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CADTH Reimbursement Review

Dupilumab (Duxipent)

Sponsor: Sanofi Genzyme, a division of Sanofi-Aventis Canada Inc.

Therapeutic area: Type 2 or eosinophilic asthma

Clinical Review

Pharmacoeconomic Review

CADTH

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

ACQ	Asthma Control Questionnaire
ACQ-5	Asthma Control Questionnaire, 5-item
ACQ-7	Asthma Control Questionnaire, 7-item
AQLQ	Asthma Quality of Life Questionnaire
BCLA	British Columbia Lung Association
CI	confidence interval
CrI	credible interval
EMA	European Medicines Agency
EQ-5D	EuroQol 5-Dimensions questionnaire
EQ-5D-3L	EuroQol 5-Dimensions 3-Levels questionnaire
EQ-5D-5L	EuroQol 5-Dimensions 5-Levels questionnaire
EQ VAS	EuroQol Visual Analogue Scale
FeNO	fractional exhaled nitric oxide
FEV_1	forced expiratory volume in the first second
FTP	fluticasone propionate
GINA	Global Initiative for Asthma
ICS	inhaled corticosteroid
IgE	immunoglobin E
IL	interleukin
ITC	indirect treatment comparison
LABA	long-acting beta2-agonist
LAMA	long-acting muscarinic antagonist
LHF	Lung Health Foundation
LSM	least squares mean
MAIC	matching-adjusted indirect comparison
MID	minimally important difference
MMRM	mixed-effect model with repeated measures
MPPI	minimal patient perceivable improvement
NMA	network meta-analysis
OCS	oral corticosteroid
PEF	peak expiratory flow
PICOS	population, intervention, comparator, outcome, and study
PMM-MI	pattern mixture modelling–multiple imputation
ppb	parts per billion
RCT	randomized controlled trial
RQLQ	Rhinoconjunctivitis Quality of Life Questionnaire
RQLQ(S)	Standardized Rhinoconjunctivitis Quality of Life Questionnaire
RR	relative risk
SE	standard error
SNOT-22	Sino-Nasal Outcomes Test, 22 items

Executive Summary

An overview of the submission details for the drug under review is provided in Table 1.

Introduction

Asthma is a chronic respiratory disorder characterized by reversible airway obstruction. Hallmarks of asthma include inflammation, bronchoconstriction, and airway remodelling, as well as hyper-responsive airways and mucous production. Symptoms of asthma include wheezing, dyspnea, chest tightness, sputum production, and coughing, and these symptoms can be exacerbated by exogenous influences such as allergens, upper respiratory tract infections, or environmental factors such as smoke or cold air. Eosinophils are believed to be a major contributor to the inflammatory processes that are characteristic of the disease. It is estimated that 2.4 million Canadians 12 years or older suffer from asthma, or 12% of all children and 8% of adults.

The management of asthma is carried out using (i) medications for the acute relief of exacerbations (colloquially, "asthma attacks"), often referred to as "relievers" or "rescue medications," and (ii) controllers, or maintenance drugs, which are used on a regular or chronic basis in an effort to prevent the onset of exacerbations. The reliever medications are typically rapid-acting, short-acting bronchodilators, such as the beta2-agonist salbutamol. It is well understood, though, that the chronic use of maintenance medications such as inhaled corticosteroids (ICSs) is critical in the management of asthma. The second maintenance medications typically used are long-acting bronchodilators, most commonly the long-acting beta2-agonists (LABAs), always in combination with ICSs. Other medications used include other bronchodilators, such as the long-acting muscarinic antagonists (LAMAs) and, less commonly, methylxanthines such as theophylline, which have numerous safety and

Table 1: Submitted for Review

Item	Description
Drug product	Dupilumab (Dupixent), 200 mg or 300 mg, single use syringe, solution for subcutaneous injection
Indication	Indicated as add-on maintenance treatment in patients aged 12 years and older with severe asthma with a type 2/eosinophilic phenotype or oral corticosteroid–dependent asthma
Reimbursement request	For patients with type 2 or eosinophilic asthma characterized by the following: • 2 or more clinically significant asthma exacerbations in the last 12 months and ◦ Blood eosinophils ≥ 150 cells/μL, or ◦ FeNO ≥ 25 ppb, or ◦ Treatment with maintenance oral corticosteroids, or ◦ Clinically allergen-driven asthma.
Health Canada approval status	NOC
Health Canada review pathway	Standard
NOC date	November 12, 2020
Sponsor	Sanofi Genzyme

FeNO = fractional exhaled nitric oxide; NOC = notice of compliance; ppb = parts per billion.

tolerability issues. Leukotriene receptor antagonists, which are considered to be "steroid sparing," tend to be reserved for those with an allergic phenotype and have modest efficacy. Monoclonal antibodies are the newest entrants into the asthma treatment paradigm, beginning with immunoglobin E (IgE) inhibitors (omalizumab) and, more recently, interleukin (IL)-5 inhibitors (mepolizumab, reslizumab, and benralizumab) and now, an IL-4 and IL-13 inhibitor (dupilumab). None of the monoclonal antibodies are intended to be used first line but, rather, are reserved for those patients whose asthma is not well-controlled with moderate-to-high doses of ICS or ICS + LABA.

Dupilumab is an IL-4 and IL-13 inhibitor, administered by subcutaneous injection, at a dose of either 200 mg (patients with severe asthma with a type 2 or eosinophilic phenotype) or 300 mg (patients with oral corticosteroid [OCS]–dependent asthma or with comorbid moderate-to-severe atopic dermatitis and/or severe chronic rhinosinusitis with nasal polyposis) every 2 weeks. The 200 mg dose may be increased to 300 mg, if needed, at the discretion of the prescriber. Dupilumab is indicated as add-on maintenance treatment in patients 12 years and older with severe asthma with a type 2 or eosinophilic phenotype or with OCS-dependent asthma. Dupilumab is also indicated for atopic dermatitis and for chronic rhinosinusitis with nasal polyposis. It was reviewed previously by CADTH for the atopic dermatitis indication and, in July 2018, received a recommendation of do not list.

The sponsor has requested that dupilumab be reimbursed for patients with type 2 or eosinophilic asthma characterized by 2 or more clinically significant asthma exacerbations in the past 12 months and (i) blood eosinophils greater than or equal to 150 cells/μL, or (ii) fractional exhaled nitric oxide (FeNO) greater than or equal to 25 parts per billion (ppb), or (iii) treatment with maintenance OCSs, or (iv) clinically allergen-driven asthma. These criteria are in addition to the Health Canada indication.

The objective of this report was to perform a systematic review of the beneficial and harmful effects of dupilumab for patients 12 years and older with a type 2 or eosinophilic phenotype or with OCS-dependent asthma.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups who responded to CADTH's call for patient input and from the clinical expert consulted by CADTH for the purpose of this review.

Patient Input

- Input was provided by the British Columbia Lung Association and Lung Groups and the Lung Health Foundation (LHF). Input was obtained through the use of an LHF online survey, with 16 respondents with asthma and 2 caregivers.
- Respondents indicated shortness of breath and breathlessness as key symptoms, as well as fatigue, chest tightness, wheezing, and coughing. Asthma impacts their ability to play sports, exercise, work, travel, and participate in hobbies and leisure activities. Patients with severe asthma experience anxiety and depression, as do their caregivers.
- Patients expect new therapies will relieve symptoms, prolong life, reduce disability, stabilize lung function, and slow disease progression.
- Patients identified the adverse effects associated with chronic use of OCSs as particularly problematic and that even short-term use can cause problems such as sleep disturbances

and increased risk of infection and thromboembolism. Therefore, any strategies that would help reduce the need for OCSs are important to patients.

Clinician Input

Input From Clinical Expert Consulted by CADTH

- According to the clinical expert consulted by CADTH, the goals of therapy are to improve daily symptoms and to reduce the risk of severe exacerbations. The needs of the majority of patients are met with current therapies; however, approximately 5% to 10% of patients are poorly controlled despite maximized pharmacological and nonpharmacological treatment (inhaler education, improved medication adherence).
- Patients with severe asthma with type 2 inflammation are now treated with biologics. These may be drugs that target eosinophilic inflammation, like dupilumab or the IL-5 inhibitors. The clinical expert believed that dupilumab should be useful in patients with type 2 inflammation who remain uncontrolled despite moderate- to high-dose ICS with a second controller added, or in patients who require OCS to maintain control.
- The patients most likely to benefit from monoclonal antibody treatment are those with uncontrolled asthma despite treatment with moderate- to high-dose ICS + LABA or OCS. The clinical expert believed that dupilumab will also likely be considered in patients with concomitant atopic dermatitis and/or chronic rhinosinusitis with nasal polyps. The product monograph for dupilumab includes an indication for these common comorbidities of asthma; therefore, the presence of these comorbidities may drive its use ahead of other biologics.
- In asthma, the drug should not be used on patients with non–type 2 inflammation. Currently, peripheral blood eosinophils act as a surrogate for identifying patients with type 2 inflammation because the preferred method using sputum eosinophil counts is not readily accessible, Biologics such as dupilumab would be considered for patients with blood eosinophil counts of equal to or greater than 150 cells/μL.
- Elimination of airflow reversibility to a bronchodilator and reduction of nighttime and daytime symptoms would be measured over time to assess response, improvement, or stabilization of forced expiratory volume in the first second (FEV_1). Validated instruments, such as the Asthma Control Questionnaire (ACQ), can be used to assess asthma control. For patients on regular OCS, gradual reduction in OCS dose or elimination of OCS would be a clinically important outcome. A period of 12 months is typically needed to assess whether a treatment is effective in meeting treatment goals. This is the minimum duration needed to assess the effects on asthma exacerbations.
- The clinical expert believed that the primary factor in deciding whether to discontinue treatment would be lack of improvement in asthma control over time. Serious adverse events (such as keratitis) would also be an indication to stop treatment. Patients may still have asthma exacerbations while on treatment for a variety of reasons unrelated to lack of efficacy of dupilumab, such as intercurrent rhinovirus infection.
- The clinical expert believed that inclusion of the concurrent treatment of atopic dermatitis or chronic rhinosinusitis is an important outcome for some patients with asthma. There is no clear mechanism or scoring system to account for the beneficial effects in these patients.

Clinician Group Input

- One group, the Family Physician Airways Group of Canada, provided input.

- There is no clear indication of any contrary views between the clinician group and the clinical expert.
- The clinician group did not specifically describe experience with dupilumab. Its members noted that biologics are now used in asthma for severe, uncontrolled disease.

Drug Program Input

Input was obtained from the jurisdictions participating in CADTH reimbursement reviews. The following were identified as key clinical factors that could impact the implementation:

- The definition of type 2 asthma and the threshold of blood eosinophils at which clinicians would initiate treatment with dupilumab.
- The place in therapy of dupilumab relative to currently available treatments for severe asthma, including the sequencing of treatments.

The clinical expert consulted by CADTH weighed evidence from the trials and other clinical considerations to provide responses, which can be found in the Drug Program Input section.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

Three studies were included in this review: QUEST, VENTURE, and DRI12544. The included studies were all multinational, manufacturer-sponsored, double-blind randomized controlled trials that compared dupilumab to placebo in patients with asthma who were already receiving standard of care. QUEST was a 52-week phase III trial that randomized 1,902 adults and adolescents with moderate-to-severe asthma in a 2:2:1:1 ratio to 1 of 2 doses of dupilumab (200 mg or 300 mg) every 2 weeks or matching placebo every 2 weeks. The co-primary outcomes of QUEST were the annualized rate of severe asthma exacerbations and the absolute change from baseline in pre-bronchodilator FEV_1 at week 12. VENTURE was a 24-week phase III study whose objective was to investigate the efficacy and tolerability of dupilumab in reducing the use of OCSs while maintaining asthma control in patients with severe refractory asthma. VENTURE randomized 210 adults and adolescents with severe asthma and regular use of systemic steroids in the 6 months before screening to dupilumab 300 mg every 2 weeks or placebo. The primary outcome of VENTURE was the percent reduction in OCS dose at week 24. DRI12544 was a 24-week dose-ranging study that randomized adults with moderate-to-severe uncontrolled asthma to 1 of 4 dosages of dupilumab (dupilumab 200 mg or dupilumab 300 mg, every 2 weeks or every 4 weeks) or placebo. Only the 2 every 2 week dosing regimens that are approved in Canada, as well as placebo, comprising 465 patients, are reported in this review. The primary outcome was the change from baseline in FEV_1 at week 12.

Patients across studies were in their late 40s to early 50s, on average (range: 48 to 51 years of age), and the majority were female (> 60%) and White (approximately 80%). In QUEST, approximately half were on a high dose of ICS at baseline, while most of the remainder were on a medium dose (approximately 1% were on a low dose). Across the studies, patients had an average of approximately 2 severe asthma exacerbations in the past year, with the highest average in DRI12544 (approximately 2.15/year). On an annual basis, patients averaged less than 1 severe exacerbation requiring hospitalization or urgent medical attention, with a range between studies of approximately 0.7 in QUEST and DRI12544 to approximately 1 in VENTURE.

Efficacy Results

There were few deaths across the included studies and no clear differences in mortality between groups within studies.

The annualized rate of severe exacerbations was the primary outcome in QUEST. At the lower dose (200 mg), the annualized rate of severe asthma exacerbations was 0.456 with dupilumab versus 0.871 with placebo, for a relative risk (RR) of 0.523 (95% confidence interval [CI], 0.413 to 0.662; P < 0.0001). At the higher dose (300 mg), the rate was 0.524 dupilumab versus 0.970 placebo, for an RR of 0.540 (95% CI, 0.430 to 0.680; P < 0.0001). Similar results were seen in VENTURE, where the rate in the dupilumab 300 mg group was 0.649 (95% CI, 0.442 to 0.0955) and in the placebo group was 1.597 (95% CI, 1.248 to 2.043), for an RR versus placebo of 0.407 (95% CI, 0.263 to 0.630; P < 0.0001) (Table 2). Similar results were also seen in the DRI12544 study, where severe exacerbations were a secondary outcome, with an RR versus placebo in the dupilumab 200 mg dose group of 0.300 (95% CI, 0.159 to 0.565; P = 0.0002) and in the 300 mg dose group of 0.295 (95% CI, 0.159 to 0.546; P = 0.0001). In the pre-planned subgroup of patients based on baseline eosinophil count, larger improvements in severe exacerbation rates were seen in those with higher baseline eosinophils (> 300 cells/μL) for 200 mg of dupilumab, with an RR of 0.342 (95% CI, 0.244 to 0.480; P < 0.0001), and for 300 mg dupilumab, with an RR of 0.326 (95% CI, 0.234 to 0.454; P < 0.0001), than in those with lower baseline eosinophils (dupilumab 200 mg: 0.759 [95% CI, 0.548 to 1.052; P = 0.0975]; dupilumab 300 mg: 0.834 [95% CI, 0.608 to 1.144; P = 0.2599]).

Percent reduction in OCS dose was the primary outcome of VENTURE. From a mean baseline daily OCS dose of 10.75 mg, the least squares mean (LSM) (standard error [SE]) percent reduction from baseline in the dupilumab 300 mg group was 70.09% (4.90) and from a mean baseline of 11.75 mg/day in the placebo group was 41.85% (4.57), for an LSM difference between groups of 28.24% (95% CI, 15.81 to 40.67; P < 0.0001). The absolute reduction in OCS dose had an LSM (SE) of 7.58 mg/day (0.58) with dupilumab 300 mg and 4.77 mg/day (0.54) with placebo, for an LSM difference between groups of 2.81 mg/day (95% CI, 1.33 to 4.29; P = 0.0002). The clinical expert consulted by CADTH on this review believed this to be a clinically significant reduction in OCS dose. A secondary outcome of VENTURE was the proportion of patients with a 50% or greater reduction in OCS dose compared to baseline, and at week 24 this had been achieved by 81.0% of dupilumab 300 mg patients and 53.3% of placebo patients, for an odds ratio of 3.98 (95% CI, 2.06 to 7.67; P < 0.0001). The proportion of patients achieving a reduction of OCS dose to less than 5 mg/day at week 24 was another secondary outcome, and by week 24 had been achieved by 72.9% in the dupilumab 300 mg group and 37.4% in the placebo group, for an odds ratio of 4.48 (95% CI, 2.39 to 8.39; P < 0.0001). Another secondary outcome was the proportion of patients no longer requiring OCS at week 24, and this was 48% with dupilumab 300 mg and 25% with placebo, for an odds ratio of 2.74 (95% CI, 1.47 to 5.10).

Health-related quality of life was assessed using the Asthma Quality of Life Questionnaire (AQLQ) in each of the studies, as a secondary outcome in QUEST and DRI12544 and as a disease-specific outcome in VENTURE. AQLQ global scores were increased (improved) across all studies. In QUEST, the LSM difference between dupilumab 200 mg and placebo after 24 weeks was 0.20 (95% CI, 0.06 to 0.34) and between dupilumab 300 mg and placebo was 0.15 (95% CI, 0.01 to 0.28). In VENTURE, after 24 weeks the LSM difference between dupilumab 300 mg and placebo was 0.35 (95% CI, 0.09 to 0.62). In DRI12544, between dupilumab 200 mg and placebo, the LSM difference was 0.31 (95% CI, 0.08 to 0.55) and between dupilumab 300 mg and placebo was 0.36 (95% CI, 0.12 to 0.59) (Table 2). Results for this outcome were

tested outside of the statistical hierarchy. None of the differences between dupilumab and placebo met the minimally important difference (MID) of 0.5 for this instrument.

The ACQ, 5-item (ACQ-5) score was a secondary outcome in QUEST and DRI12544 and a disease-specific outcome in VENTURE, where it was reduced (improved) from the baseline to week 24 in each of the dupilumab and placebo groups across the studies (Table 2). In QUEST, the LSM difference between dupilumab 200 mg and placebo was −0.35 (95% CI, −0.48 to −0.21) and between dupilumab 300 mg and placebo was −0.19 (95% CI, −0.32 to −0.05). In VENTURE, the LSM difference between dupilumab 300 mg and placebo after 24 weeks was −0.47 (95% CI, −0.76 to −0.18) and in DRI12544 for dupilumab 200 mg versus placebo was −0.35 (95% CI, −0.57 to −0.14) and for dupilumab 300 mg versus placebo was −0.31 (95% CI, −0.52 to −0.09). Results for this outcome were tested outside of the statistical hierarchy. None of the differences between dupilumab and placebo met the MID of 0.5 for this instrument.

Pre-bronchodilator FEV_1 was assessed as a secondary outcome in QUEST, was the primary outcome of DRI12544, and was assessed as a disease-specific outcome in VENTURE. In QUEST, the difference between dupilumab 200 mg and placebo at 12 weeks was 0.14 L (95% CI, 0.08 to 0.19; P < 0.0001), and between dupilumab 300 mg and placebo was 0.13 L (95% CI, 0.08 to 0.18; P < 0.0001) (Table 2). In VENTURE, the difference between dupilumab 300 mg and placebo at 24 weeks was 0.22 L (95% CI, 0.09 to 0.34) and in DRI12544 the difference between dupilumab 200 mg and placebo at 12 weeks was 0.20 L (95% CI, 0.11 to 0.28; P < 0.0001) and the difference between dupilumab 300 mg and placebo was 0.16 L (95% CI, 0.08 to 0.25; P = 0.0002). Results for this outcome in VENTURE were tested outside of the statistical hierarchy. The minimal patient perceivable improvement (MPPI) for FEV_1 is 0.23 L and is lower in older patients (0.17 L) than in younger patients (0.28 L).

Harms Results

In QUEST, with dupilumab 200 mg, 80.5% of patients experienced an adverse event versus 82.1% in placebo, and with dupilumab 300 mg, 81.5% of patients experienced an adverse event versus 84.1% with placebo (Table 2). In VENTURE, 62.1% of dupilumab 300 mg patients and 64.5% of placebo patients had an adverse event, and in DRI12544 80.4% of patients in the dupilumab 200 mg group, 77.6% of patients in the dupilumab 300 mg group, and 74.7% of patients in the placebo group had an adverse event. The most common adverse events across the studies were upper respiratory tract infection and bronchitis, with no notable differences in frequency between groups within studies.

In QUEST, serious adverse events occurred in 7.8% of the dupilumab 200 mg group versus 8.3% in the placebo group, and 8.7% in the 300 mg dose dupilumab group versus 8.4% in the placebo group (Table 2). Asthma was the most common serious adverse event. In VENTURE, 8.7% of dupilumab 300 mg patients and 5.6% of placebo patients had a serious adverse event, and in DRI12544 6.8% of patients in the dupilumab 200 mg group and 8.3% of patients in the dupilumab 300 mg group, versus 5.7% of placebo patients, had a serious adverse event through 24 weeks of treatment.

