



# Dupilumab: A Review in Moderate to Severe Asthma

Emma D. Deeks<sup>1</sup>

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## Abstract

Dupilumab (Dupixent<sup>®</sup>) is a fully human monoclonal antibody against the interleukin (IL)-4 receptor  $\alpha$  subunit of IL-4 and IL-4/IL-13 receptor complexes. IL-4 and IL-13 are key cytokines in driving type 2 inflammation, a dominant and largely eosinophilic inflammatory pathway in asthma. Trials evaluating the efficacy of dupilumab in asthma include three pivotal, placebo-controlled, phase 3 or 2b trials of 24–52 weeks' treatment duration in patients aged  $\geq 12$  years with moderate-to-severe asthma (inadequately controlled with medium-to-high dose inhaled corticosteroids) or severe asthma [dependent on oral corticosteroids (OCS) for control]. In these studies, adding subcutaneous dupilumab (200 or 300 mg every 2 weeks) to background therapy was generally well tolerated and reduced the rate of severe asthma exacerbations, improved lung function, as well as asthma control and, where specified, health-related quality of life (HR-QOL), and enabled OCS maintenance doses to be reduced without impacting asthma control. Dupilumab displayed efficacy across various patient subgroups, although those with heightened type 2 immune activity, including elevated eosinophils and fractional exhaled nitric oxide, tended to have a more prominent treatment benefit. Dupilumab is consequently widely indicated (and a valuable treatment option) as an add-on therapy in patients aged  $\geq 12$  years who have severe/moderate-to-severe asthma with a type 2 inflammation/eosinophilic phenotype despite conventional treatments or have OCS-dependent asthma.

### Dupilumab: clinical considerations as an add-on therapy in moderate to severe asthma

|                                                                                                   |
|---------------------------------------------------------------------------------------------------|
| First asthma therapy to target IL-4/IL-13 signalling                                              |
| Reduces rate of severe asthma exacerbations and improves lung function, asthma control and HR-QOL |
| Enables OCS dose reductions in patients with OCS-dependent severe asthma                          |
| Generally provides more notable benefit in patients with heightened type 2 immunity               |
| Generally well tolerated                                                                          |

Enhanced material for this Adis Drug Evaluation can be found at <https://doi.org/10.6084/m9.figshare.10252718>.

The manuscript was reviewed by: **C. Incorvaia**, Cardiac and Pulmonary Rehabilitation Unit, ASST Pini-CTO, Milan, Italy; **I. D. Pavord**, NDM Research Building, Oxford Respiratory NIHR BRC, University of Oxford, Oxford, UK.

✉ Emma D. Deeks  
demail@springer.com

<sup>1</sup> Springer Nature, Private Bag 65901, Mairangi Bay, Auckland 0754, New Zealand

## 1 Introduction

Asthma is a chronic heterogeneous lung disease typified by reversible airflow obstruction, hyper-responsiveness of the bronchi and airway inflammation [1], the latter of which determines its severity, among other characteristics [2]. The inflammatory pathways in asthma can vary between patients, although the pathway that dominates in many is type 2 inflammation [2]. This inflammation is largely eosinophilic in nature and driven by the cytokines interleukin (IL)-4, IL-5 and IL-13 [2, 3]. These cytokines have various roles in asthma pathogenesis, with, for instance, IL-5 being pivotal in eosinophil (EOS) differentiation, maturation and survival, and IL-4/IL-13 being involved in the recruitment of EOS to the airways (where they damage epithelia), stimulation of airway goblet cell development, mucus secretion and nitric oxide (NO) synthesis, and promotion of IgE production [3–5].

Type 2 inflammatory pathways contribute considerably to severe asthma [2], with around half of the patients who are unable to achieve adequate asthma control with conventional treatments having strong evidence of eosinophilic/allergic inflammation involving type 2 inflammatory cytokines [4]. Consequently, IL-4, IL-5 and IL-13 have been a focus of targeted therapy development in recent years and have helped

to identify biomarkers of type 2 inflammation [e.g. sputum/blood EOS, total serum IgE, fractional exhaled NO (FeNO) and certain bronchial epithelial proteins (e.g. periostin)] with the potential to determine which patients are likely to respond to such treatments [2, 4].

One of the more recent targeted therapies, and the first to target IL-4 and IL-13 signalling in asthma, is dupilumab (Dupixent®), a fully human monoclonal antibody against the IL-4 receptor  $\alpha$  (IL-4R $\alpha$ ) subunit common to both IL-4 and IL-4/IL-13 receptor complexes. Dupilumab is approved in various countries (including the USA [6] and those of the EU [7]) as an add-on maintenance treatment for severe/moderate-to-severe asthma with a type 2 inflammation/eosinophilic phenotype, and is also approved for a similar indication in Japan [8] (Sect. 6). This article reviews data relevant to the use of subcutaneous dupilumab in these settings, with focus on the recommended regimens of 200 or 300 mg every 2 weeks (q2w), subsequent to a respective loading dose of 400 or 600 mg (Sect. 6). Other indications for which dupilumab is currently approved [i.e. atopic dermatitis and chronic rhinosinusitis (CRS) with nasal polyps (NP)] are beyond the scope of this review.

## 2 Pharmacodynamic Properties of Dupilumab

Dupilumab binds specifically and with high affinity to the IL-4R $\alpha$  subunit shared by the type I IL-4 receptor complex (IL-4 $\alpha$ / $\gamma$ c) and type II IL-4/IL-13 receptor complex (IL-4 $\alpha$ /IL-13R $\alpha$ ), and in doing so, inhibits IL-4 and IL-13 signalling [6–8]. Given the key roles that IL-4 and IL-13 play in driving type 2 inflammation (Sect. 1), inhibition of such pathways by dupilumab may suppress the inflammatory responses induced by these cytokines, such as the release of proinflammatory cytokines, chemokines, IgE and NO [6].

