Methods Section

The EuroGuiDerm guideline on AE was developed in accordance with the EuroGuiDerm Methods Manual v1.3. For the detailed description of the guideline development process as well as an overview of the evidence referred to, please see the EuroGuiDerm guideline on AE Methods Report and the Evidence Report.

Both are available alongside the guideline document on the EDF website: https://www.edf.one/de/home/Guidelines/EDF-EuroGuiDerm.html

Nomination of experts, management of conflicts of interest

The guideline development group comprised 26 experts from twelve countries nominated by EuroGuiDerm national partner societies or the two guideline co-coordinators (AW and CF). All nominations were reviewed and confirmed by the EuroGuiDerm Board of Directors. In addition, three patient representatives participated in the guideline development.

38% of the experts declared personal-financial interests (for details on classification see EuroGuiDerm Methods Manual v1.3.). *These members were neither eligible to take the lead in a respective working group nor for voting on recommendations pertaining to systemic treatment and on the stepped-care plan.*

Development of the guideline and the consensus process

The chapters of the guideline and the recommendations had been developed by the group members, who formed a number of working groups. Each chapter and all recommendations were reviewed, discussed and amended where appropriate by the entire group. All texts and recommendations were voted on with a necessary minimal agreement of >50% during the consensus conferences. AN facilitated all four consensus conferences using a structured consensus technique. Both internal and external review were conducted. Dissemination and implementation plans were developed. For more details, see Methods Report.

The wording of the recommendations was standardized (as suggested by the GRADE Working Group [1]).

Wording of recommendations

Strength	Wording	Symbols	Implications
Strong recommendation **for** the use of an intervention	'We recommend . . .'	↑↑	We believe that all or almost all informed people would make that choice.
Weak recommendation **for** the use of an intervention	'We suggest . . .'	↑	We believe that most informed people would make that choice, but a substantial number would not.
No recommendation with respect to an intervention	'We cannot make a recommendation with respect to . . .'	0	At the moment, a recommendation in favour or against an intervention cannot be made due to certain reasons (e.g. no reliable evidence data available, conflicting outcomes, etc.)
Weak recommendation	'We suggest against . . .'	↓	We believe that most informed people would make a choice against that intervention, but a substantial number would not.

against the use of an intervention			
Strong recommendation **against** the use of an intervention	'We recommend against . . .'	↓↓	We believe that all or almost all informed people would make a choice against that intervention.

The recommendation are presented throughout this guideline as displayed below: alongside the wording of the recommendations the arrow(s) and colors indicate the direction and the strength of each recommendation. The rate of agreement (consensus strength) is also displayed as the actual percentage and in form of a category-type pie chart. For all systemic drugs, we added the dosages (according to the European Medical Agency). Additionally, the certainty of evidence was added where applicable (bold – significant difference; Associations are reported in line with Drucker et. al[2]).

We **recommend** dupilumab in AE patients who are candidates for systemic treatment.	↑↑	100%  Evidence and consensus based, see Evidence Report

dupilumab: in licence for ≥ 6 months of age;
age 6 months-6 years: from 5kg <15 kg 200 mg Q4W, 15kg <30 kg 300 mg Q4W
age 6-11: from 15kg <60kg, initially 300 mg s.c. day 1 and 15 followed by 300 mg Q4W, when ≥60 kg, initially 600 mg s.c. day 1 followed by 300 mg Q2W
age 12-17: <60 kg: initially 400 mg s.c. day 1 followed by 200 mg Q2W, when ≥60 kg: initially 600 mg s.c. day 1 followed by 300 mg Q2W
adults: initially 600 mg s.c. day 1 followed by 300 mg Q2W

Certainty of evidence: Network meta-analysis from 2024[3,4]:

Short term (up to 16 weeks) vs placebo (NMA medications used in clinical practice)

⊕⊕⊕⊕ HIGH for mean difference **EASI** -10.5 (-11.9, -9.2); **POEM** -7.3 (-8, -6.7); **peak pruritus NRS** -2.1 (-2.3, -1.8); **DLQI** (-4.9 (-5.4, -4.3)

For dupilumab versus other drugs, see Evidence Report

Update 2025

The third update of the guideline was initiated to incorporate nemolizumab. As nemolizumab received EMA approval after the previous guideline update, it had not yet been addressed in earlier versions. In addition, the guideline group decided to include guidance on vaccination prior to initiating systemic therapy and during ongoing systemic treatment, as well as guidance on switching systemic therapies and adjusting treatment frequency and intervals.