In QUEST, treatment-emergent adverse events leading to study drug discontinuation occurred in 3.0% of patients in the dupilumab 200 mg group versus 6.1% in the placebo group, and in 7.0% of patients in the dupilumab 300 mg group versus 3.1% in the placebo group. In VENTURE, adverse events leading to permanent discontinuation of treatment occurred in 1.0% of patients in the dupilumab 300 mg group and 3.7% of patients in the placebo group. In DRI12544, treatment-emergent adverse events leading to treatment discontinuation occurred

in 4.1% of patients in the dupilumab 200 mg group, 2.6% of patients in the 300 mg group, and 3.2% of patients in the placebo group.

Among notable harms, anaphylactic reactions were infrequent (< 1% of patients) across studies, with no numerical differences in frequency between groups within the studies. Serious or severe infections occurred in between 1.0% and 1.4% of patients in the dupilumab 200 mg group, between 2.7% and 3.8% of patients in the dupilumab 300 mg group, and between 1.3% and 1.9% of patients in the placebo group. There were no patients with parasitic infections across 24 weeks in either VENTURE or DRI12544, and 1 patient with parasitic infection in each of the dupilumab 300 mg and placebo groups in QUEST. In QUEST, opportunistic infections occurred in 0.2% of patients in the dupilumab 200 mg group versus 0.6% in the placebo group, and in 0.2% of patients in the dupilumab 300 mg group versus 0.9% in the placebo group.

Critical Appraisal

- Issues surrounding internal validity include the fact that patients and investigators in QUEST may have been able to determine whether they were in the 200 mg or 300 mg groups, although they would not have been able to determine whether they were receiving dupilumab or placebo. The sponsor did control for multiplicity by use of a statistical hierarchy; however, the hierarchy failed early in the QUEST analysis, meaning that many important outcomes — such as AQLQ and ACQ scores — were not controlled for multiple comparisons. The testing hierarchy for DRI12544 was developed retrospectively, after a change in status from nonpivotal to pivotal study based on a request from the European Medicines Agency (EMA). As a result of this, Health Canada decided that statistical claims beyond the primary outcome were "not permissible."
- None of the included studies had an active comparator, the most notable being the other monoclonal antibodies such as the IL-5 inhibitors. Only 1 of the included studies was 52 weeks in duration, and, overall, the studies were unlikely to be of sufficient duration to assess the longer term efficacy of dupilumab or its long-term safety and tolerability. Placebo responses were robust for many of the outcomes across the trials, suggesting that patients may have benefited from the extra training and care they received in a clinical trial setting.

Indirect Comparisons

Description of Studies

The sponsor submitted 2 indirect treatment comparisons (ITCs); 5 additional ITCs were identified after a systematic search of the literature performed by CADTH. Of the sponsor-submitted ITCs, 1 compared dupilumab to other biologics for persistent, uncontrolled (moderate-to-severe) asthma in adults and adolescents, while the other focused on a population of adults and adolescents with OCS-dependent asthma.[4-6] After a feasibility assessment recommended against a full network Bayesian analysis, a series of pairwise Bucher ITCs was performed, comparing dupilumab with other biologics, where subgroup data were generated by matching patient phenotypes for the dupilumab trials to the relevant comparators. The 5 ITCs that were identified by CADTH indirectly compared dupilumab with benralizumab, mepolizumab, and reslizumab.

Efficacy Results

For patients with uncontrolled persistent asthma, dupilumab 200 mg every 2 weeks was associated with a statistically significantly lower likelihood of severe asthma exacerbation than mepolizumab (75 mg every 4 weeks to 75 mg every 2 weeks), benralizumab (30 mg

Table 2: Summary of Key Results From Pivotal and Protocol Selected Studies

Outcomes	Quest				Venture		DR112544		
	Dupilumab 200 mg N = 631	Placebo N = 317	Dupilumab 300 mg N = 633	Placebo N = 321	Dupilumab 300 mg N = 103	Placebo N = 107	Dupilumab 200 mg N = 150	Dupilumab 300 mg N = 157	Placebo N = 158
Annualized rate of severe exacerbations (52-week follow-up in QUEST; 24 weeks in VENTURE and DRI12544)									
Adjusted annualized rate (95% CI)	0.456 (0.389 to 0.534)	0.871 (0.724 to 1.048)	0.524 (0.450 to 0.611)	0.970 (0.810 to 1.160)	0.649 (0.442 to 0.096)	1.597 (1.248 to 2.043)	0.269 (0.157 to 0.461)	0.265 (0.157 to 0.445)	0.897 (0.619 to 1.300)
RR vs. placebo (95% CI; P value)[a]	0.523 (0.413 to 0.662; < 0.0001)		0.540 (0.430 to 0.680; < 0.0001)		0.407 (0.263 to 0.630; < 0.0001)		Dupilumab 200 mg: 0.300 (0.159 to 0.565; 0.0002) Dupilumab 300 mg: 0.295 (0.159 to 0.546; 0.0001)		
Annualized rate of asthma exacerbations leading to hospitalizations or ED visits (52-week follow-up in QUEST; 24 weeks in VENTURE and DRI12544)									
Annualized rate, adjusted (95% CI)	0.024 (0.013 to 0.044)	0.051 (0.027 to 0.099)	0.011 (0.005 to 0.025)	0.017 (0.007 to 0.042)	0.114 (0.040 to 0.328)	0.198 (0.086 to 0.457)	NR	NR	NR
RR (95% CI; P value) [a]	0.468 (0.196 to 1.118; 0.0874)[b]		0.653 (0.199 to 2.144; 0.4711)[b]		0.577 (0.161 to 2.071; 0.3972) [b]		NA		
Pre-bronchodilator FEV_1, L (12 weeks in QUEST and DRI12544; 24 weeks in VENTURE)									
Baseline, mean (SD)	1.78 (0.62)	1.76 (0.61)	1.78 (0.60)	1.75 (0.57)	1.53 (0.53)	1.63 (0.61)	1.79 (0.52)	1.85 (0.53)	1.82 (0.55)
Change from baseline, LSM (SE)	0.32 (0.02)	0.18 (0.02)	0.34 (0.02)	0.21 (0.02)	0.22 (0.05)	0.01 (0.05)	0.31 (0.03)	0.28 (0.03)	0.12 (0.03)
LSM difference vs. placebo (95% CI; P value)[c]	0.14 (0.08 to 0.19; < 0.0001)		0.13 (0.08 to 0.18; < 0.0001)		0.22 (0.09 to 0.34; NR)		Dupilumab 200 mg: 0.20 (0.11 to 0.28; < 0.0001) Dupilumab 300 mg: 0.16 (0.08 to 0.25; 0.0002)[b]		
AQLQ global score at 24 weeks									
Baseline, mean (SD)	4.31 (1.08)	4.26 (1.02)	4.28 (1.05)	4.30 (1.03)	4.38 (1.24)	4.31 (1.12)	4.03 (1.15)	3.91 (1.13)	4.12 (1.10)

Outcomes	Quest				Venture		DR112544		
	Dupilumab 200 mg N = 631	Placebo N = 317	Dupilumab 300 mg N = 633	Placebo N = 321	Dupilumab 300 mg N = 103	Placebo N = 107	Dupilumab 200 mg N = 150	Dupilumab 300 mg N = 157	Placebo N = 158
Change from baseline, LSM (SE)	1.14 (0.04)	0.94 (0.06)	1.15 (0.04)	1.00 (0.06)	0.89 (0.10)	0.54 (0.10)	1.20 (0.09)	1.24 (0.08)	0.88 (0.09)
LSM difference vs. placebo (95% CI; P value)[d]	0.20 (0.06 to 0.34; 0.0039)[b]		0.15 (0.01 to 0.28; 0.0298)[b]		0.35 (0.09 to 0.62; NR)		Dupilumab 200 mg: 0.31 (0.08 to 0.55; 0.0090)[b] Dupilumab 300 mg: 0.36 (0.12 to 0.59; 0.0027)[b]		
ACQ-5 at 24 weeks									
Baseline, mean (SD)	2.76 (0.80)	2.71 (0.73)	2.77 (0.76)	2.77 (0.77)	2.42 (1.24)	2.58 (1.09)	2.73 (0.82)	2.80 (0.83)	2.69 (0.80)
Change from baseline, LSM (SE)	−1.44 (0.04)	−1.10 (0.06)	−1.40 (0.04)	−1.21 (0.06)	−1.05 (0.11)	−0.58 (0.11)	−1.49 (0.08)	−1.45 (0.08)	−1.14 (0.08)
LSM difference vs. placebo (95% CI; P)[e]	−0.35 (−0.48 to −0.21; < 0.0001)[b]		−0.19 (−0.32 to −0.05; 0.0069)[b]		−0.47 (−0.76 to −0.18; NR)		Dupilumab 200 mg: −0.35 (−0.57 to −0.14; 0.0015)[b] Dupilumab 300 mg: −0.31 (−0.52 to −0.09; 0.0049)[b]		
Harms									
AE, n (%)	508 (80.5)	257 (82.1)	515 (81.5)	270 (84.1)	64 (62.1)	69 (64.5)	119 (80.4)	121 (77.6)	118 (74.7)
SAE, n (%)	49 (7.8)	26 (8.3)	55 (8.7)	27 (8.4)	9 (8.7)	6 (5.6)	10 (6.8)	13 (8.3)	9 (5.7)
Discontinued treatment due to AE, n (%)	19 (3.0)	19 (6.1)	44 (7.0)	10 (3.1)	1 (1.0)	4 (3.7)	6 (4.1)	4 (2.6)	5 (3.2)

ACQ-5 = Asthma Control Questionnaire, 5-item; AE = adverse event; AQLQ = Asthma Quality of Life Questionnaire; CI = confidence interval; ED = emergency department; FEV_1 = forced expiratory volume in the first second; LSM = least squares mean; NA = not applicable; NR = not reported; RR = relative risk; SAE = serious adverse event; SD = standard deviation; SE = standard error; vs. = versus .

[a]RR and P value derived using negative binomial model with total number of events onset from randomization to visit 18 or last contact date (whichever comes earlier) as the response variable, with the 4 treatment groups, age, region (pooled country), baseline eosinophil strata, baseline inhaled corticosteroid dose level, and number of severe exacerbation events within 1 year before the study as covariates, and log-transformed standardized observation duration as the offset variable.

[b]P value has not been adjusted for multiple testing (i.e., the type I error rate has not been controlled).

[c]Derived from mixed-effect model with repeated measures, with change from baseline in pre-bronchodilator FEV_1 values up to week 12 as the response variable, and treatment, age, sex, baseline height, region (pooled country), baseline eosinophil strata, baseline inhaled corticosteroid dose level, visit, treatment-by-visit interaction, baseline pre-bronchodilator FEV_1 value, and baseline-by-visit interaction as covariates.

[d]Least squares mean difference (AQLQ) derived from mixed-effect model with repeated measures, with change from baseline up to week 24 as the response variable, and treatment, age, region (pooled country), baseline eosinophil strata, baseline inhaled corticosteroid dose level, visit, treatment-by-visit interaction, baseline score, and baseline-by-visit interaction as covariates.

[e]Least squares mean difference (ACQ-5) derived from mixed-effect model with repeated measures, with change from baseline in ACQ-5 up to week 24 as the response variable, and treatment, age, region (pooled country), baseline eosinophil strata, baseline inhaled corticosteroid dose level, visit, treatment-by-visit interaction, baseline ACQ-5, and baseline-by-visit interaction as covariates.

Source: Clinical Study Report for QUEST,[1] VENTURE,[2] DRI12544.[3]

every 8 weeks to 30 mg every 4 weeks), and reslizumab (3 mg/kg every 2 weeks). Dupilumab statistically significantly improved the FEV_1 at week 24 compared with reslizumab. Dupilumab showed a statistically significant improved FEV_1 at week 12 compared with omalizumab in the subgroup of patients with allergic asthma. Dupilumab 300 mg was associated with a statistically significantly lower likelihood of severe asthma exacerbation than benralizumab and omalizumab in the allergic asthma subgroup and the allergic eosinophilic asthma subgroup. Dupilumab statistically significantly improved the FEV_1 compared with reslizumab at 24 weeks and compared with benralizumab at 12 weeks. Dupilumab also showed a statistically significantly improved FEV_1 at week 12 compared with omalizumab in the overall patient population and in the subgroup of patients with allergic asthma. No statistically significant differences were identified between dupilumab and mepolizumab, benralizumab, reslizumab, and omalizumab in terms of ACQ and AQLQ score. For children and adults 12 years or older with moderate-to-severe OCS-dependent asthma, no statistically significant difference was found between dupilumab and other recommended biologics in terms of reducing the dose of OCS or reducing the rate of annual exacerbations, or in terms of FEV_1, ACQ, or AQLQ scores.

In the ITC by Ando et al. (2020),[7] in terms of annual exacerbation rate, dupilumab was superior to benralizumab in patients with inadequately controlled asthma who had blood eosinophil counts greater than or equal to 150 cells/μL but less than 300 cells/μL, and greater than or equal to 300 cells/μL. In the anchored matching-adjusted indirect comparison (MAIC) by Bourdin et al. (2020),[8] following matching of patient baseline characteristics, benralizumab demonstrated similar efficacy to dupilumab for OCS dosage reduction, OCS elimination, and annual exacerbation rate reduction. In the network meta-analysis (NMA) by Ramonell et al. (2020),[9] in terms of annual exacerbation rate, dupilumab was superior to benralizumab. In the NMA by Edris et al. (2019),[10] and the NMA by Iftikhar et al. (2018),[11] no statistically significant difference was observed in any outcome (e.g., FEV_1) between dupilumab and benralizumab, mepolizumab, or reslizumab.

Harms Results

Safety outcomes were not assessed in the sponsor-submitted ITCs due to variation in terms of follow-up duration, with inconsistent definitions of adverse events across included trials. Only 1 of the published ITCs (Ando et al. [2020])[7] reported data on harms, finding no statistically significant difference in the risk of adverse events or serious adverse events between dupilumab 300 mg and benralizumab 30 mg every 8 weeks.

Critical Appraisal

There were several limitations of the sponsor-submitted ITCs, including the fact that there was considerable heterogeneity across the included studies. Despite matching specific subgroups of patients with dupilumab to the comparator studies, considerable differences remained in the distributions of potential treatment effect modifiers (e.g., severity of the included patients).

Compared with the sponsor-submitted ITCs, the scope of the 5 ITCs identified by the CADTH literature search were relatively narrow, as they were focused on specific asthma populations, had fewer comparators, and assessed fewer outcomes. Overall, heterogeneity across studies was the most important limitation in all 5 ITCs. In the MAIC by Bourdin et al. (2020),[8] not all effect factors could be matched and adjusted (e.g., which patients were eligible for OCS elimination varied between the 2 included studies).

In summary, due to various methodological limitations, no robust conclusions can be drawn about the comparative clinical efficacy of dupilumab versus mepolizumab, benralizumab, reslizumab, and omalizumab in the treatment of patients with uncontrolled persistent or OCS-dependent asthma. Methodological issues also limit the conclusions that can be drawn from the 5 ITCs identified in the literature by CADTH; thus, no robust conclusions can be drawn about the comparative clinical efficacy of dupilumab compared with benralizumab, mepolizumab or reslizumab in the treatment of uncontrolled asthma, including severe type 2 inflammation asthma and severe eosinophilic asthma.

Other Relevant Evidence

Description of Studies

Study LTS12551 was an open-label extension study that evaluated the long-term safety and tolerability of dupilumab in patients with asthma who participated in 1 of the 4 previous dupilumab asthma clinical studies (QUEST,[1] VENTURE,[2] DRI12544,[3] and EXPEDITION [PDY14192]).[4,12] EXPEDITION (PDY14192) was an exploratory, randomized, double-blind, placebo-controlled study of the effects of dupilumab 300 mg subcutaneously every 2 weeks for 12 weeks on the airway inflammation of adults with uncontrolled persistent asthma.[4,12] EXPEDITION (PDY14192) was not a pivotal study and is not included in this submission.

A total of 1,315 patients (69.1%) from QUEST, 534 patients (68.6%) from DRI12544, and 139 patients (66.2%) from VENTURE were enrolled in study LTS12551. Information about patients from EXPEDITION (PDY14192) was not provided in the Clinical Study Report.[12]

Efficacy Results

The findings of study LTS12551 indicated that the long-term sustained efficacy of dupilumab 300 mg in patients with asthma — in particular, a low event rate of severe asthma exacerbation (the unadjusted annualized event rate of severe asthma exacerbation was 0.347); a durable effect in FEV_1, ACQ-5, and AQLQ scores; and a reduction in the use of rescue inhalers — was maintained when compared to the baseline of the parent studies.

Overall, 83.4% of patients enrolled from studies DRI12544 and QUEST who participated in LTS12551 had no asthma exacerbation over a mean exposure to dupilumab 300 mg of 634 days and 140 days, respectively. The unadjusted annualized event rate in the overall population was 0.347. The low asthma exacerbation event rate was maintained throughout the study duration.

A mean FEV_1 improvement of greater than or equal to 0.30 L from the baseline of the parent study was observed from week 2 of the open-label extension study, and the improvement was sustained up to week 96 for patients enrolled from DRI12544 and up to week 24 for patients enrolled from QUEST.

The author of the study LTS12551 concluded that long-term treatment of adult and adolescent asthma patients with dupilumab 300 mg every 2 weeks was generally well tolerated, with a long-term safety profile similar to that observed in the respective parent studies. It was also suggested that long-term dupilumab 300 mg use was associated with a sustained clinical benefit to adult and adolescent patients with asthma who had previously participated in controlled dupilumab clinical trials.

Harms Results

Overall, the most frequent adverse events were upper respiratory tract infections. Eosinophilia adverse events were observed in between 3.1% and 3.6% of patients enrolled from DRI12544, between 0.1% to 0.9% of patients enrolled from QUEST, and 4.4% of patients enrolled from VENTURE. The incidence of these events was generally lower than in the parent studies. It was noted that most adverse events of eosinophilia were laboratory findings without any associated symptoms. Most of the cases were of mild and moderate intensity and did not require corrective treatment or treatment interruption.

The most frequently reported treatment-emergent serious adverse events were asthma and pneumonia, and no patients were discontinued due to serious adverse events or adverse events.

Three patients, all of them enrolled from DRI12544 and previously treated with dupilumab in this study, experienced treatment-emergent adverse events leading to death.

In the 70 adolescent patients who participated in the study, the safety profile of dupilumab was similar to that observed in the overall population, and no new safety signals were identified in this population.

Critical Appraisal

The limitations of this study are its open-label design and its single arm without a control group. In addition, this was an interim analysis, and subgroup efficacy results for patients from VENTURE were not well reported. Furthermore, no subgroup data for patients from EXPEDITION (PDY14192) were provided in the Clinical Study Report.

Conclusions

Three sponsor-funded, multinational, double-blind randomized controlled trials were included in this review. Both the 200 mg and 300 mg biweekly doses of dupilumab reduced the annualized rate of severe exacerbations compared to placebo. In a population with severe OCS-dependent asthma, dupilumab 300 mg every 2 weeks reduced the daily OCS dose requirements versus placebo, a clinically significant reduction according to the clinical expert, and this is important given the serious adverse effects associated with this class of drugs. Dupilumab also improved FEV_1 versus placebo. However, although numerical improvements in health-related quality of life and symptoms were reported, the between-group differences were not controlled for multiple comparisons, and the difference between the dupilumab and placebo groups did not exceed the MID. There was no indication of any clear or consistent differences in serious harms or tolerability issues between dupilumab and placebo. Findings from several ITCs, both sponsor submitted and published, were inconclusive with respect to the relative efficacy of dupilumab compared to other monoclonal antibodies due to methodological issues associated with each. A longer term extension study did not identify any new safety issues and appeared to suggest that efficacy results are durable, including reduction in risk of severe exacerbations. However, the lack of control group limits any conclusions that can be drawn from these data.

