

Dupilumab: First Global Approval

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Abstract Dupilumab (Dupixent[®]) is a fully human monoclonal antibody directed against the interleukin (IL)-4 receptor α (IL-4R α) subunit. Dupilumab inhibits the signalling of the type 2 cytokines IL-4 and IL-13 and was co-developed by Regeneron Pharmaceuticals and Sanofi as a potential therapeutic agent for the treatment of atopic or allergic diseases. In March 2017 dupilumab received its first global approval, in the USA, for use in the treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Dupilumab is in preregistration for this indication in the EU. In addition, dupilumab is currently under phase III development across the world for the treatment of asthma and nasal polyposis as well as for atopic dermatitis in paediatric patients. The agent has also entered phase II development in the USA for the treatment of eosinophilic oesophagitis. This article summarizes the milestones in the development of dupilumab leading to this first approval for the treatment of moderate-to-severe atopic dermatitis in adults.

This profile has been extracted and modified from the *AdisInsight* database. *AdisInsight* tracks drug development worldwide through the entire development process, from discovery, through pre-clinical and clinical studies to market launch and beyond.

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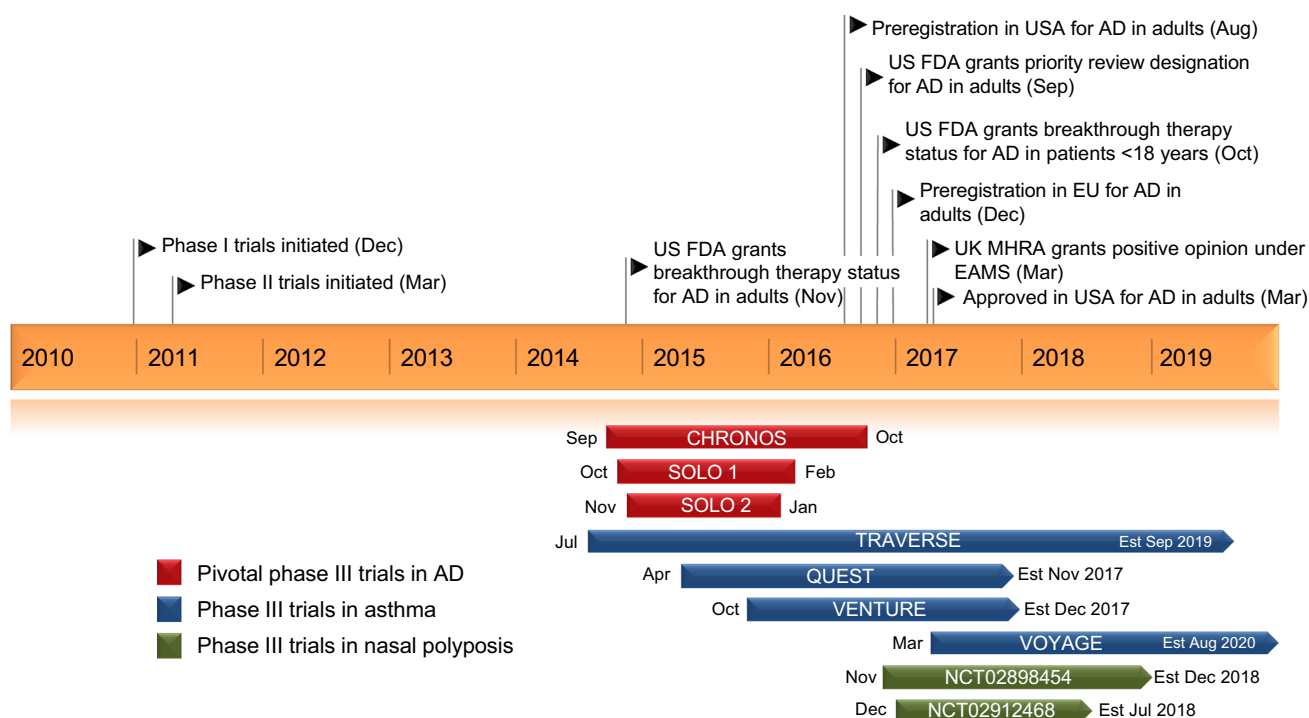
1 Introduction

