with insufficient detail

33	Lee SH, Lee SH, Lee SY, Lee B, Lee SH, Park YL. Psychological Health Status and Health-related Quality of Life in Adults with Atopic Dermatitis: A Nationwide Cross-sectional Study in South Korea. Acta Derm Venereol. 2018 Jan 12; 98(1): 89-97	AD severity unclear. Authors contacted with no response
34	Lio PA, Wollenberg A, Thyssen JP, Pierce EJ, Rueda MJ, DeLozier AM, Ross Terres JA, Anderson P, Milligan G, Piercy J, Silverberg JI, Paul C. Impact of Atopic Dermatitis Lesion Location on Quality of Life in Adult Patients in a Real-world Study. J Drugs Dermatol. 2020 Oct 1;19(10):943-948	Irrelevant population
35	Marron SE, Alcalde-Herrero VM, Garcia-Latasa FJ, Moncin-Torres Dpharm, CA, Fuentelsaz-del-Barrio MV, Alvarez-Salafranca M, Tomas-Aragones L. Dupilumab for the treatment of adult atopic dermatatis patients in routine clinical practice. J. Am. Acad. Dermatol. 2019; 81(4): AB48	Abstract with insufficient detail
36	Marron SE, Tomas-Aragones L, Moncin-Torres CA, Gomez-Barrera M, Aranibar FJG. Patient Reported Outcome Measure in Atopic Dermatitis Patients Treated with Dupilumab: 52-Weeks Results. Life (Basel). 2021 Jun 25; 11(7): 617	Irrelevant outcome
37	Mastey V, Simpson E, Bieber T, Eckert L, Wu R, Ardeleanu M, Graham N, Pirozzi G, Sutherland E. The patient burden of atopic dermatitis: insights from a dupilumab phase 2 clinical trial in adults with moderate-to-severe disease. Experimental Dermatology. 2014; 23: 4	Abstract with insufficient detail
38	Misery L, Seneschal J, Reguiai Z, Merhand S, Héas S, Huet F, Taieb C, Ezzedine K. The impact of atopic dermatitis on sexual health. J Eur Acad Dermatol Venereol. 2019 Feb;33(2):428-432	Irrelevant outcome
39	Misery L, Seneschal J, Ezzedine K, Heas S, Merhand S, Reguiai Z, Taieb C. PSS40 Atopic dermatitis is associated with poor quality of life in adult patients. Value in Health. 2017: A399-A811	Abstract with insufficient detail
40	Misery L, Reguiai Z, Seneschal J, Heas S, Merhand S, Taieb C, Ezzedine K. Atopic dermatitis is associated with poor quality of life in adult patients. J. Am. Acad. Dermatol. 2018; 79(3): AB50	Abstract with insufficient detail
41	Nguyen SH, Nguyen LH, Vu GT, Nguyen CT, Le THT, Tran BX, Latkin CA, Ho CSH, Ho RCM. Health-Related Quality of Life Impairment among Patients with Different Skin Diseases in Vietnam: A Cross-Sectional Study. Int J Environ Res Public Health. 2019 Jan 23; 16(3): 305	AD severity unclear. Authors contacted with no response.
42	Ock M, Han JW, Lee JY, Kim SH, Jo MW. Estimating quality-adjusted life-year loss due to noncommunicable diseases in Korean adults through to the year 2040. Value Health. 2015 Jan; 18(1): 61-6	Irrelevant outcome
43	Park YL, Lee SH, Kim HJ, Hong KR, Young Park A, Lee JS. Psychologic health status and health-related quality of life in adults with atopic dermatitis. J. Am. Acad. Dermatol. 2018; 79(3): AB234	Abstract with insufficient detail
44	Rencz F, Baji P, Gulácsi L, Kárpáti S, Péntek M, Poór AK, Brodszky V. Discrepancies between the Dermatology Life Quality Index and utility scores. Qual Life Res. 2016 Jul; 25(7): 1687-96	Irrelevant population
45	Schwartzman G, Lei D, Yousaf M, Janmohamed SR, Vakharia PP, Chopra R, Chavda R, Gabriel S, Patel KR, Singam V, Kantor R, Hsu DY, Silverberg JI. Validity and reliability of Patient-Reported Outcomes Measurement Information System Global Health scale in adults with atopic dermatitis. J Am Acad Dermatol. 2021 Jan 20: S0190-9622(21)00180-8.	Irrelevant outcome
46	Seneschal J, Ezzedine K, Reguiai Z, Heas S, Merhand S, Misery L, Taieb C. PSS41 Atopic dermatitis in adults: Impact on sexuality. Value in Health. 2017:	Irrelevant outcome

	A399-A811	
47	Seneschal J, Misery L, Reguiai Z, Heas S, Merhand S, Taieb C, Ezzedine K. Atopic dermatitis in adults: Impact on sexuality. J. Am. Acad. Dermatol. 2018; 79(3): AB50	Irrelevant outcome
48	Silverberg J, Gelfand JM, Margolis D, Boguniewicz M, Fonacier L, Grayson M, Ong P, Fuxench ZC, Simpson EL. 245 Validation and interpretation of short form 12 and comparison with dermatology life quality index in adult atopic dermatitis. Journal of Investigative Dermatology. 2019; 139(5): S42	Irrelevant outcome
49	Silverberg JI, Gelfand JM, Margolis DJ, Boguniewicz M, Fonacier L, Grayson MH, Ong PY, Chiesa Fuxench ZC, Simpson EL. Validation and Interpretation of Short Form 12 and Comparison with Dermatology Life Quality Index in Atopic Dermatitis in Adults. J Invest Dermatol. 2019 Oct; 139(10): 2090-2097	Irrelevant outcome
50	Silverberg JI, Kragh N, Guttman-Yassky E, Wollenberg A. Tralokinumab with topical corticosteroids (TCS) improves health-related quality of life (HRQoL) in adults with moderate-to-severe atopic dermatitis (AD): A Phase 2b, randomized, double-blind, placebo-controlled study. Experimental dermatology. 2018; 27: 41-42	Irrelevant outcome
51	Silverberg JI, Margolis DJ, Boguniewicz M, Fonacier L, Grayson MH, Ong PY, Fuxench ZC, Simpson EL. Validation of five patient-reported outcomes for atopic dermatitis severity in adults. Br J Dermatol. 2020 Jan; 182(1): 104-111	Irrelevant outcome
52	Silverberg JI, Gelfand JM, Margolis DJ, Boguniewicz M, Fonacier L, Grayson MH, Simpson EL, Ong PY, Chiesa Fuxench ZC. Patient burden and quality of life in atopic dermatitis in US adults: A population-based cross-sectional study. Ann Allergy Asthma Immunol. 2018 Sep; 121(3): 340-347	Irrelevant outcome
53	Silverberg JI, Guttman-Yassky E, Gooderham M, Worm M, Rippon S, O'Quinn S, van der Merwe R, Kragh N, Kurbasic A, Wollenberg A. Health-related quality of life with tralokinumab in moderate-to-severe atopic dermatitis: A phase 2b randomized study. Ann Allergy Asthma Immunol. 2021 May; 126(5): 576-583	Irrelevant outcome
54	Silverberg JI, Simpson EL, Guttman-Yassky E, Cork MJ, de Bruin-Weller M, Yosipovitch G, Eckert L, Chen Z, Ardeleanu M, Shumel B, Hultsch T, Rossi AB, Hamilton JD, Orengo JM, Ruddy M, Graham NMH, Pirozzi G, Gadkari A. Dupilumab Significantly Modulates Pain and Discomfort in Patients With Atopic Dermatitis: A Post Hoc Analysis of 5 Randomized Clinical Trials. Dermatitis. 2020 Nov 5.	Irrelevant outcome
55	Silverberg JI, Chiesa-Fuxench Z, Margolis D, Boguniewicz M, Fonacier L, Grayson M, Simpson E, Ong P. Sleep Disturbances in Atopic Dermatitis in US Adults, Dermatitis: March 5, 2021	Irrelevant population Irrelevant outcome
56	Simpson E, Worm M, Soong W, Blauvelt A, Eckert L, Wu R, Ardeleanu M, Graham N, Pirozzi G, Sutherland ER, Mastey V. 544 Dupilumab improves patient-reported outcomes (PROS) in a phase 2 study in adults with moderate-to-severe atopic dermatitis. J Allergy Clin Immunol. 2015; 135(2): AB617	Abstract with insufficient detail
57	Steinke S, Langenbruch A, Ständer S, Franzke N, Augustin M. Therapeutic benefits in atopic dermatitis care from the patients' perspective: results of the German national health care study 'Atopic Health'. Dermatology. 2014; 228(4): 350-9	Irrelevant outcome
58	Takenaka M, Matsumoto M, Murota H, Inoue S, Shibahara H, Yoshida K, Takigawa S, Ishimoto A. Cost- effectiveness analysis of delgocitinib in adult patients with atopic dermatitis in Japan. J Cutan Immunol Allergy. 2021; 00: 1–9.	Irrelevant outcome

59	Thaci D, Deleuran M, De Bruin-Weller M, Chen Z, Tomondy P, Ardeleanu M, Boklage S, Shumel B, Surendranathan T. 009 Dupilumab treatment for up to 100 weeks demonstrates sustained improvement in quality of life in adult patients with moderate-to-severe atopic dermatitis (LIBERTY AD OLE). British Association of Dermatologists. 2020; 183(Suppl. 1): 9–25	Abstract with insufficient detail
60	Thaçi D, L Simpson E, Deleuran M, Kataoka Y, Chen Z, Gadkari A, Eckert L, Akinlade B, Graham NMH, Pirozzi G, Ardeleanu M. Efficacy and safety of dupilumab monotherapy in adults with moderate-to-severe atopic dermatitis: a pooled analysis of two phase 3 randomized trials (LIBERTY AD SOLO 1 and LIBERTY AD SOLO 2). J Dermatol Sci. 2019 May; 94(2): 266-275	Irrelevant outcome
61	Vilsbøll A, Kragh N, Hahn-Pedersen J, Jensen CE. An algorithm to generate EQ-5D-5L utility scores from the dermatology life quality index: A direct mapping study in a population with atopic dermatitis. Qual. Life Res. 2018; 27(0): S28-S29	Abstract with insufficient detail
62	Vilsbøll AW, Kragh N, Hahn-Pedersen J, Jensen CE. Mapping Dermatology Life Quality Index (DLQI) scores to EQ-5D utility scores using data of patients with atopic dermatitis from the National Health and Wellness Study. Qual Life Res. 2020 Sep; 29(9): 2529-2539	Irrelevant population
63	Whiteley J, Emir B, Seitzman R, Makinson G. The burden of atopic dermatitis in US adults: results from the 2013 National Health and Wellness Survey. Curr Med Res Opin. 2016 Oct; 32(10): 1645-1651	Abstract with insufficient detail

3 Quality assessments

3.1 Randomised controlled trials informing the clinical effectiveness

3.1.1 Abrocitinib

Table 6. Quality assessment of studies evaluating abrocitinib

Component	Rating for risk of bias			Comments
	Low	Unclear	High	
Phase IIb (Study B7451006)				
Random sequence generation	✓			Randomisation by interactive response technology system.
Allocation concealment	✓			Blinded study drugs and matching placebo delivered to the study sites in blister packs.
Blinding (who [participants, personnel], and method)	✓			Double blind. Patients, investigators and sponsors were blinded to study treatment.
Blinding of outcome assessment	✓			Investigators and sponsors blinded to study treatment
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)			✓	High rate of discontinuation from randomised set. Higher rate of discontinuation in placebo, 10mg and 30mg abrocitinib groups (~50% attrition) compared to 100 and 200mg abrocitinib

				groups (33% attrition).
Selective reporting	✓			Outcomes for which data are available were pre-specified.
JADE MONO-1 and JADE MONO-2				
Random sequence generation	✓			Randomisation administered by interactive response technology system.
Allocation concealment	✓			Randomised using computer generated randomisation schedule using interactive response technology.
Blinding (who [participants, personnel], and method)	✓			Patients, investigators and sponsors were blinded to treatment.
Blinding of outcome assessment	✓			Investigators and sponsors were blinded to treatment.
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			Loss to follow up was low. Treatment discontinuation was higher in the placebo group than the abrocitinib groups. Discontinuations were mainly due to adverse events, lack of efficacy and withdrawal of consent
Selective reporting	✓			Outcomes for which data are available were pre-specified.
JADE TEEN				
Random sequence generation		✓		Random allocation. Randomization stratified by baseline disease severity.
Allocation concealment		✓		Method of concealment not reported
Blinding (who [participants, personnel], and method)	✓			Double blind study design
Blinding of outcome assessment	✓			Assessments will be conducted at the investigator site by a clinical assessor blinded to treatment assignment.
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			Loss to follow up was low across all study arms.
Selective reporting		✓		NA (conference abstract).
JADE COMPARE				
Random sequence generation		✓		Described as “Randomised”
Allocation concealment	✓			Patients, investigators, and representatives of the sponsor were unaware of the trial-group assignment.
Blinding (who [participants, personnel], and method)	✓			Double-blind, double dummy study
Blinding of outcome assessment	✓			Most outcome measures were subjective but investigators and patients were blinded to treatment allocation and there were few treatment related side effects that could

				give an indication of treatment allocation. Thus, risk of bias for outcome assessment was deemed to be low.
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			Loss to follow up was low across all study arms. The main reasons for discontinuation were withdrawal by subject and adverse events, although these were low across all groups.
Selective reporting	✓			Outcomes for which data are available were pre-specified.
JADE DARE				
Random sequence generation		✓		Described as "Randomised"
Allocation concealment		✓		Described as double-blind
Blinding (who [participants, personnel], and method)		✓		Described as double-blind
Blinding of outcome assessment	✓			Most outcome measures were subjective but investigators and patients were blinded to treatment allocation and there were few treatment related side effects that could give an indication of treatment allocation. Thus, risk of bias for outcome assessment was deemed to be low.
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			Loss to follow up was low across both study arms.
Selective reporting	✓			Outcomes for which data are available were pre-specified.

3.1.2 Tralokinumab

Table 7. Quality assessment of studies evaluating tralokinumab

Component	Rating for risk of bias			Comments
	Low	Unclear	High	
Phase IIb dose ranging study				
Random sequence generation		✓		Method of randomisation not reported
Allocation concealment		✓		Method to maintain concealment of allocation not reported
Blinding (who [participants, personnel], and method)	✓			Participant, Care Provider, Investigator, and Outcomes Assessor were masked to treatment assignment
Blinding of outcome assessment	✓			Most outcome measures are subjective. However, investigators and participants

				were masked to treatment allocation, and there was low occurrence of treatment-related side effects that could suggest treatment allocation, thus, outcome assessment was deemed to be at low risk of bias
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			Loss to follow up was low
Selective reporting	✓			Based on outcomes reported for the study on ClinicalTrials.gov, outcomes for which data are available were pre-specified
ECZTRA 1 and ECZTRA 2				
Random sequence generation	✓			Randomisation was carried out using an interactive response system, with randomisation stratified by region ((ECZTRA 1: North America, Japan and Europe; ECZTRA 2: North America, Europe, Australia and Korea) and baseline disease severity (IGA 3 or 4)
Allocation concealment	✓			Interactive response system used to allocate treatment, which together with use of placebo, minimises risk of allocation bias However, tralokinumab and placebo are visually distinct and not matched for viscosity. To minimise risk of revealing allocation, investigational medicinal products were handled and administered by a qualified, unblinded health-care professional at the site who was not involved in the management of trial participants and who did not perform any of the assessments
Blinding (who [participants, personnel], and method)	✓			Participant and Investigator, were masked to treatment assignment
Blinding of outcome assessment	✓			Most outcome measures are subjective. However,

				investigators and participants were masked to treatment allocation. There was low occurrence of treatment-related side effects that could suggest treatment allocation, thus, outcome assessment was deemed to be at low risk of bias
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			Loss to follow up was low. Treatment discontinuation was higher in the placebo group than the tralokinumab group. Discontinuations were mainly due to lack of efficacy and withdrawal of consent
Selective reporting	✓			Based on outcomes reported in the publication for ECZTRA 1 and 2, outcomes for which data are available were pre-specified
ECZTRA 5				
Random sequence generation		✓		Method of randomisation not reported
Allocation concealment	✓			Method to maintain concealment of allocation not reported
Blinding (who [participants, personnel], and method)	✓			Participant and Investigator, were masked to treatment assignment
Blinding of outcome assessment	✓			The study was designed to evaluate whether tralokinumab affects the body's immune response to vaccines. Most outcomes were based on results from laboratory assessments. For the outcomes of interest to the MTA, investigators and participants were masked to treatment allocation and, for this reason, risk of compromising masking of outcome assessment has been categorised as low risk
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			Loss to follow up was low
Selective reporting	✓			Based on outcomes reported in the publication for

				ECZTRA 5, outcomes for which data are available were pre-specified
ECZTRA 3				
Random sequence generation	✓			Randomisation was carried out using an interactive response system, with randomisation stratified by region (North America and Europe) and baseline disease severity (IGA 3 or 4)
Allocation concealment	✓			Interactive response system used to allocate treatment, which together with use of placebo, minimises risk of allocation bias However, tralokinumab and placebo are visually distinct and not matched for viscosity. To minimise risk of revealing allocation, investigational medicinal products were handled and administered by a qualified, unblinded health-care professional at the site who was not involved in the management of trial participants and who did not perform any of the assessments
Blinding (who [participants, personnel], and method)	✓			Participant and Investigator, were masked to treatment assignment
Blinding of outcome assessment	✓			Most outcome measures are subjective. However, investigators and participants were masked to treatment allocation. There was low occurrence of treatment-related side effects that could suggest treatment allocation, thus, outcome assessment was deemed to be at low risk of bias
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			Loss to follow up was low. Treatment discontinuation was higher in the placebo group than the tralokinumab group. Discontinuations were mainly due to lack of efficacy and

				withdrawal of consent
Selective reporting	✓			Based on outcomes reported in the publication for ECZTRA 3, outcomes for which data are available were pre-specified
ECZTRA 7				
Random sequence generation	✓			Randomisation was carried out using an interactive response system, with randomisation stratified by prior cyclosporin A use, country (Germany, yes or no) and baseline disease severity (IGA 3 or 4)
Allocation concealment	✓			Interactive response system used to allocate treatment, which together with use of placebo, minimises risk of allocation bias
Blinding (who [participants, personnel], and method)	✓			Participant and Investigator, were masked to treatment assignment
Blinding of outcome assessment	✓			Most outcome measures are subjective. However, investigators and participants were masked to treatment allocation, and there was low occurrence of treatment-related side effects that could suggest treatment allocation, thus, outcome assessment was deemed to be at low risk of bias
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			Loss to follow up was low. Treatment discontinuation was higher in the placebo group than the tralokinumab group. Discontinuations were mainly due to lack of efficacy and withdrawal of consent
Selective reporting	✓			Based on outcomes reported on the record for ECZTRA 7 on ClinicalTrials.gov, outcomes for which data are available were pre-specified

3.1.3 Upadacitinib

Table 8. Quality assessment of studies evaluating upadacitinib

Component	Rating for risk of bias			Comments
	Low	Unclear	High	
Phase IIb study				
Random sequence generation	✓			An interactive response system referring to a schedule previously generated via computer by statisticians from the study sponsor was used to randomize qualifying patients 1:1:1:1
Allocation concealment	✓			Each study drug kit was labelled with a unique code that was linked to the randomization schedule.
Blinding (who [participants, personnel], and method)	✓			Patients, investigators, and the sponsor were blinded to allocation. The placebo and upadacitinib tablets were identical in appearance to maintain blinding of treatment assignment.
Blinding of outcome assessment	✓			Most outcome measures were subjective but investigators and patients were blinded to treatment allocation and there were few-treatment related side effects that could give an indication of treatment allocation. Thus, risk of bias for outcome assessment was deemed to be low.
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			Loss to follow up was low. Treatment discontinuation seems to be dose dependent with higher discontinuation in the placebo and the low dose (7.5mg) upadacitinib groups.
Selective reporting	✓			Results for all specified outcomes were reported
HEADS UP				
Random sequence generation	✓			Randomisation was carried out using interactive response technology, a unique identification number was issued at the screening visit, which encoded the patient's treatment group according to a randomisation schedule generated by the statistics department at AbbVie.
Allocation concealment	✓			Interactive response system used to allocate treatment, which together with use of placebo, minimises risk of allocation bias
Blinding (who [participants, personnel], and method)	✓			Participant, Care Provider, Investigator, and Outcomes Assessors were all masked to treatment assignment

Blinding of outcome assessment	✓			Most outcome measures were subjective but as investigators and patients were blinded to treatment allocation and there were few treatment related side effects that could give an indication of treatment allocation, risk of bias for outcome assessment was deemed to be low.
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)		✓		Patient flow diagram not available
Selective reporting		✓		N/A (no publication)
MEASURE UP1 and MEASURE UP2				
Random sequence generation	✓	✓		Randomisation was carried out using interactive response technology, a unique identification number was issued at the screening visit, which encoded the patient's treatment group according to a randomisation schedule generated by the statistics department at AbbVie.
Allocation concealment	✓			Interactive response system used to allocate treatment, which together with use of placebo, minimises risk of allocation bias
Blinding (who [participants, personnel], and method)	✓			Participant, Care Provider, Investigator, and Outcomes Assessors were all masked to treatment assignment
Blinding of outcome assessment	✓			Most outcome measures were subjective but as investigators and patients were blinded to treatment allocation and there were few treatment related side effects that could give an indication of treatment allocation, risk of bias for outcome assessment was deemed to be low.
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			Loss to follow up was low. Treatment discontinuations were higher in the placebo group than in either upadacitinib group. Discontinuations were mainly due to lack of efficacy and withdrawal of consent.
Selective reporting				N/A (no publication available at the time of writing)
AD UP				
Random sequence generation	✓			Randomisation was carried out using interactive response technology, a unique identification number was issued at the screening visit, which encoded the patient's treatment group according to a randomisation schedule generated by the statistics department at AbbVie.

Allocation concealment	✓			Interactive response system used to allocate treatment, which together with use of placebo, minimises risk of allocation bias
Blinding (who [participants, personnel], and method)	✓			Participant, Care Provider, Investigator, and Outcomes Assessors were all masked to treatment assignment
Blinding of outcome assessment	✓			Most outcome measures were subjective but as investigators and patients were blinded to treatment allocation and there were few treatment related side effects that could give an indication of treatment allocation, risk of bias for outcome assessment was deemed to be low.
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			Loss to follow up was low. Treatment discontinuations were higher in the placebo group than in either upadacitinib group.
Selective reporting				N/A (no publication)
RISING UP				
Random sequence generation		✓		Study described as RCT but no details reported about random sequence generation
Allocation concealment		✓		Study described as RCT but no details reported about allocation concealment
Blinding (who [participants, personnel], and method)	✓			Participant, Care Provider, Investigator, Outcomes Assessor were all blinded to treatment assignment
Blinding of outcome assessment	✓			Participant, Care Provider, Investigator, Outcomes Assessor were all blinded to treatment assignment
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)		✓		Details not available
Selective reporting		✓		N/A (no publication and no CSR provided)

3.1.4 Baricitinib

Table 9. Quality assessment of studies evaluating baricitinib

Component	Rating for risk of bias			Comments
	Low	Unclear	High	
BREEZE-AD1 and BREEZE AD2				
Random sequence generation	✓			Randomised by an interactive web response system.
Allocation concealment	✓			Interactive response system used to allocate treatment, which together with use of

				placebo, minimises risk of allocation bias
Blinding (who [participants, personnel], and method)	✓			Double blind – matched placebo tablets
Blinding of outcome assessment	✓			Outcome assessors blind to treatment allocation
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			Loss to follow up was low across all study arms. The main reasons for discontinuation were withdrawal by subject and lack of efficacy, although these were low across all groups.
Selective reporting	✓			Outcomes for which data are available were pre-specified.
Phase II (Guttman-Yassky 2019)				
Random sequence generation	✓			Randomised by an interactive response system.
Allocation concealment	✓			Blocked randomisation generated and maintained centrally with interactive response technology.
Blinding (who [participants, personnel], and method)	✓			Double blind – matched placebo tablets
Blinding of outcome assessment	✓			Outcome assessors blind to treatment allocation
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)			✓	Loss to follow up was relatively high across all study arms, highest in the placebo group (41%). The main reasons for discontinuation were withdrawal by subject and lack of efficacy and adverse events.
Selective reporting	✓			Outcomes for which data are available were pre-specified.
BREEZE-AD4				
Random sequence generation	✓			Randomised by an interactive web response system.
Allocation concealment	✓			Interactive response system used to allocate treatment, which together with use of placebo, minimises risk of allocation bias
Blinding (who [participants, personnel], and method)	✓			Double blind – matched placebo tablets
Blinding of outcome assessment	✓			Outcome assessors blind to

				treatment allocation
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			Loss to follow up was low across all study arms. Treatment discontinuation was higher in the placebo group than the baricitinib groups.
Selective reporting	✓			Outcomes for which data are available were pre-specified.
BREEZE-AD7				
Random sequence generation	✓			Randomised by an interactive web response system.
Allocation concealment	✓			Interactive response system used to allocate treatment, which together with use of placebo, minimises risk of allocation bias
Blinding (who [participants, personnel], and method)	✓			Double blind – matched placebo tablets
Blinding of outcome assessment	✓			Outcome assessors blind to treatment allocation
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			Loss to follow up was low across all study arms. The main reasons for discontinuation were withdrawal by subject and adverse events, although these were low across all groups.
Selective reporting	✓			Outcomes for which data are available were pre-specified.

3.1.5 Dupilumab

Table 10 Quality assessment of studies evaluating dupilumab

Component	Rating for risk of bias			Comments
	Low	Unclear	High	
Phase IIb				
Random sequence generation	✓			Randomisation was performed using a central randomisation scheme provided by an interactive voice-response system, and stratified by disease severity and region.
Allocation concealment	✓			Blinded study drug kits coded providing masking to treatment assignment.

Blinding (who [participants, personnel], and method)	✓			The study remained blinded to all individuals (including patients, investigators, sponsors and study personnel) until the time of prespecified unblinding.
Blinding of outcome assessment	✓			The study remained blinded to principal investigators and study centre personnel until the time of prespecified unblinding.
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			Loss to follow-up was low across all groups.
Selective reporting	✓			Results for all specified outcomes were reported
AD ADOL				
Random sequence generation		✓		"Randomised"
Allocation concealment	✓			Blinded study drug kits coded with a medication numbering system were used. To maintain blinding, lists linking codes with product lot numbers were not accessible to individuals involved in study conduct.
Blinding (who [participants, personnel], and method)	✓			The study remained blinded to all individuals (including patients, investigators, and study personnel) until the time of prespecified unblinding.
Blinding of outcome assessment	✓			The study remained blinded to study personnel until the time of prespecified unblinding, except for independent data monitoring committee members.
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			Loss to follow-up was low across all groups.
Selective reporting	✓			Results for all specified outcomes were reported
SOLO-1 and SOLO-2				
Random sequence generation	✓			Randomization was conducted by means of a central interactive voice-response system, and stratified by disease severity and by region

Allocation concealment	✓			Blinded, coded kits containing dupilumab or placebo were used to mask the assigned treatment
Blinding (who [participants, personnel], and method)	✓			Double-blind study design with matched placebo to ensure blinding of participants and care providers.
Blinding of outcome assessment	✓			Most outcome measures were subjective but as investigators and patients were blinded to treatment allocation and there were few treatment related side effects that could give an indication of treatment allocation, risk of bias for outcome assessment was deemed to be low.
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			Loss to follow up was low. Treatment discontinuations were higher in the placebo groups than in dupilumab groups for both studies.
Selective reporting	✓			Results for all specified outcomes were reported
CAFE				
Random sequence generation	✓			Randomisation was performed using a central randomisation scheme provided by an interactive voice-response system, and stratified by disease severity, region, prior CSA exposure and candidate for CSA treatment.
Allocation concealment	✓			Interactive response system used to allocate treatment, which together with use of placebo, minimises risk of allocation bias
Blinding (who [participants, personnel], and method)	✓			Double-blind study design with matched placebo to ensure blinding of participants and care providers.
Blinding of outcome assessment	✓			Most outcome measures were subjective but as investigators and patients were blinded to treatment allocation and there were few treatment related side effects that could give an

				indication of treatment allocation, risk of bias for outcome assessment was deemed to be low.
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			Loss to follow-up was low across all groups.
Selective reporting	✓			Results for all specified outcomes were reported
CHRONOS				
Random sequence generation	✓			Randomisation was performed using a central randomisation scheme provided by an interactive voice-response system, and stratified by disease severity and by region
Allocation concealment	✓			Interactive response system used to allocate treatment, which together with use of placebo, minimises risk of allocation bias
Blinding (who [participants, personnel], and method)	✓			Double-blind study design with matched placebo to ensure blinding of participants and care providers.
Blinding of outcome assessment	✓			Most outcome measures were subjective but as investigators and patients were blinded to treatment allocation and there were few treatment related side effects that could give an indication of treatment allocation, risk of bias for outcome assessment was deemed to be low.
Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			Loss to follow up was low. Treatment discontinuations were higher in the placebo groups than in dupilumab groups.
Selective reporting	✓			Results for all specified outcomes were reported

3.1.6 *Summary of risk of bias assessments of RCTs included in the clinical effectiveness review*

Table 11. Summary of risk of bias assessments of RCTs included in the review

Study	Sequence generation	Allocation concealment	Masking of participants and personnel	Masking of outcome assessment	Incomplete outcome data	Selective reporting	Overall risk of bias
Abrocitinib							
Study B7451006[95]	✓	✓	✓	✓	X	✓	Some concerns
JADE MONO-1[96]	✓	✓	✓	✓	✓	✓	Low
JADE MONO-2[97]	✓	✓	✓	✓	✓	✓	Low
JADE TEEN[98]	?	?	✓	✓	✓	?	Some concerns
JADE COMPARE[99]	?	✓	✓	✓	✓	✓	Low
JADE DARE[100]	?	?	?	✓	✓	✓	Some concerns
Tralokinumab							
Phase IIb[101]	?	?	✓	✓	✓	✓	Some concerns
ECZTRA 1[102]	✓	✓	✓	✓	✓	✓	Low
ECZTRA 2[102]	✓	✓	✓	✓	✓	✓	Low
ECZTRA 3[103]	✓	✓	✓	✓	✓	✓	Low
ECZTRA 5[104]	?	✓	✓	✓	✓	✓	Low
ECZTRA 7[105]	✓	✓	✓	✓	✓	✓	Low
Upadacitinib							
Phase IIb[106]	✓	✓	✓	✓	✓	✓	Low
AD UP[107]	✓	✓	✓	✓	✓	?	Low
HEADS UP[108]	✓	✓	✓	✓	?	?	Some concerns
MEASURE UP1[109]	✓	✓	✓	✓	✓	?	Low
MEASURE UP2[109]	✓	✓	✓	✓	✓	?	Low
RISING UP[110]	?	?	✓	✓	?	?	Some concerns
Baricitinib							
Phase II[111]	✓	✓	✓	✓	X	✓	Some concerns
BREEZE-AD1[112]	✓	✓	✓	✓	✓	✓	Low

BREEZE-AD2[112]	✓	✓	✓	✓	✓	✓	Low
BREEZE-AD4[113]	✓	✓	✓	✓	✓	✓	Low
BREEZE-AD7[114]	✓	✓	✓	✓	✓	✓	Low
Dupilumab							
Phase IIb[115 116]	✓	✓	✓	✓	✓	✓	Low
LIBERTY AD-ADOL[117]	?	✓	✓	✓	✓	✓	Low
LIBERTY AD CAFE[118]	✓	✓	✓	✓	✓	✓	Low
LIBERTY AD CHRONOS[119]	✓	✓	✓	✓	✓	✓	Low
LIBERTY AD SOLO-1[120]	✓	✓	✓	✓	✓	✓	Low
LIBERTY AD SOLO-2[120]	✓	✓	✓	✓	✓	✓	Low
Key for risk assessment: ✓ = low risk of bias; ? = unclear risk of bias; and x = high risk of bias.							

3.2 Observational study informing clinical effectiveness

Table 12. Assessment of the quality of Ariens *et al.*[121] using the Newcastle Ottawa tool for Case–Control studies[122]

Component	Response
Selection	
Is the Case Definition Adequate?	* Yes, population for analysis is defined
Representativeness of the Cases	* Yes, population derived from trial registry and receiving CsA is comparable, in terms of baseline characteristics, to the population enrolled in the RCT informing the comparator group. No evidence of election bias.
Selection of Controls	* Comparator group is derived from an RCT.
Definition of Controls	N/A. Both groups have moderate-severe AD, which is appropriate for the primary objective of the study.
Comparability	
Comparability of Cases and Controls on the Basis of the Design or Analysis	* Comparator group is derived from an RCT and has similar baseline characteristics to those of the group receiving CsA. The authors used logistic regression analysis to assess outcomes and included sex, baseline EASI, and baseline TARC level as regressors.
Exposure	
Ascertainment of Exposure	* Data on group receiving CsA were selected based on information in secure records collated in a clinical database
Same method of ascertainment for cases and controls	* Yes.
Non-Response Rate	Not applicable to the objective of the study. The study compares active

	interventions and does not include a placebo group.

Abbreviations: EASI, Eczema Area and Severity Index; TARC, thymus and activation-regulated chemokine.

3.3 Economic evaluations

Table 13. Economic evaluations – Drummond checklist

Paper	Canadian Agency for Drugs and Technologies in Health. 2020. Canada	Kuznik, A. et al, 2017. USA	Fanelli, F. et al, 2020. Italy (abstract)	Zimmermann, M. et al, 2018. USA	National Institute for Health and Care Excellence - TA534	National Institute for Health and Care Excellence - TA681	Healthcare Improvement Scotland. Scottish Medicines Consortium (SMC2011 & SMC2232)	Healthcare Improvement Scotland. Scottish Medicines Consortium (SMC2337)	Institute for Clinical and Economic Review
Study design									
1. The research question is stated.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. The economic importance of the research question is stated.	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
3. The viewpoint(s) of the analysis are clearly stated and justified.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. The rationale for choosing alternative programmes or interventions	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

compared is stated.									
5. The alternatives being compared are clearly described.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. The form of economic evaluation used is stated.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. The choice of form of economic evaluation is justified in relation to the questions addressed.	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Data collection									
8. The source(s) of effectiveness estimates used are stated.	Yes	Yes	No	Not clear	Yes	Yes	Yes	Yes	Yes
9. Details of the design and results of effectiveness study are given (if based on a single study).	Not appropriate	Not appropriate	Not clear	Not appropriate	Not appropriate	Not appropriate	Yes	Yes	Not appropriate

10. Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies).	Yes	Yes	Not clear	No	Yes	Yes	Yes	Yes	Not clear
11. The primary outcome measure(s) for the economic evaluation are clearly stated.	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
12. Methods to value benefits are stated.	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
13. Details of the subjects from whom valuations were obtained were given.	Yes	Yes	No	Not clear	Yes	Yes	No	No	No
14. Productivity changes (if included) are reported separately.	Not appropriate	Not appropriate	Not appropriate	Not appropriate	Not appropriate	Not appropriate	Not appropriate	Not appropriate	Not appropriate

15. The relevance of productivity changes to the study question is discussed.	Not appropriate	Not appropriate	Not appropriate	Not appropriate	Not appropriate	Not appropriate	Not appropriate	Not appropriate	Not appropriate
16. Quantities of resource use are reported separately from their unit costs.	No	No	No	Not clear	Yes	Yes	No	No	Not clear
17. Methods for the estimation of quantities and unit costs are described.	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
18. Currency and price data are recorded.	Yes	Yes	No	Yes	Yes	Yes	Not clear	Not clear	Yes
19. Details of currency of price adjustments for inflation or currency conversion are given.	No	Yes	No	Yes	Yes	Yes	No	No	Yes
20. Details of any model used are given.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
21. The choice of	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes

model used and the key parameters on which it is based are justified.									
Analysis and interpretation of results									
22. Time horizon of costs and benefits is stated.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
23. The discount rate(s) is stated.	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes
24. The choice of discount rate(s) is justified.	No	Yes	No	No	Yes	Yes	No	No	No
25. An explanation is given if costs and benefits are not discounted.	Not appropriate	Not appropriate	Not appropriate	Not appropriate	Not appropriate	Not appropriate	No	No	Not appropriate
26. Details of statistical tests and confidence intervals are given for stochastic data.	Yes	Yes	No	No	Yes	Yes	No	No	No
27. The approach to sensitivity analysis is given.	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes

28. The choice of variables for sensitivity analysis is justified.	Yes	Yes	No	No	Yes	Yes	No	No	No
29. The ranges over which the variables are varied are justified.	Yes	Yes	No	No	Yes	Yes	No	No	No
30. Relevant alternatives are compared.	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes
31. Incremental analysis is reported.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
32. Major outcomes are presented in a disaggregated as well as aggregated form.	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes
33. The answer to the study question is given.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
34. Conclusions follow from the data reported.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

35. Conclusions are accompanied by the appropriate caveats.	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes

4 Data abstraction tables

4.1 Randomised controlled trials informing clinical effectiveness

4.1.1 Abrocitinib

4.1.1.1 Interventions assessed in the included studies

Table 14. Summary of interventions assessed in studies evaluating abrocitinib

Study name	Intervention		Comparator(s)		Duration of treatment	Additional information
	Dose	N	Name	N		
Phase IIb	Abrocitinib 200 mg QD	55	Placebo	56	12 weeks	–
	Abrocitinib 100 mg QD	56				
	Abrocitinib 30 mg QD	51				
	Abrocitinib 10 mg QD	49				
JADE MONO-1	Abrocitinib 200 mg QD	154	Placebo	77	12 weeks	–
	Abrocitinib 100 mg QD	156				
JADE MONO-2	Abrocitinib 200 mg QD	155	Placebo	78	12 weeks	–
	Abrocitinib 100 mg QD	158				
JADE TEEN	Abrocitinib 200 mg QD plus TCS	94	Placebo plus TCS	96	12 weeks	Topical therapies allowed during the trial included low or medium potency TCS, TCIs, and topical phosphodiesterase 4-inhibitors. People were allowed to use more than one topical therapy.
	Abrocitinib 100 mg QD plus TCS	95				

JADE COMPARE	Abrocitinib 200 mg QD plus TCS	226	Dupilumab 300 mg Q2W plus TCS	242	20 weeks for abrocitinib regimens and placebo versus 16 weeks for dupilumab	Those allocated to abrocitinib and placebo received a placebo injection and those in the dupilumab group received a placebo tablet. Topical therapies allowed during the trial included low or medium potency TCS, TCIs, and topical phosphodiesterase 4-inhibitors. People were allowed to use more than one topical therapy.
	Abrocitinib 100 mg QD plus TCS	238	Placebo QD plus TCS	131		
JADE DARE	Abrocitinib 200 mg QD plus TCS	362	Dupilumab 300 mg Q2W plus TCS	365	26 weeks	Topical therapies allowed during the trial included low or medium potency TCS, TCIs, and topical phosphodiesterase 4-inhibitors.
Abbreviations: QD, once daily; Q2W, every 2 weeks; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.						

4.1.1.2 Study characteristics

Table 15. Characteristics of studies evaluating abrocitinib

Characteristic	Phase II study	JADE MONO-1	JADE MONO-2	JADE TEEN	JADE COMPARE	JADE DARE
Study references	Gooderham 2019[95]	Simpson 2020[96]	Silverberg 2020[97]	Eichenfield 2021[98]	Bieber 2021[123]	ClinicalTrials.gov[100]
Country(ies) where the clinical trial was conducted	5 countries – USA, Australia, Canada, Germany, Hungary.	8 countries – UK, USA, Australia, Canada, Czechia, Germany, Hungary, Poland.	13 countries – UK, USA, Australia, Bulgaria, Canada, China, Czechia, Germany, Hungary, Japan, South Korea, Latavia, Poland.	14 countries – UK, USA, Australia, China, Czechia, Germany, Hungary, Italy, Japan, Latvia, Mexico, Poland, Spain, Taiwan.	18 countries – UK, USA, Australia, Bulgaria, Canada, Chile, Czechia, Germany, Hungary, Italy, Japan, Republic of Korea, Latvia, Mexico, Poland, Slovakia, Spain, Taiwan.	15 countries - Australia, Bulgaria, Canada, Chile, Finland, Germany, Hungary, Italy, Latvia, Poland, Slovakia, South Korea, Spain, Taiwan, USA.