Introduction

Disease Background

Asthma is a chronic respiratory disorder characterized by reversible airway obstruction. Hallmarks of asthma include inflammation, bronchoconstriction, and airway remodelling, as well as hyper-responsive airways and mucous production. Symptoms of asthma include wheezing, dyspnea, chest tightness, sputum production, and coughing, and these symptoms can be exacerbated by exogenous influences such as allergens, upper respiratory tract infections, or environmental factors such as smoke or cold air. It is estimated that 2.4 million Canadians 12 years or older suffer from asthma, or 12% of all children and 8% of adults.[13]

There are several asthma phenotypes, 1 of which is characterized by an increased peripheral blood eosinophil count, and this may persist despite treatment with moderate- to high-dose ICS. Eosinophils, among other functions, promote airway inflammation and contribute to airway hyper-responsiveness and remodelling. According to the clinical expert consulted by CADTH for this review, tissue eosinophilia is present in 40% to 60% of patients with asthma and the use of ICS typically reduces eosinophils in these patients. However, a subset of patients (5% to 10% overall, and 50% of patients with severe asthma) continue to experience exacerbations, despite treatment with high-dose ICS.

Standards of Therapy

Traditionally, the management of asthma is carried out using (i) medications for the acute relief of exacerbations (colloquially, "asthma attacks"), often referred to as "relievers" or "rescue medications," and (ii) controllers, or maintenance drugs, which are used on a regular or chronic basis in an effort to prevent the onset of exacerbations. According to the clinical expert consulted by CADTH for this review, the pharmacologic management of asthma in Canada has recently evolved, based on the updated Global Initiative for Asthma (GINA) guidelines.[14] In step 1, patients begin using a low-dose ICS whenever a reliever medication is used. As symptoms persist, step 2 involves daily low-dose ICS or ICS plus formoterol on an as needed basis. From there, patients may need to escalate to regular use of low-dose (step 3) or medium-dose (step 4) ICS + LABA. Finally, step 5 involves the use of daily high-dose ICS + LABA, and if control of asthma is not achieved at that point, then additional treatments are considered, such as low-dose OCS, inhaled tiotropium, and/or biologics. Other drugs that may be considered as add-on therapy include leukotriene receptor antagonists and long-term therapy with macrolides, with the latter considered off label. Although methylxanthines like theophylline were once used extensively, they are now rarely prescribed for asthma. Nonpharmacologic therapies include education, improvement of inhaler technique, allergen avoidance, and a written asthma action plan. The treatment of comorbidities such as tobacco dependence, depression, and obstructive sleep apnea are also important in the management of asthma. With respect to harms associated with pharmacologic therapies, ICSs have short-term side effects such as oral candidiasis ("thrush") and dysphonia; however, a number of concerning adverse effects, including osteoporosis, are associated with their long-term use, particularly at high doses. The use of systemic corticosteroids heightens the risk of harms, and their chronic use is avoided. According to the clinical expert, the approach to managing asthma has evolved, such that patients are now routinely grouped into those who have type 2 inflammation and those who do not. Type 2 inflammation is mediated by cytokines such as IL-4, IL-5, and IL-13, and this explains why this phenotype may be more responsive to the biologics that target this cytokine. Monoclonal antibodies are the newest entrants into the

asthma treatment paradigm, beginning with an IgE inhibitor (omalizumab) and, more recently, IL-5 inhibitors (mepolizumab, reslizumab, benralizumab) and now, an IL-4 and IL-13 inhibitor (dupilumab). None of the monoclonal antibodies are intended to be used first line but, rather, are reserved for those patients whose asthma is not well-controlled with moderate-to-high doses of ICS + LABA.

According to the clinical expert consulted by CADTH, the goals of asthma therapy are to maintain control of asthma, indicated by an absence of exacerbations and improved symptoms. Improving these symptoms should improve health-related quality of life. The longer term goal is to prevent airway remodelling, thus preventing future risk from severe exacerbations and, ultimately, reducing the risk of death. Reducing risk of harms from pharmacologic therapies is also an important goal.

Drug

Dupilumab is an IL-4 and IL-13 inhibitor. Both IL-4 and IL-13 are thought to play a role in inflammation and in the pathophysiology of asthma, and thus dupilumab is a monoclonal antibody that targets both. Dupilumab is administered by subcutaneous injection, at a dose of either 200 mg (patients with severe asthma with a type 2 or eosinophilic phenotype) or 300 mg (patients with OCS-dependent asthma or with comorbid moderate-to-severe atopic dermatitis and/or severe chronic rhinosinusitis with nasal polyposis) every 2 weeks. The 200 mg dose may be increased to 300 mg if needed, at the discretion of the prescriber. Dupilumab is indicated as add-on maintenance treatment in patients 12 years and older with severe asthma with a type 2 or eosinophilic phenotype or with OCS-dependent asthma. Dupilumab is also indicated for atopic dermatitis and for chronic rhinosinusitis with nasal polyposis. It was reviewed previously by CADTH for the atopic dermatitis indication and, in July 2018, received a recommendation of do not list.

The sponsor has requested that dupilumab be reimbursed for patients with type 2 or eosinophilic asthma characterized by 2 or more clinically significant asthma exacerbations in the past 12 months and (i) blood eosinophils greater than or equal to 150 cells/μL, or (ii) FeNO greater than or equal to 25 ppb, or (iii) treatment with maintenance OCSs, or (iv) clinically allergen-driven asthma. These criteria are in addition to the Health Canada indication.

Stakeholder Perspectives

Patient Group Input

This section was prepared by CADTH staff based on the input provided by patient groups.

About the Patient Group(s) and Information Gathered

Two patient groups, British Columbia Lung Association and Lung Groups and the LHF, have provided input for this review.

The British Columbia Lung Association (BCLA) is a major Canadian charitable organization with more than a century of experience and leadership in lung disease prevention, treatment, and management. The BCLA's mission is to improve lung health and to lead lung health initiatives. The BCLA's vision is healthy lungs for everyone. The BCLA's role is to improve

Table 3: Key Characteristics of IL-4 and IL-13 Inhibitors, IL-5 Inhibitors, and IgE Inhibitors

Characteristic	IL-4 and IL-13 inhibitors	IL-5 inhibitors	IgE inhibitors
Mechanism of action	Blocking IL-4RAlpha, which inhibits IL-4 and IL-13 signalling. These ILs promote the release of a variety of pro-inflammatory cytokines; therefore, dupilumab blocks the actions of these cytokines, resulting in an anti-inflammatory effect.	IL-5 inhibition results in destruction of eosinophils, and eosinophils are thought to participate in the inflammatory component of asthma. Therefore, IL-5 inhibitors act as anti-inflammatories in asthma.	IgE facilitates degranulation of mast cells, which leads to release of numerous mediators of the allergic component of asthma. IgE inhibitors therefore prevent mast cell degranulation and inhibit the allergic component of asthma.
Indication[a]	Add-on maintenance treatment in patients 12 years and older with severe asthma with a type 2 or eosinophilic phenotype or with OCS-dependent asthma.	Add-on maintenance treatment for adult patients with severe eosinophilic asthma. The following criteria are added for mepolizumab and reslizumab: • Patients who are inadequately controlled with medium- to high-dose ICS and an additional asthma controller (or controllers) (e.g., LABA) For mepolizumab: • Patients with blood eosinophils ≥ 150 cells/μL at initiation of treatment with mepolizumab or ≥ 300 cells/μL in the past 12 months For reslizumab: • Patients with blood eosinophils ≥ 400 cells/μL at initiation of treatment	Treatment of adults and adolescents with moderate-to-severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled on ICS.
Route of administration	SC	SC: benralizumab, mepolizumab IV infusion: reslizumab	SC
Recommended dose	Patients with severe asthma with a type 2 or eosinophilic phenotype: • Initial dose of 400 mg followed by 200 mg every other week (may be increased to 300 mg every other week based on clinical judgment)	Benralizumab: 30 mg once every 4 weeks for the first 3 doses, then once every 8 weeks thereafter Mepolizumab: 100 mg every 4 weeks Reslizumab: 3 mg/kg every 4 weeks	150 mg to 375 mg every 2 or 4 weeks depending on body weight and serum IgE

Characteristic	IL-4 and IL-13 inhibitors	IL-5 inhibitors	IgE inhibitors
	Patients with OCS-dependent asthma or with comorbid moderate-to-severe AD or adults with comorbid severe chronic rhinosinusitis with nasal polyposis for which dupilumab is indicated: • Initial dose of 600 mg followed by 300 mg every other week		
Serious adverse effects or safety issues	Anaphylaxis, injection site reactions, eosinophilia, helminth infections, eye disorders	Anaphylaxis, injection site reactions, infection	Anaphylaxis, injection site reactions, infection

AD = atopic dermatitis; ICS = inhaled corticosteroid; IgE = immunoglobulin E; IL = interleukin; LABA = long-acting beta2-agonist; OCS = oral corticosteroid; SC = subcutaneous.

[a]Health Canada–approved indication.

Source: Product monographs for dupilumab, mepolizumab, benralizumab, reslizumab, and omalizumab.[15]

respiratory health and overall quality of life through programs, education, research, training, treatment, advocacy, and prevention of lung disease. The BCLA works together with the Canadian Lung Association and other partners to help Canadians who have breathing problems. The BCLA provides approximately $1.2 million each year to internationally recognized physicians and scientists doing research in British Columbia on lung diseases. The BCLA is significantly invested and involved in asthma research and the provision of patient services and programs.

The LHF, previously called the Ontario Lung Association (www.lunghealth.ca), is a leading health charity dedicated to improving lung health through an integrated approach that identifies gaps and fills them by developing the agenda and strategically investing in research; drives policy, system, and practice change; invests in urgently needed programs and supports; and promotes awareness about lung health issues affecting everyone. The information provided from the LHF in this submission was obtained from 16 online surveys completed by people living with asthma and 2 caregivers of people living with asthma (input received in December 2020). All respondents live in Ontario. Information on age and gender was not collected within this survey. Input from a certified respiratory educator, whose role at the LHF includes answering the Lung Health Line and educating people living with lung disease, was also obtained for this submission.

Declared funding support for each patient group may be found on the CADTH web page for the dupilumab review.

Disease Experience

The patient groups indicated that wheezing, shortness of breath, chest tightness, fatigue, and cough that vary over time, together with variable expiratory airflow limitation, are the main features of asthma. These symptoms restrict peoples' day-to-day activities such as showering, climbing stairs, getting dressed, eating, playing sports, exercising, working, travelling, and participating in hobbies and leisure activities. Depression and feelings of hopelessness are also common among patients with severe asthma. A few examples of the direct quotes in the LHF input are provided here:

- "Not being able to do activities I want to do because of daily breathing issues."
- "Exercise can be difficult for me and I am unable to lead a really active life."
- "This condition negatively effects my emotional and social life."
- "My cough can be frustrating, especially at night."
- "When my allergies are triggered, they cause wheezing and shortness of breath."

The LHF indicated that, as the condition progresses, patients' independence is further compromised and there are implications for caregivers. Financial challenges are key challenges. Patients with severe asthma and their caregivers experience anxiety and depression, which has a negative impact on the caregiver's health and well-being.

Experiences With Currently Available Treatments

The BCLA indicated that side effects are particularly common and problematic with OCSs, which in the past were a mainstay of treatment for severe asthma. Even short-term use of OCSs is associated with sleep disturbance and increased risk of infection and thromboembolism. Strategies to minimize the need for OCSs are therefore a high priority.

Input from the LHF reported that treatments tried by those who completed the LHF online survey had included budesonide and formoterol fumarate dihydrate, albuterol sulphate, fluticasone propionate and salmeterol pressurized inhalation, tiotropium, prednisone, fluticasone furoate–umeclidinium–vilanterol, indacaterol maleate, ciclesonide, salbutamol, fluticasone furoate–vilanterol, and "puffers." Nasal corticosteroids and antihistamines are used for allergies as needed. Current treatments do provide some relief for fatigue, shortness of breath, wheezing, cough, and reduced energy. But participants expressed dissatisfaction with their treatments in terms of improving their ability to exercise. The side effects indicated from using these drugs included voice hoarseness, dry mouth, appetite loss, impact on mood, and difficulty sleeping.

The patient groups indicated that regardless of effective treatments being widely available and the existence of treatment guidelines, a large population of severe asthma cases remain uncontrolled. Achieving and maintaining asthma control in this group of patients is, therefore, of utmost importance. Patients hope that additional therapies will go beyond symptom relief and improve overall lung function.

Improved Outcomes

Both groups indicated that key outcomes to be improved include relieving symptoms (e.g., shortness of breath, fatigue, cough), improving ability to exercise, and improving quality of life. Ideally, these patients would like to experience improved overall lung function. In LHF's input, when asked about the most important benefit or outcome they would like to experience from a new medication or treatment for their asthma, respondents indicated the following: reduced symptoms (85%), improved quality of life (77%), and improved symptom management (46%).

Experience With Drug Under Review

The BCLA indicated that in 2 British Columbia Severe Asthma Clinics, respirologists had several patients with severe asthma who had participated in clinical trials for dupilumab. The BCLA spoke with 8 patients who are members of the British Columbia Lung Support Group that are taking Dupixent. The BCLA reported that the patients are very happy and excited about the maintained effects of the new biologic medication as a maintenance therapy.

The BCLA mentioned that some side effects of Dupixent (reactions at injection site) are common but minor.

The LHF indicated that no patients from their submission had used Dupixent.

Clinician Input

Input From Clinical Expert Consulted by CADTH

All CADTH review teams include at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). The following input was provided by 1 clinical specialist with expertise in the diagnosis and management of asthma.

Unmet Needs

The clinical expert consulted by CADTH indicated that the goals of asthma therapy can be achieved in many patients with available medications and treatments. None of these therapies cure asthma, but for many patients, long-term control can be achieved. Even patients with mild disease can experience exacerbations, with an annualized rate for severe exacerbations of 0.11.[16] Therefore, treatments are needed to improve the outcomes for patients who have few daily symptoms but who are still at risk of severe exacerbations. Most patients with uncontrolled asthma can regain control with current treatments, focusing on medication adherence, self-management techniques, and inhaler education. Approximately 5% to 10% of patients will remain poorly controlled despite this and require additional treatment. Simplified inhaler regimens may improve adherence to ICS use and thereby improve asthma control, but there is little good-quality evidence to support this contention.[17] In addition, these patients may benefit from add-on therapies to the standard ICS + LABA inhalers.

Place in Therapy

Dupilumab will be used as add-on therapy for those with type 2 inflammation and whose asthma is uncontrolled despite using high-dose ICS + LABA. Patients may also be receiving another add-on therapy, such as a LAMA. As well, patients who require treatment with maintenance OCS would be considered. In addition, patient adherence to therapies and proper inhaler use should be assessed, as well as ensuring that environmental allergen exposures are dealt with and that comorbidities that might worsen asthma have been appropriately addressed.[18]

Patient Population

Patients 12 years and older with type 2 inflammation (blood eosinophil count of ≥ 150 cells/μL) severe asthma that is uncontrolled (patient has experienced 2 or more clinically significant asthma exacerbations in the past 12 months) despite high-dose ICS + LABA (and 1 or more additional asthma controllers) would be the target population for dupilumab. As well, patients who require maintenance treatment with OCS would be considered in practice. Dupilumab will also be considered for patients with concomitant atopic dermatitis and/or chronic rhinosinusitis with nasal polyps. These are common comorbidities of asthma, and dupilumab is already Health Canada–approved for these indications. Therefore, the presence of these comorbidities may drive the use of dupilumab ahead of other biologic medications.

The use of this drug for patients with diseases of airway obstruction should be restricted to patients with asthma. Within the population of patients with asthma, dupilumab would not be used in patients with non–type 2 inflammation-based asthma.

The standard approaches to the diagnosis and management of asthma, as outlined in the older Canadian Thoracic Society Guidelines and the more current GINA recommendations, describe appropriate diagnosis of asthma.[14,19] The approaches described in these publications are within the scope of most dedicated asthma clinics but may be more problematic for a family physician office.

Assessing Response to Treatment

The outcomes used clinically are typically measurements of gaining control of asthma symptoms. This can be quantified with validated tools such as the ACQ. Often, asthma control is assessed less rigorously with routine clinical questioning. Reduction in nocturnal symptoms, increase in physical activity, and reduction of rescue medication use are often used to assess gaining control. Measurement of peak expiratory flow (PEF) at home or improvement of spirometric indices in an office provide additional information regarding treatment effectiveness. Stepping down other asthma therapies (e.g., elimination of tiotropium, elimination of OCS) while maintaining control would also be meaningful. Because of dupilumab's broader indication in patients with atopic dermatitis and chronic rhinosinusitis with polyps, improvement in these comorbid conditions would also constitute a meaningful therapeutic response. Finally, reduction in exacerbation frequency is a major sign of stabilization of disease but might only be noted in patients who had frequent and severe exacerbations (e.g., emergency department visits several times per year) before treatment initiation.

Response would be assessed initially every 6 to 8 weeks, then — once clinical stability is achieved — every 4 to 6 months.

Discontinuing Treatment

Treatment reduction (stepping down) and potential discontinuation should be considered once asthma control has been achieved and maintained for at least 3 months. There are currently no high-quality data guiding stepping down therapy with dupilumab or other biologics.

Prescribing Conditions

Dupilumab can be prescribed and administered in a community setting. It should be restricted to being initiated by a pulmonary medicine or allergy specialist. The other indications should be restricted to ear, nose, and throat (chronic rhinosinusitis with polyps) or dermatology (atopic dermatitis) specialists. Broader access to telehealth makes patients in rural or remote areas able to be assessed by specialists, and therefore location should not limit access.

Clinician Group Input

This section was prepared by CADTH staff based on the input provided by clinician groups.

One clinician group, the Family Physician Airways Group of Canada, provided input on the dupilumab submission.

The Family Physician Airways Group of Canada's mandate is to help all family physicians develop and maintain their skills in assisting individuals with airway diseases like asthma and

chronic obstructive pulmonary disease. The group maintains resources such as a speaker bank, a data bank, and practical tools and information to aid physicians. The following input was developed after a meeting at the group's annual general meeting in November 2020. Gaps in care were seen when creating programs on asthma and severe asthma.

Unmet Needs

The Family Physician Airways Group of Canada noted that severe asthma affects less than 10% of asthmatics; however, it is responsible for greater than 90% of the medical costs, such as exacerbations, emergency department visits, oral steroids, and associated long-term ramifications.

Usual care for asthma includes relievers and controllers, or preventive medicine. These medications are intended to prevent symptoms and exacerbations and include ICSs, LAMAs, LABAs, and leukotriene receptor antagonists. The Family Physician Airways Group of Canada noted that when usual care with ICSs, LABAs, and LAMAs is not sufficient for asthma control, a biologic agent can be considered. However, this should only be after a review of accurate diagnosis, proper adherence, device technique, and comorbidities.

The Family Physician Airways Groups of Canada noted that the classes of biologics currently available are effective in achieving control for many of the phenotypes of severe asthma. However, the group noted that some phenotypes are not properly covered by existing biologic therapy and therefore are at risk for poor outcomes such as exacerbations.

Treatment goals would be to improve asthma control, prevent exacerbations, improve lung function, and allow patients to reduce and hopefully stop the use of OCSs. The goal of the anti-IL4 to 13 therapy would be to fill the treatment gap where current therapies do not work to respond to certain phenotypes of severe asthma patients, since the anti-IL4 to 13 treatment works at different places in the asthma cytokine cascade. The clinician group also noted that individuals with moderate blood eosinophils (> 150 cells/μL), elevated FeNO, and severe asthma symptoms have the greatest unmet need. It was also noted that atopic dermatitis and chronic rhinosinusitis with nasal polyps are frequent comorbidities with asthma. Dupilumab may offer additional benefits in a single therapy for these patients because it is approved for these indications as well as for severe asthma.

Place in Therapy

The Family Physician Airways Group of Canada noted that anti-IL4 to 13 therapies work with a unique mechanism, different than other biologic asthma therapies. Prior to initiating therapy, patients should have severe asthma (defined as patients who are exacerbating or uncontrolled despite proper diagnosis, have good adherence to medications, have good techniques, and are appropriate dealing with triggers and comorbidities). Input from the clinician group noted that dupilumab would likely replace other biologics that might not be as efficacious in certain patients. The group noted that dupilumab has multiple actions and may alleviate the costs of other therapies, such as those for rhinitis and dermatitis, as well as surgical costs for nasal polyps, which frequently accompany asthma.

Patient Population

The Family Physician Airways Group of Canada noted that patients with severe asthma and type 2 inflammation on at least a moderate dose of ICS + LABA (with or without other treatments) with elevated blood eosinophils (> 150 cells/μL) and/or elevated FeNO (> 20 ppb), would be the target population for treatment with dupilumab. The group also noted that

biologics including dupilumab are not expected to provide benefit in patients with mild-to-moderate asthma and that the treatment would be ineffective if blood eosinophils are less than 150 cells/μL and FeNO is less than 20 ppb.

