EAACI Biologicals Guidelines – dupilumab for children and adults with moderate-to-severe atopic dermatitis

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Short title: EAACI Guideline for the use dupilumab in adults and children with atopic dermatitis

Abstract

Atopic dermatitis imposes a significant burden on patients, families and healthcare systems. Management is difficult, due to disease heterogeneity, comorbidities, complexity in care pathways and differences between national or regional healthcare systems. Better understanding of the mechanisms has enabled a stratified approach to the management of atopic dermatitis, supporting the use of targeted treatments with biologicals. However, there are still many issues that require further clarification. These include the definition of response, strategies to enhance the responder rate, the duration of treatment and its regimen (in the clinic or home-based), its cost-effectiveness and long-term safety. The EAACI Guidelines on the use of dupilumab in atopic dermatitis follow the GRADE approach in formulating recommendations for each outcome and age group. In addition, future approaches and research priorities are discussed.

Abbreviations
AD = atopic dermatitis
ADA = anti-drug antibodies
ADTA = Atopic Dermatitis Control Tool
AE = adverse events
AR = allergic rhinitis
CTACK = cutaneous T-cell attracting chemokine
COI = conflict of interest
CRSwNP = chronic rhinosinusitis with nasal polyps
DAC = dupilumab associated conjunctivitis
DCs = dendritic cells
EAACI = European Academy of Allergy and Clinical Immunology
EASI = Eczema Area and Severity Index
ED = emergency department
EMA = European Medicines Agency
EtD = evidence-to-decision
Fab = antigen-binding fragment
Fc = fragment crystallizable
FcεRI = IgE high affinity receptor
FDA = Food and Drug Administration
GDG = guidelines development group
GRADE = Grading of Recommendations Assessment, Development, and Evaluation
HCP = healthcare professional
ICERs = incremental cost-effectiveness ratios
ICS = inhaled corticosteroids
Ig = immunoglobulin
IGA = Investigator´s Global Assessment
IL = interleukin
IL-4Rα = the α subunit of the IL-4 receptor
IL-5Rα = the α subunit of the IL-5 receptor
IV = intravenous
JAK = Janus kinase
LDH = lactate dehydrogenase
Mab = monoclonal antibody
NICE = National Institute for Health and Care Excellence
OCS = oral corticosteroids
PICO (population, intervention, comparator, and outcomes)
PI3K = phosphoinositide 3 kinase
PROs = patient-reported outcomes
QALY = quality adjusted life-years
QoL = quality of life
ROB = risk of bias
SCS = systemic corticosteroids
SIS = systemic immunosupressants
SMD = small molecule drug
SOF = summary of findings
SRs = systematic literature reviews
STAT= signal transducer and activator of transcription
TARC = thymus- and activation-regulated chemokine
T2 = type 2 immune response
TCS = topical corticosteroids
TEWL = transepidermal water loss
Th = T helper

TNF = tumor necrosis factor
TSLP = Thymic stromal lymphopoietin
vIGA = validated Investigator´s Global Assessment

I.   Introduction

a. *The current landscape of atopic dermatitis*

i.   *Definition and burden*

Atopic dermatitis (AD) is a common chronic systemic inflammatory disease with skin manifestations affecting children and adults. AD is characterized by pruritus, inflammatory erythematous skin lesions, and skin-barrier defect (1,2). The prevalence of adult AD ranges from 2.1% to 4.9% across countries (3). Up to 20% of children are affected. A recent systematic review reported an overall point prevalence of AD symptoms ranging from 1.7% to 32.8% in children and from 1.2% to 9.7% in adults (4). AD usually evolves as a chronic remitting-relapsing inflammatory skin disease, with flares triggered by viral, bacterial or fungal infections, food allergens, cosmetics, fragrance, aeroallergens, irritants, weather, contact allergens and psychosocial factors (5). The diagnosis is made clinically through history and physical examination. Pruritus, or itching, is the leading symptom. Excessive rubbing or scratching can result in crusted erosions, excoriation, and subsequent development of secondary infections. The intense pruritus and rash can be debilitating, significantly impairing quality of life (QoL). The burden of disease is frequently experienced by the patient's family as well. Direct costs include, but are not limited to, prescription and non-prescription costs, healthcare provider visits, hospital and emergency department visits, and hospitalisations. Indirect costs associated with AD include absenteeism from work, school, and physical activities; decreased productivity (presenteeism) and QoL, primarily due to sleep disturbance from itching, and time related to care (6,7,8,9,10).

ii.   *Atopic dermatitis phenotypes and endotypes - practical implications for management*

AD has highly complex pathophysiology and heterogeneous clinical presentations, which are illustrated by different features such as age of disease onset, variable IgE sensitisations to allergens, spectrum of severity, potential of IgE autoreactivity and comorbidities (asthma, rhinitis, food allergy, infections and others) (11,12,13,14).

Improved understanding of the contribution of immune-inflammatory mechanisms in AD has encouraged the development of biologicals and small molecules specifically targeting the key pathogenetic mechanisms. The use of targeted treatment is facilitated by the concept of phenotypes (visible properties) and endotypes (pathogenetic mechanisms). The most common endotypes for AD are type-2 (T2) and non-T2. However, recent data point to a role of inflammasome pathways, barrier defect, type-17 and type 22 subtypes and mixed types such as T2/type 1 and T2/type 17 (15,16,17,18,19,20). Expression profiling of skin biopsies and tape strips has established molecular features of the skin in patients with AD. Both immune and epidermis-related genes separate patients with AD from healthy subjects, with 50% of patients with AD exhibiting a T2 endotype associated with more severe disease (21,22,23, 24).

IL-4 and IL-13 are both pivotal cytokines involved in the pathogenesis of T2 allergic diseases (25,26). The expression of IL-4 is upregulated in the affected skin of AD patients, with basophils as one of the producers of IL-4, alongside other cells including Th2 cells and type 2 innate lymphoid cells (27). IL-13 shows even higher expression in the lesional skin and has a significant impact on skin biology, including the recruitment of inflammatory cells, alteration of the skin microbiome, and decrease in the epidermal barrier function (28). The IL-13-rich local milieu causes barrier dysfunction by downregulating the OVOL1-filaggrin axis and by upregulating the periostin-IL-24 axis (29). There is the emerging hypothesis that IL-13 is critical in the skin and IL-4 in the circulation (28) The upstream role of IL-33 in modulating skin inflammatory cascades in AD has recently been described (30). Type 2 cytokines directly activate sensory nerves, with a critical role of neuronal IL-4Rα and JAK1 signaling in chronic itch (31).