Multicentre trial (number, location)	58 locations	69 sites (UK 5 sites: London, 2x South Yorkshire, Devon, Birmingham	106 sites (UK 6 sites)	99 sites (UK two sites:)	194 sites (UK 11 sites: London x5, Devon, Peterborough, Warwickshire, Yorkshire, Corby, Glasgow)	151 sites
Trial sponsors	Pfizer	Pfizer		Pfizer	Pfizer	Pfizer
Date the clinical trial was conducted	April 2016 to April 2017	December 2017 to March 2019	June 2018 to August 2019	February 2019 to April 2020	October 2018 to December 2019	June 2020 to July 2021
Trial design (e.g. parallel, crossover, or cluster trial)	Phase IIb parallel assignment RCT, double-blind	Phase III, multicentre, randomised, double-blind, placebo-controlled studies			Phase III parallel assignment RCT, double-blind	Phase IIIb parallel assignment RCT, double-blind
Trial duration (treatment duration and follow-up)	35-day screening period, 12-week intervention with additional 4-week follow-up	28-day screening period 12-week intervention and follow-up		12-week intervention and follow-up	28-day screening period 20-week intervention phase 16-week follow-up (primary endpoint measured at 12 weeks	26-week intervention and follow-up
Inclusion criteria	Subjects aged 18 years or older with diagnosis of AD with: • clinical diagnosis of chronic AD for at least 1 year; • inadequate response to treatment with topical	• ≥12 years of age with body weight of ≥40 kg • Diagnosis of AD for ≥1 year and current status of moderate to severe disease • Recent history of inadequate response or inability to tolerate topical AD treatments or require systemic treatments for AD control		• Aged between 12 and to 17 with a minimum body weight of 40 kg • Diagnosis of AD for at least 1 year and current status of moderate to severe disease	• Subjects aged 18 years or older with diagnosis of moderate to severe AD for at least 1 year. • Documented recent history of inadequate response to treatment with	• 18 years of age or older • Diagnosis of chronic AD for at least 6 months • Moderate to severe AD (BSA at least 10%, IGA at least 3, EASI

	medications given for at least 4 weeks, or for whom topical treatments are otherwise medically inadvisable within 12 months; • Moderate to severe AD.			medicated topical therapy for AD or required systemic therapies.	at least 16, and PP-NRS severity score at least 4) • Recent history of inadequate response to treatment with medicated topical therapy for AD, or who have required systemic therapies for control of their disease
Exclusion criteria	• History of HIV or positive HIV serology at screening • Infected with hepatitis B or hepatitis C viruses • Have evidence of active or latent or inadequately treated infection with TB	• Unwilling to discontinue current AD medications prior to the study or require treatment with prohibited medications during the study • Prior treatment with JAK inhibitors • Other active non-AD inflammatory skin diseases or conditions affecting skin • Medical history including thrombocytopenia, coagulopathy or platelet dysfunction, Q wave interval abnormalities, current or history of certain infections, cancer, lymphoproliferative	• Acute or chronic medical or laboratory abnormality that may increase the risk associated with study participation • Unwilling to discontinue current AD medications prior to the study or require treatment with prohibited medications	• Medical history including thrombocytopenia, coagulopathy or platelet dysfunction, Q wave interval abnormalities, current or history of certain infections, cancer, lymphoproliferative disorders and other medical conditions at the	• Acute or chronic medical or laboratory abnormality that may increase the risk associated with study participation • Have increased risk of developing venous thromboembol

		disorders and other medical conditions at the discretion of the investigator • Pregnant or breastfeeding women, or women of childbearing potential who are unwilling to use contraception	during the study • Prior treatment with JAK inhibitors • Other active non-AD inflammatory skin diseases or conditions affecting skin • Medical history including thrombocytopenia, coagulopathy or platelet dysfunction, malignancies, current or history of certain infections, lymphoproliferative disorders and other medical conditions at the discretion of the investigator • Pregnant or breastfeeding women, or women of childbearing potential who are unwilling to use	discretion of the investigator. • Other active non-AD inflammatory skin diseases or conditions affecting skin • Prior treatment with JAK inhibitors • Previous treatment with dupilumab • Pregnant or breastfeeding women, or women of childbearing potential who are unwilling to use contraception	ism • Unwilling to discontinue current AD medications prior to the study or require treatment with prohibited medications during the study • Prior treatment with systemic JAK inhibitors or IL-4 or IL-13 antagonists including dupilumab, lebrikizumab or tralokinumab • Other active non-AD inflammatory skin diseases or conditions affecting skin • Medical history

			contraception		including thrombocytopenia, coagulopathy or platelet dysfunction, malignancies, current or history of certain infections, lymphoproliferative disorders and other medical conditions at the discretion of the investigator • Pregnant or breastfeeding women, or women of childbearing potential who are unwilling to use contraception
Concomitant medications	Not reported	Background medicated topical therapy was not permitted in the MONO trials.	Background therapy (medicated and non-medicated topical therapy) must have been applied	Emollient BD. Topical therapies that were allowed during the trial included low or medium	Standardised background topical therapy was required to be used during the

			BD for the duration of the treatment period.	potency glucocorticoids, topical calcineurin inhibitors and topical phosphodiesterase 4-inhibitors.	study.
Rescue therapy	Patients were allowed to use oral antihistamines and nonmedicated emollient; or Aquaphor and sunscreen.	Additional rescue therapy was prohibited	Additional rescue therapy was prohibited	Additional rescue therapy was prohibited	After Week 4, rescue therapy for AD with high-potency TCS or systemic corticosteroids was permitted.
Outcomes	Primary endpoint: • % achieving IGA response of 0 or 1 and a reduction of ≥2 points at week 12. Secondary endpoints: • Change in EASI score from baseline at week 12; • % achieving IGA response of 0 or 1 and a reduction of ≥2 points at other time points; • % EASI score change from	Primary endpoints: • % achieving IGA response of 0 or 1 and a reduction of ≥2 points at week 12; • % achieving EASI response ≥75% improvement at week 12. Secondary endpoints: • Response based on a ≥50% and ≥90% improvement in EASI (EASI-50, EASI-90) from baseline at all scheduled time points; • Response based on ≥50% and ≥75% improvement in SCORAD (SCORAD-50, SCORAD-75) from baseline at all scheduled time points; • SCORAD subjective assessments of itch and sleep loss;	Primary endpoints: • % achieving IGA response of 0 or 1 and a reduction of ≥2 points at week 12; • % achieving EASI response ≥75% improvement at week 12. Secondary endpoints: • % with ≥4 improvement in the PP-NRS; • Change in PSAAD at week 12; • % achieving IGA response of 0 or	Primary endpoints: • % achieving IGA response of 0 or 1 and a reduction of ≥2 points at week 12 • % achieving EASI response ≥75% improvement at week 12 Secondary endpoints: • % with ≥4 improvement in the PP-NRS • IGA and EASI-75 response at week 16 • Improvement of ≥50%, ≥90% and	Primary endpoints: • Response based on achieving at least a 4-point improvement in the severity of PP-NRS from baseline at Week 2; • Response based on achieving EASI-90 (≥90% improvement from baseline) at Week 4 Secondary endpoints: • Response

	baseline; • Patients achieving ≥3 and ≥4 point improvement on PP-NRS; • Change from baseline of PP-NRS; • Change from baseline of SCORAD; • % change in BSA; • Adverse events; • POEM score; • HADS score. More secondary endpoints listed on clinicaltrials.gov	• Change in DLQI or CDLQI at Week 12 or all other scheduled time points; • Change in HADS score at Week 12 and all other scheduled time points; • Change in POEM at Week 12 and all other scheduled time points; • Change of PtGA at Week 12 and all other scheduled time points; • Change of EQ-5D-5L or EQ-5D-Y at Week 12 and all other scheduled time points; • CHANGE in SF-36v2, acute, at Week 12 and all other scheduled time points; • Response based on PP-NRS; • Time from baseline to achieve PP-NRS; • Adverse events. More secondary endpoints listed on clinicaltrials.gov	1 and a reduction of ≥2 points at other time points; • % achieving EASI response ≥75% improvement at other timepoints; • Improvement of ≥50%, ≥90% and 100% of EASI; • % change in EASI from baseline; • PSAAD score; • DLQI score; • HADS score; • EQ-5D; • Adverse events. More secondary endpoints listed on clinicaltrials.gov	100% of EASI • Time to itch response • % change in BSA • POEM score • PSAAD score • DLQI score • HADS score • % with SCORAD response ≥50% and ≥75% improvement • EQ-5D More secondary endpoints listed on clinicaltrials.gov	based on achieving EASI-90 (≥90% improvement from baseline) at Week 16; • Response based on achieving a ≥90% improvement in the EASI total score at all other scheduled time points up to Week 26; • Response based on achieving a ≥75% improvement in the EASI total score at all scheduled time points up to Week 26; • Response based on IGA score of clear (0) or almost

					clear (1) (on a 5- point scale) and a reduction from baseline of ≥2 points at all scheduled time points up to Week 26; • Response based on achieving at least a 4-point improvement in the severity of PP-NRS from baseline at all scheduled time points except Week 2; • % change from Baseline in SCORAD; • Change from baseline in HADS; • Change from baseline in DLQI; • Change from

					baseline in EQ-5D-5L; • Change from baseline in POEM; • Adverse events More secondary endpoints listed on clinicaltrials.gov
Subgroups	None	None	None	None	None
Criteria for determination of moderate to severe AD	• IGA ≥3 • EASI ≥12 • BSA involvement ≥10%	• IGA ≥3 • EASI ≥16 • BSA involvement ≥10% • PP-NRS ≥4	• IGA ≥3 • EASI ≥16 • BSA involvement ≥10% • PP-NRS ≥4	• IGA ≥3 • EASI ≥16 • BSA involvement ≥10% • PP-NRS ≥4	• BSA ≥10% • IGA ≥3 • EASI ≥16 • PP-NRS severity score ≥4

Abbreviations: AD, atopic dermatitis; BD, twice daily; BSA, body surface area; CDLQI, Children's Dermatology Life Quality Index; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; HADS, Hospital Anxiety and Depression Scale; HIV, human immunodeficiency virus; IGA, Investigator's Global Assessment; JAK, Janus kinase inhibitor; POEM, Patient-Oriented Eczema Measure; PP-NRS, Peak Pruritus Numerical Rating Scale; PSAAD, Pruritus and Symptoms Assessment for Atopic Dermatitis; PtGA, Patient Global Assessment; RCT, randomised controlled trial; SCORAD, Scoring Atopic Dermatitis; TB, mycobacterium tuberculosis.

4.1.1.3 Baseline characteristics

Data for the adult generalisable and restricted populations of the abrocitinib trials are academic in confidence and are not presented in this report.

Table 16. Baseline characteristics of trial populations in studies evaluating abrocitinib

Characteristic	Phase IIb (study B7451006) Full trial population				
	Abrocitinib 200 mg QD (N=55)	Abrocitinib 100 mg QD (N=56)	Abrocitinib 30 mg QD (N=51)	Abrocitinib 10 mg QD (N=49)	Placebo (N=56)
Mean age (SD), years	38.7 (17.6)	41.1 (15.6)	37.6 (15.9)	44.3 (15.9)	42.6 (15.1)
Gender, n (%)	Female: 27 (49.1)	Female: 25 (44.6)	Female: 29 (56.9)	Female: 28 (57.1)	Female: 35 (62.5)
Duration of AD, years Median (range)	19.6 (1.9–68.8)	23.8 (1.1–66.7)	20.5 (1.2–66.6)	30.2 (1.8–60.6)	25.6 (1.1–67.1)
Race					
• White, n (%)	37 (67.3)	40 (71.4)	39 (76.5)	38 (77.6)	40 (71.4)
• Black or African American, n (%)	13 (23.6)	7 (12.5)	4 (7.8)	5 (10.2)	10 (17.9)
• Asian, n (%)	5 (9.1)	8 (14.3)	5 (9.8)	5 (10.2)	4 (7.1)
Mean EASI score (SD)	24.6 (13.5)	26.7 (11.8)	22.1 (10.7)	28.1 (13.1)	25.4 (12.9)
Mean IGA score	NR	NR	NR	NR	NR
Mean DLQI score	NR	NR	NR	NR	NR
Mean SCORAD score (SD)	62.7 (13.7)	65.4 (13.7)	62.4 (13)	65.3 (13.2)	65 (12.1)
Mean peak pruritus NRS score	6.9 (2.7)	7.4 (2.2)	7.6 (1.9)	7.6 (1.7)	7.6 (1.8)
Mean % BSA affected (SD)	38 (23.3)	41.9 (22.3)	34.1 (22.3)	44.2 (22.7)	40.1 (22.3)
Prior treatment					
OCS	NR	NR	NR	NR	NR
Immunosuppressant	NR	NR	NR	NR	NR
TCS	NR	NR	NR	NR	NR

TCI	NR	NR	NR	NR	NR

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NR, not reported; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; QD, once daily; SD, standard deviation; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

Characteristic	JADE MONO-1 Full trial population		
	Abrocitinib 200 mg QD (N=154)	Abrocitinib 100 mg QD (N=156)	Placebo (N=77)
Mean age (SD), years	33.0 (17.4)	32.6 (15.4)	31.5 (14.4)
Gender, n (%)	Female: 73 (47.4)	Female: 66 (42.3)	Female: 28 (36.4)
Mean duration of AD (SD), years	22.7 (14.5)	24.9 (16.1)	22.5 (14.4)
Race			
• White, n (%)	104 (67.5)	113 (72.4)	62 (80.5)
• Black or African American, n (%)	11 (7.1)	15 (9.6)	6 (7.8)
• Asian, n (%)	26 (16.9)	26 (16.7)	6 (7.8)
Mean EASI score (SD)	30.6 (14.1)	31.3 (13.6)	28.7 (12.5)
IGA, % moderate/severe	59.1/40.9	59.0/41.0	59.7/40.3
Baseline IGA score of 4, n (%)	–	–	–
Mean DLQI score (SD)	14.6 (6.8)	14.6 (6.5)	13.9 (7.3)
Mean SCORAD score (SD)	64.3 (13.1)	67.1 (13.7)	64.5 (13.2)
Mean peak pruritus NRS score (SD)	7.1 (1.9)	6.9 (2.0)	7.0 (1.8)

Mean % BSA affected (SD)	49.9 (24.4)	50.8 (23.4)	47.4 (22.7)
Mean baseline EQ-5D Score (SD)	–	–	–
Prior treatment, n (%)			
Any	154 (100)	155 (99)	77 (100)
Topical (TCS or TCI)	82 (53)	69 (44)	34 (44)
Systemic with or without topical treatment	68 (44)	78 (50)	41 (53)
Dupilumab	9 (6)	13 (8)	8 (10)
Oral/injectable corticosteroids, n (%)	–	–	–
Other non-biologic systemics (i.e., ciclosporin or other)	–	–	–
Biologics (i.e., dupilumab and other)	–	–	–
TCS, n (%)	–	–	–
TCI, n (%)	–	–	–

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NR, not reported; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; QD, once daily; SD, standard deviation; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

Characteristic	**JADE MONO-2 Full trial population**		
	Abrocitinib 200 mg QD (N=155)	Abrocitinib 100 mg QD (N=158)	Placebo (N=78)
Mean age (SD), years	33.5 (14.7)	37.4 (15.8)	33.4 (13.8)
Gender, n (%)	Male: 88 (56.8)	Male: 94 (59.5)	Male: 47 (60.3)
Mean duration of AD (SD), years	20.5 (14.8)	21.1 (14.8)	21.7 (14.3)

Race			
• White, n (%)	91 (58.7)	101 (63.9)	40 (51.3)
• Black or African American, n (%)	6 (3.9)	9 (5.7)	6 (7.7)
• Asian, n (%)	54 (34.8)	46 (29.1)	29 (37.2)
Mean EASI score (SD)	29.0 (12.4)	28.4 (11.2)	28.0 (10.2)
Baseline IGA score of 4, n (%)	49 (31.6)	51 (32.3)	26 (33.3)
Mean DLQI score (SD)	14.8 (6.0)	15.4 (7.3)	15.0 (7.1)
Mean SCORAD score (SD)	64.1 (13.1)	63.8 (11.4)	64.3 (12.4)
Mean peak pruritus NRS score (SD)	7.0 (1.6)	7.1 (1.6)	6.7 (1.9)
Mean % BSA affected (SD)	47.7 (22.3)	48.7 (21.4)	48.2 (20.8)
Mean baseline EQ-5D Score (SD)	–	–	–
Prior treatment, n (%)			
Any	153 (99)	157 (99)	78 (100)
Topical (TCS or TCI)	93 (60)	87 (55)	46 (59)
Systemic with or without topical treatment	60 (39)	70 (44)	32 (41)
Dupilumab	5 (3)	7 (4)	2 (3)
Oral/injectable corticosteroids, n (%)	–	–	–
Other non-biologic systemics (i.e., ciclosporin or other)	–	–	–
Biologics (i.e., dupilumab and other)	–	–	–
TCS, n (%)	–	–	–
TCI, n (%)	–	–	–

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NR, not reported; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; SD, standard deviation; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

Characteristic	JADE TEEN Full trial population		
	Abrocitinib 200 mg QD plus TCS (N=94)	Abrocitinib 100 mg QD plus TCS (N=95)	Placebo plus TCS (N=96)
Gender, n (%)	Female: 38 (40.4)	Female: 50 (52.6)	Female: 52 (54.2)
Mean duration of AD (SD), years	9.7 (5.3)	9.8 (5.4)	10.5 (4.8)
Race			
• White, n (%)	52 (55.3)	52 (54.7)	56 (58.3)
• Black or African American, n (%)	5 (5.3)	9 (9.5)	3 (3.1)
• Asian, n (%)	31 (33)	31 (32.6)	32 (33.3)
Mean EASI score (SD)	29.5 (12.2)	31.0 (12.8)	29.2 (12.7)
Mean SCORAD score (SD)	–	–	–
Mean % BSA affected (SD)	–	–	–
Mean EQ-5D score (SD)	NR	NR	NR
Prior treatment			
Oral/injectable corticosteroids, n (%)	NR	NR	NR
Other non-biologics systemic (i.e., ciclosporin or other)	NR	NR	NR
Biologic (i.e. dupilumab or other)	NR	NR	NR
TCS, n (%)	NR	NR	NR
TCI, n (%)	NR	NR	NR

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NR, not reported;

NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

Characteristic	JADE COMPARE Full trial population			
	Abrocitinib 200 mg QD plus TCS (N=226)	Abrocitinib 100 mg QD plus TCS (N=238)	Dupilumab 300 mg Q2W plus TCS (N=242)	Placebo plus TCS (N=131)
Mean age (SD), years	38.8 (14.5)	37.3 (14.8)	37.1 (14.6)	37.4 (15.2)
Gender, n (%)	Female: 122 (54)	Female: 118 (49.6)	Female: 134 (55.4)	Female: 54 (41.2)
Mean duration of AD (SD), years	23.4 (15.6)	22.7 (16.3)	22.8 (14.8)	21.4 (14.4)
Race				
• White, n (%)	161 (71.2)	182 (76.5)	176 (72.7)	87 (66.4)
• Black or African American, n (%)	9 (4.0)	6 (2.5)	14 (5.8)	6 (4.6)
• Asian, n (%)	53 (23.5)	48 (20.2)	46 (19)	31 (23.7)
Mean EASI score (SD)	32.1 (13.1)	30.3 (13.5)	30.4 (12)	31 (12.6)
IGA, % moderate/severe	61.1/38.9	64.3/35.7	66.9/33.1	67.2/32.8
Baseline IGA score of 4, n (%)	–	–	–	–
Mean DLQI score (SD)	16.3 (6.6)	15.5 (6.4)	15.6 (6.7)	15.2 (6.9)
Mean SCORAD score (SD)	69.3 (12.7)	66.8 (13.8)	67.9 (11.4)	67.9 (12.0)
Mean peak pruritus NRS score (SD)	7.6 (1.5)	7.1 (1.7)	7.3 (1.7)	7.1 (1.8)
Mean % BSA affected (SD)	50.8 (23)	48.1 (23.1)	46.5 (22.1)	48.9 (24.9)
Mean baseline EQ-5D Score (SD)	NR	NR	NR	NR

Prior treatment, n (%)				
Oral/injectable corticosteroids, n (%)	NR	NR	NR	NR
Other non-biologic systemics (i.e., ciclosporin or other)	NR	NR	NR	NR
Biologics (i.e., dupilumab and other)	NR	NR	NR	NR
TCS, n (%)	NR	NR	NR	NR
TCI, n (%)	NR	NR	NR	NR

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NR, not reported; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; SD, standard deviation; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

Characteristic	**JADE DARE** **Full trial population**	
	Abrocitinib 200 mg QD plus TCS (N=362)	Dupilumab 300 mg Q2W plus TCS (N=2365)
Mean age (SD), years	36.6 (14.6)	35.5 (13.3)
Gender, n (%)	Female 169 (46.7%) Male 193 (53.3%)	Female 161 (44.1%) Male 204 (55.9%)
Mean duration of AD (SD), years		
Race		
• White, n (%)	269 (74.3%)	248 (67.9%)
• Black or African American, n (%)	25 (6.9%)	26 (7.1%)
• Asian, n (%)	62 (17.1%)	83 (22.7%)
Mean EASI score (SD)	NR	NR
IGA, % moderate/severe	NR	NR

Baseline IGA score of 4, n (%)	NR	NR
Mean DLQI score (SD)	NR	NR
Mean SCORAD score (SD)	NR	NR
Mean peak pruritus NRS score (SD)	NR	NR
Mean % BSA affected (SD)	NR	NR
Mean baseline EQ-5D Score (SD)	NR	NR
Prior treatment, n (%)	NR	NR
Oral/injectable corticosteroids, n (%)	NR	NR
Other non-biologic systemics (i.e., ciclosporin or other)	NR	NR
Biologics (i.e., dupilumab and other)	NR	NR
TCS, n (%)	NR	NR
TCI, n (%)	NR	NR

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NR, not reported; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; SD, standard deviation; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

4.1.1.4 Data extracted on outcomes of interest

Data on clinical effectiveness from studies evaluating abrocitinib and for populations of interest to the MTA are academic in confidence and are therefore not presented in this report. However, data on the proportion of people achieving EASI 75 and who discontinue treatment at week 16 from JADE TEEN are public and presented in Table 17.

Table 17. Data on clinical effectiveness from JADE TEEN

Outcome	JADE TEEN		
	Abrocitinib 200 mg QD plus TCS (N=94)	Abrocitinib 100 mg QD plus TCS (N=95)	Placebo plus TCS (N=96)
Proportion of people achieving EASI 75, n (%)	67/93 (72.0)	61/89 (68.5)	39/94 (41.5)
Proportion of patients who discontinue treatment at week 16 (additional request from clarification meeting), n/N (%)	3/94 (3.2)	3/95 (3.2)	6/96 (6.3)

Abbreviations: AD, atopic dermatitis; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; TCS, topical corticosteroid.

4.1.2 Tralokinumab

4.1.2.1 Interventions assessed in the included studies

Table 18. Summary of interventions assessed in studies evaluating tralokinumab

Study name	Intervention		Comparator(s)		Duration of treatment	Additional information
	Dose[a]	N	Name	N		
ECZTRA 1	Tralokinumab 300 mg Q2W	603	Placebo	199	16 weeks	Initial treatment given for 16 weeks, after which people entered a maintenance phase[b]
ECZTRA 2	Tralokinumab 300 mg Q2W	593	Placebo	201	16 weeks	Initial treatment given for 16 weeks, after which people entered a maintenance phase[b]
ECZTRA 5	Tralokinumab 300 mg Q2W	107	Placebo	108	16 weeks	Treatment phase followed by 14-week off-treatment follow-up period for the assessment of safety.

						Dependent on eligibility, people could transfer to an open-label, long-term trial at week 16 or later.
Phase IIb	Tralokinumab 300 mg Q2W plus TCS	52	Placebo	51	12 weeks	Leo Pharma confirmed that people did not receive a loading dose of tralokinumab.
	Tralokinumab 150 mg Q2W plus TCS	51				
	Tralokinumab 45 mg Q2W plus TCS	50				
ECZTRA 3	Tralokinumab 300 mg Q2W plus TCS	252	Placebo plus TCS	126	16 weeks	TCS was mometasone furoate 0.1% cream daily until control was achieved.
ECZTRA 7	Tralokinumab 300 mg Q2W plus TCS	140	Placebo plus TCS	137	26 weeks	TCS was mometasone furoate 0.1% cream daily until control was achieved.

[a] First dose of tralokinumab given at a dose of 600 mg, which is the loading dose.

[b] Those allocated to tralokinumab and achieving EASI 75 or IGA 0/1 were re-randomised 2:2:1 to tralokinumab 300 mg Q2W, tralokinumab 300 mg Q4W or placebo. People allocated to placebo arm and achieving EASI 75 or IGA 0/1 continued to receive placebo. People not reaching EASI 75 or IGA 0/1 in either the tralokinumab or placebo groups received tralokinumab 300 mg Q2W.

Abbreviations: EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; Q2W, every 2 weeks; TCS, topical corticosteroid.

4.1.2.2 Study characteristics

Table 19. Characteristics of studies evaluating tralokinumab

Characteristic	Phase IIb	ECZTRA 1	ECZTRA 2	ECZTRA 5	ECZTRA 3	ECZTRA 7
Study references	Wollenberg 2019[101]	Wollenberg 2021[102]	Wollenberg 2021[102]	ClinicalTrials.gov[104]	Silverberg 2021[103]	ClinicalTrials.gov[105]
Country(ies) where the clinical trial was conducted	6 countries – Australia, Canada, Germany, Japan, Poland, USA	5 countries – France, Germany, Japan, Spain, USA	9 countries – Australia, Canada, Denmark, Italy, Republic of Korea, Poland, Russian Federation, UK, USA	2 countries – Canada, USA	8 countries – Belgium, Canada, Germany, Netherlands, Poland, Spain, UK, USA	7 countries – Belgium, Czechia, France, Germany, Poland, Spain, UK
Multicentre trial (number, location)	57 sites	124 sites	108 sites	51 sites	64 sites	68 sites
Trial sponsors	MedImmune LLC	LEO Pharma	LEO Pharma	LEO Pharma	LEO Pharma	LEO Pharma

Date the clinical trial was conducted	23 January 2015 to 27 November 2015	30 May 2017 to 7 August 2018	12 June 2017 to 4 September 2018	13 July 2018 to 17 September 2019	22 February 2018 to 8 March 2019	28 December 2018 to 28 September 2020
Trial design (e.g. parallel, crossover, or cluster trial)	Phase IIb parallel assignment RCT, double blind Four arms: 3 arms evaluating different doses of tralokinumab (45 mg, 150 mg or 300 mg QW) and a placebo arm Patients randomised 1:1	Phase III parallel assignment RCT, double blind Patients randomised 3:1		Phase III parallel assignment RCT, double blind Patients randomised 1:1	Phase III parallel assignment RCT, double blind Patients randomised 2:1	Phase III parallel assignment RCT, double blind Patients randomised 1:1
Trial duration (treatment duration and follow-up)	Post randomisation: initial treatment period of 12 weeks	Post randomisation: initial treatment period of 16 weeks. Those achieving a clinical response at week 16 (defined as IGA of 0 or 1 or at least 75% reduction EASI score from baseline) moved onto maintenance treatment that continued until week 52		Screening period of 2 to 6 weeks, followed by a treatment period of 16 weeks and a 14-week off-treatment follow-up period for the assessment of safety. Dependent on eligibility, people could transfer to an open-label, long-term trial at week 16 or later.	Post randomisation: Initial 16-week treatment period followed by re-randomisation of responders and a 16-week treatment period	Pre-randomisation: 6-week washout period of AD medication, with the exception of TCS and TCI Post-randomisation: 26-week treatment period
Inclusion criteria	• Age 18 to 75 years • Physician diagnosis of AD for greater than 1 year	• Age 18 and above • Diagnosis of AD as defined by the Hanifin and Rajka (1980) criteria for AD • EASI ≥12 at screening and ≥16 at baseline		• Age 18 to 54 years • Diagnosis of AD as defined by Hanifin and Rajka (1980)	• Age 18 and above • Diagnosis of AD as defined by the Hanifin	• Age 18 and above • Diagnosis of AD as defined by the Hanifin and Rajka

	• AD involvement of ≥10% BSA • EASI score of ≥12 • SCORAD of ≥25 • IGA score of ≥3 • Effective birth control in line with protocol details	• IGA 3 or 4, and worst daily pruritis NRS score ≥4 • AD involvement of ≥10% body surface area at screening and baseline • Diagnosis of AD for ≥1 year • Subjects who have a recent history of inadequate response to treatment with topical medications or for whom topical treatments are otherwise medically inadvisable • Subjects must have applied a stable dose of emollient twice daily (or more, as needed) for at least 14 days before randomisation	criteria for AD • History of AD for ≥1 year • Subjects who have a recent history of inadequate response to treatment with topical medications or for whom topical treatments are otherwise medically inadvisable • AD involvement of ≥10% BSA at screening and baseline • EASI score of ≥12 at screening and 16 at baseline • An IGA score of ≥3 at screening and at baseline • Subjects must have applied a	and Rajka (1980) criteria for AD • EASI ≥12 at screening and ≥16 at baseline • IGA 3 or 4, and worst daily pruritis NRS score ≥4 • AD involvement of ≥10% body surface area at screening and baseline • History of AD for ≥1 year • Recent history of inadequate response to treatment with topical medications • Stable dose of emollient twice daily	(1980) criteria for AD • EASI score at screening and baseline of ≥20 • IGA 3 or 4, and worst daily pruritis NRS score ≥4 • AD involvement of 10% (or more) BSA at screening and baseline (visit 3) according to component A of SCORAD • History of AD for 1 year or more • Subjects with a history within 1 year prior to screening of inadequate response to treatment with topical

			stable dose of emollient twice daily (or more, as needed) for at least 14 days before randomisation	(or more, as needed) for at least 14 days before randomisation	medications or subjects for whom topical treatments are otherwise medically inadvisable • Documented history of either no previous CsA exposure and not currently a candidate for CsA treatment OR previous exposure to CsA in which case CsA treatment should not be continued or restarted • Subjects must have applied a stable dose of emollient twice daily (or more, as needed) for at least 14 days before

					randomisation
Exclusion criteria	• History of anaphylaxis following any biologic therapy • Hepatitis B, C or human immunodeficiency virus • Pregnant or breastfeeding • History of cancer • Previous receipt of tralokinumab	• Active dermatologic conditions that may confound the diagnosis of AD • Use of tanning beds or phototherapy within 6 weeks prior to randomisation • Treatment with systemic immunosuppressive/immunomodulating drugs and/or systemic corticosteroid within 4 weeks prior to randomisation • Treatment with TCS and/or TCI within 2 weeks prior to randomisation • Active skin infection within 1 week prior to randomisation • Clinically significant infection within 4 weeks prior to randomisation • A helminth parasitic infection within 6 months prior to the date informed consent is obtained • History of anaphylaxis following any biologic therapy • Tuberculosis requiring treatment within the 12 months prior to screening • Known primary immunodeficiency disorder • Alanine aminotransferase or aspartate aminotransferase level ≥2.0 times the upper limit of normal at screening • Positive hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody or hepatitis C virus	• Subjects for whom administration of the meningococcal vaccine provided in this trial is contraindicated or medically inadvisable, according to local label of the vaccine • Subjects for whom administration of the tetanus, diphtheria, and pertussis vaccine provided in this trial is contraindicated or medically inadvisable, according to local label of the vaccine • Active dermatologic	• Subjects for whom TCS are medically inadvisable e.g., due to important side effects or safety risks in the opinion of the investigator • Active dermatologic conditions that may confound the diagnosis of AD • Use of tanning beds or phototherapy within 6 weeks prior to randomisation • Treatment with systemic immunosuppressive/immu	• Subjects for whom TCSs are medically inadvisable in the opinion of the investigator • Use of tanning beds or phototherapy (NBUVB, UVB, UVA1, PUVA), within 6 weeks prior to randomisation • Treatment with immunomodulatory medications or bleach baths within 4 weeks prior to randomisation • Treatment with topical phosphodiesterase-4 (PDE-4)

		antibody serology at screening	conditions that may confound the diagnosis of AD or would interfere with assessment of treatment • Use of tanning beds or phototherapy within 6 weeks prior to randomisation • Treatment with systemic immunosuppressive/immunomodulating medications and/or systemic corticosteroids within 4 weeks prior to randomisation • Treatment with the topical medications TCS, TCI or phosphodiesterase 4 (PDE-4) inhibitor within	nomodulating drugs and/or systemic corticosteroid within 4 weeks prior to randomisation • Treatment with TCS, topical calcineurin inhibitors (TCI), or topical phosphodiesterase 4 (PDE-4) inhibitor within 2 weeks prior to randomisation • Receipt of any marketed biological therapy (i.e. immunoglobulin, anti-immunoglobu	inhibitor within 2 weeks prior to randomisation • Receipt of any marketed or investigational biologic agent (e.g. cell-depleting agents or dupilumab) within 6 months prior to randomisation or until cell counts return to normal, whichever is longer • History of any active skin infection within 1 week prior to randomisation • History of a clinically significant infection

			2 weeks prior to randomisation • Receipt of any vaccine (except influenza virus vaccines) within 3 months prior to screening, any meningococcal vaccine within 1 year prior to screening, or any tetanus-, diphtheria-, or pertussis-containing vaccine within 5 years prior to screening> • Receipt of any marketed (i.e. immunoglobulin, anti-IgE) or investigational biologic agent, including dupilumab> • History of any active skin	lin E) including dupilumab or investigational biologic agents within 3 months or 5 half-lives, whichever is longer prior to randomisation • Active skin infection within 1 week prior to randomisation • Clinically significant infection within 4 weeks prior to randomisation • A helminth parasitic infection within 6 months prior	(systemic infection or serious skin infection requiring parenteral treatment) within 4 weeks prior to randomisation • A helminth parasitic infection within 6 months prior to the date informed consent is obtained that has not been treated with, or has failed to respond to, standard of care therapy • Tuberculosis requiring treatment within the 12 months prior to screening. Evaluation will be

			infection within 1 week prior to randomisation • History of a clinically significant infection (systemic infection or serious skin infection requiring parenteral treatment) within 4 weeks prior to randomisation	to the date informed consent is obtained • Tuberculosis requiring treatment within the 12 months prior to screening • Known primary immunodeficiency disorder	according to local guidelines as per local standard of care • History of any known primary immunodeficiency disorder including a positive HIV test at screening, or the subject taking antiretroviral medications
Concomitant medications	TCS	None	• Tdap vaccine: tetanus (lockjaw), diphtheria (infection of the nose and throat), and pertussis (whooping cough) vaccines • Meningococcal vaccine	None reported, other than combination TCS	None reported, other than combination TCS

Rescue therapy	Unclear	Patients receiving topical rescue treatment continued treatment with the study drug. Patients receiving systemic rescue treatment discontinued study drug, but could resume at least five half-lives after the last dose of systemic rescue treatment	Unclear	Patients receiving topical rescue treatment continued treatment with the study drug. Patients receiving systemic rescue treatment discontinued study drug, but could resume at least five half-lives after the last dose of systemic rescue treatment	Patients receiving topical rescue treatment continued treatment with the study drug. Patients receiving systemic rescue treatment discontinued study drug, but could resume at least five half-lives after the last dose of systemic rescue treatment
Outcomes	Primary outcomes: • Absolute change from baseline in EASI score at week 12; • Percentage of participants achieving IGA of 0 (Clear) or 1 (Almost Clear) and at least a 2-grade reduction from baseline at week 12. Secondary outcomes of interest to MTA:	Primary outcomes: • Proportion of patients with EASI 75 at week 16; • Proportion of patients with IGA 0/1 at week 16. Additional outcomes used in model: • EASI 50 at week 16 and during maintenance treatment; • EASI 75 during maintenance treatment; • Combined endpoint: EASI 50 + ΔDLQI ≥4 at week 16 and during maintenance treatment; • EQ-5D-5L at week 16; • Reduction in Worst Daily Pruritis NRS at week 16.	Primary outcomes: • Positive anti-tetanus response at week 16; • Positive anti-meningococcal response at week 16. Secondary outcomes of interest to MTA: • Proportion of patients with EASI 75 at week 16; • Adverse effects.	Primary outcomes: • Proportion of patients with EASI 75 at week 16; • Proportion of patients with IGA 0/1 at week 16. Additional outcomes used in model: • EASI 50 at week 16 and during maintenance treatment • EASI 75 during	Primary outcome: • Proportion of patients with EASI 75 at week 16. Additional outcomes used in model: • EASI 50 at week 16 and during maintenance treatment; • EASI 75 during maintenance treatment; • Combined endpoint:

	EASI 75 at week 12 are reported			maintenance treatment • Combined endpoint: EASI 50 + ΔDLQI ≥4 at week 16 and during maintenance treatment • EQ-5D-5L at week 16 • Reduction in Worst Daily Pruritis NRS at week 16	EASI 50 + ΔDLQI ≥4 at week 16 and during maintenance treatment ; • EQ-5D-5L at week 16 • Reduction in Worst Daily Pruritis NRS at week 16
Subgroups	None	None planned	None	None planned	None planned
Criteria for determination of moderate to severe AD	EASI score at baseline of ≥12 and IGA score of 3 or 4	EASI score at baseline of ≥16 and IGA score of 3 or 4	EASI score at baseline of ≥16 and IGA score of 3 or 4	EASI score at baseline of ≥16 and IGA score of 3 or 4	EASI score at screening and baseline of ≥20 and IGA score of 3 or 4

Abbreviations: AD, atopic dermatitis; BSA, body surface area; CsA, cyclosporin A; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D, EuroQol 5 dimensions; IGA, Investigator's Global Assessment; NRS, Numerical Rating Scale; PUVA, psoralen and ultraviolet A radiation; SCORAD, Scoring Atopic Dermatitis; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

4.1.2.3 Baseline characteristics

Data from the ECZTRA-7 like population of ECZTRA 1, ECZTRA 2 and ECZTRA 3 are commercial in confidence and are not presented in this report.

Table 20. Baseline characteristics of trial populations in studies evaluating tralokinumab

Characteristic	Phase IIb dose ranging study[a] Full trial population		ECZTRA 5 Full trial population	
	Tralokinumab Q2W (N=52)	Placebo (N=51)	Tralokinumab Q2W (N=107)	Placebo (N=108)
Median age, years (IQR)	Mean age: 35.7 (SD 14.6)	Mean age: 39.4 (SD 14.5)	Mean age: 34.0 (SD 11.2)	Mean age: 34.4 (SD 10.8)
Gender, Male, n (%)	33 (63.5)	22 (43.1)	54 (50.5)	35 (32.4)
Median duration of AD, years (IQR)	N/A	N/A	N/A	N/A
Race				
• White, n (%)	28 (53.8)	31 (60.8)	62 (57.9)	56 (51.9)
• Black or African American, n (%)	7 (13.5)	8 (15.7)	25 (23.4)	27 (25.0)
• Asian, n (%)	16 (30.8)	10 (19.6)	16 (15.0)	18 (16.7)
Median EASI score (IQR)	N/A	N/A	Mean EASI: 26.26 (SD 10.79)	Mean EASI: 26.75 (SD 11.23)
Baseline IGA score of 4	N/A	N/A	34 (31.8)	36 (33.3)
Median DLQI score (IQR)	N/A	N/A	N/A	N/A
Median SCORAD score (IQR)	N/A	N/A	N/A	N/A
Median weekly average worst peak pruritus NRS score (IQR)	N/A	N/A	N/A	N/A
Median % BSA affected (IQR)	N/A	N/A	N/A	N/A
Mean baseline EQ-5D-3L score (SD) [N]	N/A	N/A	N/A	N/A
Prior treatment				
OCS, n (%)	N/A	N/A	N/A	N/A

Immunosuppressant	N/A	N/A	N/A	N/A
•CsA	N/A	N/A	N/A	N/A
•Methotrexate	N/A	N/A	N/A	N/A
•Azathioprine	N/A	N/A	N/A	N/A
•Mycophenolate	N/A	N/A	N/A	N/A
•Other immunosuppressant	N/A	N/A	N/A	N/A
TCS, n (%)	N/A	N/A	N/A	N/A
TCI, n (%)	N/A	N/A	N/A	N/A

[a] Baseline characteristics are not available in Wollenberg 2019. Baseline characteristics are reported on ClinicalTrails.gov. However, tralokinumab groups are not labelled by dose given and so it unclear which baseline characteristics apply to the group receiving the 300 mg dose. Based on reporting in Wollenberg 2019, the EAG has assumed that group 3 in the record available on ClinicalTrials.gov has received the 300 mg dose of tralokinumab.

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; IQR, interquartile range; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

Characteristic	ECZTRA 1 Full trial population		ECZTRA 2 Full trial population	
	Tralokinumab Q2W (N=603)	Placebo (N=199)	Tralokinumab Q2W (N=593)	Placebo (N=201)
Median age, years (IQR)	37·0 (27·0–48·0)	37·0 (26·0–49·0)	34·0 (25·0–48·0)	30·0 (23·0–46·0)
Gender, Male, n (%)	351 (58.2)	123 (61.8)	359 (60.5)	114 (56.7%)
Median duration of AD, years (IQR)	27.0 (19.0–38.0)	28.0 (18.0–41.0)	25.5 (17.0–39.0)	25.0 (18.0–36.0)
Race				

• White, n (%)	426 (70.6)	138 (69.3)	374 (63.1)	123 (61.2)
• Black or African American, n (%)	41 (6.8)	18 (9.0)	43 (7.3)	17 (8.5)
• Asian, n (%)	120 (19.9)	40 (20.1)	154 (26.0)	52 (25.9)
Median EASI score (IQR)	28.2 (21.3–40.0)	30.3 (22.0–41.5)	28.2 (19.8–40.8)	29.6 (20.6–41.4)
Baseline IGA score of 4	305 (50.6)	102 (51.3)	286 (48.2)	101 (50.2)
Median DLQI score (IQR)	17.0 (12.0–22.0)	16.0 (13.0–22.0)	18.0 (13.0–23.0)	18.0 (12.5–24.0)
Median SCORAD score (IQR)	69.2 (61.5–79.1)	70.8 (63.8–81.0)	69.5 (60.5–79.1)	69.9 (61.9–79.1)
Median weekly average worst peak pruritus NRS score (IQR)	7.9 (6.7–8.9)	7.9 (6.9–8.7)	8.0 (7.0–9.0)	8.1 (7.1–9.0)
Median % BSA affected (IQR)	50.0 (33.0–70.0)	52.5 (31.0–77.0)	50.0 (31.0–74.0)	50.0 (31.0–74.0)
Mean baseline EQ-5D-3L score (SD) [N]	N/A	N/A	N/A	N/A
Prior treatment				
OCS, n (%)	357 (59.2)	119 (59.8)	410 (69.1)	125 (62.2)
Immunosuppressant				
•CsA	227 (37.6)	65 (32.7)	204 (34.4)	65 (32.3)
•Methotrexate	77 (12.8)	26 (13.1)	127 (21.4)	38 (18.9)
•Azathioprine	39 (6.5)	7 (3.5)	72 (12.1)	25 (12.4)
•Mycophenolate	27 (4.5)	9 (4.5)	37 (6.2)	14 (7.0)
•Other immunosuppressant	29 (4.8)	11 (5.5)	31 (5.2)	10 (5.0)

TCS, n (%)	591 (98.0)	195 (98.0)	584 (98.5)	200 (99.5)
TCI, n (%)	298 (49.4)	103 (51.8)	271 (45.7)	98 (48.8)

[a] Baseline characteristics are not available in Wollenberg 2019. Baseline characteristics are reported on ClinicalTrails.gov. However, tralokinumab groups are not labelled by dose given and so it unclear which baseline characteristics apply to the group receiving the 300 mg dose. Based on reporting in Wollenberg 2019, the EAG has assumed that group 3 in the record available on ClinicalTrials.gov has received the 300 mg dose of tralokinumab.

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; IQR, interquartile range; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

Characteristic	ECZTRA 3 Full trial population	
	Tralokinumab Q2W plus TCS (N=253)	Placebo plus TCS (N=127)
Median age, years (IQR)	37.0 (28.0–52.0)	34.0 (24.0–50.0)
Gender, Male, n (%)	125 (49.4)	84 (66.1)
Median duration of AD, years (IQR)	27.0 (17.0–39.0)	26.0 (18.0–39.0)[c]
Race		
• White, n (%)	203 (80.2)	85 (66.9)
• Black or African American, n (%)	23 (9.1)	12 (9.4)
• Asian, n (%)	17 (6.7)	24 (18.9)
Median EASI score (IQR)	24.7 (18.4–35.9)[c]	26.5 (19.9–39.3)[c]
Baseline IGA score of 4	116 (45.8)	60 (47.2)
Median DLQI score (IQR)	18.0 (12.0–23.0)[b]	18.0 (12.0–23.0)[a]
Median SCORAD score (IQR)	66.2 (57.6–76.3)[c]	67.9 (59.4–79.0)[c]

Median weekly average worst peak pruritus NRS score (IQR)	8.0 (6.6–8.7)[a]	8.0 (7.0–9.0)[c]
Median % BSA affected (IQR)	41.0 (30.0–63.0)	40.0 (26.0–74.0)
Mean baseline EQ-5D-3L score (SD) [N]	N/A	N/A
Prior treatment		
OCS, n (%)	148 (58.5)	86 (67.7)
Immunosuppressant		
•CsA	75 (29.6)	43 (33.9)
•Methotrexate	29 (11.5)	30 (23.6)
•Azathioprine	13 (5.1)	12 (9.4)
•Mycophenolate	7 (2.8)	5 (3.9)
•Other immunosuppressant	6 (2.4)	0
TCS, n (%)	251 (99.2)	122 (96.1)
TCI, n (%)	127 (50.2)	69 (54.3)

[a] Data missing for two patients.

[b] Data missing for three patients.

[c] Data missing for one patient.

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; IQR, interquartile range; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

4.1.2.4 Data extracted on outcomes of interest

Data on clinical effectiveness from studies evaluating tralokinumab and for populations of interest to the MTA are commercial in confidence and are therefore not presented in this report.

4.1.3 Upadacitinib

4.1.3.1 Interventions assessed in the included studies

Table 21. Summary of interventions assessed in studies evaluating upadacitinib

Study name	Intervention		Comparator(s)		Duration of treatment	Additional information
	Dose	N	Name	N		
Phase IIb	Upadacitinb 30 mg QD	42	Placebo	41	16 weeks	16-week double-blind, randomised treatment period followed by 72-week double-blind, randomised withdrawal period
	Upadacitinb 15 mg QD	42				
	Upadacitinb 7.5 mg QD	42				
HEADS UP	Upadacitinb 30 mg QD	325	Dupilumab 300 mg Q2W	325	24 weeks	Treatment period followed by 12-week follow-up
MEASURE UP1	Upadacitinb 30 mg QD	285	Placebo	281	16 weeks	Treatment phase followed by blinded extension period for up to 120 weeks of treatment
	Upadacitinb 15 mg QD	281				
MEASURE UP2	Upadacitinb 30 mg QD	282	Placebo	278	16 weeks	Treatment phase followed by blinded extension period for up to 120 weeks of treatment
	Upadacitinb 15 mg QD	276				

AD UP	Upadacitinb 30 mg QD plus TCS	297	Placebo plus TCS	304	16 weeks	Initial concomitant TCS was of medium potency (clinician choice), moving to low potency for 7 days once lesions became "clear" or "almost clear" or after 3 weeks, whichever occurred sooner. 16-week double-blind, randomised treatment period followed by 120-week blinded extension period
	Upadacitinb 15 mg QD plus TCS	300				
RISING UP	Upadacitinb 30 mg QD plus TCS	?	Placebo plus TCS	?	16 weeks	Study carried out in Japan and enrolled 272 people. Additional information not available.
	Upadacitinb 15 mg QD plus TCS	?				
Abbreviations: QD, once daily; Q2W, every 2 weeks; TCS, topical corticosteroid.						

