Table 1a. Summary of biological Therapies for Atopic Dermatitis of IL-4/IL-13 inhibitors

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| type of therapy, source | biological therapies and dose | study region | publish  year | study length and design | no. | baseline severity level | comparison treatment | study results |
| IL-4/IL-13 Inhibitors | | | | | | | | |
| Hamilton *et al*[14] | **dupliumab 150 mg, 300 mg, or placebo, s.c. weekly** | **United States** | **2014** | **4 wk; randomized, double-blinded, placebo-controlled** | **18** | **mean EASI scores:**  **placebo: 23.6**  **150mg dupilumab : 30.5**  **300mg dupilumab:28.2** | **placebo** | **expression of genes upregulated in ad decreased in dupilumab group by 26 % and 65 %, gene downregulated in ad lesions increased by 21 % and 32 % (150 mg and 300 mg, respectively)**  **42.9 % and 85.7 % achieved EASI-50** |
| Halling *et al*[18] | **dupilumab s.c. for 16 weeks, most studies started with 600 mg loading dose followed by a maintenance dose of 300 mg every second week** | **Denmark** | **2020** | **a meta-analysis of 22 RCTs** | **22 studies, 3303 patients** | **NA** | **various** | **after 16 weeks of dupilumab therapy, the pooled proportion of patients achieving EASI-50, EASI-75, and EASI-90 was 85.1 %, 59.8 %, and 26.8 %. the weighted mean reduction in EASIEASI was 69.6 %.** |
| Ferrucci *et al*[19] | **dupilumab s.c. for 16 weeks, most studies started with 600 mg loading dose followed by a maintenance dose of 300 mg every other week** | **Italy** | **2020** | **16 wk; observational study** | **117** | **baseline EASI**  24 | **NA** | **a significant response to dupilumab in EASI-75 at week 4. reductions in EASI, DLQI, POEM, HADS, NRS-itch, and VASs-sleep were found between week 4 and week 16. (p<0.0001 for all)** |
| Deleuran *et al*[20] | **dupilumab s.c. 300 mg weekly for 76 weeks** | **Denmark** | **2019** | **76wk; open-label extension (OLE) study** | **1491** | **adult patients who participated in phase 1-3 clinical trials of dupilumab in ad** | **NA** | **92.9 % of patients remained on cut off. mean EASIEASI at week 76 was 3.11 and continuous progressive improvement inEASI from week 2 to week 24. 70.7 % patients had** 1 AE, <5 % reported SAE |
| Cork *et al*[21] | **dupilumab s.c. 2 mg/kg or 4 mg/kg weekly for 4 weeks with 8 weeks follow-up** | **United Kingdom** | **2020** | **8wk; pharmacokinetic sampling, 4wk+8wk phase 2a and ole open-label study; 52wk long-term follow-up** | **40 in phase 2a and 36 in OLE** | **pediatric patients (aged** to <18 years**) investigator global assessment (IGA) of 3 or4** | **NA** | **mean dupilumab concentration in serum at week 48 (ole) were 74mg/l and 16160 mg/l, in 2mg group and 4 mg group, respectively. EASI scores improved further at week 52 85 % 12 %versus 84 %20 %.** |
| Cork *et al*[22] | **dupilumab s.c. 2 mg/kg or 4 mg/kg weekly for 4 weeks with 8 weeks follow-up** | **United Kingdom** | **2020** | **8wk; pharmacokinetic sampling, 4wk+8wk phase 2a and ole open-label study; 52wk long-term follow-up** | **37 in phase 2a and 33 in OLE** | **pediatric patients (aged** to <12 years**) investigator global assessment (IGA) of 3 or4** | **NA** | **mean dupilumab concentration in serum at week 24-48 (ole) were 61-77 mg/l and 143-181 mg/l, in 2 mg group and 4 mg group, respectively. EASI and pp-NRS scores improved further 37 %/33 %versus 17 %/20 % (week 2) and 92 %/84 % versus 70 %/58 % (week52).** |
| Simpson *et al*[25] | **lebrikizumab s.c. 125 mg single dose (sd), 250 mg sd, 125 mg once every 4 weeks(q4w), or placebo q4w for 12 weeks** | **Austria** | **2018** | **12wk+8wk follow-up randomized, placebo-controlled phase 2 trial** | **209** | **moderate-to-severe ad defined as EASI** 14, IGA3, BSA10%, VAS3 | **placebo, topical corticosteroids (TCS) apply as needed** | **at week 12, significantly more patients achieved EASI-50 with 125 mg q4w (82.4%; p=0.026). patients got sd showed no statistically significant improvements in EASI-50.** |
| Guttman-Yassky *et al*[26] | **lebrikizumab s.c. 125 mg q4w with 250 mg loading dose (ld), 250 mg q4w with 500 mg (ld), 250 every 2 weeks (q2w) with 500 mg ld at baseline and week 2, or placebo q2w** | **United States** | **2020** | **16 wk; phase 2b double-blind, placebo-controlled dose-ranging randomized clinical trial** | **280** | **adults moderate-to-severe ad patients defined EASI** 16, IGA 3, BSA10% | **placebo, TCS apply as needed** | **lebrikizumab groups showed dose-dependent, statistically significant improvement at week 16 versus placebo in EASI (-41.1 %): 125 mg q4w -62.3 %, 250 mg q4w -69.2 %, 250 mg q2w -72.1 %. the most adverse events were herpesvirus infection 3.5 %, and conjunctivitis 2.6 %.** |
| Wollenberg *et al*[30] | **tralokinumab s.c. 45, 150, 300 mg or placebo, q2w for 12 weeks** | **United States** | **2018** | **12 wk; phase 2b double-blind, placebo-controlled randomized clinical trial** | **204** | **adults, moderate-to-severe ad patients defined EASI** 12, IGA 3, BSA10%, SCORAD25 | **placebo, with concomitant TCS** | **300 mg group significantly improved in EASI versus placebo (mean difference -4.94; p=0.01) and IGA 26.7 % versus 11.8 %. upper respiratory tract infection was reported as the most frequent treatment-emergent ae 3.9 % in each group.** |
| Pharma leo[31]  Nct03160885 | **tralokinumab, s.c. 300 mg q2w, 300 mg q4w, and placebo** | **United States** | **2020** | **16 wk; phase 3 double-blinded placebo-controlled randomized clinical trial followed by the 42-week open-label observational study** | **794** | **adult ad patients with mean EASI 32.2, DLQI 17.7, BSA 52.7 %.** | **placebo** | **at week 16, 22.2 % of 300 mg q2w patients achieve IGA 0 or 1 versus 10.9 % in the placebo group. 32.3 % of patients achieved EASI-75 in the 300 mg q2w group versus 11.4 %in the placebo group. at week 52, 55.8 % and 51.4 % of patients achieved EASI-75 in 300 mg q2w and q4w groups.** |