Dupilumab (Dupixent[®]) is a fully human IgG4 monoclonal antibody directed against the interleukin (IL)-4 receptor α (IL-4R α) subunit [1]. Binding of dupilumab to the IL-4R α subunit inhibits the signalling of IL-4 and IL-13, two type 2 (Th2) cytokines. Dupilumab was developed by Regeneron Pharmaceuticals and Sanofi as a potential therapeutic antibody for the treatment of atopic and allergic diseases where IL-4 and IL-13 are proposed to be important drivers of disease [2].

On 28 March 2017, dupilumab received its first global approval, in the USA, for use in the treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable [1, 2]. Dupilumab thus became the first targeted biologic therapy approved for the treatment of atopic dermatitis.

Dupilumab is supplied in a single-dose pre-filled syringe and is to be administered by subcutaneous injection into the thigh, abdomen or upper arm [1]. The recommended dosage is a loading dose of 600 mg (two 300-mg injections at different sites) followed by 300 mg every other week, with rotation of the injection site. Dupilumab can be used with or without concomitant topical corticosteroids (TCS); topical calcineurin inhibitors may also be used for problem areas [1].

Approval of dupilumab in the treatment of adults with moderate-to-severe atopic dermatitis was based on the results of the pivotal phase III SOLO 1 (NCT02277743), SOLO 2 (NCT02277769) and CHRONOS (NCT02260986) trials which investigated the safety and efficacy of the (subsequently) approved dupilumab dosage regimen compared with placebo [2]. These trials each included a third randomized treatment arm of dupilumab 300 mg once weekly; however, this dosage regimen provided no additional benefit over dupilumab 300 mg once every 2 weeks (see Sect. 2.3.1).



Clinical development of dupilumab. *AD* atopic dermatitis, *EAMS* Early Access to Medicines Scheme, *Est* estimated date of completion, *MHRA* Medicines and Healthcare Products Regulatory Agency

A Marketing Authorization Application for dupilumab for the treatment of adult patients with moderate-to-severe atopic dermatitis who are candidates for systemic therapy was accepted for review by the EMA in December 2016 [3]. Dupilumab has also been granted a positive scientific opinion by the UK's Medicines and Healthcare Products Regulatory Agency through the Early Access to Medicines Scheme [4]. Under the scheme, dupilumab is being made available to eligible adult patients with severe atopic dermatitis throughout the UK. Dupilumab was granted Breakthrough Therapy designation by the US FDA for the treatment of moderate-to-severe atopic dermatitis in adults in November 2014, and Priority Review was granted in this indication in September 2016 [5]. In October 2016 Breakthrough Therapy designation was also granted by the FDA for dupilumab for the treatment of moderate-to-severe atopic dermatitis in patients 12 to <18 years of age and for severe atopic dermatitis in patients 6 months to <12 years of age when topical medications are inadequate or inappropriate [5].

Dupilumab is in ongoing phase III clinical development for the treatment of atopic dermatitis in adults and paediatric patients. It is also in phase III development across the world for the treatment of asthma and nasal polyposis, while phase II development in eosinophilic oesophagitis is underway in the US. Earlier development of an intravenous formulation of dupilumab has been discontinued.

1.1 Company Agreements

Dupilumab was originated using Regeneron Pharmaceuticals' proprietary VelocImmune[®] technology and was co-developed by Regeneron and Sanofi (formerly Sanofi-Aventis) [2]. Regeneron and Sanofi entered a collaboration in 2007 to develop and commercialize fully human therapeutic antibodies, whereby development costs and profits are shared. The collaboration was expanded and extended in November 2009.

2 Scientific Summary

Dupilumab is a fully human IgG4 monoclonal antibody that selectively binds the IL-4R α subunit [1]. It is produced in Chinese hamster ovary cell suspension culture using recombinant DNA technology and has a molecular weight of ~147 kDa [1].

