



Dupilumab in the treatment of moderate-to-severe atopic dermatitis

Magdalena Kraft & Margitta Worm

To cite this article: Magdalena Kraft & Margitta Worm (2017): Dupilumab in the treatment of moderate-to-severe atopic dermatitis, Expert Review of Clinical Immunology, DOI: [10.1080/1744666X.2017.1292134](https://doi.org/10.1080/1744666X.2017.1292134)

To link to this article: <http://dx.doi.org/10.1080/1744666X.2017.1292134>



Accepted author version posted online: 06 Feb 2017.
Published online: 15 Feb 2017.



[Submit your article to this journal](#) 



Article views: 50



[View related articles](#) 



[View Crossmark data](#) 

DRUG PROFILE

Dupilumab in the treatment of moderate-to-severe atopic dermatitis

Magdalena Kraft and Margitta Worm

Department of Dermatology and Allergology, Allergy-Center-Charité, Charité – Universitätsmedizin Berlin, Berlin, Germany

ABSTRACT

Introduction: Atopic dermatitis is a common inflammatory skin disease with an increasing prevalence. Treatment of patients suffering from mild or moderate disease includes the use of emollients and topical glucocorticoids or topical calcineurin inhibitors. Patients with chronic and severe atopic dermatitis where topical therapy is usually insufficient require the use of systemic immunosuppressive drugs, which is often limited due to toxicity and severe adverse effects.

Areas covered: This review summarizes the literature on the mechanism of action, clinical efficacy and safety of dupilumab, a monoclonal antibody that targets the α -subunit of the interleukin-4 receptor (IL-4R α) leading to the inhibition of both the IL-4 and IL-13 pathways. A literature search was performed on Pubmed and ClinicalTrials.gov using key words 'dupilumab', 'REGN668', 'IL-4'/IL-13' and 'atopic dermatitis'.

Expert commentary: Dupilumab offers an innovative therapeutic approach for moderate-to-severe atopic dermatitis. It is not approved for clinical use in any country yet; however, due to its excellent clinical efficacy and a favorable safety profile, dupilumab may revolutionize the treatment of moderate-to-severe atopic dermatitis in the next upcoming years.

ARTICLE HISTORY

Received 10 December 2016
Accepted 3 February 2017

KEYWORDS

Atopic dermatitis; atopic eczema; biologics; dupilumab; IL-4; IL-13; REGN668

1. Introduction

Atopic dermatitis is a common inflammatory skin disease. The prevalence rates worldwide are up to 2–5% for adults [1–3] and up to 10–20% for children [4–6]. Typically, the disease occurs for the first time in early childhood, but also an adult onset of atopic dermatitis (AD) is not uncommon [7]. Most of the children presenting with AD outgrow the disease; however, approximately one in four (or even more) of them continues to suffer from AD during adulthood [8,9]. Atopic dermatitis is often the beginning of the *atopic march* – meaning children with AD are much more likely to develop food allergies, asthma, and allergic rhinitis [10]. Atopic dermatitis seems to be more common in well-developed countries (including the USA and Europe) than in the developing ones [4,11]. Longitudinal data suggest that the prevalence of AD over the last decades has been increasing [11–13].

The pathogenesis of AD is multifactorial and is not completely understood. However, in the last years, enormous efforts have been made to explore the underlying mechanisms of the disease, which has led to deeper insights into its pathophysiology and development of new treatment approaches. The abnormalities in the skin of AD patients include an activation of the immune system (especially the Th2-pathway) without an adequate stimulus, epithelial barrier dysfunction (often associated with a mutation of filaggrin gene), and an imbalance in the skin microbiota composition [14–18]. The strong activation of Th2 cells with overexpression of the cytokines interleukin (IL)-4, IL-5, IL-13, and IL-31 is a hallmark of AD [19,20]. However, the activation of other T-cells

pathways (Th17, Th22, and Th1 in a chronic disease) has been observed in lesional skin as well [15,19].

Clinical manifestations of AD include erythema, edema, oozing, and papulation in the early stages and excoriations, crusting, lichenification, and rhagades in subchronic and chronic skin lesions [21]. Patients suffer from pruritus, frequently leading to sleeping disturbances and an impairment of concentration. Moreover, AD patients tend to develop more frequently severe skin infections by *Staphylococcus aureus* or herpes viruses than individuals with healthy skin [16].

The standard treatment for AD consists of emollients to improve the impaired skin barrier combined with topical immunosuppressive substances, such as glucocorticoids or calcineurin inhibitors, in mild-to-moderate cases and systemic immunosuppression in severe cases.

According to the guidelines of the American Academy of Dermatology, and also the European guidelines, the use of moisturizers as a fundamental part of therapy for all AD patients is highly recommended [22]. The use of wet-wrap therapy can be recommended for moderate-to-severe AD. Topical glucocorticoids and calcineurin inhibitors (pimecrolimus and tacrolimus) should be used when emollients therapy is insufficient to control the disease. A proactive therapy with these agents (applied 1–3 times per week) reduces the frequency of flares. No topical antimicrobials and antiseptics are recommended (except for bleach baths and intranasal mupirocin in patients with clinical symptoms of secondary bacterial infection) [22]. A second-line treatment for patients with the disease not being adequately controlled by topical agents includes phototherapy, cyclosporine, azathioprine,

methotrexate, or in certain cases, mycophenolate mofetil or interferon gamma; all of these drugs are off-label treatment options in the United States. Cyclosporine is the only licensed systemic drug for the treatment of severe AD in some European countries and Japan [23–25]. Systemic glucocorticoids should be used only as a short-time therapy for acute, severe exacerbations or as a bridge therapy to other systemic treatment [23]. Adjuvant therapy in form of educational and/or psychological interventions has been shown to be beneficial for patients with AD [26].

The European *Guidelines for the treatment of atopic eczema* are similar in most aspects to the American ones and differ only in some minor recommendations [24,27].

Following these recommendations, the therapy of patients with mild AD usually causes no difficulties. However, treatment of patients with moderate-to-severe disease still remains challenging. All systemic drugs listed above suppress the immune system in an unselective/broad way and their use is limited due to their toxicity and sometimes serious side effects. The high prevalence of AD and the absence of satisfying therapeutic options for its severe forms cause an enormous unmet medical need in the disease treatment.

Due to novel findings on the pathophysiology of the disease, many new therapeutic approaches have been developed in the last years. Currently, there are numerous ongoing trials studying various substances in AD patients, including several biologics (targeting, for instance IL4R α , IL-5, IL-13, IL-17, IL-22, IL-12/IL-23p40, IL-31R, IL-31, and TSLP), histamine-4 receptor inhibitors, CRTh2 antagonists, phosphodiesterase (PDE)-4 inhibitors, and Janus kinase (JAK) inhibitors [28,29]. Based on the currently published studies, the most promising substance among these is the IL-4–13R antibody dupilumab (also known as REGN668), which has the potential to revolutionize the therapy of moderate-to-severe AD in the next few years.