Furthermore, an update of the network meta-analysis by Drucker et al. was published in May 2025.[5] The updated data from the network meta-analysis from May 2025 were summarised in an updated evidence report.

The new evidence from the updated network meta-analysis, and the updated chapters on systemic treatment and on pregnancy, breastfeeding, and family planning and new versions of the stepped-care plans and drug tables were presented to the GDG and put to the vote in an online survey.

All experts were asked to vote (agree, abstain, reject). Alternative suggestions could be entered as a reply option. Experts could not see how others had voted. Only the EuroGuiDerm team had access to the results. All authors could participate but the votes of those with personal financial conflicts of interest did not count.

All recommendations that did not achieve full approval in the online vote, as well as background-text changes requiring further discussion, were reconsidered during an online consensus conference on 30 September 2025. The process was moderated by Ricardo N. Werner, a certified guideline facilitator, using the nominal group technique. He first presented the anonymised results, comments, and suggested modifications from the pre-voting survey, then opened the floor for discussion. Benefits, harms, processes, and procedures were discussed in detail. Final voting followed, with experts choosing to agree, disagree, or abstain for each recommendation. All GDG members were asked to participate. As before, the definitive evaluation included only the votes of members without COIs.

For the second update in 2025, the group comprised experts from twelve countries. Thirteen experts (46.4%) declared personal financial conflicts of interest, see below.

Title	First name	Last name	Relevant personal- financial conflicts of interest
	Bernd	Arents	None
Dr.	Nora	Aszodi	None
Prof. Dr.	Sebastien	Barbarot	Abbvie, Almirall, Galderma, Lilly, Leo, Pfizer, Sanofi
Prof. Dr.	Thomas	Bieber	Abbvie, Almirall, Galderma, Lilly, Leo, Pfizer, Sanofi
Dr.	Helen A.	Brough	Leo
Prof. Dr.	Piergiacomo	Calzavara Pinton	None
Dr.	Stéphanie	Christen-Zäch	None
Dr.	Mette	Deleuran	Abbvie, Almirall, Lilly, Leo, Pfizer, Sanofi
Prof. Dr.	Carsten	Flohr	Almirall, Leo, Pfizer, Sanofi
Dr.	Nicole	Fosse	None
Dr.	Krisztián	Gáspár	Abbvie, Sanofi
Dr.	Louise	Gerbens	None
Prof. Dr.	Uwe	Gieler	None
Prof. Dr.	Giampiero	Girolomoni	Abbvie, Almirall, Lilly, Leo, Pfizer, Sanofi
Prof. Dr.	Stamatis	Gregoriou	None

	Holland	Suzi	None
Prof. Dr.	Charlotte	Mortz	None
MD PhD	Uffe	Nygaard	None
MD PhD	Eva Maria	Rehbinder	None
Prof. Dr. Dr.	Johannes	Ring	Abbvie, Sanofi
Dr.	Mariateresa	Rossi	None
Dr.	Esther	Serra-Baldrich	Abbvie, Almirall, Galderma, Lilly, Leo, Pfizer, Sanofi
Prof. Dr.	Dagmar	Simon	None
Prof. Dr.	Zsuzsanna	Szalai	None
Prof. Dr.	Jacek C.	Szepietowski	Almirall, Leo, Pfizer, Sanofi
Dr.	Antonio	Torrelo	Abbvie, Lilly, Pfizer, Sanofi
Prof. Dr.	Thomas	Werfel	Abbvie, Almirall, Galderma, Sanofi
Prof. Dr. med. Dr. h.c.	Andreas	Wollenberg	Abbvie, Almirall, Galderma, Lilly, Leo, Pfizer, Sanofi

The updated guideline document (chapters on systemic treatment, chapter on pregnancy, breastfeeding, and family planning, the stepped-care plans and the drug tables) were send to all members of the guideline development group for internal review. After the review phase all comments were combined in a word documents by the EuroGuiDerm Team. Editorial comments were directly resolved by the EuroGuiDerm Team. All other comments were sent to the coordinators AW and CF to be resolved. All changes to the guideline were made using the `track changes'function. All reviewers received feedback to their comments. Changes resulting from the commenting phase were clearly visible. An anonymised version of all comments, feedback and action taken are available from euroguiderm@debm.de.