T2 is the predominant endotype in AD, but subendotypes vary by age, race and ethnicity. In adults, the Th22, Th17, and Th1 pathways are involved, and a weakened epidermal barrier is characteristic. In paediatric patients Th17/Th22 skewing and alterations in epidermal lipid metabolism contribute to the barrier defect, while Th1 activation is less pronounced. European American patients have higher Th2/Th22 activation and lower expression of the Th1/Th17, together with suppression of filaggrin and loricrin gene expressions. Asian patients have accentuated polarity of the Th22/Th17 pathways, and also exhibit epidermal barrier defects despite relative maintenance of filaggrin and loricrin expression. African American patients exhibit less frequently studied filaggrin mutations and less Th17/Th1 inflammatory pathways (19,32,33,34,35,36).

The link between the endotype and the phenotype is facilitated by biomarkers (12,14,37, 38,39,40). Stratified medicine is the endotype/biomarker-driven approach that classifies individuals into subpopulations differing in their susceptibility to a particular disease or their response to a particular treatment. It is facilitated by a subgroup of biomarkers serving to stage diseases based on prognosis or underlying biological mechanism, thus enabling the concept of enrichment. Enrichment implies selection of theratypes, a patient population in which a successful intervention effect is more likely than in an unselected population (37,38,39,40). Stratified medicine can identify patients who are more likely to benefit or experience an adverse reaction in response to a given therapy and anticipate their long-term outcome. In addition, this approach potentially facilitates drug development and prevention strategies (37, 38,39,40). Whether this stratified approach will improve the burden of AD remains to be proven by real-life studies and registry data (37). There are several critical points impacting the efficacy of the stratified approach, from the complexity of disease endotypes to its effectiveness in real-world settings. Given the relatively high costs of biological therapies, cost-effectiveness analyses are a prerequisite for coverage and reimbursement. Carefully targeting biological therapy to specific populations, such as high-responders, or discounting the acquisition price in order to further improve value are currently advocated.

iii. Biologicals

Biologic products (biologicals) include a wide range of products such as vaccines, blood and blood components, allergen vaccines, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. They are isolated from a variety of natural sources - human, animal, or microorganism - and may be produced by biotechnology methods and other cutting-edge technologies. For the purpose of this guideline we refer to monoclonal antibodies (mAb) as biologicals. In contrast to chemical compounds and small-molecule agonists or antagonists, biologicals bind a specific determinant, for example, a cytokine or receptor. Owing to this selectivity, biologicals are ideal for 'personalised' or 'precision' medicine (41).

iv. Current management of atopic dermatitis

Current AD therapeutic armamentarium includes emollients/skin care, topical or systemic corticosteroids, phototherapy, topical calcineurin inhibitors, crisaborole, delgocitinib, systemic immunosuppressants and biologicals (42). The most recently approved class of therapies for AD are crisaborole and dupilumab (43,44,45,46). Dupilumab is approved in the United Stated for adults, adolescents (12-17 years old) and children 6-11 years old with moderate and severe AD. In the European Union dupilumab is currently approved for use in adults and adolescents 12 years and older with moderate-to-severe AD who are candidates for systemic therapy. The European Medicines Agency's Committee for Medicinal Products for Human Use has adopted in October 2020 a positive opinion for dupilumab, recommending to extend its approval to include children aged 6 to 11 years with severe AD who are candidates for systemic therapy. The recommended dose for adults and for adolescents > 60 kg is an initial dose of 600 mg, followed by 300 mg given every other week. For adolescents < 60 kg the initial dose is 400 mg, followed by 200 mg given every other week. For the 6-11 years of age children dupilumab

is given either every two weeks (200 mg) or four weeks (300 mg), based on weight, following an initial loading dose.

A systematic literature review of 41 studies showed that the strongest evidence for systemic treatment of AD currently exists for dupilumab and cyclosporine in improving clinical disease severity (47).

b. *Purpose of the EAACI Guidelines for the use of dupilumab in atopic dermatitis*

Delivering high-quality clinical care is a central priority for allergists, dermatologists, paediatricians, internal medicine and other specialities caring for patients with AD. The European Academy of Allergy and Clinical Immunology (EAACI) develops and updates each year resources to help healthcare professionals (HCP) and researchers to design the best interventions, deliver high standard care and to assess their actions and decisions for purposes of quality improvement and/or reporting.

EAACI guidelines include recommendations for the management of patients with particular conditions or diseases. Guidelines are developed using a systematic process, and are based on available evidence and the clinical experience and expertise of all interested stakeholders. Following the rapid accrual of evidence for dupilumab in AD together with an advancement of guideline development methodologies a guideline focused on the use of dupilumab in AD was therefore needed.

The current EAACI guideline for the use of dupilumab in AD is focussed only on treatment with dupilumab for AD. It does not address any topics related to AD diagnosis, concurrent treatment, or monitoring adherence.

The EAACI Guideline for the use of dupilumab in AD is not intended to impose a standard of care. Instead, it provides the framework for rational decisions for the use of dupilumab in AD by HCPs, patients, third-party payers, institutional review committees and other stakeholders. Statements regarding the underlying values and preferences as well as qualifying remarks accompanying each recommendation are an integral part of the Guidelines and aim to facilitate more accurate interpretation. They should never be omitted or ignored when quoting Guidelines recommendations.

i. *Target audience*

The target audience includes all HCPs involved in the management of AD, patients and caregivers, basic scientists involved in biologicals development, regulatory authorities and policy makers.

ii. *Biologicals included - rationale for choosing*

This EAACI guideline provide recommendations for the use of dupilumab in patients with AD. Dupilumab is currently the only biological with regulatory approval for the treatment of AD. Additional comments are provided for the biologicals currently tested and not yet approved and for doses/routes not approved by regulatory authorities.

II. Methods

This EAACI guidelines followed the GRADE methodology (available at www.gradeworkinggroup.org). Training was conducted with all members of the guidelines development group (GDG) to prepare them for their roles, including specific sessions on the GRADE methodology.

a. *The Guidelines Development Group*

A Core Leadership Team (table S1) supervised the project and was responsible for defining the project scope, drafting the clinical question to be addressed by the guideline, coordinating the search, and drafting the manuscript together with the Voting Panel (table S1). The project was led by three chairs with both content and methodologic expertise. The Core Leadership Team received support from a methodologist team, who advised on the process and provided

input on the GRADE summary of findings (SOF) tables. The methodologist team conducted the systematic literature review (SR) for the clinical question, graded the quality of evidence, developed the SOF tables, and provided the evidence reports. Narrative reviews were conducted by different content specialist subgroups for each topic to be covered to complement the SR.