Assessing Response to Treatment

The Family Physician Airways Group of Canada noted that the following are used to determine whether a patient is responding in clinical practice: FEV_1 generally improves within the first few months, and exacerbation reduction is visible over the first year. OCS dose reduction occurs as tolerated by the individual. Information with respect to clinically meaningful response for these outcomes was not provided.

Discontinuing Treatment

The clinician input noted that treatment should be discontinued when a lack of response in symptoms, asthma control, FEV_1, and exacerbation reduction are not seen.

Prescribing Conditions

The Family Physician Airways Group of Canada commented that outpatient settings are the most appropriate for treatment with dupilumab. Patients will require injection every 2 weeks, which can be done at home. The specialists required to diagnose, treat, and monitor patients who might receive the drug include respirologists; ear, nose, and throat specialists; allergists; dermatologists; and family physicians with expertise.

Additional Considerations

The Family Physician Airways Group of Canada noted that the price of dupilumab is in line with other biologic agents and gives an additional treatment choice to treat severe asthma patients.

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's Reimbursement Review processes by identifying issues that may impact their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical expert consulted by CADTH are summarized in Table 4.

Clinical Evidence

The clinical evidence included in the review of dupilumab is presented in 3 sections. The first section, the systematic review, includes pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those studies that were selected according to an a priori protocol. The second section includes indirect evidence from the sponsor and indirect evidence selected from the literature that met the selection criteria specified in the review. The third section includes sponsor-submitted long-term extension studies and additional relevant studies that were considered to address important gaps in the evidence included in the systematic review.

Systematic Review: Pivotal and Protocol Selected Studies

Objectives

To perform a systematic review of the beneficial and harmful effects of dupilumab for patients 12 years and older with a type 2 or eosinophilic phenotype or with OCS-dependent asthma.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those meeting the selection criteria presented in Table 5. Outcomes included in the CADTH review protocol reflect outcomes considered to be important to patients, clinicians, and drug plans.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the PRESS (Peer Review of Electronic Search Strategies) checklist (https://www.cadth.ca/resources/finding-evidence/press).[20]

Table 4: Summary of Drug Plan Input and Clinical Expert Response

Drug program implementation questions	Clinical expert response
Should patients be required to have failed high-dose ICS and an additional controller (e.g., LABA) before treatment with dupilumab is reimbursed?	Patients should be using high-dose ICS + LABA and remain uncontrolled before treatment with dupilumab therapy.
Will dupilumab be used in patients with moderate asthma? And/or for patients < 12 years old?	Patients should have type 2 inflammation (peripheral blood eosinophil counts ≥ 150 cells/μL), uncontrolled asthma despite treatment with high-dose ICS + LABA or oral corticosteroids to receive dupilumab therapy. Typically, this would mean patients who have step 5 severe asthma per the GINA recommendations. Patients at this step may receive treatment with a LAMA before trying a biologic like dupilumab. Dupilumab should not currently be used in patients younger than 12 years of age and with non–type 2 inflammation.
What factors would be considered when choosing 1 biologic (e.g., IL-5 inhibitor or anti-IgE therapy) vs. another (e.g., dupilumab)? How will these be sequenced?	Current practice in Canada relies on the IL-5 inhibitors mepolizumab and benralizumab. Reslizumab is not used much because it is not generally reimbursed, has IV administration (others are subcutaneous), and may not be as effective as the other 2. Omalizumab may be used in the same population but would generally be targeted to those with another phenotype: severe allergic asthma. The choice between dupilumab, mepolizumab, or benralizumab will depend on several clinical factors, including patient preference. Dupilumab may be considered before the IL-5 inhibitors based on the presence of concomitant atopic dermatitis and/or chronic rhinosinusitis with nasal polyps. Dupilumab has a Health Canada–approved indication for these common comorbidities of asthma. Therefore, the presence of these comorbidities may drive prescribing of dupilumab ahead of other biologics with less robust clinical data for treating these comorbidities. There are currently few data to guide treatment sequencing of the biologics; however, if a patient's asthma remains uncontrolled on 1 of the biologics (and all other interventions and adherence are optimized), then switching to another biologic with a different receptor target may be reasonable. At the moment, there are no high-quality data to guide initial biologic and subsequent biologic treatments.

GINA = Global Initiative for Asthma; ICS = inhaled corticosteroid; IgE = immunoglobin E; IL = interleukin; LABA = long-acting beta2-agonist; LAMA = long-acting muscarinic antagonist.

Table 5: Inclusion Criteria for the Systematic Review

Criteria	Description
Patient population	Patients 12 years and older with severe asthma with a type 2 or eosinophilic phenotype or with oral corticosteroid–dependent asthma • baseline eosinophils • type 2 or oral corticosteroid–dependent asthma • number of asthma exacerbations in the past year
Intervention	For patients with a type 2 or eosinophilic phenotype: Dupilumab 400 mg initial dose, followed by 200 mg every 2 weeks by subcutaneous injection. The dose may be increased to 300 mg every 2 weeks based on clinical judgment. For patients with oral corticosteroid–dependent asthma or with comorbid moderate-to-severe atopic dermatitis and/or comorbid severe chronic rhinosinusitis with nasal polyposis: Dupilumab 600 mg initial dose, followed by 300 mg every 2 weeks by subcutaneous injection.
Comparators	Inhaled corticosteroids in combination with long-acting beta2-agonists alone or in combination with 1 or more of the following: • IL-5 inhibitors • IgE inhibitors • leukotriene receptor antagonists • oral corticosteroids (chronic) • long-acting muscarinic antagonists • rescue medications (SABA, SAMA) for acute exacerbations
Outcomes	**Key efficacy outcomes:** • mortality • acute asthma exacerbations • hospitalizations, emergency department visits, physician visits due to asthma exacerbation • use of oral corticosteroids (acutely for exacerbations or chronic use) • health-related quality of life, as measured by a validated scale[a] • change in pulmonary function (e.g., PEF, FEV_1) • asthma symptoms (e.g., ACQ)[a] • change in number of asthma symptom–free days or nights[a] • incidence of nocturnal awakenings[a] • use of ICS[a] • use of rescue medication[a] • days of missed school or work[a] • symptoms of rhinosinusitis and/or atopic dermatitis **Harms:** Adverse events, serious adverse events, withdrawal due to adverse event **Notable Harms:** Hypersensitivity reactions, helminth infections, conjunctivitis and keratitis, hypereosinophilic pneumonia, injection site reactions
Study design	Published and unpublished phase III and IV RCTs

ACQ = Asthma Control Questionnaire; FEV_1 = forced expiratory volume in the first second; ICS = inhaled corticosteroid; IgE = immunoglobulin E; IL = interleukin; PEF = peak expiratory flow; RCT = randomized controlled trial; SABA = short-acting beta2-agonist; SAMA = short-acting muscarinic antagonist.

[a]These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid and Embase (1974–) via Ovid. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Dupixent (dupilumab) and asthma. Clinical trial registries were searched: the US National Institutes of Health's clinicaltrials.gov, WHO's International Clinical Trials Registry Platform search portal, Health Canada's Clinical Trials Database, and the European Union Clinical Trials Register.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See Appendix 1 for the detailed search strategies.

The initial search was completed on December 23, 2020. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee on April 21, 2021.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the *Grey Matters: A Practical Tool for Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters).[21] Included in this search were the websites of regulatory agencies (the US FDA and the EMA). Google was used to search for additional internet-based materials. See Appendix 1 for more information on the grey literature search strategy.

These searches were supplemented through contacts with appropriate experts. In addition, the sponsor of the drug was contacted for information regarding unpublished studies.

Two CADTH clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least 1 reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Findings From the Literature

Description of Studies

Three studies were included in this review: QUEST, VENTURE, and DRI12544 (Table 6, Table 7, and Table 8). The included studies were all multinational, manufacturer-sponsored, double-blind randomized controlled trials that compared dupilumab to placebo in patients with asthma who were already receiving standard of care. There were 15 Canadian sites in QUEST, 6 Canadian sites in VENTURE, and no Canadian sites in DRI12544. QUEST was a phase III trial that randomized 1,902 adults and adolescents with moderate-to-severe asthma in a 2:2:1:1 to 1 of 2 doses of dupilumab (200 mg or 300 mg) every 2 weeks or matching placebo every 2 weeks. Randomization was stratified by age (< 18 years or ≥ 18 years), blood eosinophil count (< 300 cells/μL or ≥ 300 cells/μL) by central laboratory, ICS dose level (medium or high), and country at screening. VENTURE was a phase III study whose objective was to investigate the efficacy and tolerability of dupilumab in reducing the use of OCSs while maintaining asthma control in patients with severe refractory asthma. VENTURE randomized 210 adults and adolescents with severe asthma and regular use of systemic steroids in the 6 months before screening to dupilumab 300 mg every 2 weeks or placebo. Randomization was stratified by optimized OCS dose (prednisone or prednisolone) at week 0 (≥ 10 mg/day or > 10 mg/day) and by country. DRI12544 was a dose-ranging study that randomized adults with moderate-to-severe uncontrolled asthma to 1 of 4 doses of dupilumab (dupilumab 200

mg or 300 mg, every 2 weeks or every 4 weeks) or placebo. Randomization was stratified by blood eosinophils at visit 1 (≥ 300 cells/μL, 200 to 299 cells/μL, or < 200 cells/μL). Only the 2 every 2 week dose regimens that are approved in Canada, as well as placebo, comprising 465 patients, are reported in this review.

QUEST consisted of a screening phase (3 to 5 weeks), a treatment phase of 52 weeks, and a follow-up of 12 weeks. An open-label extension was also available to patients. VENTURE consisted of a 4-week induction phase, where patients remained on their optimized dose of OCS and their baseline asthma medication; a 24-week treatment phase; and a 12-week post-treatment follow-up period. The purpose of this phase was to ensure that patients entered the randomized treatment period on the lowest possible OCS dose while maintaining asthma control. DRI12544 had a screening period of 14 to 21 days, a randomized treatment period of 24 weeks, and a 16-week post-treatment period.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

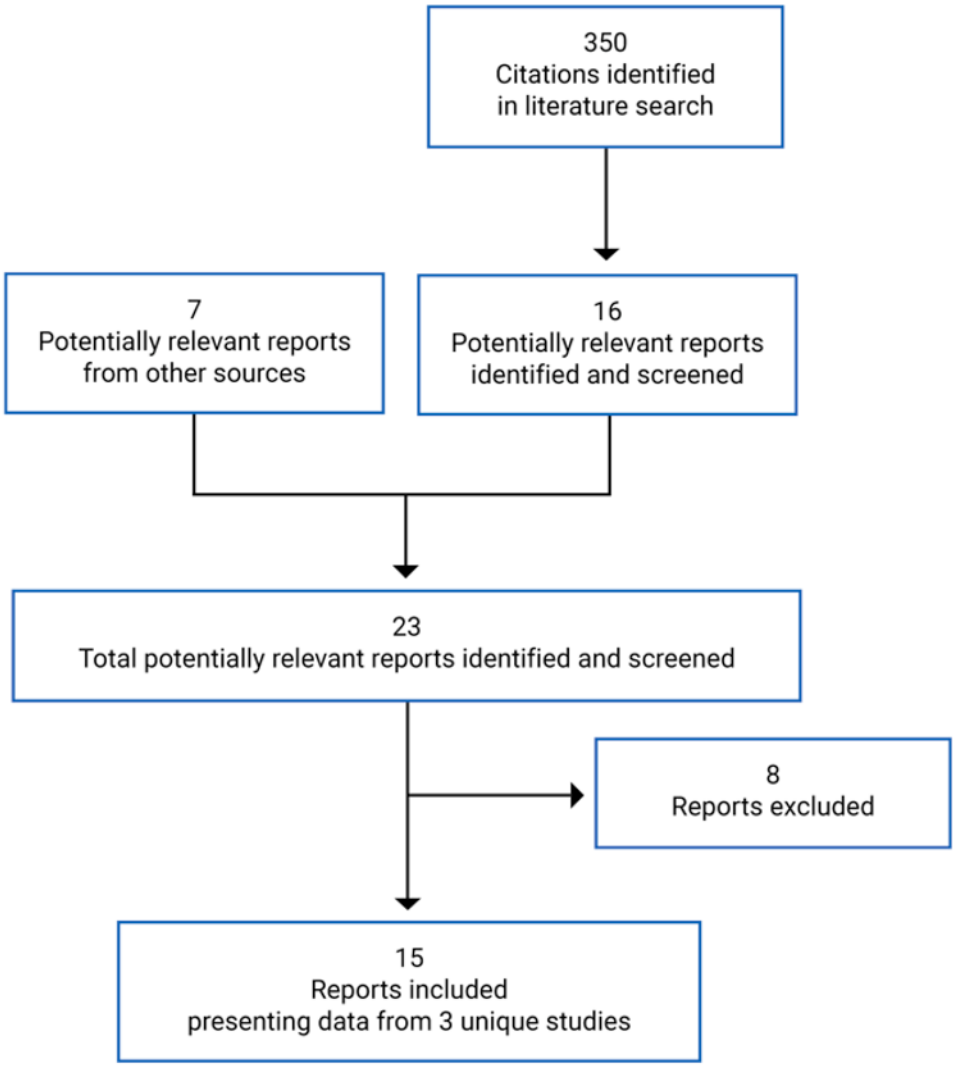


Table 6: Details of Included Studies: QUEST

	Criteria	Description
Designs and populations	**Study design**	DB RCT
	Locations	331 centres, 21 countries (North America [Canada], South America, EU, Japan, Korea, Australia, Taiwan)
	Study period	April 2015 to July 2017
	Randomized (N)	1,902
	Inclusion criteria	• Adults and adolescents (12 years and older) with diagnosis of asthma for ≥ 12 months (based on GINA 2014) • Existing treatment with medium- to high-dose ICS (250 mcg FTP b.i.d. or equipotent ICS daily dose to a maximum of 2,000 mcg/day FTP or equivalent) in combination with a second controller (e.g., LABA, LTRA) for at least 3 months with a stable dose ≥ 1 month before visit 1 ◦ Japan only — 18 years and older: ICS ≥ 200 mcg FTP b.i.d. or equivalent; 12 to 17 years: ICS ≥ 100 mcg FTP b.i.d. or equivalent ◦ Patients requiring a third controller were eligible (also for at least 3 months with a stable dose ≥ 1 month before visit 1) • Pre-bronchodilator FEV_1 ≤ 80% of predicted normal (adults) and ≤ 90% for adolescents at visits 1 and 2, before randomization • ACQ-5 score 1.5 at visits 1 and 2, before randomization • Reversibility of at least 12% and 200 mL in FEV_1 after administration of 200 mcg to 400 mcg salbutamol or levosalbutamol • Experienced any of the following within 1 year before visit 1: ◦ Treatment with a systemic steroid (oral or parenteral) for worsening asthma at least once ◦ Hospitalization or emergency medical care visit for worsening asthma
	Exclusion criteria	COPD or other lung diseases (e.g., idiopathic pulmonary fibrosis, Churg-Strauss syndrome) that may impair lung function Severe asthma exacerbation (defined as a deterioration of asthma resulting in emergency treatment, hospitalization due to asthma, or treatment with systemic steroids at any time from 1 month before the screening visit up to and including the baseline visit) Lung disease other than asthma (clinical evidence or imaging) Current smoking or stopped smoking within 6 months before visit 1 Previous smoking history of > 10 pack-years Comorbid disease that might interfere with evaluation of study drug
Drugs	**Intervention**	Dupilumab 200 mg q.2.w. (1.14 mL) after a 400 mg loading dose Dupilumab 300 mg q.2.w. (2 mL) after a 600 mg loading dose
	Comparator(s)	Placebo matched to dupilumab 200 mg (1.14 mL) SC q.2.w. after a loading dose (2 × 1.14 mL) Placebo matched to dupilumab 300 mg (2.0 mL) SC q.2.w. after a loading dose (2 × 2.0 mL)

	Criteria	Description
Duration	**Phase**	
	Screening	4 weeks
	DB	52 weeks
	Follow-up	12 weeks
Outcomes	**Primary end point**	Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period; a severe exacerbation event was defined as a deterioration of asthma requiring: • use of systemic corticosteroids for ≥ 3 days, or • hospitalization or emergency department visit because of asthma, requiring systemic corticosteroids Absolute change from baseline in pre-bronchodilator FEV_1 at week 12
	Other end points	Key secondary: Percent change from baseline in pre-bronchodilator FEV_1 at week 12 Additional secondary end points: • Analyses of the 2 primary end points and the key secondary end point in subgroups of patients with baseline eosinophil counts ≥ 300 cells/μL, ≥ 150 to < 300 cells/μL, and < 150 cells/μL, and a high dose of ICS at baseline • Change from baseline in AQLQ-S at week 24 (in the ITT population and in the subgroup of patients with baseline eosinophil counts ≥ 300 cells/μL) • Change from baseline in ACQ-5 at week 24 • Annualized rate of severe exacerbation events resulting in hospitalization or emergency department visit during the 52-week placebo-controlled treatment period • Annualized rate of LOAC events during the 52-week placebo-controlled period. An LOAC event was defined as any of the following: ◦ ≥ 6 additional reliever puffs of salbutamol (albuterol) or levosalbutamol (levalbuterol) in a 24-hour period (compared to baseline) on 2 consecutive days ◦ ≥ 20% decrease in pre-bronchodilator FEV_1 compared with baseline ◦ ncrease in ICS dose ≥ 4 times the dose at visit 2 ◦ decrease in morning or evening peak flow of 30% or more on 2 consecutive days of treatment, based on the defined stability limit (treatment period stability limit was defined as the respective mean morning or evening PEF obtained over the last 7 days before randomization [day 1]) ◦ severe exacerbation event

	Criteria	Description
		• Time to first severe exacerbation event; time to first LOAC event • Change from baseline in other lung function measurements: percent predicted FEV_1, morning and evening PEF, FVC, FEF 25% to 75%, and post-bronchodilator FEV_1 at weeks 2, 4, 8, 12, 24, 36, and 52 • Change from baseline at weeks 2, 4, 8, 12, 24, 36, and 52 in the following: ◦ ACQ scores (5 and 7 question versions) ◦ morning and evening asthma symptom score (patients used a numeric rating scale) ◦ nocturnal awakenings ◦ use of daily puffs of rescue medication. • Change from baseline at weeks 12, 24, 36, and 52 in the following: ◦ health care resource use ◦ other patient-reported outcomes: EQ-5D-5L, HADS, SNOT-22 in those patients with comorbid bilateral nasal polyposis and/or chronic rhinosinusitis, RQLQ(S) + 12 in those patients with comorbid allergic rhinitis Safety: • Adverse events, serious adverse events • Vital signs, physical, ECG
Notes	**Publications**	Castro et al. (2020),[22] Castro et al. (2018),[23] Busse et al. (2018)[24]

ACQ = Asthma Control Questionnaire; ACQ-5 = Asthma Control Questionnaire, 5-item; AQLQ-S = Asthma Quality of Life Questionnaire with Standardized Activities; b.i.d. = twice daily; COPD = chronic obstructive pulmonary disease; DB = double blind; ECG = electrocardiogram; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; EU = European Union; FEF = forced expiratory flow; FEV_1 = forced expiratory volume in the first second; FTP = fluticasone propionate; FVC = forced vital capacity; GINA = Global Initiative for Asthma; HADS = Hospital Anxiety and Depression Scale; ICS = inhaled corticosteroid; ITT = intention to treat; LABA = long-acting beta2-agonist; LOAC = loss of asthma control; LTRA = leukotriene receptor antagonist; PEF = peak expiratory flow; q.2.w. = every 2 weeks; RCT = randomized controlled trial; RQLQ(S) + 12 = Standardized Rhinoconjunctivitis Quality of Life Questionnaire, ages 12 + ; SC = subcutaneous; SNOT-22 = Sino-Nasal Outcomes Test, 22 items.

Note: Five additional reports were included (Clinical Study Report for QUEST,[1] FDA clinical and statistical review,[25,26] Health Canada reviewer's report,[27] sponsor's submission[4]).

Source: Clinical Study Report for QUEST.[1]

In QUEST, 54% of patients were screened out of the study. The most common reason for exclusion from the study was exceeding the pre-bronchodilator FEV_1, having an ACQ-5 score lower than the minimum, having FEV_1 reversibility lower than the minimum, and exhibiting noncompliance with use of background therapy during the screening period. In VENTURE, 46% of patients screened were excluded, the most common reasons being active hepatitis, hepatitis B, or hepatitis C; enrolment or randomization stopped at the study level; and FEV_1 lower than the minimum required. In DRI12544, 49% of patients screened were excluded from the study, and the leading reasons were failure to meet inclusion for FEV_1 reversibility, and treatment with systemic corticosteroids within 28 days of screening or any time during screening.