Table 1b Summary of biological Therapies for Atopic Dermatitis in JAK inhibitors

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| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Type of Therapy, Source | Biological Therapies and Dose | Study Region | Publish  Year | Study Length and Design | No. | Baseline Severity Level | Comparison Treatment | Study Results |
| Bissonnette *et al*[42] | **2 % Tofacitinib ointment, tropical, twice daily** | **Canada** | **2016** | **4 wk; phase 2a, randomized, double-blind, vehicle-controlled study** | **69** | **Mean EASI 14.7** | **Vehicle ointment** | **The change of EASI percentage at week 4 was significantly greater for tofacitinib (-81.7 %) vs. vehicle (-29.9 %) (p < 0.001)** |
| Guttman-Yassky *et al*[44] | **Baricitinib, oral, 2 mg, 4 mg, and placebo once daily for 16 weeks** | **United States and Japan** | **2018** | **16 wk; phase 2, randomized, double-blind, placebo-controlled study** | **124** | **Moderate-to-severe AD defined as EASI** 12, BSA10%, diagnosis years | **0.1% Triamcinolone cream applied 4 weeks prior. Placebo with TCS as needed** | **More 4 mg baricitinib patients achieved EASI-50 versus placebo (61 % vs 37 %, p=0.027) at week 16. Pruritus and sleep loss also improved.** |
| Eli L company[45]  NCT03334396 | **Baricitinib, oral, 1 mg, 2 mg, 4 mg, and placebo once daily for 16 weeks** | **Multiple** | **2020** | **16wk; phase 3, randomized, double-blind, placebo-controlled study** | **660** | **Moderate-to-severe Adult AD patients.** diagnosis of year | **placebo** | **Percentage of patients achieving IGA 0 or 1 or with** 2 improvement: 4.8 %, 11.8 %,11.4 %, and 16.8 % in placebo, 1mg, 2mg, 4mg group, respectively. More patients achieve EASI-75 in 4mg group. (24.8 %) 16.0 % reached EASI-90 at week 16. |
| Eli L company[46]  NCT03334422 | **Baricitinib, oral, 1 mg, 2 mg, 4 mg, and placebo once daily for 16 weeks** | **Multiple** | **2020** | **16wk; phase 3, randomized, double-blind, placebo-controlled study** | **615** | **Moderate-to-severe Adult AD patients.** diagnosis of year | **placebo** | **Percentage of patients achieving IGA 0 or 1 or with** 2 improvement: 4.5 %, 8.8 %,10.6 %, and 13.8 % in placebo, 1 mg, 2 mg, 4 mg group, respectively. More patients achieve EASI-75 in 4 mg group. (21.1%) |
| Eli L company[47]  NCT037333301 | **Baricitinib, oral, 2 mg, 4 mg, and placebo in combination with TCS once daily for 16 weeks** | **Multiple** | **2020** | **16wk; phase 3, randomized, double-blind, placebo-controlled study** | **329** | **Moderate-to-severe Adult AD patients.** | **Placebo in combination with TCS** | **Percentage of patients achieving IGA 0 or 1 or with** 2 improvements: 14.7 %, 23.9 %, and 30.6 % in placebo, 2 mg, 4 mg group, respectively. More patients achieve EASI-75 in the 4 mg group. (47.7 %) |
| Gooderham *et al*[52] | **Abrocitinib, oral, 200 mg, 100 mg, 30 mg, 10 mg, or placebo, once daily for 12 weeks** | **Multiple** | **2019** | **12wk; phase 2b, randomized, double-blinded, placebo-controlled, parallel-group trial** | **267** | **Adult Moderate-to-severe AD defined as EASI** 12, BSA10%, IGAdiagnosis years | **placebo** | **At week 12, 43.8 %(p < 0.001) patients in 200 mg group; 29.6 %(p<0 .001) in 100 mg group; 5.8% in placebo group achieve IGA 0 or 1. EASI reduction in 200 mg and 100 mg groups is 59 % vs. 35.2 %.** |