The Voting Panel, composed of content experts, decided which clinical questions are to be asked and which outcomes are critical, important and of low importance, and voted for the final recommendations after reviewing the evidence provided by the methodology team and the narrative reviews. The Voting Panel included specialists with expertise and clinical experience in treating AD, biologists and clinical immunology experts, as well as patient representatives.

In accordance with EAACI policy, everyone who was intellectually involved in the project (i.e., considered for guideline authorship) disclosed all potential conflict of interest (COIs) in writing at the beginning, middle, and end of the project. The Guideline Oversight Committee (table S1) was responsible for developing and implementing rules related to COIs.

b. Definitions

For the purpose of the SR (48) that informed the recommendations, the AD population was defined as patients (≥12 years or older) with confirmed diagnosis of moderate-to-severe AD. Moderate-to-severe disease was defined as an Investigator´s Global Assessment (IGA) score of three or higher at baseline or an Eczema Area and Severity Index (EASI) score of 12 or higher at baseline.

For the recommendations the population was defined as in the clinical trials that informed the regulatory approval.

c. Systematic review questions, prioritisations of key outcomes and clinical questions not covered by the SR

Clinically relevant interventions and comparators were developed balancing comprehensiveness with feasibility (Table 1). The most challenging decision in framing the question was how broadly the patients and intervention should be defined. The underlying biology of AD suggested that across the range of patients and interventions it is plausible that the magnitude of effect on the key outcomes is different, thus the GDG defined subpopulations based on age (6-11 years old, 12-17 years old, ≥ 18 years old) and on dupilumab dose.

As required by the GRADE approach AD-related outcomes were prioritised in a first step by the GDG using a 1 to 9 scale (7 to 9 critical; 4 to 6 important; 1 to 3 of limited importance). The critical outcomes were changes in: SCORAD; EASI 50 or 75; pruritus and safety (drug-related adverse events (AE) and drug-related serious AE (SAE). The important outcomes were IGA, resource utilisation, rescue medication use, pain, sleep disturbance, symptoms of anxiety and depression, and Quality of life (QoL) (Table 2). After reviewing the evidence, the prioritisation of the outcomes was reassessed to ensure that important outcomes that were not initially considered are included and to reconsider the relative importance of outcomes in light of the available evidence. All AD-related relevant outcomes were addresses simultaneously.

The GDG also framed a cost-effectiveness question to assess the economic impact of dupilumab versus standard of care or the best standard of care. The selected outcomes of interest were costs, resource use, and the incremental cost-effectiveness ratios (ICERs) per quality adjusted life-years (QALY).

The GDG also defined and addressed clinical questions not covered by the systematic review (Table 3).

d. The minimal important difference

To evaluate the imprecision for each outcome their minimal important difference (MID) thresholds were considered: 8.7 points for Scoring Atopic Dermatitis (SCORAD) (49,50); 6.6 points for Eczema Area and Severity Index (EASI) (51); 4 points for Patient-Oriented Eczema

Measure (POEM) (50,52); 4 points for the Dermatology Life Quality Index (DLQI) (53); 6 points for Children's DLQI (CDLQI) (54); 3 points for numerical rating scale (NRS) for adults (55,56) and 4 points for adolescents (54); 8 points or less for the Hospital Anxiety and Depression Scale of anxiety (HAD-A) or depression (HADS-D) (57).

e. The GRADE approach (search, appraisal of the evidence)

Key principles and provisions, key terms, descriptions, drug categories, PICO (population, intervention, comparator, and outcomes) questions, search methodology and evidence reporting used in the guideline development process were predefined.

A systematic review was conducted to inform the recommendations (48). A GRADE SOF table was provided for the PICO question. The quality of evidence was evaluated based on GRADE quality assessment criteria by two independent reviewers and discordance resolved by consensus. Quality assessment includes the risk of bias (ROB) of included trials, the likelihood of publication bias, inconsistency between trial results, indirectness of the evidence (e.g., differences between populations, interventions, or outcomes of interest in the group to whom the recommendation applies versus those who were included in the studies referenced), and imprecision (wide confidence intervals, usually due to a small number of patients or events, or those situations where clinical decision-making would differ at the extremes of the confidence interval) (58, 59,60). The quality of evidence for each outcome was rated as high, moderate, low, or very low. In the absence of any data, the level of evidence was rated as very low, based on clinical experience only. Search results were pooled in an evidence report as SOF tables and accompanied by a qualitative summary of the evidence the PICO question. The Content Panel reviewed the drafted evidence report to address evidence gaps prior to presentation to the Voting Panel.

f. Additional evidence

In support of formulated recommendations, the GDG performed narrative reviews collecting evidence on phase IV, observational, real-world trials and registries and on clinical questions not addressed by the SRs (table S2).

g. Consensus building and formulating recommendations

After reviewing the evidence report and the additional evidence, the Voting Panel discussed and consented by voting in a hybrid meeting (face-to-face and online, on 12.01.2020) the final recommendations of this Guideline. For each outcome, the Voting Panel heard an oral summary of the evidence and voted on the wording, direction and strength of the related recommendation. A 70% consensus threshold was reached for all recommendations presented below. The recommendations follow the data included in the evidence-to-decision (EtD) tables and take into consideration the balance of desirable and undesirable consequences, the quality of evidence, patients' values and preferences, feasibility, and acceptability of various interventions, use of resources paid for by third parties, equity considerations, impacts on those who care for patients, and public health impact (58,59,60). A strong recommendation was made in favour of an intervention when the GDG was certain that the desirable consequences outweighed the undesirable consequences. A conditional recommendation was provided if there were reasons for uncertainty on the benefit-risk profile, especially for low or very low quality of evidence. The underlying values and preferences played a key role in formulating recommendations. As the key target audience of this EAACI Guideline are HCPs and the patients they treat, the perspective chosen when formulating recommendations was mainly that of the HCPs and of the patient, although the health systems perspective was also evaluated, as per WHO recommendations for guidelines development (61). Recommendations are formulated separate by outcome. The recommendations formulated in this guideline should be used following the GRADE interpretation (table 4). These recommendations should be reconsidered when new evidence becomes available and an update of this guideline is planned for 2025.