2. Biological properties, mechanism of action, and pharmacokinetics of dupilumab

Dupilumab is a fully human monoclonal IgG4 antibody targeting the α -subunit of the interleukin-4 receptor (IL-4R α) [30,31]. IL-4R α is a part of type I and type II IL-4 receptors and the IL-13 receptor; therefore, blocking it inhibits the downstream signaling of IL-4 and IL-13 [31]. IL-4 and IL-13, both crucial cytokines of the Th2 pathway, have partly overlapping effects and are essential for the IgE production [32]. Besides that key function, they exhibit multiple inflammatory immune reactions like the recruitment of eosinophils [20] into inflamed tissues. IL-4 also plays an essential role in the differentiation of Th2 cells [33]. Moreover, both cytokines disturb the skin barrier, for example, by suppressing the expression of barrier proteins (involucrin, loricrin, and filaggrin) and antimicrobial peptides [34–39]. Figure 1 summarizes the most important mechanisms of action of IL-4/IL-13 in AD.

Patients treated with dupilumab show significant dose-dependent changes in gene expression of lesional skin. The differences in the transcriptome between lesional and non-lesional skin of patients with AD diminished after 4 weeks of therapy with 150 or 300 mg of dupilumab; this effect was not present in the placebo-treated group [30,40]. The reduction of expression of genes associated with hyperplasia (keratin 16, MK167), Th2-related chemokines (CCL13, CCL17, CCL18, and CCL26), and many others immune markers was described [40]. Also, an upregulation of genes related to lipid metabolism and barrier function in the skin samples from dupilumab-treated patients has been reported [40]. However, there were no significant changes of mRNA expression regarding the major Th2 cytokines (IL-4, IL-5, IL-13, and IL-31), Th1 cytokines, IL-17A, or IL-22, although many IL17/IL22-modulated genes were suppressed as well [40]. The decrease of mRNA expression of CCL26, CCL13, and keratin 16 correlated with the improvement of the clinical score EASI [40].

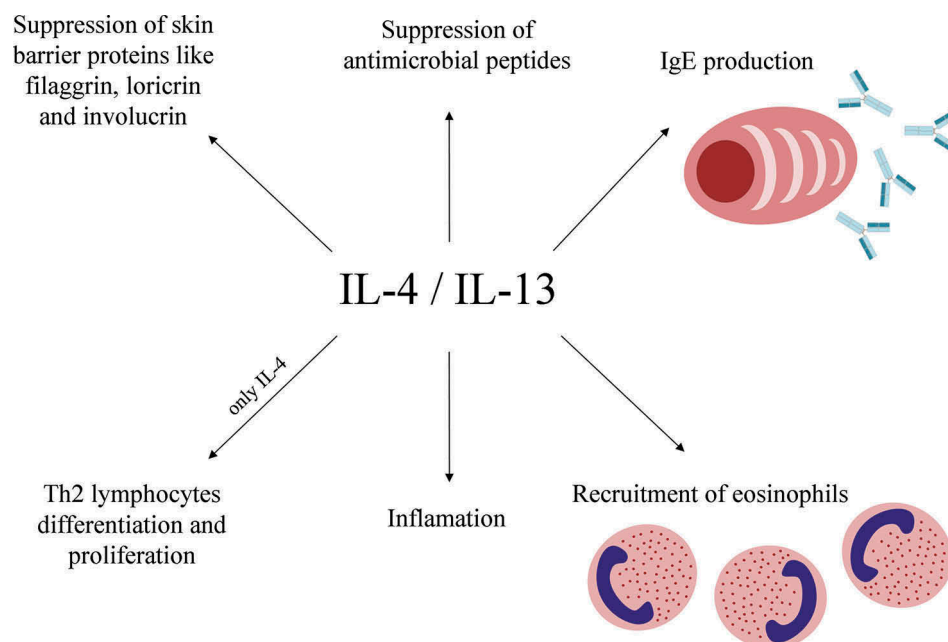


Figure 1. Overview of the most important mechanisms of action of IL-4/IL-13 in atopic dermatitis.

Dupilumab therapy also has an effect on blood biomarkers associated with the Th2 pathway. The levels of TARC (also known as CCL17) started to drop after the first injection of dupilumab and after 12 weeks of therapy with 300 mg, an 83% reduction, compared with the baseline, was observed. Also, 4 weeks of treatment was sufficient to reduce in a dose-dependent manner the levels of TARC (by 67–76% for the 300-mg dose, approximately 48% for the 150-mg dose, and with no effect for the 75-mg dose) [30]. The IgE reduction occurred delayed so that after 4 weeks, roughly no difference between patients administered placebo or dupilumab could be observed; however, after 12 weeks of treatment with 300 mg of dupilumab, 39% less IgE, compared with the baseline, was measured [30].

Elimination of dupilumab seems to occur (in a similar way to that of other human monoclonal antibodies) mostly due to binding to its target, followed by complex internalization [31]. There has been only one publication describing pharmacokinetics of dupilumab. The presented estimations of parameters were based on 2518 serum samples from 197 participants (healthy volunteers and AD patients) from six phase 1 and phase 2 clinical trials [31]. To describe the pharmacokinetics of dupilumab, the authors estimated ‘a two-compartment model with parallel linear and Michaelis-Menten elimination from the central compartment’ [31]. No differences in pharmacokinetics of dupilumab according to gender or patients with AD versus healthy volunteers were noted. The weight affected the central volume; this, however, does not seem to be relevant in the clinical practice [31].

3. Clinical efficacy of dupilumab

3.1. Clinical trials overview

Assessing the clinical efficacy of dupilumab for the treatment of AD started with two small phase 1 studies comparing different dosages of dupilumab with placebo, followed by three phase 2 trials [30,41–43]. In the phase 2 trials, a total number of 520 patients were recruited. Two phase 3 studies

with the same design enrolled 1379 patients [44]. All participants were adults with moderate or severe AD (defined as score 3 or 4 on the Investigator’s Global Assessment [IGA] scale). In almost all trials (with the exception of one small phase 2a study), dupilumab was used as a monotherapy. No data comparing the efficacy of dupilumab in patients with intrinsic versus extrinsic phenotype of AD have been published. The longest course of treatment for which the data have been published is 16 weeks.