Indeed, in phase 3 [9, 10] and 2b [11] trials in adults and adolescents with moderate to severe asthma discussed in Sect. 4 (i.e. QUEST [9], VENTURE [10, 12] and DRI12455 [11, 13]), subcutaneous treatment with dupilumab 200 or 300 mg q2w for up to 52 weeks suppressed levels of FeNO [9–13] and various other biomarkers of type 2 inflammation, including serum/plasma total IgE, TARC (i.e. thymus and activation-regulated chemokine), eotaxin-3 and/or periostin [9, 12, 13], relative to placebo ( $p < 0.001$  where specified [11–13]). Suppression of these biomarkers was near maximal after 2 weeks of dupilumab therapy [10, 11, 13] (with the exception of IgE, for which the decline was slower [13]) and was largely maintained throughout treatment [6, 7, 9–11, 13]. Similar benefit was evident with these dupilumab dosages in asthma patients with or without comorbid allergic rhinitis (AR) [14] or CRS with or without NP [15] in post hoc analyses of QUEST. However, the exact mechanism(s)

underlying the efficacy of dupilumab in asthma (Sect. 4) is yet to be determined [6].

Dupilumab reduced EOS lung infiltration, goblet cell metaplasia and lung dysfunction in a mouse model of allergen-induced type 2 inflammation [8]. Although patients with asthma had transient increases in blood EOS count following initiation of dupilumab in QUEST, the elevations were generally without clinical consequence or adverse events (AEs) and EOS counts returned to near baseline after 52 weeks of therapy [9]. A similar phenomenon was observed with dupilumab in patients with a baseline blood EOS count of  $\geq 300/\mu\text{L}$  in DRI12544 [11]. Eosinophilia is discussed further in Sect. 5.

Some recipients of dupilumab may develop antibodies against the drug [6, 7, 9, 10]. For instance, persistent anti-dupilumab antibodies were present in 4.2%, 2.1% and 1.1% of asthma patients who received dupilumab 200 mg q2w, dupilumab 300 mg q2w or placebo, respectively, in the 52-week QUEST trial [9]. However, anti-dupilumab antibodies are generally of low titre [6] and do not impact the exposure, efficacy or safety of the drug [7].

## 3 Pharmacokinetic Properties of Dupilumab

Concentrations of dupilumab (in serum where specified [7]) peak  $\approx 7$  days after subcutaneous administration of a 600 or 400 mg loading dose [6] and in a median of 3–7 days after single subcutaneous doses of 75–600 mg [7]. Exposure to dupilumab increases in a greater than dose-proportional fashion across this dose range [6, 7] (due to non-linear clearance [7]) and the drug reaches steady-state concentrations by week 16 with the recommended regimens (600 mg loading dose, then 300 mg q2w; 400 mg loading dose, then 200 mg q2w) [6].

Dupilumab has an estimated volume of distribution of almost 5 L [6, 7], suggesting it distributes predominantly in the vascular system [7]. The drug is likely degraded into small peptides and amino acids [6, 7], with elimination occurring mainly via a linear proteolytic pathway at high concentrations and a non-linear saturable IL-4R $\alpha$  target-mediated pathway at low concentrations [7]. The median time taken to reach a non-detectable dupilumab concentration after the last steady-state dose with the 200 and 300 mg q2w regimens is 9 and 10–11 weeks, respectively, according to population pharmacokinetic (popPK) analysis [7].

As dupilumab is an antibody, its hepatic and renal elimination is not expected to be significant [7]. Consequently, studies have not formally assessed whether hepatic or renal impairment may impact dupilumab pharmacokinetics, although a popPK analysis found no clinically meaningful impact of mild or moderate renal impairment on dupilumab exposure [7]. Although trough concentrations of dupilumab

are lower in individuals with higher body weight, this has no meaningful effect on its efficacy [7]. Race, gender and age had no clinically relevant effects on dupilumab exposure in popPK analyses, and no age-related differences in dupilumab pharmacokinetics were evident in the adolescent (aged 12–17 years) participants of QUEST after correction for body weight [7]. The dosage of dupilumab does not require adjustment on the basis of body weight, being elderly (aged  $\geq 65$  years) or having mild or moderate renal impairment (data in severe renal impairment are limited) [7].

The pharmacokinetics of dupilumab are not impacted by medications commonly co-administered in patients with moderate to severe asthma, according to popPK analysis [7]. Moreover, dupilumab does not appear to have any clinically relevant impact on the activity of key CYP enzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6 or CYP3A4) [6, 7] and is thus not expected to impact the pharmacokinetics of co-administered agents [7].

## 4 Therapeutic Efficacy of Dupilumab

This section focuses on three double-blind, placebo-controlled studies with randomized treatment periods of 24–52 weeks' duration that evaluated the efficacy of adding subcutaneous dupilumab to background therapy in adults [9–11] and adolescents [9, 10] with moderate-to-severe [9, 11] or severe [10] asthma. These phase 3 (QUEST [9] and VENTURE [10]) and phase 2b (DRI12544 [11]) trials from the LIBERTY ASTHMA clinical development programme enrolled patients aged  $\geq 12$  [9, 10] or  $\geq 18$  [11] years with persistent asthma for  $\geq 12$  months and certain lung function parameters, including a pre-bronchodilator forced expiratory volume in 1 s ( $FEV_1$ ) of  $\leq 80\%$  [9, 10] or 40–80% [11] of predicted (if adult) or  $\leq 90\%$  of predicted (if aged 12–17 years) [9, 10], plus  $FEV_1$  reversibility of  $\geq 12\%$  and 200 ml [9–11] or airway hyper-responsiveness in the last 12 months [10]. There was no requirement for a minimum level of blood EOS or other biomarkers of type 2 inflammation to participate in any of the studies [6, 7], although the phase 3 trials excluded patients with a screening blood EOS count of  $> 1500$  cells/ $\mu$ L [6].