Populations

Inclusion and Exclusion Criteria

QUEST included patients on existing treatment with medium- to high-dose ICS (250 mcg to 2,000 mcg fluticasone propionate [FTP] twice daily or equivalent) in combination with a second controller for at least 3 months, pre-bronchodilator FEV_1 80% or less of predicted normal, reversibility of at least 12% and 200 mL, and within the past year had either been treated with a systemic steroid or been hospitalized or visited an emergency department for

Table 7: Details of Included Studies: VENTURE

	Criteria	Description
Designs and populations	**Study design**	DB RCT
	Locations	68 centres (17 countries: Canada, US, EU, South America, Israel)
	Study period	October 2015 to Sep 2017
	Randomized (N)	210
	Inclusion criteria	• Adults and adolescents (12 years and older) with diagnosis of asthma for ≥ 12 months (based on GINA 2014). • Severe asthma, documented regular prescribed treatment of maintenance SCS in 6 months before visit 1 and using a stable OCS dose 4 weeks before visit 1. Patients were to be taking 5 mg to 35 mg a day of prednisone equivalent at visit 1 and the randomization visit. Patients had to agree to switch to study-required prednisone or prednisolone as their OCS at visit 1 and use it for duration of study. • Existing treatment with high-dose ICS (> 500 mcg FTP [or equivalent]) in combination with a second controller (e.g., LABA, LTRA) for at least 3 months with a stable dose ≥ 1 month before visit 1. Patients requiring a third controller were eligible (also for at least 3 months with a stable dose ≥ 1 month before visit 1). • FEV_1 < 80% of predicted normal (adults) and ≤ 90% for adolescents at visit 1. • Evidence of asthma, as documented by either: ◦ reversibility of at least 12% and 200 mL in FEV_1 after administration of 200 mcg to 400 mcg salbutamol or levosalbutamol, or ◦ airway hyper-responsiveness (methacholine challenge)
	Exclusion criteria	COPD or other lung diseases (e.g., idiopathic pulmonary fibrosis, Churg-Strauss syndrome) that may impair lung function Deterioration of asthma resulting in emergency treatment, or hospitalization due to asthma within 4 weeks of screening visit 1 Required ≥ 12 puffs rescue medication on any day in the week before visit 1 Lung disease other than asthma (clinical evidence or imaging) Current smoking or stopped smoking within 6 months before visit 1 Previous smoking history of > 10 pack-years Comorbid disease that might interfere with evaluation of study drug
Drugs	**Intervention**	Dupilumab 300 mg SC q.2.w. after a 600 mg loading dose
	Comparator(s)	Placebo matched to dupilumab 300 mg SC q.2.w. after a loading dose

	Criteria	Description
Duration	**Phase**	
	Screening	10 weeks (included OCS optimization)
	DB	24 weeks
	Follow-up	12 weeks
Outcomes	**Primary end point**	Percent reduction in investigator-prescribed OCS dose at week 24 while still maintaining asthma control (lack of control was defined as ACQ ≥ 0.5, a severe asthma exacerbation, or a clinically significant event required an OCS dose adjustment)
	Other end points	Key secondary: • Patients achieving a reduction of 50% or greater in OCS dose at week 24 compared to baseline while still maintaining asthma control • Patients achieving a reduction in OCS dose to < 5 mg/day at week 24 while maintaining asthma control Other secondary: • Patients achieving their maximum possible reduction of OCS dose per protocol at week 24 while still maintaining asthma control • Absolute reduction of OCS dose at week 24 compared to baseline dose while still maintaining asthma control Additional disease-specific efficacy end points: • Annualized rate of severe exacerbation events • Time to first severe exacerbation event • Change from baseline in pre-bronchodilator FEV_1, weeks 2, 4, 8, 12, 16, 20, and 24 • Percent change from baseline in pre-bronchodilator FEV_1, weeks 2, 4, 8, 12, 16, 20, and 24 • Change from baseline in other lung assessments (percent predicted FEV_1, morning and evening PEF, FVC, FEF 25% to 75%), weeks 2, 4, 8, 12, 16, 20, and 24

	Criteria	Description
		• Absolute change from baseline in post-bronchodilator FEV_1, weeks 12 and 24 • Change from baseline in ACQ-5 score at weeks 2, 4, 8, 12, 16, 20, and 24 • Change from baseline in AQLQ at week 24 • Annualized rate of severe asthma exacerbations requiring hospitalizations or ED visit • Time to first severe asthma exacerbation requiring hospitalization or ED visit • Change from baseline to weeks 12 and 24 in: ◦ SNOT-22 in patients with bilateral nasal polyposis and/or chronic rhinosinusitis ◦ HADS ◦ EQ-5D-5L • Change from baseline at weeks 2, 4, 8, 12, 16, 20, and 24 in: ◦ morning and evening asthma symptom score and nocturnal awakenings (e-diary) ◦ use of rescue medication ◦ health care resource use • Safety: ◦ Adverse events, serious adverse events ◦ Vital signs, physical, ECG
Notes	**Publications**	Rabe et al. (2018)[28]

ACQ = Asthma Control Questionnaire; ACQ-5 = Asthma Control Questionnaire, 5-item; AQLQ = Asthma Quality of Life Questionnaire; COPD = chronic obstructive pulmonary disease; DB = double blind; ECG = electrocardiogram; ED = emergency department; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; EU = European Union; FEF = forced expiratory flow; FEV_1 = forced expiratory volume in the first second; FTP = fluticasone propionate; FVC = forced vital capacity; GINA = Global Initiative for Asthma; HADS = Hospital Anxiety and Depression Scale; ICS = inhaled corticosteroid; LABA = long-acting beta2-agonist; LTRA = leukotriene receptor antagonist; OCS = oral corticosteroid; PEF = peak expiratory flow; q.2.w. = every 2 weeks; RCT = randomized controlled trial; SC = subcutaneous; SCS = systemic corticosteroid; SNOT-22 = Sino-Nasal Outcomes Test, 22 items.

Note: Five additional reports were included (Clinical Study Report for VENTURE, FDA clinical and statistical review,[25,26] Health Canada reviewer's report,[27] sponsor's submission[4]).

Source: Clinical Study Report for VENTURE.[2]

Table 8: Details of Included Studies: DRI12544

	Criteria	Description
Designs and populations	**Study design**	DB RCT
	Locations	US, Europe
	Study period	June 2013 to April 2015
	Randomized (N)	465

	Inclusion criteria	• Physician-diagnosed moderate-to-severe asthma, uncontrolled for ≥ 12 months (GINA 2009)
		• Existing treatment with moderate- to high-dose ICS (250 mcg FTP [or equivalent]) with a stable dose of ICS + LABA for ≥ 1 month before visit 1
		• FEV_1 40% to 80% of predicted normal at visit 1 and visit 2 before first dose of investigational product
		• ACQ-5 score ≥ 1.5 at visit 1 and 2
		• Reversibility of ≥ 12% and 200 mL in FEV_1 after 200 mcg to 400 mcg of salbutamol at visit 1
		• Experienced within 1 year of visit 1:
		  ○ Treatment with ≥ 1 systemic steroid bursts for worsening asthma
		  ○ Hospitalization or an emergency or urgent medical care visit for worsening asthma

	Exclusion criteria	< 18 years old COPD or other lung diseases (e.g., idiopathic pulmonary fibrosis, Churg-Strauss syndrome) that may impair lung function Lung disease other than asthma (clinical evidence or imaging) Current smoking or stopped smoking within 6 months before visit 1 Previous smoking history of > 10 pack-years Comorbid disease that might interfere with evaluation of study drug Treatment with systemic corticosteroids (> 10 mg of oral prednisone or equivalent) within 28 days of screening and at any time during screening
Drugs	**Intervention**	Dupilumab 300 mg SC q.2.w. after a 600 mg loading dose Dupilumab 200 mg SC q.2.w. after a 400 mg loading dose
	Comparator(s)	Placebo matched to dupilumab 300 mg SC q.2.w. after a loading dose

	Criteria	Description
Duration	**Phase**	
	Screening	2 to 3 weeks
	DB	24 weeks
	Follow-up	16 weeks
Outcomes	**Primary end point**	Change from baseline to week 12 in FEV_1
	Other end points	• Relative change (%) from baseline to week 12 in FEV_1 • Annualized rate of loss of asthma control events during the treatment period • Annualized rate of severe exacerbation events during the treatment period • Time to LOAC events during the treatment period and overall study period • Time to severe exacerbation events during the treatment period and overall study period • Change from baseline to week 12 in FVC • Relative change (%) from baseline to week 12 in FVC • Change from baseline to week 12 in FEV_1-FVC ratio • Change from baseline to week 12 in FEF 25% to 75% • Health care resource use • Change from baseline at week 12 in: ◦ Morning and evening asthma symptom scores ◦ ACQ-5 score ◦ AQLQ score ◦ Morning and evening PEF ◦ Number of inhalations per day of salbutamol or levosalbutamol for symptom relief ◦ Nocturnal awakenings

	Criteria	Description
		• Change from baseline at week 12 and week 24 in: ◦ SNOT-22 ◦ HADS ◦ EQ-5D-3L • Safety: ◦ adverse events, serious adverse events, AESIs (anaphylactic reactions, serious injection site reactions, severe infections, parasitic infections, ALT elevation) ◦ pregnancy ◦ symptomatic overdose
Notes	**Publications**	Corren et al. (2019),[29] Corren et al. (2019),[30] Weinstein et al. (2018),[31] Wenzel et al. (2016)[32]

ACQ-5 = Asthma Control Questionnaire, 5-item; AESI = adverse event of special interest; ALT = alanine transaminase; AQLQ = Asthma Quality of Life Questionnaire; COPD = chronic obstructive pulmonary disease; DB = double blind; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels questionnaire; FEF = forced expiratory flow; FEV_1 = forced expiratory volume in the first second; FTP = fluticasone propionate; FVC = forced vital capacity; GINA = Global Initiative for Asthma; HADS = Hospital Anxiety and Depression Scale; ICS = inhaled corticosteroid; LABA = long-acting beta2-agonist; LOAC = loss of asthma control; PEF = peak expiratory flow; q.2.w. = every 2 weeks; RCT = randomized controlled trial; SC = subcutaneous; SNOT-22 = Sino-Nasal Outcomes Test, 22 items.

Note: Five additional reports were included (Clinical Study Report for DRI12544,[3] FDA clinical and statistical review,[25,26] Health Canada reviewer's report,[27] sponsor's submission[4]).

Source: Clinical Study Report for DRI12544.[3]

worsening asthma (Table 6). It was not explicitly stated what the cut-off was for medium- versus high-dose ICS; however, this is often considered to be greater than 250 mcg FTP and greater than 500 mcg, respectively. VENTURE enrolled patients with severe asthma and with documented regular use of systemic corticosteroids in the 6 months before visit 1, as well as high-dose ICS (> 500 mcg FTP or equivalent) in combination with a second controller (Table 7). Otherwise, patients had the same requirements for reversibility and FEV_1 as in QUEST. The inclusion criteria for DRI12544 were similar to that of QUEST (Table 8).

Patients were excluded if they had other lung diseases that would impair pulmonary function (like chronic obstructive pulmonary disease), if they were current smokers or had recently (within 6 months of visit 1) stopped smoking or had a smoking history of more than 10 pack-years. Patients with signs of recent deterioration in asthma were excluded; evidence of deterioration might include emergency treatment or hospitalization within 4 weeks of visit 1, or having required 12 puffs or more of rescue medication in the week before visit 1. In QUEST and in DRI12544, this recent deterioration included use of systemic corticosteroids for asthma, while in VENTURE patients using systemic corticosteroids were being sought.

Baseline Characteristics

Patients across studies were in their late 40s to early 50s, on average (range: 48 to 51 years of age), and the majority were female (> 60%) and White (approximately 80%) (Table 9, Table 10, and Table 11). In QUEST, approximately half were on a high dose of ICS at baseline, while most of the remainder were on a medium dose (approximately 1% were on low dose). Across the studies, patients had an average of approximately 2 severe asthma exacerbations in the past year, with the highest average in DRI12544 (approximately 2.15/year). On an annual basis, patients averaged less than 1 severe exacerbation requiring hospitalization or urgent medical attention, with a range between studies from approximately 0.7 in QUEST and DRI12544 to approximately 1 in VENTURE.

With respect to differences between groups within studies, there were numerically more exacerbations in the placebo group that was matched to dupilumab 300 mg (2.31 versus a range between 2.02 and 2.07 in the other groups), but otherwise there were no noteworthy differences in baseline characteristics between groups. In VENTURE, there was a numerically higher number of severe asthma exacerbations in the past year in the placebo group (2.17 versus 2.01 with dupilumab), a higher number of inhalations of salbutamol or levosalbutamol per day (4.94 versus 4.29 with dupilumab), and a higher optimized dose of OCS (11.75 mg/day versus 10.75 mg/day with dupilumab). In DRI12544, the mean number of asthma exacerbations differed between dupilumab 200 mg (1.85), dupilumab 300 mg (2.37), and placebo (2.27).

Interventions

Across the included studies, dupilumab was administered by subcutaneous injection every 2 weeks, at doses of either 200 mg or 300 mg, initiated with a loading dose that was twice the strength (2 injections) of the maintenance dose (i.e., a 400 mg loading dose for a 200 mg biweekly maintenance dose). Patients were trained to self-administer the doses, and after a certain amount of time (e.g., 12 weeks in QUEST) were permitted to self-inject at their home if they wished to do so. In QUEST, the dupilumab 200 mg dose was administered in a 1.14 mL syringe and the 300 mg dose was administered in a 2.0 mL syringe; therefore, to maintain blinding, the 200 mg dose was matched to a 1.14 mL placebo and the 300 mg dose was matched to a 2.0 mL placebo.

Table 9: Summary of Baseline Characteristics: QUEST

Characteristic	Dupilumab 200 mg q.2.w. N = 631	Placebo N = 317	Dupilumab 300 mg q.2.w. N = 633	Placebo N = 321
Mean age, years (SD)	47.9 (15.3)	48.2 (15.6)	47.7 (15.6)	48.2 (14.7)
Male, n (%)	244 (38.7)	119 (37.5)	239 (37.8)	103 (32.1)
Race, n (%)				
White	510 (80.8)	265 (83.6)	529 (83.6)	273 (85.0)
Black/African descent	33 (5.2)	14 (4.4)	21 (3.3)	12 (3.7)
Asian	78 (12.4)	33 (10.4)	79 (12.5)	33 (10.3)
American Indian/Alaska Native	0	1 (0.3)	0	0
Native Hawaiian/Other Pacific Islander	1 (0.2)	0	0	0
Other	9 (1.4)	4 (1.3)	4 (0.6)	3 (0.9)
Mean BMI (SD)	29.05 (6.52)	29.76 (7.25)	29.07 (6.68)	29.21 (6.95)
ICS dose at baseline, n (%)				
High	317 (50.2)	172 (54.3)	323 (51.0)	167 (52.0)
Medium	310 (49.1)	144 (45.4)	303 (47.9)	151 (47.0)
Low	4 (0.6)	1 (0.3)	7 (1.1)	3 (0.9)
Age at onset of asthma, years, mean (SD)	27.1 (19.2)	27.2 (19.1)	26.6 (19.4)	27.4 (18.6)
Time since first diagnosis of asthma, years, mean (SD)	20.85 (15.54)	21.01 (15.25)	21.10 (15.19)	20.74 (15.48)
With ongoing medical conditions, n (%)	509 (80.7)	266 (83.9)	524 (82.8)	266 (82.9)
Smoking history				
Former, n (%)	126 (20.0)	59 (18.6)	116 (18.3)	67 (20.9)
Never, n (%)	505 (80.0)	258 (81.4)	517 (81.7)	254 (79.1)
Time since cessation, years, mean (SD)	17.88 (13.30)	15.86 (12.82)	18.18 (12.39)	16.10 (12.21)
Pack-years, mean (SD)	3.89 (2.69)	3.96 (2.81)	4.15 (3.04)	4.07 (3.12)
Time since last severe asthma exacerbation, months, mean (SD)	5.53 (2.97)	5.59 (3.06)	5.67 (2.91)	5.58 (2.83)
Number of severe asthma exacerbations in the past year, mean (SD)	2.07 (2.66)	2.07 (1.57)	2.02 (1.86)	2.31 (2.07)
Number, n (%)				
1	340 (53.9)	150 (47.3)	330 (52.1)	144 (44.9)
2	163 (25.8)	91 (28.7)	158 (25.0)	93 (29.0)
3	64 (10.1)	39 (12.3)	48 (15.0)	65 (10.3)
≥ 4	64 (10.1)	37 (11.7)	65 (10.3)	48 (15.0)

Characteristic	Dupilumab 200 mg q.2.w. N = 631	Placebo N = 317	Dupilumab 300 mg q.2.w. N = 633	Placebo N = 321
Number of severe asthma exacerbations requiring hospitalizations or urgent medical care, past year, mean (SD)	0.69 (1.41)	0.62 (1.15)	0.66 (1.21)	0.82 (1.59)
0	393 (62.3)	205 (64.9)	385 (60.8)	190 (59.2)
1	155 (24.6)	64 (20.3)	170 (26.9)	80 (24.9)
2	45 (7.1)	31 (9.8)	35 (5.5)	27 (8.4)
3	16 (2.5)	7 (2.2)	25 (3.9)	7 (2.2)
≥ 4	22 (3.5)	9 (2.8)	18 (2.8)	17 (5.3)
Pre-bronchodilator FEV_1, L, mean (SD)	1.78 (0.62)	1.76 (0.61)	1.78 (0.60)	1.75 (0.57)
Pre-bronchodilator FEV_1, % predicted, mean (SD)	58.38 (13.52)	58.43 (13.22)	58.51 (13.52)	58.35 (13.87)
Post-bronchodilator FEV_1, L, mean (SD)	2.16 (0.74)	2.16 (0.71)	2.17 (0.72)	2.14 (0.69)
FEV_1 reversibility, mean (SD)	27.39 (22.79)	26.45 (17.65)	25.73 (23.79)	26.45 (17.65)
Morning PEF, L/min, mean (SD)	281.37 (112.1)	286.84 (111.7)	294.55 (15.9)	281.27 (107.6)
Evening PEF, L/min, mean (SD)	293.55 (115.3)	298.31 (110.6)	306.93 (116.4)	294.75 (109.2)
Inhalations of salbutamol or levosalbutamol, mean (SD)	3.45 (4.2)	3.15 (3.6)	3.14 (3.5)	3.13 (4.0)
Hypersensitivity to Aspirin or other NSAID, n (%)	53 (8.4)	24 (7.6)	69 (10.9)	25 (7.8)
Ongoing atopic medical condition, n (%)	509 (80.7)	266 (83.9)	524 (82.8)	266 (82.9)
Ongoing atopic dermatitis, n (%)	61 (9.7)	35 (11.0)	62 (9.8)	38 (11.8)
Ongoing allergic conjunctivitis, n (%)	83 (13.2)	44 (13.9)	89 (14.1)	49 (15.3)
Ongoing allergic rhinitis, n (%)	421 (66.7)	221 (69.7)	438 (69.2)	225 (70.1)
Ongoing eosinophilic esophagitis, n (%)	0	1 (0.3)	0	2 (0.6)
Mean eosinophils, cells/μL (SD)	350 (350)	370 (340)	350 (370)	390 (420)
Patients with eosinophils < 150 cells/μL, n (%)	193 (30.6)	85 (26.8)	181 (28.6)	83 (25.9)
≥ 150 to < 300 cells/μL	173 (27.5)	84 (26.5)	175 (27.6)	95 (29.7)
≥ 300 cells/μL	264 (41.9)	148 (46.7)	277 (43.8)	142 (44.4)
ICS total daily dose, FTP equivalent, mcg, mean (SD)	748.74 (301.7)	772.67 (331.0)	745.14 (297.5)	757.83 (299.7)
Non-ICS controller, n (%)				
LABA	620 (98.3)	312 (98.4)	623 (98.4)	308 (96.0)
LAMA	45 (7.1)	30 (9.5)	42 (6.6)	36 (11.2)
Antileukotrienes	173 (27.4)	87 (27.4)	189 (29.9)	88 (27.4)
Methylxanthines	27 (4.3)	11 (3.5)	22 (3.5)	18 (5.6)
Other	1 (0.2)	0	2 (0.3)	0

Characteristic	Dupilumab 200 mg q.2.w. N = 631	Placebo N = 317	Dupilumab 300 mg q.2.w. N = 633	Placebo N = 321
Two types of controllers, n (%)	413 (65.5)	204 (64.4)	404 (63.8)	201 (62.6)
ICS + LABA	405 (64.2)	200 (63.1)	395 (62.4)	192 (59.8)
Other	8 (1.3)	4 (1.3)	9 (1.4)	9 (2.8)
Three types of controllers, n (%)	202 (32.0)	104 (32.8)	211 (33.3)	112 (34.9)
ICS + LABA + LAMA	31 (4.9)	21 (6.6)	28 (4.4)	29 (9.0)
ICS + LABA + antileukotrienes	150 (23.8)	74 (23.3)	163 (25.8)	71 (22.1)
Other	21 (3.3)	9 (2.8)	20 (3.2)	12 (3.7)

BMI = body mass index; FEV_1 = forced expiratory volume in the first second; FTP = fluticasone propionate; ICS = inhaled corticosteroid; LABA = long-acting beta2-agonist; LAMA = long-acting muscarinic antagonist; NSAID = nonsteroidal anti-inflammatory drug; PEF = peak expiratory flow; q.2.w. = every 2 weeks; SD = standard deviation.
Source: Clinical Study Report for QUEST.[1]

In QUEST, concomitant use of controllers such as ICS, LABA, LAMA, antileukotrienes, and methylxanthines was permitted. Patients supplied their own controllers. Prior to study entry, patients were to be on a stable dose of medium- to high-dose ICS (≥ 250 mcg twice daily FTP equivalent to a maximum of 2,000 mcg total daily dose) for at least 3 months with at least 1 month of stable dose before visit 1. If any other controllers were used, they also needed to be at a stable dose before entering the study. Changes to dosing during the study were only permitted on a temporary basis for the management of acute symptoms of asthma. Rescue medication could be used as needed for symptom control, and all use of controllers and rescue medication was to be recorded. A similar protocol was followed for DRI12544, and all patients received a 2 mL syringe of placebo or dupilumab to maintain blinding.