4.1.3.2 Study characteristics

Table 22. Characteristics of studies evaluating upadacitinib

Characteristic	Phase IIb	HEADS UP	MEASURE UP1	MEASURE UP2	AD UP	Rising UP
Study references	Guttman-Yassky 2020[106]	CS, clinicaltrials.gov (NCT03738397)[108]	Guttman-Yassky 2021,[109] CS, clinicaltrials.gov (NCT03569293)	Guttman-Yassky 2021,[109] CS, clinicaltrials.gov (NCT03607422)	Reich 2021,[107] CS, clinicaltrials.gov (NCT03568318)	CS, clinicaltrials.gov (NCT03661138)[110]
Country(ies) where the clinical trial was conducted	8 countries – Australia, Canada, Finland, Germany, Japan, the Netherlands, Spain, USA	23 countries – UK, Croatia, Czech Republic, Finland, France, Germany, Hungary, Ireland, Israel, Italy, Netherlands, Norway, Poland, Spain, Sweden, Ukraine, Canada, USA, Australia, New Zealand, Malaysia, Singapore,	24 countries – UK, Bosnia & Herzegovina, Bulgaria, Croatia, Denmark, Finland, France, Germany, Italy, Romania, Turkey, Switzerland, Canada, USA (including Puerto	23 countries – UK, Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, France, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Portugal, Spain, Canada, USA, Australia, New	22 countries – UK, Austria, Belgium, Czech Republic, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Netherlands, Norway, Slovakia, Spain, Sweden, Canada, USA (including Puerto Rico), Australia, New	Japan

		Taiwan	Rico), Argentina, Columbia, Australia, New Zealand, Ukraine, Russia, Estonia, China, Japan, Malaysia	Zealand, Singapore, South Korea, Taiwan	Zealand, China, Japan	
Multicentre trial (number, location)	Not reported	142 locations UK (6 sites: Brighton, Cardiff, Glasgow, 2 x London, Fife)	151 locations UK (4 sites: 3 x London, Manchester,)	154 locations UK (4 sites: London, Newcastle, Plymouth, Southampton)	171 locations UK (5 sites: Dundee, Leeds, 2 x London, Oxford)	43 sites in Japan
Trial sponsors	AbbVie	AbbVie	AbbVie	AbbVie	AbbVie	AbbVie
Date the clinical trial was conducted	Unknown	February 2019 to December 2020	August 2018 to October 2025	July 2018 to December 2025	August 2018 to November 2025	October 2018 to August 2022
Trial design (e.g. parallel, crossover, or cluster trial)	Phase IIb, double-blind, parallel-group, dose-ranging RCT	Phase III parallel assignment RCT, double-blind	Phase III parallel assignment RCT, double-blind	Phase III parallel assignment RCT, double-blind	Phase III parallel assignment RCT, double-blind	Phase 3 parallel assignment RCT, double-blind
Trial duration (treatment duration and follow-up)	16-week double-blind, randomised treatment period followed by 72-week double-blind, randomised withdrawal period	24-week double-blind, double-dummy treatment period followed by 12-week follow-up	16-week double-blind, randomised treatment period followed by 120-week blinded extension period			16-week double blind period followed by a long-term extension
Inclusion criteria	Adults aged 18-75 years, Moderate to severe AD, inadequate response to TCS or TCI within a year of screening, or patients for whom topical	• Adults aged 18-75 years • Moderate to severe AD who are candidates for systemic	• Adolescents and adults aged 12–75 years • Moderate to severe AD who are candidates for systemic therapy or have recently required systemic therapy			• Adolescents and adults aged 12-75 years • Moderate to severe AD who are candidates

	treatment were medically inadvisable	therapy or have recently required systemic therapy		for systemic therapy or have recently required systemic therapy and are able to tolerate TCS
Exclusion criteria	Not reported	• Prior exposure to any JAK inhibitor • Prior exposure to dupilumab. • Unable or unwilling to discontinue current AD treatments prior to the study. • Requirement of prohibited medications during the study. • Other active skin diseases or skin infections requiring systemic treatment or would interfere with appropriate assessment of AD lesions. • Female	• Prior exposure to any JAK inhibitor • Unable or unwilling to discontinue current AD treatments prior to the study • Requirement of prohibited medications during the study • Other active skin diseases or skin infections requiring systemic treatment or would interfere with appropriate assessment of AD lesions • Female subject who is pregnant, breastfeeding, or considering pregnancy during the study	• Prior exposure to any JAK inhibitor • Unable or unwilling to discontinue current AD treatments prior to the study. • Requirement of prohibited medications during the study. • Female participant who is pregnant, breastfeeding, or considering pregnancy during the study.

		participant who is pregnant, breastfeeding, or considering pregnancy during the study				
Concomitant medications	Emollient BD	Emollient BD	Emollient BD	Emollient BD	• Emollient BD • TCS	TCS
Rescue therapy	Not reported	Rescue therapy could be provided from week 4 at the discretion of the investigator if participants had EASI response of <50% at any two consecutive study visits. The first step was to limit rescue therapy to topical treatments and escalate to systemic treatments if participants did not respond adequately after at least 7 days of topical treatment. Study drug was discontinued if a systemic treatment or phototherapy was required.				Not reported
Outcomes	Primary endpoint: • % improvement from baseline at week 16 in EASI. Secondary outcomes: • EASI 50/75/90 at weeks 8 and 16; • IGA 0/1 (%) at week 16; • % improvement from baseline at week 8 in	Primary endpoint: • EASI 75 (%) at week 16 Secondary endpoints: • % change from baseline in WP-NRS at week 16; • EASI 100 (%) at week 16; • EASI 90 (%) at week 16; • % change from baseline in WP-NRS at week 4; • EASI 75 (%) at week 2; • % change from	Primary endpoints: • IGA 0/1 (%) with at least two grades of reduction from baseline at week 16; • EASI 75 (%) at week 16. Secondary endpoints: • % of participants with WP-NRS ≥4 at Baseline with a change of ≥4 in WP-NRS at week 16; • EASI 100 (%) at week 16; • EASI 90 (%) at week 16; • EASI 75 (%) at week 2; • % of participants with WP-NRS ≥4 at Baseline and Randomized to Dose A with a change of ≥4 in WP-NRS at Day 2; • % of participants with WP-NRS		Primary endpoints: • IGA 0/1 (%) with at least two grades of reduction from baseline at week 16; • EASI 75 (%) at week 16 Secondary endpoints: • % of participants with WP-NRS ≥4 at Baseline with a change of ≥4 in WP-NRS at week	Primary endpoint: • number of patients experiencing AE

	EASI; • % improvement from baseline in pruritus NRS by week; • % of patients achieving pruritus NRS improvement from baseline of ≥4 at each visit (among patients with baseline NRS >4 points); • % improvement from baseline in SCORAD at weeks 8 and 16; • SCORAD 50/75/90) at weeks 8 and 16; and change from baseline in BSA at week 16.	baseline in WP-NRS at week 1. Additional outcomes used in model: • % of participants achieving EASI 50 at week 16; • % of participants aged ≥16 years old at screening achieving an improvement (reduction) in DLQI ≥4 from baseline at week 16 for participant with DLQI ≥4 at baseline.	≥4 at Baseline and Randomized to Dose B with a change of ≥4 in WP-NRS at Day 3; • % experiencing a flare at week 16; • % with a change of ≥12 in ADerm-SS Sleep Domain Score at week 16; • % with a change of ≥4 in ADerm-SS Skin Pain Score at week 16; • % with a change of ≥28 in ADerm-SS Total Symptom Score at week 16; • % with a change of ≥11 in ADerm-IS Emotional State Domain Score at week 16; • % with a change of ≥14 in ADerm-IS Daily Activities Score at week 16; Additional outcomes used in model: • % of participants achieving EASI 50 at week 16; • % of participants aged ≥16 years old at screening achieving an improvement (reduction) in DLQI ≥4 from baseline at week 16 for participant with DLQI ≥4 at baseline.	16; • EASI 100 (%) at week 16 for participants in Arm A and Arm C ; • EASI 90 (%) at week 16; • EASI 75 (%) at week 2. Additional outcomes used in model: • % of participants achieving EASI 50 at week 16; • % of participants aged ≥16 years old at screening achieving an improvement (reduction) in DLQI ≥4 from baseline at week 16 for participant with DLQI ≥4 at baseline.	

Subgroups	Baseline IGA of 3 or 4	• Age: <40 years, ≥40 to <65 years, ≥65 years • Gender: male, female • BMI: normal (<25), overweight (≥25 to <30), obese (≥30) • Race: White, Asian, Black, other • Weight: <median, ≥median • Geographic region: US/Puerto Rico/Canada and other • Baseline IGA-AD: <4, ≥4 • Baseline EASI: <median, ≥median • High-sensitivity C-reactive protein: <median, ≥median	• Age: adolescents vs adults <18 years, ≥18 years • Age: <18 years, ≥18 to <40 years, ≥40 to <65 years, ≥65 years • Gender: male, female • BMI: normal (<25), overweight (≥25 to <30), obese (≥30) • Race: White, Asian, Black, other • Weight: <median, ≥median • Geographic region: US/Puerto Rico/Canada and other • Baseline IGA-AD: <4, ≥4) • Baseline EASI: <median, ≥median • High-sensitivity C-reactive protein: <median, ≥median • Previous systemic therapy: with, without • Participants who reported an intolerance to at least one prior TCS or TCI therapy • Participants who reported an inadequate response to at least one prior topical treatment	Not reported

		• Previous systemic therapy: with, without		
Criteria for determination of moderate to severe AD	• IGA ≥3 • EASI ≥16 • BSA involvement ≥10%	• IGA ≥3 • EASI ≥16 • BSA involvement ≥10% • WP-NRS ≥4		Unclear

Abbreviations AD, atopic dermatitis; BSA, body surface area; CsA, cyclosporin A; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D, EuroQol 5 dimensions; IGA, Investigator's Global Assessment; NRS, Numerical Rating Scale; PUVA, psoralen and ultraviolet A radiation; SCORAD, Scoring Atopic Dermatitis; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid; WP-NRS, Worst Pruritus-Numerical Rating Scale.

4.1.3.3 Baseline characteristics

Data from HEADS UP are academic in confidence and are not presented in this report. Additionally, data from MEASURE UP 1 for the adolescent and adult first- and second-line populations are academic in confidence and are not presented in this report.

Table 23. Baseline characteristics of trial populations in studies evaluating upadacitinib

Characteristic	Phase IIb Full trial population			
	Upadacitinib 30 mg QD (N=42)	Upadacitinib 15 mg QD (N=42)	Upadacitinib 7.5 mg QD (N=42)	Placebo (N=41)
Mean age (SD), years	39.9 (15.3)	38.5 (15.2)	41.5 (15.4)	39.9 (17.5)
Gender, female, n (%)	20 (48)	12 (29)	14 (33)	17 (41)
Mean duration of AD since diagnosis (SD), years	24.2 (13.6)	22.6 (15.8)	30.4 (18.1)	26.8 (18.8)
Race				

• White, n (%)	23 (55)	21 (50)	24 (57)	28 (68)
• Black or African American, n (%)	6 (14)	10 (24)	7 (17)	6 (15)
• Asian, n (%)	13 (31)	9 (21)	9 (21)	7 (17)
Mean EASI score (SD)	28.2 (11.6)	31.4 (12.3)	31.4 (15.8)	32.6 (14.5)
Baseline IGA score of 4, n (%)	11 (26)	23 (55)	13 (31)	23 (56)
Mean or median DLQI score	NR	NR	NR	NR
Mean or median SCORAD score	NR	NR	NR	NR
Mean pruritus NRS score (SD)	6.3 (2.1)	6.4 (1.7)	6.8 (1.8)	6.5 (1.9)
Mean % BSA affected (SD)	42.1 (20.4)	50.6 (21.5)	46.9 (24.9)	45.7 (22.8)
Prior treatment				
OCS	NR	NR	NR	NR
Immunosuppressant	NR	NR	NR	NR
TCS	NR	NR	NR	NR
TCI	NR	NR	NR	NR

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

Characteristic	MEASURE UP1 Full trial population		
	Upa 30 mg QD (N=285)	Upa 15 mg QD (N=281)	Placebo (N=281)
Mean age (SD), years	33.6	34.1	34.4

	(15.8)	(15.7)	(15.5)
Gender, male, n (%)	155 (54.4)	157 (55.9)	144 (51.2)
Mean EASI score (SD)	28.98 (11.1)	30.57 (12.8)	28.84 (12.6)
Baseline IGA score of 4, n (%)	131 (46.0)	127 (45.2)	125 (44.5)
Mean DLQI score (SD)	16.4 (7.0)	16.2 (7.0)	17.0 (6.9)
Mean Weekly worst pruritus NRS score (SD)	7.28 (1.5)	7.23 (1.6)	7.27 (1.7)
Mean % BSA affected (SD)	NR	NR	NR
Mean baseline EQ-5D Score (SD)	NR	NR	NR
Prior treatment			
OCS	NR	NR	NR
Immunosuppressant	NR	NR	NR
TCS	NR	NR	NR
TCI	NR	NR	NR

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

Note: Data on mean duration of AD, race, mean SCORAD score and prior systemic treatment from the full trial population of MEASURE UP 1 are academic in confidence, thus are not presented in this report.

Characteristic	MEASURE UP2 Full trial population		
	Upa 30 mg QD (N=282)	Upa 15 mg QD (N=276)	Placebo (N=278)
Mean age (SD), years	34.1 (16.0)	33.3 (15.7)	33.4 (14.8)
Gender, male, n (%)	162 (57.4)	155 (56.2)	154 (55.4)
Mean EASI score (SD)	29.65 (12.2)	28.60 (11.7)	29.08 (12.1)
Baseline IGA score of 4, n (%)	156 (55.3)	150 (54.3)	153 (55.0)
Mean DLQI score (SD)	16.7 (6.93)	16.9 (7.04)	17.1 (7.17)
Mean Weekly worst pruritus NRS score (SD)	7.26 (1.6)	7.15 (1.6)	7.34 (1.6)
Mean % BSA affected (SD)	47.02 (23.2)	45.12 (22.4)	47.61 (22.7)
Mean baseline EQ-5D Score (SD)	NR	NR	NR
Prior treatment			
OCS	NR	NR	NR
Immunosuppressant	NR	NR	NR
TCS	NR	NR	NR
TCI	NR	NR	NR

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

Note: Additionally, data on mean duration of AD, race, mean SCORAD score and prior systemic treatment from the full trial population of MEASURE UP 2 are also academic in confidence, thus are

not presented in this report.

Characteristic	AD UP Full trial population		
	Upa 30 mg QD plus TCS (N=297)	Upa 15 mg QD plus TCS (N=300)	Placebo plus TCS (N=304)
Mean age (SD), years	35.5 (15.8)	32.5 (14.0)	34.3 (15.1)
Gender, male, n (%)	190 (64.0)	179 (59.7)	178 (58.6)
Mean EASI score (SD)	29.72 (11.8)	29.16 (11.8)	30.26 (13.0)
Baseline IGA score of 4, n (%)	157 (52.9)	157 (52.3)	163 (53.6)
Mean DLQI score (SD)	17.1 (7.0)	16.4 (7.2)	16.3 (7.0
Mean Weekly worst pruritus NRS score (SD)	7.36 (1.7)	7.06 (1.8)	7.14 (1.6)
Mean % BSA affected (SD)	48.53 (23.1)	46.68 (21.7)	48.57 (23.1)
Mean baseline EQ-5D Score (SD)	NR	NR	NR
Prior treatment			
OCS	NR	NR	NR
Immunosuppressant	NR	NR	NR
TCS	NR	NR	NR
TCI	NR	NR	NR

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

Note: Data on mean duration of AD, race, mean SCORAD score and prior systemic treatment from the full trial population of AD UP 1 are also academic in confidence, thus are not presented in this report.

4.1.3.4 Data extracted on outcomes of interest

Data on clinical effectiveness from studies evaluating upadacitinib (except for HEADS UP) and for populations of interest to the MTA are academic in confidence and are therefore not presented in this report. Clinical effectiveness data from HEADS UP are presented in Table 24.

Table 24. Data on clinical effectiveness HEADS UP

Outcome at 16 weeks	**HEADS UP** Second-line adults – monotherapy			
	Censoring for receipt of rescue medication		**No censoring for receipt of rescue medication**	
	Upa 30 mg QD (N=50)	DUPI 300 mg Q2W (N=56)	Upa 30 mg QD (N=50)	DUPI 300 mg Q2W (N=56)
Proportion of people achieving EASI 50 + ΔDLQI ≥4, n (%)	NR	NR	NR	NR
Change in EQ-5D score from baseline	NR	NR	NR	NR
Proportion of people who discontinue treatment (including those who discontinue treatment after a response at a set time point as defined in the study)	NR	NR	NR	NR
Proportion of people requiring use of rescue therapy during treatment (present by treatment type, if available)	NR	NR	NR	NR
Number of days free from TCS during treatment	NR	NR	NR	NR
Proportion of people maintaining for a set period of time the	NR	NR	NR	NR

level of response (as defined in the study) initially achieved				
Serious adverse effects of treatment	NR	NR	NR	NR

Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; TCS, topical corticosteroid.

Note: Data on proportion of people achieving EASI 75 are academic in confidence and are not presented in this report.

4.1.4 Baricitinib

4.1.4.1 Interventions assessed in the included studies

Table 25. Summary of interventions assessed in studies evaluating baricitinib

Study name	Intervention		Comparator(s)		Duration of treatment	Additional information
	Dose	N	Name	N		
BREEZE-AD1	Baricitinib 4 mg QD	125	Placebo	249	16 weeks	–
	Baricitinib 2 mg QD	123				
	Baricitinib 1 mg QD	127				
BREEZE-AD2	Baricitinib 4 mg QD	123	Placebo	244	16 weeks	–
	Baricitinib 2 mg QD	123				
	Baricitinib 1 mg QD	125				
Phase II	Baricitinib 4 mg QD plus TCS	38	Placebo plus TCS	49	16 weeks	Concomitant TCS was triamcinolone 0.1%.
	Baricitinib 2 mg QD plus TCS	37				

BREEZE-AD4	Baricitinib 4 mg QD plus TCS	92	Placebo plus TCS	93	52 weeks	Background TCS therapy with moderate-potency and/or low-potency TCS.
	Baricitinib 2 mg QD plus TCS	185				
	Baricitinib 1 mg QD plus TCS	93				
BREEZE-AD7	Baricitinib 4 mg QD plus TCS	111	Placebo plus TCS	109	16 weeks	Patients were allowed to use concomitant TCS that were of moderate or low potency.
	Baricitinib 2 mg QD plus TCS	109				
Abbreviations: QD, once daily; TCS, topical corticosteroid.						

4.1.4.2 Study characteristics

Table 26. Characteristics of studies evaluating baricitinib

Characteristic	BREEZE-AD1 (JAHL)	BREEZE-AD2 (JAHM)	Phase II	BREEZE-AD4 (JAIN)	BREEZE-AD7 (JAIY)
Study references	Committee papers for NICE recommendation for Baricitinib in AD	Committee papers for NICE recommendation for Baricitinib in AD	Guttman-Yassky 2019	Committee papers for NICE recommendation for Baricitinib in AD	Committee papers for NICE recommendation for Baricitinib in AD
Country(ies) where the clinical trial was conducted	10 countries – Czechia, Denmark, France, Germany, India, Italy, Japan, Mexico, Russian Federation, Taiwan	10 countries – Argentina, Australia, Austria, Hungary, Israel, Japan, Republic of Korea, Poland, Spain, Switzerland	2 countries – Japan, USA	14 countries –Austria, Belgium, Brazil, Finland, France, Germany, Italy, Japan, The Netherlands, Poland, Russian Federation, Spain, Switzerland, UK	10 countries –Argentina, Australia, Austria, Germany, Italy, Japan, Republic of Korea, Poland, Spain, Taiwan
Multicentre trial (number, location)	93 locations (9 sites in).	80 locations	13 locations	103 locations (6 sites in UK)	68 locations
Trial sponsors	Eli Lilly and Company	Eli Lilly and Company	Eli Lilly and Company	Eli Lilly and Company	Eli Lilly and Company
Date the clinical trial was conducted	November 2017 to January 2019	November 2017 to December 2018	February 2016 to March 2017	May 2018 to November 2019	November 2018 to August 2019
Trial design (e.g. parallel, crossover, or cluster trial)	BREEZE-AD1 (JAHL) and BREEZE-AD2 (JAHM) were concurrent multicentre, randomised, double-blind, placebo-controlled, parallel-group Phase III		Multicentre, randomised, double-blind, placebo-controlled, parallel-group	An international Phase III, multicentre, long-term	Multicentre, randomised, double-blind, placebo-controlled, parallel-group

	studies.	Phase IIb study.	extension study.	Phase III study.
Trial duration (treatment duration and follow-up)	4-week wash-out for systemic treatments and 2 weeks for topical treatments 16-week intervention 4-week post-treatment follow-up	16-week intervention and follow-up	5-week wash-out 52-week treatment period (followed by a 52-week double-blind long-term extension which included a down-titration sub-study for responders and re-randomisation for non-responders) 4-week post-treatment follow-up	5-week wash-out 16-week intervention 4-week post-treatment follow-up
Inclusion criteria	Adult patients with moderate-to-severe AD, an AD diagnosis at least 12 months prior according to the American Academy of Dermatology definition with a history of clinically significant adverse reactions to topical therapy or a history of inadequate response to topical or systemic therapies.	• Adults with moderate-to-severe AD. • Diagnosed with AD at least 2 years prior • Have a history of inadequate clinical response to other eczema treatments	Adult patients with moderate-to-severe AD, an AD diagnosis at least 12 months prior according to the American Academy of Dermatology definition, a history of inadequate response to topical therapy and a history of intolerance to, contraindication to, or inadequate response to ciclosporin.	Adult patients with moderate-to-severe AD, an AD diagnosis at least 12 months prior according to the American Academy of Dermatology definition and a history of inadequate response to topical or systemic therapy.
Exclusion criteria	• Currently experiencing, or have a history of, other concomitant skin conditions, including psoriasis or lupus erythematosus, which would interfere with evaluation of the effect of the study medication on AD, or which requires frequent hospitalisation and/or	• Females who are pregnant or nursing • Participants who do not agree to use adequate	• Currently experiencing, or have a history of, other concomitant skin conditions which would	• Currently experiencing, or have a history of, other concomitant skin conditions,

	intravenous treatment for skin infections. • Eczema herpeticum within 12 months prior to screening or more than twice in the past. • Any serious concomitant illness anticipated to require the use of systemic corticosteroids or require active frequent monitoring	contraception • Are currently experiencing or have a history of: • Skin conditions such as psoriasis or lupus erythematosus • Skin disease that requires frequent hospitalizations or intravenous treatment • Serious illness that could interfere with study participation, • Active or latent tuberculosis • Have received certain types of vaccination	interfere with evaluation of the effect of the study medication on AD, or which requires frequent hospitalisation and/or intravenous treatment for skin infections. • Have an important side effect to TCS which would prevent further use. • Eczema herpeticum within 12 months prior to screening or more than twice in the past • Any serious concomitant illness anticipated to require the use of systemic corticosteroids or require active frequent monitoring.	including psoriasis or lupus erythematosus, which would interfere with evaluation of the effect of the study medication on AD, or which requires frequent hospitalisation • and/or intravenous treatment for skin infections. • Eczema herpeticum within 12 months prior to screening or more than twice in the past • Any serious concomitant illness anticipated to require the use of systemic corticosteroids or require active

				frequent monitoring • Have an important side effect to TCS (e.g. intolerance to treatment or hypersensitivity reactions) which would prevent further use
Concomitant medications	Systemic and topical treatments were allowed as rescue therapy at the investigator's discretion if patients experienced worsening or unacceptable AD symptoms.	• Triamcinolone cream was provided to patients to use throughout the study according to the labelling or as recommended by the investigator	All concomitant therapies for AD were prohibited throughout the trial except for: • Daily use of emollients • Background TCS therapy with moderate-potency and/or low-potency TCS • TCIs, or topical PDE-4 inhibitor in place of TCS on areas where application of TCS is considered inappropriate • Intranasal or	• Background TCS therapy with moderate-potency and/or low-potency TCS. • High- or ultra-high potency TCS permitted only as rescue therapy. • TCIs or topical PDE-4 inhibitor were permitted in place of TCS on areas where application of TCS was considered inappropriate by the investigator

			inhaled steroids • Topical anaesthetics and topical and systemic anti-infective medications • Non-live seasonal vaccines and/or emergency vaccinations • Antihistamine ophthalmic preparations	• Ophthalmic drugs containing antihistamines, corticosteroids or other immunosuppressants
Rescue therapy	Emollient	As above	Emollient	Emollient
Outcomes	Primary endpoint: • % of patients achieving IGA ≤1 with a ≥2-point improvement at week 16 Secondary endpoints: • Signs and symptoms of AD at Week 16; • EASI scores; • SCORAD scores; • Atopic Dermatitis Sleep Scale Item 2 score; • Itch NRS; • Skin Pain NRS; • DLQI; • EQ-5D-5L; • Adverse events, serious adverse events and treatment-emergent adverse events by	Primary endpoint: • Percentage of participants with a ≥50% reduction in the EASI 50 Secondary endpoints: • Change in EASI • Change in SCORAD • Change in IGA • Change in DLQI • Change in itch NRS • Adverse events	Primary endpoints • Proportion of patients in the ITT population achieving EASI 75 at Week 16 of treatment. Secondary endpoints: Improvement in signs and symptoms at Week 16: • EASI75; • EASI90; • Percent change in EASI score; • SCORAD75.	Primary endpoint: • % of patients achieving IGA ≤1 with a ≥2-point improvement at week 16. Secondary endpoints: • Patients achieving EASI75 and EASI90 at week 16; • Itch NRS; • ADSS score;

	Week 16		Improvement in signs and symptoms at Week 24: • IGA of 0 or 1 with a ≥2-point; improvement • EASI75. Patient-reported outcome measures at Week 16: • 4-point improvement in Itch NRS at Week 1, 2, 4 and 16 of treatment; • Mean change in Item 2 of ADSS score at Week 1 or 16 of treatment; • Mean change from baseline in Skin Pain NRS at Week 16 of treatment. HRQoL outcomes at Week 16: • DLQI; • EQ-5D-5L. Other outcomes listed on clinicaltrials.gov	• Skin pain NRS. Additional outcomes listed in supplement 2 of study paper and on clinicaltrials.gov
Subgroups	• Gender	None reported	• Gender	As for BREEZE AD1 and

	• Age group (<65, ≥65, ≥65 to <75, ≥75 to <85, ≥85 years old) • Baseline weight (<60, ≥60 to <100, ≥100 kg) • Baseline BMI (<25, ≥25 to <30, ≥30 kg/m2) • Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple) • Baseline renal function status: impaired (eGFR <60 mL/min/1.73m2) or not impaired (eGFR ≥60 mL/min/1.73m2) • Region (Europe, Japan, rest of world) • Specific regions (Europe, other) • Specific country (Japan, other) • Prior systemic therapy use (Yes/No) • Baseline disease severity (IGA 3 or 4)		• Age group (<65, ≥65, ≥65 to <75, ≥75 to <85, ≥85 years old) • Baseline weight (<60, ≥60 to <100, ≥100 kg) • Baseline BMI (<25, ≥25 to <30, ≥30 kg/m2) • Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple) • Ethnicity (Hispanic, non-Hispanic) • Baseline renal function status: impaired (eGFR <60 mL/min/1.73m2) or not impaired (eGFR ≥60 mL/min/1.73m2) • Region (Europe, Japan, rest of	BREEZE AD2

			world) • Specific regions (Europe, other) • Specific country (Japan, other) • Prior TCI use • Prior systemic therapy use • Baseline disease severity (IGA 3 or 4)	
Criteria for determination of moderate to severe AD	• EASI score ≥16 • IGA score ≥3 • BSA involvement ≥10%	• EASI score ≥12 • BSA involvement ≥10%	• EASI score ≥16 • IGA score ≥3 • BSA involvement ≥10%	• EASI score ≥16 • IGA score ≥3 • BSA involvement ≥10%

Abbreviations: AD, atopic dermatitis; BD, twice daily; BSA, body surface area; CDLQI, Children's Dermatology Life Quality Index; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; eGFR, Estimated Glomerular Filtration Rate; HADS, Hospital Anxiety and Depression Scale; HIV, human immunodeficiency virus; IGA, Investigator's Global Assessment; JAK, Janus kinase inhibitor; POEM, Patient-Oriented Eczema Measure; PP-NRS, Peak Pruritus Numerical Rating Scale; PSAAD, Pruritus and Symptoms Assessment for Atopic Dermatitis; PtGA, Patient Global Assessment; RCT, randomised controlled trial; SCORAD, Scoring Atopic Dermatitis; TB, mycobacterium tuberculosis; TCI, Topical calcineurin inhibitors.

4.1.4.3 Baseline characteristics

Table 27. Baseline characteristics of trial populations in studies evaluating baricitinib

Characteristic	BREEZE-AD1 (JAHL) Full trial population[b]				BREEZE-AD2 (JAHM) Full trial population[b]			
	Baricitinib 4 mg QD (N=125)	Baricitinib 2 mg QD (N=123)	Baricitinib 1 mg QD (N=127)	Placebo (N=249)	Baricitinib 4 mg QD (N=123)	Baricitinib 2 mg QD (N=123)	Baricitinib 1 mg QD (N=125)	Placebo (N=244)
Mean, years (SD)	37 (12.9)	35 (13.7)	36 (12.4)	35 (12.6)	34 (14.1)	36 (13.2)	33 (10.0)	35 (13.0)

Gender, n (%)	Female: 42 (33.6)	Female: 41 (33.3)	Female: 49 (38.6)	Female: 101 (40.6)	Female: 41 (33.3)	Female: 58 (47.2)	Female: 45 (36.0)	Female: 90 (36.9)
Duration of AD	25 (14.9)	25 (14.6)	27 (14.9)	26 (15.5)	23 (15)	24 (14)	24 (13)	25 (14)
Race								
• White, n (%)	70 (56.5)	75 (61.0)	74 (58.3)	147 (59.5)	82 (66.7)	85 (69.1)	85 (68.0)	169 (69.3)
• Asian, n (%)	41 (33.1)	35 (28.5)	40 (31.5)	73 (29.6)	38 (30.9)	37 (30.1)	36 (28.8)	72 (29.5)
• Other, n (%)	14 (11.2)	13 (10.6)	13 (10.2)	27 (10.9)	2 (2.4)	1 (0.8)	4 (3.2)	3 (1.2)
Mean EASI score (SD)	32 (12.7)	31 (11.7)	29 (11.8)	32 (13.0)	33 (12.7)	35 (16.0)	33 (12.7)	33 (12.8)
IGA of 4 at baseline, n (%)	51 (40.8)	52 (42.3)	53 (41.7)	105 (42.2)	63 (51.2)	62 (50.4)	63 (50.8)	121 (49.6)
Mean DLQI score (SD)	14 (7.1)	13 (7.7)	13 (6.9)	14 (7.4)	14 (8.4)	14 (7.7)	15 (8.1)	15 (8.1)
Mean SCORAD score (SD)	68 (13.0)	68 (13.0)	66 (14.3)	68 (14.0)	68 (13.6)	69 (13.3)	67 (12.9)	68 (12.7)
Mean peak pruritus NRS score (SD)	NR	NR	NR	NR	NR	NR	NR	NR
Mean % BSA affected (SD)	52 (21.8)	50 (22.1)	47 (21.2)	53 (23.1)	54 (21.5)	55 (26.1)	55 (21.9)	52 (21.7)
Prior treatment								
OCS	Unavailable[a]	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable
Immunosuppressant	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable
TCS	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable
TCI	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable

[a] Data were redacted from the Committee papers available for baricitinib.

[b] Data on subgroups of interest from relevant trials were redacted from the Committee papers available for baricitinib.

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

Characteristic	Phase II (Guttman-Yassky 2019) Full trial population[a]			BREEZE-AD4 (JAIN) Full trial population[a]				BREEZE-AD7 (JAIY) Full trial population[a]		
	Baricitinib 4 mg QD plus TCS (N=38)	Baricitinib 2 mg QD plus TCS (N=37)	Placebo plus TCS (N=49)	Baricitinib 4 mg QD plus TCS (N=92)	Baricitinib 2 mg QD plus TCS (N=185)	Baricitinib 1 mg QD plus TCS (N=93)	Placebo plus TCS (N=93)	Baricitinib 4 mg QD plus TCS (N=111)	Baricitinib 2 mg QD plus TCS (N=109)	Placebo plus TCS (N=109)
Median, years (IQR)	32.5 (26–48)	42 (26–52)	35 (28–48)	Mean age (SD)				Mean age (SD)		
				39 (13)	37 (14)	39 (14)	39 (14)	33.9 (11.4)	33.8 (12.8)	33.7 (13.2)
Gender, n (%)	Male: 22 (58)	Male: 22 (59)	Male: 24 (49)	Female: 35 (38)	Female: 52 (28)	Female: 35 (38)	Female: 44 (47)	Female: 36 (32)	Female: 39 (36)	Female: 38 (35)
Median duration of AD (IQR)	22 (6.4–30.7)	26.4 (18.3–40.5)	17.7 (7.3–29.5)	NR	NR	NR	NR	Mean duration of AD (SD)		
								25.5 (13.2)	24.6 (14.8)	22 (12.2)
Race										
• White, n (%)	18 (47)	20 (54)	23 (47)	71 (77)	144 (78)	70 (75)	74 (80)	54 (49)	50 (46)	46 (42)
• Asian, n (%)	9 (24)	9 (24)	7 (14)	NR	NR	NR	NR	54 (49)	57 (52)	57 (52)
• Black, n (%)	9 (24)	8 (22)	16 (33)	NR	NR	NR	NR	3 (3)	2 (2)	6 (6)
• Other, n (%)	2 (5)	0	3 (6)							
Median (IQR) EASI score	19.5 (13.7–25.9)	22.1 (16.8–32.3)	22.1 (15.3–28)	Mean EASI score (SD)				Mean EASI score (SD)		
				33 (13.7)	31 (12.4)	34 (13.5)	31 (11.6)	30.9 (12.6)	29.3 (11.9)	28.5 (12.3)
Median IGA score	3 (3–4)	3 (3–4)	3 (3–4)	IGA of 4 at baseline, %				IGA of 4 at baseline, n (%)		

(IQR)				51	51	51	54	50 (45)	50 (46)	48 (44)
Median DLQI score (IQR)	11 (8–17)	10 (7–17)	15 (10–19)	Mean DLQI score (SD)				Mean DLQI score (SD)		
				14.0 (8.1)	13.6 (7.4)	14.3 (8.3)	14.5 (6.9)	14.7 (7.9)	15 (7.7)	15 (7.9)
Median SCORAD score (IQR)	57.6 (49.5–64.9)	53.3 (49.9–61.1)	55 (44.9–63.8)	Mean SCORAD score (SD)				Mean SCORAD score (SD)		
				69 (13.4)	68 (13.4)	71 (14.1)	69 (13.0)	68.3 (13.2)	66.8 (14)	66.6 (13.8)
Median peak pruritus NRS score	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mean % BSA affected (SD)	NR	NR	NR	NR	NR	NR	NR	52.1 (23.3)	50.6 (21.6)	48.1 (24.4)
Prior treatment				NR	NR	NR	NR	NR	NR	NR
OCS	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Immunosuppressant	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
TCS	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
TCI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

[a] Data on subgroups of interest from relevant trials were redacted from the Committee papers available for baricitinib.

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

4.1.4.4 Data extracted on outcomes of interest

Table 28. Data on clinical effectiveness from studies evaluating baricitinib and for populations of interest to the MTA

Outcome	BREEZE AD4 Second-line adults – combination therapy			
	Bar 4 mg QD plus TCS (N=92)	Bar 2 mg QD plus TCS (N=185)	Bar 1 mg QD plus TCS (N=93)	Placebo plus TCS (N=93)
Proportion of people achieving EASI 75	29	51	21	16

Abbreviations: AD, atopic dermatitis; EASI, Eczema Area and Severity Index; QD, once daily; TCS, topical corticosteroid.

Table 29. Data on adverse effects and adverse effects of special interest informing the model for bariticinib

Outcome	BREEZE AD 4				BREEZE AD 7		
	Placebo plus TCS (N=93)	Bar 1 mg QD plus TCS (N=NR)	Bar 2 mg QD plus TCS (N=NR)	Bar 4 mg QD plus TCS (N=92)	Placebo +TCS (N=108)	Bar 2 mg QD plus TCS (N=109)	Bar 4 mg QD plus TCS (N=111)
SAEs n (%)	2	NR	NR	6 (1 allergic conjunctivitis)	4	2	4
Injection site reaction	NA	NA	NA	NA	NA	NA	NA
Allergic conjunctivitis	NR	NR	NR	NR	NR	NR	NR
Conjunctivitis	NR	NR	NR	NR	2	3	0
URTI	NR	NR	NR	NR	2	8	3
Acne	NR	NR	NR	NR	1	1	4
Oral herpes	3	NR	NR	5	0	4	4

Abbreviations: AE adverse effect; NA, not applicable; NR, not reported; QD, once daily; Q2W, every 2 weeks; SAE, serious adverse effect; TCS, topical corticosteroid; URTI, urinary tract infection.

4.1.5 Dupilumab

4.1.5.1 Interventions assessed in the included studies

Table 30. Summary of interventions assessed in studies evaluating dupilumab

Study name	Intervention[a]		Comparator(s)		Duration of treatment	Additional information
	Dose	N	Name	N		

Phase IIb	Dupilumab 300 mg Q4W	65	Placebo	61	16 weeks	–
	Dupilumab 300 mg Q2W	64				
	Dupilumab 300 mg QW	63				
	Dupilumab 200 mg Q2W	61				
	Dupilumab 100 mg Q4W	65				
AD ADOL	Dupilumab 300 mg Q4W	84	Placebo	82	16 weeks	In the dupilumab Q2W group, dose was weight-based, with those weighing <60 kg receiving 200 mg Q2W after a loading dose of 400 mg. Those weighing ≥60 kg received 300 mg Q2W after a loading dose of 600 mg.
	Dupilumab 200 mg or 300 mg Q2W	82				
SOLO-1	Dupilumab 300 mg Q2W	224	Placebo	224	16 weeks	–
	Dupilumab 300 mg QW	223				
SOLO-2	Dupilumab 300 mg Q2W	233	Placebo	236	16 weeks	–
	Dupilumab 300 mg QW	239				
CAFE	Dupilumab 300 mg Q2W plus TCS	107	Placebo plus TCS	108	16 weeks	Initial concomitant TCS was of medium potency applied once daily to active lesions. Low-potency TCS could be applied to areas of thin skin.
	Dupilumab 300 mg QW plus TCS	110				
CHRONOS	Dupilumab 300 mg Q2W plus TCS	106	Placebo plus TCS	315	52 weeks	Topical therapies allowed during the trial included low or medium potency TCS and TCI. People were allowed to use more than one topical therapy. Initial concomitant TCS was of medium potency, moving to low potency for 7 days once lesions became “clear” or “almost clear”.
	Dupilumab 300 mg QW plus TCS	319				

[a] Initial dose of dupilumab was 600 mg, which was a loading dose

Abbreviations: QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks; TCS, topical corticosteroid.

4.1.5.2 Study characteristics

Table 31. Characteristics of studies evaluating dupilumab

Characteristic	Phase IIb	AD ADOL	SOLO-1	SOLO-2	CAFE	CHRONOS
Study references	Simpson 2016b/Thaci 2016	Simpson 2020[117]	Simpson 2016[120] TA534[124]	Simpson 2016[120] TA534[124]	de Bruin-Weller 2018[118] TA534[124]	Blauvelt 2017[125] TA534[124]
Country(ies) where the clinical trial was conducted	7 countries – USA, Canada, Czechia, Germany, Hungary, Japan, Poland	2 countries – USA, Canada	10 countries – USA, Bulgaria, Canada, Denmark, Estonia, Finland, Germany Japan, Singapore, Spain	11 countries – USA Canada, France, Germany, Hong Kong, Italy, Korea, Lithuania, Poland, Sweden, UK	Countries where systemic CsA was approved for the treatment of AD including Austria, Belgium, Germany, Ireland, The Netherlands, Poland, Russian Federation, Slovakia, Spain, UK.	14 countries – USA, Australia, Canada, Czech Republic, Hungary, Italy, Japan, Republic of Korea, The Netherlands, New Zealand, Poland, Romania, Spain, UK
Multicentre trial (number, location)	84 locations	45 locations	101 locations	93 locations	Approximately 115 study sites	149 locations
Trial sponsors	Regeneron Pharmaceuticals & Sanofi	Regeneron Pharmaceuticals & Sanofi	Regeneron Pharmaceuticals & Sanofi	Regeneron Pharmaceuticals & Sanofi	Regeneron Pharmaceuticals & Sanofi	Regeneron Pharmaceuticals & Sanofi
Date the clinical trial was conducted	May 2015 and Jan 2014	March 2017 to June 2018	October 2014 to February 2016	November 2014 to January 2016	January 2016 to March 2017	September 2014 to October 2016
Trial design (e.g. parallel, crossover, or cluster trial)	Phase IIb, double-blind, randomised, placebo-controlled, parallel-group	Phase III, double-blind, randomised, placebo-controlled, parallel-group	Identical Phase III studies, 16-week, multicentre, randomised, double-blind, placebo-controlled, parallel-group studies.		Phase III, double-blind, randomised, placebo-controlled, parallel-group	Phase III, multicentre, randomised, double-blind, placebo-controlled study
Trial duration (treatment duration and	16-week intervention phase plus 16-week follow-up	16-week intervention phase plus 12-week follow-up	16-week intervention phase plus 12-week follow-up		16-week intervention phase plus 16 week follow-up	64 weeks 52 weeks of treatment plus 12 weeks of follow-

follow-up)					up
Inclusion criteria	Adults (age >18 years) with moderate to severe AD, defined by IGA score 3 or higher, with disease not adequately controlled by topical medications or for whom topical treatment was inadvisable. Patients were required to have chronic AD, defined by consensus criteria, present for 3 or more years before screening; an EASI score of 12 or higher at screening and 16 or higher at baseline; an IGA score of 3 or higher; and AD involvement 10% or more of BSA.	Eligible patients were 12 years or older to younger than 18 years with moderate to severe AD inadequately controlled by topical treatment or for whom topical treatment was medically inadvisable. Patients had chronic AD, as per American Academy of Dermatology criteria for 1 year or more before screening.	Adult patients with moderate-to-severe AD whose disease is not adequately controlled with topical medications or for whom topical treatment was medically inadvisable.	Adult patients with moderate-to-severe AD who are not adequately controlled with, or are intolerant to oral ciclosporin, or when this treatment is not medically advisable	Adult patients with moderate-to-severe AD who had an inadequate response to medium or higher potency TCS
			Additionally, eligible patients presented with chronic AD (present for at least 3 years and meeting the American Academy of Dermatology Consensus Criteria and with a documented recent history (within 6 months before the screening visit) of an inadequate response to topical prescription medications, or in whom those therapies were not advisable. In addition, an average maximum itch intensity of ≥3 on the pruritus NRS was required at baseline. The studies therefore represent a patient population with AD lesions affecting a large portion of their BSA and experienced high levels of AD symptoms, including pruritus, which are not adequately controlled by topical prescription therapies alone, and were candidates for systemic AD therapies.		
Exclusion criteria	• Active acute or chronic infections; use of topical medications for AD (other than bland emollients) within 1 week of baseline;	• Participation in a prior dupilumab clinical study • Treatment with a systemic investigational drug before the baseline visit • Treatment with a topical	• Participation in a prior Dupilumab clinical study • Treatment with an investigational drug within 8 weeks or within 5 half-lives • Having used immunosuppressive/ immunomodulating drugs or phototherapy within 4 weeks before the baseline visit	• Participation in a prior dupilumab clinical study • Treatment with an investigational drug within 8 weeks or within 5 half-lives (if known), whichever is longer, before the screening visit	• Participation in a prior Dupilumab clinical trial; • Important side effects of topical medication • Having used immunosuppressive/ immunomodulati

	• Systemic immunosuppressive/ immunomodulating drugs within 4 weeks of baseline; or significant comorbidities or laboratory abnormalities	investigational agent within 4 weeks or within 5 half-lives • Treatment with TCS or TCI within 2 weeks before the baseline visit • Having used immunosuppressive/ immunomodulating drugs or phototherapy within 4 weeks before the baseline visit • Treatment with live vaccine within 4 weeks • Body weight <30kg • Regular use of tanning booths • Known history of HIV • Pregnant or breastfeeding women • Women	• Regular use of a tanning booth/ parlour within 4 weeks of the screening visit • Treatment with a live vaccine within 12 weeks before the baseline visit • Known or suspected history of immunosuppression • Pregnant or breastfeeding women • Women unwilling to use adequate birth control, if of reproductive potential and sexually active	• Hypersensitivity and/or intolerance to corticosteroids or to any other ingredients contained in the TCS product used in the study • Systemic CSA, systemic corticosteroids, or phototherapy within 4 weeks prior to screening, and azathioprine (AZA), methotrexate (MTX), mycophenolate mofetil (MMF), or Janus kinase (JAK) inhibitors within 8 weeks prior to screening • Treatment with TCI within 1 week before the screening visit • Regular use of a tanning booth/ parlour within 4 weeks of the screening visit	ng drugs or phototherapy within 4 weeks before the baseline visit • Treatment with a live vaccine within 12 weeks before the baseline visit; • Positive hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or hepatitis C antibody at the screening visit; • Active or acute infection requiring systemic treatment within 2 weeks before baseline visit; • Known or suspected history of immunosuppression;

		unwilling to use adequate birth control, if of reproductive potential and sexually active		• Known or suspected history of immunosuppression • Pregnant or breastfeeding women • Women unwilling to use adequate birth control, if of reproductive potential and sexually active	• Pregnant or breastfeeding women • Women unwilling to use adequate birth control, if of reproductive potential and sexually active
Concomitant medications	–	–	• Basic skin care emollients, topical anaesthetics, topical and systemic antihistamines, and topical and systemic anti-infective medications for any duration. • Medications used to treat chronic disease such as diabetes, hypertension, and asthma were permitted.	Basic skin care (cleansing and bathing), emollients, bleach baths, topical anaesthetics, and antihistamines for any duration. Low to medium dose TCS.	• Basic skin care (cleansing and bathing), emollients, bleach baths, topical anaesthetics, and antihistamines for any duration. Use of TCS restricted to locally approved products and according local country guidelines. • Use of TCI was reserved for problem areas.