QUEST [9] and DRI12544 [11] were primarily designed to assess asthma exacerbations [9] and/or lung function [9, 11] and required patients to have asthma that had worsened in the last year (resulting in hospitalization, emergency/urgent medical care or systemic corticosteroid therapy) and to be receiving medium-to-high-dose inhaled corticosteroids (ICS) plus additional controller medication(s). By contrast, VENTURE [10] was primarily designed to assess oral corticosteroid (OCS) sparing, and required patients to have been treated regularly with systemic corticosteroids in the last 6 months and high-dose ICS plus up to two controller

medications for the last  $\geq 3$  months. Prior to randomization, VENTURE participants had their current OCS dosage adjusted over 3–10 weeks to the minimum capable of managing their symptoms. This OCS optimization phase was followed by a 24-week randomized treatment period consisting of three parts: an induction phase (week 0–4) during which patients (now randomized to study drug) received their optimized OCS dosage; an OCS-reduction phase (week 4–20) during which the optimized OCS dosage was reduced every 4 weeks, based on asthma control changes and severe exacerbation incidence (as per prespecified schedule); and a maintenance phase (week 20–24) during which the OCS dosage established at the end of the OCS-reduction phase was continued unchanged.

Across the studies [9–11], patients had a mean age of  $\approx 50$  years, a mean (pre-bronchodilator [9, 10])  $FEV_1$  52–61% of predicted, a mean blood EOS count of 347–360 cells/ $\mu$ L and had experienced a mean of 2.1–2.2 (severe [10]) asthma exacerbations in the past year. Around 50% of patients in QUEST and DRI12544 were receiving a high-dose ICS-containing regimen [9, 11]; patients in VENTURE had received their first OCS prescription a mean of 1.7 years previously and their current dosage was 11.8 mg/day before adjustment [10].

### 4.1 Exacerbations

Adding subcutaneous dupilumab to background asthma therapy was effective in reducing the rate of severe asthma exacerbations in adults and adolescents whose asthma was inadequately controlled with medium-to-high-dose ICS [9, 11] or dependent on OCS for control [10] (Table 1). Relative to placebo, dupilumab (200 or 300 mg q2w) significantly reduced the yearly rate of these exacerbations per patient by almost 50% over 52 weeks in QUEST (primary endpoint) [9], with 24-week data from DRI12544 [11] and VENTURE [10] generally supporting these findings (Table 1). The corresponding rate of hospitalizations and/or emergency room visits because of severe exacerbations was also almost 50% lower with dupilumab than with placebo in QUEST (46.8% for dosages combined) [9]; a pooled analysis of QUEST and DRI12544 reported reductions of 25.5% with dupilumab 200 mg q2w and 46.9% with dupilumab 300 mg q2w [7].

### 4.2 Lung Function and Corticosteroid Use

Dupilumab improved lung function across the studies, with each dosage (200 or 300 mg q2w) being associated with significant increases in  $FEV_1$  relative to placebo over 12 weeks' therapy [9, 11] (primary endpoint [9]), which were sustained over 24 [9–11] and 52 [9] weeks (Table 1). This parameter markedly improved after only 2 weeks of dupilumab therapy in all trials [10, 16, 17] ( $p < 0.001$  vs. placebo where reported [16, 17]) and

**Table 1** Efficacy of subcutaneous dupilumab in reducing asthma exacerbations and improving lung function in patients with moderate-to-severe asthma in phase 2b [11] or 3 [9, 10] trials; *p*-values are provided where available

| Trial                      | Regimen (mg q2w <sup>a</sup> ) [no. of ITT pts] | Severe asthma exacerbations per pt-year (RR vs. PL; 95% CI) <sup>b,c</sup> | LSM change from BL in FEV <sub>1</sub> [L] (difference vs. PL; 95% CI) |                           |                           |
|----------------------------|-------------------------------------------------|----------------------------------------------------------------------------|------------------------------------------------------------------------|---------------------------|---------------------------|
|                            |                                                 |                                                                            | At 12 weeks <sup>c</sup>                                               | At 24 weeks <sup>d</sup>  | At 52 weeks <sup>d</sup>  |
| QUEST [9]                  | DUP 200 [631]                                   | 0.46 (0.52; 0.41–0.66)*                                                    | 0.32 (0.14; 0.08–0.19)*                                                | 0.34 (0.17; 0.11–0.22)*** | 0.36 (0.20; 0.14–0.25)*** |
|                            | PL [317]                                        | 0.87                                                                       | 0.18                                                                   | 0.17                      | 0.16                      |
|                            | DUP 300 [633]                                   | 0.52 (0.54; 0.43–0.68)*                                                    | 0.34 (0.13; 0.08–0.18)*                                                | 0.33 (0.11; 0.06–0.17)*** | 0.35 (0.13; 0.08–0.19)*** |
|                            | PL [321]                                        | 0.97                                                                       | 0.21                                                                   | 0.22                      | 0.22                      |
| DRI12544 <sup>e</sup> [11] | DUP 200 [150]                                   | 0.27**                                                                     | 0.31 (0.20; 0.11–0.28)***                                              | 0.29 (0.16; 0.07–0.24)**  |                           |
|                            | DUP 300 [157]                                   | 0.27***                                                                    | 0.28 (0.16; 0.08–0.25)**                                               | 0.28 (0.16; 0.07–0.24)**  |                           |
|                            | PL [158]                                        | 0.90                                                                       | 0.12                                                                   | 0.13                      |                           |
| VENTURE [10]               | DUP 300 [103]                                   | 0.65 (0.41; 0.26–0.63)                                                     |                                                                        | 0.22 (0.22; 0.09–0.34)    |                           |
|                            | PL [107]                                        | 1.60                                                                       |                                                                        | 0.01                      |                           |

The mean FEV<sub>1</sub> at BL in the overall trial population was 1.8 L in QUEST and DRI12544 and 1.6 L in VENTURE

BL baseline, DUP dupilumab, FEV<sub>1</sub> forced expiratory volume in 1 s (pre-bronchodilation, where specified [9, 10]), ITT intent-to-treat, LSM least-squares mean, PL volume-matched placebo, pt(s) patient(s), q<sub>xw</sub> every x weeks, RR rate ratio

\**p* < 0.001, \*\**p* ≤ 0.0005, \*\*\**p* ≤ 0.0001 vs. PL

<sup>a</sup>Maintenance dosage, subsequent to a loading dose of 400 mg (for 200 mg q2w) or 600 mg (for 300 mg q2w)

<sup>b</sup>Adjusted rates for the randomized treatment period (24 [10, 11] or 52 [9] weeks)

<sup>c</sup>Primary endpoint in QUEST

<sup>d</sup>Data for QUEST are from an abstract [17]

<sup>e</sup>This trial also contained DUP 200 mg (*n* = 154) and 300 mg (*n* = 157) q4w arms

was generally supported by other lung function measures, such as forced vital capacity (FVC), forced expiratory flow 25–75% of FVC, and morning/evening peak expiratory flow [9, 16, 18] (analyses were pre-specified [10, 17] or post hoc [16] where reported).