Where no evidence was available the GDG formulated expert-based recommendations.

The Guideline was available on the EAACI website for two weeks (7-21 September 2020) for public comment and it underwent external peer-review. All comments received were carefully reviewed by the GDG and incorporated where applicable.

h. Final review and approval of the guideline by EAACI

In addition to journal and external peer review, the EAACI Scientific Committee and Executive Committee reviewed the manuscript. These EAACI over-sight groups did not mandate that certain recommendations be made within the guideline, but rather serve as peer reviewers.

III. Key recommendations

Dupilumab is an IgG4 human monoclonal antibody that binds to the α subunit of the IL-4 receptor (IL-4Rα) shared by IL-4 and IL-13 receptor complexes, thus simultaneously inhibiting both IL-4- and IL-13-mediated signalling pathways. Simultaneous blocking of Type I receptor (IL-4Rα/γc) and Type 2 receptor (IL-4Rα/IL-13Rα) inhibit at the same time T2 responses dependent on IL-4 and IL-4/IL-13, respectively, in hematopoietic and non-hematopoietic cells. Dupilumab targets several important disease mechanisms in the skin of AD patients, including the skin barrier defect, the chronic itch, the microbiome, and the T2 inflammation, both in clinical trials and in real life (38,39, 62,63,64,65,66). Accumulating experience with dupilumab treatment for AD confirmed its effectiveness and safety, by reducing AD severity, reliever and background medication, and improving QoL, both in the paediatric population 12-17 years old and in adults (67,68,69,70,71,72,73,74,75,76). Recent evidence was published for the efficacy and safety in the 6-11 years old population (77).

The summary of the supportive evidence is presented in tables S3, S4, S5 and S6. Recommendations for adults and the 12-17 years old paediatric population are based on the evidence-to-decision tables 5 and 6.

Recommendations are formulated together for the adult and 12-17 years old population included in the SR (Box 1) and separate for the 6-11 years old population (Box 2)

Box 1: Recommendation for dupilumab treatment in adults and in the paediatric population 12-17 years old with uncontrolled atopic dermatitis

1. Dupilumab is recommended in adults and in the pediatric population 12-17 years old with atopic dermatitis* to:	Reduce disease activity as reflected by SCORAD, EASI, IGA	Strong recommendation
	Reduce rescue** and background*** medication	Strong recommendation
	Improve quality of life	Strong recommendation
2. Dupilumab has demonstrated a good safety profile however drug-related AEs should be periodically monitored		Conditional recommendation

* population: moderate to severe AD not adequately controlled with topical prescription therapies or when those therapies are not advisable
** Rescue refers to „on demand"
*** Background medication includes systemic and topical treatment

Box 2: Recommendation for dupilumab treatment in the paediatric population 6-11 years old with uncontrolled atopic dermatitis

1. Dupilumab is recommended in the	Reduce disease activity as reflected by EASI and IGA	Conditional recommendation

paediatric population 6-11 years old with atopic dermatitis* to:		as per expert opinion
	Improve quality of life	Conditional recommendation as per expert opinion
2. Dupilumab has demonstrated a good safety profile however drug-related AEs should be periodically monitored		Conditional recommendation as per expert opinion

* population: severe AD not adequately controlled with topical prescription therapies or when those therapies are not advisable

Justification

There is high certainty for adults and 12-17 years old patients with AD for reducing disease activity, rescue and background medication and for improving QoL. The evidence on safety treatment-related AEs in adults is of low certainty and very uncertain both for adults and adolescents for treatment-related SAEs, thus the GDG formulated a conditional recommendation.

As the evidence for the 6-11 years old group (16 weeks trial, severe AD only) (77) was published after the completion of the SR the CGD formulated conditional recommendations as per expert opinion based on the results of this trial showing significantly improving signs, symptoms, and QOL for dupilumab added to topical corticosteroids

Subgroups: stratified by co-morbidities

The GDG evaluated the evidence for dupilumab efficacy in AD associated with other T2 diseases or other co-morbidities not included in the SR (table S2) and formulated a conditional recommendation, expert opinion based on the efficacy of dupilumab in patients with AD and other T2 co-morbidities (box 3). Emerging evidence on the associations between AD and alopecia areata (78, 79, 80), may also need to be considered, when considering treatments for patients with both diseases.

Box 3: Recommendation for dupilumab in adults and 12-17 years old patients with both AD associated with other T2 allergic diseases or other co-morbidities

Dupilumab may be of particular benefit in adults and 12-17 years old patients with both AD associated with other T2 allergic diseases (asthma, chronic rhinosinusitis with nasal polyposis, eosinophilic esophagitis	Conditional recommendation, expert opinion based

Implementation considerations

The GDG formulated strong recommendations for the reduction in disease activity, rescue and background medication and for improving QoL and conditional recommendations for safety-related outcomes. According to GRADE for strong recommendations most individuals should receive the intervention and the recommendation can be adapted as policy or performance measure in most situations (table 4). However, the GDG cautions on several unsolved key pillars supporting the implementation of these recommendations, such as independent high-quality cost-effectiveness studies, selection of responders, documentation of the disease modifying effect together with long-term safety data, studies addressing a priori AD together with its co-morbidities. The cost-effectiveness of dupilumab based on real-world treatment patterns is unknown. Including broader evidence on treatment discontinuation, caregiver

burden, and background and rescue medication reduction from real-world studies and AD registries may better reflect the effects and value of biologicals for all healthcare stakeholders (81,82). Last but not least the value of the recommendations depends also on the setting in which the current guideline will be implemented, as recommendation suitable for resource-rich environments might change from strong to conditional in resource-poor environments (Box 4).