Rescue therapy	Rescue treatment (medication and/ or phototherapy) was allowed at the investigator's discretion; patients who received such therapy were discontinued from study treatment, but were asked to continue with assessments.	Systemic nonsteroidal immunosuppressants, systemic or topical corticosteroids, topical calcineurin inhibitors, and topical crisaborole could be used only as rescue treatment by patients with intolerable AD symptoms at the discretion of the investigator.	Rescue treatment for AD if medically necessary (i.e., to control intolerable AD symptoms), was provided to study patients at the discretion of the investigator after week 2. Patients who received rescue treatment prior to week 2 were to permanently discontinue study treatment. Patients who received rescue treatment continued study treatment if rescue consisted of topical medications. TCI could be used for rescue, but were reserved for problem areas only. Patients could be rescued directly with higher potency topical medications or with systemic treatments. If a patient received rescue treatment with systemic corticosteroids or nonsteroidal systemic immunosuppressive/ immunomodulating drugs study treatment was immediately, temporarily discontinued. After the treatment with these medications was completed, study treatment could be resumed but not sooner than 5 half-lives after the last dose of systemic rescue medication. Dose modification for an individual patient was not allowed. Patients who were discontinued from study drug were to remain in the study and complete all study visits and assessments.		
Outcomes	Primary endpoint: • % improvement in EASI score from baselines to Week 16. Secondary endpoints: • Participants who achieved IGA response; • Percent change in weekly average of peak; • daily pruritus NRS from baseline; • Percent change in EASI score from baseline;	Primary endpoints: • Proportion of patients with an IGA score of 0 or 1 and a reduction from baseline of ≥2 points at Week 16; • Proportion of patients with ≥75% improvement in EASI score (EASI-75) from baselines to Week 16. Secondary endpoints: • Percentage changes from	Primary endpoints: • Proportion of patients with an IGA score of 0 or 1 and a reduction from baseline of ≥2 points at Week 16; • Proportion of patients with ≥75% improvement in EASI score (EASI-75) from baselines to Week 16. Secondary endpoints: • Percent change in EASI score from baseline; • Proportion of patients who achieved EASI-50; • Percent change in weekly average of peak daily pruritus NRS from baseline; • Proportion of patients achieving a reduction of ≥4 points in	Primary endpoint: • Proportion of patients with ≥75% improvement in EASI score (EASI-75) from baselines to Week 16. Secondary endpoints: • Percent change in EASI score from baseline; • Proportion of patients who achieved EASI-50; • Percent change in weekly average of peak daily pruritus NRS from baseline; • Proportion of	Primary endpoints: • Proportion of patients with an IGA score of 0 or 1 and a reduction from baseline of ≥2 points at Week 16; • Proportion of patients with ≥75% improvement in EASI score (EASI-75) from baselines to Week 16. Secondary endpoints: • Percent change in EASI score

	• percentage change in SCORAD; • >50%, >75% and >90% improvement from baseline in EASI (EASI-50/EASI-75/EASI-90); • Change from baseline in POEM.	baseline in EASI and Peak Pruritus NRS • Proportion of patients with a 3-point or more or 4-point or more improvement from baseline in Peak Pruritus NRS • 50% or more or 90% or more improvement from baseline in EASI • (EASI-50/EASI-90) • percentage change in SCORAD • Changes in Children's Dermatology Life • Quality Index • POEM scores • HADS scores	weekly average of peak daily pruritus NRS from baseline; • Change from baseline in weekly average of peak daily pruritus NRS; • Change from baseline in DLQI; • Change from baseline in POEM; • Change from baseline in HADS; • Change from baseline in EQ-5D; • Incidence of AEs; • Sick leave/missed school days assessment.	patients achieving a reduction of ≥4 points in weekly average of peak daily pruritus NRS from baseline; • Change from baseline in weekly average of peak daily pruritus NRS; • Change from baseline in DLQI; • Change from baseline in POEM; • Change from baseline in HADS; • Change from baseline in EQ-5D; • Incidence of AEs; • Sick leave/missed school days assessment.	from baseline; • Proportion of patients who achieved EASI-50; • Percent change in weekly average of peak daily pruritus NRS from baseline; • Proportion of patients achieving a reduction of ≥4 Points in weekly average of peak daily pruritus NRS from baseline; • Change from baseline in weekly average of peak daily pruritus NRS; • Change from baseline in DLQI; • Change from baseline in POEM;

					• Change from baseline in HADS; • Change from baseline in EQ-5D; • Incidence of AEs; • Sick leave/missed school days assessment.
Subgroups	None reported	Bodyweight (<60 kg vs ≥60 kg)	SOLO CAFÉ-like: patients from SOLO-1 and SOLO-2 who showed an inadequate efficacy response to oral ciclosporin, inadequate efficacy response or were intolerant to oral ciclosporin or patients who did not receive prior oral ciclosporin treatment because ciclosporin was contraindicated or otherwise medically inadvisable. • Age (≥18 to <40 years, ≥40 to <65 years, ≥65 years) • Sex (male, female) • Ethnicity (Hispanic or Latino, not Hispanic or Latino) • Race (White, Black or African American, Asian, or other) • Duration of AD (<26 years, ≥26 years)	CSA prior exposure vs CSA naïve • Age (≥18 to <40 years, ≥40 to <65 years, ≥65 years) • Sex (male, female), • Ethnicity (Hispanic or Latino, not Hispanic or Latino) • Race (White, Black or African American, Asian, or other) • Duration of AD (<26 years, ≥26 years) • Baseline weight (<70 kg, ≥70 kg to	CHRONOS CAFÉ-like: patients who showed an inadequate efficacy response to oral ciclosporin, patients who showed an inadequate efficacy response or were intolerant to oral ciclosporin, plus patients who did not receive prior oral ciclosporin treatment because ciclosporin was contraindicated or because treatment with oral ciclosporin was otherwise medically inadvisable. • Age (≥18 to <40 years, ≥40 to

			• Baseline weight (<70 kg, ≥70 kg to <100 kg, ≥100 kg) • BMI at baseline (≥15 to <25 kg/m^2, ≥25 to <30 kg/m^2, ≥30 kg/m^2) • Region for global submission (Asia-Pacific, Eastern Europe, North and South America, Western Europe) • Region for Japan submission (Japan, rest of world).	<100 kg, ≥100 kg) • BMI at baseline (≥15 to <25 kg/m^2, ≥25 to <30 kg/m^2, ≥30 kg/m^2) • Region for global submission (Asia-Pacific, Eastern Europe, North and South America, Western Europe) • Region for Japan submission (Japan, rest of world).	<65 years, ≥65 years) • Sex (male, female), • Ethnicity (Hispanic or Latino, not Hispanic or Latino) • Race (White, Black or African American, Asian, or other) • Duration of AD (<26 years, ≥26 years) • Baseline weight (<70 kg, ≥70 kg to <100 kg, ≥100 kg) • BMI at baseline (≥15 to <25 kg/m^2, ≥25 to <30 kg/m^2, ≥30 kg/m^2) • Region for global submission (Asia-Pacific, Eastern Europe, North and South

						America, Western Europe) • Region for Japan submission (Japan, rest of world).
Criteria for determination of moderate to severe AD	• IGA ≥3 • EASI ≥16 • ≥10% BSA involvement	• IGA ≥3 • EASI ≥16 • ≥10% BSA involvement	• IGA ≥3 • ≥10% BSA involvement	• IGA ≥3 • ≥10% BSA involvement	• IGA ≥3 • EASI ≥ 20 • ≥10% BSA involvement	• IGA ≥3 • EASI ≥16 • ≥10% BSA involvement
Abbreviations: AD, atopic dermatitis; BD, twice daily; BSA, body surface area; CDLQI, Children's Dermatology Life Quality Index; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; HADS, Hospital Anxiety and Depression Scale; HIV, human immunodeficiency virus; IGA, Investigator's Global Assessment; JAK, Janus kinase inhibitor; POEM, Patient-Oriented Eczema Measure; PP-NRS, Peak Pruritus Numerical Rating Scale; PSAAD, Pruritus and Symptoms Assessment for Atopic Dermatitis; PtGA, Patient Global Assessment; RCT, randomised controlled trial; SCORAD, Scoring Atopic Dermatitis; TB, mycobacterium tuberculosis.						

4.1.5.3 Baseline characteristics

Table 32. Baseline characteristics of trial populations in studies evaluating dupilumab

Characteristic	Phase IIb Full trial population					
	Dupilumab 300 mg Q2W	Dupilumab 300 mg QW	Dupilumab 200 mg Q2W	Dupilumab 300 mg Q4W	Dupilumab 100 mg Q4W	Placebo QW
N patients	63	64	61	65	65	61
Mean age, years (SD)	36.2 (10.7)	39.4 (12.1)	35.8 (14.9)	36.8 (10.8)	36.6 (11.6)	37.2 (13.1)
Gender male, n (%)	43 (68.3)	41 (64.1)	36 (59.0)	40 (61.5)	34 (52.3)	40 (65.6)
Duration of AD (years), mean (SD)	25.8 (12.2)	28.6 (16.5)	25.6 (13.2)	27.1 (11.6)	28.0 (14.7)	31.2 (14.2)

Race						
• White, n (%)	NR	NR	NR	NR	NR	NR
• Black or African American, n (%)	NR	NR	NR	NR	NR	NR
• Asian, n (%)	NR	NR	NR	NR	NR	NR
• Other, n (%)	NR	NR	NR	NR	NR	NR
Mean EASI score (SD)	30.1 (11.2)	33.8 (14.5)	32.9 (15.5)	29.4 (11.5)	32.2 (13.5)	32.9 (13.8)
IGA score, n (%)						
• 3	32 (50.8)	34 (53.1)	31 (50.8)	37 (56.9)	34 (52.3)	32 (52.5)
• 4	31 (49.2)	30 (46.9)	30 (49.2)	28 (43.1)	31 (47.7)	29 (47.5)
Mean DLQI score (SD)	NR	NR	NR	NR	NR	NR
Mean SCORAD score (SD)	65 (12.2)	68.5 (12.6)	68.3 (14)	67.2 (12.3)	68.2 (15)	67.1 (13.6)
Weekly average peak daily pruritus NRS score, Mean (SD)	NR	NR	NR	NR	NR	NR
% BSA affected, mean (SD)	48.4 (20.9)	53.2 (24.8)	50.8 (25.4)	50.8 (22.6)	48.7 (23.9)	51.1 (23.5)
Prior treatment						
Corticosteroids	NR	NR	NR	NR	NR	NR
Immunosuppressant	NR	NR	NR	NR	NR	NR

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

Characteristic	AD ADOL Full trial population			SOLO-1 Full trial population			SOLO-2 Full trial population			SOLO-1 and SOLO-2 Pooled CAFÉ-like population		
	Dup 200/300 mg Q2W (N=82)	Dup 300 mg Q4W (N=84)	Placebo (N=85)	Dup 300 mg Q2W (N=224)	Dup 300 mg QW (N=223)	Placebo (N=224)	Dup 300 mg Q2W (N=233)	Dup 300 mg QW (N=239)	Placebo (N=236)	Dup 300 mg Q2W (N=104)	Dup 300 mg QW (N=96)	Placebo (N=88)
Mean age, years (SD)	14.5 (1.7)	14.4 (1.6)	14.5 (1.8)	39.8 (14.7)	39.3 (14.4)	39.5 (13.9)	36.9 (14.0)	37.1 (14.5)	37.4 (14.1)	38.0 (13.5)	37.6 (12.5)	38.8 (12.9)
Gender male, n (%)	43 (52.4)	52 (61.9)	53 (62.4)	130 (58.0)	142 (63.7)	118 (52.7)	137 (58.8)	139 (58.2)	132 (55.9)	75 (72.1)	56 (58.3)	55 (62.5)
Duration of AD (years), mean (SD)	12.5 (3.0)	11.9 (3.2)	12.3 (3.4)	28.5 (16.1)	27.9 (15.8)	29.5 (14.5)	27.2 (14.2)	27.4 (15.0)	28.2 (14.4)	29.0 (14.4)	28.3 (15.3)	29.9 (14.7)
Race												
• White, n (%)	54 (65.9)	55 (65.5)	48 (56.5)	155 (69.2)	149 (66.8)	146 (65.2)	165 (70.8)	168 (70.3)	156 (66.1)	75 (72.1)	69 (71.9)	52 (59.1)
• Black or African American, n (%)	7 (8.5)	8 (9.5)	15 (17.6)	10 (4.5%)	20 (9.0%)	16 (7.1%)	13 (5.6%)	15 (6.3%)	20 (8.5%)	1 (1.0%)	2 (2.1)	0
• Asian, n (%)	12 (14.6)	13 (15.5)	13 (15.3)	54 (24.1)	51 (22.9)	56 (25.0)	44 (18.9)	45 (18.8)	50 (21.2)	23 (22.1)	23 (24.0)	30 (34.1)
• Other, n (%)	NR	NR	NR	5 (2.2)	3 (1.3)	6 (2.7)	6 (2.6)	4 (1.7)	7 (3.0)	5 (4.8)	2 (2.0)	6 (6.8)
Mean EASI score	35.3	35.8	35.5	33.0	33.2	34.5	31.8	31.9	33.6	36.9	35.7	35.6

(SD)	(13.8)	(14.8)	(14.0)	(13.6)	(14.0)	(14.5)	(13.1)	(12.7)	(14.31	(14.6)	(14.7)	(14.3)
Mean IGA score (SD)	NR	NR	NR	3.5 (0.50)	3.5 (0.50)	3.5 (0.50)	3.5 (0.50)	3.5 (0.50)	3.5 (0.50)	3.7 (0.5)	3.6 (0.5)	3.6 (0.5)
Proportion with IGA score of 3/4 at baseline, n (%)	39 (47.6)/43 (52.4)	38 (45.2)/46 (54.8)	39 (45.9)/46 (54.1)	Score of 4: 108 (48.2)	Score of 4: 106 (47.5)	Score of 4: 110 (49.1)	Score of 4: 115 (49.4)	Score of 4: 112 (46.9)	Score of 4: 115 (48.7)	NR	NR	NR
Mean DLQI score (SD)	13.0 (6.2)	14.8 (7.4)	13.1 (6.7)	13.9 (7.4)	14.1 (7.5)	14.8 (7.2)	15.4 (7.1)	16.0 (7.3)	15.4 (7.7)	15.7 (6.8)	16.8 (7.8)	16.6 (7.9)
Mean SCORAD score (SD)	70.6 (13.9)	69.8 (14.1)	70.4 (13.3)	66.9 (14.0)	67.5 (13.6)	68.3 (14.0)	67.2 (13.5)	67.5 (13.1)	69.2 (14.9)	72.2 (13.9)	70.9 (13.4)	72.8 (13.4)
Peak pruritus NRS score, Mean (SD)	7.5 (1.5)	7.5 (1.8)	7.7 (1.6)	Weekly average Peak daily pruritus NRS score, Mean (SD)								
				7.2 (1.9)	7.2 (2.1)	7.4 (1.8)	7.6 (1.6)	7.5 (1.8)	7.5 (1.9)	7.6 (1.6)	7.4 (1.8)	7.8 (1.5)
% BSA affected, mean (SD)	56.0 (21.4)	56.9 (23.5)	56.4 (24.1)	54.7 (23.2)	56.1 (23.0)	57.5 (23.4)	52.7 (21.2)	52.2 (21.5)	54.3 (23.1)	58.8 (21.9)	59.0 (22.7)	59.9 (23.7)
Prior treatment												
Corticosteroids	21 (25.6)	27 (32.5)	21 (24.7)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Immunosuppressant	20 (24.4)	15 (18.1)	17 (20.0)	NR	NR	NR	NR	NR	NR	NR	NR	NR

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; Dup, dupilumab; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

Characteristic	CAFÉ			CHRONOS Full trial population			Pooled data for CAFÉ & CHRONOS-CAFÉ-like		
	Dupilumab 300 mg Q2W plus TCS (N=107)	Dupilumab 300 mg QW plus TCS (N=110)	Placebo plus TCS (N=108)	Dupilumab 300 mg Q2W plus TCS (N=106)	Dupilumab 300 mg QW plus TCS (N=319)	Placebo plus TCS (N=315)	Dupilumab 300 mg Q2W plus TCS (N=130)	Dupilumab 300 mg QW plus TCS (N=163)	Placebo plus TCS (N=169)

Mean age, years (SD)	37.5 (12.9)	38.7 (13.2)	38.9 (13.4)	39.6 (14.0)	36.9 (13.7)	36.6 (13.0)	37.8 (12.9)	38.4 (12.9)	38.1 (13.0)
Gender male, n (%)	65 (60.7)	66 (60.0%	68 (63.0)	62 (58.5)	191 (59.9)	193 (61.3)	77 (59.2)	98 (60.1)	102 (60.4)
Duration of AD (years), mean (SD)	29.6 (15.6)	32.3 (14.0)	29.2 (14.7)	30.1 (15.5)	27.9 (14.5)	27.5 (14.3)	29.9 (15.4)	31.6 (14.5)	28.9 (15.1)
Race									
• White, n (%)	104 (97.2)	105 (95.5)	104 (96.3)	74 (69.8)	208 (65.2)	208 (66.0)	121 (93.1)	145 (89.0)	152 (89.9)
• Black or African American, n (%)	0	2 (1.8)	0	2 (1.9)	13 (4.1)	19 (6.0)	1 (0.8)	2 (1.2)	3 (1.8)
• Asian, n (%)	2 (1.9)	2 (1.8)	2 (1.9)	29 (27.4)	89 (27.9)	83 (26.3)	7 (5.4)	14 (8.6)	12 (7.1)
• Other, n (%)	1 (0.9)	1 (0.9)	2 (1.9)	1 (0.9)	9 (2.8)	5 (1.6)	0	2 (1.2)	2(1.2)
Mean EASI score (SD)	33.3 (9.9)	33.1 (11.0)	32.9 (10.8)	33.6 (13.3)	32.1 (12.8)	32.6 (12.9)	33.6 (10.5)	34.2 (11.7)	34.8 (12.0)
Mean IGA score (SD)	3.5 (0.5)	3.5 (0.5)	3.5 (0.5)	3.5 (0.5)	3.5 (0.5)	3.5 (0.5)	3.5 (0.5)	3.5 (0.5)	3.5 (0.5)
Mean DLQI score (SD)	14.5 (7.6)	13.8 (8.0)	13.2 (7.6)	14.5 (7.3)	14.4 (7.2)	14.7 (7.4)	14.6 (7.5)	15.0 (8.0)	14.8 (7.7)
Mean SCORAD score (SD)	68.6 (11.9)	66.0 (12.7)	67.0 (12.2)	69.3 (15.2)	65.9 (13.6)	66.0 (13.5)	69.3 (12.9)	67.6 (13.4)	68.7 (12.8)
Weekly average peak daily pruritus	6.6 (2.1)	6.2 (2.0)	6.4 (2.2)	7.4 (1.7)	7.1 (1.9)	7.3 (1.8)	6.9 (2.1)	6.6 (2.0)	6.9 (2.1)

NRS score, Mean (SD)									
% BSA affected, mean (SD)	56.1 (17.8)	56.0 (19.3)	55.0 (20.5)	59.5 (20.8)	54.1 (21.8)	56.9 (21.7)	57.3 (18.5)	57.3 (20.5)	58.9 (21.7)
Prior treatment									
OCS	NR	NR	NR	NR	NR	NR	NR	NR	NR
Immunosuppressant	NR	NR	NR	NR	NR	NR	NR	NR	NR
TCS	NR	NR	NR	NR	NR	NR	NR	NR	NR
TCI	NR	NR	NR	NR	NR	NR	NR	NR	NR

Abbreviations: AD, atopic dermatitis; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; NRS, numerical rating scale; OCS, oral corticosteroid; POEM, Patient-Oriented Eczema Measure; QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

4.1.5.4 Data extracted on outcomes of interest

Table 33. Data on clinical effectiveness from studies evaluating dupilumab and for populations of interest to the MTA

Outcome at 16 weeks	**Ariens et al** First-line adults – combination therapy		**CHRONOS** Full trial population		
	CsA with or without TCS (N=39)	Dup 300 mg Q2W plus TCS (N=106)	Dup 300 mg Q2W plus TCS (N=106)	Dup 300 mg QW plus TCS (N=319)	Placebo plus TCS (N=315)
Proportion of people achieving EASI 75, n (%)	20	80	78	226	102

Abbreviations: CsA, ciclosporin A; EASI, Eczema Area and Severity Index; QW, every week; Q2W, every 2 weeks; TCS, topical corticosteroid.

Outcome at 16 weeks	Pooled analysis of SOLO-1 and SOLO-2 Second-line adults - monotherapy						Pooled analysis of CAFÉ and CHRONOS CAFÉ-LIKE Second-line adults – combination therapy					
	Censoring for receipt of rescue medication			No censoring for receipt of rescue medication			Censoring for receipt of rescue medication			No censoring for receipt of rescue medication		
	Dup 300 mg Q2W (N=104)	Dup 300 mg QW (N=95)	Placebo (N=88)	Dup 300 mg Q2W (N=104)	Dup 300 mg QW (N=95)	Placebo (N=88)	Dup 300 mg Q2W plus TCS (N=130)	Dup 300 mg QW plus TCS (N=163)	Placebo plus TCS (N=169)	Dup 300 mg Q2W plus TCS (N=130)	Dup 300 mg QW plus TCS (N=163)	Placebo plus TCS (N=169)
Proportion of people achieving EASI 50 + ΔDLQI ≥4, n (%)	54	–	10	61	58	21	89	–	35	95	117	47
Proportion of people achieving EASI 75, n (%)	42	–	10	47	49	15	83	–	43	87	103	51

Abbreviations: Dup, dupilumab; EASI, Eczema Area and Severity Index; QW, every week; Q2W, every 2 weeks; TCS, topical corticosteroid.

Outcome at 16 weeks	AD ADOL Adolescents					
	Censoring for receipt of rescue medication			No censoring for receipt of rescue medication		
	Dup 200 mg or 300 mg Q2W (N=82)	Dup 300 mg Q4W (N=84)	Placebo (N=85)	Dup 200 mg or 300 mg Q2W (N=82)	Dup 300 mg Q4W (N=84)	Placebo (N=85)
Proportion of people achieving EASI 75, n (%)	34	32	7	34	32	7

Abbreviations: EASI, Eczema Area and Severity Index; Q2W, every 2 weeks; Q4W, every 4 weeks.

Table 34. Data on adverse effects and adverse effects of special interest informing the model for dupilumab

Outcome	SOLO 1			SOLO 2			CAFE			CHRONOS		
	Placebo (N=222)	Dup 300 mg Q2W (N=229)	Dup 300 mg QW (N=218)	Placebo (N=234)	Dup 300mg Q2W (N=236)	Dup 300mg QW (N=237)	Placebo plus TCS (N=108)	Dup 300 mg Q2W plus TCS (N=107)	Dup 300 mg QW plus TCS (N=110)	Placebo plus TCS (N=315)	Dup 300 mg Q2W plus TCS (N=110)	Dup 300 mg QW plus TCS (N=315)
Treatment discontinuations n (%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
SAEs n (%)	11	7	2	13	4	8	2	2	2	6	3	4
AEs of special interest												
Injection site reaction	13	19	41	15	32	31	0	1	4	18	11	51
Allergic conjunctivitis	2	12	7	2	2	3	7	16	10	9	7	19
Conjunctivitis	2	11	7	1	9	9	3	12	8	2	0	3
URTI	5	6	11	5	7	9	1	1	3	20	7	21
Acne										6	0	6
Oral herpes	4	9	4	4	8	9	0	3	5	5	3	8

Abbreviations: AE adverse effect; Dup, dupilumab; NA, not applicable; NR, not reported; QD, once daily; QW, every week; Q2W, every 2 weeks; SAE, serious adverse effect; TCS, topical corticosteroid; URTI, urinary tract infection.

Outcome	AD ADOL		
	Placebo (N=85)	Dupilumab 300 mg Q4W (N=83)	Dupilumab 200/300 mg Q2W (N=82)
SAEs n (%)	1	0	0
Injection site reaction	3	5	7
Allergic conjunctivitis	3	4	3
Conjunctivitis	1	3	4
URTI	15	6	10
Acne	NR	NR	NR
Oral herpes	NR	NR	NR

Abbreviations: AE adverse effect; NA, not applicable; NR, not reported; Q2W, every 2 weeks; Q4W, every 4 weeks; SAE, serious adverse effect; TCS, topical corticosteroid; URTI, urinary tract infection.

4.2 Economic evaluations

Table 35. Economic evaluation publications

Author, year, country	Perspective, discounting & cost year	Model type	Patient population	Intervention/ comparator	Outcomes	Results ICER (per QALY gained) incl. uncertainty
Canadian Agency for Drugs and Technologies in Health. 2020. Canada	Perspective: Canadian public healthcare payer Discounting: annual	Short-term 1-year decision tree followed by a long-term maintenance Markov model. Short-term model included 16- and 52-week assessments points for	Patients aged 12 years or older with moderate-to-severe AD for whom topical prescription therapies failed to achieve effective disease control or were not advisable.	Intervention: dupilumab plus standard of care (SOC). In adolescents aged 12 to 17 years old who weigh <60kg, two subcutaneous injections of 200 mg in the first	Response to treatment was based on 50% or more improvement in EASI score compared with baseline (EASI 50). Response at 16 weeks was based on AD-1526 for dupilumab + SOC	In the sponsor base case, dupilumab+SOC versus SOC resulted in incremental costs and QALYs of $127,607 and 2.55 QALYs, respectively. The ICER was estimated to be $50,133 per QALY gained.

	discount rate of 1.5% for costs and QALYS Cost year: 2019	response based on data from the AD-1526, SOLO 1, SOLO 2, LIBERTY AD CHRONOS AND LIBERTY AD CAFE trials. Non-responders in the short-term model transitioned to best supportive care (BSC) in the long-term model. In the long-term model, BSC was split by response status. Responders at 16 and 52 weeks transitioned to the response state in the long-term model and could discontinue to BSC during any cycle. The Markov-model included annual cycles with half-cycle correction.	Analysis includes a subgroup of patients who were refractory to, or ineligible for, systemic immunosuppressant therapies (reimbursement population)	week (loading dose), then one 200 mg subcutaneous injection Q2W. For adolescents who weigh >60 kg, two 300 mg subcutaneous injections, followed by 300 mg subcutaneous injections Q2W. Comparator: SOC, assumed to be topical therapy (type of topical treatments not listed in study). However, the cost of topical treatment was not included in the model.	(61.0%) and SOC (12.9%). Conditional response at 52-weeks for those who achieved a response at 16 weeks was taken from the CHRONOS study, but data are redacted. CADTH implemented alternative response data for their base case, which was based on pooled data from the SOLO trials that estimated 67% of dupilumab+SOC patients and 23.3% of SOC patients achieved EASI 50 as week 16. CADTH also explored the use of EASI 75 for response. CADTH were unable to verify the sponsor's 52-week conditional probability response and instead implemented the following based on data from the CHRONOS study: 97.2% for dupilumab + SOC and 81.4% for SOC. Long-term response was informed from clinical expert feedback that	The CADTH ICER was $136,025 per QALY gained. For a subgroup of patients who were refractory to, or ineligible for, systemic immunosuppressant therapies the sponsor ICER was $52,168 per QALY gained.

					suggested the probability for sustaining a response to dupilumab was 98% in year 2, reducing to 92% in year 5 and beyond. For SOC, the probability of long-term response was estimated to be 37% in year 2, reducing to 0% in year 4 and beyond. CADTH disagreed with the sponsor's treatment waning assumptions for SOC and instead preferred to assume the following: year 2 = 43%; year 3 = 18%; year 4 = 8%; and year 5+ = 3%. A treatment discontinuation rate of 6.3% per model cycle was applied for patients on dupilumab and was based on data from the SOLO trials. The impact of adverse events was only modelled to affect costs. Adverse events in the model included allergic conjunctivitis, infectious conjunctivitis, oral herpes,	

					and skin infections. The source of adverse event rates was not reported.	
Kuznik *et al*. 2017. USA	Perspective: US payer Discounting: annual discount rate of 3% for costs and QALYS Cost year: 2016	16-week decision tree, followed by a lifetime horizon Markov model. Patients enter the model on either dupilumab 300 mg or standard care (SC). At 16 weeks, patients are assessed for treatment response. Responders to dupilumab treatment enter the long-term Markov model in the maintenance health state and dupilumab non-responders move to the SC health state. Patients on SC in the short-term model remain in the SC health state in the long-term model. A 4-month cycle length was used for the Markov model.	Adult patients with moderate-to-severe AD	Intervention: dupilumab (administered as a 300-mg subcutaneous injection Q2W) plus emollients Comparator: standard care, assumed to be emollients as required.	Therapeutic response was used as the main outcome in the model and was defined as a 75% improvement in EASI score (EASI 75). Based on pooled data from the SOLO trials, 48% and 13% of dupilumab q2w and SC patients, respectively, achieved the EASI 75 response. Dupilumab treatment discontinuation was included in the model and was based on data from the open label extension studies for SOLO 1 and SOLO 2, where 6.3% of previously responding patients discontinued by 52 weeks. This annual value was converted to a constant 4-month probability for use in the model. Adverse events associated with dupilumab treatment	For the base case, dupilumab was estimated to produce 1.12 more QALYs over the lifetime horizon compared with SC (15.95 vs. 14.83) and result in cost savings of approximately $32,000 for other medical costs. The annual maintenance price for dupilumab therapy to be considered cost-effective at a threshold of $100,000 per QALY gained would be $28,769 and $39,941 when the threshold increases to $150,000 per QALY gained.

					were included in the model and were based on data from the SOLO trials. The primary adverse events modelled were injection site reaction, included once in the first cycle of the model and infectious conjunctivitis, which was included in every model cycle.	
Fanelli *et al*. 2020. Italy (abstract)	Perspective: Italian National Healthcare Service Discounting: Not reported Cost year: Not reported	1-year decision tree, followed by a lifetime horizon Markov model.	Adolescents (aged 12-17) with uncontrolled moderate-to-severe AD	Intervention: Dupilumab Comparator: Current supportive care	In the base-case, dupilumab generated 1.53 additional QALYs compared with current supportive care. However, dupilumab was associated with an increase in treatment costs (+ €61,121.17), but a decrease in the costs of disease management and the management of complications of the disease (respectively - €8,349.80 and - €907.84). The abstract does not report what measure of treatment effectiveness was used to estimate costs and QALYs for the cost-effectiveness analysis.	The ICER was €33,918.29 per QALY gained

Zimmermann . 2018. USA	Perspective: US health system Discounting: annual discount rate of 3% for costs and QALYS Cost year: 2017	Lifetime Markov model with 4-month cycles. Model health states were based on treatment response using the EASI score (EASI 50, EASI 75 or EASI 90). All patients enter the model in the no response (usual care) health state and can transition to any of the responder health states based on their response to treatment defined by EASI score. Patients could not transition between the different EASI category health states. Over time, patients can discontinue treatment or experience treatment waning and thus transition to the no response (usual care) health state.	Adults with moderate-to-severe AD inadequately controlled with topical therapy, or for whom topical therapies were medically inadvisable.	Intervention: Dupilumab 300 mg dose Q2W (with a 600 mg loading dose) Comparator: Usual care (emollients)	Treatment response in the model was defined as an initial response to treatment with a reduction in the EASI score of at least 50%, ≥75% or ≥90%, stratified by severity. Data for response came from the dupilumab trials and were provided by Sanofi. For moderate AD patients, the percentage achieving EASI 75 scores were 17.6% and 8.3% for dupilumab and usual care, respectively. For severe AD patients, the percentage achieving EASI 75 scores were 14.2% and 3.9% for dupilumab and usual care, respectively. EASI 50 and EASI 90 data are also reported in Table 1 of the publication. Dupilumab treatment discontinuation was assumed to be 6.3% annually (data provided by Sanofi). For responders on usual care, the probability of transitioning to the non-response health state was assumed to be 65.8% every	For the base case, dupilumab was estimated to produce an incremental QALY gain of 1.91 and incremental costs of $238,132 (list price) over the lifetime horizon compared with usual care. The ICER was estimated to be $124,541 per QALY gained (list price). The cost-effectiveness results for the 95% credible interval range are as follows: Incremental QALYs = 1.24-1.91 Incremental cost (list price) = $135,800 - $219,200 ICER (list price) = $66,400 - $116,400 per QALY gained

					model cycle. Adverse events were modelled with rates obtained from the literature. Adverse events included injection site reaction (DUP=11%), allergic conjunctivitis (DUP=3%; usual care=0.9%) and infectious conjunctivitis (DUP=4.3%; usual care=0.7%).	
National Institute for Health and Care Excellence - TA534. 2018. UK	Perspective: UK NHS Discounting: annual discount rate of 3.5% for costs and QALYS Cost year: 2016	Short-term 1-year decision tree followed by a long-term three-state Markov model. Short-term model included 16- and 52- week assessment points for response to treatment. Responders to dupilumab at 16 weeks continued treatment up to 52 weeks and non-responders discontinued to BSC. Patients on BSC remain on BSC irrespective of response status. At the 52-week assessment point, if response to dupilumab is maintained,	Adult patients with moderate-to-severe AD who are contraindicated to, intolerant of, had an inadequate response to or for whom it is otherwise medically inadvisable to receive treatment with a systemic immunosuppressant.	Intervention: Dupilumab 300 mg dose Q2W (with a 600 mg loading dose). However, the appraisal committee only considered evidence for dupilumab in combination with topical corticosteroids. Comparator: BSC, which includes emollients, low-to-mid potency topical corticosteroids, and rescue therapy which may include higher potency topical corticosteroids, oral corticosteroids or	The appraisal committee's preferred definition of treatment response for the economic model was EASI-50 (reduction in of at least 50% in the EASI score from baseline) plus an improvement in the DLQI of at least 4. Data on response was obtained from the CAFE study and the CAFE-like population from the CHRONOS study, which compared dupilumab+TCS with BSC. From the trials, the all-observed dataset was used, which does not exclude patients who	The ICER range considered plausible by the appraisal committee was £27,410 to 28,495 per QALY gained.

		patients enter the Markov maintenance treatment health state. If response to dupilumab treatment is lost at 52 weeks, patients enter the Markov BSC health state. All BSC patients and dupilumab patients who discontinued to BSC at the 16-week assessment point continue to the Markov BSC health state. The cycle length in the Markov model is annual, with half-cycle correction. At the end of each cycle, patients in the maintenance treatment health state can discontinue treatment and transition to the BSC health state or die.		topical calcineurin inhibitors. After the first appraisal committee meeting, the company revised BSC to also include phototherapy and psychological support.	received rescue treatment. At week 16 the proportion of patients on dupilumab+TCS and BSC responding to treatment was 73.1% and 27.8%, respectively. Response to treatment at 52 weeks was conditional on response to treatment at 16 weeks. The 52-week conditional response probability for dupilumab+TCS and BSC was 0.939 and 0.767, respectively. In the long-term model, an annual treatment discontinuation rate of 3.7% for patients on dupilumab+TCS was accepted by the appraisal committee. The annual rate of treatment discontinuation was based on data from the CHRONOS study and reflected the proportion of patients who responded to treatment at week 16 but who withdrew from the trial by 52 weeks.	

					In addition to treatment discontinuation, loss of response was considered in the model. The appraisal committee accepted that patients on dupilumab+TCS have a sustained response and that by year 5 onwards, 8% of patients would lose response. For patients on BSC, the committee considered that by year 5 onwards, up to 97% of patients would lose response to treatment. Adverse events included in the model were injection site reaction, allergic conjunctivitis, infectious conjunctivitis and oral herpes.	
National Institute for Health and Care Excellence - TA681. 2021. UK.	Perspective: UK NHS Discounting: annual discount rate of 3.5% for costs and QALYS Cost year:	A four-state, lifetime (62-year) Markov model. Health states included 'induction', representing a series of tunnel states for the short-term initial treatment phase, 'maintenance' which reflects long-term	Adult patients with moderate-to-severe AD who have previously failed one or more systemic therapies.	Intervention: Baricitinib 4 mg once daily in combination with topical corticosteroids Comparators: BSC, which includes emollients, low-to-mid potency topical corticosteroids,	The appraisal committee's preferred definition of treatment response for the economic model was EASI-50 (reduction in of at least 50% in the EASI score from baseline) plus an improvement in the DLQI of at least 4, in line with the	The cost-effectiveness results demonstrated that baricitinib + TCS was associated with cost savings and QALY loss compared with dupilumab + TCS, but the committee's preferred ICER was not presented in the final appraisal document. For the

	2019	treatment, 'non-response' and 'death'. The model cycle length was 4 weeks and no half cycle correction was applied. All patients enter the model in the induction health state and remain there for 16 weeks. At week 16, patients can transition to the maintenance health state and remain on treatment or transition to the non-response health state and receive BSC. Transitions at week 16 are determined by patients' response to their allocated treatment. Between week 16 and 52, patients in the maintenance health state receive continuous treatment until they lose response and from year 2 onwards can discontinue treatment for other reasons such as adverse events (based on all cause discontinuation) and move to the non-response health state,		phototherapy, psychological support and rescue therapy. Dupilumab 300 mg dose Q2W (with a 600 mg loading dose) in combination with topical corticosteroids	recommendations in TA534. Data on response was based on an indirect treatment comparison and included data for baricitinib from the BREEZE-AD4 (JAIN) study and a subgroup of patients from the BREEZE-AD7 (JAIY) study who had previously failed on, or were intolerant or contraindicated to ciclosporin (JAIN-like JAIY). Equivalent data for dupilumab was obtained from the CAFE study and a subpopulation from the CHRONOS study (CAFE-like CHRONOS population). Response rates at week 16 for baricitinib, dupilumab and BSC were 49.0%, 79.3% and 31.3% respectively. The ERG produced alternative estimates of response, but these data are redacted. For response at week 52, the appraisal committee preferred the use of all-cause discontinuation being applied post week 16, as	comparison of baricitinib + TCS with BSC, the appraisal committee considered that assumptions around quality of life waning made the ICERs uncertain and as such did not state a preferred ICER but concluded baricitinib is likely to be cost-effective.

		where they start 1st line BSC and start a second set of induction tunnel states, with response to treatment measured at 16 weeks post induction.			per the ERG's recommendation instead of conditional response probabilities applied at week 52 based on response at week 16. The ERG preferred discontinuation data for baricitinib from the JAHN extension study, but data are redacted. The ERG preferred per cycle rate of discontinuation for dupilumab was obtained from the CHRONOS study and estimated to be 0.29% discontinuation per model cycle. For BSC, an annual discontinuation rate of 57% was assumed for BSC.	
Healthcare Improvement Scotland. Scottish Medicines Consortium (SMC2011 & SMC2232). UK. 2019	Perspective: Scottish National Health Service health system Discounting: Not reported Cost year: Not reported	Short-term (1 year) decision tree, followed by a long-term (lifetime) Markov model with annual cycles. In the decision tree, response to treatment was evaluated at 16 weeks. Patients on dupilumab who did not respond to treatment at week 16 discontinued to BSC. However, it is not	Patients who have had an inadequate response to existing systemic immunosuppressants such as ciclosporin, or in whom such treatment is considered unsuitable. The adult population was assessed in SMC2011 and the adolescent population was assessed in SMC2232	Intervention: Dupilumab 300 mg dose Q2W (with a 600 mg loading dose) Comparator: BSC (not defined)	A composite response outcome of EASI 50 plus DLQI >4 at week 16 was used in the short-term model. Response data was based on pooled data from CAFE study and the CAFE-life population from the CHRONOS study for dupilumab in combination with TCS. For dupilumab monotherapy, data were	The base case results including PAS discount (not reported) for dupilumab+TCS and dupilumab monotherapy compared with BSC were £63,911 and £41,532, respectively. The SMC considered alternative assumptions (reported in Table 6 of the publication) and produced

		reported what happens to responders between week 16 and 52. The Markov model was based on three health states: maintenance treatment with dupilumab, BSC treatment and death. Costs and benefits for dupilumab patients in the maintenance health state were differentiated by response status. However, for the BSC arm, costs were differentiated based on response status, but benefits were based on an average of responder and non-responder utility values.			taken from the CAFE-like population from the SOLO trials. From all trials, the "all observed dataset" was used instead of the primary analysis dataset, where patients were considered non-responders after rescue medication. Dupilumab treatment discontinuation was assumed to be 3.7% annually, but the source of the data was not reported. Adverse events were included in the model but only in terms of costs. Types and rates of adverse events were not reported. It should be noted that the above results only correspond to the adult population. In SMC2232, data for the adolescent population are not provided.	what it considered was a more plausible cost-effectiveness base case. The SMC results (including PAS) for dupilumab+TCS and dupilumab monotherapy compared with BSC were £40,089 and £31,560, respectively. It should be noted that the above results only correspond to the adult population. In SMC2232, ICERs for the adolescent population are not provided.
Healthcare Improvement Scotland. Scottish	Perspective: Scottish National Health	Lifetime Markov model consisting of four health states, including induction, maintenance,	Adult patients with moderate-to-severe AD who are candidates for systemic therapy who have	Intervention: Baricitinib 4 mg once daily (with or without topical corticosteroids)	Treatment response in the model was defined as an initial response to treatment with a reduction in the EASI	The base case results for baricitinib compared with BSC and dupilumab were £65,466 and £113,459 (SW quadrant),

Medicines Consortium (SMC2337). UK. 2021.	Service health system Discounting: Not reported Cost year: Not reported	non-response and death. All patients enter the model in the induction health state and remain there for the first 16 weeks of the model, after which they can transition to the maintenance phase if they achieve an EASI 75 response. For patients who do not achieve a response, they can transition to the next line of treatment and enter the second induction phase or move to no response at the third line of treatment. Over time, patients can discontinue maintenance treatment and move to the next line of treatment. In the BSC maintenance state, no discontinuation was assumed to reflect the waxing and waning nature of response to BSC.	failed at least one current systemic immunosuppressant due to intolerance, contraindication or inadequate disease control.	Comparators: Dupilumab, BSC (not defined)	score of ≥75% (EASI 75) at week 16. Response data were derived from a pooled analysis of BREEZE-AD4 and the BREEZE-AD4-like population from the BREEZE-AD7 study. An indirect comparison was used to derive treatment response data for dupilumab. At week 16, the percentage of patients achieving EASI 75 was 42%, 57% and 22% for baricitinib, dupilumab and BSC, respectively. Between week 16 and 52, a conditional probability of EASI 75 response in patients achieving a week 16 response was applied for the baricitinib and dupilumab arms of the model. After year 1, all cause discontinuation rate at week 52 was used to calculate a constant rate of discontinuation (data not reported).	respectively.
Institute for Clinical and	Perspective: US health	Lifetime Markov model with 4-month cycles.	Adults with moderate-to-severe AD inadequately	Intervention: Dupilumab 300 mg dose Q2W (with	Treatment response in the model was defined as an	For the base case, dupilumab was estimated to produce an

Economic Review. USA. 2017	system Discounting: annual discount rate of 3% for costs and QALYS Cost year: 2017	Model health states were based on treatment response using the EASI categories (EASI 50, EASI 75 or EASI 90). All patients enter the model in the non-responder health state. After the first cycle, patients can transition to any of the responder health states based on their response to treatment defined by EASI score. In subsequent cycles, patients could transition to the non-responder health state due to treatment discontinuation or treatment waning. Patients could not transition between the different EASI category health states.	controlled with topical therapy, or for whom topical therapies were medically inadvisable.	a 600 mg loading dose) Comparator: Usual care (emollients)	initial response to treatment with a reduction in the EASI score of at least 50%, ≥75% or ≥90%, stratified by severity. Data for response was supplied by Sanofi. For moderate AD patients, the percentage achieving EASI 75 scores were 17.6% and 8.3% for dupilumab and usual care, respectively. For severe AD patients, the percentage achieving EASI 75 scores were 14.2% and 3.9% for dupilumab and usual care, respectively. EASI 50 and EASI 90 data are also reported in Table 5 and Table 6 of the publication. Dupilumab treatment discontinuation was assumed to be 6.3% annually (data from Sanofi). For responders on usual care, the probability of transitioning to the non-response health state was assumed to be 65.8% every model cycle. Adverse events were	incremental QALY gain of 1.91 and incremental costs of $238,132 (list price) over the lifetime horizon compared with usual care. The ICER was estimated to be $124,541 per QALY gained (list price). The cost-effectiveness results for the 95% credible interval range are as follows: Incremental QALYs = 1.23-2.64 Incremental cost (list price) = $101,073 - $436,399 ICER (list price) = $49,805 - $247,604 per QALY gained

					modelled and included injection site reaction (DUP=11%), allergic conjunctivitis (DUP=3%; usual care=0.9%) and infectious conjunctivitis (DUP=4.3%; usual care=0.7%). Data were provided by Sanofi.	
Institute for Clinical and Economic Review. USA. 2021.	Perspective: US health system Discounting: annual discount rate of 3% for costs and QALYS Cost year: 2021	5-year Markov model with 4-month cycles. Model health states were based on treatment response using the EASI categories (EASI 50, EASI 75 or EASI 90). All patients enter the model in the non-responder health state. After the first cycle, patients can transition to any of the responder health states based on their response to treatment defined by EASI score. In subsequent cycles, patients could transition to the non-responder health state due to treatment discontinuation or treatment waning. Patients could not	Patients with moderate-to-severe atopic dermatitis.	Interventions: - Abrocitinib 200 mg once daily - Tralokinumab 300 mg Q2W - Upadacitinib 30 mg once daily - Baricitinib 2 mg once daily Comparator: Standard of care (emollients), dupilumab 300 mg Q2W	Treatment response in the model was defined as an initial response to treatment with a reduction in the EASI score of at least 50%, ≥75% or ≥90%, stratified by severity. Data on response by EASI score is redacted. Treatment specific per-cycle treatment discontinuation rates (all cause) for the first year after initial treatment and then for all subsequent years over the model time horizon where data was available was used in the model. Per cycle discontinuation rates were derived from long-term follow-up data for patients who achieved a minimum of	ICERs - intervention vs SoC Abrocitinib - $148,300 Tralokinumab - $129,400 Upadacitinib - $248,400 Baricitinib - $71,600 Dupilumab - $110,300 ICERs - intervention vs dupilumab Abrocitinib - $303,400 Tralokinumab - dominated Upadacitinib - $1,912,200 Baricitinib - dominated

		transition between the different EASI category health states.			EASI 50 at their initial 16-week assessment. Long-term discontinuation data for AD patients were not available for upadacitinib and such rate equal to the highest rate within the class was assumed. Dupilumab treatment discontinuation was assumed to be 3.77% in the first year and then 4.87% thereafter. For tralokinumab, treatment discontinuation was 5.04% annually. Discontinuation data for all other treatments are redacted. For responders on usual care, the probability of transitioning to the non-response health state was assumed to be 25.4% annually. Adverse events were not included in the model as the authors did not identify evidence of any serious adverse events occurring in >5% of subjects among any of the clinical trials.	