There have also been two trials investigating the efficacy of dupilumab for the treatment of asthma [45,46] and one for the treatment of nasal polyposis [47], published in the last years. Many other studies are being conducted currently to access the efficacy and safety of dupilumab for treating children, long-time therapy regimes, and combinations with other drugs in AD. There is also growing interest in applying dupilumab in the therapy of asthma, nasal polyposis, and eosinophilic esophagitis. Table 1 provides an overview of published phase 2 and 3 trials and Table 2 of ongoing dupilumab trials in patients with AD; Table 3 presents all studies for other indications.

3.2. Phase 1 and 2 studies

The aim of phase 1 trials was mainly to assess the safety of dupilumab treatment in patients with AD. In the M4A study (ClinicalTrials.gov number NCT01259323), 30 adults from the United States were randomized to four groups and were administered 75, 150, 300 mg of dupilumab or a placebo. In the multinational M4B study (ClinicalTrials.gov number NCT01385657), 37 patients received 150 or 300 mg of dupilumab, or a placebo. In both studies, the inclusion criteria were moderate-to-severe AD not sufficiently controlled by topical immunosuppressive therapy. The drug or placebo was administered sc once a week during the 4-week period of time [30].

In the combined analysis of both trials, a dose-dependent reduction of the symptoms within 1 month of dupilumab

Table 1. Overview of completed and published dupilumab phase 2 and 3 trials in patients with atopic dermatitis [30,41,44].

Trial	Phase	Population	Design	Outcome
M12 NCT01548404	2a	Adults with moderate-to-severe AD from Europe <i>N</i> = 109	Randomized, double-blind, placebo-controlled, multicenter trial; patients received 300 mg of dupilumab or a placebo once a week for 12 weeks	Patients receiving dupilumab had a 74% reduction of EASI score versus a 23% reduction in the placebo group (<i>P</i> < 0.001)
C4 NCT01639040	2a	Adults with moderate-to-severe AD from Europe <i>N</i> = 31	Randomized, double-blind, placebo-controlled, multicenter trial; patients received 300 mg of dupilumab or a placebo once a week combined with a standardized regimen of topical glucocorticoids treatment (duration: 4 weeks)	No safety concerns. Patients receiving dupilumab and topical glucocorticoids had a 76% reduction of EASI score versus a 53% reduction in the group treated with a placebo and topical glucocorticoids
NCT01859988	2b	Adults with moderate-to-severe AD from North America, Europe, and Japan <i>N</i> = 380	Randomized, double-blind, placebo-controlled, multicenter trial; patients received 300 mg of dupilumab every week or every other week, 200 mg every other week or every 4 weeks, 100 mg every 4 weeks or a placebo for 16 weeks	Patients treated with dupilumab achieved a significantly better reduction of EASI score than the placebo group (–74% for 300 mg of dupilumab every week, –45% for 100 mg every 4 weeks versus –18% for placebo; <i>P</i> < 0.0001 for all dupilumab groups)
SOLO 1 NCT02277743	3	Adults with moderate-to-severe AD from North America, Europe, and Asia <i>N</i> = 671	Randomized, double-blind, placebo-controlled multicenter trial; patients received 300 mg of dupilumab every week or every other week or a placebo for 16 weeks	Score 0 or 1 on IGA scale was achieved by 37% of patients receiving dupilumab every week, 38% patients receiving dupilumab every other week, and 10% patients in the placebo group (<i>P</i> < 0.001)
SOLO 2 NCT02277769	3	Adults with moderate-to-severe AD from North America, Europe, and Asia <i>N</i> = 708		Score 0 or 1 on IGA scale was achieved by 36% of patients receiving dupilumab every week and every other week and 8% patients in the placebo group (<i>P</i> < 0.001)

Trial	Phase	Population	Description
NCT02407756	2a	Adolescents ≥ 12 – <18 years of age with moderate-to-severe AD or children ≥ 6 – <12 years of age with severe AD	Non-randomized, open-label study to investigate the safety, pharmacokinetics, and efficacy of dupilumab in children
NCT02612454	3		Non-randomized, open-label extension study to investigate the long-term safety and efficacy of dupilumab in children
NCT02647086	1	Adult patients with moderate-to-severe AD	Non-randomized, open-label study to investigate the effects of dupilumab on the pharmacokinetics of some cytochrome P450 substrates (midazolam, omeprazole, warfarin, caffeine, and metoprolol)
NCT02210780	2	Adult patients with moderate-to-severe AD	Randomized, double-blind, placebo-controlled study assessing vaccination responses under dupilumab treatment
LIBERTY AD SOLO-CONTINUE NCT02395133	3		Maintenance trial of SOLO 1 and SOLO 2 to access long-term safety and efficacy of dupilumab (total duration: 36 weeks)
LIBERTY AD MAINTAIN NCT01949311	3		Open-label extension study for patients who participated in earlier dupilumab AD trials
NCT02755649	3	Adult patients with severe AD with no response or contraindications to oral cyclosporine A treatment	Randomized, double-blind, placebo-controlled trial investigating dupilumab combined with standardized regimen of topical glucocorticoids treatment
NCT02260986	3	Adult patients with moderate-to-severe AD	Randomized, double-blind, placebo-controlled study to investigate the efficacy and long-term safety of dupilumab therapy in combination with topical glucocorticoids

Trial	Condition	Phase	Population	Outcome
NCT01312961	Asthma	2	Adults with persistent, moderate-to-severe asthma	Significant reduction of the occurrence of asthma exacerbations under withdrawal of long-acting beta-agonists and inhaled glucocorticoids
NCT01854047	Asthma	2	Adults with uncontrolled asthma despite use of inhaled glucocorticoids and a long-acting β_2 agonist	Increased lung function and reduced rate of severe exacerbations under dupilumab therapy
NCT02573233	Asthma	2	Adults with persistent asthma	Ongoing
LIBERTY ASTHMA TRAVERSE	Asthma	2/3	Adults and adolescents ≥ 12 who participated in previous dupilumab asthma studies	Ongoing
NCT02134028	Asthma	3	Adults and adolescents ≥ 12 with persistent asthma	Ongoing
LIBERTY ASTHMA QUEST	Asthma	3	Adults and adolescents ≥ 12 with severe, steroid-dependent asthma	Ongoing
NCT02414854	Asthma	3	Adults and adolescents ≥ 12 with severe, steroid-dependent asthma	Ongoing
VENTURE NCT02528214	Asthma	3	Children ≥ 6 – <12 with uncontrolled, persistent asthma	Starts 2017
LIBERTY ASTHMA VOYAGE	Eosinophilic esophagitis	2	Adults with active, moderate-to-severe eosinophilic esophagitis	Ongoing
NCT02948959	Nasal polyposis	2	Adults with nasal polyposis and chronic symptoms of sinusitis	Patients treated with dupilumab achieved significant reduction of endoscopic nasal polyp score and disease symptoms compared with the placebo group
NCT02379052	Nasal polyposis	3	Adults with nasal polyposis	Ongoing
NCT01920893	Nasal polyposis	3	Adults with nasal polyposis	Ongoing