Box 4: Factors impacting the implementation of recommendations for the use of dupilumab in atopic dermatitis (adults and 12-17 years old)

1. Cost-effectiveness, especially independent real-world evidence
2. Long-term safety data
3. Immune modulation/disease modifying effect
4. Stratification* based on biomarkers**
5. Patient's preference
6. Availability of resources
7. Duration of treatment

* Stratification – safety and efficacy
**Biomarkers include both clinical and laboratory features

IV. Practical approach
a. Definition of response; continuation and stopping rules

Box 5: Recommendations for practical use of dupilumab in adults and 12-17 years old patients with AD

The evaluation of response should be done after 16 weeks of treatment	Conditional recommendation, expert opinion based
As there are no validated criteria for defining response to dupilumab in AD the GDG recommends a composite end-point combing clinical parameters (disease severity and QoL) with biomarkers related to disease activity and severity (box 6)	Conditional recommendation, expert opinion based
For the clinical end-points a pre-established cut-off reached through shared decision making with the patient should be used	Conditional recommendation, expert opinion based
Stopping dupilumab should be considered if a significant AE occurs	Conditional recommendation, expert opinion based

Box 6: Recommended composite end-point

Clinical end-points	AD activity/severity: SCORAD, EASI 50 and 75, vIGA, pruritus (NRS), use of rescue medication; POEM
	Quality of life: DLQI; GISS; HADS
	Adverse events of special interest: conjunctivitis

Potential future biomarkers	Serum/blood: blood eosinophils, total IgE, allergen-specific IgE, LDH, TARC/CCL-17, PARC/CCL18, periostin, IL-22, eotaxin-1, eotaxin-3, CTACK, E-selectin, MDC, IL-18, IL-31, IL-13 and VEGF (82, 83,84,85,86,87,88, 89,90)
	A composite panel of biomarkers might be considered in relation to disease endotypes: PARC/TIMP-1/sCD14; IFN-γ/TIMP-1/VEGF; IFN-β, IL-1, and epithelial cytokines; IL-1, IL-4, IL-13, and TSLP (91)
	Skin: microbial colonisation (63, 92, 93,94)
	Skin: barrier function (transepidermal water loss)

In addition, adherence to background treatment and to avoidance of AD triggers measures should be evaluated before deciding to stop dupilumab due to lack of efficacy.

b. Monitoring treatment
i. Eye inflammation

The most frequent reported AE associated with dupilumab treatment in AD is eye inflammation, notably dupilumab associated conjunctivitis (DAC). Patients with AD, especially with more severe form of disease, are already at increased risk of developing conjunctivitis, however clinical trials and real-world evidence have shown a greater incidence of conjunctivitis in individuals with AD treated with dupilumab (95).

An analysis of 6 RCTs including a total of 2629 patients focused on DAC and reported a higher incidence of conjunctivitis (8.6–22.1%) in patients treated with dupilumab as compared to placebo (2.1–11.1%) for all RCTs included with the exception of SOLO-CONTINUE (96). Most cases of DAC were mild-to-moderate in severity, and less than 0.5% of patients treated with dupilumab had severe conjunctivitis. Of note, the conjunctivitis was diagnosed by dermatologists or allergists, and not by ophthalmologists, with no differentiation between allergic, infectious, or chemical aetiology. AD patients with a self-reported history of conjunctivitis or with an increased baseline level of serum biomarkers, such as thymus- and activation-regulated chemokine (TARC)/CCL-17, IgE, or with increased blood eosinophils, had a higher incidence of conjunctivitis regardless of whether they received dupilumab or placebo (95,96, 97). DAC appears to be singular to patients with AD as for patients with asthma, chronic rhinosinusitis with nasal polyps, or eosinophilic esophagitis treated with dupilumab there was no significant increase in the incidence of conjunctivitis. DAC occurred more frequently in patients with low serum levels of dupilumab (95).

Compared with the results from clinical trials, the majority of real-world studies reported higher rates of DAC (up to 62%) (98, 99, 100, 101, 102). Upon referral to an ophthalmologist the diagnosis of conjunctivitis was confirmed in a lower percentage, suggesting that there may exist a overestimation of DAC by dermatologists (98). In addition, the awareness of DAC being a commonly reported AE in AD patients receiving dupilumab may have increased the reporting of DAC over time. The analysis of DAC risk factors coming from the real-world evidence showed that the principal predictor for the occurrence of DAC was a history of conjunctivitis. Additional risk factors were family history of allergic conjunctivitis, presence of other atopic conditions, a SCORAD score of 76.6, baseline IgE levels > 3637, and baseline blood eosinophil counts > 350 (102).

Recently, two types of DAC were reported by ophthalmologists: a mild nonspecific conjunctivitis and keratitis with dry eyes and a more specific dupilumab-induced follicular conjunctivitis and limbitis. Both types were mild or moderate, and the majority did not have

any history of conjunctivitis (103). A 15% decrease in DAC incidence was reported following standard ophthalmological assessment before initiating treatment with dupilumab in AD (104).

Box 7: Recommendations for managing eye inflammation under dupilumab treatment for AD

The occurrence of eye inflammation following treatment with dupilumab in AD is an event of special interest that should be reported appropriately in order to improve the post-marketing surveillance data	Conditional recommendation, expert opinion based
Consultation with an ophthalmologist is encouraged	Conditional recommendation, expert opinion based
As most cases are mild/moderate and respond well to topical treatment dupilumab should not be discontinued	Conditional recommendation, expert opinion based

ii.   Eosinophilia and other laboratory parameters

Eosinophilia was related to a reduced response to dupilumab as reflected by EASI and POEM scores and to the increased risk of DAC (86, 101).

The evaluation of clinical laboratory findings from three randomized, double-blinded, placebo-controlled phase III trials (LIBERTY AD SOLO 1 & 2 and LIBERTY AD CHRONOS) showed small transient increases in eosinophils in some dupilumab-treated patients. Grade 3 eosinophilia was reported in < 1% of dupilumab-treated and placebo-treated patients and no adverse events were associated with eosinophilia. Platelets and neutrophils showed mild decreases from baseline in dupilumab vs. placebo groups. No clinically meaningful changes were observed between treatment groups in other haematology, chemistry or urinalysis parameters (105).

Box 8: Recommendation for routine laboratory monitoring for dupilumab treatment for AD

No routine laboratory monitoring is recommended for dupilumab in AD	Conditional recommendation, moderate quality evidence

iii.   Infections and response to vaccination

Pooled data from 7 RCTs with dupilumab in adults with moderate-to-severe AD assessed the exposure-adjusted infection rates. Treatment groups had similar skin and non-skin infection rates. Serious/severe infections were reduced with dupilumab (risk ratio 0.43; $p < 0.05$), as were bacterial and other non-herpetic skin infections (risk ratio 0.44; $p < 0.001$). Although the infection rates with non-cutaneous herpes virus were overall slightly higher with dupilumab than placebo, clinically important infections such as eczema herpeticum or herpes zoster were less common with dupilumab (risk ratio 0.31; $p < 0.01$). Systemic anti-infective medication use was lower with dupilumab (91).