In addition, dupilumab had OCS-sparing benefits in patients with OCS dependence in VENTURE [10]. While maintaining asthma control, dupilumab (300 mg q2w) enabled the OCS daily dose to be reduced to a significantly greater extent than placebo, according to a comparison of the OCS dosage at week 24 (i.e. end of OCS maintenance phase) with that at baseline (i.e. after OCS dosage optimization) [primary endpoint; Table 2] [10]. In similar analyses, dupilumab also provided significant benefit over placebo for key secondary measures of OCS-sparing, including the proportion of patients whose OCS daily dose was reduced by ≥ 50%, to < 5 mg or by the maximum possible, or the proportion who no longer required OCS (Table 2) [10].

### 4.3 Other Outcomes

As with lung function (Sect. 4.2), improvements in asthma control [as measured by the 5-item Asthma Control Questionnaire (ACQ-5) total score] were evident with dupilumab (200 or 300 mg q2w) relative to placebo at 2 weeks [9], as well as 24 [9–11] and 52 [9] weeks in the pivotal trials (*p* < 0.005 where specified [11]). Moreover, where reported,

asthma-related health-related quality of life (HR-QOL) had also improved with each of the dupilumab regimens versus placebo at the latter timepoints [as assessed by Asthma Quality of Life Questionnaire (AQLQ) global scores [9, 11]; *p* < 0.01 where specified [11]]. Notably, in a post hoc analysis of one of the studies (DRI12544), significantly (*p* < 0.05) more recipients of these dupilumab regimens than of placebo achieved a response (i.e. a clinically meaningful improvement from baseline) in these measures of asthma control (73–77 vs. 60–61%) and HR-QOL (61–65 vs. 48–51%) at week 24 (i.e. a score improvement of either ≥ 0.5 or ≥ 0.6; scale range 0–6 for ACQ-5 and 1–7 for AQLQ) [19]. Workplace productivity also improved with dupilumab in this analysis, with the unadjusted annualized number of sick-leave days due to severe exacerbations being significantly lower with dupilumab 200 or 300 mg q2w than with placebo (0.61 and 0.62 vs. 2.24; adjusted *p* < 0.0001) [19].

### 4.4 Raised Type 2 Immune Activity and Other Subgroups

Patients with heightened baseline type 2 immune activity, including elevated levels of blood EOS or FeNO, tended to have a more prominent treatment benefit with dupilumab (200 or 300 mg q2w) relative to placebo in the phase 3 [9, 10] and 2b [11] trials, with the phase 2b study assessing the change from baseline in FEV<sub>1</sub> at 12 weeks in patients with ≥ 300 EOS/μL as a primary endpoint [11]. Key data

**Table 2 Oral corticosteroid-sparing efficacy of subcutaneous dupilumab in adults and adolescents with oral corticosteroid-dependent severe asthma in the phase 3 VENTURE trial [10]. Data are at week 24**

| Regimen (no. of intent-to-treat pts) | Least-squares mean ↓ from BL in OCS daily dose (%) <sup>a,b</sup> | Pts (%) with a ↓ from BL in OCS daily dose |                        |                     | Pts (%) no longer requiring OCS |
|--------------------------------------|-------------------------------------------------------------------|--------------------------------------------|------------------------|---------------------|---------------------------------|
|                                      |                                                                   | Of ≥ 50% <sup>a</sup>                      | To < 5 mg <sup>a</sup> | Of the max possible |                                 |
| DUP (103)                            | 70.1**                                                            | 79.6**                                     | 71.8**                 | 52.4*               | 52.4*                           |
| PL (107)                             | 41.9                                                              | 53.3                                       | 37.4                   | 29.9                | 29.2                            |
| OR [vs. PL; 95% CI]                  |                                                                   | 3.98 [2.06–7.67]                           | 4.48 [2.39–8.39]       | 2.57 [1.40–4.73]    | 2.74 [1.47–5.10]                |

BL baseline (i.e. after OCS dosage optimization), *max* maximum, DUP dupilumab 300 mg every 2 weeks (subsequent to a loading dose of 600 mg), OCS oral corticosteroid, OR odds ratio, PL placebo, *pts* patients, ↓ reduction

\* $p = 0.002$ , \*\* $p < 0.001$  vs. PL

<sup>a</sup>While maintaining asthma control

<sup>b</sup>Primary endpoint

for these populations are provided in Table 3. Notably, dupilumab had no significant benefit over placebo for primary endpoint measures in patients with < 150 EOS/ $\mu$ L or FeNO < 25 ppb in QUEST [9] or in patients with < 150 EOS/ $\mu$ L in VENTURE [10].

When treatment-by-biomarker interactions were assessed post hoc in QUEST, EOS and FeNO were the only biomarkers to consistently have a significant ( $p < 0.001$ ) impact on the benefit of dupilumab versus placebo in terms of primary efficacy outcomes, with the greatest benefit being seen in patients with both  $\geq 150$  EOS/ $\mu$ L and FeNO  $\geq 25$  ppb [9]. By contrast, in VENTURE,  $p$ -interaction values for key outcomes with dupilumab versus placebo were generally not significant across EOS or FeNO subgroups, with the exception being the annualized severe exacerbation rate, which was significantly (overall  $p < 0.05$ ) impacted by FeNO (being more favourable when baseline FeNO was  $\geq 50$  ppb or  $\geq 25$  to < 50 ppb than < 25 ppb) [10]. Whether the VENTURE findings may have been confounded by the use of OCS (which can modify biomarkers of type 2 inflammation [20]) is unclear.