2.1 Pharmacodynamics

Dupilumab is an IL-4R α antagonist [1]. Binding of dupilumab to the IL-4R α subunit inhibits IL-4 and IL-13 signalling (IL-4 signalling via the Type I receptor; IL-4 and IL-13 signalling via the Type II receptor), thereby

inhibiting the release of proinflammatory cytokines, chemokines and IgE [1]. Consistent with IL-4R α blockade, an increase in serum levels of IL-4 and IL-13 is observed following dupilumab treatment [1].

In clinical trials in patients with atopic dermatitis, asthma or nasal polyposis, dupilumab suppressed levels of key Th2-associated biomarkers, including thymus and activation-regulated chemokine (TARC), eotaxin-3 (CCL26), serum IgE and the fraction of exhaled nitric oxide (FeNO) [6–10]. Some patients in clinical trials had a transient increase in eosinophil counts following initiation of dupilumab treatment [8, 10].

Vaccine immune responses were not impacted by dupilumab treatment in a study in patients with atopic dermatitis [11]. However, use of live vaccines should be avoided in patients receiving dupilumab [1].

2.2 Pharmacokinetics

Subcutaneous dupilumab exhibits non-linear target-mediated pharmacokinetics [1, 12], with greater than dose-proportional increases in exposure (an eightfold dose increase from 75 to 600 mg produced a 30-fold increase in systemic exposure) [1]. There do not appear to be any time-dependent changes in dupilumab pharmacokinetics during longer-term treatment (up to 68 weeks) based on data from phase III trials in patients with atopic dermatitis [13].

Subcutaneous dupilumab has an estimated bioavailability of 64% [1]. Mean peak dupilumab concentrations of 70.1 μ g/mL were reached approximately 1 week following a 600-mg subcutaneous dose. With a 600-mg loading dose followed by dupilumab 300 mg once weekly or once every 2 weeks,

steady-state pharmacokinetics are reached by week 16. Across clinical trials, regimens of dupilumab 300 mg once weekly and once every 2 weeks produced mean steady-state trough concentrations of 173–193 and 73.3–79.9 μ g/mL, respectively. Dupilumab has an estimated total volume of distribution of approximately 4.8 L [1].

Although the specific pathways have not been characterized, dupilumab is expected to undergo catabolism to small peptides and amino acids in the same manner as endogenous IgG [1]. Following the final steady-state dose with regimens of dupilumab 300 mg once weekly and once every 2 weeks, dupilumab reached non-detectable concentrations (<78 ng/mL) in median times of 13 and 10 weeks, respectively [1].

Higher body weight was associated with lower dupilumab trough concentrations [1, 12]; however, dosage adjustment based on body weight does not appear to be necessary in adults [12]. When controlling for body weight, gender had no apparent impact on dupilumab pharmacokinetics [12].

Based on limited available data, elderly age does not appear to affect dupilumab pharmacokinetics to a clinically relevant extent [1]. Furthermore, the pharmacokinetic profile for dupilumab in paediatric patients appears to be consistent with that in adults [14]. No formal studies have been conducted to investigate any possible impact of hepatic or renal impairment on dupilumab pharmacokinetics, nor have formal drug interaction studies been conducted [1]. However, comparisons of pharmacokinetic data from trials in which patients with atopic dermatitis received dupilumab with or without TCS indicate that dupilumab pharmacokinetics are not affected by concomitant use of TCS [13].