Abbreviations: AD, atopic dermatitis; BMI, body mass index; BSC, best supportive care; CADTH, Canadian Agency for Drugs and Technologies in Health; CI, confidence interval; CS, company submission; DLQI, Dermatology Life Quality Index; DUP, dupilumab; EASI, Eczema Area and Severity Index; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; kg, kilogram; mg, milligram; NHS, National Health Service; PAS, patient access scheme; QALY, quality-adjusted life year; qw, once weekly; q2w, every 2 weeks; q4w, every 4 weeks; SC, standard care; SD, standard deviation; SE, standard error; SMC, Scottish Medicines Consortium; SoC, standard of care; SW, south-west; TCS, topical corticosteroids; TE, technical engagement; UK, United Kingdom; US, United States

4.1 HRQoL – articles

Table 36. HRQoL publications

#	Author, year, country	Sample size	Patient population	Instrument (Valuation)	Utility results
1	Andersen, 2020, Europe (France, Germany, the UK) and the USA	Of the 1,098 respondents with moderate-to-severe AD, 118 were from the UK. Sample size according to severity (PO-SCORAD score), all countries (UK): Mild (<25): 134 (23)	People with AD, recruited from the 2016 NHWS (US also the 2015 NHWS). Mean age (SD) according to severity (PO-SCORAD score), years: Mild (<25): 47.4 (17.2) Moderate (25-30): 48.5 (15.3) Severe 1 (51-60): 49.3 (13.1) Severe 2 (61-70): 46.7 (12.7) Severe 3 (71+): 45.5 (12.4)	HRQoL measured using the EQ-5D-5L. Valuation method unclear (all EQ-5D index scores were calculated using their respective 5L value sets).	The unadjusted mean (SD) utility in the UK across all severity categories was 0.62 (0.30). The unadjusted mean (SD) utility across all countries in respondents with moderate-to-severe AD was 0.70 (0.26) and with mild AD 0.88 (0.16) Utility according to severity (PO-SCORAD score): Europe adjusted mean; USA adjusted mean Mild: NR

		Moderate (25-30): 825 (77) Severe 1 (51-60): 141 (19) Severe 2 (61-70): 83 (12) Severe 3 (71+): 49 (10)			Moderate (25-30): 0.77; 0.74 Severe 1 (51-60): 0.69; 0.67 Severe 2 (61-70): 0.64; 0.66 Severe 3 (71+): 0.42; 0.56 The mean was adjusted for country, age, sex, alcohol use, smoking, body mass index category, household income, CCI and years since atopic dermatitis diagnosis.
2	Girolomoni, 2021, EU5 (France, Germany, Italy, Spain, and the UK).	Of the 1,014 respondents with moderate-to-severe AD, 283 were from the UK. Sample size according to severity (DLQI score), all countries (UK): Moderate (6-10): 597 (177) Severe 1 (11-20): 348 (83) Severe 2 (21-30): 69 (23)	People with moderate-to-severe AD, recruited from the 2017 EU5 NHWS. Mean age (SD) according to severity (DLQI score), years: Moderate (6-10): 42.3 (16.3) Severe 1 (11-20): 40.3 (14.2) Severe 2 (21-30): 39.7 (13.5)	HRQoL measured using the EQ-5D-5L. Valuation method unclear.	Adjusted utility means by comorbidity category across EU5 countries Sleep difficulties: none, 0.66; mild, 0.63; moderate, 0.52; severe, 0.46 Anxiety: no, 0.76; yes, 0.66 Depression (PHQ-9): none-minimal, 0.76; mild, 0.70; moderate, 0.65; moderately severe, 0.56; severe, 0.42 Adjusted for age, sex, country, income, employment status, BMI, CCI score, and presence of other atopic conditions.
3	Hsieh, 2021, Taiwan	Sample size according to severity (SCORAD score): Mild (<25): 70 Moderate (25-50): 72 Severe (>50): 58	People with AD recruited from two regional hospital clinics in Taiwan from April 2018 to April 2019. Mean age (SD) according to severity (SCORAD score), years: Mild (<25): 35.3 (13.7) Moderate (25-50): 35.0 (12.2)	HRQoL measured using the EQ-5D-5L. Valued using the value set for Taiwan (Lin 2018).	Mean (SD) utility according to severity (SCORAD score): Severe (<25): 0.70 (0.22) Moderate (25-50): 0.82 (0.19) Mild (>50): 0.91 (0.12)

			Severe (>50): 32.3 (10.9)		
4	Kwatra, 2021, US	1,017 respondents with moderate-to-severe AD.	People with moderate-to-severe AD, recruited from the 2017 US NHWS. Mean age 37.4 years (SD 14.5 years).	HRQoL measured using the EQ-5D-5L. Valuation method unclear.	Adjusted utility means by comorbidity category Sleep difficulties: none, 0.67; mild, 0.63; moderate, 0.60; severe, 0.51 Anxiety: no, 0.76; yes, 0.68 Depression (PHQ-9): none-minimal, 0.75; mild, 0.68; moderate, 0.64; moderately5severe, 0.59; severe, 0.49 Adjusted means were calculated based on the results of generalised linear models that controlled for age, sex, race/ethnicity, education, income, employment status, body mass index, smoking status, alcohol use, CCI, and the presence of other atopic conditions.
5	Misery, 2018, France	Sample size according to severity (PO-SCORAD score): Mild (<25): 283 Moderate (25-50): 414 Severe (>50): 327	People with AD were members of the French Association of Eczema or outpatients recruited in 4 dermatology centres in France. Known as the ECLA study. Mean age 42.7 years (SD 15.2 years).	HRQoL measured using the EQ-5D (3L assumed based on reference to Essink-Bot 1993). Valuation method unclear.	Mean (SD) utility according to severity (PO-SCORAD score): Mild (<25): 0.79 (0.24) Moderate (25-50): 0.68 (0.28) Severe (>50): 0.60 (0.32)
6	Nyberg, 2018, Europe (France, Germany, the UK) and the USA (abstract)	Of the 1,098 respondents with moderate-to-severe AD, 548 were from Europe and 550 were from the US. Sample size according to severity (PO-SCORAD score),	People with moderate-to-severe AD, recruited from the NHWS. Mean (SD) age, years: Europe, 45.3 (13.5); US, 51.3 (15.3).	HRQoL measured using the EQ-5D-5L. Valuation method unclear.	Unadjusted mean (SD) utility according to severity (PO-SCORAD score), Europe; US: Moderate (25-50): 0.788 (0.204); 0.786 (0.128) Severe (>50): 0.606 (0.293); 0.684 (0.190) Severe 1 (51-60): 0.680 (0.244); 0.713 (0.151) Severe 2 (61-70): 0.612 (0.262); 0.697 (0.164) Severe 3 (71-80): 0.535 (0.305); 0.596 0.263) Severe 4 (81+): 0.204 (0.404); 0.385 (0.376) Adjusted mean utility according to severity (PO-

		Europe; US: Moderate (25-50): 413; 412 Severe (>50): 135; 138 Severe 1 (51-60): 62; 79 Severe 2 (61-70): 46; 37 Severe 3 (71-80): 18; 18 Severe 4 (81+): 9; 4			SCORAD score), Europe; US: Moderate (25-50): 0.77; 0.74 Severe (>50): NR Severe 1 (51-60): 0.69; 0.67 Severe 2 (61-70): 0.64; 0.66 Severe 3 (71-80): 0.42; 0.56 Severe 4 (81+): NR Adjusted for age, gender, country, smoking behaviour, alcohol use, BMI category, CCI, household income, and years since AD diagnosis.
7	Retzler, 2018, NR (abstract)	484 respondents from the general population	Seven vignettes described different skincare regimens for people with moderate-to-severe AD. These were developed with input from healthcare professionals. No further details reported.	HRQoL was valued using the TTO.	As skincare regimens increased in intensity (0.7968 for the most intense; 0.9999 for the least), utility values decreased. There were no significant differences between skincare regimens followed by patients with good disease control (0.9862 to 0.9999), however, when compared with those involving corticosteroid and emollient combinations (0.7968 to 0.8835), significant differences were observed ($p<0.001$). The largest disutilities (0.1521 to 0.1705) were between skincare regimens describing the use of corticosteroid plus emollient and those followed by patients with good disease control.
8	Retzler, 2019, UK	484 respondents from the general population	Seven vignettes described different skincare regimens for people with moderate-to-severe AD. These were developed with input from healthcare professionals.	HRQoL was valued using the TTO (with 10 years to live).	Skincare regimen: N; mean (SD) 1 Steroid twice daily and emollient four times daily: 473; 0.7968 (0.2159) 2 Steroid twice daily and emollient twice daily:

			44% of respondents reported having used TCS to treat skin conditions. 89.9% of respondents White or White British. Age of respondents, years, n(%): 18–24: 55 (11.4%) 25–34: 85 (17.6%) 35–44 : 80 (16.5%) 45–54 : 90 (18.6%) 55–64 : 70 (14.5%) 65 and over: 104 (21.5%)		466; 0.8471 (0.1744) 3 Steroid once daily and emollient twice daily: 446; 0.8835 (0.1469) 4 Light emollient twice daily: 404; 0.9862 (0.0340) 5 Light emollient once daily: 396; 0.9906 (0.0267) 6 Light emollient once every other day: 370; 0.9997 (0.0021) 7 Light emollient on occasion, as needed: 371; 0.9999 (0.0012)
9	Silverberg, 2019, USA	602 participants with AD and 2,291 participants without AD. Sample size according to self-reported AD severity: Mild 289 Moderate 172 Severe 34	Adults from the GfK knowledge panel were invited to participate. Participants with AD; without AD: Mean age, years (SD): 51.0 (15.7); 52.2 (16.4) Caucasian/White, n (%): 396 (65.8%); 1,684 (73.5%)	HRQoL measured using the SF-6D. Valued using the Brazier scoring method and US population-based weights (Brazier 2002).	Mean SF-6D scores (95% CI) according to self-reported global AD severity: Severe 0.59 (0.54-0.64) Moderate 0.64 (0.62-0.66) Mild 0.73 (0.72-0.75) Overall mean SF-6D score in adults with AD and without AD: 0.69 (0.68-0.70) and 0.79 (0.77-0.79), respectively.
10	Silverberg, 2019, USA (abstract)	602 participants	Adults with AD. No further details reported.	HRQoL measured using the SF-6D. Valuation method unclear.	Overall mean SF-6D score in adults with AD and without AD: 0.69 (0.68-0.70) and 0.79 (0.77-0.79), respectively. Moderate-to-severe AD was associated with a mean SF-6D score of 0.53 to 0.66.
11	Simpson, 2017, Multiple study locations	1,379 patients with moderate-to-severe AD. Number of patients according to treatment arm:	Patients enrolled in two phase 3 clinical trials which included adults with moderate-to-severe AD whose disease was inadequately controlled by topical treatment (SOLO 1 NCT02277743 and SOLO 2 NCT02277769, Simpson 2016). These trials compared placebo, subcutaneous dupilumab 300 mg qw or q2w.	HRQoL measured using the EQ-5D-3L. Valuation method unclear.	Mean utility according to treatment arm with censoring after rescue treatment and last-observation-carried-forward for imputation of missing data (full analysis set). All patients: baseline (SD); LS mean change at

		Placebo, n = 460 Dupilumab 300 mg qw, n = 462 Dupilumab 300 mg q2w, n = 457	Both trials are included in a pooled analysis. Mean age 38.3 years (SD 14.3 years).		week 16 (SE): Placebo: 0.611 (0.340); 0.031 (0.012) Dupilumab 300 mg qw: 0.607 (0.338); 0.207 (0.012) Dupilumab 300 mg q2w: 0.629 (0.319); 0.210 (0.012) Responders (EASI =>50): N; baseline (SD); LS mean change at week 16 (SE): Placebo: 107; 0.693 (0.34); 0.189 (0.016) Dupilumab 300 mg qw: 282; 0.636 (0.314); 0.255 (0.010) Dupilumab 300 mg q2w: 306; 0.627 (0.325); 0.253 (0.010) Responders (EASI =>75): N; baseline (SD); LS mean change at week 16 (SE): Placebo: 61; 0.712 (0.347); 0.251 (0.020) Dupilumab 300 mg qw: 232; 0.629 (0.314); 0.262 (0.010) Dupilumab 300 mg q2w: 218; 0.631 (0.327); 0.257 (0.011)
12	Simpson, 2016, Multiple study locations	380 patients with moderate-to-severe were randomized and 379 received 1 or more doses of study treatment. Number of patients according to treatment arm: Placebo qw, n = 61	Patients enrolled in a phase 2b, dose-ranging study of dupilumab (NCT01859988, Thaci 2015). This study included adults with moderate-to-severe AD that was inadequately controlled by topical treatment. Mean (SD) age, years: Placebo qw: 37.2 (12.1) Dupilumab 100 mg q4w: 36.6 (11.6) Dupilumab 300 mg q4w: 36.8 (10.8) Dupilumab 200 mg q2w: 35.8 (14.9)	HRQoL measured using the EQ-5D-3L. Valued using UK-based preferences (Dolan 1997).	Mean utility according to treatment arm (full analysis set, defined as all randomized patients who received 1 or more doses of study drug, with last observation carried forward for imputation of missing continuous variables). All patients: baseline (SD); LS mean change at week 16 (SE): Placebo qw: 0.654 (0.310); 0.028 (0.034) Dupilumab 100 mg q4w: 0.578 (0.336); 0.106

		Dupilumab 100 mg q4w, n = 65 Dupilumab 300 mg q4w, n = 65 Dupilumab 200 mg q2w, n = 61 Dupilumab 300 mg q2w, n = 64 Dupilumab 300 mg qw, n = 63	Dupilumab 300 mg q2w: 39.4 (12.1) Dupilumab 300 mg qw: 36.2 (10.7) Rescue treatment (medication and/ or phototherapy) was allowed at the investigator's discretion; patients who received such therapy were discontinued from study treatment, but were asked to continue with assessments.		(0.034) Dupilumab 300 mg q4w: 0.590 (0.327); 0.176 (0.031) Dupilumab 200 mg q2w: 0.608 (0.339); 0.166 (0.034) Dupilumab 300 mg q2w: 0.587 (0.351); 0.230 (0.032) Dupilumab 300 mg qw: 0.658 (0.288); 0.240 (0.031)
13	Simpson, 2016, Multiple study locations	380 patients with moderate-to-severe AD (number randomized at screening)	Patients enrolled in a phase 2b, dose-ranging study of dupilumab (NCT01859988, Thaci 2015). This study included adults with moderate-to-severe AD that was inadequately controlled by topical treatment. Mean age: 37.0 years (SD 12.2 years). White race: n = 257 (67.6%)	HRQoL measured using the EQ-5D-3L. Valued using UK-based preferences (Dolan 1997).	The overall mean utility was 0.659 (SD 0.305).
14	Song, 2019, Korea	155 participants from the general public	Recruited people aged 20-60 years from the general population in Korea. 19 participants had AD. Mean age was 39.7 years.	HRQoL measured using the TTO and EQ-5D-5L. EQ-5D-5L valued using the Korean value set (Kim 2016).	Two health states were described in detail: response and no response. These were developed from in-depth interviews with 20 dermatologists and 10 patients with AD. Mean (SD) utility values, all participants: response; no response TTO based on 10 years: 0.847 (0.120); 0.380 (0.218) TTO based on life expectancy: 0.865 (0.119); 0.476 (0.271) EQ-5D-5L: 0.814 (0.074); 0.279 (0.128) Mean utiltiy values, participants with AD:

					response; no response TTO based on 10 years: 0.898; 0.440 TTO based on life expectancy: 0.902; 0.552 EQ-5D-5L: 0.826; 0.276
15	Vietri, 2017, France, Germany, the UK (abstract)	Of the 548 respondents with moderate-to-severe AD, 118 were from the UK. Sample size according to severity (PO-SCORAD score): Moderate (25-50): 413 Severe (>50): 135	People with moderate-to-severe AD. Respondents had a mean age of 45 years.	HRQoL measured using the EQ-5D-5L. Valuation method unclear.	Mean utility according to severity (PO-SCORAD score): Moderate (25-50): 0.79 Severe (>50): 0.61
16	Zimmerman, 2018, USA	NR (population described in Sanofi-Regeneron data on file)	The target population for the economic model was adults in the US with moderate-to-severe AD inadequately controlled with topical therapy, or for whom topical therapies were medically inadvisable. Utility values were collected in three dupilumab clinical trials. Population described in Sanofi-Regeneron data on file. The modelled population had a mean age of 38 years.	HRQoL measured using the EQ-5D (levels unclear). Valuation method unclear.	Utilities were collected at baseline and 16 weeks for three clinical trials, and were consistent across the three trials. Mean utility, moderate patients; severe patients: Baseline / no response: 0.684; 0.535 EASI 50: 0.892; 0.882 EASI 75: 0.893; 0.890 EASI 90: 0.907; 0.911

Abbreviations: AD, atopic dermatitis; BMI, body mass index; BSC, best supportive care; CCI, Charlson Comorbidity Index; CI, confidence interval; CS, company submission; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; ERG, Evidence Review Group; EU, European Union; HRQoL, health-related quality of life; LS, least squares; mg, milligram; MMRM, mixed model repeated measurement; NHWS, National Health and Wellness Survey; PHQ, patient health questionnaire; PO-SCORAD, Patient-Oriented SCORing Atopic Dermatitis; qw, once weekly; q2w, every 2 weeks; q4w, every 4 weeks; SD, standard deviation; SE, standard error; TCS, topical corticosteroids; TE, technical engagement; TTO, time trade-off

4.2 HRQoL – HTA submissions

Table 37. HTA submissions

#	Author, year	Sample size	Patient population	Instrument (Valuation)	Utility results
1	SMC2011, 2018	HRQoL data was obtained from the 'all observed' dataset and regressions were conducted at the trial level using CAFÉ, CHRONOS and SOLO and not at the base case population level (CHRONOS- CAFÉ like or SOLO CAFÉ like subgroups). Trial sample sizes CHRONOS: Dupilumab + TCS, n = 106; Placebo + TCS, n = 315 SOLO 1: Dupilumab, n = 204; Placebo, n = 224 SOLO 2: Dupilumab, n = 233; Placebo, n = 236 CAFÉ: Dupilumab + TCS, n = 107; Placebo + TCS, n = 108	Adults with moderate-to-severe AD included in the CHRONOS, CAFÉ and SOLO studies: CHRONOS: patients had an inadequate response to medium or higher potency TCS CAFE: patients who are not adequately controlled with, or are intolerant to oral ciclosporin, or when this treatment is not medically advisable SOLO 1 and SOLO 2: patients whose disease is not adequately controlled with topical medications or for whom topical treatment was medically inadvisable.	HRQoL measured using the EQ-5D (levels unclear). Valuation method unclear.	Regression analyses were used to estimate utilities in the various states of the model. The baseline utility was 0.66 for patients in the CAFÉ and CHRONOS- CAFÉ like group, rising to 0.898 for a dupilumab responder or 0.797 for both a non-responder to dupilumab or a patient treated with BSC (regardless of whether a responder to BSC or not).
2	SMC2237, 2021	It is unclear which dataset was used to analyse HRQoL data and how the data from the trials was pooled.	Adults with moderate-to-severe AD included in the BREEZE-AD4 and BREEZE-AD7 studies: In BREEZE-AD7, patients had an inadequate response to topical therapies or failure to respond	HRQoL measured using the EQ-5D-5L and mapped to the EQ-5D-3L using a	Patient-level utilities were included in a mixed-model repeated measures analysis to estimate the change in utility score at week 16 for an EASI response and non-response. This resulted in mean health state

		Trial sample sizes BREEZE-AD4: Baricitinib 4 mg + TCS, n = 92; Placebo + TCS, n = 93 BREEZE-AD7: Baricitinib 4 mg + TCS, n = 111; Placebo + TCS, n = 109	to systemic immunosuppressant therapies. In BREEZE-AD4, patients had an inadequate response to topical therapies and a documented history of an inadequate response, intolerance, or contraindication to ciclosporin.	cross walk algorithm (van Hout 2021). Valued using the UK value set (Dolan 1997).	utility values of: Induction: 0.62 Maintenance: 0.84 Non-response: 0.76
3	NICE TA534, 2018	HRQoL data was obtained from the 'all observed' dataset and regressions were conducted at the trial level using CAFÉ, CHRONOS and SOLO and not at the base case population level (CHRONOS- CAFÉ like or SOLO CAFÉ like subgroups). Trial sample sizes CHRONOS: Dupilumab + TCS, n = 106; Placebo + TCS, n = 315 SOLO 1: Dupilumab, n = 204; Placebo, n = 224 SOLO 2: Dupilumab, n = 233; Placebo, n = 236 CAFÉ: Dupilumab + TCS, n = 107; Placebo + TCS, n = 108	Patients included in the LIBERTY trial programme: CHRONOS: adults patients with moderate-to-severe AD who had an inadequate response to medium or higher potency TCS CAFE: adult patients with moderate-to-severe AD who are not adequately controlled with, or are intolerant to oral ciclosporin, or when this treatment is not medically advisable SOLO 1 and SOLO 2: adult patients with moderate-to-severe AD whose disease is not adequately controlled with topical medications or for whom topical treatment was medically inadvisable Mean (SD) years of age, % Caucasian: CHRONOS: Dupilumab + TCS, 40 (14), 70%; Placebo + TCS, 37 (13), 66% SOLO 1: Dupilumab, 40 (15), 69%; Placebo, 40 (14), 65% SOLO 2: Dupilumab, 37 (14), 71%; Placebo, 37 (14), 66% CAFÉ: Dupilumab + TCS, 38 (13), 97%; Placebo + TCS, 39 (13), 96%	HRQoL measured using the EQ-5D-3L. Valued using UK-based preferences (Dolan 1997).	Mixed regression models were fitted for each trial using a forward selection process, controlling for baseline age, gender, baseline EQ-5D utility score, total EASI score, weekly average of peak daily pruritus, EASI-pruritus interaction and treatment. Results included in the CS, base case (included in the model according to the ERG): All observed dataset, CHRONOS-CAFÉ-like (combination therapy with TCS) Baseline: 0.66 Week 16, dupilumab: 0.898 (0.891) Week 16, BSC: 0.811 (0.797) EASI-50 + DLQI=>4 responder, dupilumab: 0.904 (0.898) All observed dataset, SOLO-CAFÉ-like (monotherapy) Baseline: 0.55 Week 16, dupilumab: 0.830 (0.817) Week 16, BSC: 0.718 (0.6986) EASI-50 + DLQI=>4 responder, dupilumab: 0.855 (0.845) Beyond week 16 in the BSC arm of the model, and

					beyond week 16 for non-responders to dupilumab, all patients share the same overall utility value; i.e. that estimated for all patients in the BSC arm at week 16. In the original economic model, dupilumab non-responders accrued the generalised BSC utility value. The committee suggested that it was more appropriate to use the utility value specific to people whose condition had not responded to dupilumab at 16 weeks than the utility value from everyone having BSC. In response, the company revised their base case: Week 16 - dupilumab non-responders accrue the average of the dupilumab and the BSC non-responder utility value (0.8205) From Week 52 onwards - dupilumab non-responders accrue the BSC non-responder utility value (0.7732)
4	NICE TA681, 2021	HRQoL data was obtained from the pooled population of JAIN + JAIN-like JAIY patients. All observed values across patients receiving all baricitinib dose groups and placebo were included in the analysis. Trial sample sizes BREEZE-AD4 (JAIN) Placebo, n = 93 Baricitinib 1 mg + TCS, n = 93 Baricitinib 2 mg + TCS, n = 185 Baricitinib 4 mg + TCS, n = 92	Patients included in the BREEZE-AD4 (JAIN) and BREEZE-AD7 (JAIY) trials: BREEZE-AD4 (JAIN) is an ongoing multicentre, double-blind, randomised, placebo-controlled Phase III study in adult patients with moderate-to-severe AD. Patients were required to have a documented history of inadequate response to topical treatment and a documented history of failed ciclosporin treatment, defined as an inadequate response following its administration, or a documented contraindication, intolerance or unacceptable toxicity to its use. BREEZE-AD7 (JAIY) was a multicentre,	HRQoL measured using the EQ-5D-5L and mapped to the EQ-5D-3L using a cross walk algorithm (van Hout 2021). Valued using the UK value set (Dolan 1997).	A MMRM approach was used to generate health state utility values. Model parameters included: response variable, gender, visit, age, EQ-5D baseline score, visit-EQ-5D baseline score interaction. Results included in the CS, base case: Induction/baseline: 0.5979 Maintenance (EASI-50 + DLQI=>4 responder): 0.7800 Non-response: 0.5979 The ERG conducted two scenario analysis

		Number of patients in BREEZE-AD7 (JAIY) redacted.	randomised, double-blind, placebo-controlled Phase III trial in adult patients with moderate-to-severe AD. Patients were required to have a documented history of an inadequate response to, or intolerance to, topical medication. BREEZE-AD4 (JAIN): Placebo; 1 mg; 2 mg; 4 mg Mean age, years (SD): 39 (14;) 39 (14); 37 (14); 39 (13) Caucasian: 80%; 75%; 78%; 77% Baseline characteristics in BREEZE-AD7 (JAIY) redacted.		a) HRQoL data from the JAIN and JAIN-like JAIY patients and modelled considering a more appropriate comparative analysis. This scenario intends to illustrate the issues with the values provided and how they serve to undermine the model structure used by the company Induction/baseline: 0.5979 Maintenance/response: 0.7800 Non-response: 0.8021 b) values based on those reported in TA534. In this scenario, treatment specific utilities are applied such that patients on maintenance baricitinib and dupilumab are assigned the reported utility of responders to dupilumab. Patients on BSC, including patients classified as non-responders are assigned a single utility value based on the average of all placebo patients at week 16 Induction/baseline: 0.66 Maintenance/response, baricitinib/dupilumab: 0.898 Maintenance/response, BSC: 0.797 Non-response: 0.797 Results included in the company's TE response: Induction/baseline: 0.6182 Change from baseline at Week 16, mean LS: response (EASI-75) 0.2310 Change from baseline at Week 16, mean LS: non-response 0.1445 The committee concluded that, given the flaws with the company's utility values, the utility values from TA534 were preferable.

Abbreviations: AD, atopic dermatitis; BSC, best supportive care; CS, company submission; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; ERG, Evidence Review Group; HRQoL, health-related quality of life; LS, least squares; mg, milligram; MMRM, mixed model repeated measurement; SD, standard deviation; TCS, topical corticosteroids; TE, technical engagement

5 Assessment of clinical effectiveness

5.1 Network meta-analysis model fit statistics

5.1.1 First-line systemic treatments – adult population

Table 38. Summary of NMA model characteristics - EASI 75

Characteristic	Primary analysis		Sensitivity analysis					
	Ariens/CHRONOS separate studies		Ariens/CHRONOS analysed as one study		All lines of therapy in AD UP		Censoring of patients receiving rescue therapy	
	RE	FE	RE	FE	RE	FE	RE	FE
Deviance information criterion	101.7	102.3	51.75	51.73	59.25	59.26	58.68	58.63
Total residual deviance	14.4	16.5	7.0	7.0	8.0	8.0	8.1	8.0
Number of data points	14	14	7	7	8	8	8	8

Abbreviations: FE, fixed effect model; RE, random effects model

5.1.2 Monotherapies as second-line treatment - adult population

Table 39. Summary of NMA model characteristics - EASI 50 + ΔDLQI ≥4

Characteristic	Primary analysis		Sensitivity analysis				
			Censoring of patients receiving rescue therapy		Abrocitinib generalisable population		Placebo risk adjustment
	RE	FE	RE	FE	RE	FE	RE
Deviance information criterion	121.1	120.7	111.4	111.1	130.1	130.4	115.8
Total residual deviance	25.0	26.4	23.6	25.0	27.7	30.4	20.2
Number of data points	22	22	21	21	22	22	22

Abbreviations: FE, fixed effect model; RE, random effects model.

Table 40. Summary of NMA model characteristics - EASI 75

Characteristic	Primary analysis		Sensitivity analysis				
			Censoring of patients receiving rescue therapy		Abrocitinib generalisable population		Placebo risk adjustment
	RE	FE	RE	FE	RE	FE	RE
Deviance information criterion	127.6	133.2	119.2	123	137.8	142.2	123.3
Total residual deviance	24.6	33.6	23.5	30.4	24.1	32.5	22.6
Number of data points	24	24	23	23	24	24	24

Abbreviations: FE, fixed effect model; RE, random effects model.

5.1.3 Second-line systemic treatments in combination with TCS – adult population

Table 41. Summary of NMA model characteristics - EASI 50 + ΔDLQI ≥4

Characteristic	Primary analysis		Sensitivity analysis			
			Censoring of patients receiving rescue therapy		Abrocitinib generalisable population	
	RE	FE	RE	FE	RE	FE
Deviance information criterion	96.14	95.3	79.78	78.69	88.83	88.07
Total residual deviance	15.4	16.2	12.4	12.5	13.6	14.2
Number of data points	16	16	13	13	14	14

Abbreviations: FE, fixed effect model; RE, random effects model.

Table 42. Summary of NMA model characteristics - EASI 75

Characteristic	Primary analysis		Sensitivity analysis			
			Censoring of patients receiving rescue therapy		Abrocitinib generalisable population	
	RE	FE	RE	FE	RE	FE
Deviance information criterion	116.5	115.3	108.8	107.4	119.4	118.7
Total residual deviance	17.8	17.8	16.6	16.3	17.9	18.6
Number of data points	18	18	17	17	18	18

Abbreviations: FE, fixed effect model; RE, random effects model.

5.1.4 Adolescents

Table 43. Summary of NMA model characteristics - EASI 75

Characteristic	Primary analysis		Sensitivity analysis		
			Censoring of patients receiving rescue therapy		Placebo risk adjustment
	RE	FE	RE	FE	RE
Deviance information criterion	81.94	82.92	79.33	78.92	57.03
Total residual deviance	17.2	20.0	15.6	16.3	13.9
Number of data points	15	15	15	15	15

Abbreviations: FE, fixed effect model; RE, random effects model.

5.2 NMA results EASI 75 second-line treatments – adult population

5.2.1 Monotherapies as second-line treatment

The trials contributing to the NMA of monotherapies on EASI 75 in the second line adult population are presented in Figure 5.

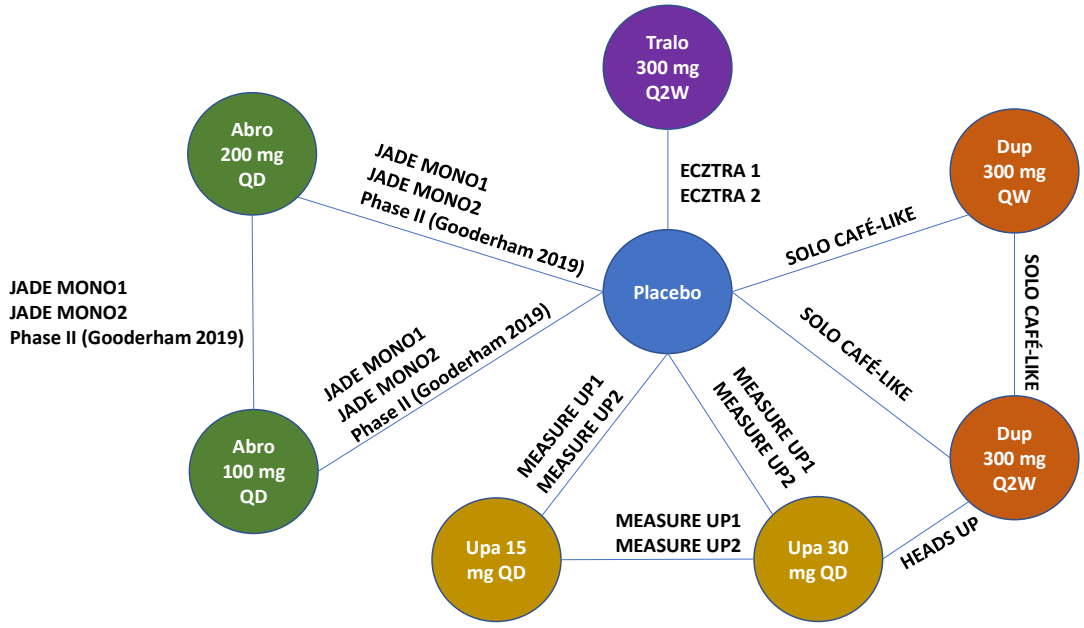

Figure 5. Network plot second line adult population, monotherapy, EASI 75

Abbreviations: Abro, abrocitinib; Dup, dupilumab; QD, once daily; Q2W, every 2 weeks; QW, every week; Tralo, tralokinumab; Upa, upadacitinib.

For the primary analysis and all sensitivity analyses of EASI 75, the goodness of model fit of the FE and RE models were similar, but the residual deviance for the RE models were considerably closer to

the number of unconstrained data points than the FE models in all analyses, which reinforces the EAG's preference for the RE model.

Treatment with any of the interventions assessed (abrocitinib, dupilumab, tralokinumab or upadacitinib) led to a statistically significant OR in favour of active treatment compared with placebo. Results from the NMA were broadly in agreement with findings from standard pair-wise analyses, in which all interventions analysed were found to be more effective than placebo. Although, for abrocitinib 200 mg and 100 mg, the NMA resulted in substantially higher ORs compared with the underlying trial data.

For the comparison with dupilumab, the results of the primary analysis for EASI 75 were similar to those for EASI 50 + ΔDLQI ≥4 for tralokinumab, which resulted in a lower improvement in response than dupilumab, and both dose of upadacitinib, which were more effective than dupilumab, though, the results were only statistically significant for upadacitinib 30 mg. The benefit of abrocitinib treatment (either dose) over dupilumab treatment was larger when response was assessed as EASI 75 than as EASI 50 + ΔDLQI ≥4, but the results did not reach statistical significance.

There was one loop in the NMA of EASI 75 consisting of upadacitinib 30 mg, dupilumab and placebo, for which the direct and indirect estimates of the ORs generated for the interventions were compared to assess possible inconsistency. The results of the inconsistency assessments demonstrated no evidence of statistically significant inconsistency (inconsistency estimate -0.88, 95% CI: -2.28 to 0.53).

Censoring patients receiving rescue therapy in the dupilumab, tralokinumab and upadacitinib trials led to a smaller benefit of each of the treatments compared with dupilumab, with the exception of tralokinumab; the benefit of dupilumab over tralokinumab therapy increased compared with the primary analysis. None of the relative differences between the interventions and dupilumab were statistically significant.

The sensitivity analysis based on the generalisable population for abrocitinib resulted in a markedly smaller benefit of treatment with abrocitinib 200 mg compared with dupilumab, than seen in the restricted population used in the primary analysis. The OR of the comparison of abrocitinib 100 mg versus dupilumab changed direction, favouring dupilumab in the generalisable population. The 95% CrIs for the comparisons of both abrocitinib doses were substantially narrower for the generalisable population likely due to the larger sample size.

There was variation in placebo response across the included trials, from no responders to just under a quarter of patients on placebo being responders at 16 weeks. The sensitivity analysis adjusting for differences in placebo response gave a marginally lower DIC than the primary, unadjusted analysis, however, the total residual deviance for this analysis, was lower than the number of unconstrained data points, indicating that the model may be "overfitting" the data. As such, the observed data were preferred to inform the primary cost effectiveness analysis.

5.2.2 Second-line systemic treatments in combination with TCS

The trials contributing to the NMA of combination therapies on EASI 75 in the second line adult population are presented in Figure 6.

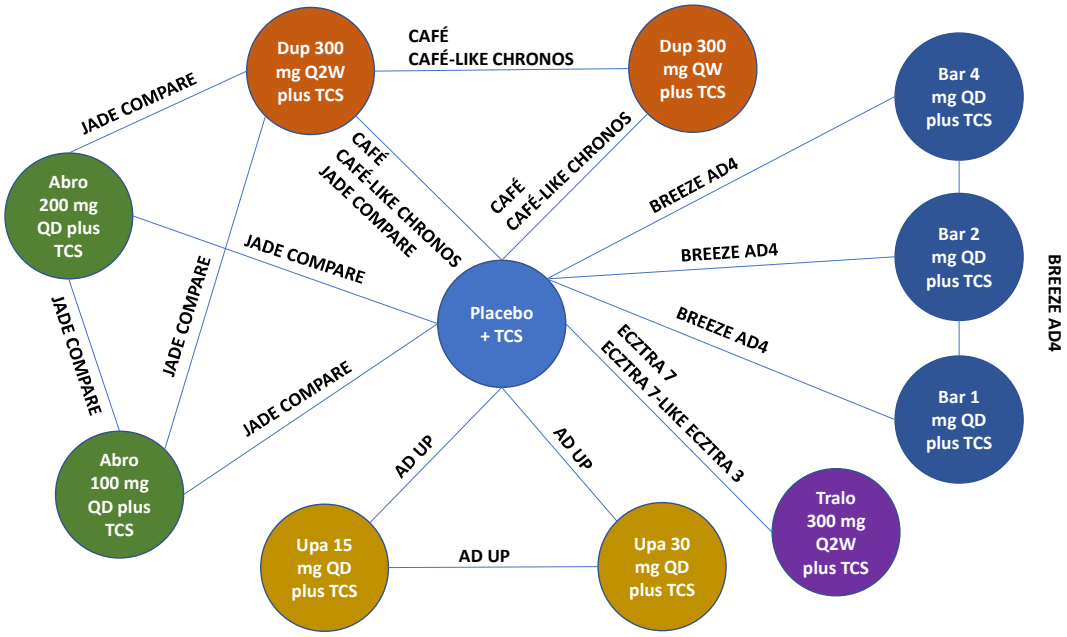

Figure 6. Network plot second line adult population, combination therapy, EASI 75

Abbreviations: Abro, abrocitinib; Bar, baricitinib; Dup, dupilumab; QD, once daily; Q2W, every 2 weeks; QW, every week; TCS, topical corticosteroid; Tralo, tralokinumab; Upa, upadacitinib.

For the NMAs of EASI 75, the RE and FE models for the primary and all sensitivity analyses were similar in terms of goodness of model fit (similar DIC) and residual deviance.

The primary analysis showed that treatment with any of the interventions assessed, which for this outcome also included baricitinib 1mg, 2mg or 4mg, led to an improvement in EASI 75 compared with placebo. The results versus placebo were statistically significant for abrocitinib 200 mg, dupilumab, and either dose of upadacitinib (15 mg or 30 mg), but not for abrocitinib 100 mg, tralokinumab, or baricitinib 1, 2, or 4 mg. Results from the NMA were broadly in agreement with

findings from standard pair-wise analyses. Although, for abrocitinib 200 mg and 100 mg the NMA resulted in a substantially lower ORs, that is, the benefit over placebo was less pronounced compared with the underlying trial data. Also, in contrast to the NMA results, in the pair-wise analyses the comparisons of abrocitinib 100 mg and baricitinib 4mg with placebo were both statistically significant.