After the internal review the updated guideline chapters, the Evidence Report and the Methods Report were send to: EDF Board, all supporting societies and pharmaceutical companies for external review. After the review phase all comments from the reviewer were combined in an word documents. Editorial comments were resolved by the EuroGuiDerm Team. All other comments were sent to the clinical coordinators AW and CF to be resolved. All changes to the guideline were made using the "track changes" function. All reviewers received feedback to their comments and all changes resulting from the commenting phase are clearly visible. An anonymised version of all comments, feedback and action taken are available from euroguiderm@debm.de

Evidence

The living systematic review by Drucker and colleagues[3-5] was used as the evidence base based on which we created an evidence-to-decision framework (see Evidence Report). Furthermore, challenges exist with comparing clinical trials in AE due to their differences in trial design, including study comparators, rules for rescue treatment, washout periods for topical and systemic treatments, inclusion criteria, and the duration of the screening period.[6] Finally, this analysis does not take into consideration the overall management plan that targets long-term stabilization, flare prevention and avoidance of side-effects beyond 16 weeks[7]. We only summarize the results here. For limitations please refer to the website.

For each recommendations that is evidence-based, we added the certainty of the evidence when compared to placebo[2]. The assessment of the certainty of evidence leads to four grades, see Figure 1 (Table 5.1. GRADE Handbook[8]).

High ⨁⨁⨁⨁: we are **very confident** that the true effect lies close to that of the estimate of the effect.
Medium ⨁⨁⨁◯: we are **moderately confident** in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low ⨁⨁◯◯: our **confidence in the effect estimate is limited: The true effect may be substantially different** from the estimate of the effect.
Very low ⨁◯◯◯: we have **very little confidence** in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Figure 1 Definitions of "certainty of evidence" [8]

Excerpt from the publication of the network meta-analysis 'Living network meta-analysis to compare nemolizumab against other available targeted systemic treatments for atopic dermatitis ' by Aaron M. Drucker and colleagues, May 2025.[5]

„[…] Our analysis shows that nemolizumab improves the signs of AD measured by the Eczema Area and Severity Index (EASI) by 6 fewer points [95% credible interval (CrI) 3.7–8.5 fewer] than dupilumab, indicating that dupilumab is probably associated with a small important reduction in EASI scores compared with nemolizumab (moderate certainty; see https://doi.org/10.6084/m9.figshare.29066576). According to GRADE, certainty was downgraded from high to moderate because the credible intervals include 6.6, the MID for EASI,8 indicating that it is possible that dupilumab may be associated with a large (rather than small) important reduction in EASI scores compared with nemolizumab.

We also found that dupilumab is probably associated with a large important reduction in Patient-Oriented Eczema Measure (POEM) scores (moderate certainty), a measure of symptoms, and is probably associated with a small but important reduction in Dermatology Life Quality Index (DLQI, moderate certainty), a measure of skin-specific health-related quality of life vs. nemolizumab.

One outcome for which dupilumab was not more efficacious compared with nemolizumab is the Peak Pruritus Numeric Rating Scale (PP-NRS). We found no difference between dupilumab and nemolizumab [–0.1 points (95% CrI –0.6 to 0.4), Figure 1d], leading us to conclude that dupilumab is probably associated with no important difference in reduction in PP-NRS scores compared with nemolizumab (moderate certainty). Nemolizumab has the best pathophysiological rationale for this symptom given that IL-31 is considered an 'itch cytokine'. […] page 549-550, Drucker et al. 2025[5]

Linking evidence to recommendations

In the table below, we link the evidence from the NMA directly to the recommendations made. For additional information and justifications, please see the corresponding chapters.