Two phase 2a trials (M12 ClinicalTrials.gov number NCT01548404 and C4 ClinicalTrials.gov number NCT01639040), both conducted in Europe, and one multinational phase 2b trial (ClinicalTrials.gov number NCT01859988) recruited a total number of 520 patients with moderate-to-severe AD.

according to the baseline IgE (with levels below 150 kU/L standing for intrinsic and levels above 150 kU/L for extrinsic type of AD). The clinical efficacy of dupilumab was assessed after 12 weeks of treatment. Compared with the 4-week data, further reduction of the symptoms of AD could be shown. In the group receiving 300 mg of dupilumab for 12 weeks, EASI-50 occurred in 85% of patients versus 35% of patients in the placebo group. Forty percent of patients treated with dupilumab had, at the end of the study, no or almost no disease activity (IGA 0 or 1). In the placebo group, this outcome was achieved by only 7% of the patients. The reduction in itching (measured as the difference in the score on pruritus numerical-rating scale between the baseline and week 12) was 56% in the dupilumab and 15% in the placebo group [30]. No data regarding any differences between patients with intrinsic versus extrinsic AD were provided.

In the smaller C4 study, the efficacy of dupilumab with additional topical glucocorticoids treatments was assessed. The patients were randomized 2:1; one group was administered 300 mg dupilumab ($N = 21$) and the other received a placebo ($N = 10$) once weekly for 4 weeks. Additionally, both groups were applying topical glucocorticoids according to a standardized regimen. All of the patients receiving dupilumab and undergoing treatment with topical glucocorticoids achieved EASI-50. In the group treated only with topical glucocorticoids and a placebo, the 50% reduction of the EASI score occurred only in one half of the patients. Furthermore, the dupilumab group needed 50% less topical glucocorticoids than the placebo group; however, this difference was not statistically significant [30].

In the phase 2b trial, 380 patients from Japan, Europe, and North America were randomized 1:1:1:1:1 (stratified by score on IGA and region Japan vs. North America/Europe) into six groups and administered the following doses: 300 mg of dupilumab once a week, 300 mg of dupilumab every other week, 200 mg of dupilumab every other week, 300 mg of dupilumab every 4 weeks, 100 mg of dupilumab every 4 weeks, or a placebo once a week for 16 weeks. On the first day of treatment, all patients being randomized to one of the dupilumab groups received a loading dose of 600 or 400 mg of dupilumab. All participants were asked to use emollients twice a day. Topical immunosuppressants and systemic drugs for the treatment of AD (apart from antihistamines and antibiotics) were not allowed. The primary end outcome was a percentage reduction of EASI score between baseline and week 16 [41–43].

All groups treated with dupilumab achieved significantly better reduction of the symptoms than the placebo group. The improvement was dose-dependent; the greatest reduction of EASI (74%) was attained by the treatment with 300 mg of dupilumab once a week; the administration of 200 mg of dupilumab every other week reduced EASI by 65% and a dose of 100 mg of dupilumab every 4 weeks reduced EASI by 45%. In the placebo group, the EASI reduction rate was at the level of 18%. All dupilumab regimes apart from the 100-mg dose every 4 weeks were able to significantly reduce itching (measured by the improvement in peak weekly pruritus NRS score). The most effective here was also the treatment with 300 mg of dupilumab every week (47% reduction) or every other week (40% reduction) [41].

3.3. Phase 3 studies

Two randomized, placebo-controlled, double-blinded phase 3 studies with the same design, SOLO 1 (ClinicalTrials.gov number NCT02277743) and SOLO 2 (ClinicalTrials.gov number NCT02277769), were recently published [44]. Both studies enrolled adult patients with moderate-to-severe (IGA 3 or 4), chronic (symptoms for at least 3 years before screening) AD not sufficiently controlled by topical immunosuppressive therapy. Patients ($N = 671$ in SOLO 1 and $N = 708$ in SOLO 2) were randomized 1:1:1 into three groups, one was administered 300 mg of dupilumab every week, one was administered 300 mg of dupilumab every other week, and one was administered a placebo. Patients in both dupilumab groups started with a single 600-mg loading dose on the first day. Treatment continued for 16 weeks. In addition

to the injections, patients were asked to use emollients twice a day. Topical or systemic immunosuppressive drugs were principally forbidden and allowed only as rescue medication [44].

The primary end point of both trials was an IGA score of 0 and 1 after 16 weeks of treatment and a reduction of at least 2 points on the IGA scale (range 0–4) comparing the baseline with the 16-week time point. Key secondary end points were the fraction of patients achieving EASI-75 (75% reduction of score on Eczema Area and Severity Index; this was a coprimary end point in the European Union and Japan), the improvement of pruritus, defined as at least a 4-point reduction in the weekly average of peak pruritus scores measured on the NRS (numerical rating scale; range 0–10) at weeks 2, 4, and 16 or at least a 3 point reduction at week 16. Other secondary end points included: EASI-50, EASI-90, mean percent change on the pruritus numerical rating scale score, mean percent change on the EASI score, the Scoring Atopic Dermatitis score (SCORAD), the Global Individual Sign Score (GISS), the score on the Patient-Oriented Eczema Measure (POEM), the score on the Dermatology Life Quality Index (DLQI), the total score on the Hospital Anxiety and Depression Scale (HADS), and the mean percent change of affected body-surface area. Both trials achieved all primary and secondary end points [44].

The primary outcome (IGA of 0 or 1 at week 16 and reduction of at least 2 points between baseline and week 16) was achieved in 37% (SOLO 1) and 36% (SOLO 2) of patients administered 300 mg of dupilumab every week. Patients receiving 300 mg of dupilumab every 2 weeks responded similarly: 38% (SOLO 1) and 36% (SOLO 2) of them had after 16 weeks of treatment no or almost no disease activity (IGA of 0 or 1). The responder rates were significantly lower ($P < 0.001$) in the placebo groups (10% in SOLO 1 and 8% in SOLO 2).

The 75% improvement of the EASI score (comparing baseline with week 16) occurred in 52% (SOLO 1)/48% (SOLO 2) of the patients treated with dupilumab every week and in 51% (SOLO 1)/44% (SOLO 2) of the patients treated with dupilumab every 2 weeks versus in 15% (SOLO 1)/12% (SOLO 2) of the patients in the placebo groups.