A randomized, double-blinded, placebo-controlled study evaluated the T-cell-dependent and T-cell-independent humoral immune responses to tetanus and meningococcal vaccines, in

adults with moderate-to-severe AD receiving dupilumab or placebo weekly for 16 weeks, and single doses of vaccines at week 12. Similarly, efficient immune responses were achieved both in the dupilumab and placebo groups, both for the tetanus and meningococcal polysaccharide vaccines (84).

Box 9: Recommendation for management of infections and vaccinations under dupilumab treatment for AD

Dupilumab should not be discontinued in case of cutaneous or non-cutaneous infections or in case a vaccination is required, however, an unexpected outcome such as serious infection or vaccination failure should be reported appropriately in order to improve the post-marketing surveillance data	Conditional recommendation, moderate quality evidence

V.   Other biologicals currently tested for atopic dermatitis

Anti IL-13 mAbs lebrikizumab and tralokinumab showed promising results in phase II trials (106,107,108). In exploratory analyses, additional anti IL-13 mAbs benefits were observed in the DPP-4- and periostin-high subgroups.

Thymic stromal lymphopoietin (TSLP) is a critical upstream epithelial derived cytokine inducing T2 inflammation. TSLP activates distinct immune cell cascades in the context of innate and adaptive immune-mediated T2 inflammation (11,36). TSLP's importance in human AD has been repeatedly documented (11,109,110,111,112). Targeting of TSLP-mediated signalling is a potential therapeutic strategy for AD. Tezepelumab (anti-TSLP) resulted in numerically better but statistically not significantly improvements over placebo in a recent phase II study (113).

The involvement of the IgE pathway in AD is well known (11,13,17, 114). Total serum IgE levels are significantly elevated in subjects with AD. A recent molecular profiling study showed that IgE was upregulated across 4 allergen subsets (food, perennial, seasonal, and mixed), and each allergen subset was associated with a distinct inflammatory signature marked by a specific suite of upregulated proteins. IgE antibodies against *Staphylococcus aureus* toxic shock syndrome toxin-1 were significantly upregulated in subjects with seasonal and perennial allergy (115). Omalizumab, has been used for almost two decades, mainly in allergic asthma and chronic spontaneous urticaria, for which it is highly beneficial. Two small RCTs did both not find omalizumab to be superior to placebo in AD (116). In a recent RCT in paediatric AD omalizumab significantly reduced AD severity and improved QoL in a paediatric population with atopy and severe eczema despite highly elevated total IgE levels at baseline. Its efficacy was associated with a potent topical corticosteroid sparing effect (117).

In addition to T2 immune response, the Th17 driven immune response is becoming increasingly important in AD together with the contribution of IL-22, IL-12/IL-23, IL-31, IL-33 and the Ox40 pathways (11,13,17,118).

Targeting IL-17 with sekuninumab did not show benefit in a randomized trial in AD patients (119). Fezakinumab (anti IL-22) showed benefit in a subset of patients with increased IL-22 expression at baseline (120,121). For ustekinumab, an IL-12/IL-23p40 antagonist that suppresses Th1 and Th17 activation, the clinical outcomes might have been obscured by a profound "placebo" effect, most likely due to background topical glucocorticosteroids and possibly insufficient dosing for AD (122). Larger randomized controlled trials need to be conducted to identify a suitable regimen for AD and provide more evidence for clinical application. The use of subcutaneous IL-31Rα antagonist nemolizumab resulted in significant improvement in skin inflammation and pruritus, together with evidence for short-term safety (123,124,125). Anti OX40 antagonists are also investigated (126,127).

A recent SR (128) evaluated 13 RCTs and 10 observational studies with nine biologicals in AD (dupilumab, lebrikizumab, infliximab, omalizumab, nemolizumab, rituximab, tralokinumab, tezepelumab, ustekinumab). High-quality evidence was available for dupilumab, nemolizumab and ustekinumab. Nemolizumab had similar EASI-75 responses as placebo, but significantly improved pruritus. In online reports, lebrikizumab demonstrated superior EASI-50 responses versus placebo, while tralokinumab had superior SCORAD-50 responses versus placebo, with borderline significance. In two RCTs each, omalizumab and ustekinumab were comparable with placebo, while tezepelumab, infliximab, and rituximab lacked adequate evidence of efficacy.

VI.   Discussion
a. *Relevance of this EAACI Guideline compared to other guidelines*

The EAACI Guidelines recommendations for the use of dupilumab in AD are formulated per outcome and age group, with a careful description of the population where the recommendation is applicable. The GRADE approach was used to rate the certainty of the evidence. The outcomes included were prioritised beforehand and the minimal important difference was considered when available for all AD-related outcomes. Besides judging the risk of bias, the recommendations considered all relevant aspects related with the certainty of evidence like heterogeneity, indirectness or imprecision of the results. An evaluation of cost-effectiveness and a critical appraisal of the evidence not included the SR provided additional support for the GDG in formulating recommendations. The recommendations follow the data included in the evidence-to-decision tables and take into consideration the balance of desirable and undesirable consequences, quality of evidence, cost-efetiveness, patients' values and preferences, feasibility, and acceptability of various interventions, use of resources paid for by third parties, equity considerations, impacts on those who care for patients, and public health impact

The consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part II recommends dupilumab as a disease-modifying drug for patients with moderate-to-severe AD, in whom topical treatment is not sufficient and other systemic treatment is not advisable (level of evidence 1, a) (42). They also recommend that dupilumab should be combined with daily emollients and may be combined with topical anti-inflammatory drugs as needed. (level of evidence 2, b). These consensus-based guidelines used a different methodology for appraising the evidence, no systematic literature review had been performed and no separate recommendations per outcome and per age group were provided. Another difference is that for this EAACI Guidelines the GDG did not consider that there is enough evidence for the disease-modifying effect of dupilumab in AD and included the need to demonstrate its long-term efficacy as a research priority.