For the comparison with dupilumab, there were no comparisons that were statistically significant. Similar to the assessment of the EASI 50 + ΔDLQI ≥4, the largest relative treatment effects favouring the interventions were for upadacitinib 30 mg. However, the relative benefit of upadacitinib 30 mg was substantially smaller when response was assessed as EASI 75 compared with the composite outcome. The NMA results also indicate that there may be a benefit of treatment with abrocitinib 200 mg over dupilumab, in terms of EASI 75. The results for abrocitinib 100 mg, upadacitinib 15 mg and tralokinumab were similar for EASI 75 and EASI 50 + ΔDLQI ≥4; a large relative treatment effect favouring dupilumab was observed for tralokinumab and the OR of upadacitinib 15 mg and abrocitinib 100 mg were closer to 1, favouring dupilumab for both.

Similarly, none of the comparisons versus baricitinib 2mg or 4 mg were statistically significant. Tralokinumab therapy led to a lower EASI 75 response than baricitinib 2 mg and 4 mg, although the difference was smaller than compared with dupilumab. A dose dependent benefit was observed for both upadacitinib and abrocitinib compared with baricitinib 4 mg and 2mg.

Censoring patients receiving rescue therapy in the dupilumab, tralokinumab and upadacitinib trials only had a very limited impact on the comparisons with dupilumab and the comparisons with baricitinib. In this sensitivity analysis, the benefit of dupilumab over tralokinumab was statistically significant. Similarly, there was little impact of the sensitivity analysis based on the generalisable population for abrocitinib; the benefit of dupilumab over tralokinumab reached statistically significance, and the credible intervals for the comparisons of either dose of abrocitinib versus dupilumab or baricitinib narrowed.

Placebo response varied between 8% and 49% in the studies contributing to EASI 75 analysis. However, the models for the baseline risk-adjusted sensitivity analysis did not converge despite attempts to increase convergence by thinning the sampling and increasing the number of model iterations.

5.3 Additional outcomes

5.3.1 First-line systemic treatments – adult population

5.3.1.1 Quality of life (EQ-5D)

In the upadacitinib trials Measure UP 1, Measure UP 2, and AD UP, EQ-5D-5L was captured throughout to measure the impact of upadacitinib therapy on general QoL. For each of the sub-populations, including the first-line population in the upadacitinib trials, EQ-5D data were provided as the mean at baseline and week 16. The results show a larger improvement in EQ-5D from baseline to week 16 in patients treated with upadacitinib than for patients receiving placebo, irrespective of upadacitinib dose or if used as a monotherapy or in combination with TCS.

5.3.1.2 Use of rescue medication

Use of rescue therapy was not captured for the CsA data in Ariens *et al*. and for CHRONOS rescue therapy use was only reported at 52 weeks. However, data on the use of rescue therapy were provided by the company for upadacitinib used in the first line setting either as a monotherapy (Measure UP 1, Measure UP 2, and Heads UP) and in combination with TCS (AD UP).

The proportion of people treated with upadacitinib as a first line monotherapy, who required rescue therapy during the first 16 weeks of treatment, seems to be dose dependent with a lower proportion on upadacitinib 30 mg compared with upadacitinib 15 mg. A similar dose-related effect was not seen when upadacitinib was given in combination with TCS in AD UP. The rates were relatively similar for upadacitinib used as a monotherapy (Measure UP 1 and Measure UP 2) and combination therapy (AD UP), whereas patients given placebo as a monotherapy received substantially more rescue therapy than people given placebo with concomitant TCS. That is, the difference in use of rescue medication between upadacitinib and placebo was substantially higher in the monotherapy trials (Measure UP 1 and Measure UP 2) than in the combination therapy trial (AD UP). Interestingly, the rate of patients needing rescue therapy in HEADS UP, the head-to-head trial of upadacitinib and dupilumab monotherapy, were similar for the two treatments and higher than the proportion in the other monotherapy trials.

The allowed rescue therapy was the same for the monotherapy and combination therapy upadacitinib trials; the first step was to limit rescue therapy to topical treatments and escalate to systemic treatments if participants did not respond adequately after at least 7 days of topical treatment. In AD UP, patients requiring rescue therapy mainly received high potency TCS. In

Measure UP 1 and 2, where a larger proportion required rescue therapy, especially in the placebo arms, the most frequently used types of rescue therapy included TCS of varying potency (low, medium or high) and non-biologic systemic treatments. Similarly, patients who needed rescue therapy in Heads UP mainly received TCS of varying potency.

5.3.1.3 Number of days free from TCS during treatment

Data on the number of days free from TCS during treatment were reported for the subgroup of the adult population of AD UP who received upadacitinib as a first-line systemic therapy in combination with TCS.

5.3.2 Monotherapies as second-line treatment – adult population

5.3.2.1 Quality of life (EQ-5D)

EQ-5D data for people receiving monotherapy treatment for AD in the second line setting were available or provided by the companies for abrocitinib, dupilumab, tralokinumab and upadacitinib. Data were reported as change from baseline, with the exception of upadacitinib, where data were provided at baseline and at week 16. In the upadacitinib and abrocitinib trials, general QoL was captured using EQ-5D-5L, whereas EQ-5D-3L was used in the dupilumab trials.

The results for dupilumab, tralokinumab and upadacitinib show a larger improvement in EQ-5D from baseline to week 16 in patients treated with active monotherapy than for patients receiving placebo. For upadacitinib this was irrespective of dose. The results for abrocitinib, which are based on the restricted population and assessed after 12 weeks of treatment, are less clear; treatment with abrocitinib 200 mg, but not abrocitinib 100 mg, seems to result in an improvement in EQ-5D compared with placebo. However, the relevant sample sizes are very small.

5.3.2.2 Use of rescue medication

Data on the use of rescue therapy for monotherapies used in the second line setting were provided by the company for upadacitinib (Measure UP 1, Measure UP 2, and Heads UP) and for tralokinumab (ECZTRA 1 and ECZTRA 2). Data on the use of rescue medication needed with dupilumab monotherapy were available from SOLO 1 and SOLO2 but for the full trial populations rather than the subgroup of patients treated in the second line setting. Limited data were also available for baricitinib on the use of rescue therapy used in BREEZE AD1 and BREEZE AD2. Table 44 presents data on the use of rescue therapy for dupilumab and baricitinib only.

The use of rescue medication was markedly reduced in patients receiving active treatment (baricitinib, dupilumab, tralokinumab or upadacitinib) compared with placebo. The proportion of people treated with upadacitinib in combination with TCS as a second line therapy, who required rescue therapy during the first 16 weeks of treatment, seems to be dose dependent with a lower proportion on upadacitinib 30 mg compared with upadacitinib 15 mg.

TCSs were the most common form of rescue medication in the upadacitinib and tralokinumab trials. In the upadacitinib trials this was followed by non-biologic systemic therapy, and in the tralokinumab trials by other topical therapies for people treated with tralokinumab and either systemic corticosteroids or immunosuppressants for people treated with placebo. The most common form of rescue therapy in the dupilumab trials was systemic corticosteroids.

Table 44. Use of rescue medication during the double-blind period for adults treated with monotherapy in the second line setting

Proportion of people requiring use of rescue therapy during treatment n (%)			
Dupilumab trials	Dupilumab 300 mg Q2W	Dupilumab 300 mg QW	Placebo
SOLO 1	N=224	N=223	N=224
	47 (21.0%)	52 (23.3%)	115 (51.3%)
SOLO 2	N=233	N=239	N=236
	35 (15.0%)	49 (20.5%)	123 (52.1%)
Baricitinib trials	Baricitinib 4 mg	Placebo	
BREEZE-AD1	NR	NR	NA
	51 (40.8)	166 (66.7)	NA
BREEZE-AD2	NR	NR	NA
	72 (58.5)	187 (76.6)	NA

Abbreviations: NA, not applicable; NR, not reported; Q2W, every 2 weeks; QD, once daily; Upa, upadacitinib.

5.3.3 Second-line systemic treatments in combination with TCS – adult population

5.3.3.1 Quality of life (EQ-5D)

EQ-5D data for people receiving combination therapy for AD in the second line setting were available or provided by the companies for abrocitinib, dupilumab, tralokinumab and upadacitinib. Data were reported as change from baseline, with the exception of upadacitinib, where data were provided at baseline and at week 16. In the upadacitinib and abrocitinib trials, general QoL was captured using EQ-5D-5L, whereas EQ-5D-3L was used in the dupilumab trials.

The results show a larger improvement in EQ-5D from baseline to week 16 (week 12 for abrocitinib) in patients treated with any of the active therapies in combination with TCS than for patients receiving placebo and TCS. For upadacitinib and abrocitinib this was irrespective of dose. The results for abrocitinib, are based on the restricted population with low patient numbers in each treatment arm.

5.3.3.2 Use of rescue medication

Data on the use of rescue therapy for each of the treatments used in combination with TCS in the second line setting were provided by the company for upadacitinib (AD UP) and for tralokinumab (ECZTRA 3 and ECZTRA 7). Data on the use of rescue medication needed with dupilumab combination therapy were available from CHRONOS and CAFE but for the full trial population for CHRONOS rather than the subgroup of patients treated in the second line setting. Table 45 presents data on the use of rescue therapy for dupilumab only.

The use of rescue medication was markedly reduced in patients receiving active treatment (dupilumab, tralokinumab or upadacitinib) compared with placebo. The only exception was ECZTRA 1, in which a similar proportion of patients received rescue therapy in the tralokinumab and placebo arms of the trial. The proportion of people treated with upadacitinib as a second line monotherapy, who required rescue therapy during the first 16 weeks of treatment, seems to be dose dependent with a lower proportion on upadacitinib 30 mg compared with upadacitinib 15 mg.

TCS was the most common form of rescue medication in the dupilumab, tralokinumab and upadacitinib trials. In the dupilumab trial CHRONOS this was followed by systemic corticosteroids. In all other combination therapy trials the rates of other types of rescue therapy were low.

Table 45. Use of rescue medication during the double-blind period for adults treated with combination therapy in the second line setting

Proportion of people requiring use of rescue therapy during treatment n (%)			
Dupilumab trials	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW + TCS	Placebo QW + TCS
CHRONOS	N=106	N=319	N=315
	17 (16.0%)	64 (20.1%)	167 (53.0%)
Cafe	(N=107)	(N=110)	(N=108)
	4 (3.7%)	5 (4.5%)	19 (17.6%)

Abbreviations: NA, not applicable; Q2W, every 2 weeks; QD, once daily; TCS topical corticosteroid; Upa, upadacitinib.

5.3.3.3 Number of days free from TCS during treatment

In the restricted subgroup of JADE COMPARE, the number of days free from TCS during treatment varied. Data on the number of days free from TCS during treatment were not reported for dupilumab and baricitinib in TA534 and TA681, respectively.

5.3.4 Adolescents

5.3.4.1 Quality of life (EQ-5D)

EQ-5D-5L data for adolescents receiving monotherapy or combination therapy for AD were provided by the companies for abrocitinib and upadacitinib. Data were reported as change from baseline to week 12 for abrocitinib and at baseline and week 16 separately for upadacitinib.

The results show a larger improvement in EQ-5D from baseline to week 12/16 in patients treated with upadacitinib or abrocitinib than for patients receiving placebo, irrespective of dose or if used as a monotherapy or in combination with TCS. The results for abrocitinib are based on the full adolescent trial populations. Therefore, the number of patients in the analyses was not as low as for some of the other populations.

5.3.4.2 Use of rescue medication

Rescue therapy was not permitted in the abrocitinib trials, including JADE MONO 1, JADE MONO 2, and JADE TEEN.

The proportion of people treated with upadacitinib requiring use of rescue therapy during the first 16 weeks of treatment were dose dependent with a lower proportion on upadacitinib 30 mg compared with upadacitinib 15 mg. The rates were relatively similar for upadacitinib used as a monotherapy (Measure UP 1 and Measure UP 2) and combination therapy (AD UP), whereas patients given placebo as a monotherapy received substantially more rescue therapy than people given placebo with concomitant TCS. That is, the difference in use of rescue medication between upadacitinib and placebo was substantially higher in the monotherapy trials (Measure UP 1 and Measure UP 2) than in the combination therapy trial (AD UP).

The allowed rescue therapy was the same for the monotherapy and combination therapy upadacitinib trials; the first step was to limit rescue therapy to topical treatments and escalate to systemic treatments if participants did not respond adequately after at least 7 days of topical

treatment. In AD UP, patients requiring rescue therapy mainly received high potency TCS. In Measure UP 1 and 2, where a larger proportion required rescue therapy, especially in the placebo arms, the most frequently used types of rescue therapy included TCS of varying potency (low, medium or high) and non-biologic systemic treatments.

Dupilumab data in the adolescent population were only available from AD ADOL, where dupilumab was used as a monotherapy. Similar to the data for upadacitinib, AD ADOL showed that a substantially smaller proportion of patients treated with dupilumab needed to use rescue medication compared with placebo (Table 46).

Table 46. Use of rescue medication during the double-blind period for adults treated with combination therapy in the second line setting

Proportion of people requiring use of rescue therapy during treatment n (%)			
Dupilumab trials	Dupilumab 200/300 Q2W	Dupilumab 300 Q4W	Placebo
AD ADOL	82	84	85
	17 (20.7)	27 (32.1%)	50 (58.8)

Abbreviations: Q2W, every 2 weeks; Q4W, once every four weeks; QD, once daily; Upa, upadacitinib.

5.3.4.3 Number of days free from TCS during treatment

Data on the number of days free from TCS during treatment were reported for JADE TEEN and for the adolescent population of AD UP in which abrocitinib and upadacitinib, respectively, were used in combination with TCS.

5.4 Subgroup by skin colour

In the full-text publications identified by the EAG, clinical effectiveness of interventions that are the focus of the MTA was not reported by racial subgroup. One publication was identified,[126] which was cited as a related publication that reported clinical effectiveness of dupilumab by racial subgroup, as self-reported by the patient, based on evidence derived from three RCTs (SOLO-1, SOLO-2, and CHRONOS). The racial subgroups considered, from a total number of 2,058 people enrolled across the studies, were White (1,429 [69.4%]), Asian (501 [24.3%]) and Black/African American (128 [6.2%]). The authors reported that baseline demographics and disease characteristics were generally well balanced across treatment groups and among racial subgroups. The authors focused on mean change from baseline for the outcomes assessed, commenting that continuous outcomes are the most sensitive for subgroup analyses. Across the cohorts, dupilumab 300 mg Q2W, with or without TCS, statistically significantly improved mean change (least squares) in EASI score from baseline:[126]

- White: -25.35 (standard error [SE] 0.69) with dupilumab versus -14.91 (SE 0.70) with placebo, p <0.0001;
- Asian: -24.23 (standard error [SE] 1.62) with dupilumab versus -10.97 (SE 1.66) with placebo, p <0.0001;
- Black/African/American: -20.02 (standard error [SE] 2.72) with dupilumab versus -11.88 (SE 1.95) with placebo, p=0.0161.

Clinical improvements were noted for other measures of the signs and symptoms of AD for the White and Asian cohorts, including IGA, POEM, Peak Pruritus NRS, and DLQI, with differences between dupilumab 300 mg Q2W and placebo reaching statistical significance for all outcomes. Level of improvement was reported to be comparable to that achieved for the full trial populations of SOLO-1, SOLO-2 and CHRONOS. For the Black/African American racial subgroup, dupilumab 300 mg Q2W was associated with a statistically significant improvement over placebo for only weekly Peak Pruritus NRS, DLQI, and POEM, in addition to EASI 75. Effectiveness of dupilumab 300 mg QW was also evaluated. Dupilumab 300 mg QW was associated with statistically significant improvements over placebo in most outcomes evaluated for the three cohorts. The authors commented that results for the Black/African American cohort be interpretated with caution due to the small sample size informing the analysis. Overall, the authors considered dupilumab to be clinically effective in treating AD, irrespective of racial subgroup.

6 Summary of TA534, TA681 and company submissions

Table 47. Summary of TA534, TA681 and the company submission and EAG approach

	Committee decisions (TA534 &TA681)	Abrocitinib (Pfizer)	Tralokinumab (Leo Pharma)	Upadacitinib (AbbVie)	EAG approach
Population	TA534 - dupilumab in combination with TCS is recommended for treating moderate-to-severe AD in adults if the disease has not responded to at least 1 other systemic therapy, such as CsA, methotrexate, azathioprine and mycophenolate, or these are contraindicated or not tolerated. The data informing the assessment were based on the subgroup of patients who had an inadequate response to CsA, or where CsA was not tolerated or was contraindicated. Patients who had failed on other systemic therapies such as methotrexate, azathioprine and mycophenolate, were excluded. TA681 - Baricitinib is recommended for treating	Patients with moderate-to-severe AD who have not responded to, or have lost response to, at least one systemic immunosuppressant therapy, or in whom these are contraindicated or not tolerated. The company submission includes both adults and adolescents (aged 12 and older). However, the clinical data informing the company's base case is for patients who were previously treated with at least one systemic treatment for AD (referred to as the "generalisable population"). The company's sensitivity analyses were conducted using the "restricted" population for abrocitinib based on the subgroup of	Adult patients with moderate-to-severe AD that has not responded to at least one other systemic therapy, or in cases where systemic therapies are contraindicated or not tolerated. The clinical data informing the company's base case are for patients who had inadequate control with, or intolerance or contraindications to CsA.	The population considered by the company is adults and adolescents (12 years and older) with moderate-to-severe AD who are candidates for systemic therapy. The company split the population by line of therapy, as follows: - In people who are candidates for conventional systemic treatment (referred to as 'systemic eligible'). - In people in whom the disease has not responded to at least one other conventional systemic therapy (CsA, methotrexate, azathioprine or mycophenolate mofetil) or conventional systemic therapy is not suitable (referred to as 'systemic	The populations considered of relevance to the MTA are adolescents aged 12 to 18 years and adults aged 18 years and older. The definition of the populations in the MTA are as follows: - First-line systemic therapy denotes those who are eligible for systemic treatment on inadequate response to topical treatments, and; - Second-line systemic therapy captures those who achieve inadequate response to, cannot tolerate, or are contraindicated to their first systemic therapy (often CsA azathioprine or methotrexate). Abrocitinib, tralokinumab

	moderate-to-severe AD in adults if the disease has not responded to at least 1 other systemic immunosuppressant, such as CsA, methotrexate, azathioprine and mycophenolate mofetil, or these are not suitable. The data informing the NMA were based on the subgroup of patients who had an inadequate response to CsA, or where CsA was not tolerated or was contraindicated. Patients who had failed on other systemic therapies such as methotrexate, azathioprine and mycophenolate, were excluded.	patients who have failed or were intolerant to CsA. However, contraindication to CsA was not captured in trials evaluating abrocitinib and, therefore, the restricted population is limited to those who did not achieve an adequate response to CsA.		exposed'). The clinical data informing the adult systemic eligible population includes patients who have been treated with conventional systemic therapies and thus overlaps with the adult exposed population. With regards to the adolescent systemic-eligible population, clinical data include patients who have had systemic therapy and may not be generalisable to the adolescent exposed population that received dupilumab in clinical practice. The adult systemic-exposed is limited to those who had received CsA or were intolerant of or experienced a medical complication of CsA as contraindication to CsA was not captured in trials evaluating upadacitinib.	and upadacitinib will be assessed in the population position proposed by the company of each drug. Dupilumab and baricitinib will be included as comparators as per the population position in the NICE recommendations in TA534 and TA681. The clinical data informing the different populations includes: • adults with moderate-to-severe AD and inadequate response to topical treatments receiving first-line systemic treatment, • adults with moderate-to-severe AD receiving second-line systemic treatment after inadequate response to CsA, or where CsA was not tolerated or was contraindicated; • adolescents, irrespective of prior therapy.
Interventions	Dupilumab 600mg loading dose followed by 300mg Q2W.	Abrocitinib 200mg once daily (tablet). 100mg dose available for patients aged	Tralokinumab 600mg loading dose followed by 300mg Q2W. Option for	Upadacitinib 15mg or 30 mg once daily (tablet). 2 doses (15/30mg) either	Abrocitinib 200mg or 100mg once daily (tablet).

	Baricitinib 4mg once daily. Dupilumab and baricitinib, both as monotherapy and in combination with TCS. However, combination therapy was considered more clinically relevant for both TA534 and TA681.	>65 years. Separate analyses were performed to model abrocitinib as a 100 mg or 200 mg dose. The company assessed abrocitinib as both monotherapy and in combination with medicated topical therapy. The company's primary analysis is for the combination therapy as that is how they anticipate abrocitinib will be used in clinical practice	tralokinumab maintenance therapy to be given as 300mg Q4W for patients who achieve clear or almost clear skin. The company assess tralokinumab as both monotherapy and in combination with TCS. Furthermore, the company includes a base case assumption that a percentage of patients switched to Q4W dosing at week 52.	given as a monotherapy or in combination with TCS. The company present results for both doses of upadacitinib and the licensed dose for adolescents expected to be 15mg. However, the company did not explore dose escalation to upadacitinib 30mg for adult patients on upadacitinib 15mg in the presence of treatment effect waning.	Tralokinumab 600mg loading dose followed by 300mg Q2W. Upadacitinib 15mg or 30 mg once daily (tablet) Each treatment will be considered as monotherapy and in combination with TCS. Where appropriate, dose reductions will be considered.
Comparators	BSC was the accepted comparator for both TA534 and TA681. In TA681, dupilumab was also considered as a comparator. TA534 - CsA modelled as 5 mg/kg daily week 1 to 6 and 3 mg/kg daily week 6 to 52.	Dupilumab 300mg Q2W with an initial loading dose based on weight of 600mg (>60kg) or 400mg (<60kg) Baricitinib 4mg once daily. Both comparators assessed as monotherapy and in combination with TCS.	Dupilumab 600mg loading dose followed by 300mg Q2W, assessed as both monotherapy and in combination with TCS. BSC, defined as a combination of emollients, low-to-mid potency TCS in the case of combination therapy, and rescue therapy (such as higher potency topical or oral corticosteroids and TCIs).	CsA (systemic eligible only) 3 mg/kg daily for weeks 1-16 followed by 5 mg/kg daily for the remainder of the year. Company's dosing of CsA based on clinical expert opinion. Dupilumab 600mg loading dose followed by 300mg Q2W, assessed as both monotherapy and in combination with TCS. BSC, defined as a combination of emollients, low-to-mid potency TCS and rescue therapy (such as higher potency topical or oral corticosteroids or	For adult patients with moderate-to-severe AD that has not responded to at least one other systemic therapy, or in cases where systemic therapies are contraindicated or not tolerated, dupilumab and baricitinib are both recommended and will be considered as comparators in this position. Each treatment will be considered as both monotherapy and in combination with TCS. Dupilumab is also provided for adolescents under the NHS England Medicines for

				TCIs) phototherapy and psychological support.	Children Policy and will be considered as a comparator in the adolescent analyses. For patients eligible for systemic treatment, CsA (using the licensed dose regimen) will be considered as the comparator as it is the only licensed treatment for this position.
Model structure	TA534 - One year decision tree with outcomes based on response, followed by a 3-state Markov Model with annual cycles. Health states in the Markov model included maintenance, BSC and death. TA681 - 4-state Markov model with 4-week cycles. Health states in the model include induction, maintenance, non-response and death. For both TA534 and TA681, the committee accepted the model structures as suitable for decision making. However, for TA681, the committee considered the	1 year decision tree followed by a 3-state Markov model, with annual cycles. Response timepoints in short-term model were 16 and 52 weeks. Health states in the Markov model include, maintenance, BSC and death. The BSC health state in the Markov model is a weighted average of responders and non-responders.	1 year decision tree followed by a 3-state Markov chain with annual cycles. Response timepoints in short-term model were 16 and 52 weeks. Health states in the Markov model include maintenance, BSC and death. In the tralokinumab, baricitinib and dupilumab model engines, there is a single health state for BSC non-responders. Patients who switch from maintenance therapy to BSC are assumed to remain BSC non responders for the remainder of the modelled time horizon. In the BSC model engine, the BSC health state is subdivided into BSC responders and	1 year decision tree followed by a 4-state Markov chain with annual cycles. Response timepoints in short-term model were 16 and 52 weeks. Health states in the Markov model include maintenance, BSC non-responders, BSC responders and death. Patients who switch from maintenance therapy to BSC can only transition to the BSC non responder health state.	As per TA534, the model structure will be based on a one-year decision tree with outcomes based on response, followed by a 3-state Markov Model with annual cycles. Health states in the Markov model included maintenance, BSC and death. The BSC health state will be one overall BSC health state composed of responders and non-responders and these proportions will be informed by week 16 data.

	model structure was similar to the structure accepted in TA534.		BSC non-responders.		
Time horizon	TA534 - Lifetime (up to a maximum age of 100 years) TA681 - Lifetime (model time horizon was 62 years)	Lifetime (up to a maximum age of 100 years).	Lifetime (100 years)	Lifetime (up to a maximum age of 100 years)	Lifetime (up to a maximum age of 100 years)
Efficacy (outcomes)	Treatment response at 16 weeks based on EASI 50 and DLQI>4. TA534 - response to treatment at 52 weeks was conditional on response to treatment at 16 weeks (week 16 responders who lose response by week 52). TA681 - sustained response at 52 weeks should be based on all cause stopping rate for people whose condition responded to treatment at week 16 but withdrew from treatment at week 52.	Treatment response at 16 weeks based on EASI-50 and DLQI>4. The company assumed that the average time to response for "responders" is 8 weeks. The company use data for the generalisable population, defined as people who have failed systemic treatment (not restricted to CsA) for the base case. However, scenario analyses are conducted for the restricted populated, defined as people who have failed CsA. Furthermore, rescue medication was prohibited in the abrocitinib clinical trials and as such may not reflect the patient population seen in UK clinical practice. For the adolescent population combination	Treatment response at week 16 based on EASI-50 and DLQI>4. Non-responder imputation used for the company base case, which means that any patient who used rescue therapy was treated as a non-responder. Scenario analysis conducted for all-observed population, where patients who used rescue therapy were still included in the analysis. Sustained response at week 52 conditional on response at week 16.	Treatment response at week 16 based on EASI-50 and DLQI>4 was used for the adult systemic-exposed population. To capture early response to treatment, efficacy was applied from week 8 in the model. For the adult and adolescent systemic-eligible population, the composite outcome could not be obtained from the key trials and as such treatment response at week 16 was based on EASI 75. For the company base case, clinical data for the all-observed population has been used. The all-observed population patients were classed as responding to treatment, regardless of whether they received rescue	Treatment response at 16 weeks based on EASI 50 and DLQI>4, using the all-observed populations (defined as patients classed as responders irrespective of rescue medication use) from the key clinical trials. The committee for TA681 preferred the use of conditional discontinuation rates instead of conditional response (accepted in TA534) for week 52 outcomes. As TA681 supersedes TA534, assumption of conditional discontinuation for week 52 outcomes will be used in the model. Conditional response will be explored in a scenario.

		treatment analyses, the company assumed that the adult combination treatment composite outcome holds for adolescents. Adolescent combination treatment data for abrocitinib are available, however equivalent data for dupilumab are unavailable and thus could not be included in the NMA. Sustained response at 52 weeks estimated using conditional discontinuation data (proportion of patients discontinuing treatment at week 52 from those who achieve response at week 16). Data taken from EXTEND for full trial population. Discontinuation defined as lack of efficacy, adverse event or withdrawal by patient. However data reflects week 44 (compare) and week 48 (mono 1 +2)		medication. Sustained response at week 52 was conditional on response at week 16, calculated as the ratio of the proportion of responders at week 52 by the proportion of responders at week 16. For CsA, the company used the efficacy of BSC at week 16 (32.3%) as a proxy to estimate the proportion of patients who respond to BSC when they discontinue CsA at week 52.	
Network meta-analysis	TA534 - the key comparator was BSC which was captured in the dupilumab trials. Therefore no NMA was necessary. An indirect comparison with CsA was	Abrocitinib 200 mg and 100 mg were compared with dupilumab 300 mg and baricitinib 4 mg and 2 mg Separate NMAs were performed for adolescents	NMAs were conducted for data at 12 or 16 weeks follow up (induction phase) and at 26 weeks or later (maintenance phase). The comparators in the NMAs	Separate NMAs were performed for each subpopulation: adolescents, adult systemic-exposed and adult systemic-eligible	Separate NMAs were conducted for adolescents, 1L adults and 2L adults at 12- or 16-weeks follow-up. The comparator in the adolescent population was

	made through a MAIC. The data sources for CsA were Haeck 2011[127] and Jin 2015[128]. TA681 - NMAs were conducted to compare baricitinib 4 mg with dupilumab. Primary analysis based on censoring patients following initiation of rescue therapy. Used FE model as no between-study heterogeneity identified, outcomes analysed included EASI 50, EASI 75, EASI 90, NRS > 4 and EASI 50 + DLQI >4. Sensitivity analysis using 1) including patients who receive therapy with TCS, 2) European patients only for JAIN. Results reported as OR, RR and risk difference.	and adult for data at 12 or 16 weeks follow up. Long-term comparisons with dupilumab were performed through unanchored STC. Separate NMAs were conducted using the restricted population (patients who had failed on CsA), generalisable population (patients who had failed on at least one systemic therapy) and the full trial population for abrocitinib. The comparator in the adolescent NMA was dupilumab, and for the adult population it was dupilumab and baricitinib. Primary analysis based on censoring patients who received rescue therapy in the dupilumab and baricitinib trials as rescue therapy was not allowed in the abrocitinib trials. Both FE and RE models were assessed, with either informative priors or non-informative prior used for between-trial heterogeneity for RE models. Meta-regression performed to identify evidence of covariate effects on any of the	were dupilumab, baricitinib and BSC. Primary analyses reported for both censoring patients who received rescue therapy (non-responder imputation) and including patients who received rescue therapy (as observed). Both FE and RE models were assessed. A half-normal prior was used for between-trial heterogeneity for RE models. Outcomes analysed included EASI 50, EASI 75, IGA 0/1 and EASI 50 + DLQI >4. Sensitivity analysis included baseline-risk adjustment. Results reported as median RR with 95% CrI.	populations. The comparators in the adolescent and adult systemic-exposed NMAs were dupilumab and BSC, and for the adult systemic-eligible it was CsA. Primary analysis based on including patients who received rescue therapy. Both FE and RE models were assessed. Vague prior used for between-trial heterogeneity for RE models. Outcomes analysed included EASI 50, EASI 75, and EASI 50 + DLQI >4. Sensitivity analysis included 1) censoring patients who receive rescue therapy, 2) baseline-risk adjustment (DSU TSD3).[129] Results reported as OR with 95% CrI.	dupilumab, in the 1L adult population it was CsA, and in the 2L adult population it was dupilumab or baricitinib. The primary analysis was based on including patients who received rescue therapy (where possible). Both FE and RE models were assessed. Informative prior was used for between-trial heterogeneity for RE models. Outcomes analysed included EASI 75 and EASI 50 + DLQI >4. Sensitivity analysis included 1) censoring patients who receive rescue therapy, 2) using the generalisable population for abrocitinib, 3) baseline-risk adjustment (DSU TSD3).[129] Results reported as OR with 95% CrI

		outcomes in the full trial populations. Outcomes analysed included EASI 50/75/90 alone, EASI 50/75/90 + DLQI >4, PP-NRS 4, PP-NRS CFB, and DLQI CFB. Sensitivity analysis included RE models with informative priors for the heterogeneity SD. Results reported as mean effect (OR or CFB difference) with 95% CrI			
Other outcomes	TA534 - From year 2 onwards, an annual treatment discontinuation probability of 3.7% for dupilumab was accepted by committee. The discontinuation rate was based on the observed probability of week 16 responders discontinuing treatment by week 52. With regards to treatment waning, the appraisal committee accepted that patients on dupilumab have a sustained response and that by year 5 onwards, 8% of patients would lose response. Upon loss of response, dupilumab patients transition to the BSC health state. For	Long-term treatment discontinuation modelled using conditional discontinuation data at week 52 from the EXTEND trial, modelled as a constant rate converted to annual probabilities. Treatment effect waning applied as loss of utility in the maintenance and BSC Markov model health states. Data on the probability of sustained response for abrocitinib was unavailable and so the company applied assumptions from TA534 and TA681 to the base case. In TA534, the appraisal	Long-term treatment discontinuation for all biologics based on discontinuation data (due to adverse events or loss of efficacy) from the ECZTEND trial Treatment waning based on loss of response associated with biologics. The company assumed that 2-3% of patients would lose response annually up to year 4, with 1% losing response annually from year 5 onwards. Tralokinumab patients who lose response discontinue to BSC. For all patients on BSC, loss of treatment	Long-term treatment discontinuation modelled as an annual rate at which patients discontinue active treatment due to lack of long-term efficacy, adverse events, patient preference of physician preference. Treatment discontinuation data for upadacitinib+TCS is taken from 52-week data from AD UP and for dupilumab+TCS data was from a dupilumab open label extension study (6.4%). For all monotherapy treatments, discontinuation data are from SOLO-CONTINUE (6.3%). Discontinuation	The EAG's approach to long-term discontinuation will be consistent with the committee's preferences in TA534 and TA681. That is, treatment-specific all cause discontinuation rates at week 52 for responders at week 16 based will be applied from year 2 onwards. Treatment waning assumptions will be based on the committee's preferred approach in TA534, as no definitive recommendation was provided in TA681. However, treatment-waning

	patients on BSC, the committee considered that by year 5 onwards, up to 97% of patients would lose response to treatment and this was applied in the model as a return to baseline utility by year 5. TA681 - Consistent with TA534, all-cause discontinuation rates applied in the post-52-week period were accepted by committee. For treatment waning, proportions losing response to treatment and BSC were taken from TA534. Upon loss of response, patients returned to baseline utility. The ERG considered the company overestimated treatment waning for BSC patients and the approach separated utilities from costs in both arms of the model. However, the committee considered that the impact of treatment-waning for BSC on cost-effectiveness was likely to be between the company and ERG's estimates. Furthermore, the committee	committee accepted that patients on dupilumab have a sustained response and that by year 5 onwards, 8% of patients would lose response and this was used to estimate treatment waning for abrocitinib. For patients on BSC, the company assumed that by year 5 onwards, up to 96% of patients would lose response to treatment and this was used for the abrocitinib base case. Upon treatment waning, patients accrued a non-responder utility value for their respective treatment.	benefit assumed to occur linearly with all benefit lost by 5 years and patients returning to baseline utility.	data was based on all patients Treatment waning is assumed for both active treatment and BSC. For BSC responders and non-responders, all patients (regardless of response) return to baseline utility and incur non-responder costs over a 5-year period. For patients on CsA, BSC waning assumptions were applied, as treatment is given for a maximum of 1 year and then patients receive BSC thereafter. For patients on upadacitinib and dupilumab, treatment waning rates are taken from TA534 and are applied from years 1 to 5. From years 6 to 10, an annual treatment waning rate of 1% was assumed. After 10 years, no treatment waning is assumed. Upon treatment waning, upadacitinib and dupilumab patients move to the BSC non-responder health state and first incur	assumptions will be explored in scenarios to account for the points made in the committee discussion for TA681.

	considered that treatment waning assumptions for the active treatment arms had little impact on the cost-effectiveness results.			the utility of BSC non-responders then gradually return to the baseline utility following BSC non-responders waning rates.	
Utility values and sources	TA534 - treatment specific utility values preferred. Key assumptions accepted by the committee included at week 16 after starting treatment, dupilumab non-responders accrued the average utility of a dupilumab non-responder and BSC non-responder (0.82) and after week 52 accrued the utility value of BSC non-responders (0.77). TA681 - treatment-specific utility values from TA534 were preferred by committee.	EQ-5D-5L (mapped to EQ-5D-3L) and EQ-5D-Y from the abrocitinib trials (COMPARE, TEEN and MONO-1/2). Utilities presented in the submission are based on the full trial populations. Treatment was included as a covariate in the utility regressions to allow for treatment specific utility values to be estimated. **Key utility assumptions:** - Baseline utility is applied between weeks 0 and 8, regardless of treatment or response. - Treatment specific utilities applied between week 8 and 16, using utility at week 16 assessment point, regardless of response. - For non-responders on abrocitinib/ comparator, between week 16 and 52, average utility of non-	EQ-5D-5L data (mapped to EQ-5D-3L) collected in the ECZTRA trials. **Key utility assumptions:** - Treatment specific utilities included in the model. - Responders at week 16 accrue the mean of the biologic/ BSC responder utility and baseline utility between week 0 and 16. - Non-responders to biologic therapy accrue the mean of the biologic non-responder utility and BSC non-responder utility. - A proportion of BSC patients revert to baseline utility each year and by year 5, all BSC patients accrue baseline utility. - Disutility associated with AEs not included.	EQ-5D-5L data (mapped to EQ-5D-3L) collected in Measure UP 1 & 2 and AD UP trials (all-observed dataset). **Key utility assumptions:** - Utility values applied in the model are not treatment specific. - Upadacitinib-treated patients only incur the baseline utility for weeks 0-7. At week 8 they incur the initial response utility (regardless of response) until week 16. - Patients on the comparator treatments never incur the initial response utility as they move directly from the baseline utility to the responder or non-responder utility at week 16. - BSC non-responder" health state is sub-divided	The companies for abrocitinib, tralokinumab and upadacitinib have supplied treatment specific utility data from their respective key trials. However, due to missing data, uncertainty due to small numbers and relevance of the populations for utility values, the EAG has decided to implement utilities based on drug class using UK representative trial data. For JAK inhibitors, utilities based on upadacitinib data from Measure UP 1 & 2 (mono) and AD UP (combo) will be used for the first- and second-line population. This is because mono and combo upadacitinib utility data are available for adults and mono data are available for the adolescent population for both the

		responder and BSC applied regardless of response at week 16, and beyond week 52 average utility of BSC at week 16 regardless of response. - For patients on BSC between after week 16 and for the remainder of the model time horizon, weighted average utility of BSC responders and non-responders. - Disutility associated with AEs not included.		into “recent” non-responders and non-responders in their baseline state. The “recent” non-responders incur a non-responder utility which is in-between the utility of responders and baseline while non-responders in their baseline state incur the baseline utility - Disutility associated with AEs not included.	composite outcome and EASI 75. For monoclonal antibody drugs, utilities based on tralokinumab data will be used for the adult second line population and adolescents. The key reason tralokinumab utility data was selected over dupilumab data for monoclonal antibodies is because the dupilumab CS does not consistently report utility data for treatment as a monotherapy or using the EASI 75 response outcome whereas the data are available from the tralokinumab trials Scenario analyses will be conducted using accepted utility values from TA534.
Costs and sources	TA534 - Costs sourced from the BNF (2017), eMIT, PSSRU and the National Reference Costs (2015) and the National Schedule of Reference Costs (2015-2016), and NHS Reference Costs (2014). Resource use for AEs were based on dupilumab clinical trials	Costs sourced from NHS reference costs (2018-19), PSSRU 2020, BNF and eMIT. Resource use assumptions taken from TA534 and TA681. Concomitant medications consisted of TCS, emollients and TCI but excluded	Costs sourced from NHS reference costs (2018-19), PSSRU 2019, MIMS and the published literature. Resource use assumptions taken from TA534. BSC concomitant medication costs include TCS, emollients and TCI but	Costs sourced from the National schedule of reference costs, PSSRU 2019, HES 2018/19, the Drug Tariff, BNF and eMIT. Resource use assumptions taken from TA534. Concomitant medications include TCS, emollients,	Costs and resource use assumptions accepted for TA534 were used in TA681 and as such will be implemented in the model. Cost sources will reflect the most up to date cost data from standard sources such as NHS reference costs, PSSRU and the BNF.

	TA681 - Costs sourced from the BNF (2019), MIMS, PSSRU and National Reference Costs (2019) and the National Schedule of NHS Costs (2018- 2019). Resource use was based on TA534. The committee preferred to omit the cost of bathing products from the model.	bathing products.	excluded bathing products.	TCI and bathing products.	Furthermore, cost assumptions preferred by the committee for TA534 and TA681 will be taken into consideration.
Adverse events	TA534 - Key AEs reported in the dupilumab clinical trials. AEs include injection site reactions, allergic conjunctivitis, infectious conjunctivitis and oral herpes TA681 - Most frequent and serious AEs reported in the baricitinib AD trials. AEs include injection site reactions, allergic conjunctivitis, infectious conjunctivitis and oral herpes	Treatment emergent AEs occurring in >5% of patients in either arm in the full trial populations for abrocitinib. AEs include injection site reaction, allergic conjunctivitis, infectious conjunctivitis, headache, nasopharyngitis, nausea, upper respiratory tract infection, folliculitis, pharyngitis, oral herpes. Adverse events in submission are based on full trial population.	AEs based on an NMA and include injection site reactions, oral herpes, allergic conjunctivitis and infectious conjunctivitis	Treatment emergent AEs occurring in >5% of the study population in the upadacitinib and dupilumab clinical trials. AEs include injection site reactions, allergic conjunctivitis, infectious conjunctivitis, skin infections, upper respiratory tract infection, acne	Serious treatment emergent adverse events specific to treatment will be included in the model.
Company base case ICERs	**TA534 dupilumab + TCS - adults** vs. BSC - plausible ICER range of £27,410 to £28,495. Committee concluded that	List price ICERs were provided in the company submission and are presented below.	List price ICERs were not provided in the company submission. Results presented include the PAS discount for	List price ICERs were not provided in the company submission. Results presented below include the PAS discount	N/A

	dupilumab + TCS is a cost-effective use of NHS resources. **TA681 baricitinib - adults** vs. dupilumab - ICER was in the SW quadrant (less costly, less effective) and were within what NICE would consider an acceptable use of NHS resources. vs. BSC - £27,037 (scenario 1) and £28,396 (scenario 2). Committee considered that there was uncertainty related to the ICERs related to quality of life waning assumptions associated with BSC, but considered it was likely to be at the upper end of what NICE considers an acceptable use of NHS resources. As such, the committee concluded baricitinib is likely to be cost-effective compared with BSC.	**Abrocitinib 100 mg - adult combination** vs. dupilumab = £142,241 (SW quadrant) vs. baricitinib = £69,593 **Abrocitinib 200 mg - adult combination** vs. dupilumab = £218,356 (SW quadrant) vs. baricitinib = £60,757 **Abrocitinib 100 mg - adolescent combination** vs. dupilumab = £102,345 (SW quadrant) **Abrocitinib 200 mg - adolescent combination** vs. dupilumab = £168,861 (SW quadrant) **Abrocitinib 100 mg - adult monotherapy** vs. dupilumab = £125,278 (SW quadrant) vs. baricitinib = £88,344 **Abrocitinib 200 mg - adult monotherapy** vs. dupilumab = £167,991 (SW quadrant) vs. baricitinib = £53,040	tralokinumab **Tralokinumab - adult combination** vs. BSC = £26,969 vs. dupilumab = £115,545 (SW quadrant) **Tralokinumab - adult monotherapy** vs. BSC = £24,666 vs. dupilumab = £125,178	for upadacitinib. **Upadacitinib 15 mg + TCS - adult systemic eligible** vs. CsA + TCS = £13,173 **Upadacitinib 30 mg + TCS - adult systemic eligible** vs. CsA + TCS = £29,934 **Upadacitinib 15 mg + TCS - adult systemic exposed** vs. BSC = £10,583 vs. dupilumab + TCS = £128,057 (SW quadrant) **Upadacitinib 30 mg + TCS - adult systemic exposed** vs. BSC = £25,163 vs. dupilumab + TCS = Dominant **Upadacitinib 15 mg + TCS - adolescent systemic eligible** vs. dupilumab + TCS = £10,287 **Upadacitinib 30 mg +**	

		Abrocitinib 100 mg - adolescent monotherapy vs. dupilumab = £96,811 (SW quadrant) **Abrocitinib 200 mg - adolescent monotherapy** vs. dupilumab = £160,010 (SW quadrant)		**TCS - adolescent systemic eligible** vs. dupilumab + TCS = Dominant	

Abbreviations: AD, atopic dermatitis; AE, adverse events; BNF, British National Formulary; BSC, best supportive care; CFB, change from baseline; combo, combination; CsA, ciclosporin; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; eMIT, Drugs and pharmaceutical electronic market information tool; EQ-5D, EuroQoL five dimension; FE, fixed effects; HES, Hospital Episodes Statistics; IGA, Investigator's Global Assessment; mg, milligram; MIMS, Monthly Index of Medical Specialities; mono, monotherapy; NHS, National Health Service; NMA, network meta-analysis; OR, odds ratio; PP-NRS, Peak Pruritus Numerical Rating Scale; PSSRU, Personal Social Services Research Unit; Q2W, once every two weeks; Q4W, once every four weeks; RE, random effects; RR, relative risk; SD, standard deviation; SW, south-west; TA, technology assessment; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids.