In other subgroup analyses of QUEST (prespecified [21] or post hoc [22–25], where reported), dupilumab generally reduced severe exacerbation rates and improved lung function (FEV<sub>1</sub>) significantly ( $p < 0.05$ ) relative to placebo irrespective of the patient's baseline ICS dose [21], baseline FEV<sub>1</sub> [26], exacerbation history [22], age of asthma onset (i.e. late or early) [27], comorbid AR status [23], comorbid CRS/NP status [24] or whether their asthma was allergic or non-allergic in nature [25]. However, the exacerbation [22] or lung function [26] benefit was sometimes more prominent in patients with a greater number of prior exacerbations [22] or a lower baseline FEV<sub>1</sub> [26]. Subgroup analyses of VENTURE [28] and DRI12544 [29–37] generally supported these findings [28–33] and also suggested that dupilumab may (vs. placebo) improve severe exacerbation rates and/or lung function (FEV<sub>1</sub>) regardless of other patient characteristics (such as race, body mass index, smoking history [36],

post-bronchodilator reversibility [34], baseline periostin levels [37] and atopy history [35]) and reduce the OCS dose of patients with OCS-dependent asthma irrespective of their CRS/NP status [28] (analyses were post hoc where specified [28–32, 34, 35]).

Moreover, when dupilumab efficacy was assessed in adolescents (aged 12–17 years) in a prespecified analysis of QUEST [38], both the 200 mg ( $n = 21$ ) and 300 mg ( $n = 18$ ) q2w regimen significantly improved FEV<sub>1</sub> over 12 weeks relative to matched placebo ( $n = 34$  and 34) [difference vs. placebo in mean change from baseline was 0.36 and 0.27 L for the respective groups] [7, 38]. The 200 mg q2w regimen also significantly reduced the annualized rate of severe exacerbations relative to placebo by 46.4%, whereas 300 mg q2w had no treatment effect (despite an unadjusted rate of 0.46 vs. 0.76 with placebo), a finding possibly due to the subgroup being small and imbalanced with regard to the mean number of prior exacerbations (1.53 vs. 2.22 in placebo group) [38].

When the impact of dupilumab on asthma control (ACQ-5) and/or asthma-related HR-QOL (AQLQ) was assessed across various patient characteristics (e.g. exacerbation history [19, 39, 40], baseline FEV<sub>1</sub> [19] and comorbid AR [41] or CRS/NP [24, 42] status) in QUEST [24, 40], VENTURE [42] and DRI12544 [19, 39, 41], the findings of the analyses were generally consistent with those that assessed the exacerbation and lung function benefits of the drug by such patient factors. Of note, a large proportion of dupilumab recipients with elevated blood EOS ( $\geq 150$  or 300/ $\mu$ L) or FeNO ( $\geq 25$  ppb) levels at baseline achieved an ACQ-5 (70–76 vs. 64–67% of placebo recipients) or AQLQ (62–71 vs. 53–59%) response (i.e. score improvement of  $\geq 0.5$ ) after 52 weeks' treatment in QUEST [7]. Moreover, in the participants of QUEST [24, 43] and VENTURE [44] who had comorbid AR [43] or CRS [24, 44], improvements ( $p \leq 0.05$  vs. placebo) in HR-QOL measures related to the comorbidities (namely the Rhinoconjunctivitis Quality of Life Questionnaire [43] and 22-item Sino-Nasal Outcome Test [24, 44]

**Table 3** Efficacy of subcutaneous dupilumab in patients with moderate to severe asthma and raised biomarkers of type 2 inflammation in phase 2b or 3 trials

| Treatment<br>[mg q2w <sup>a</sup> ] |         | Severe exacerbations per pt per<br>year [RR vs. PL] (95% CI) |                  | LSM change from BL in pbFEV <sub>1</sub> (L) at 12<br>or 24 wk <sup>b</sup> [diff vs. PL] (95% CI) |                      | LSM ↓ from BL in OCS daily<br>dose (%) at 24 wk [diff vs. PL]<br>(95% CI) |                  |
|-------------------------------------|---------|--------------------------------------------------------------|------------------|----------------------------------------------------------------------------------------------------|----------------------|---------------------------------------------------------------------------|------------------|
| BL EOS count (cells/μL)             |         | ≥ 300                                                        | ≥ 150            | ≥ 300                                                                                              | ≥ 150                | ≥ 300                                                                     | ≥ 150            |
| QUEST [7]                           | DUP 200 | 0.34 (0.24–0.48)                                             | 0.44 (0.34–0.58) | 0.21 (0.13–0.29)                                                                                   | 0.17 (0.11–0.23)     |                                                                           |                  |
|                                     | DUP 300 | 0.33 (0.23–0.45)                                             | 0.40 (0.31–0.53) | 0.24 (0.16–0.32)                                                                                   | 0.15 (0.09–0.21)     |                                                                           |                  |
| DRI12544<br>[7]                     | DUP 200 | 0.29 (0.11–0.76)                                             | 0.28 (0.14–0.55) | 0.26 (0.11–0.40) <sup>c</sup>                                                                      | 0.19 (0.09–0.29)     |                                                                           |                  |
|                                     | DUP 300 | 0.19 (0.07–0.56)                                             | 0.27 (0.14–0.52) | 0.21 (0.06–0.36) <sup>c</sup>                                                                      | 0.16 (0.06–0.26)     |                                                                           |                  |
| VENTURE<br>[10]                     | DUP 300 | 0.29 (0.14–0.60)                                             | 0.42 (0.25–0.69) | 0.32 (0.10–0.54)                                                                                   | 0.22 (0.06–0.38)     | 36.8 (18.9–54.7)                                                          | 29.4 (15.7–43.1) |
| BL FeNO (ppb)                       |         | ≥ 50                                                         | ≥ 25 to < 50     | ≥ 50                                                                                               | ≥ 25 to < 50         | ≥ 50                                                                      | ≥ 25 to < 50     |
| QUEST [9]                           | DUP 200 | 0.31 (0.18–0.52)                                             | 0.39 (0.24–0.62) | 0.30 (0.17–0.44)                                                                                   | 0.19 (0.09–0.28)     |                                                                           |                  |
|                                     | DUP 300 | 0.31 (0.19–0.49)                                             | 0.44 (0.28–0.69) | 0.39 (0.26–0.52)                                                                                   | 0.12 (0.03–0.21)     |                                                                           |                  |
| VENTURE<br>[10]                     | DUP 300 | 0.53 (0.23–1.24)                                             | 0.20 (0.07–0.53) | 0.28 (–0.03 to 0.60)                                                                               | 0.23 (–0.01 to 0.48) | 33.6 (13.7–53.6)                                                          | 38.3 (14.8–61.8) |