Features and properties of dupilumab

Alternative names	Dupixent; REGN668; SAR 231893
Class	Antiasthmatics; monoclonal antibodies; skin disorder therapies
Mechanism of action	IL-4R α and IL-13 receptor antagonism
Route of administration	Subcutaneous injection
Pharmacodynamics	Selectively binds IL-4R α subunit, thereby inhibiting IL-4 and IL-13 signalling; reduces levels of key Th2-associated biomarkers
Pharmacokinetics	Maximum concentrations reached ~1 week after a single dose; estimated bioavailability is 64%; estimated total volume of distribution is ~4.8 L; reaches non-detectable concentrations ~10–13 weeks after the final dose
Most common adverse events (with higher incidence than placebo)	Injection-site reactions, nasopharyngitis, conjunctivitis
ATC codes	
WHO ATC codes	D11A-H; L04A-C; R01; R03D-X
EphMRA ATC codes	D11A; L4X; R1B; R3X2
Chemical name	Immunoglobulin, anti-(human IL-4R α) (human REGN668 heavy chain), disulfide with human REGN668 κ -chain, dimer

IL interleukin, IL-4R α interleukin-4 receptor α

2.3 Therapeutic Trials

2.3.1 Atopic Dermatitis

In pivotal phase III trials subcutaneous dupilumab, as monotherapy or in combination with TCS, markedly improved the signs and symptoms of atopic dermatitis in adults with moderate-to-severe disease.

The efficacy of subcutaneous dupilumab in the treatment of moderate-to-severe atopic dermatitis was evaluated in three pivotal, randomized, double-blind, placebo-controlled phase III trials. These were the 16-week SOLO 1 ($n = 671$) and SOLO 2 ($n = 708$) trials which evaluated dupilumab as monotherapy [15] and the 52-week CHRONOS trial ($n = 740$) which evaluated dupilumab in combination with TCS [16]. In each of the three trials, adult patients (aged ≥ 18 years) with moderate-to-severe atopic dermatitis not adequately controlled by topical medication(s) were randomized (1:1:1 in SOLO 1 and SOLO 2; 3:1:3 in CHRONOS) to receive subcutaneous dupilumab 300 mg once weekly, dupilumab 300 mg once every 2 weeks or placebo [15, 16]. In all trials, patients in the dupilumab groups were administered a 600-mg loading dose of dupilumab on day 1. In addition, all patients in CHRONOS were initiated on low or medium potency TCS (which could be tapered or stopped), with topical calcineurin inhibitors also permitted for use in areas where use of TCS is not advisable [16]. The primary endpoint in each of the trials was the proportion of patients with an Investigator's Global Assessment (IGA) score of 0 (clear) or 1 (almost clear) accompanied by a reduction from baseline of ≥ 2 points in the score at week 16 [15, 16].

In all three trials, significantly more patients who received dupilumab than placebo were responders for the primary efficacy outcome at week 16 (37 and 38% vs. 10% of patients in SOLO 1, 36 and 36% vs. 8% in SOLO 2 and 39 and 39% vs. 12% in CHRONOS in the dupilumab once weekly, dupilumab once every 2 weeks and placebo groups, respectively; $p < 0.001$ for all comparisons vs. placebo) [15, 16]. Among the 623 patients in CHRONOS for whom 52-week efficacy data were available, 40 and 36% of patients in the dupilumab once weekly and once every 2 weeks groups, respectively, had an IGA score of 1 or 2 with a ≥ 2 -point reduction from baseline at week 52 compared with 13% in the placebo group ($p < 0.0001$ for both comparisons vs. placebo) [16].

In a key secondary endpoint for each of the trials (considered a co-primary endpoint by EU and Japan regulatory authorities), a $\geq 75\%$ improvement from baseline in the Eczema Area and Severity Index (EASI) score at week 16 was also reported in significantly more patients treated with either regimen of dupilumab compared with placebo-treated patients [15, 16]. Both regimens of dupilumab were also associated with significant improvements in several other measures of efficacy and patient-reported

outcomes in all trials, including significant reductions in pruritus (apparent by week 2) and improvements in health-related quality of life [15, 16].

Key inclusion criteria in the trials were chronic atopic dermatitis that had been present for ≥ 3 years prior to screening, an IGA score of 3 (moderate) or 4 (severe), an EASI score ≥ 16 and $\geq 10\%$ body-surface area involvement [15, 16]. Baseline characteristics were well balanced between treatment groups in the trials [15, 16]. In each trial, approximately half of the patients had moderate (IGA score, 3) disease and half had severe (IGA score, 4) disease at baseline. Across all groups, patients had a median duration of disease of 24.0–28.0 years, a median EASI score of 28.6–31.8 points, a median of 50.0–58.8% of body-surface area affected and a median peak pruritus Numeric Rating Scale score of 7.4–7.8 at baseline [15, 16].