The improvement of the pruritus, defined as a reduction of at least 3 points on the NRS between baseline and week 16, was reported in significantly more patients, who were administered dupilumab every week (52% SOLO 1/49% SOLO 2) or every other week (47% SOLO 1/51% SOLO 2) than in the placebo group (17% SOLO 1/13% SOLO 2).

The mean reduction in SCORAD (Scoring Atopic Dermatitis Scale; range 0–103) between baseline and week 16 was 57% (SOLO 1)/54% (SOLO 2) among patients who received dupilumab every week, 58% (SOLO 1)/51% (SOLO 2) among patients who received every other week, and 29% (SOLO 1)/20% (SOLO 2) among patients receiving a placebo. Furthermore, the percent of affected body-surface area, the score on the GISS, on the POEM, on the DLQI, and the total score on the HADS improved significantly more in the treatment versus in the placebo groups. In both trials, more patients receiving placebo needed a rescue medication. The all over rate of rescue medication used in patients treated with

300 mg of dupilumab every week was 23% (SOLO 1)/21% (SOLO 2). In the placebo group, this was 51% (SOLO 1)/52% (SOLO 2) of the patients. Participants treated with a placebo needed more frequent systemic rescue treatment and it happened earlier in the study course than in the dupilumab groups [44].

3.4. Other indications

The first published study investigating the efficacy of dupilumab in the treatment of diseases other than AD was a randomized, double-blinded, placebo-controlled trial, which included 104 patients with moderate-to-severe asthma and a at least 300 eosinophils/ μ L blood or an eosinophil level in sputum of at least 3% (ClinicalTrials.gov number NCT01312961). In this trial, the treatment with dupilumab did reduce the onset of asthma exacerbations under withdrawal of long-acting beta-agonists and inhaled glucocorticoids and improved the lung function of the asthma in comparison to the patients receiving placebo [45].

In 2016, those results were confirmed by another larger phase 2b study [46]. Patients with moderate-to-severe asthma being treated with inhaled corticosteroids and long-acting beta-agonists ($N = 769$) were randomized into five groups, one of them received a placebo ($N = 158$) and the others, different doses of dupilumab ($N = 611$; 200 or 300 mg every 2 or 4 weeks). The primary end point was improvement of forced expiratory volume in 1 s (FEV1) after 12 weeks of treatment in patients with at least 300 eosinophils/ μ L in the blood.

This outcome was achieved for all treatment regimes apart from the 200-mg dose every 4 weeks: the FEV1 of patients with more than 300 eosinophils per μ L improved by 18–26% (0.26–0.43 L) in the dupilumab treatment groups compared with 11% (0.18 L) in the placebo group. This effect was stable after 24 weeks of treatment. In patients with less than 300 eosinophils per μ L, an improvement of 11–14% (0.18–0.25 L) compared with 4.8% (0.1 L) in the placebo group after 12 weeks of treatment was observed. This difference was statistically significant for treatment with 200 and 300 mg of dupilumab every 2 weeks. Dupilumab therapy also succeeded in reducing the rate of patients suffering from at least one severe exacerbation during the 24-week treatment period from 26% (placebo) to 11% (300 mg every other week), 9% (200 mg every other week), or 15% (200 mg every 4 weeks) [46].

Another recently published study investigated the efficacy of dupilumab in patients suffering from chronic sinusitis and nasal polyposis. Sixty patients were randomized 1:1 into the dupilumab (300 mg every week following a 600-mg loading dose) or placebo group. All patients were additionally using a mometasone furoate nasal spray twice a day. The dupilumab/placebo injections were continued for 16 weeks. After treatment, changes in the endoscopic nasal polyp score, sense of smell score (measured by the University of Pennsylvania Smell Identification Test), radiological changes (in computed tomography), and many other features of nasal function and quality of life parameters were assessed. The mean nasal polyp score after 16 weeks

of therapy was reduced by -1.9 (on a scale with a range of 0–8) in the group administered dupilumab, which was highly significant compared with the -0.3 reduction in the placebo group. Positive, significant changes were also noticed according to sense of smell, quality of life, radiological measurements, and daily symptoms [47].

4. Safety and tolerability profile of dupilumab

Dupilumab was well tolerated in all clinical trials. Adverse events occurred mostly similar frequent in patients administered placebo or dupilumab and most of them were mild or moderate and temporary.

In phases 1 and 2a studies, serious adverse events occurred in less than 10% ($N = 13$) of the patients and were more frequent in the placebo group ($N = 9/80$) than among dupilumab-treated patients ($N = 2/127$) [30]. The most frequent adverse events were headaches and nasopharyngitis (both more frequent among patients treated with dupilumab than the placebo group). Exacerbations of AD and skin infections were more common in patients who received the placebo and were responsible for the higher rate of serious adverse events in this group [30].

In phase 2b trial, the most common adverse events were nasopharyngitis, upper respiratory tract infections, exacerbations of AD, and headache [41]. Respiratory infections occurred similar frequent in all groups. Headaches were more frequent in the dupilumab treatment groups (8–15%) than in the placebo group (3%). Dupilumab-treated patients had a higher rate of infections with herpes viruses (5–12%), all of them being mild to moderate, as compared with the placebo group (2%). However, the total skin infection rate was similar in patients administered placebo and those treated with dupilumab. Patients receiving dupilumab experienced conjunctivitis more often (2–11%) than those receiving the placebo (3%). The total overall rate of serious adverse events was, as in previous studies, higher in the placebo group (7%) than in patients who received the trial drug (for all dupilumab groups combined: 4%) [41].

In phase 3 trials (SOLO 1 and SOLO 2), the overall incidence of adverse events was similar in the treatment and placebo groups. Serious adverse events were rare and occurred more frequent in the placebo groups of both studies (mostly due to severe exacerbations of AD). Exacerbations of AD, headache, injection-site reactions, and nasopharyngitis were the most frequent adverse events in these trials [44]. (Table 4 displays an overview of frequent adverse events from both phase 3 trials.) Laboratory values did not differ among the groups apart from a slight transient increase in the eosinophils level during the first 12 weeks of dupilumab treatment [44].

The frequencies of all infectious adverse events were similar between placebo and treatment groups. There was no difference according to the frequency of nasopharyngitis. Patients administered dupilumab were slightly more likely to suffer from upper respiratory tract infections (SOLO 1: dupilumab every week 5%, dupilumab every other week 3% vs. placebo 2%; SOLO 2: dupilumab every week 4%, dupilumab every other week 3% vs. placebo 2%), infectious conjunctivitis and conjunctivitis of unspecified cause (SOLO 1: dupilumab every week 3%,

Table 4. Common adverse events in dupilumab phase 3 trials [44].