Analyses by BL EOS/FeNO were pre-specified in QUEST [9] and DRI12544 (≥ 300 EOS/μL) [11] and exploratory in VENTURE [10]. Across endpoints, the no. of evaluable DUP (any dosage) and PL recipients differed between EOS subgroups in QUEST (437–452 and 232–237 had ≥ 150 EOS/μL; 264–277 and 142–148 had ≥ 300 EOS/μL) [7], DRI12544 (120–129 and 127; 64–65 and 68) [7] and VENTURE (81 and 69; 48 and 41) [10]. The no. of evaluable DUP (any dosage) and/or PL recipients also differed between FeNO subgroups in QUEST (113–124 and 69–75 had FeNO ≥ 50 ppb; 174–186 and 88–97 had FeNO ≥ 25 to < 50 ppb) [9] and VENTURE (23–24 and 27–29; 31–33 and 28) [10]

BL baseline, *diff* difference, DUP dupilumab, EOS blood eosinophil, FeNO fractional exhaled nitric oxide, LSM least-squares mean, OCS oral corticosteroid, pbFEV<sub>1</sub> pre-bronchodilator forced expiratory volume in 1 s, PL placebo, *pt* patient, q2w every 2 weeks, RR rate ratio, wk week, ↓ reduction

<sup>a</sup>Maintenance dosage, subsequent to a loading dose of 400 mg (for 200 mg q2w) or 600 mg (for 300 mg q2w)

<sup>b</sup>Data are at week 12 for QUEST and DRI12544 and week 24 for VENTURE

<sup>c</sup>Primary endpoint; LSM change from BL was 0.43 and 0.39 L with DUP 200 or 300 mg q2w vs. 0.18 L with PL ( $p < 0.001$  and  $p < 0.01$ ). Mean BL value was 1.82 L in the overall ≥ 300 EOS/μL subgroup

total scores) were evident with dupilumab (200 or 300 mg q2w) at all/most of the timepoints assessed (12, 24 and/or 52 weeks), with comorbid AR subgroup data from DRI12544 supporting the benefit of dupilumab (300 mg, but not 200 mg, q2w) in this regard [45]. Analyses were prespecified [43, 44] or post hoc [19, 24, 39–41, 45] where reported.

## 5 Tolerability of Dupilumab

Dupilumab, administered subcutaneously in addition to background asthma therapy for 24 or 52 weeks, was generally well tolerated in adults and adolescents with moderate to severe asthma in the three clinical trials discussed in Sect. 4 (QUEST [9], VENTURE [10] and DRI12544 [11]), and its tolerability profile at these timepoints was generally similar [9].

Across the three studies, the tolerability profile of dupilumab (200 or 300 mg q2w) was generally similar to that of placebo with regard to the incidence of AEs (62–82 vs. 64–84%), serious AEs (7–9 vs. 6–8%) and AEs that resulted in treatment discontinuation (1–7 vs. 3–6%) or death (0–0.6 vs. 0–1.0%) [9–11]. Where specified,

pneumonia was the most frequent serious AE (0.3% of dupilumab vs. 0.3% of placebo recipients) and no deaths were considered treatment related [9]. In a pooled analysis of 24-week data from two of these trials (QUEST and DRI12544), the adverse reactions that occurred most commonly with dupilumab (200 or 300 mg q2w;  $n = 779$  and 788) and with an incidence numerically greater than with placebo ( $n = 792$ ) included injection-site reactions (14 and 18 vs. 6%), oropharyngeal pain (2 and 2 vs. 1%) and eosinophilia (i.e. blood EOS ≥ 3000/μL or deemed to be an AE by the investigator) [2 and 2 vs. < 1%] [6]. When eosinophilia was defined as blood EOS > 3000/μL (as per trial protocol), the incidence was 1.2% with dupilumab (200 or 300 mg q2w; combined data) versus 0.3% with placebo (combined data) in the 52-week QUEST trial [9] and 13% with dupilumab (300 mg q2w) versus 1% with placebo in the 24-week VENTURE trial [10].

### 5.1 Adverse Events of Special Interest

There have been cases of eosinophilic pneumonia and vasculitis consistent with eosinophilic granulomatosis with polyangiitis among adults who received dupilumab in the

asthma development programme [6, 7]. As these are conditions often treated with systemic corticosteroids, they can be associated with OCS reductions [6, 7]; a causal relationship with dupilumab has not been established [6]. Clinicians are advised to be alert (in patients with eosinophilia [6, 7]) to EOS count changes [8], vasculitic rash, neuropathy, worsening pulmonary symptoms and/or cardiac complications [6–8]. However, few dupilumab (200 or 300 mg q2w) or placebo recipients (0.2 and 0.6 vs. 0.3%) experienced cardiovascular thromboembolic events (i.e. cardiovascular death or non-fatal stroke/myocardial infarction) in QUEST [6].

Hypersensitivity reactions (e.g. rash, serum sickness reaction and anaphylaxis) were uncommon with dupilumab in clinical trials (incidence < 1%), with only one recipient experiencing anaphylaxis in the asthma development programme [6]. In the event of a clinically significant hypersensitivity reaction, dupilumab should be discontinued and appropriate treatment started [6–8].