| Simpson *et al*[53] | **Abrocitinib, oral, 200 mg, 100 mg, or placebo, once daily for 12 weeks** | **Multiple** | **2020** | **12wk; phase 3, randomized, double-blinded, placebo-controlled, parallel-group trial** | **387** | **Patients aged** 12 years with **Moderate-to-severe AD defined as EASI** 16, BSA10%, IGA**NRS-itch**4 | **placebo** | **At week 12, 44 %, 37 %, and 8 % patients in 200 mg, 100mg, and placebo group achieve IGA 0/1, respectively. (p < 0.0001) 63 %, 40 %, 12 % patients achieve EASI-75. 3 %patients reported AE.** |
| Silverberg *et al*[54] | **Abrocitinib, oral, 200 mg, 100 mg, or placebo, once daily for 12 weeks** | **multiple** | **2020** | **12wk; phase 3, randomized, double-blinded, placebo-controlled, parallel-group trial** | **391** | **Patients aged** 12 years with **Moderate-to-severe AD defined as EASI** 16, BSA10%, IGA**NRS-itch**4 | **placebo** | **At week 12, 48.1 %, 28.4 %, and 9.1 % patients in 200 mg, 100 mg, and placebo group achieve IGA 0/1, respectively. (p<0.0001) 61 %, 44.5 %, 10.4 % patients achieve EASI-75. Greater proportion with abrocitinib reached EASI-90.** |
| Guttman-Yassky *et al*[55] | **Upadacitinib, oral, 7.5, 15, 30 mg or placebo, once daily for 16 weeks** | **multiple** | **2019** | **16wk; randomized, double-blinded, placebo-controlled, parallel-group trial** | **167** | **Adult Moderate-to-severe AD defined as EASI** 12, BSA 10 %, IGA diagnosis years | **placebo** | **At week 16, 39%, the improvement of EASI: 62 %, 74 % patients for the 7.5, 15, 30 mg groups, respectively. (p = 0.03, < 0.001, and < 0.001) SAE occurred in 4.8 %, 2.4 % 0% in the three groups.** |
| Kim *et al*[56] | **Ruxolitinib, 1.5 % twice daily (BID), 1.5 % once daily (QD), vehicle, or 1 % triamcinolone cream for 4 weeks** | United states and Canada | **2020** | **4wk; phase 2 randomized, double-blinded, placebo-controlled, parallel-group trial** | **307** | **Adult Mild-to-moderate AD defined as** BSA3-20%, IGA2 or , EASI7 | **Vehicle**  **1% triamcinolone cream** | **At week 4, 1.5 % BID provided greatest improvement in EASI 71.6 % (p<0.0001) and IGA 38.0 %(p < 0.0001). Rapidly reduction in VAS occurred within 36 hours.** |
| Nakagawa *et al*[64] | **0.5 % Delgocitinib ointment, or vehicle ointment, BID, for 4 weeks+24 weeks (OLE)** | **Japan** | **2019** | **4wk; phase 3 randomized, double-blinded, vehicle-controlled study; 24 wk; OLE** | **158 for trial and 138 completed OLE** | **Adult Mild-to-moderate AD defined as** BSA10-30%, IGA3 or 4 mEASI | **Vehicle ointment** | **At week 4, 44.3 % vs 1.7 % (P < 0.001) in modified EASI (mEASI) in the delgocitinib group and placebo group, respectively. The improvement of mEASI was maintained through week 24.** |
| Nakagawa *et al*[65] | **0.5 % Delgocitinib ointment, BID, for 52 weeks** | **Japan** | **2020** | **52wk; long-term observational study** | **506** | **Adult Mild-to-moderate AD defined as** BSA5-30%, IGA2 or 4 | **NA** | **Improvement of mEASI was maintained throughout the treatment period. Common AE was nasopharyngitis, contact dermatitis, acne, and folliculitis.** |
| Nakagawa *et al*[66] | **0.25 %,0.5 % Delgocitinib ointment, or vehicle ointment, BID, for 4 weeks** | **Japan** | **2019** | **4wk; phase 2 randomized, double-blinded, placebo-controlled, parallel-group trial** | **98** | **Patients aged** 12 years; **Mild-to-moderate AD defined as** BSA5-30%, IGA2, mEASI 5 | **Vehicle ointment** | **At week 4, 52.4 % vs 61.8 % (P<0.001) in modified EASI (mEASI) in 0.25 % and 0.5 %delgocitinib group, respectively, comparing to 4.8 % in placebo group. (P < 0.001)** |