In VENTURE, there was an OCS reduction phase, where the OCS dose was down-titrated every 4 weeks up to week 20, according to a specific protocol. A clinical assessment was completed before each dose reduction, and if any 1 of a list of criteria was met, the scheduled dose reduction did not occur. The criteria included a change in ACQ of greater than or equal to 0.5 from the prior month, a clinically significant asthma exacerbation, a reduction of 20% in FEV_1 from baseline stability limit, mean PEF less than 70% of the baseline stability limit, use of 4 or more puffs per day of rescue medication above the mean baseline value or 12 or more puffs on any 1 day in the week before the clinical visit, and any clinically significant event that in the judgment of the investigator required treatment by OCS dose adjustment. The OCS reduction phase was followed by a 4-week maintenance phase, where the OCS dose was not to be reduced any further; however, in the event that any of the above criteria were met, the OCS dose could be increased by 1 step. In the event of a severe asthma exacerbation, patients could be treated with oral or parenteral corticosteroids at a dose that was at least double the OCS maintenance dose being used in the study. Once the exacerbation resolved, the dose of OCS was set to be 1 step higher than the OCS dose they were on when the exacerbation occurred for at least 4 weeks, and the dose reductions were continued per the usual schedule. If a second exacerbation occurred, then the OCS dose was to be increased by 1 step; however, no further dose reductions were allowed.

Outcomes

A list of efficacy end points identified in the CADTH review protocol that were assessed in the clinical trials and included in this review is provided in Table 12. These end points are further

Table 10: Summary of Baseline Characteristics: VENTURE

Characteristic	Dupilumab 300 mg q.2.w.	Placebo
Mean age, years (SD)	51.9 (12.5)	50.7 (12.8)
Female, n (%)	62 (60.2)	65 (60.7)
Race, n (%)		
White/White	97 (94.2)	100 (93.5)
Black/African descent	4 (3.9)	1 (0.9)
Asian	0	2 (1.9)
American Indian/Alaskan Native	0	2 (1.9)
Native Hawaiian/Other Pacific Islander	1 (1.0)	0
Other	1 (1.0)	2 (1.9)
Mean BMI (SD)	28.88 (5.91)	29.77 (6.00)
Age at onset of asthma, years, mean (SD)	31.2 (18.9)	31.6 (16.4)
Time since first diagnosis of asthma, years, mean (SD)	20.76 (14.81)	19.17 (12.97)
With ongoing atopic medical condition, n (%)	74 (71.8)	77 (72.0)
Smoking history		
Former, n (%)	24 (23.3)	17 (15.9)
Never, n (%)	79 (76.7)	90 (84.1)
Time since cessation, years, mean (SD)	13.99 (10.96)	16.98 (11.01)
Pack-years, mean (SD)	4.83 (2.60)	4.17 (2.77)
Time since last severe asthma exacerbation, months, mean (SD)	10.77 (12.35)	9.12 (9.18)
Number of severe asthma exacerbations in the past year, mean (SD)	2.01 (2.08)	2.17 (2.24)
Number, n (%)		
0	21 (20.4)	18 (16.8)
1	29 (28.2)	31 (29.0)
2	24 (23.3)	27 (25.2)
3	12 (11.7)	17 (15.9)
≥ 4	17 (16.5)	14 (13.1)
Number of severe asthma exacerbations requiring hospitalizations or urgent medical care, past year, mean (SD)	1.04 (1.83)	1.00 (1.40)
Number, n (%)		
0	55 (53.4)	52 (48.6)
1	26 (25.2)	29 (27.1)
2	10 (9.7)	14 (13.1)
3	4 (3.9)	6 (5.6)

Characteristic	Dupilumab 300 mg q.2.w.	Placebo
≥ 4	8 (7.8)	6 (5.6)
Pre-bronchodilator FEV_1, L, mean (SD)	1.53 (0.53)	1.63 (0.61)
Pre-bronchodilator FEV_1, % predicted, mean (SD)	51.64 (15.28)	52.69 (15.14)
Post-bronchodilator FEV_1, L, mean (SD)	1.83 (0.60)	1.89 (0.73)
FEV_1 reversibility, %, mean (SD)	0.29 (0.31)	0.28 (0.32)
Morning PEF, L/min, mean (SD)	236.57 (100.21)	240.60 (115.50)
Evening PEF, L/min, mean (SD)	251.79 (109.15)	256.12 (117.92)
Inhalations of salbutamol or levosalbutamol per 24 hours, mean (SD)	4.29 (4.33)	4.94 (6.65)
Hypersensitivity to Aspirin or other NSAID, n (%)	15 (14.6)	9 (8.4)
Ongoing atopic medical condition, n (%)	74 (71.8)	77 (72.0)
Ongoing atopic dermatitis, n (%)	8 (7.8)	8 (7.5)
Ongoing allergic conjunctivitis, n (%)	13 (12.6)	3 (2.8)
Ongoing allergic rhinitis, n (%)	56 (54.4)	61 (57.0)
Ongoing eosinophilic esophagitis, n (%)	0	0
Mean eosinophils, cells/μL (SD)	370 (320)	330 (300)
Patients with eosinophils < 150 cells/μL, n (%)	22 (21.4)	38 (35.5)
≥ 150 to < 300 cells/μL	33 (32.0)	28 (26.2)
≥ 300 cells/μL	48 (46.6)	41 (38.3)
ICS total daily dose, FTP equivalents, mcg, mean (SD)	1,084.32 (473.94)	980.12 (473.94)
Optimized daily OCS dose at baseline, mg/day, mean (SD)	10.75 (5.9)	11.75 (6.31)
Non-ICS controller, n (%)		
LABA	102 (99.0)	106 (100)
LAMA	27 (26.2)	20 (18.9)
Antileukotrienes	28 (27.2)	24 (22.6)
Methylxanthines	6 (5.8)	13 (12.3)
Two types of controllers, n (%)		
ICS + LABA	43 (41.7)	49 (46.2)
Other	0	0
Three types of controllers, n (%)		
ICS + LABA + LAMA	24 (23.3)	19 (17.9)
ICS + LABA + antileukotrienes	25 (24.3)	23 (21.7)
Other	7 (6.8)	14 (13.2)

BMI = body mass index; FEV_1 = forced expiratory volume in the first second; ICS = inhaled corticosteroid; LABA = long-acting beta2-agonist; LAMA = long-acting muscarinic antagonist; NSAID = nonsteroidal anti-inflammatory drug; OCS = oral corticosteroid; PEF = peak expiratory flow; q.2.w. = every 2 weeks; SD = standard deviation.

Source: Clinical Study Report for VENTURE.[2]

Table 11: Summary of Baseline Characteristics: DRI12544

Characteristic	Dupilumab 200 mg q.2.w. N = 150	Dupilumab 300 mg q.2.w. N = 157	Placebo N = 158
Mean age, years (SD)	51.0 (13.4)	47.5 (12.4)	49.0 (12.7)
Female, n (%)	96 (64.0)	103 (65.6)	104 (65.8)
Race, n (%)			
White/White	114 (76.0)	129 (82.2)	119 (75.3)
Black/African descent	9 (6.0)	5 (3.2)	9 (5.7)
Asian	25 (16.7)	22 (14.0)	25 (15.8)
American Indian/Alaskan Native	1 (0.7)	0	0
Native Hawaiian/Other Pacific Islander	0	0	0
Other	1 (0.7)	1 (0.6)	5 (3.2)
Mean BMI (SD)	29.72 (5.87)	29.51 (6.37)	29.15 (6.39)
Age at onset of asthma, years, mean (SD)	27.14 (18.42)	27.01 (17.48)	27.02 (18.13)
Time since first diagnosis of asthma, years, mean (SD)	23.95 (15.73)	20.21 (13.43)	21.96 (16.46)
With atopic medical history, n (%)	118 (79.2)	113 (73.4)	119 (77.3)
Ongoing	112 (75.2)	110 (71.4)	113 (73.4)
Smoking history			
Former, n (%)	32 (21.3)	36 (22.9)	34 (21.5)
Never, n (%)	118 (78.7)	121 (77.1)	124 (78.5)
Time since cessation, months, mean (SD)	195.81 (159.14)	155.53 (137.91)	161.35 (133.43)
Pack-years, mean (SD)	4.33 (3.15)	3.88 (3.42)	4.31 (3.13)
Number of asthma exacerbations in the past year, mean (SD)	1.85 (1.43)	2.37 (2.29)	2.27 (2.25)
Number, n (%)			
1	87 (58.0)	72 (45.9)	79 (50.0)
2	27 (18.0)	43 (27.4)	35 (22.2)
3	23 (15.3)	18 (11.5)	19 (12.0)
≥ 4	13 (8.7)	24 (15.3)	25 (15.8)
Number of asthma exacerbations requiring hospitalizations or urgent medical care, past year, mean (SD)	0.57 (0.91)	0.79 (1.47)	0.65 (1.37)
n (%)			
0	93 (62.0)	92 (58.6)	105 (66.5)
1	40 (26.7)	34 (21.7)	33 (20.9)

Characteristic	Dupilumab 200 mg q.2.w. N = 150	Dupilumab 300 mg q.2.w. N = 157	Placebo N = 158
2	7 (4.7)	21 (13.4)	9 (5.7)
3	8 (5.3)	5 (3.2)	5 (3.2)
4	2 (1.3)	1 (0.6)	3 (1.9)
5	0	2 (1.3)	0
6	0	1 (0.6)	1 (0.6)
8	0	0	1 (0.6)
10	0	0	1 (0.6)
FEV_1, L, mean (SD)	1.79 (0.52)	1.85 (0.53)	1.82 (0.55)
FEV_1, % predicted, mean (SD)	61.23 (11.00)	60.76 (10.39)	60.96 (10.72)
FEV_1 reversibility, %, mean (SD)	26.66 (17.50)	27.37 (16.59)	27.94 (14.32)
Mean eosinophils, cells/µL (SD)	360 (350)	320 (250)	340 (300)
Eosinophils, cells/µL, patients n (%)			
Low (< 200)	50 (33.3)	53 (33.8)	57 (36.1)
Medium (200 to 299)	36 (24.0)	39 (24.8)	39 (24.7)
High (≥ 300)	64 (42.7)	65 (41.4)	62 (39.2)
Any atopic medical history, n (%)	118 (79.2)	113 (73.4)	119 (77.3)
Ongoing	112 (75.2)	110 (71.4)	113 (73.4)
Atopic dermatitis history, n (%)	10 (6.7)	16 (10.4)	16 (10.4)
Ongoing	7 (4.7)	13 (8.4)	12 (7.8)
Allergic conjunctivitis history, n (%)	27 (18.1)	29 (18.8)	32 (20.8)
Ongoing	21 (14.1)	27 (17.5)	29 (18.8)
Allergic rhinitis history, n (%)	99 (66.4)	94 (61.0)	102 (66.2)
Ongoing	95 (63.8)	92 (59.7)	99 (64.3)
Chronic rhinosinusitis history, n (%)	23 (15.4)	32 (20.8)	18 (11.7)
Ongoing	19 (12.8)	27 (17.5)	16 (10.4)
Nasal polyposis history, n (%)	25 (16.8)	30 (19.5)	18 (11.7)
Ongoing	18 (12.1)	19 (12.3)	11 (7.1)
Eosinophilic esophagitis history, n (%)	0	1 (0.6)	0
Ongoing	0	1 (0.6)	0
Inhalations of salbutamol or levosalbutamol per 24 hours, mean (SD)	2.98 (2.74)	3.25 (3.15)	2.72 (2.73)
ICS + LABA at baseline, n (%)			
High	75 (52.1)	79 (51.6)	77 (49.7)

Characteristic	Dupilumab 200 mg q.2.w. N = 150	Dupilumab 300 mg q.2.w. N = 157	Placebo N = 158
Medium	69 (47.9)	74 (48.4)	78 (50.3)

BMI = body mass index; FEV_1 = forced expiratory volume in the first second; ICS = inhaled corticosteroid; LABA = long-acting beta2-agonist; q.2.w. = every 2 weeks; SD = standard deviation.

Source: Clinical Study Report for DRI12544.[3]

summarized in this section. A detailed discussion and critical appraisal of the outcome measures is provided in Appendix 4.

The annualized rate of severe asthma exacerbations was the co-primary outcome of QUEST, a key secondary outcome of DRI12544, and a disease-specific outcome of VENTURE. Severe exacerbations were defined as a deterioration in asthma that required the use of systemic corticosteroids for at least 3 days or resulted in hospitalizations or emergency department visits requiring systemic corticosteroids. Severe exacerbations recorded by the investigator were reviewed and verified by the sponsor's clinical team. Data from the electronic diary, spirometry, and electronic case report form were used to confirm that the severe exacerbation was associated with changes in peak flow and pre-bronchodilator FEV_1, use of rescue medication and controllers, nocturnal awakenings due to asthma, or any other relevant signs and symptoms.

Spirometry was performed following American Thoracic Society–European Respiratory Society guidelines. FEV_1 is the maximal amount of air that can be forcefully exhaled in 1 second, and PEF is the maximum flow achieved during an expiration delivered with "maximal force starting from the level of maximal lung inflation." Change from baseline to week 12 was a co-primary outcome of QUEST and a co-primary outcome of DRI12544. In VENTURE, it was assessed across numerous weeks but was not a multiplicity-controlled outcome. Pre-bronchodilator FEV_1 was performed after a washout commensurate with the duration of action of bronchodilators. Spirometry was to be performed at the same time every day, using standardized techniques. The study sites performed the spirometry, and all recordings were transmitted electronically and reviewed centrally. There is only limited evidence with respect to an MID for FEV_1, which has been expressed as an MPPI. The MPPI for FEV_1 was reported as 230 mL from 1 study, with older patients having a lower MPPI than younger patients. For PEF, an MID of 25 L/min has been used in clinical trials previously.[33]

The AQLQ is a disease-specific instrument used to assess health-related quality of life and was administered across all studies. In QUEST the AQLQ global score was a multiplicity-controlled secondary outcome assessed at week 24, in VENTURE it was an "other" outcome assessed at week 24, and in DRI12544 it was a multiplicity-controlled secondary outcome assessed at week 24. The AQLQ includes 32 questions that are grouped into 4 domains: symptoms, activity limitations, emotional function, and environmental stimuli. Each question employs a 7-point scale ranging from 1 (severe impairment) to 7 (no impairment). An overall score is calculated using the mean of all questions, and domain scores are also reported. The MID for the AQLQ is a cut point of 0.5.[34-39]

The EuroQol 5-Dimensions questionnaire (EQ-5D), a generic instrument, was also used to assess health-related quality of life, using various versions: the EuroQol 5-Dimensions 5-Levels questionnaire (EQ-5D-5L) in QUEST and VENTURE, and the EuroQol 5-Dimensions 3-Levels questionnaire (EQ-5D-3L) in DRI12544. The EQ-5D was a non-multiplicity-controlled

outcome. The EQ-5D-5L consists of the EQ-5D descriptive system and the EuroQol Visual Analogue Scale (EQ VAS). The descriptive system includes 5 dimensions — mobility, self-care, usual activities, pain and discomfort, and anxiety and depression — each with 5 levels: level 1 = "no problems," level 2 = "slight problems," level 3 = "moderate problems," level 4 = "severe problems," and level 5 = "extreme problems" or "unable to perform." The EQ-5D-3L has 3 levels in each dimension: "no problems," "some problems," and "extreme problems." Results from the EQ-5D-5L and −3L can be converted into a single index score using a scoring algorithm, and the range of index scores depends on the scoring algorithm used. In all cases, a score of 0 represents the health state "dead" and 1.0 is "perfect health." The EQ VAS records patient self-rated health using a VAS that ranges from 0 ("worst health you can imagine") to 100 ("best health you can imagine"). Respondents are asked to mark an X on the scale at the point that best represents their health on that day. No MIDs for the EQ-5D-5L or −3L were found for asthma. The MID for the EQ-5D-3L ranges from 0.033 to 0.074.[40] The MID for the EQ-5D-5L was 0.056.[41]

The ACQ-5 and Asthma Control Questionnaire, 7-item (ACQ-7) were used to assess symptoms in the included trials. In QUEST, ACQ scores were assessed at weeks 2, 4, 8, 12, 24, 36, and 52, to be completed in each patient's electronic diary at clinic visits. In VENTURE, change from baseline in ACQ-5 scores at weeks 2, 4, 8, 12, 16, 20, and 24 were an "other" outcome (not multiplicity controlled), and in DRI12544 ACQ-5 scores at week 24 were a secondary outcome. The ACQ-7 contains 7 questions, each scored on a 7-point scale. The questions ask about 6 aspects of a patient's previous week: activity limitation, nocturnal waking, shortness of breath, wheezing, symptoms on waking, and use of a short-acting beta2-agonist. The seventh item is a calculated pre-bronchodilator FEV_1 or PEF (percent predicted). The ACQ-7 is calculated as the mean of all 7 components, with scores of 0 indicating well-controlled asthma and those at 6 indicating extremely poor asthma control. The accepted MID for in-person change is 0.5 points,[42-44] and a score of 1.5 on the ACQ is considered most appropriate for discriminating between well-controlled and not well-controlled asthma patients. The ACQ-5 is a shortened version of the ACQ-7, which focuses only on symptoms and excludes FEV_1 and the use of a short-acting beta2-agonist. The MID for the ACQ-5 is 0.5.[44]

The Sino-Nasal Outcomes Test, 22 items (SNOT-22) was used to assess health-related quality of life in patients who had comorbid chronic rhinosinusitis. The SNOT-22 includes 22 questions covering nasal symptoms, sleep, ear and facial discomfort, and emotional symptoms. The score for each question has a range of 0 ("no problem at all") to 5 ("worst possible problem"), and total scores therefore range between 0 and 110. In patients with chronic rhinosinusitis, there is a large range of MIDs, from 8.3 to 17.5, depending on the method used, while a specific estimate of 8.9 has also been used.[45,46]

The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) is used to measure health-related quality of life in patients with rhinoconjunctivitis. It is self-administered and contains 28 questions across 7 domains: activity limitations (3 questions), sleep problems (3 questions), nose symptoms (4 questions), eye symptoms (4 questions), non–nose or eye symptoms (7 questions), practical problems (3 questions), and emotional function (4 questions). It is scored on a scale from 0 (not troubled/none of the time) to 6 (extremely troubled/all the time). The overall RQLQ score is the mean of all 28 responses, and the domain scores are the means of the individual domains. A standardized version of the RQLQ has also been developed, the RQLQ(S). The MID has been established at 0.5 for either the overall score or the individual domains.[47]