The National Institute for Health and Care Excellence (NICE) in the United Kingdom recommends dupilumab as an option for treating moderate to severe AD in adults only if the disease has not responded to at least 1 other systemic therapy, such as ciclosporin, methotrexate, azathioprine and mycophenolate mofetil, or these are contraindicated or not tolerated and if the company provides dupilumab according to the commercial arrangement ((e.g. NHS patient access scheme) (129). Similar to NICE recommendations the EAACI Guideline proposes the evaluation of treatment response after 16 weeks. This arbitrary cut-off for the evaluation was chosen based on the high-cost of the drugs with the assumption that the duration of treatment is long enough to identify responders and those with a suboptimal response. Different to NICE recommendations, as no validated criteria exist for defining optimal response, this EAACI Guideline advocates for consideration of a composite end-point and for individualised predefined targets for the clinical outcomes established by informed shared decision making focused on the patient's goals to control their chronic inflammatory skin disease.

b. Future perspectives: barriers and facilitators
i. Precision medicine using multiple or upstream targets

Small molecule drug (SMD)-based therapies represent an active field in pharmaceutical research and development. SMDs expand biologicals' therapeutic targets by reaching the intracellular compartment by delivery as either an oral or topically based formulation, offering both convenience and lower costs (130). The PDE-4 inhibitors premilast and roflumilast and the CRTH2 inhibitors fevipiprant and temapiprant did not meet in phase II trials the primary endpoint, specifically reduction of AD severity (131). However, they may still hold therapeutic value in certain subpopulation of AD patients. Being pivotal for signalling for multiple AD-relevant cytokines, including IL-4, IL-5, IL-13, and TSLP, Janus kinase (JAK)/ signal transducer and activator of transcription (STAT) inhibition might be a novel intervention strategy for AD. The JAK-STAT inhibitors (baricitinib, abrocitinib, upadacitinib, gusacitinib, tofacitinib, ruxolitinib, and delgocitinib) have the most promising results from the emerging therapies (132,133,134,135,136,137,138,139,140). The EMA Committee for Medicinal Products for Human Use has recently issued a positive opinion for baricitinib for the treatment of adult patients with moderate to severe AD. Other drugs with potential include the aryl hydrocarbon receptor modulating agent tapinarof and the H4 receptor antagonists (141,142).

ii. Impact on the cutaneous microbial community structure

Normalising the skin microbiome is an important target in the management of AD. A SR of 8 RCTs including 2706 adults with moderate-to-severe AD reported a decrease in the incidence of skin infections and of eczema herpeticum following treatment with dupilumab (91). Another study assessing specifically the skin microbiome showed that dupilumab increased microbial diversity and decreased the abundance of *S. aureus*, both in the non-lesional and the lesional skin. Decreased *S. aureus* abundance during dupilumab treatment correlated with clinical improvement of AD and with the decrease in T2 biomarkers (63, 92,93). The effect is similar to the one reported topical corticosteroids with or without a bleach bath (143).

iii. Impact on skin barrier biology

Impaired skin barrier is a central mechanism in AD thus a disease-modifying intervention should aim at restoring the normal barrier function. Three unique transcriptomic programmes in keratinocytes were described, KC1, KC2, KC17, characteristic to immune signalling from disease-associated helper T cells (144). Broad spectrum treatment with ciclosporin ameliorated the KC17 response in AD lesions to a non-lesional immunophenotype, without altering KC2. Conversely, the specific anti-Th2 therapy, dupilumab, reversed the KC2 immunophenotype (144). A previous study showed similar results for dupilumab, significantly decreasing the mRNA expression of genes related to hyperplasia and potent inhibition of T2 chemokines without significant modulation of Th1-associated genes (145). Another study showed a broader effect of dupilmab. In parallel with clinical improvement and decrease in T2 biomarkers, treatment with dupilumab reduced lesional epidermal thickness and shifted the lesional transcriptome toward a non-lesional phenotype, significantly reduced the expression of genes involved in T2 inflammation, epidermal hyperplasia, dendritic cells and Th17/Th22 activation and increased expression of epidermal differentiation, barrier, and lipid metabolism genes (83).
As targeting a single axis of immune signal alone may be insufficient to resolve the keratinocyte immunophenotype abnormalities, the endotype-driven approach seems to be crucial in selecting the patient responding best to the target intervention. This approach is extremely valuable for managing the recommendation for dupilumab in a heterogeneous real-life population where endotypes vary by age, race and ethnicity (32,33,34,35).

iv. The disease modifying effect

The "holy Grail" for the use of biologicals in AD is to validate their disease modifying potential. If this proves to be true a future potential role for dupilumab in mild AD to prevent the evolution towards severe cases or for the primary prevention of AD in high risk individuals may be considered.

Currently dupilumab did not demonstrate a convincing disease modifying effect in AD, as the efficacy is lost a few weeks or months after the treatment is stopped and the efficacy seems to depend on the interval of dose administration (75). Data from mechanistic studies on the skin transcriptomics, skin barrier and microbiome are however encouraging. The sustained efficacy over 3 years (146) is also an argument for a potential disease-modifying effect. Further long-term studies are needed.

v. Long term safety

An analysis of pooled data from 7 RCTs showed that dupilumab decreased the overall infection rates versus placebo in patients with moderate-to-severe AD (94). Thus, dupilumab seems different from the other systemic treatment in AD such as systemic corticosteroids or immunosupresants regarding the increased the risk of infections

Corroborated data from RCTs and post-marketing surveillance, such as registries and spontaneous reporting are building-up a good safety profile for dupilumab in AD, both for the adult and the pediatric population.

For dupilumab in adults with AD there is evidence for long-term safety from RCTs up until 3 years (146,147). For the 12-17 years old patients with AD the safety data evaluation is available up until 52 weeks (148).

Post-marketing surveillance, especially collected through structured registries is of utmost importance. A long-term prospective observational safety study is essential to fully characterize the safety profile of systemic immunomodulating therapies for patients with AD. The TREatment of ATopic eczema (TREAT) Registry Taskforce offers a large platform to conduct such research using national registries that collect the same data using a predefined core dataset. Adult and paediatric patients who start treatment with dupilumab or another systemic immunomodulating agent for their AD will be included. The primary endpoint is the incidence of malignancies (excluding non-melanoma skin cancer) compared between the treatment groups. Secondary endpoints include other serious adverse events and adverse events of special interest, such as eye disorders and eosinophilia (149).