Table 1c Summary of biological Therapies for Atopic Dermatitis in anti-IL-13 antibodies

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| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Type of Therapy, Source | Biological Therapies and Dose | Study Region | Publish  Year | Study Length and Design | Patients, No. | Baseline Severity Level | Comparison Treatment | Study Results |
| Ruzicka *et al*[70] | **Nemolizumab, s.c. 0.1 mg, 0.5 mg, 2.0 mg/kg or placebo Q4W or 2.0 mg/kg Q8W for 12 weeks** | **United states, Japan, and Europe** | **2017** | **12wk; phase 2 randomized, double-blinded, placebo-controlled, parallel-group trial** | **216** | **Mean EASI 30.0, BSA 44.8%, VAS 75.1** | **Placebo** | **At week 12, changes on pruritus VAS were -43.7 % in 0.1mg group, -59.8 % in 0.5 mg group and -63.1% in 2.0 group. Changes on EASI were -23.0 %, -42.3 %, and -40.9 %, respectively.** |
| Mihara *et al*[71] | **Nemolizumab, s.c. 0.1mg, 0.5 mg, 2.0 mg/kg or placebo Q4W for 12 weeks or 2.0 mg/kg every 8 weeks (Q8W) +52 weeks (OLE)** | **United states, Japan** | **2019** | **12wk; phase 2 randomized, double-blinded, placebo-controlled trial; 52 wk OLE** | **264 in phase 2 RCT and 138 in OLE** | **Mean EASI 31.0, BAS 45.0%, pruritis VAS 78.0** | **NA** | **Improvements were sustained through week 64 on reduced EASI and sleeping and pruritis VAS.** |
| Silverberg *et al*[72] | **Nemolizumab, s.c. placebo, 10 mg, 30 mg, and 90 mg Q4W for 24 weeks** | **multiple** | **2019** | **24wk; phase 2b randomized, double-blinded, placebo-controlled, study** | **226** | **Adult Moderate-to-severe AD defined as EASI** 12, IGA3 to 4 NRS-itch 7 | **placebo** | **At week 24, 30 mg dose shows most effective with reduced EASI -52.1 %, p=0.16. IGA 0/1 rates were higher for 30 mg versus placebo at week 16 (33.3 %p=0.008).** |