Table 12: Summary of Outcomes of Interest Identified in the CADTH Review Protocol

Outcome measure	Hierarchy	Adjusted for multiplicity
QUEST		
Annualized rate of severe exacerbation	Primary	Yes
Change from baseline in pre-bronchodilator FEV_1, week 12	Primary	Yes
Percent change from baseline in pre-bronchodilator FEV_1, week 12	Secondary	Yes
Annualized rate of severe exacerbation events during the 52 weeks, subgroup with eosinophils ≥ 150 cells/μL	Secondary	Yes
Change from baseline in pre-bronchodilator FEV_1, week 12, subgroup with eosinophils ≥ 150 cells/μL	Secondary	Yes
Annualized rate of severe exacerbation events during the 52 weeks, subgroup with eosinophils ≥ 300 cells/μL	Secondary	Yes
Change from baseline in pre-bronchodilator FEV_1, week 12, subgroup with eosinophils ≥ 300 cells/μL	Secondary	Yes
Annualized rate of severe exacerbation events during the 52 weeks, subgroup with eosinophils < 300 cells/μL (testing stopped here)	**Secondary**	**Yes**
Annualized rate of severe exacerbation events during the 52 weeks, subgroup with high-dose ICS at baseline	Secondary	Yes
Change from baseline in pre-bronchodilator FEV_1, week 12, subgroup with high-dose ICS at baseline	Secondary	Yes
Change from baseline in AQLQ global score at week 24, ITT	Secondary	Yes
Change from baseline in AQLQ global score at week 24, subgroup with eosinophils ≥ 300 cells/μL	Secondary	Yes
Change from baseline in ACQ-5 score at week 24, ITT	Secondary	Yes
Annualized rate of severe exacerbation events resulting in hospitalization or emergency department visit during the 52 weeks	Secondary	Yes
Change from baseline in pre-bronchodilator FEV_1, week 12, subgroup with eosinophils < 300 cells/μL	Secondary	Yes
Change from baseline in other lung function measurements: percent predicted FEV_1, morning and evening PEF at weeks 2, 4, 8, 12, 24, 36, and 52	Other secondary	No
ACQ scores (5- and 7-question versions)	Other secondary	No
Morning and/or evening asthma symptom score (patients used a numeric rating scale)	Other secondary	No
Nocturnal awakenings	Other secondary	No
Use of daily puffs of rescue medication	Other secondary	No
Health care resource use	Other secondary	No
EQ-5D-5L	Other secondary	No
SNOT-22 (patients with bilateral nasal polyposis and/or chronic rhinosinusitis)	Other secondary	No

Outcome measure	Hierarchy	Adjusted for multiplicity
RQLQ(S) + 12	Other secondary	No
VENTURE		
LSM percent reduction of OCS dose at week 24	Primary	Yes
Adjusted probability of patients achieving a reduction of ≥ 50% in OCS dose at week 24	Key secondary	Yes
Adjusted probability of patients achieving a reduction of OCS dose to < 5 mg/day at week 24	Key secondary	Yes
Adjusted probability of patients achieving maximum possible reduction of OCS dose per protocol at week 24	Other secondary	Yes
Adjusted probability of patients no longer requiring OCS at week 24	Other secondary	Yes
Annualized rate of severe exacerbation events	Disease specific	No
Time to first severe exacerbation event	Disease specific	No
Change from baseline in pre-bronchodilator FEV_1, weeks 2, 4, 8, 12, 16, 20, and 24	Disease specific	No
Percent change from baseline in pre-bronchodilator FEV_1, weeks 2, 4, 8, 12, 16, 20, and 24	Disease specific	No
Change from baseline in other lung assessments (percent predicted FEV_1, morning and/or evening PEF), weeks 2, 4, 8, 12, 16, 20, and 24	Disease specific	No
Absolute change from baseline in post-bronchodilator FEV_1, weeks 12 and 24	Disease specific	No
Change from baseline in ACQ-5 score at weeks 2, 4, 8, 12, 16, 20, and 24	Disease specific	No
Change from baseline in AQLQ at week 24	Disease specific	No
Annualized rate of severe asthma exacerbations requiring hospitalizations or ED visit	Disease specific	No
Time to first severe asthma exacerbation requiring hospitalization or ED visit	Disease specific	No
SNOT-22 in patients with bilateral nasal polyposis and/or chronic rhinosinusitis	Disease specific	No
EQ-5D-5L	Disease specific	No
Change from baseline at weeks 2, 4, 8, 12, 16, 20, and 24:		
Morning/evening asthma symptom score and nocturnal awakenings (e-diary)	Disease specific	No
Use of rescue medication	Disease specific	No
Health care resource use	Disease specific	No
DRI12544[a]		
Percent change from baseline to week 12 in FEV_1	Primary	See note
Annualized rate of severe exacerbation events during the treatment period	Key secondary	See note

Outcome measure	Hierarchy	Adjusted for multiplicity
Time to severe exacerbation event	Key secondary	See note
Change from baseline in ACQ-5 global score, week 12	Key secondary	See note
Change from baseline in AQLQ global score, week 12	Key secondary	See note

ACQ = Asthma Control Questionnaire; ACQ-5 = Asthma Control Questionnaire, 5-item; AQLQ = Asthma Quality of Life Questionnaire; ED = emergency department; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; FEV_1 = forced expiratory volume in the first second; ICS = inhaled corticosteroid; ITT = intention to treat; LSM = least squares mean; OCS = oral corticosteroid; PEF = peak expiratory flow; RQLQ(S) + 12 = Standardized Rhinoconjunctivitis Quality of Life Questionnaire, ages 12 + ; SNOT-22 = Sino-Nasal Outcomes Test, 22 items.

[a]For DRI12544, there was originally no accounting for multiplicity for outcomes; rather, the focus for multiplicity was on testing multiple doses within each end point. After a number of regulatory bodies agreed to consider DRI12544 as a pivotal study, the multiplicity approach used for the QUEST study was adopted.

Source: Clinical Study Report for QUEST,[1] VENTURE,[2] DRI12544.[3]

Statistical Analysis

Primary Outcomes of the Studies

Power Calculation

In QUEST, the sample size was calculated based on a comparison between dupilumab 300 mg every 2 weeks and placebo with respect to the 2 primary outcomes. Originally, at least 1,638 patients were to be randomized, with at least 690 patients with blood eosinophils greater than or equal to 300 cells/µL. Recruitment for patients on medium-dose ICS was stopped at approximately 819 to ensure that at least 50% would be on high-dose ICS. A protocol amendment added another 220 patients to provide additional exposure to dupilumab with the intended commercial process and stipulated that the data cut-off for the primary analysis would occur when the originally planned 1,638 patients completed the 52-week treatment period. In VENTURE, for the primary outcome (percent reduction from baseline of OCS dose at week 24), the sponsor assumed a standard deviation of 50% and 90 patients randomized per group, yielding 94% power to detect a treatment difference of 27% at the 2-tailed significance level of alpha = 0.05. For the key secondary outcome (patients achieving a 50% reduction from baseline to week 24 in OCS dose while maintaining asthma control), with a sample of 90 patients per group, there was 81% power to detect a difference (at a 2-sided alpha of 0.05), assuming proportions of 54% with dupilumab and 33% with placebo. In DRI12544, sample size was based on the primary outcome (change from baseline to week 12 in FEV_1 in the high-eosinophil population). The outcome was calculated using a common standard deviation of 0.35 (based on data from the ACT11457 study), a 0.2 L mean difference between the highest dupilumab dose and placebo for the primary outcome, and a t-test with a 2-sided significance of 5% and 83% power. The expected percentage of early withdrawals was 10%, and high-eosinophil patients were expected to make up 40% of the population.

Statistical Test or Model

In QUEST, the annualized rate of severe asthma exacerbations was analyzed using a negative binomial regression model, which included the total number of events occurring during the observation period (response variable) with the 4 treatment groups, age, region (pooled country), baseline eosinophil stratum, baseline ICS dose, and number of severe exacerbation events within 1 year before the study as covariates. The log-transformed duration of observation was the offset variable. In this primary approach, off-treatment measurements of patients who prematurely discontinued treatment were included in the analysis, with all severe exacerbation events that happened up until week 52 included in the analysis, regardless of whether the patient was on treatment.

In VENTURE, the primary efficacy outcome was assessed using analysis of covariance; the model included the percent reduction in the response variable, and the treatment groups, optimized OCS at baseline, regions (pooled countries), and baseline eosinophil level subgroups (< 150 cells/μL, ≥ 150 cells/μL) were covariates. Missing data were handled using pattern mixture modelling–multiple imputation (PMM-MI). In DRI12544, analysis of the primary outcome used a mixed-effect model with repeated measures (MMRM) analysis and included change from baseline to week 12 as response variables, and factors (fixed effect) for treatment, baseline eosinophil strata, pooled countries or regions, visit, treatment-by-visit interaction, FEV_1 baseline value, and baseline-by-visit interaction. An unstructured correlation matrix was used to model the within-patient errors, and parameters were estimated using the restricted maximum likelihood method with the Newton-Raphson algorithm. No imputation for missing data was performed for the MMRM. FEV_1 measurements that were collected while patients were using systemic corticosteroids (for exacerbations), plus 30 days, were excluded from the analysis.

Multiplicity

In QUEST, a hierarchical testing procedure was used to account for multiple statistical comparisons, where each hypothesis was only formally tested if the preceding 1 was statistically significant at the 5% alpha level. The hierarchy for the co-primary outcomes went in this order: (i) annualized exacerbation rate for 300 mg every 2 weeks versus placebo, (ii) absolute change from baseline in FEV_1 at week 12 for 300 mg every 2 weeks versus placebo, (iii) annualized severe exacerbation rate for 200 mg every 2 weeks versus placebo, (iv) absolute change from baseline in FEV_1 at week 12 for 200 mg every 2 weeks versus placebo. Multiple secondary outcomes were also assessed in a hierarchical fashion, summarized in Table 13. VENTURE and DRI12544 followed a similar hierarchical testing procedure, although the number of outcomes tested in the hierarchy in VENTURE was much smaller than in QUEST. The statistical hierarchy in DRI12544 was planned after the interim analysis, in response to feedback from the EMA, and as a result the Health Canada reviewers report determined statistical claims beyond the primary outcome to be "not permissible."[27]

Subgroup Analyses

In QUEST, pre-specified subgroups of relevance to our protocol included baseline blood eosinophils (≥ 300 cells/μL, < 300 cells/μL; ≥ 150 cells/μL, < 150 cells/μL). These subgroups were analyzed for the primary outcome of annualized rate of severe asthma events during the 52-week treatment period. Treatment by subgroup interaction and P values were derived from a negative binomial model. The total number of events that occurred during the observation period was the response variable, and the 4 treatment groups, age, region (pooled country), baseline eosinophil strata, baseline ICS dose, number of severe exacerbation events within 1 year before the study, subgroup (if different than the aforementioned covariates), and treatment by subgroup interaction were covariates. The log-transformed observation duration was the offset variable. If quantitative treatment by subgroup interaction was detected with a nominal P value less than 0.05 for any subgroup factor, the Gail-Simon test was to be performed to evaluate possible qualitative interaction. Subgroup analyses for baseline eosinophils (≥ 300 cells/μL, < 300 cells/μL) were also tested as part of the statistical hierarchy and thus were controlled for multiplicity. In VENTURE, subgroup analyses were performed for the primary outcome based on the same baseline eosinophil strata as QUEST. An analysis of covariance model that incorporated subgroup-by-treatment interactions was built for each subgroup factor and included all the covariates in the main statistical model plus the subgroup variable (if not 1 of the covariates adjusted in the main model) and the subgroup-

by-treatment interaction. In DRI12544, the high-eosinophil subgroup (blood eosinophils ≥ 300 cells/μL) was the primary population for efficacy analyses.

Sensitivity Analyses

QUEST included an analysis to assess efficacy in patients who adhered to therapy, using a similar negative binomial model with the same covariates as in the primary analysis. Sensitivity analyses for missing data included PMM-MI, control-based PMM-MI, and tipping point analyses. To examine the potential impact of loading dose on response, sensitivity analyses were conducted that excluded severe exacerbation events that occurred during the first 4 weeks and the first 12 weeks of randomization. Only on-treatment events were included in this analysis. For FEV_1, sensitivity analyses were also conducted for patients who adhered to therapy, and on-treatment FEV_1 measurements were analyzed using an MMRM similar to the primary analyses, including the same set of covariates and estimation algorithm. A sensitivity analysis was also performed to account for potential confounding from use of systemic corticosteroids to treat asthma exacerbations. Sensitivity analyses for missing data also included a PMM-MI, a control-based PMM-MI, and a tipping point analysis. In VENTURE, for the primary outcome, sensitivity analyses for missing data for the primary outcome was conducted using PMM-MI and also "worst of the last 2 observations carried forward," as well as tipping point analysis. For the key secondary outcomes, for missing data a control-based PMM-MI, an analysis where discontinuations were counted as nonresponders, and the main logistic regression model were applied to the complete dataset. In DRI12544, analyses for the primary outcome, FEV_1, were conducted and included all measurements regardless of systemic corticosteroid use, as well as excluding all FEV_1 measurements collected on or after the first day of systemic corticosteroid use. Additional sensitivity analyses for the primary outcome included PMM-MI and control-based PMM. For secondary outcomes, any events occurring on study were included in the analysis, regardless of whether the patient remained on treatment or not. For missing data, a PMM and control-based PMM were performed, as well as a tipping point analysis.

Secondary Outcomes of the Studies

In QUEST, absolute change from baseline in FEV_1 at week 12 was analyzed using an MMRM and included change from baseline in pre-bronchodilator FEV_1 values up to week 12 as the response variable and treatment, age, sex, baseline height, region (pooled country), baseline eosinophil stratum, baseline ICS dose, visit, visit-by-treatment interaction, baseline pre-bronchodilator FEV_1 value, and baseline-by-visit interaction as covariates. For patients who discontinued the study drug before week 12, any off-treatment FEV_1 measurements up to week 12 were included in the analysis. Other continuous outcomes such as ACQ-5 and AQLQ at week 24 were analyzed using MMRM, including change from baseline up to week 24 as response variables, regardless of the patient's treatment status when the outcome was measured.

Key secondary dichotomous outcomes in VENTURE, such as patients achieving a 50% or greater reduction in OCS dose or patients achieving reduction in dose to less than 5 mg/day, were analyzed using a logistic regression with the binary status of whether or not the patient achieved the corresponding dose reduction criterion as the response variable and with treatment groups, optimized OCS dose at baseline, regions (pooled countries), and baseline eosinophil level subgroups as covariates. In DRI12544, the annualized rate of severe exacerbations was a key secondary outcome and a negative binomial regression model was used, with the total number of events as the response variable, and treatment group, baseline eosinophil strata, pooled countries or regions, and number of asthma exacerbations

in the year before study as covariates; the log-transformed observation duration was the offset variable.

Analysis Populations

Across the studies, the efficacy populations were the intention-to-treat population, analyzed according to the group to which the patients were randomized. The safety population included all patients who received at least 1 dose of the study drug. In DRI12544, the primary efficacy analysis population was originally the high-eosinophil population, or those with baseline blood eosinophils greater than or equal to 300 cells/μL. After advice from the EMA after the interim analysis, the intention-to-treat population became the primary analysis population.

Results

Patient Disposition

Study discontinuations ranged from 4% to 7% in the 52-week QUEST study to 0% to 1% in VENTURE and 5% to 8% in DRI12544. The most common reason for discontinuing a study was adverse event (Table 14, Table 15, Table 16). There were no clear numerical differences between groups within studies for overall withdrawal.

Exposure to Study Treatments

The duration of study treatment was similar for dupilumab 200 mg and matched placebo in QUEST, and numerically lower for dupilumab 300 mg versus matched placebo (333.4 days versus 344.4 days). In VENTURE and in DRI12544, treatment duration was similar for dupilumab and placebo.

Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported here. See Appendix 3 for detailed efficacy data.

Mortality

There were 5 deaths in the dupilumab groups and 3 deaths in the placebo group in QUEST. In DRI12544, there were 2 deaths in dupilumab patients, both at the 300 mg dose, and none with placebo. There were no deaths in VENTURE.

Asthma Exacerbations

The annualized rate of severe exacerbations was the primary outcome in QUEST. At the 200 mg dose, the annualized rate of severe asthma exacerbations was 0.456 with dupilumab versus 0.871 with placebo, for an RR of 0.523 (95% CI, 0.413 to 0.662; P < 0.0001). At the 300 mg dose, it was 0.524 versus 0.970 for placebo, for an RR of 0.540 (95% CI, 0.430 to 0.680; P < 0.0001). Similar results were seen in VENTURE: 0.649 in the dupilumab group (95% CI, 0.442 to 0.0955) and 1.597 in the placebo group (95% CI, 1.248 to 2.043), for an RR versus placebo of 0.407 (95% CI, 0.263 to 0.630; P < 0.0001). Similar results were also seen in the DRI12544 study, with an RR versus placebo in the dupilumab 200 mg group of 0.300 (95% CI, 0.159 to 0.565; P = 0.0002) and in the dupilumab 300 mg group of 0.295 (95% CI, 0.159 to 0.546; P = 0.0001).

In QUEST, in the subgroup of patients based on baseline eosinophil count, larger improvements in severe exacerbation rates were seen in those with higher baseline eosinophils (> 300 cells/μL) at the 200 mg dose, with an RR of 0.342 (95% CI, 0.244 to 0.480;

Table 13: Statistical Analysis of Efficacy End Points

End point	Statistical model	Adjustment factors	Sensitivity analyses
QUEST			
Annualized rate of severe asthma exacerbations	Negative binomial regression model	Total number of events occurring during observation period (response variable) Four treatment groups, age, region (pooled country), baseline eosinophil stratum, baseline ICS dose, number of severe exacerbation events within 1 year before study as covariates Log-transformed duration of observation as the offset variable	Analysis performed in patients who adhered to therapy, using a similar negative binomial model with the same covariates as the primary analysis Sensitivity analysis for missing data included PMM-MI, control-based PMM-MI, and tipping point analyses To account for the potential effect of loading dose on response, sensitivity analyses were conducted that excluded severe exacerbation events that occurred during the first 4 weeks and the first 12 weeks of randomization
Absolute change from baseline in FEV_1 at week 12	MMRM	Change from baseline in pre-bronchodilator FEV_1 to week 12 as response variable Treatment, age, sex, baseline height, region (pooled country), baseline eosinophil stratum, baseline ICS dose, visit, visit-by-treatment interaction, baseline pre-bronchodilator FEV_1 value, and baseline-by-visit interaction as covariates	As above, sensitivity analysis conducted in those who adhered to therapy Sensitivity analysis performed to account for the potential confounding from use of systemic corticosteroids to treat exacerbations Missing data, as above (PMM-MI, control-based PMM-MI, and tipping point)
VENTURE			
Percent reduction in investigator-prescribed OCS dose at week 24 while maintaining asthma control	ANCOVA	Percent reduction in OCS dose (response variable) Treatment groups, optimized OCS dose at baseline, regions (pooled countries), and baseline eosinophil level subgroups (< 150 cells/μL, ≥ 150 cells/μL) as covariates	Missing data were handled using PMM-MI Also “worse of the last 2 observations carried forward” and tipping point analysis

End point	Statistical model	Adjustment factors	Sensitivity analyses
Key secondary: Patients achieving a ≥ 50% reduction in OCS dose Patients achieving a reduction in OCS dose to < 5 mg/day	Logistic regression model	Binary status of whether or not a patient achieved the corresponding OCS reduction criterion as response variable Treatment groups, optimized OCS dose at baseline, regions (pooled countries), and baseline eosinophil level subgroups (< 150 cells/μL or ≥ 150 cells/μL) as covariates	For missing data, a control-based PMM-MI, an analysis where discontinuation = nonresponders, and the main logistic regression model were applied to the complete dataset On-treatment analysis: for those who permanently discontinued treatment but continued to be followed, data collected after treatment discontinuation were not used; rather, imputed data from the on-treatment analysis were used
DRI12544			
Change from baseline to week 12 in FEV_1	MMRM	Change from baseline to week 12 (response variable) Factors (fixed effects) for treatment, baseline eosinophil strata, pooled countries or regions, visit, treatment-by-visit interaction, FEV_1 baseline value, and baseline-by-visit interaction	MMRM including all FEV_1 measurements regardless of use of systemic corticosteroids Excluding all FEV_1 measurements collected on or after first day of systemic corticosteroid use Using all on-study data, regardless of whether the patient was on treatment PMM-MI Control-based PMM

End point	Statistical model	Adjustment factors	Sensitivity analyses
Annualized rate of severe exacerbations	Negative binomial regression model	Total number of confirmed events as response variable Treatment group, baseline eosinophil strata, pooled countries or regions, and number of asthma exacerbations in year before study as covariates Log-transformed observation duration as the offset variable	24 weeks on-study data: if patient discontinued study treatment, events happening during the post-treatment period (within 24 weeks of randomization) were included in the analysis PMM: for patients who discontinued study, events happening during the post-study period within 24 weeks of randomization were replaced by the mean of the number of observed events occurring during the same time period in patients in the same treatment group and with the same missing pattern Control-based PMM: as above, but observed events in placebo were used to impute number of events happening after study discontinuation for each treatment group Tipping point analysis

ANCOVA = analysis of covariance; FEV_1 = forced expiratory volume in the first second; ICS = inhaled corticosteroid; MMRM = mixed-effect model with repeated measures; OCS = oral corticosteroid; PMM-MI = pattern mixture modelling–multiple imputation.