7 BSC treatment waning – TA534, TA681 and company assumptions

In TA534 and explored in TA681, the two sensitivity analyses were presented around the proportion of BSC patients that lost treatment benefit over 5 years which were deemed plausible by the committee (see Table 48). However, the ERG for TA681 did not agree that treatment waning should be applied to BSC patients, but preferred to model BSC response and non-response in one health state to capture the waxing and waning nature of AD for patients on BSC. In the abrocitinib model, BSC treatment waning in the base case was informed by sensitivity analysis 1 in TA534. The assumptions in the tralokinumab and upadacitinib models deviated from the committee preferred assumptions in TA534 and TA681 as 100% of BSC patients were assumed to lose response by year 5.

All of the company models, including TA534 and TA681, implemented BSC treatment waning as a loss of utility benefit. With the exception of the abrocitinib model, BSC patients who experience a loss of response return to baseline utility. In the abrocitinib model, BSC patients who lose response accrue the BSC non-responder utility value. The upadacitinib model goes one step further to also assume that BSC patients who lose response also incur non-responder BSC costs. Furthermore, in the upadacitinib model, treatment waning for CsA was assumed to be the same as BSC.

Table 48. Treatment waning proportions scenario analyses

Year	Active treatment	BSC – TA534 sensitivity analysis 1	BSC – TA534 sensitivity analysis 2
2	2%	82%	57%
3	5%	90%	82%
4	7%	94%	92%
5+	8%	96%	97%

Abbreviations: BSC, best supportive care

8 Adverse events in TA534, TA681 and the company models

Table 49 presents a comparison of AEs included in TA534, TA681 and the company models as well as those included in the EAG's analysis.

Table 49. Comparison of AEs included in models

Adverse events	TA534	TA681	Abrocitinib	Tralokinumab	Upadacitinib	EAG approach
Injection site reaction	✓	✓	✓	✓	✓	✓
Allergic	✓	✓	✓	✓	✓	✓

conjunctivitis						
Infectious conjunctivitis	✓	✓	✓	✓	✓	✓
Oral herpes	✓	✓	✓	✓	-	✓
Upper respiratory tract infection	-	✓	✓	-	✓	✓
Acne	-	-	-	-	✓	✓
Skin infection	-	-	-	-	✓	-
Folliculitis	-	-	✓	-	-	-
Headache	-	-	✓	-	-	-
Nausea	-	-	✓	-	-	-
Pharyngitis	-	-	✓	-	-	-
Nasopharyngitis	-	-	✓	-	-	-

Abbreviations: AE, adverse events; EAG, evidence assessment group.

9 Additional health related quality of life information

9.1.1 Utility regressions

As discussed in Section **Error! Reference source not found.**, the EAG has used a drug class approach for the utility data. For the Janus Kinase (JAK) inhibitors, utility data provided by the company for upadacitinib was used. Company utility data for tralokinumab was used for the monoclonal antibodies. The following subsections describe the companies utility data and regression analysis.

Upadacitinib utility data

The EQ-5D-5L was used to capture HRQoL data in the Measure UP 1, Measure UP 2 and AD-UP trials at baseline, week four, week 16, week 32, week 52 and every 24 weeks post the week 52 visit. In line with NICE guidance, the company mapped the EQ-5D-5L responses onto the EQ-5D-3L value set using the van Hout *et al.* 2012 algorithm.[130] Measure UP 1 and Measure UP 2 assessed upadacitinib monotherapy 15 mg and 30 mg in both adults and adolescents. Upadacitinib 15 mg and 30 mg in combination with TCS 15 in both adults and adolescents was assessed in AD UP.

The EAG requested the company to run utility regression models according to the subgroups assessed in the MTA model (adult first-line systemic treatment, adult second-line systemic treatment and adolescents). All-observed baseline and week-16 data from the upadacitinib trials informed the regressions. Utility data from Measure UP 1 and Measure UP 2 were used for the upadacitinib monotherapy analyses and for the combination therapy analyses, data from AD UP were used. Additionally the company provided separate analyses for EASI 50 + DLQI ≥4 and EASI 75 for the adult second-line systemic treatment population. Only EASI 75 data were available for adult first-line systemic treatment and adolescent populations, but this is aligned with the MTA model outcomes for these populations.

Model selection was performed using backward selection and covariates included age, baseline Investigator Global Assessment (IGA), baseline EASI, sex, TCI/TCS intolerance and treatment (at the request of the EAG). Baseline utility was included for the week 16 regressions. Covariates were included in the model if they met the statistical significance threshold of $p<0.1$. However, for the results by treatment and/or response status, respective covariates were retained in the model irrespective of statistical significance. Mean utility values and standard errors were estimated using the least squared means approach using equal weights for covariates across groups.

Table 50. Covariates included in regression models

Population and outcome	Monotherapy	Combination therapy
Adult first-line systemic treatment - EASI 75	N/A	**Baseline**: treatment, age, baseline EASI **Responder & non-responder**: treatment, EASI 75 response at week 16, crosswalk UK baseline
Adult second-line systemic treatment - EASI 50 + DLQI ≥4	**Baseline**: treatment, baseline EASI **Responder & non-responder**: treatment, EASI 50 + DLQI ≥4 response at week 16, crosswalk UK baseline	**Baseline**: treatment, baseline EASI **Responder & non-responder**: treatment, EASI 50 + DLQI ≥4 response at week 16, crosswalk UK baseline
Adult second-line systemic treatment - EASI 75	**Baseline**: treatment, age, baseline EASI **Responder & non-responder**: treatment, EASI 75 response at week 16, crosswalk UK baseline	**Baseline**: treatment, age, baseline EASI **Responder & non-responder**: treatment, EASI 75 response at week 16, crosswalk UK baseline
Adolescents - EASI 75	**Baseline**: treatment, baseline EASI **Responder & non-responder**: treatment, EASI 75 response at week 16, crosswalk UK baseline, age	N/A

Abbreviations: DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; N/A, not applicable; UK, United Kingdome.

Tralokinumab utility data

The EQ-5D-5L was used to capture HRQoL data in the ECZTRA 1, ECZTRA 2, ECZTRA 3 and ECZTRA 7 trials at baseline and every two weeks up to the week 16 assessment point and week 16 in ECZTRA 7. In line with NICE guidance, the company mapped the EQ-5D-5L responses onto the EQ-5D-3L value set using the van Hout *et al.* 2012 algorithm.[130] ECZTRA 1 and ECZTRA 2 assessed tralokinumab monotherapy in adults who are candidates for systemic therapy. ECZTRA 3 assessed tralokinumab in combination with TCS also in adults who are candidates for systemic therapy. ECZTRA 7 assessed tralokinumab in combination with TCS in adults who do not have adequate control with, or have intolerance or contraindications to, CSA.

The EAG requested the company to run utility regression models for the adult second-line systemic treatment population (known as the ECZTRA-7 like subgroup). The company used a mixed model with repeated measures (MMRM) on mapped EQ-5D-3L data. To make full use of the utility data available, all-observed data (all patient population) from ECZTRA 1 and 2 (monotherapy analyses)

and ECZTRA 3 and 7 (combination therapy analyses) using ECZTRA 7-like inputs informed the regressions. The company provided separate analyses for EASI 50 + DLQI ≥4 and EASI 75 for the adult second-line systemic treatment population. Only statistically significant covariates were included in the final model.

Covariates assessed were based on those used in TA534 and included baseline EQ-5D, age, sex, EASI score and treatment. In the company submission, worst pruritus and an interaction term with worst pruritus and EASI score was included, but as pruritus is not an outcome in the MTA model, the EAG requested the company to exclude these covariates from the regressions.

ECZTRA 7-like baseline inputs for the regressions (age, proportion male, baseline EASI and baseline EQ-5D) were based on the mean across all ECZTRA 7-like patients in ECZTRA 1 and 2 for the monotherapy analyses and ECZTRA 3 and 7 for the combination analyses.

The company provided utility data for week 0 to 16 (induction) and week 16 to 52 (maintenance). The company noted limitations with the maintenance period data as only tralokinumab responders could be included and only EASI 75 responders were eligible for inclusion and re-randomisation, thus maintenance data could not be generated for the composite outcome. To align with the upadacitinib data, the EAG focussed only on the induction period utility data.

9.1.2 Utility data for scenarios

Table 51. TA534 utility values

BSC	Active treatment	Best supportive case	Assumptions
Baseline	0.663	-	-
Responder	0.898	0.797	Patients who are non-responders to systemic treatment transition to BSC. Patients on BSC are assigned a weighted utility value based on the proportion of patients who respond to BSC at Week 16
Non-responder	-		Patients on BSC are assigned a weighted utility value based on the proportion of patients who respond to BSC at Week 16

Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index; JAK, Janus Kinase.

10 Additional cost and resource use information

Table 52. Concomitant medication costs included in the model

Drug	Pack cost	Pack size	Source[131 132]
TCI			
Protopic 0.1% ointment, tacrolimus	£45.56	60	BNF drug tariff, Part VIIIA Category M, last updated August 2021
TCS			
Mometasone 0.1% ointment	£2.58	100	eMIT last updated March 2021
Emollient			
Aveeno cream (Johnson & Johnson Ltd)	£6.47	500	BNF NHS indicative price, last updated August 2021
Cetraben ointment (Thornton & Ross Ltd)	£5.39	450	BNF NHS indicative price, last updated August 2021
Dermol cream (Dermal Laboratories Ltd)	£6.63	500	BNF NHS indicative price, last updated August 2021
Diprobase ointment (Bayer Plc)	£5.99	500	BNF NHS indicative price and drug tariff, Part VIIIA Category C, last updated August 2021
Epaderm ointment (Molnlycke Health Care Ltd)	£12.42	1000	BNF NHS indicative price, last updated August 2021
Hydromol ointment (Alliance Pharmaceuticals Ltd)	£8.31	1000	BNF NHS indicative price, last updated August 2021
White soft paraffin 50% / Liquid paraffin 50% ointment (A A H Pharmaceuticals Ltd)	£4.32	500	BNF NHS indicative price and drug tariff, Part VIIIA Category C, last updated August 2021
Oilatum cream (Thornton & Ross Ltd)	£5.28	500	BNF NHS indicative price and drug tariff, Part VIIIA Category C, last updated August 2021

Abbreviations: BNF, British National Formulary; NHS, National Health Service; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids.

Table 53. Concomitant medication resource use included in the model (amount per week)

Drug	Systemic treatment (responders)	BSC (responders and non-responders)	Source
TCI			
Protopic 0.1% ointment, tacrolimus	NA	1.75g	CS for TA534 (Table 3.27) and CS for TA681 (Table 96)
TCS			
Mometasone 0.1% ointment	56.70g	112.04g	CS for TA534 (Table 3.26) and CS for TA681 (Table 96)
Emollient			

Aveeno cream (Johnson & Johnson Ltd)	0.50	1.00	CS for TA534 (Table 3.25) and CS for TA681 (Table 96)
Cetraben ointment (Thornton & Ross Ltd)	0.50	1.00	
Dermol cream (Dermal Laboratories Ltd)	0.50	1.00	
Diprobase ointment (Bayer Plc)	0.50	1.00	
Epaderm ointment (Molnlycke Health Care Ltd)	0.25	0.50	
Hydromol ointment (Alliance Pharmaceuticals Ltd)	0.25	0.50	
White soft paraffin 50% / Liquid paraffin 50% ointment (A A H Pharmaceuticals Ltd)	0.50	1.00	
Oilatum cream (Thornton & Ross Ltd)	0.25	0.50	

Abbreviations: BSC, best supportive care; CS, company submission; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids.

Table 54. Monitoring unit costs included in the model

Visit/ test	Unit cost	Source[133 134]
Dermatologist outpatient consultation	£124.83	National Schedule of NHS Costs - Year 2019-20 - NHS trusts and NHS foundation trusts. Service code 330, dermatology, consultant led, weighted average WF01A-WF01D, WF02A-WF02D
Dermatologist nurse visit	£31.25	Unit Costs of Health and Social Care 2020. 15 minutes of a band 6 hospital-based nurse (£50 per working hour). Note: each hour spent with a client requires 2.5 paid hours
GP consultation	£39.00	Unit Costs of Health and Social Care 2020. Per surgery consultation lasting 9.22 minutes. Including direct care staff costs and qualifications
A&E visit	£170.98	National Schedule of NHS Costs - Year 2019-20 - NHS trusts and NHS foundation trusts. Weighted average VB06Z-VB09Z
Hospitalisation	£1,611.14	National Schedule of NHS Costs - Year 2019-20 - NHS trusts and NHS foundation trusts. Skin Disorders: Non-elective short stay, weighted average JD07A-JD07K (134,484 at £587) Non-elective long stay, weighted average JD07A-JD07K (99,096 at £3,001)
Day case	£439.00	National Schedule of NHS Costs - Year 2019-20 - NHS trusts and NHS foundation trusts. Day case, Skin Disorders, weighted average JD07A-JD07K
FBC	£2.58	National Schedule of NHS Costs - Year 2019-20 - NHS trusts and NHS foundation trusts. DAPS05 Haematology
Phototherapy	£107.24	National Schedule of NHS Costs - Year 2019-20 - NHS trusts and NHS foundation trusts. JC47Z Total HRGs & Currencies

		Phototherapy or Photochemotherapy
Psychological support	£324.88	National Schedule of NHS Costs - Year 2019-20 - NHS trusts and NHS foundation trusts. Service code 656, clinical psychology, consultant led, weighted average WF01A-WF01D, WF02A-WF02B

Abbreviations: A&E, accident and emergency; FBC, full blood count; GP, General Practitioner; NHS, National Health Service

Table 55. Monitoring resource use included in the model (number per year)

Visit/ test	Non-responders	Responders	Source
Dermatologist outpatient consultation	6.00	4.32	ERG for TA534 (Table 38), CS for TA681 (Table 100)
Dermatologist nurse visit	0.46	0.35	ERG for TA534 (Table 38), CS for TA681 (Table 100)
GP consultation	12.81	6.15	ERG for TA534 (Table 38), CS for TA681 (Table 100)
A&E visit	0.082	0.021	ERG for TA534 (Table 38), CS for TA681 (Table 100)
Hospitalisation	0.13	0.017	ERG for TA534 (Table 38), CS for TA681 (Table 100)
Day case	0.20	0.00	CS for TA534, ERG for TA534 (Table 38), CS for TA681 (Table 100)
FBC (biologic treatment)	4.00	NA	CS for TA534, ERG for TA534 (Table 38), CS for TA681 (Table 100)
FBC (BSC)	4.00	4.00	CS for TA534, ERG for TA534 (Table 38), CS for TA681 (Table 100)
Phototherapy	0.06	NA	Company ACD response for TA534, CS for TA681 (Table 101)
Psychological support	0.07	NA	Company ACD response for TA534, CS for TA681 (Table 101)

Abbreviations: ACD, Appraisal Committee document; CS, company submission; ERG, Evidence Review Group; NA, not applicable.

Table 56. Flare medication acquisition costs

Drug	Pack cost	Pack size	Source[131 132]
TCS potent			
Betamethasone valerate cream	£2.71	100	eMIT last updated March 2021
Cutivate 0.005% ointment (GlaxoSmithKline UK Ltd)	£4.24	30	BNF NHS indicative price and drug tariff, Part VIIIA Category C, last updated August 2021
TCS very potent			
Eumovate 0.05% ointment	£5.44	100	BNF NHS indicative price and drug tariff, Part VIIIA Category C, last updated August 2021
Dermovate 0.05% cream (GlaxoSmithKline UK Ltd)	£7.90	100	BNF NHS indicative price and drug tariff, Part VIIIA Category C, last updated August 2021
Systemic steroid			

Prednisolone 5 mg	£0.40	28	eMIT last updated March 2021
TCI			
Protopic 0.1% ointment, tacrolimus	£45.56	60	BNF drug tariff, Part VIIIA Category M, last updated August 2021

Abbreviations: BNF, British National Formulary; NHS, National Health Service; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids.

Table 57. Flare medication resource use

Drug	Number of packs per flare	Source
TCS potent		
Betamethasone valerate cream	1	CS for TA681 (Table 98)
Cutivate 0.005% ointment (GlaxoSmithKline UK Ltd)	3.33	CS for TA681 (Table 98)
TCS very potent		
Eumovate 0.05% ointment	1	CS for TA681 (Table 98)
Dermovate 0.05% cream (GlaxoSmithKline UK Ltd)	1	CS for TA681 (Table 98)
Systemic steroid		
Prednisolone 5 mg	1	CS for TA681 (Table 98)
TCI		
Protopic 0.1% ointment, tacrolimus	0.40	CS for TA681 (Table 98)

Abbreviations: BNF, British National Formulary; CS, company submission; NHS, National Health Service; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids.

11 One-way sensitivity plots

11.1 Adults first-line systemic treatment population

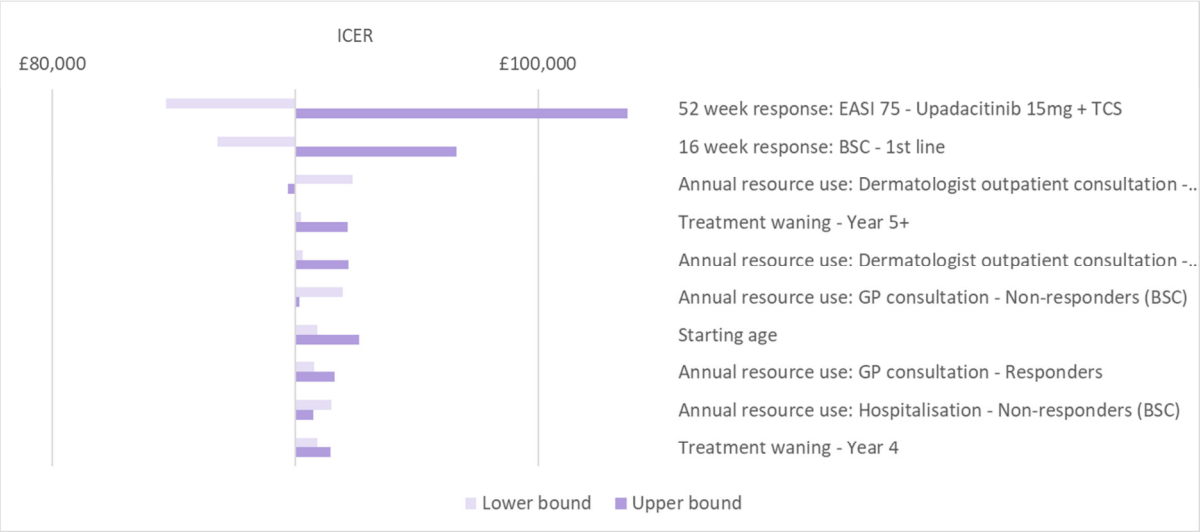

Figure 7. Tornado diagram for abrocitinib 100 mg + TCS vs CsA + TCS: adult first-line - EASI 75 – combination therapy (list prices)

Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index; CsA, ciclosporin; ICER, incremental cost-effectiveness ratio; mg, milligram; mg, milligram; TCS, topical corticosteroids.

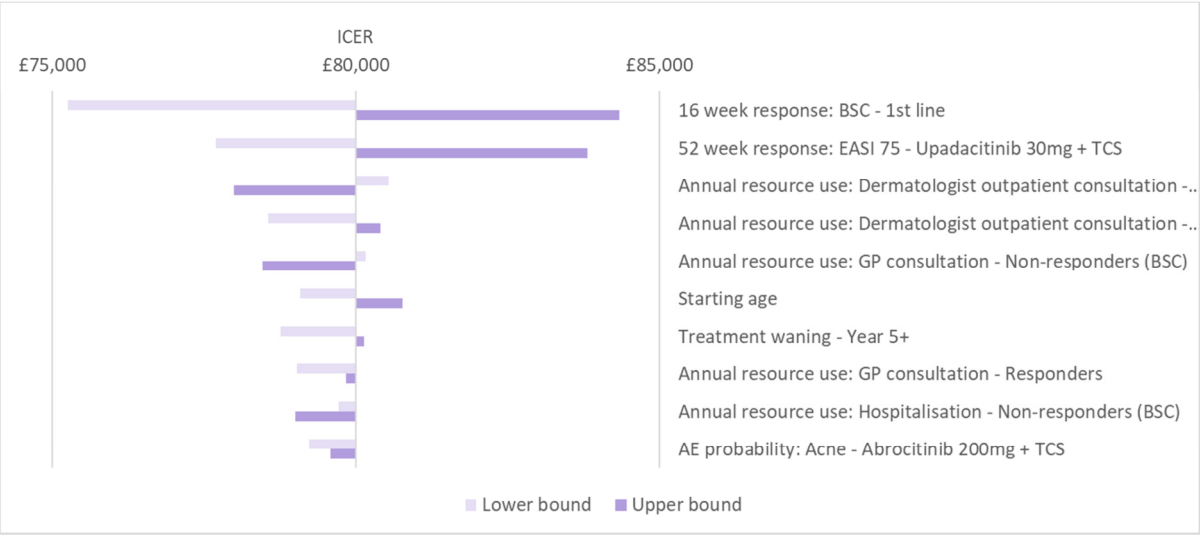

Figure 8. Tornado diagram for abrocitinib 200 mg + TCS vs CsA + TCS: adult first-line - EASI 75 – combination therapy (list prices)

Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index; CsA, ciclosporin; ICER, incremental cost-effectiveness ratio; mg, milligram; mg, milligram; TCS, topical corticosteroids.

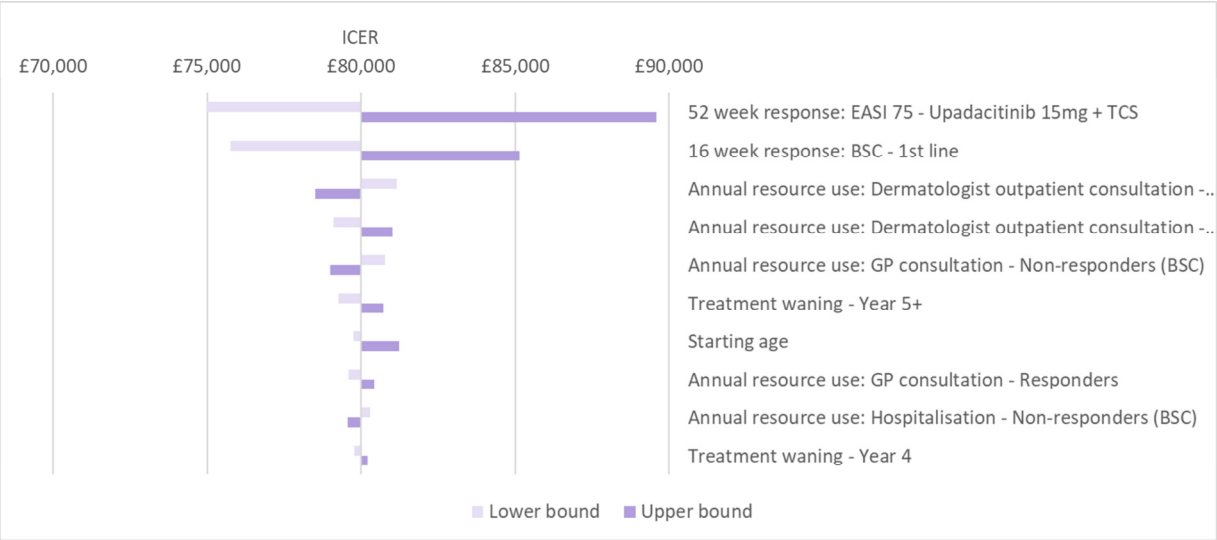

Figure 9. Tornado diagram for upadacitinib 15mg + TCS vs CsA + TCS: adult first-line - EASI 75 – combination therapy (list prices)

Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index; CsA, ciclosporin; ICER, incremental cost-effectiveness ratio; mg, milligram; mg, milligram; TCS, topical corticosteroids.

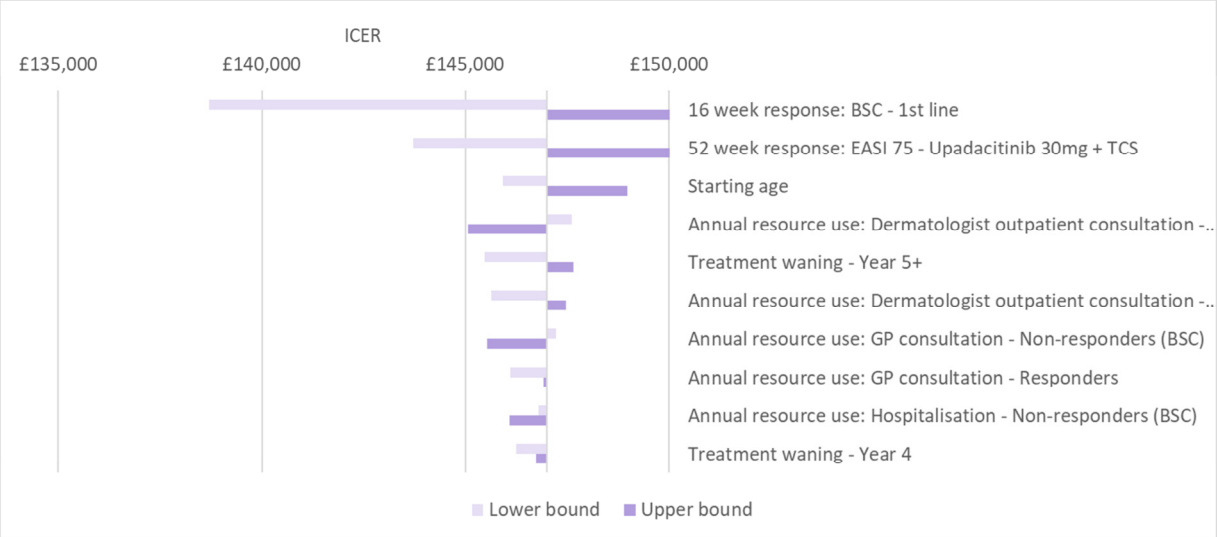

Figure 10. Tornado diagram for upadacitinib 30mg + TCS vs CsA + TCS: adult first-line – EASI 75 – combination therapy (list prices)

Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index; CsA, ciclosporin; ICER, incremental cost-effectiveness ratio; mg, milligram; mg, milligram; TCS, topical corticosteroids.

11.2 Adults second-line systemic treatment population – monotherapy

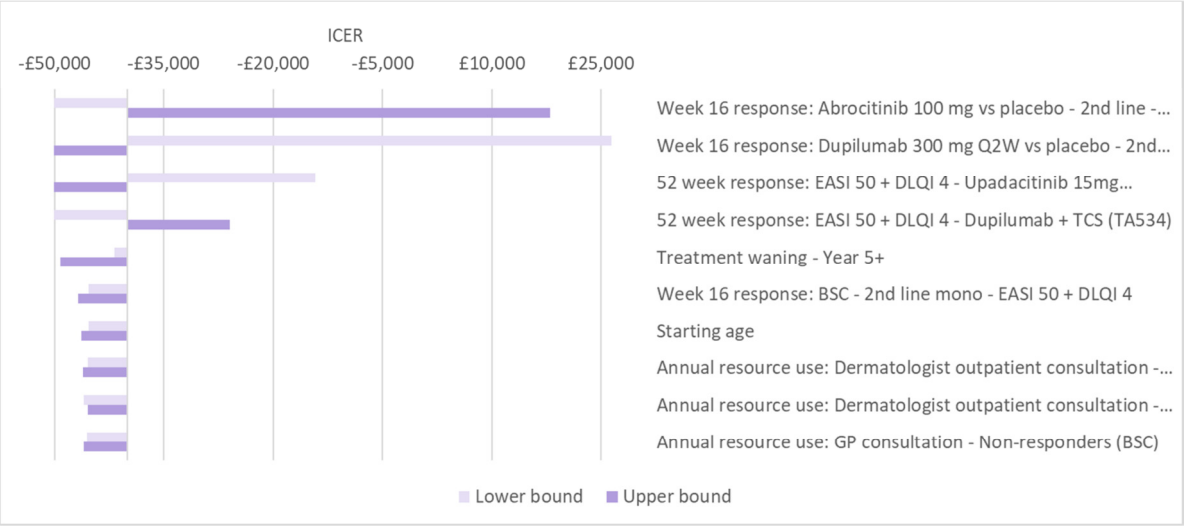

Figure 11. Tornado diagram for abrocitinib 100mg vs dupilumab: adults second-line - EASI 50 + DLQI ≥4 - monotherapy therapy (list prices)

Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; ICER, incremental cost-effectiveness ratio; mg, milligram; Q2W, twice weekly; TCS, topical corticosteroids.

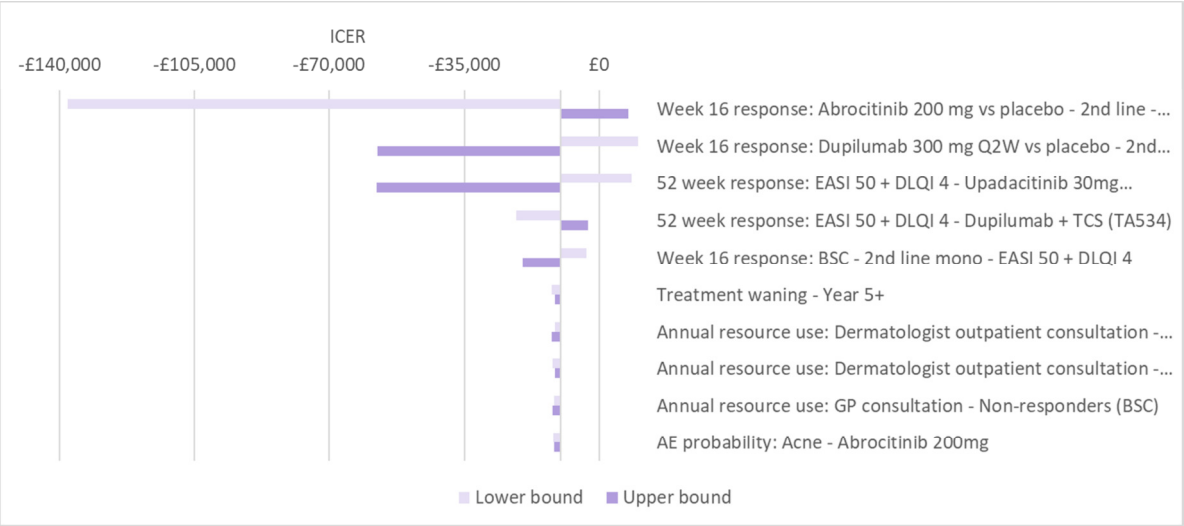

Figure 12. Tornado diagram for abrocitinib 200mg vs dupilumab: adults second-line - EASI 50 + DLQI ≥4 - monotherapy therapy (list prices)

Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; ICER, incremental cost-effectiveness ratio; mg, milligram; Q2W, twice weekly; TCS, topical corticosteroids.

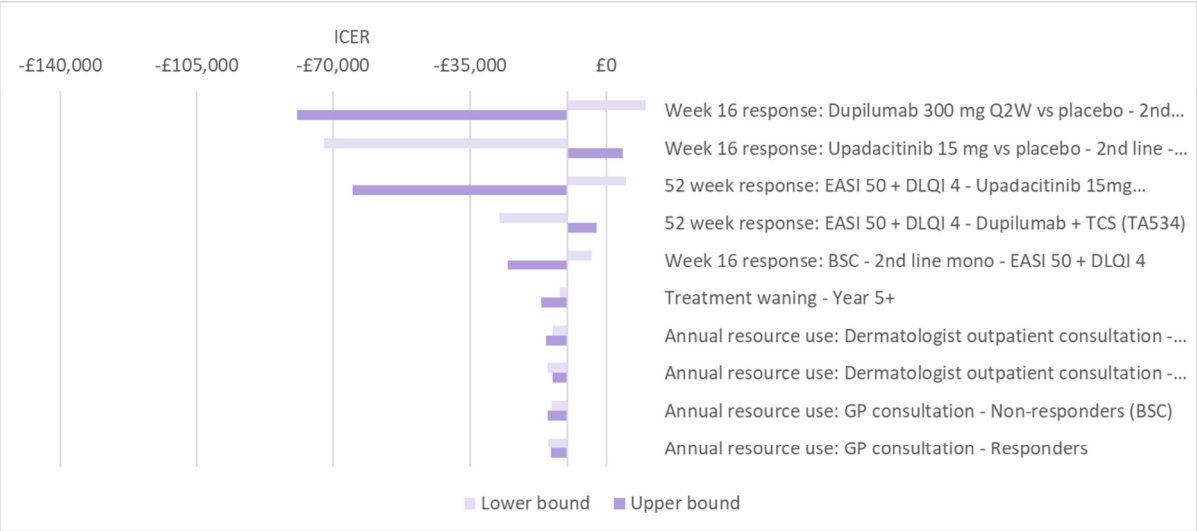

Figure 13. Tornado diagram for upadacitinib 15mg vs dupilumab: adults second-line - EASI 50 + DLQI ≥4 - monotherapy therapy (list prices)

Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; ICER, incremental cost-effectiveness ratio; mg, milligram; Q2W, twice weekly; TCS, topical corticosteroids.

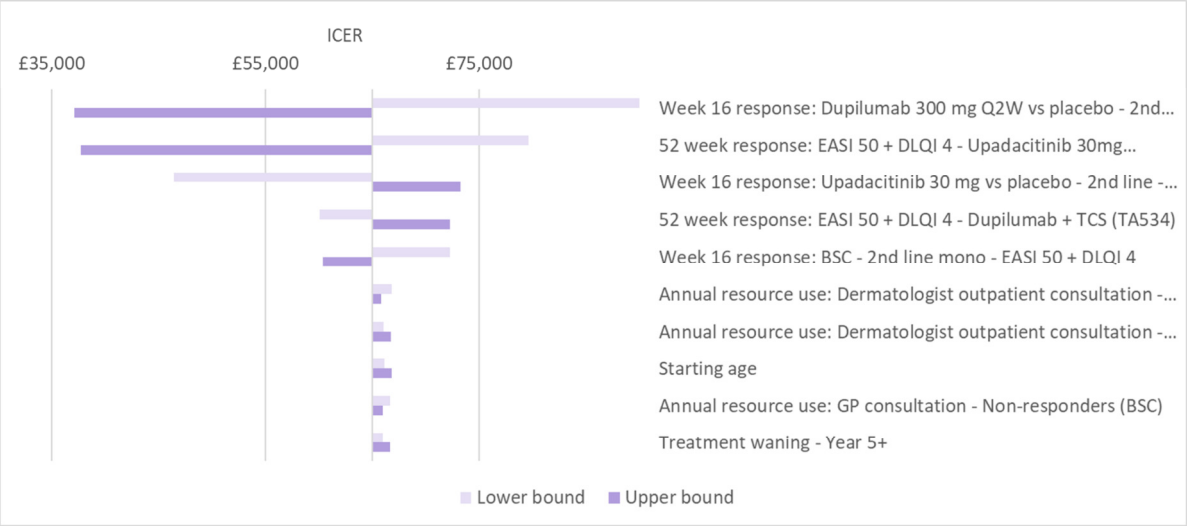

Figure 14. Tornado diagram for upadacitinib 30mg vs dupilumab: adults second-line - EASI 50 + DLQI ≥4 - monotherapy therapy (list prices)

Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; ICER, incremental cost-effectiveness ratio; mg, milligram; Q2W, twice weekly; TCS, topical corticosteroids.

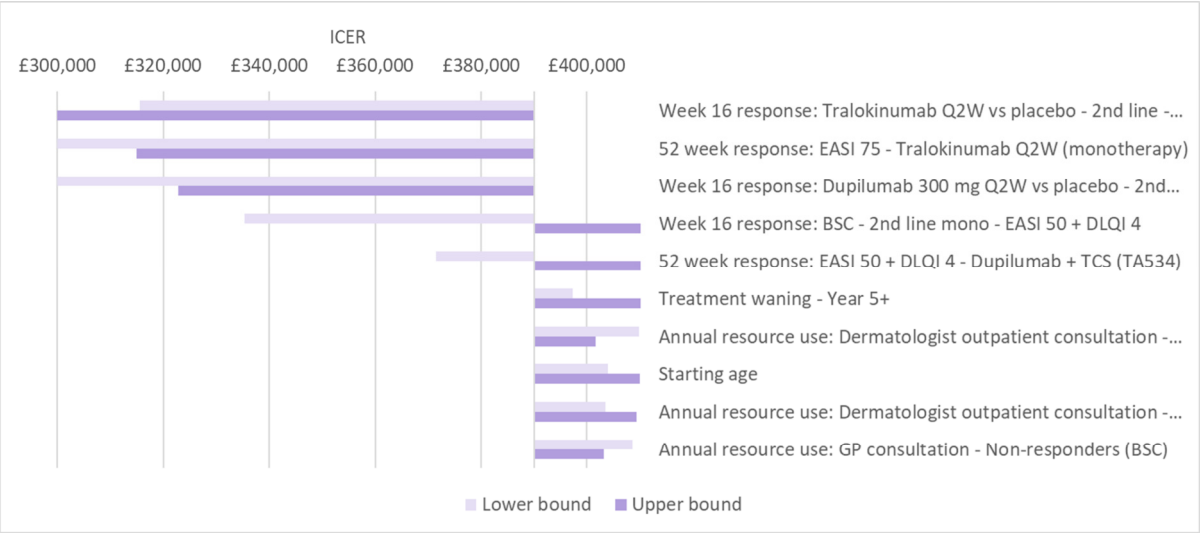

Figure 15. Tornado diagram for tralokinumab vs dupilumab: adults second-line - EASI 50 + DLQI ≥4 - monotherapy therapy (list prices)

Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; ICER, incremental cost-effectiveness ratio; mg, milligram; Q2W, twice weekly; TCS, topical corticosteroids.

11.3 Adults second-line systemic treatment population – combination therapy

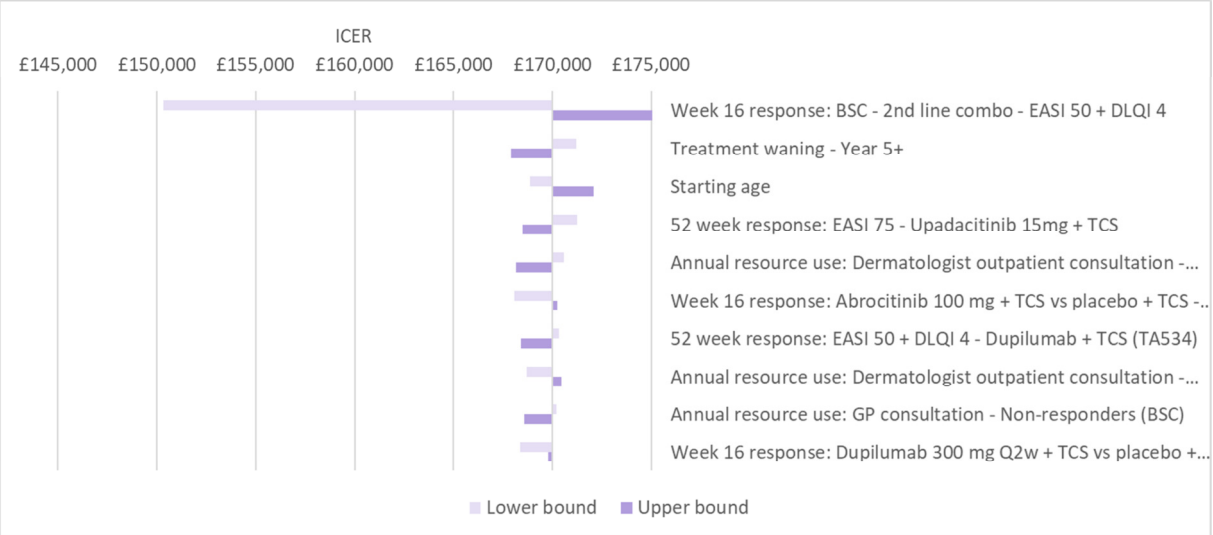

Figure 16. Tornado diagram for abrocitinib 100mg + TCS vs dupilumab + TCS: adults second-line - EASI 50 + DLQI ≥4 - combination therapy (list prices)

Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; ICER, incremental cost-effectiveness ratio; mg, milligram; Q2W, twice weekly; TCS, topical corticosteroids.

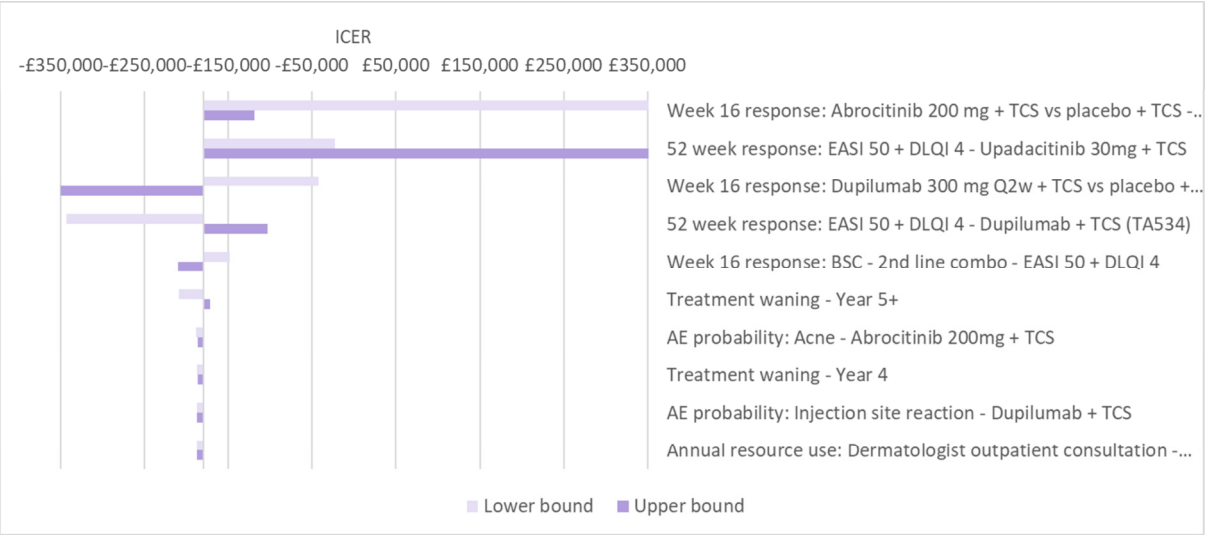

Figure 17. Tornado diagram for abrocitinib 200mg + TCS vs dupilumab + TCS: adults second-line - EASI 50 + DLQI ≥4 - combination therapy (list prices)

Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; ICER, incremental cost-effectiveness ratio; mg, milligram; Q2W, twice weekly; TCS, topical corticosteroids.