Dupilumab did not increase the risk of conjunctivitis relative to placebo in patients with asthma in key clinical studies [9, 10]; however, dupilumab recipients should report new or worsening eye symptoms to their healthcare provider [6]. If standard treatment does not resolve conjunctivitis, ophthalmological examination is advised [7]; withdrawal/discontinuation of dupilumab may be necessary [8].

It is not yet known if dupilumab (through inhibition of IL-4/IL-13 signalling) could impact immune responses against parasitic (helminth [6, 7]) infections [6–8]. Consequently, such infections should be treated before initiating the drug, although if they occur during dupilumab therapy and do not respond to appropriate treatment, dupilumab should be temporarily discontinued [6–8].

## 6 Dosage and Administration of Dupilumab

The asthma indications for which dupilumab is approved in key global regions are summarized in Table 4, along with the recommended dosage and administration details for the drug. Dupilumab is administered by the patient/caregiver (after appropriate training) or healthcare professional via subcutaneous injection into the thigh or abdomen [6–8], with the upper arm also an option [8] if administered by someone other than the patient [6, 7]; injection-site rotation is advised [6–8]. Dupilumab should not be injected into skin 5 cm around the navel or skin that is bruised [6–8], scarred/damaged [6, 7], tender/sensitive [6, 7] or severely inflamed due to atopic dermatitis [8]. For patients taking concomitant OCS who experience clinical improvement with dupilumab, the OCS dosage may be reduced [7], although any reductions in corticosteroid dosage after initiating dupilumab therapy should be made gradually [6–8]. Dupilumab should not be used for the treatment of acute asthma symptoms/

exacerbations [6–8], acute bronchospasm [6, 7] or status asthmaticus [6, 7]. Local prescribing information should be consulted for detailed information regarding preparation and administration, use in special populations, contraindications and other warnings and precautions.

## 7 Place of Dupilumab in the Management of Asthma

Key goals of treating asthma include reducing the likelihood of airway damage, exacerbations and drug-related AEs and, thus, the overall burden of disease [46]. To this end, a stepwise treatment approach is recommended, with the most appropriate starting regimen being chosen on the basis of the disease's current severity and then adjusted as needed thereafter [46, 47]. Although most patients achieve asthma control with conventional treatment regimens [48] (such as ICS plus long-acting  $\beta$ -adrenoceptor agonists (LABA), with or without long-acting muscarinic antagonists, leukotriene receptor antagonists, theophylline and/or OCS [46, 47]), some patients do not, and for a proportion of these patients with more severe forms of asthma, targeted biological therapies have been a major treatment advance [2].

The targeted agents approved for use to date are monoclonal antibodies against specific components of type 2 inflammation, namely IgE (omalizumab), IL-5 signalling (mepolizumab, reslizumab, benralizumab) and IL-4/IL-13 signalling (dupilumab) [49]. Given their varying target mechanisms, the asthma indications for which these agents are approved also differ, being, in EU/US markets for instance, severe (or moderate-to-severe) persistent allergic asthma for omalizumab, severe eosinophilic asthma for the anti-IL-5-signalling agents, and severe (or moderate to severe) type 2 inflammatory/eosinophilic asthma or OCS-dependent asthma for dupilumab. The importance of these agents in asthma is particularly evident in the recent GINA guidelines for difficult-to-treat and severe asthma [49], which recommends they are considered as add-on therapies in patients with severe asthma with type 2 inflammation who have exacerbations/poor symptom control on a high-dose ICS plus LABA regimen and also have eosinophilic/allergic biomarkers or a requirement for OCS maintenance therapy. The most appropriate initial targeted agent can then be selected on the basis of its treatment criteria (including particular type 2 inflammation biomarker characteristics), taking into account the presence of factors likely to predict a good treatment response [49].

Dupilumab is the first drug to target IL-4/IL-13 signalling in asthma and, consistent with this mechanism, it reduces levels of a range of type 2 inflammation biomarkers (Sect. 2), suggesting its effects on type 2 inflammation may be broader than those of anti-IL-5-signalling agents (which

**Table 4** Approved indication and dosage recommendations for subcutaneous dupilumab in key global regions

| Region    | Indication                                                                                                                                                                                                                                                          | Dosage recommendations                                                                                                                                                                                                             |
|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| EU [7]    | Add-on maintenance treatment for severe asthma with type 2 inflammation (characterized by raised blood eosinophils and/or raised FeNO) in adults and adolescents aged $\geq 12$ years inadequately controlled with high-dose ICS plus another maintenance treatment | 600 mg loading dose <sup>a</sup> then 300 mg q2w, for pts with severe asthma on OCS or with severe asthma and comorbid moderate-to-severe atopic dermatitis<br>400 mg loading dose <sup>a</sup> then 200 mg q2w, for all other pts |
| USA [6]   | Add-on maintenance treatment in pts with moderate-to-severe asthma aged $\geq 12$ years with an eosinophilic phenotype or with OCS-dependent asthma                                                                                                                 | 600 mg loading dose <sup>a</sup> then 300 mg q2w (recommended initial regimen for pts with OCS-dependent asthma, or with comorbid moderate-to-severe atopic dermatitis)<br>400 mg loading dose <sup>a</sup> then 200 mg q2w        |
| Japan [8] | Add-on treatment in pts aged $\geq 12$ years with severe or intractable bronchial asthma not controlled with existing treatment who have appropriate bio-markers of type 2 inflammation                                                                             | Usually 600 mg loading dose <sup>a</sup> then 300 mg q2w                                                                                                                                                                           |

FeNO fractional exhaled nitric oxide, ICS inhaled corticosteroid, OCS oral corticosteroid, pts patients, q2w every 2 weeks

<sup>a</sup>Loading dose is administered in two injections of 300 mg (i.e. 600 mg dose) or 200 mg (i.e. 400 mg dose) where specified [6, 7]

solely impact EOS). In the pivotal QUEST, VENTURE and DRI12544 trials of  $\leq 52$  weeks' duration, adding subcutaneous dupilumab (200 or 300 mg q2w) to the background asthma therapy of adults and adolescents aged  $\geq 12$  years with moderate-to-severe asthma (inadequately controlled with medium-to-high dose ICS) or severe asthma (dependent on OCS for control) reduced the rate of severe asthma exacerbations (Sect. 4.1) and provided rapid and sustained lung function improvements (Sect. 4.2), as well as improvements in asthma control and HR-QOL (Sect. 4.3). Dupilumab also enabled patients with OCS-dependent asthma to reduce their maintenance dose of OCS without impacting asthma control (Sect. 4.2), which is important given that considerable systemic AEs (e.g. cataracts, diabetes and osteoporosis) can occur with OCS, especially when used often or continuously [49].