The BioDay registry, a prospective multicenter registry, published recently its first real-world evaluation of dupilumab in AD and showed a significantly improved disease severity and decreased severity-related serum biomarkers in patients with very difficult-to-treat AD (patients who failed treatment on ≥2 immunosuppressive drugs) in a daily practice setting. The most frequent AE was DAC reported in 34% of patients (82).

vi. Efficacy versus effectiveness in a real-world setting

Several retrospective real-life cohorts and AD registries report similar impact of dupilumab on AD severity as in RCTs with an acceptable safety profile (82, 85, 86, 150, 151).

vii. Efficacy and safety in the paediatric population

Data on the efficacy and safety of dupilumab in the 12-17- and 6-11-years old AD patients are limited and evidence for long-term use (> 1 year) is lacking. The development of new drugs for the treatment of paediatric AD proves difficult due to the limited availability of a very heterogenous population to enter randomised placebo-controlled trials in combination with the stringent requirements of the Paediatric Investigational Plan (EMA) or Paediatric Study Plan (FDA). Registries and large-scale international consortia evaluating paediatric AD could help to overcome this major unmet need in the field of dupilumab for AD.

The Paediatric Study in Atopic Dermatitis (PEDISTAD) is a prospective, observational, longitudinal study in paediatric patients with moderate-to-severe AD who are currently

receiving systemic or topical treatment and whose disease is not adequately controlled by topical prescription therapies or for whom those therapies are not medically advisable. Data collected will include disease characteristics and comorbidities, current therapy for AD and initiation of new treatments/changes in current treatment, safety and biomarkers, patient-oriented outcomes and health-economics parameters (152).

viii. Overall efficacy on AD co-morbidities

There is high incidence of T2-driven co-morbidity in AD cases such as chronic rhinosinusitis with nasal polyps (CRSwNP), asthma, allergic rhinitis, food allergy, anaphylaxis, allergic conjunctivitis (1,2). As dupilumab is systemically bio available improving the overall patient wellbeing by acting on the non-skin targets in AD patients should be further explored, both in RCTs and in real life studies. Currently dupilumab is approved for asthma, AD and CRSwNP.

A recent multicentre, prospective, observational, real-life study including adult patients with moderate/severe AD treated with dupilumab in 16 Italian care centres evaluated the impact on the associated perennial AR and asthma. Dupilumab significantly improved disease control and QoL both in AR and in asthma, in parallel with AD (153).

The EAACI guidelines provide conditional recommendation (expert opinion based) for the use of dupilumab for AD and associated T2 co-morbidities (Box 3).

c. Additional major unmet needs and research priorities

The GDG proposed several key areas of interest both for the clinician and the basic researcher and from the health-care point of view (box 10). Unmet needs have been assessed from the perspectives of different stakeholders.

Box 10: Gaps in evidence for the use of dupilumab in AD and plan to address		
Gaps in evidence	**Plan to address**	**Priority**
Standardising the use in clinical practice 1. Criteria for responders and suboptimal response (early stopping rules) 2. When to assess response 3. The difference between fast and slow responders 4. Switching rules 5. Duration of treatment in responders (late stopping rules) 6. Long-term treatment regimen in responders: longer interval, down-dosing, possibility of stopping treatment, switch to strategies like topical application, etc. 7. How to switch from other systemic treatment, such as ciclosporin 8. Identification of factors related to failure 9. Routine measurement of ADA	Prospective trials testing the clinical question followed by validation in independent population	High
Implementation of guidelines for the use of biologicals in clinical practice	In-depth education of HCPs on AD pathogenic mechanisms and in recogonising the T2 endotype recognising the involvement of both the innate and the adaptive immune system.	High
Improving evaluation by combining clinical and molecular outcomes	Multidimensional endotyping validating skin and systemic biomarker profiles	High
Long-term safety data (> 5 years)	Well-structured post-marketing surveillance using AD registries	High
Assess the long-term efficacy/disease modifying effect (after treatment cessation)	Identify biomarkers related to the course of AD Well-designed RCT and real-life studies focusing on long-term efficacy	High

	Mechanistic studies at a single cell level	
Efficacy and safety data in the paediatric population	RCT and RWE trials/registries focused primarily on the paediatric population	High
Efficacy and safety in selected populations (pregnancy,) and in high-risk populations	RCT and RWE trials/registries focused primarily on these populations	High
Cost-effectiveness	Sectoral and generalised cost-effectiveness analysis, including the real-word perspective Long-term perspective as disease modifying intervention and thereby influence long-term cost	High
Use of biomarkers for stratification	Proof of concept studies evaluating patient selection based on biomarkers	High
Validation of disease phenotypes and endotypes	Proof of concept studies evaluating patient selection based on phenotypes and/or endotypes	High
Impact of multi- morbidities (allergic rhinitis, asthma, CRSwNP, food allergy, etc)	Studies evaluating the global effect of biologicals on multi- morbidities	High
Fair accessibility to AD correct diagnosis and optimal targeted treatment	Reorganisation of AD care Implementation of the patients' perspective from research to models of care Implementation of management pathways/clinical decision systems	High
Comparison between biologicals available for AD (approved and currently tested)	Independent head-to-head comparison between biologicals, ideally with cross-over design	High
Alignment of studies (including RWE) with guidance from regulatory bodies.	Work in partnership with regulatory bodies to continuously review trial methodology and outcomes.	Medium
The impact of age/race/ethnicity/phenotype on the short and the long-term effects (efficacy and safety)	Well-designed RCT, example for personalised medicine	Medium
Does 'resistance' occur as in antibiotic or anti-cancer therapy and what are the underlying molecular mechanisms?	Well-designed RCT, example for personalised medicine	Medium
Validation of different regimens: shorter or longer intervals ('pulse-wise') rather than as a chronic ('maintenance') therapy (e.g. to prevent resistance)?	RCTs and real-life studies testing different approaches in terms of dose, duration and route	Medium
Combination of dupilumab with other immune modulation interventions (allergen immunotherapy), other biologicals, immunosuppresants	RCTs and real-life studies	Medium
The need for a background topical treatment in responders	RCTs and real-life studies	Medium

VII.   Conclusion

The addition of dupilumab for the treatment of patients with moderate and severe atopic dermatitis is supported by improved understanding of disease mechanisms and has proved so far efficacious and safe in adults and the 12-17 years old population. Evidence is accumulating for the 6-11 years old population.

There are several critical points that need further evaluation, from the effectiveness in real-world settings to the sustainability by the healthcare systems, especially if long-term administration is warranted.

This EAACI Guideline on the use of dupilumab for atopic dermatitis offer a desk reference tool for healthcare providers, patients, regulators and healthcare systems based on a critical appraisal of the current evidence and a structured approach in formulating recommendations in alignment with the key principles of personalised medicine and implementation science.

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