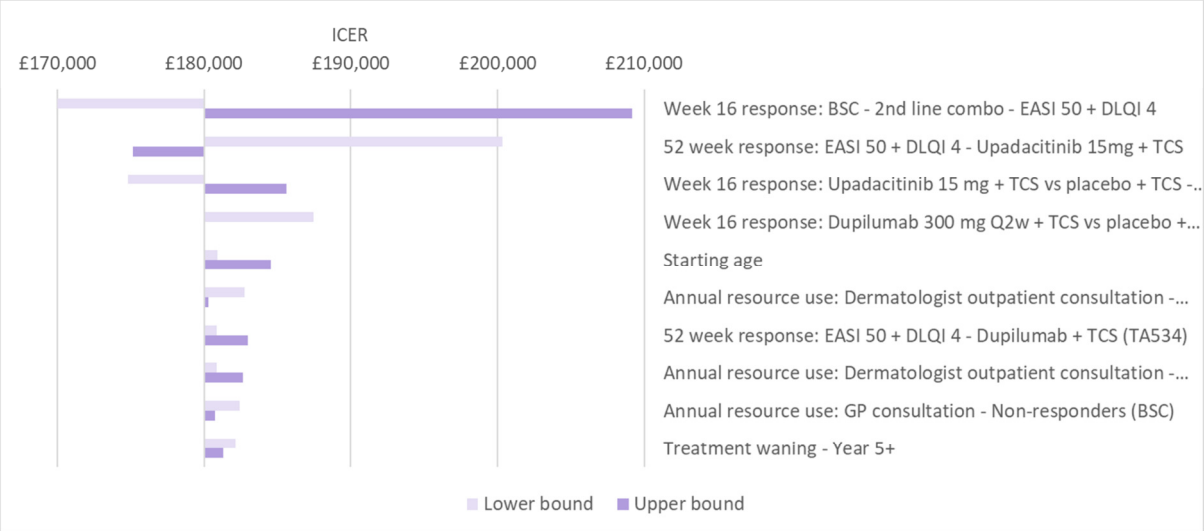

Figure 18. Tornado diagram for upadacitinib 15mg + TCS vs dupilumab + TCS: adults second-line - EASI 50 + DLQI ≥4 - combination therapy (list prices)

Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; ICER, incremental cost-effectiveness ratio; mg, milligram; Q2W, twice weekly; TCS, topical corticosteroids.

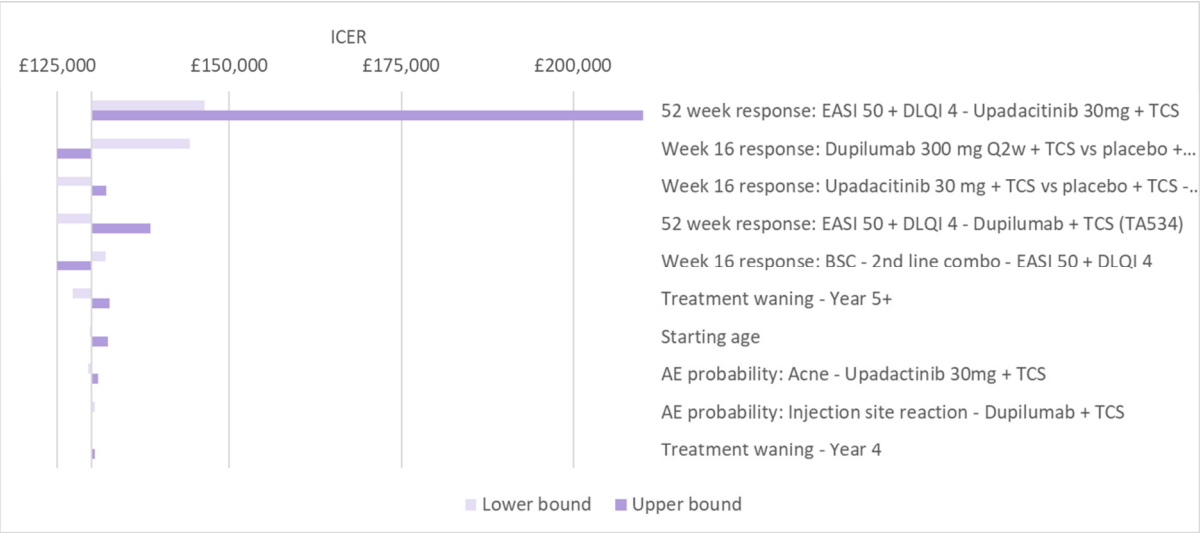

Figure 19. Tornado diagram for upadacitinib 30mg + TCS vs dupilumab + TCS: adults second-line - EASI 50 + DLQI ≥4 - combination therapy (list prices)

Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; ICER, incremental cost-effectiveness ratio; mg, milligram; Q2W, twice weekly; TCS, topical corticosteroids.

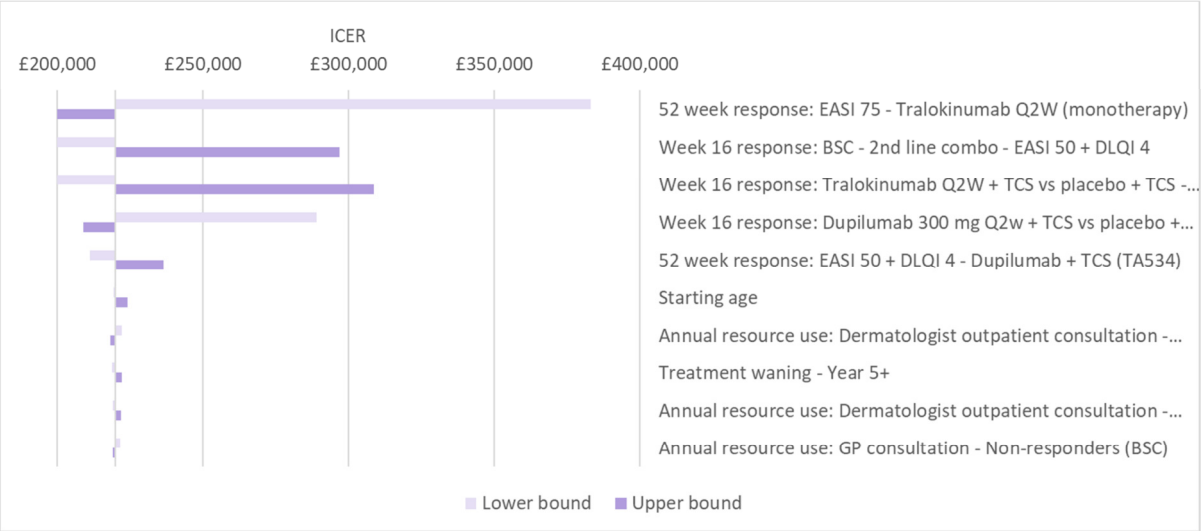

Figure 20. Tornado diagram for tralokinumab + TCS vs dupilumab + TCS: adults second-line - EASI 50 + DLQI ≥4 - combination therapy (list prices)

Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; ICER, incremental cost-effectiveness ratio; mg, milligram; Q2W, twice weekly; TCS, topical corticosteroids.

11.4 Adolescents

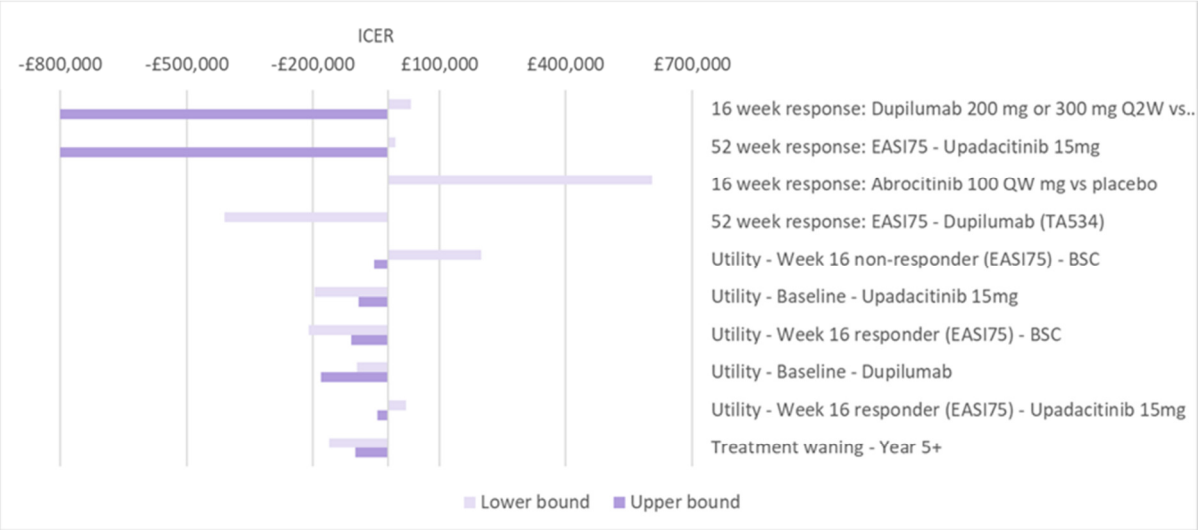

Figure 21. Tornado diagram for abrocitinib 100mg vs dupilumab: adolescents - EASI 75 - monotherapy (list prices)

Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; ICER, incremental cost-effectiveness ratio; mg, milligram; Q2W, twice weekly.

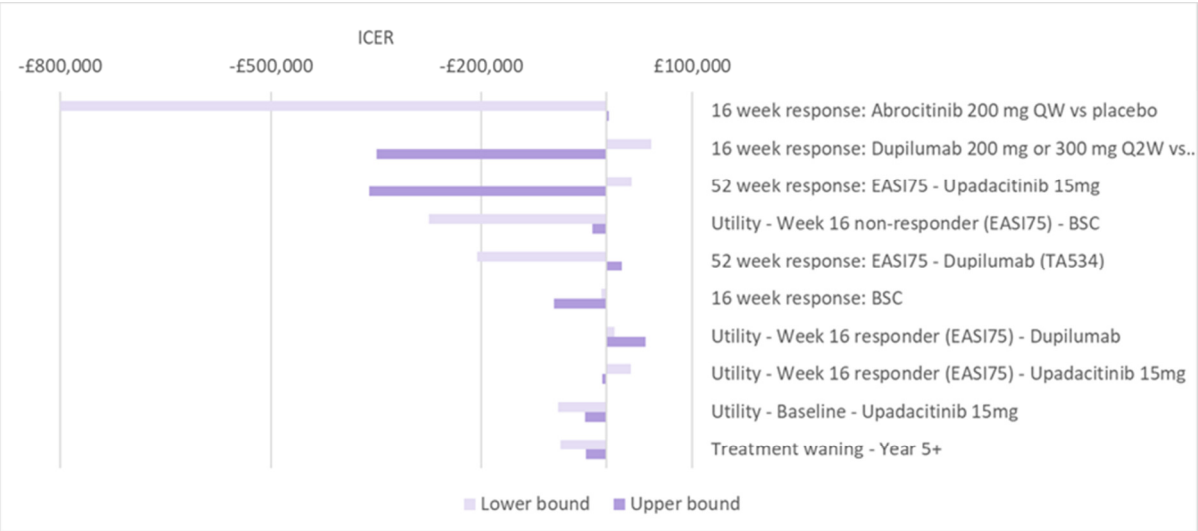

Figure 22. Tornado diagram for abrocitinib 200mg vs dupilumab: adolescents - EASI 75 - monotherapy (list prices)

Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; ICER, incremental cost-effectiveness ratio; mg, milligram; OD, once daily; Q2W, twice weekly.

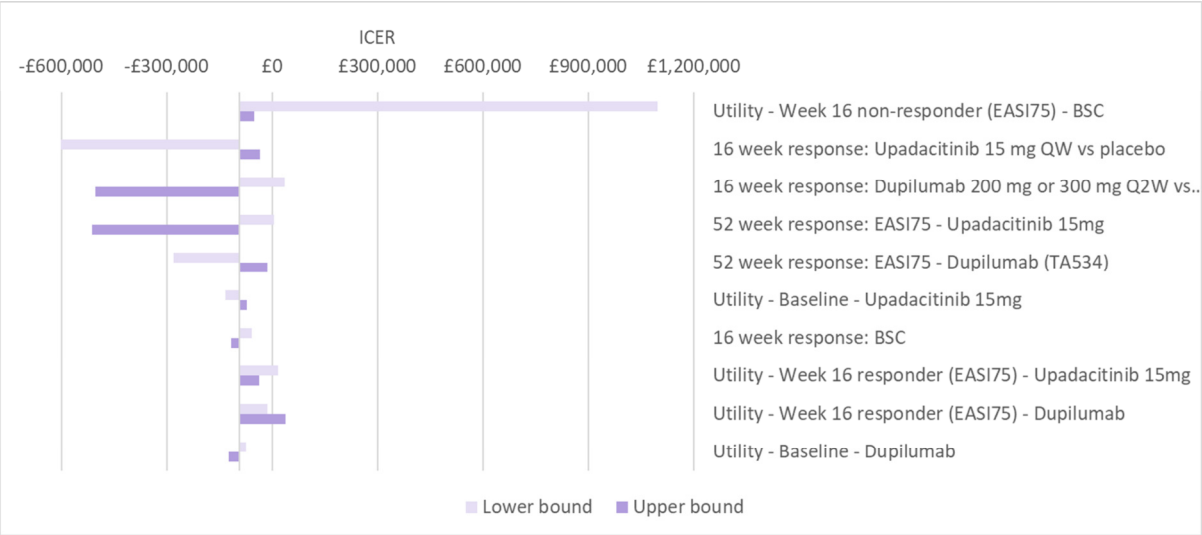

Figure 23. Tornado diagram for upadacitinib 15mg vs dupilumab: adolescents - EASI 75 - monotherapy (list prices)

Abbreviations: BSC, best supportive care; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; ICER, incremental cost-effectiveness ratio; mg, milligram; OD, once daily; Q2W, twice weekly.

12 Probabilistic sensitivity plots

12.1 Adult first-line systemic treatment population

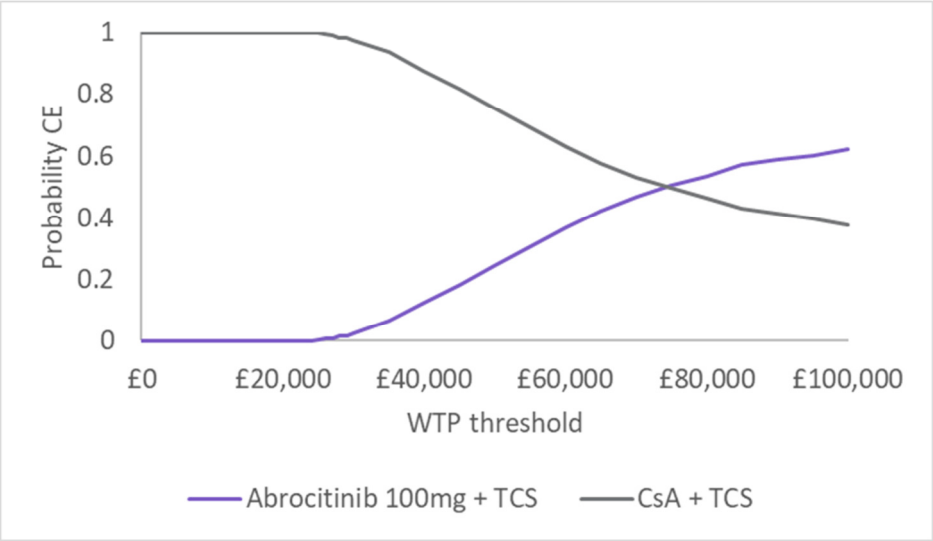

Figure 24. CEAC for abrocitinib + TCS vs CsA + TCS: adults first-line - EASI 75 – combination therapy (list price)

Abbreviations: CEAC, cost-effectiveness acceptability curve; CE, cost-effectiveness; CsA, ciclosporin; EASI, Eczema Area and Severity Index; mg, milligram; TCS, topical corticosteroids; WTP, willingness to pay.

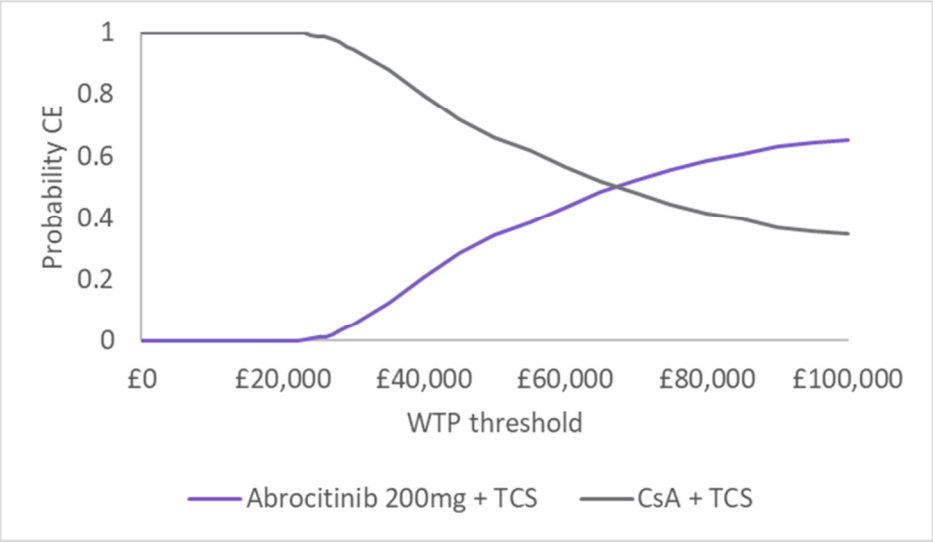

Figure 25. CEAC for abrocitinib 200 mg + TCS vs CsA + TCS: adults first-line - EASI 75 – combination therapy (list price)

Abbreviations: CEAC, cost-effectiveness acceptability curve; CE, cost-effectiveness; CsA, ciclosporin; EASI, Eczema Area and Severity Index; mg, milligram; TCS, topical corticosteroids; WTP, willingness to pay.

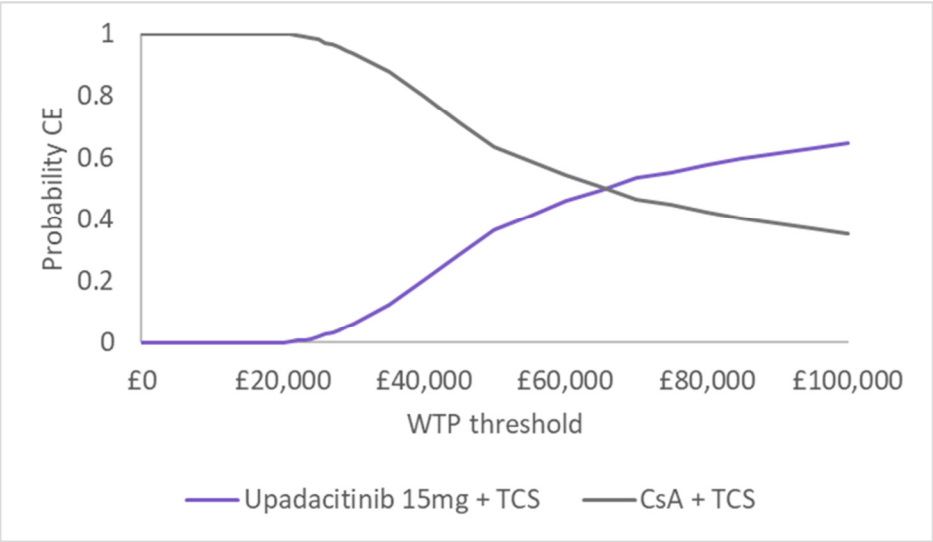

Figure 26. CEAC for upadacitinib 15 mg + TCS vs CsA + TCS: adults first-line - EASI 75 – combination therapy (list price)

Abbreviations: CEAC, cost-effectiveness acceptability curve; CE, cost-effectiveness; CsA, ciclosporin; EASI, Eczema Area and Severity Index; mg, milligram; TCS, topical corticosteroids; WTP, willingness to pay.

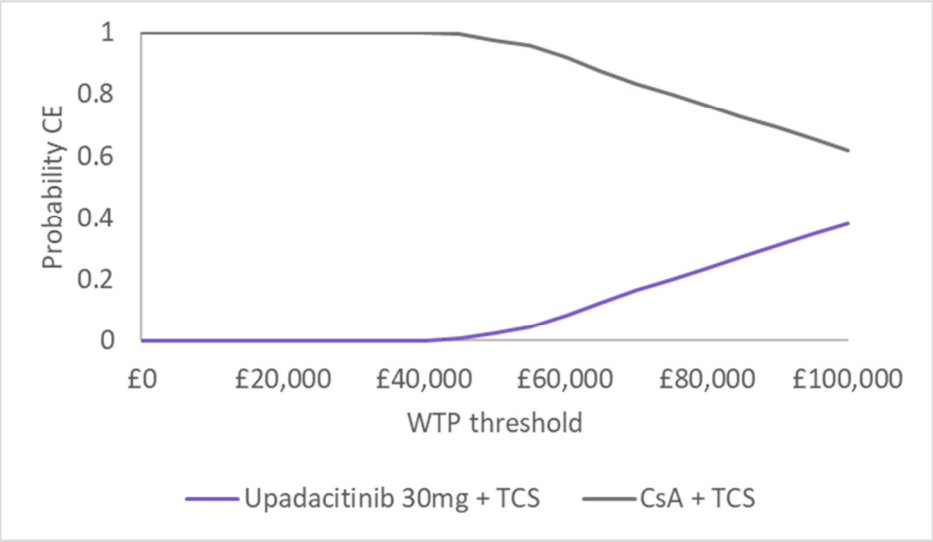

Figure 27. CEAC for upadacitinib 30 mg + TCS vs CsA + TCS: adults first-line - EASI 75 – combination therapy (list price)

Abbreviations: CEAC, cost-effectiveness acceptability curve; CE, cost-effectiveness; CsA, ciclosporin; EASI, Eczema Area and Severity Index; mg, milligram; TCS, topical corticosteroids; WTP, willingness to pay.

12.2 Adult second-line systemic treatment population – monotherapy

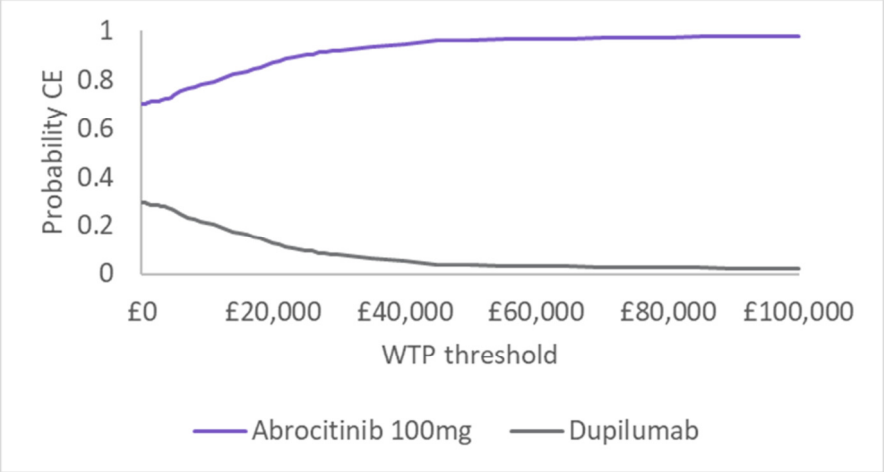

Figure 28. CEAC for abrocitinib 100mg vs dupilumab: adults – second-line - EASI 50 + DLQI ≥4 – monotherapy (list prices)

Abbreviations: CEAC, cost-effectiveness acceptability curve; CE, cost-effectiveness; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; mg, milligram; WTP, willingness to pay.

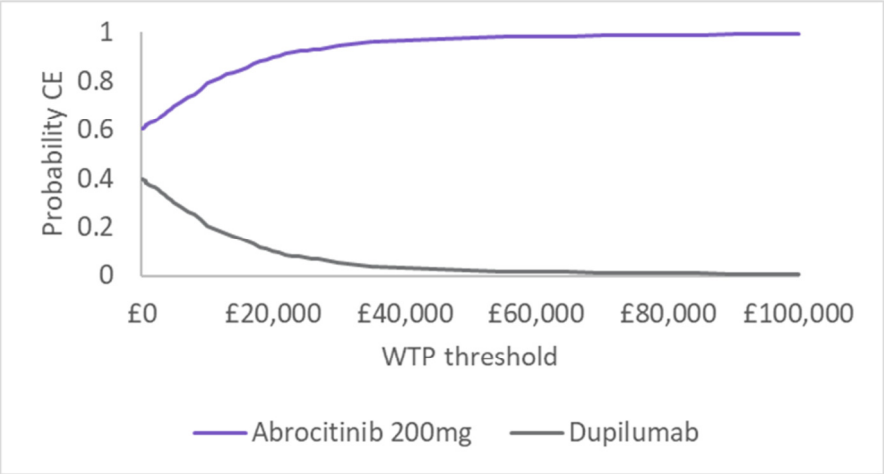

Figure 29. CEAC for abrocitinib 200mg vs dupilumab: adults – second-line - EASI 50 + DLQI ≥4 – monotherapy (list prices)

Abbreviations: CEAC, cost-effectiveness acceptability curve; CE, cost-effectiveness; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; mg, milligram; WTP, willingness to pay.

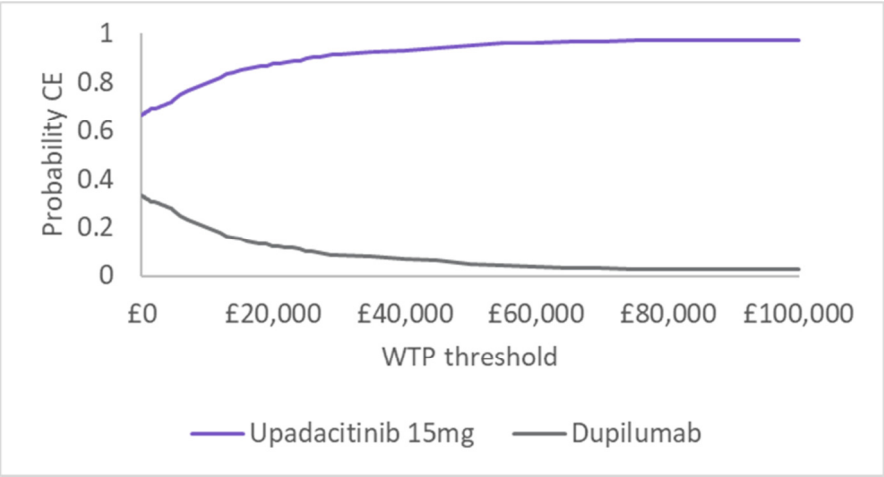

Figure 30. CEAC for upadacitinib 15mg vs dupilumab: adults – second-line - EASI 50 + DLQI ≥4 – monotherapy (list prices)

Abbreviations: CEAC, cost-effectiveness acceptability curve; CE, cost-effectiveness; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; mg, milligram; WTP, willingness to pay.

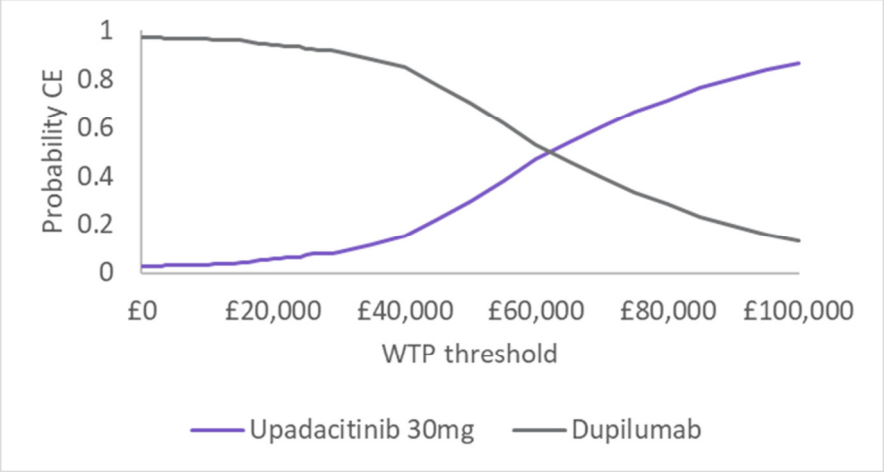

Figure 31. CEAC for upadacitinib 30mg vs dupilumab: adults – second-line - EASI 50 + DLQI ≥4 – monotherapy (list prices)

Abbreviations: CEAC, cost-effectiveness acceptability curve; CE, cost-effectiveness; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; mg, milligram; WTP, willingness to pay.

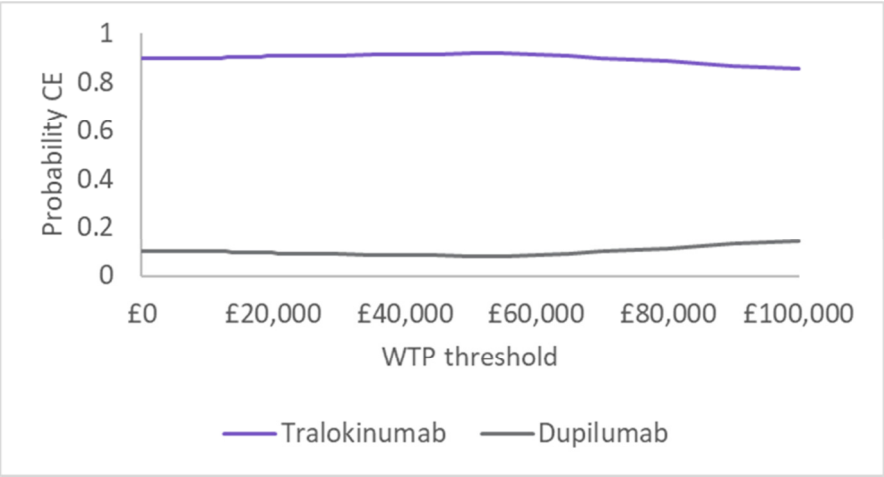

Figure 32. CEAC for tralokinumab vs dupilumab: adults – second-line - EASI 50 + DLQI ≥4 – monotherapy (list prices)

Abbreviations: CEAC, cost-effectiveness acceptability curve; CE, cost-effectiveness; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; mg, milligram; WTP, willingness to pay.

12.3 Adult second-line systemic treatment population – combination therapy

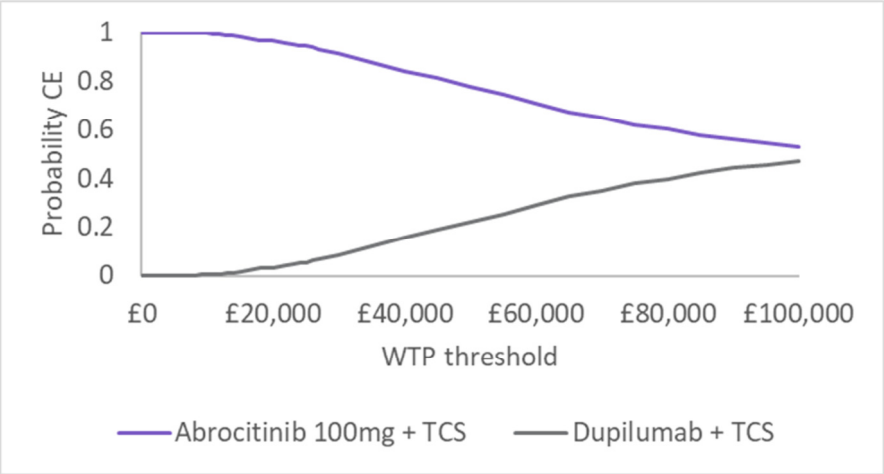

Figure 33. CEAC for abrocitinib 100 mg + TCS vs dupilumab + TCS: adults second-line - EASI 50 + DLQI ≥4 – combination therapy (list price)

Abbreviations: CEAC, cost-effectiveness acceptability curve; CE, cost-effectiveness; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; mg, milligram; TCS, topical corticosteroids; WTP, willingness to pay.

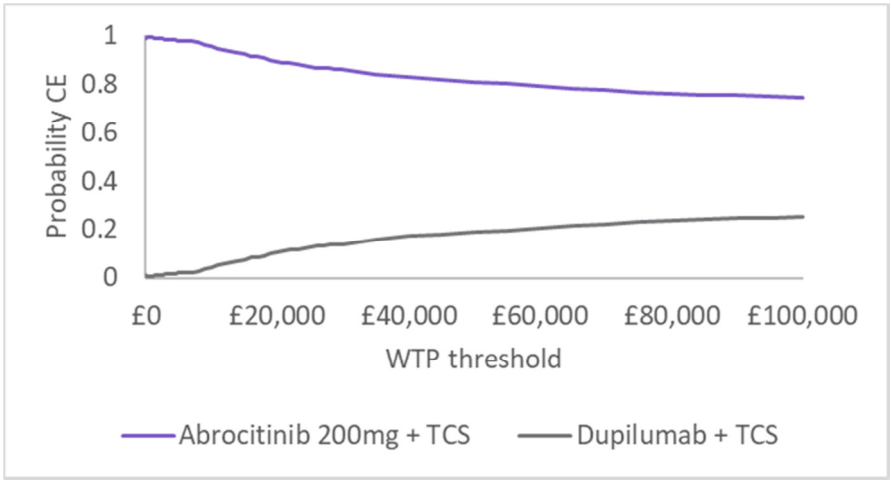

Figure 34. CEAC for abrocitinib 200 mg + TCS vs dupilumab + TCS: adults second-line - EASI 50 + DLQI ≥4 – combination therapy (list price)

Abbreviations: CEAC, cost-effectiveness acceptability curve; CE, cost-effectiveness; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; mg, milligram; TCS, topical corticosteroids; WTP, willingness to pay.

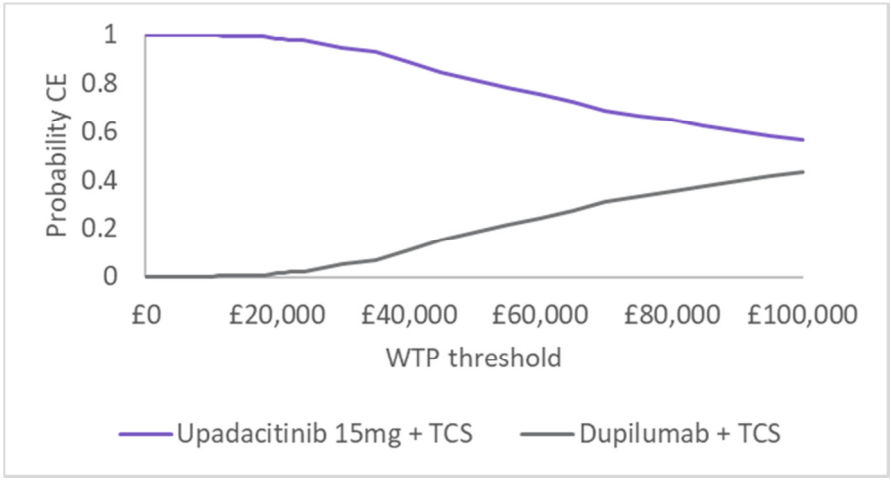

Figure 35. CEAC for upadacitinib 15 mg + TCS vs dupilumab + TCS: adults second-line - EASI 50 + DLQI ≥4 – combination therapy (list price)

Abbreviations: CEAC, cost-effectiveness acceptability curve; CE, cost-effectiveness; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; mg, milligram; TCS, topical corticosteroids; WTP, willingness to pay.

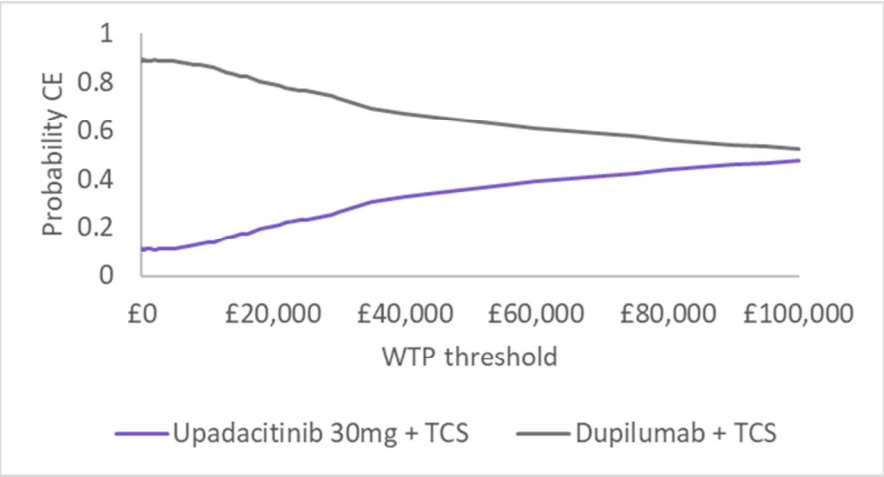

Figure 36. CEAC for upadacitinib 30 mg + TCS vs dupilumab + TCS: adults second-line - EASI 50 + DLQI ≥4 – combination therapy (list price)

Abbreviations: CEAC, cost-effectiveness acceptability curve; CE, cost-effectiveness; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; mg, milligram; TCS, topical corticosteroids; WTP, willingness to pay.

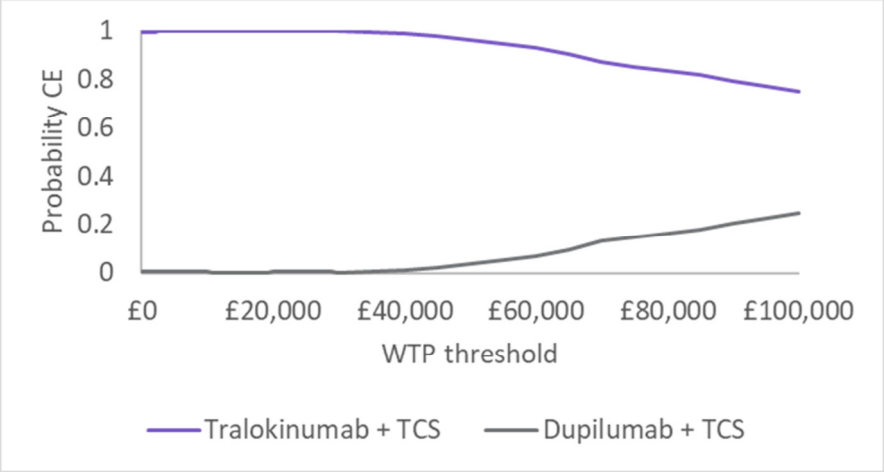

Figure 37. CEAC for tralokinumab + TCS vs dupilumab + TCS: adults second-line - EASI 50 + DLQI ≥4 – combination therapy (list price)

Abbreviations: CEAC, cost-effectiveness acceptability curve; CE, cost-effectiveness; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; mg, milligram; TCS, topical corticosteroids; WTP, willingness to pay.

12.4 Adolescents

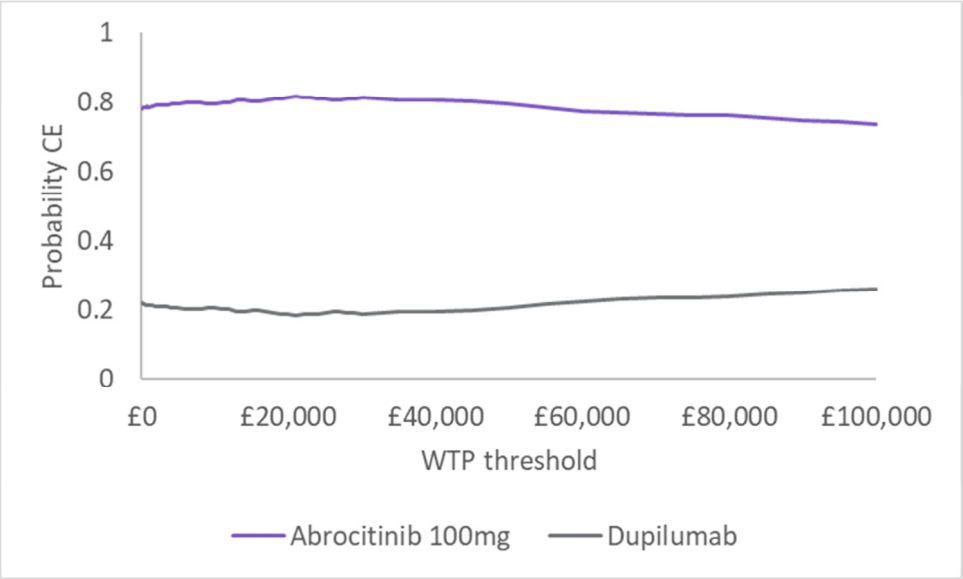

Figure 38. CEAC for abrocitinib 100 mg vs dupilumab: adolescents - EASI 75 - monotherapy (list prices)

Abbreviations: CEAC, cost-effectiveness acceptability curve; CE, cost-effectiveness; EASI, Eczema Area and Severity Index; mg, milligram; WTP, willingness to pay.

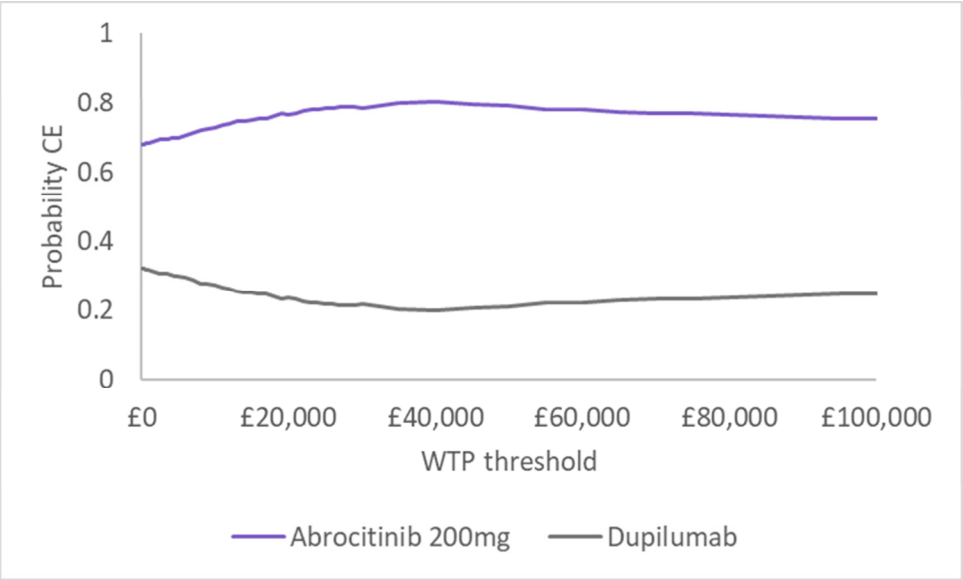

Figure 39. CEAC for abrocitinib 200 mg vs dupilumab: adolescents - EASI 75 - monotherapy (list prices)

Abbreviations: CEAC, cost-effectiveness acceptability curve; CE, cost-effectiveness; EASI, Eczema Area and Severity Index; mg, milligram; WTP, willingness to pay.

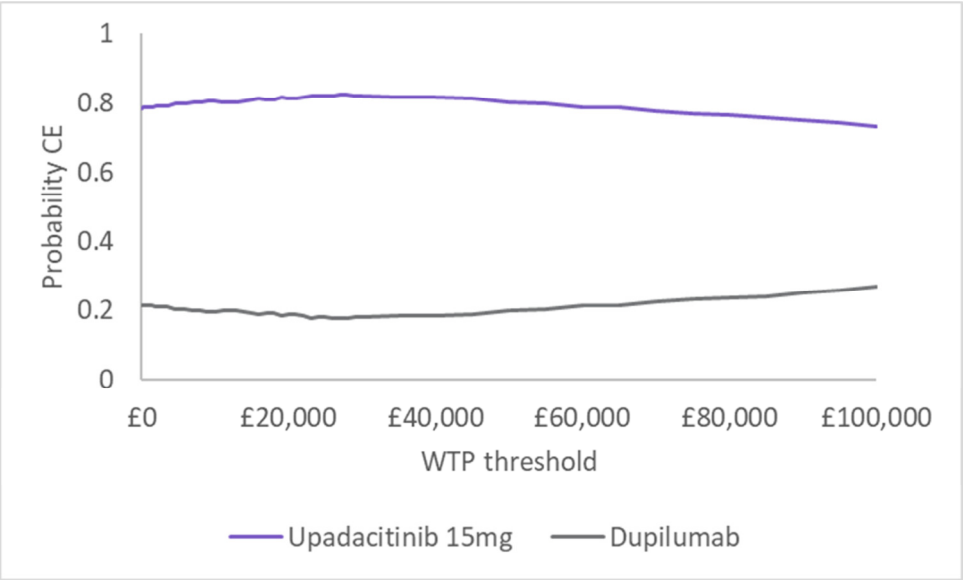

Figure 40. CEAC for upadacitinib 15 mg vs dupilumab: adolescents - EASI 75 - monotherapy (list prices)

Abbreviations: CEAC, cost-effectiveness acceptability curve; CE, cost-effectiveness; EASI, Eczema Area and Severity Index; mg, milligram; WTP, willingness to pay.

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