Dupilumab displayed efficacy across various patient subgroups (Sect. 4.4). However, patients with heightened type 2 immune activity, including elevated baseline levels of blood EOS and FeNO, tended to have a more prominent treatment benefit with the drug (Sect. 4.4), a finding that is reflected in the asthma populations for which dupilumab is approved (Sect. 6) and guideline-recommended [49] for use. Indeed, GINA guidelines recommend dupilumab for patients with severe asthma with a type 2 inflammation/eosinophilic phenotype (i.e. exacerbations in the last year, blood EOS  $\geq 150/\mu\text{L}$  or FeNO  $\geq 25$  ppb) or who require OCS maintenance therapy, and they consider higher blood EOS and higher FeNO levels to be factors that may predict a good response [49].

Of note, patients who receive dupilumab for the treatment of asthma with a type 2 inflammation/eosinophilic phenotype may also experience improvements in comorbid diseases that are likewise driven by type 2 inflammation (Sect. 4.4). Further clinical experience will likely help to determine the extent of this potential benefit, although a

similar phenomenon has been observed with dupilumab in patients with atopic dermatitis and comorbid asthma and chronic sinus-nasal conditions, with all three conditions improving with the drug [50].

Dupilumab was generally well tolerated in the asthma trials and did not increase the risk of conjunctivitis (Sect. 5), an AE that has been associated with dupilumab therapy in patients with atopic dermatitis [51]. Although transient elevations in circulating EOS levels were seen with the drug, they were generally without clinical consequence or AEs (Sect. 2) and may have been due to dupilumab inhibiting IL-4 and IL-13-mediated migration of EOS into the tissues without impacting EOS production in/egress from the bone marrow. Few dupilumab recipients experienced eosinophilia in a pooled analysis of QUEST and DRI12544 or when it was defined as  $> 3000$  EOS/ $\mu\text{L}$  in QUEST (Sect. 5). Although the latter definition of eosinophilia occurred with markedly greater incidence with dupilumab than with placebo in VENTURE (Sect. 5), this may have been due, at least in part, to the OCS-sparing benefits of dupilumab versus placebo in this study (Sect. 4.2), as circulating EOS can be suppressed by corticosteroids [52].

The financial burden of severe asthma is very high, due to costs associated with OCS-related AEs, as well as physician visits, hospitalizations and medications [49]. Indeed, the targeted biological agents approved for use in asthma are expensive (e.g. average wholesale price  $\approx$  \$US 1100–5700 per vial/syringe/dose) [53], making pharmacoeconomic data for them important. For dupilumab, such data are currently limited to an analysis of DRI12544, in which dupilumab 200 or 300 mg q2w reduced direct medical costs by 39 and 95%, productivity-related costs by 68 and 71% and overall exacerbation-related costs by 52 and 84%, relative to placebo [54]. Cost-utility studies for dupilumab would therefore be of interest, as would longer-term efficacy and tolerability data for the drug; data are

awaited from a 1-year open-label extension study (TRAV-ERSE; NCT02134028) conducted in participants of previous dupilumab trials, including QUEST, VENTURE and DRI12544.

Clinical studies directly comparing dupilumab with other type 2 inflammation-targeting agents (such as omalizumab and anti-IL-5-signalling agents) would also be informative because, although indicated for different asthma phenotypes, some patients may be eligible for more than one of the agents. To date, dupilumab has only been compared with these agents indirectly in network meta-analyses [55–57], the findings of which require cautious interpretation due to the nature of the comparisons and the likely heterogeneity of the studies/patient populations assessed. Switching trials may also be of interest, given that GINA guidelines for difficult-to-treat and severe asthma recommend trying a different type 2 inflammation-targeting agent if a good asthma response is not achieved after  $\geq 4$  months' treatment with the first, provided the patient is eligible for another targeted agent [49].

Although dupilumab requires administration q2w (which is more frequent than most other type 2 inflammation-targeting agents), it can be self-administered at home if appropriate (Sect. 6), which some patients may find more convenient than administration by a healthcare professional (as is generally required for the other type 2 inflammation-targeting agents).

In conclusion, subcutaneous dupilumab is a valuable add-on treatment option for patients aged  $\geq 12$  years who have severe/moderate-to-severe asthma with a type 2 inflammation/eosinophilic phenotype despite conventional treatments or who are dependent on OCS for asthma control.

#### Data Selection Dupilumab: 283 records identified

|                                                                                                                                                                                                                                                                                                         |           |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| Duplicates removed                                                                                                                                                                                                                                                                                      | 78        |
| Excluded during initial screening (e.g. press releases; news reports; not relevant drug/indication; preclinical study; reviews; case reports; not randomized trial)                                                                                                                                     | 110       |
| Excluded during writing (e.g. reviews; duplicate data; small patient number; nonrandomized/phase I/II trials)                                                                                                                                                                                           | 38        |
| <b>Cited efficacy/tolerability articles</b>                                                                                                                                                                                                                                                             | <b>36</b> |
| <b>Cited articles not efficacy/tolerability</b>                                                                                                                                                                                                                                                         | <b>21</b> |
| Search Strategy: EMBASE, MEDLINE and PubMed from 1946 to present. Clinical trial registries/databases and websites were also searched for relevant data. Key words were dupilumab, Dupixent, REGN 668, asthma. Records were limited to those in English language. Searches last updated 21 October 2019 |           |

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