Further supportive evidence for the efficacy of subcutaneous dupilumab in the treatment of moderate-to-severe atopic dermatitis is available from several earlier phase clinical studies [6, 17, 18].

2.3.2 Asthma

In a randomized, double-blind, placebo-controlled phase IIb dose-ranging trial in patients with uncontrolled persistent asthma (NCT01854047), subcutaneous dupilumab increased lung function and reduced severe asthma exacerbations when given as add-on therapy to medium-to-high-dose inhaled corticosteroids plus long-acting β_2 -agonist (LABA) therapy [8]. In the trial, 776 patients aged ≥ 18 years were randomized (1:1:1:1:1) to receive subcutaneous dupilumab 200 mg or 300 mg every 2 weeks or every 4 weeks, or placebo, for a duration of 24 weeks. Patients in a dupilumab 200 or 300 mg group received a loading dose of dupilumab 400 or 600 mg, respectively, at week 0. In addition, all patients continued stable dose inhaled corticosteroids plus LABA therapy throughout the study. Randomization was stratified based on eosinophil count at screening (<200 , 200–299 and $\geq 300/\mu\text{L}$). The primary endpoint was the change from baseline in forced expiratory volume in 1 s (FEV_1) at week 12 assessed in the subpopulation of patients with a high ($\geq 300/\mu\text{L}$) eosinophil count ($n = 325$; 62–68 patients per treatment group). In the primary endpoint analysis, regimens of dupilumab 200 or 300 mg every 2 weeks or dupilumab 300 mg every 4 weeks were associated with significant ($p < 0.05$) increases in FEV_1 , ranging from 0.17 to 0.26 L relative to placebo, from baseline at week 12. In these three treatment groups, improvements in FEV_1 were sustained over the 24-week treatment period, with increases of 0.15–0.16 L relative to placebo ($p < 0.05$) observed at week 24. Dupilumab 200 or 300 mg every 2 weeks was also associated with significant increases in FEV_1 at 12 weeks in the

overall population and in the subpopulation with eosinophil counts $<300/\mu\text{L}$, with the improvements again sustained at week 24. Over the 24-week treatment period, both dose regimens of dupilumab every 2 weeks also significantly reduced the annualized rates of severe asthma exacerbations (70.0–70.5% reduced risk vs. placebo in the overall population) [8].

In an earlier 12-week, randomized, double-blind, placebo-controlled phase IIa trial in adults ($n = 104$) with persistent, moderate-to-severe eosinophilic asthma, it was shown that, relative to placebo, treatment with subcutaneous dupilumab (300 mg once weekly) was associated with significantly fewer asthma exacerbations when LABA therapy and inhaled corticosteroids were withdrawn [9]. Dupilumab treatment was also associated with significant improvements in several measures of lung function, including FEV_1 [9].

2.3.3 Nasal Polyposis

The efficacy of subcutaneous dupilumab in the treatment of nasal polyposis has been investigated in a randomized,

double-blind, placebo-controlled, proof-of-concept phase II trial in adult patients ($n = 60$) with chronic sinusitis and nasal polyposis refractory to intranasal corticosteroids (NCT01920893) [10]. In the trial, the addition of subcutaneous dupilumab (a 600-mg loading dose followed by 300 mg once weekly) to mometasone furoate nasal spray for 16 weeks reduced endoscopic nasal polyp burden relative to mometasone furoate alone. Dupilumab was also associated with significant improvements in other objective measures of clinical efficacy and patient-reported outcomes [10].

2.4 Adverse Events

Currently available clinical data indicate that subcutaneous dupilumab is generally well tolerated in patients with atopic dermatitis [6, 15, 16, 18, 19]. In clinical trials, most adverse events were of mild to moderate severity, and incidences of adverse events leading to treatment discontinuation were low. Longer-term data (including from post-marketing surveillance) will be required to more fully establish the safety and tolerability of the agent.