Adverse event	Placebo SOLO 1/SOLO 2	Dupilumab 300 mg sc every other week SOLO 1/SOLO 2	Dupilumab 300 mg sc every week SOLO 1/SOLO 2
	Percent of patients		
Injection-site reactions	6/6	8/14	19/13
Nasopharyngitis and upper respiratory tract infections	10/11	13/11	16/12
Headache	6/5	9/8	5/9
Adjudicated skin infections	8/11	6/6	6/6
Any herpes viral infections	4/3	7/4	4/5
Allergic conjunctivitis	1/1	5/1	3/1
Infectious conjunctivitis and conjunctivitis of unspecified cause	1/<1	5/4	3/4

dupilumab every other week 5% vs. placebo 1%; SOLO 2: dupilumab every week 4%, dupilumab every other week 4% vs. placebo <1%), and herpes infections (SOLO 1: dupilumab every week 4%, dupilumab every other week 7% vs. placebo 4%; SOLO 2: dupilumab every week 5%, dupilumab every other week 4% vs. placebo 3%). Adjudicated skin infections occurred more often in the placebo group (SOLO 1: dupilumab every week 6%, dupilumab every other week 6% vs. placebo 8%; SOLO 2: dupilumab every week 6%, dupilumab every other week: 6% vs. placebo 11%) [44].

The rate of injection-site reactions was approximately twice as much in the dupilumab treatment comparing with placebo group, most of them being mild or moderate. A more frequent occurrence of allergic conjunctivitis was observed in SOLO 1 (dupilumab every week 3%, dupilumab every other week 5% vs. placebo 1%) but not in the SOLO 2 trial (1% in all groups); however, in both trials, more patients receiving dupilumab suffered from infectious conjunctivitis and a conjunctivitis of an unspecified cause [44]. The mechanism of this adverse events is unknown. It is a subject of speculation whether the conjunctivitis is a part of the allergic systemic disorder not being well targeted with dupilumab treatment or if the blockade of IL-4/IL-13 causes the conjunctivitis e.g. via impaired or aberrant tear production or immunosuppression.

The assessed safety profile of dupilumab in asthma and nasal polyposis trials was similar to those established in AD studies [45–47].

In conclusion, dupilumab has been shown to be a well-tolerated drug with an adverse event rate similar to that of placebo. The combined analysis of phase 2b and both phase 3 AD trials for 300 mg dupilumab every week or every other week treatment groups (including data from 1046 dupilumab-treated patients and 521 patients who received placebo) shows that the dupilumab seems to cause a significant increase in the incidence of injection-site reactions (mostly mild or moderate; dupilumab 12.6% vs. placebo 5.8%), headache (dupilumab 8% vs. 5% placebo), and allergic and nonallergic conjunctivitis (dupilumab 6.6% vs. 1.7% placebo). The rate of upper respiratory tract infections (including nasopharyngitis) was very similar between patients treated with 300 mg of dupilumab (16%) and the placebo group (14%). The difference in the occurrence of herpes infections was small and statistically nonsignificant (5.2% vs. 3.5% in the placebo group; statistical significance was tested with a chi-squared test). The incidence of serious herpes infections, such as eczema herpeticum, was comparably low (there were only a few cases described); therefore, this drug may also be safely administered to patients with a history of eczema herpeticum. However, one still must be careful using dupilumab in this group of patients, as the data from long-term treatment

regimens are not yet published, and the number of patients included in the completed trials may not be sufficient to evaluate properly the risk of this rare condition.

5. Conclusions

The results from the dupilumab trials in almost 2000 patients with moderate-to-severe AD have confirmed its clinical efficacy. A vast majority of patients who received dupilumab benefited from treatment. In approximately half of the patients studied, an up to 75% improvement in skin condition, measured by EASI score, was observed. Moreover, dupilumab treatment leads to a significant and clinically relevant decrease of pruritus, a key symptom being responsible for the significant reduction of the quality of life in the vast majority of patients. In addition, compared to other systemic therapies for AD, dupilumab has a favorable safety profile with mostly mild or moderate adverse reactions reported and an adverse event rate similar to placebo. Furthermore, patients with asthma and nasal polyposis appear to benefit from dupilumab therapy. The available data are based on results from a treatment period of 16 weeks; long-term studies are underway but the results have not yet been published [44].

6. Expert commentary

Dupilumab is not currently approved for use; however, the Biologics License Application submitted by Regeneron Pharmaceuticals and Sanofi for dupilumab was accepted for priority review by the US FDA [49]. Based on the published data from the phase 2 and phase 3 clinical trials, dupilumab has a high potential to revolutionize the treatment of AD in the upcoming coming years. It will most likely become the first biological treatment for AD allowing a targeted treatment approach as it has been introduced for psoriasis another chronic inflammatory skin disease many years ago.

Despite the preliminary findings on its safety and efficacy, many questions about a dupilumab-based treatment in AD remain. We do not yet have data on the long-term efficacy, tolerability, and the safety profile of dupilumab. Also, the mechanism of conjunctivitis, which was a surprisingly frequent adverse event, even leading to discontinuation of treatment, is unclear. The data analysis of different phenotypes of AD (intrinsic vs. extrinsic) was not published; therefore, we cannot be sure if the drug has the same efficacy in both patient groups. Nevertheless, because AD is even more common among children, the efficacy and safety of dupilumab treatment in this patient group is of high interest. Studies investigating these questions are

ongoing and their results, combined with experience in handling of dupilumab in everyday settings of clinical practice, will help determine its significance for the therapy of AD. Whether and to what extent the treatment of AD patients with dupilumab has a disease-modifying effect will need to be studied as well as its efficacy in other allergic conditions like allergic rhinitis or food allergy.

In phase 3 studies, little less than 40% patients achieved 0 or 1 on the IGA scale, meaning no or almost no disease activity; therefore, 60% of patients continued to experience some symptoms under dupilumab therapy. This number can be probably remarkably reduced with an additional treatment using topical agents, which must be further assessed in clinical trials. However, even when dupilumab is approved for use, the unmet need for new therapeutic options for AD will remain.

7. Five-year view

The first revolution in the treatment of AD in clinical practice will probably occur this year and the next with the approval of dupilumab. Another new drug available for this condition is crisaborole – a topical PDE-4 inhibitor that was approved by FDA for the treatment of mild-to-moderate AD in adults and children (from the age of 2 years) in December 2016 [50]. However, crisaborole is much more likely to be an alternative to topical steroids and topical calcineurin inhibitors than to systemic therapy with dupilumab or cyclosporine A.