Table 1Table 1d Summary of biological Therapies for Atopic Dermatitis in other targeted therapies

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| Type of Therapy, Source | Biological Therapies and Dose | Study Region | Publish  Year | Study Length and Design | No. | Baseline Severity Level | Comparison Treatment | Study Results |
| Anti-IL-22 antibodies | | | | | | | | |
| Guttman-Yassky et al[74] | **Fezakinumab, i.v. every 2 weeks for 10 weeks, a follow-up to week 20** | **United states** | **2018** | **20wk; phase 2b randomized, double-blinded, placebo-controlled, study** | **60** | **Adult Moderate-to-severe AD defined as IGA** , SCORAD | **placebo** | **In week 12, the mean declines in SCORAD for fezakinumab is 13.82.7 and 8.03.1in placebo. Progressive improvement after the last dosing at week 10 until week 20.** |
| Anti-IL-33 antibodies | | | | | | | | |
| Chen et al [78] | **Etokimab, i.v. 300 mg single dose** | **United states** | **2019** | **Phase 2a, Unblinded Observational study** | **12** | **EASI** 14 | **NA** | **At day 29, 83 % of patients achieved EASI-50 and 33 % achieved EASI-75** |
| Thymic stromal lymphopoietin inhibitor (TSLP) | | | | | | | | |
| Simpson et al[80] | **Tezepelumab, s.c. 280 mg, or placebo, Q2W, plus TCS for 16 weeks** | **United Kingdom** | **2019** | **16 wk, phase 2a, randomized, double-blind, placebo-controlled study** | **113** | **Adult Moderate-to-severe AD defined as IGA** , SCORAD, EASI12, BSA10% | **Placebo plus TCS** | **At week 12, 64.7 % versus 48.2 %(p=0.091) achieved EASI 50 in tezepelumab plus TCS group and Placebo Plus TCS group, respectively. Further improvement was sustained at week 16.** |
| OX40 antibody | | | | | | | | |
| Guttman-Yassky et al[84] | **GBR 830, i.v. 10 mg/kg, and placebo on day 1 and day 29** | **United States and Canada** | **2019** | **phase 2a, randomized, double-blind, placebo-controlled study** | **64** | **Adult Moderate-to-severe AD defined as** EASI12, BSA10 % | **Placebo** | **At day 71, patients achieve EASI 50 were 76.9 % versus 37.5 % in GBR 830 group and placebo group.** |
| H4R-antagonist | | | | | | | | |
| Murata et al[89] | **JNJ-39758979, orally, 300 mg, 100 mg. or placebo once daily for 6 weeks** | **Japan** | **2014** | **6wk; phase 2a, randomized, double-blind, placebo-controlled study** | **105** | **Adult Moderate-to-severe AD defined as** BSA10-50 %, IGA 3 | **Placebo** | **Numerical improvements in median EASI were observed at week 6, with 100 mg (-3.7), 300 mg (-3.0), placebo (-1.3).** |

Table 2 Abbreviations of the tables

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| **AD=atopic dermatitis**  **EASI=Eczema Area and Severity Index, IGA= Investigator Global Assessment, BSA= body surface area, VAS= Pruritus Visual Analog Scale**  **DLQI= Dermatology Life of Quality Index, SCORAD= SCORing of Atopic Dermatitis**  **POEM= Patient-Oriented Eczema Measure**  **HADS=Hospital Anxiety and Depression Scale**  **NRS-itch=Peak Pruritus Numerical Rating Scale**  **AE= adverse event, SAE= severe adverse event** |