Key clinical trials of dupilumab (Regeneron Pharmaceuticals/Sanofi)

Identifier	Phase	Indication	Drug(s)	Location(s)	Status
SOLO 1; NCT02277743	III	Atopic dermatitis in adults	Dupilumab, placebo	Multinational	Completed
SOLO 2; NCT02277769	III	Atopic dermatitis in adults	Dupilumab, placebo	Multinational	Completed
CHRONOS; NCT02260986	III	Atopic dermatitis in adults	Dupilumab, topical corticosteroids, placebo	Multinational	Completed
SOLO-Continue; NCT02395133	III	Atopic dermatitis in adults	Dupilumab, placebo	Europe	Ongoing
MAINTAIN; NCT01949311	III	Atopic dermatitis in adults	Dupilumab	Multinational	Ongoing
NCT02755649	III	Atopic dermatitis in adults	Dupilumab, placebo	Europe	Ongoing
NCT02612454	III	Atopic dermatitis in patients aged 6–17 years	Dupilumab	Canada, Czech Republic, Germany, Hungary, Poland, UK	Ongoing
NCT03054428	III	Atopic dermatitis in patients aged 12–17 years	Dupilumab, placebo	USA	Ongoing
QUEST; NCT02414854	III	Asthma in patients aged ≥ 12 years	Dupilumab, placebo	Multinational	Ongoing
VENTURE; NCT02528214	III	Asthma in patients aged ≥ 12 years	Dupilumab, asthma controller therapies, placebo	Multinational	Ongoing
TRAVERSE; NCT02134028	II/III	Asthma in patients aged ≥ 12 years	Dupilumab	Multinational	Ongoing
VOYAGE; NCT02948959	III	Asthma in patients aged 6–11 years	Dupilumab, asthma reliever and asthma controller therapies, placebo	USA	Ongoing
NCT02898454	III	Nasal polyposis in adults	Dupilumab, mometasone furoate, placebo	Multinational	Ongoing
NCT02912468	III	Nasal polyposis in adults	Dupilumab, mometasone furoate, placebo	Multinational	Ongoing

In the 16-week SOLO 1 and SOLO 2 dupilumab monotherapy trials, adverse events that occurred more commonly among dupilumab recipients than among placebo recipients included injection-site reactions (8–19% vs. 6%) and conjunctivitis (3–5% vs. 0.4–0.9%), whereas exacerbation of atopic dermatitis (10–16% vs. 30–35%) and skin infections (6% vs. 8–11%) were more common among placebo recipients [15]. Nasopharyngitis was reported with a similar incidence in each group (8–11% vs. 8–9%). The most common serious adverse event in the trials was a serious exacerbation of atopic dermatitis, which occurred in three dupilumab recipients (0.3%) and eight placebo recipients (1.8%) across SOLO 1 and SOLO 2. Two deaths occurred in SOLO 2, neither of which were considered to be related to the study drug; there were no deaths in SOLO 1 [15].

The safety and tolerability profile of dupilumab used in combination with TCS in the 52-week CHRONOS trial was consistent with that observed in the SOLO 1 and SOLO 2 trials [15, 16]. The most commonly reported adverse events (incidence $\geq 15\%$ in any treatment group) in CHRONOS were atopic dermatitis exacerbation (17–18% in dupilumab groups vs. 46% in the placebo group), nasopharyngitis (19–23% vs. 19%), injection-site reaction (15–19% vs. 8%), conjunctivitis (14–19% vs. 8%) and non-herpetic skin infections (8–11% vs. 18%) [16]. There was one death in CHRONOS, not considered to be related to the study drug [16].