Numerous other topical and systemic drugs are currently being tested in patients with AD. The majority of substances meant to treat moderate-to-severe AD are biologics (i.e. against IL-5, IL-13, IL-17, IL-22, IL-12/IL-23p40, IL-31R, IL-31, and TSLP), but there are also ongoing trials with small molecules such as histamine-4 receptor, PDE-4, or JAK inhibitors [28,48,51]. There are numerous phase 3 clinical studies (some of them including children from the age of 3 months) of topical products for the treatment of AD; therefore, one may expect more alternatives to topical glucocorticoids in the near future. However, all systemic pharmaceutical approaches listed above are in phase 1 and/or 2 trials; therefore, we must wait to find out which of them may have the potential to revolutionize the therapy of AD, similar to that of dupilumab [48,51].

Key issues

- Atopic dermatitis is a common inflammatory skin disease with the prevalence rates worldwide up to 2–5% for adults and up to 10–20% for children.
- There is an immense unmet need for new therapy concepts for moderate-to-severe atopic dermatitis.
- Due to better understanding of pathophysiology of the disease multiple new therapeutic approaches were developed and are currently a subject of ongoing clinical trials.
- Dupilumab is a monoclonal antibody that targets the α -subunit of the interleukin-4 receptor (IL-4R α) leading to the inhibition of the IL-4 and IL-13 pathways and offering a new treatment possibility for patients with atopic dermatitis.
- Dupilumab showed in several clinical trials efficacy. In phase 3 trials 40% patients treated with dupilumab

achieved 0 or 1 on the IGA scale, meaning no or almost no disease activity. Approximately half of them had a 75% improvement in skin condition, measured by EASI score.

- Dupilumab is a well tolerated drug with an adverse event rate similar to that of the placebo. Most of adverse events which occurred in the clinical trials were mild or moderate. Injection-site reactions, allergic and nonallergic conjunctivitis, headache, and perhaps upper respiratory tract infections (including nasopharyngitis) and herpes infections appear to be the main adverse reactions of the treatment.
- Conjunctivitis seems to be one of the major problems occurring during dupilumab therapy. The pathogenic mechanism of this adverse event is unclear and is a subject of a new ongoing sub-trial.
- Long-term safety and efficacy of dupilumab, treatment of children and its efficacy together with topical anti-inflammatory therapies have not yet been established.
- Other future promising indications for dupilumab in clinical practice are allergic rhinitis and food allergy.

Funding

This article was not funded.

Declaration of interest

M Worm served as an investigator in the dupilumab phase II and phase III studies, received consulting honoraria from Regeneron and Sanofi and lecture honoraria from Sanofi. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

References

Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.

1. Silverberg JI, Hanifin JM. Adult eczema prevalence and associations with asthma and other health and demographic factors: a US population-based study. *J Allergy Clin Immunol*. 2013;132(5):1132–1138.
2. Harrop J, Chinn S, Verlato G, et al. Eczema, atopy and allergen exposure in adults: a population-based study. *Clin Exp Allergy*. 2007;37(4):526–535.
3. Plunkett A, Merlin K, Gill D, et al. The frequency of common nonmalignant skin conditions in adults in central Victoria, Australia. *Int J Dermatol*. 1999;38(12):901–908.
4. Odhiambo JA, Williams HC, Clayton TO, et al. Global variations in prevalence of eczema symptoms in children from ISAAC phase three. *J Allergy Clin Immunol*. 2009;124(6):1251–1258.
5. Shaw TE, Currie GP, Koudelka CW, et al. Eczema prevalence in the United States: data from the 2003 National Survey of Children's Health. *J Invest Dermatol*. 2011;131(1):67–73.
6. Schultz LF, Diepgen T, Svensson A. The occurrence of atopic dermatitis in north Europe: an international questionnaire study. *J Am Acad Dermatol*. 1996;34(5 Pt 1):760–764.
7. Bannister MJ, Freeman S. Adult-onset atopic dermatitis. *Australas J Dermatol*. 2000;41:225–228.
8. Williams HC, Strachan DP. The natural history of childhood eczema: observations from the British 1958 birth cohort study. *Br J Dermatol*. 1998;139(5):834–839.