Recommendation	Short term (8-16 weeks) vs placebo Bold = statistically significant difference
We recommend ciclosporin to achieve disease control in AE patients who are candidates for systemic treatment.	Network meta-analysis from 2022[2,9]: Higher dose ⊕⊕⊕◯ MODERATE for standardized mean difference **change in signs** -1 (-1.6, -0.4) ⊕⊕⊕◯ MODERATE for standardized mean difference **QoL** -0.7 (-1.3, -0.1) ⊕⊕◯◯ LOW for standardized mean difference itch -0.7 (-1.5, 0.2) Lower dose ⊕⊕⊕◯ MODERATE for standardized mean difference **change in signs** -0.7 (-1.4, -0.1) ⊕⊕◯◯ LOW for standardized mean difference QoL -0.5 (-1.1, 0.2) ⊕⊕◯◯ LOW for standardized mean difference itch -0.7 (-1.6, 0.3)
We suggest methotrexate in AE patients who are candidates for systemic treatment.	Network meta-analysis from 2022[2,9]: ⊕⊕◯◯ LOW for standardized mean difference change in signs -0.6 (-1, -0.2), Qol -0.4 (-0.9, 0.1), itch -0.6 (-1.2, 0)
We recommend dupilumab in AE patients who are candidates for systemic treatment.	Network meta-analysis from 2024[9,10]: ⊕⊕⊕⊕ HIGH for mean difference **EASI** -10.5 (-11.9, -9.2); **POEM** -7.3 (-8, -6.7); **peak pruritus NRS** -2.1 (-2.3, -1.8); **DLQI** (-4.9 (-5.4, -4.3)
We recommend lebrikizumab in AE patients, who are candidates for systemic treatment.	Network meta-analysis from 2024[9,10]: ⊕⊕⊕⊕ HIGH for mean difference **POEM** -6.2 (-7.4, -5.1) ⊕⊕⊕◯ MODERATE for mean difference **EASI** -8.5 (-10.4, -6.5); **DLQI** -4.7 (-6.4, -2.8) ⊕⊕◯◯ LOW for mean difference **peak pruritus NRS** -2.1 (-2.6, -1.7)
We recommend nemolizumab in AE patients, who are candidates for systemic treatment.	Network meta-analysis from 2025[5]: ⊕⊕⊕◯ MODERATE for mean difference **EASI** -4.4 (-6.5, -2.4); **POEM** -3.9 (-5.1, -2.8); **DLQI** -2.4 (-3.4, -1.3); **peak pruritus NRS** -2 (-2.4, -1.6)
We recommend tralokinumab in AE patients, who are candidates for systemic treatment.	Network meta-analysis from 2024[9,10]: ⊕⊕⊕⊕ HIGH for mean difference **POEM** -4.2 (-5, -3.4) ⊕⊕⊕◯ MODERATE for mean difference **peak pruritus NRS** -1 (-1.2, -0.7); **DLQI** -2.4 (-3.1, -1.6) ⊕⊕◯◯ LOW for mean difference **EASI** -6.2 (-7.8, -4.7)
We recommend abrocitinib in AE patients who are candidates for systemic treatment.	Network meta-analysis from 2024[9,10]: 100 mg ⊕⊕⊕⊕ HIGH for mean difference **EASI** -8.5 (-10.3, -6.7); **POEM** -5.1 (-6.1, -4.1) ⊕⊕⊕◯ MODERATE for mean difference **peak pruritus NRS** -1.6 (-2.1, -1.1); **DLQI** -3.4 (-4.3, -2.6) 200 mg ⊕⊕⊕⊕ HIGH for mean difference **EASI** -12.8 (-14.6, -11.1); **POEM** -8.4 (-9.3, -7.5); **DLQI** -5.6 (-6.3, -4.8) ⊕⊕⊕◯ MODERATE for mean difference **peak pruritus NRS** -2.4 (-3, -1.8)
We recommend baricitinib in AE patients who are candidates for systemic treatment.	Network meta-analysis from 2024[9,10]: 2 mg ⊕⊕⊕◯ MODERATE for mean difference **EASI** -5.1 (-6.9, -3.4); **POEM** -3.8 (-4.9, -2.7); **peak pruritus NRS -1**.2 (-1.6, -0.9); **DLQI** -2.3 (-3.1, -1.4) 4 mg ⊕⊕⊕⊕ HIGH for mean difference **POEM** -5.4 (-6.6, -4.2); **peak pruritus NRS** -1.6 (-2, -1.3) ⊕⊕⊕◯ MODERATE for mean difference **EASI** -7.5 (-9.4, -5.6); **DLQI** -3.5 (-4.4, -2.6)
We recommend upadacitinib in AE patients who are candidates for systemic treatment	Network meta-analysis from 2024[9,10]: 15 mg ⊕⊕⊕⊕ HIGH for mean difference **EASI** -11 (-12.6, -9.4) ⊕⊕⊕◯ MODERATE for mean difference **POEM** -7 (-11.2, -2.9); **peak pruritus NRS** -2.4 (-2.8, -2) 30 mg ⊕⊕⊕⊕ HIGH for mean difference **EASI** -13.5 (-15.2, -11.9); **POEM** -10.7 (-14.8, -6.5); **peak pruritus NRS** -3.3 (-3.6, -3.1)

AE = atopic eczema; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; NMA = network meta analysis; OR = Odds ratio; POEM = Patient-Oriented Eczema Measure; PPNRS = Peak Pruritus Numerical Rating Scale; RoB = Risk of Bias; VAS = visual analog scale

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