Available clinical data suggest that subcutaneous dupilumab is also generally well tolerated in patients with asthma [8, 9] or nasal polyposis [10]. In the trial NCT01854047 the most common adverse events in dupilumab recipients (all regimens combined) were upper respiratory tract infection (14% vs. 18% of placebo recipients), injection-site erythema (13 vs. 8%), headache (10 vs. 13%) and nasopharyngitis (10 vs. 9%) [8]. In the trial NCT01920893 the most common adverse events were nasopharyngitis (47% of dupilumab recipients vs. 33% of placebo recipients), injection-site reaction (40 vs. 7%) and headache (20 vs. 17%) [10].

As for all therapeutic proteins, dupilumab has a potential for immunogenicity. Anti-drug antibodies were developed by approximately 7% of patients with atopic dermatitis who received dupilumab 300 mg every 2 weeks for 16 weeks in SOLO 1 and 2 [1, 20]. Approximately 30% of patients with anti-drug antibodies (2% overall) had neutralizing antibodies [1]. Similarly, approximately 7% of patients who received dupilumab 300 mg once every 2 weeks (plus TCS) for 52 weeks in CHRONOS developed antibodies to dupilumab, with approximately 14% of these patients (1% overall) having neutralizing antibodies [1]. Anti-dupilumab antibodies were also detected in approximately 2 and 8% of patients in the placebo and placebo

plus TCS groups, respectively. Among dupilumab recipients, the development of anti-dupilumab antibodies was associated with lower serum drug concentrations. Hypersensitivity reactions (including serum sickness, serum sickness-like reaction and generalized urticaria) occurred in $<1\%$ of dupilumab recipients in clinical trials [1].

2.5 Ongoing Clinical Trials

Regeneron and Sanofi are continuing clinical development of subcutaneous dupilumab in an extensive range of ongoing clinical trials.

Ongoing phase III trials in atopic dermatitis include: SOLO-Continue (NCT02395133), a randomized, double-blind, placebo-controlled trial investigating the maintenance of the treatment response achieved by patients in SOLO 1 or SOLO 2 over 36 weeks; MAINTAIN (NCT01949311), an open-label extension study for patients who participated in placebo-controlled dupilumab atopic dermatitis trials to investigate the safety, immunogenicity and efficacy of dupilumab over a longer term (up to 164 weeks); NCT02755649, a randomized, double-blind, placebo-controlled trial investigating dupilumab in adults with severe atopic dermatitis that is not adequately controlled with oral cyclosporine A or when cyclosporine A is not medically advisable; NCT03054428, a randomized, double-blind, placebo-controlled phase III trial in patients aged 12–17 years; and NCT02612454, an open-label, long term extension study in patients aged 6–17 years who have participated in a prior dupilumab study.

Ongoing trials in asthma include: the pivotal QUEST trial (NCT02414854), a 52-week randomized, double-blind, placebo-controlled phase III trial that is investigating dupilumab in adult and adolescent patients (≥ 12 years old) with inadequately controlled, persistent asthma; the TRAVERSE trial (NCT02134028), an open-label 1-year extension study evaluating the longer-term safety, tolerability and efficacy of dupilumab in patients who participated in a previous dupilumab asthma study; the VENTURE trial (NCT02528214), a randomized, double-blind, placebo-controlled phase III trial evaluating the reduction in use of oral corticosteroids in patients with severe steroid-dependent asthma; the EXPEDITION trial (NCT02573233), an exploratory, double-blind, placebo-controlled phase IIa trial investigating the effects of dupilumab on airway inflammation; and the VOYAGE trial (NCT02948959), a randomized, double-blind, placebo-controlled phase III trial evaluating the safety and efficacy of dupilumab in children 6–11 years old.

Dupilumab is also being investigated in the treatment of adults with nasal polyposis in two randomized, double-blind, placebo-controlled phase III trials (NCT02898454 and NCT02912468) in patients with bilateral nasal

polyposis on background therapy with intranasal corticosteroids. Finally, an ongoing, randomized, double-blind, placebo-controlled phase II trial (NCT02379052) is investigating dupilumab in adult patients with active, moderate-to-severe eosinophilic oesophagitis.

3 Current Status

Dupilumab received its first global approval on 28 March 2017, in the USA, for use in the treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable [1, 2].

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