9. Margolis JS, Abuabara K, Bilker W, et al. Persistence of mild to moderate atopic dermatitis. *JAMA Dermatol.* **2014**;150(6):593–600.
10. Spergel JM, Paller AS. Atopic dermatitis and the atopic march. *J Allergy Clin Immunol.* **2003**;112(6 Suppl):S118–27.
11. Garg N, Silverberg JL. Epidemiology of childhood atopic dermatitis. *Clin Dermatol.* **2015**;33(3):281–288.
12. Jackson KD, Howie LD, Akinbami LJ. Trends in allergic conditions among children: United States, 1997–2011. *NCHS Data Brief.* **2013**;121:1–8.
13. Hansen TE, Evjenth B, Holt J. Increasing prevalence of asthma, allergic rhinoconjunctivitis and eczema among schoolchildren: three surveys during the period 1985–2008. *Acta Paediatr.* **2013**;102(1):47–52.
14. Bieber T. Atopic dermatitis. *N Engl J Med.* **2008** Apr 3;358(14):1483–1494.
15. Werfel T, Allam JP, Biedermann T, et al. Cellular and molecular immunologic mechanisms in patients with atopic dermatitis. *J Allergy Clin Immunol.* **2016** Aug;138(2):336–349.
16. Boguniewicz M, Leung DY. Atopic dermatitis: a disease of altered skin barrier and immune dysregulation. *Immunol Rev.* **2011**;242(1):233–246.
17. Williams MR, Gallo RL. The role of the skin microbiome in atopic dermatitis. *Curr Allergy Asthma Rep.* **2015**;15(11):65.
18. Cabanillas B, Novak N. Atopic dermatitis and filaggrin. *Curr Opin Immunol.* **2016**;42:1–8.
19. Mansouri Y, Guttman-Yassky E. Immune pathways in atopic dermatitis, and definition of biomarkers through broad and targeted therapeutics. *J Clin Med.* **2015**;4(5):858–873.
20. Brandt EB, Sivaprasad U. Th2 cytokines and atopic dermatitis. *J Clin Cell Immunol.* **2011**;2(3):pii: 110.
21. Williams HC. Clinical practice. Atopic dermatitis. *N Engl J Med.* **2005**;352(22):2314–2324.
22. Eichenfield LF, Tom WL, Berger TG, et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol.* **2014**;71(1):116–132.
23. Sidbury R, Davis DM, Cohen DE, et al. Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. *J Am Acad Dermatol.* **2014**;71(2):327–349.
24. Ring J, Alomar A, Bieber T, et al. Guidelines for treatment of atopic eczema (atopic dermatitis) Part II. *J Eur Acad Dermatol Venereol.* **2012**;26(9):1176–1193.
25. Saeki H, Nakahara T, Tanaka A, et al. Clinical practice guidelines for the management of atopic dermatitis 2016. *J Dermatol.* **2016**;43(10):1117–1145.
26. Sidbury R, Tom WL, Bergman JN, et al. Guidelines of care for the management of atopic dermatitis: section 4. Prevention of disease flares and use of adjunctive therapies and approaches. *J Am Acad Dermatol.* **2014** Dec;71(6):1218–1233.
27. Ring J, Alomar A, Bieber T, et al. Guidelines for treatment of atopic eczema (atopic dermatitis) part I. *J Eur Acad Dermatol Venereol.* **2012** Aug;26(8):1045–1060.
28. Heratizadeh A, Werfel T. Anti-inflammatory therapies in atopic dermatitis. *Allergy.* **2016**;71(12):1666–1675.
- **Overview of various anti-inflammatory drugs being currently investigated in clinical trials in AD patients.**
29. Werfel T, Biedermann T. Current novel approaches in systemic therapy of atopic dermatitis: specific inhibition of cutaneous Th2 polarized inflammation and itch. *Curr Opin Allergy Clin Immunol.* **2015**;15(5):446–452.
30. Beck LA, Thaçi D, Hamilton JD, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. *N Engl J Med.* **2014**;371(2):130–139.
- **Results from phase 1 and 2a dupilumab trials in AD patients.**
31. Kovalenko P, DiCioccio AT, Davis JD, et al. Exploratory population PK analysis of dupilumab, a fully human monoclonal antibody against IL-4R α , in atopic dermatitis patients and normal volunteers. *CPT Pharmacometrics Syst Pharmacol.* **2016**;5(11):617–624.
- **The analysis of pharmacokinetics of dupilumab.**
32. Berker M, Frank LJ, Geßner AL, et al. Allergies - A T cells perspective in the era beyond the TH1/TH2 paradigm. *Clin Immunol.* [cited 2016 Nov 12]. DOI:10.1016/j.clim.2016.11.001
33. Mowen KA, Glimcher LH. Signaling pathways in Th2 development. *Immunol Rev.* **2004**;202:203–222.
34. Hamilton JD, Ungar B, Guttman-Yassky E. Drug evaluation review: dupilumab in atopic dermatitis. *Immunotherapy.* **2015**;7(10):1043–1058.
35. Howell MD, Kim BE, Gao P, et al. Cytokine modulation of atopic dermatitis filaggrin skin expression. *J Allergy Clin Immunol.* **2007**;120(1):150–155.
36. Kim BE, Leung DY, Boguniewicz M, et al. Loricrin and involucrin expression is down-regulated by Th2 cytokines through STAT-6. *Clin Immunol.* **2008**;126(3):332–337.
37. Zheng-Hong D, Lei M, Rui-Qun Q, et al. T Helper 1 and T Helper 2 cytokines differentially modulate expression of filaggrin and its processing proteases in human keratinocytes. *Chin Med J (Engl).* **2016**;129(3):295–303.
38. Howell MD, Fairchild HR, Kim BE, et al. Th2 cytokines act on S100/A11 to downregulate keratinocyte differentiation. *J Invest Dermatol.* **2008**;128(9):2248–2258.
39. Hönzke S, Wallmeyer L, Ostrowski A, et al. Influence of Th2 cytokines on the cornified envelope, tight junction proteins, and β -defensins in filaggrin-deficient skin equivalents. *J Invest Dermatol.* **2016**;136(3):631–639.
40. Hamilton JD, Suárez-Fariñas M, Dhingra N, et al. Dupilumab improves the molecular signature in skin of patients with moderate-to-severe atopic dermatitis. *J Allergy Clin Immunol.* **2014**;134(6):1293–1300.
- **The analysis of changes in mRNA expression profile in the lesional skin of AD patients after 4 weeks of treatment with dupilumab.**
41. Thaçi D, Simpson EL, Beck LA, et al. Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial. *Lancet.* **2016**;387(10013):40–52.
- **Results from the phase 2b dupilumab trial in AD patients.**
42. Simpson EL, Gadkari A, Worm M, et al. Dupilumab therapy provides clinically meaningful improvement in patient-reported outcomes (PROs): a phase IIb, randomized, placebo-controlled, clinical trial in adult patients with moderate to severe atopic dermatitis (AD). *J Am Acad Dermatol.* **2016**;75(3):506–515.
43. Simpson EL, Bieber T, Eckert L, et al. Patient burden of moderate to severe atopic dermatitis (AD): insights from a phase 2b clinical trial of dupilumab in adults. *J Am Acad Dermatol.* **2016**;74(3):491–498.
44. Simpson EL, Bieber T, Guttman-Yassky E, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N Engl J Med.* **2016** [cited 2016 Sep 30]. DOI:10.1056/NEJMoa1610020
- **Results from SOLO 1 and SOLO 2 – two phase 3 dupilumab trials in AD patients.**
45. Wenzel S, Ford L, Pearlman D, et al. Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med.* **2013**;368(26):2455–2466.
46. Wenzel S, Castro M, Corren J, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β 2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet.* **2016**;388(10039):31–44.
47. Bachert C, Mannent L, Naclerio RM, et al. Effect of subcutaneous dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal polyposis: a randomized clinical trial. *JAMA.* **2016**;315(5):469–479.
48. ClinicalTrials.gov - A service of the U.S. National Institutes of Health [Internet]. Bethesda (MD): National Library of Medicine (US). [cited 2017 Jan 25]. Available from: <https://clinicaltrials.gov>
49. Regeneron and sanofi announce dupilumab biologics license application accepted for priority review by U.S. FDA. Regeneron Pharmaceuticals, Inc., **2016** [cited 2016 Nov 30]. Available from: <http://www.prnewswire.com/news-releases/regeneron-and-sanofi-announce-dupilumab-biologics-license-application-accepted-for-priority-review-by-us-fda-300333529.html>

50. Pfizer receives FDA approval for EUCRISA™ (crisaborole), a novel non-steroidal topical ointment for mild to moderate atopic dermatitis (Eczema). Pfizer Inc., 2016 [cited 2017 Jan 25]. Available from: http://www.pfizer.com/news/press-release/press-release-detail/pfizer_receives_fda_approval_for_eucrisa_crisaborole_a_novel_non_steroidal_topical_ointment_for_mild_to_moderate_atopic_dermatitis_eczema
51. EU Clinical Trials Register [Internet]. London: The European Medicines Agency. [cited 2017 Jan 25]. Available from: <https://www.clinicaltrialsregister.eu>