Source: Clinical Study Report for QUEST,[1] VENTURE,[2] DRI12544.[3]

Table 14: Patient Disposition: QUEST

Characteristic	Dupilumab 200 mg q.2.w.	Placebo	Dupilumab 300 mg q.2.w.	Placebo
Screened, N	4,148			
Screen failures, n	2,246			
Randomized, N	631	317	633	321
Randomized and treated, n (%)	629 (99.7)	315 (99.4)	632 (99.8)	321 (100)
Completed treatment, n (%)	487 (77.2)	230 (72.6)	469 (74.1)	248 (77.3)
Ongoing treatment, n (%)	72 (11.4)	47 (14.8)	78 (12.3)	38 (11.8)
Discontinued treatment, n (%)	**70 (11.1)**	**38 (12.0)**	**85 (13.4)**	**35 (10.9)**
Treatment discontinued per patient request	54 (8.6)	24 (7.6)	51 (8.1)	27 (8.4)
Reason for study treatment discontinuation				
Adverse event	21 (3.3)	19 (6.0)	46 (7.3)	10 (3.1)
Lack of efficacy	4 (0.6)	3 (0.9)	3 (0.5)	5 (1.6)
Poor compliance to protocol	3 (0.5)	4 (1.3)	1 (0.2)	3 (0.9)
Other reason	42 (6.7)	12 (3.8)	35 (5.5)	17 (5.3)
Completed randomized treatment period	535 (84.8)	256 (80.8)	523 (82.6)	273 (85.0)
Discontinued study before week 52, n (%)	**28 (4.4)**	**17 (5.4)**	**41 (6.5)**	**17 (5.3)**
Per patient request	23 (3.6)	14 (4.4)	31 (4.9)	16 (5.0)
Reason for study discontinuation before week 52				
Adverse event	4 (0.6)	8 (2.5)	12 (1.9)	0
Poor compliance to protocol	1 (0.2)	1 (0.3)	2 (0.3)	2 (0.6)
Other reason	23 (3.6)	8 (2.5)	27 (4.3)	15 (4.7)
Continued into LTS12551 study, n (%)	**444 (70.4)**	**215 (67.8)**	**429 (67.8)**	**229 (71.3)**

Characteristic	Dupilumab 200 mg q.2.w.	Placebo	Dupilumab 300 mg q.2.w.	Placebo
Patients who did not continue into LTS12551				
Ongoing in follow-up period	40 (6.3)	13 (4.1)	33 (5.2)	16 (5.0)
Completed follow-up period	32 (5.1)	20 (6.3)	44 (7.0)	19 (5.9)
Discontinued from follow-up period	41 (6.5)	20 (6.3)	48 (7.6)	19 (5.9)
Study discontinuation per patient request	33 (5.2)	16 (5.0)	37 (5.8)	16 (5.0)
Reason for study discontinuation				
Adverse event	8 (1.3)	9 (2.8)	14 (2.2)	1 (0.3)
Poor compliance to protocol	1 (0.2)	1 (0.3)	2 (0.3)	2 (0.6)
Other reason	32 (5.1)	10 (3.2)	32 (5.1)	16 (5.0)
Efficacy population, n (%)	631 (100)	317 (100)	633 (100)	321 (100)
Safety population, n (%)	631 (100)	313 (98.7)	632 (99.8)	321 (100)

q.2.w = every 2 weeks.

Source: Clinical Study Report for QUEST.[1]

P < 0.0001), and at the 300 mg dose, with RR of 0.326 (95% CI, 0.234 to 0.454; P < 0.0001), than in those with lower baseline eosinophils (200 mg dose: 0.759 [95% CI, 0.548 to 1.052; P = 0.0975]; 300 mg dose: 0.834 [95% CI, 0.608 to 1.144; P = 0.2599])(Table 47).

Hospitalizations or Emergency Visits due to Asthma Exacerbations

Annualized rate of severe exacerbations resulting in hospitalizations or emergency department visits was a secondary outcome of QUEST. There was no statistically significant difference in adjusted exacerbation rates between dupilumab and placebo in either the 200

Table 15: Patient Disposition: VENTURE

Characteristic	Dupilumab 300 mg q.2.w.	Placebo
Screened, N	390	
Screen failures, n	180	
Randomized, N	103	107
Randomized and treated, N	103	107
Completed the randomized treatment period regardless of whether on treatment or not, n	**101**	**102**
Discontinued study treatment, n (%)	**2 (1.9)**	**5 (4.7)**
Treatment discontinuation per patient request	2 (1.9)	1 (0.9)
Reason for treatment discontinuation		
Adverse event, n,(%)	1 (1.0)	4 (3.7)
Other reason, n (%)	1 (1.0)	1 (0.9)
Discontinued study, n (%)	**1 (1.0)**	**0**
Per patient request, n(%)	1 (1.0)	0
Continued into LTS12551 study, n (%)	**92 (89.3)**	**97 (90.7)**
Patients who did not continue into LTS12551		
Ongoing in follow-up period, n(%)	1 (1.0)	5 (4.7)
Completed the follow-up period, n(%)	7 (6.8)	5 (4.7)
Discontinued from the follow-up period, n(%)	3 (2.9)	0
Study discontinuation per patient request, n(%)	2 (1.9)	0
Reason for study discontinuation		
Adverse event, n(%)	1 (1.0)	0
Poor compliance to protocol, n(%)	1 (1.0)	0
Other reason, n(%)	1 (1.0)	0
Intention to treat, n(%)	103 (100)	107 (100)
Safety, n (%)	103 (100)	107 (100)

q.2.w = every 2 weeks.

Source: Clinical Study Report for VENTURE.[2]

mg (RR versus placebo of 0.468 [0.196 to 1.118; P = 0.0874]) or 300 mg (RR versus placebo of 0.653 [0.199 to 2.144; P = 0.4711]) dose groups. Similarly, in VENTURE, there was no statistically significant difference in the annualized rate of severe exacerbations resulting in hospitalizations or emergency department visits over 24 weeks, with an RR versus placebo of 0.577 (95% CI, 0.161 to 2.071; P = 0.3972).

Use of OCSs

Percent reduction in OCS dose was the primary outcome of VENTURE. The LSM (SE) percent reduction from baseline in the dupilumab group was 70.09% (4.90) and in placebo was

Table 16: Patient Disposition: DRI12544

Characteristic	Dupilumab 200 mg q.2.w.	Dupilumab 300 mg q.2.w.	Placebo
Screened, N	1,532		
Screen failures, n	756		
Randomized, N	150	157	158
Randomized and treated, n (%)	148 (98.7)	156 (99.4)	158 (100)
Completed 12-week study treatment period, n (%)	141 (94.0)	149 (94.9)	153 (96.8)
Completed study treatment period, n (%)	137 (91.3)	149 (94.9)	146 (92.4)
Discontinued study treatment period, n (%)	11 (7.3)	7 (4.5)	12 (7.6)
Treatment discontinued per patient request	3 (2.0)	5 (3.2)	2 (1.3)
Reason for study treatment discontinuation			
Adverse event	6 (4.0)	4 (2.5)	5 (3.2)
Lack of efficacy	0	0	1 (0.6)
Poor compliance to protocol	2 (1.3)	0	3 (1.9)
Other reason	3 (2.0)	3 (1.9)	3 (1.9)
Completed study period	141 (94.0)	147 (93.6)	147 (93.0)
Discontinued study period	7 (4.7)	9 (5.7)	11 (7.0)
Patient request for study discontinuation	5 (3.3)	7 (4.5)	7 (4.4)
Reason for study discontinuation			
Adverse event	1 (0.7)	3 (1.9)	2 (1.3)
Poor compliance to protocol	0	0	1 (0.6)
Other reason	6 (4.0)	6 (3.8)	8 (5.1)
Analysis populations			
ITT, N	150	157	158
HEos ITT, n (%)	65 (43.3)	64 (40.8)	68 (43.0)
Safety, n (%)	148 (98.7)	156 (99.4)	158 (100)

HEos = high eosinophil; ITT = intention to treat; q.2.w. = every 2 weeks.
Source: Clinical Study Report for DRI12544.[3]

41.85% (4.57), for an LSM difference between groups of 28.24% (95% CI, 15.81 to 40.67; P < 0.0001). The absolute reduction in OCS dose was an LSM (SE) of 7.58 mg/day (0.58) with dupilumab and 4.77 mg/day (0.54) with placebo, for an LSM difference between groups of 2.81 mg/day (95% CI, 1.33 to 4.29; P = 0.0002).

A secondary outcome of VENTURE was the proportion of patients with a 50% or greater reduction in OCS dose compared to baseline, and at week 24 this had been achieved by 81.0% of dupilumab patients and 53.3% of placebo patients, for an odds ratio of 3.98 (95% CI, 2.06 to 7.67; P < 0.0001). The proportion of patients achieving a reduction of OCS dose to less than 5 mg/day at week 24 was another secondary outcome, and by week 24 72.9% had reached this reduction with dupilumab and 37.4% with placebo, for an odds ratio of 4.48 (95% CI, 2.39 to 8.39; P < 0.0001). An "other" secondary outcome was the proportion of patients no longer requiring OCS at week 24, and with dupilumab this was 48% and with placebo 25%, for an odds ratio of 2.74 (95% CI, 1.47 to 5.10; P = 0.0015).

Table 17: Duration of Study Treatment

	Dupilumab		Placebo	
Study	Mean Duration, Days (SD)	N	Mean Duration, Days (SD)	N
QUEST 200 mg	340.4 (73.9)	631	337.3 (75.5)	313
QUEST 300 mg	333.4 (83.8)	632	344.4 (64.7)	321
VENTURE	166.1 (17.8)	103	165.1 (18.4)	107
DRI12544 200 mg	161.7 (27.3)	148	161.7 (25.7)	158
DRI12544 300 mg	162.1 (28.8)	156		

SD = standard deviation.

Source: Clinical Study Report for QUEST,[1] VENTURE,[2] DRI12544.[3]

Table 18: Annualized Rate of Severe Asthma Exacerbations

	Dupilumab		Placebo			Follow up
Study	Rate (95% CI)	N	Rate (95% CI)	N	RR (95% CI; P value)	(weeks)
QUEST 200 mg	0.456 (0.389 to 0.534)	631	0.871 (0.724 to 1.048)	317	0.523 (0.413 to 0.662; < 0.0001)	52
QUEST 300 mg	0.524 (0.450 to 0.611)	633	0.970 (0.810 to 1.160)	321	0.540 (0.430 to 0.680; < 0.0001)	52
VENTURE	0.649 (0.442 to 0.096)	103	1.597 (1.248 to 2.043)	107	0.407 (0.263 to 0.630; < 0.0001)	24
DRI12544 200 mg	0.269 (0.157 to 0.461)	148	0.897 (0.619 to 1.300)	158	0.300 (0.159 to 0.565; 0.0002)	24
DRI12544 300 mg	0.265 (0.157 to 0.445)	156	0.897 (0.619 to 1.300)	158	0.295 (0.159 to 0.546; 0.0001)	24

CI = confidence interval; RR = relative risk.

Note: QUEST: RR and P value derived using negative binomial model, with total number of events onset from randomization to visit 18 or last contact date (whichever comes earlier) as the response variable, and with the 4 treatment groups, age, region (pooled country), baseline eosinophil strata, baseline inhaled corticosteroid dose level, and number of severe exacerbation events within 1 year before the study as covariates, and log-transformed standardized observation duration as the offset variable.

Source: Clinical Study Report for QUEST,[1] VENTURE,[2] DRI12544.[3]

Health-Related Quality of Life

Health-related quality of life was assessed using the AQLQ in each of the studies. AQLQ global scores were increased (improved) across all studies. In QUEST, the LSM difference between dupilumab 200 mg and placebo after 24 weeks was 0.20 (95% CI, 0.06 to 0.34) and between dupilumab 300 mg and placebo was 0.15 (95% CI, 0.01 to 0.28). In VENTURE, after 24 weeks the LSM difference between dupilumab and placebo was 0.35 (95% CI, 0.09 to 0.62) and in DRI12544 between dupilumab 200 mg and placebo was 0.31 (95% CI, 0.08 to 0.55) and between dupilumab 300 mg and placebo was 0.36 (95% CI, 0.12 to 0.59). In QUEST, a responder analysis was reported, with patients who achieved an increase from baseline of at least 0.5 (the MID for the AQLQ is 0.5), and at 24 weeks in the dupilumab 200 mg group 63.7%

Table 19: Annualized Rate of Severe Asthma Exacerbations Leading to Hospitalizations or ED Visits

Study	Dupilumab		Placebo		RR (95% CI; P value)	Follow-up (weeks)
	Rate (95% CI)	N	Rate (95% CI)	N		
QUEST 200 mg	0.024 (0.013 to 0.044)	631	0.051 (0.027 to 0.099)	317	0.468 (0.196 to 1.118; 0.0874)	52
QUEST 300 mg	0.011 (0.005 to 0.025)	633	0.017 (0.007 to 0.042)	321	0.653 (0.199 to 2.144; 0.4711)	52
VENTURE	0.114 (0.040 to 0.328)	103	0.198 (0.086 to 0.457)	107	0.577 (0.161 to 2.071; 0.3972)	24

CI = confidence interval; ED = emergency department; RR = relative risk.

Note: QUEST: Derived using negative binomial model with the total number of events onset from randomization up to visit 18 or last contact date (whichever comes earlier) as the response variable, and with the 4 treatment groups, age, region (pooled country), baseline eosinophil strata, baseline inhaled corticosteroid dose level, and number of severe exacerbation events within 1 year before the study as covariates, and log-transformed standardized observation duration as an offset variable.

Source: Clinical Study Report for QUEST,[1] VENTURE.[2]

Table 20: AQLQ Global Score, Change From Baseline

Study	Dupilumab			Placebo			Between-group LSM difference (95% CI; P value)	Follow up (weeks)
	Baseline, mean (SD)	Change, LSM (SE)	N	Baseline, mean (SD)	Change, LSM (SE)	N		
QUEST 200 mg	4.31 (1.08)	1.14 (0.04)	560	4.26 (1.02)	0.94 (0.06)	281	0.20 (0.06 to 0.34; 0.0039)	24
QUEST 300 mg	4.28 (1.05)	1.15 (0.04)	569	4.30 (1.03)	1.00 (0.06)	295	0.15 (0.01 to 0.28; 0.0298)	24
VENTURE	4.38 (1.24)	0.89 (0.10)	100	4.31 (1.12)	0.54 (0.10)	98	0.35 (0.09 to 0.62)	24
DRI12544 200 mg	4.03 (1.15)	1.20 (0.09)	132	4.12 (1.10)	0.88 (0.09)	127	0.31 (0.08 to 0.55; 0.0090)	24
DRI12544 300 mg	3.91 (1.13)	1.24 (0.08)	141	4.12 (1.10)	0.88 (0.09)	127	0.36 (0.12 to 0.59; 0.0027)	24

AQLA = Asthma Quality of Life Questionnaire; CI = confidence interval; LSM = least squares mean; SD = standard deviation; SE = standard error.

Note: QUEST: LSM difference (AQLQ) derived from a mixed-effect model with repeated measures, with change from baseline up to week 24 as the response variable, and treatment, age, region (pooled country), baseline eosinophil strata, baseline inhaled corticosteroid dose level, visit, treatment-by-visit interaction, baseline score, and baseline-by-visit interaction as covariates.

Source: Clinical Study Report for QUEST,[1] VENTURE,[2] DRI12544.[3]

of patients achieved this response, versus 57.1% in the placebo group (RR = 1.48; 95% CI, 1.09 to 1.99). At the dupilumab 300 mg dose, 66.2% of patients achieved this response, versus 64.8% of patients in the placebo group (RR = 1.16; 95% CI, 0.86 to 1.57). Results for all these outcomes were tested outside of the statistical hierarchy.

EQ-5D-5L and EQ-5D-3L scores increased (improved) from baseline in both groups across all studies. In QUEST, after 52 weeks the LSM difference between dupilumab 200 mg and placebo was 0.03 (95% CI, 0.01 to 0.06) and between dupilumab 300 mg and placebo was 0.01 (95% CI, −0.01 to 0.04). In VENTURE, after 24 weeks the LSM difference between dupilumab and placebo was 0.01 (95% CI, −0.03 to 0.06), and in DRI12544 for the EQ-5D-3L after 24 weeks between dupilumab 200 mg and placebo, it was 0.00 (95% CI, −0.04 to 0.04) and between dupilumab 300 mg and placebo was 0.03 (95% CI, −0.01 to 0.07). Neither the EQ-5D-5L scores nor the EQ-5D-3L scores met the MID for these instruments, of 0.056 and 0.033 to 0.074, respectively, although neither of these MIDs are specific to asthma. Results for this outcome were tested outside of the statistical hierarchy.

EQ VAS scores were reported in QUEST and in VENTURE. In QUEST, the LSM difference between dupilumab 200 mg and placebo after 52 weeks was 3.30 (95% CI, 0.96 to 5.63) and for dupilumab 300 mg versus placebo was 2.68 (95% CI, 0.40 to 4.96). In VENTURE, after 24 weeks the LSM difference between dupilumab and placebo was 5.78 (95% CI, 1.67 to 9.90). Results for this outcome were tested outside of the statistical hierarchy.

Table 21: EQ-5D-5L or EQ-5D-3L Index Score, Change From Baseline

	Dupilumab			Placebo				
Study	Baseline, mean (SD)	Change, LSM (SE)	N	Baseline, mean (SD)	Change, LSM (SE)	N	Between-group LSM difference (95% CI; P value)	Follow up (weeks)
EQ-5D-5L								
QUEST 200 mg	0.74 (0.19)	0.10 (0.01)	457	0.74 (0.18)	0.07 (0.01)	220	0.03 (0.01 to 0.06; 0.0133)	52
QUEST 300 mg	0.74 (0.19)	0.10 (0.01)	448	0.74 (0.19)	0.09 (0.01)	238	0.01 (−0.01 to 0.04; 0.2896)	52
VENTURE	0.74 (0.18)	0.06 (0.02)	98	0.72 (0.19)	0.04 (0.02)	100	0.01 (−0.03 to 0.06; 0.5518)	24
EQ-5D-3L								
DRI12544 200 mg	0.80 (0.19)	0.06 (0.01)	131	0.78 (0.20)	0.06 (0.01)	127	0.00 (−0.04 to 0.04; 0.9299)	24
DRI12544 300 mg	0.78 (0.19)	0.09 (0.01)	139	0.78 (0.20)	0.06 (0.01)	127	0.03 (−0.01 to 0.07; 0.1316)	24

CI = confidence interval; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels questionnaire; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; LSM = least squares mean; SD = standard deviation; SE = standard error.

Note: QUEST: Derived from mixed-effect model with repeated measures, with change from baseline in EQ-5D-5L single index score up to week 52 as the response variable, and treatment, age, region (pooled country), baseline eosinophil strata, baseline inhaled corticosteroid dose level, visit, treatment-by-visit interaction, baseline EQ-5D-5L single index score, and baseline-by-visit interaction as covariates.

Source: Clinical Study Report for QUEST,[1] VENTURE,[2] DRI12544.[3]

Table 22: EQ VAS, Change From Baseline

Study	Dupilumab			Placebo				
	Baseline, mean (SD)	Change, LSM (SE)	N	Baseline, mean (SD)	Change, LSM (SE)	N	Between-group LSM difference (95% CI; P value)	Follow up (weeks)
QUEST 200 mg	65.32 (17.62)	12.37 (0.70)	457	66.03 (16.16)	9.07 (0.99)	220	3.30 (0.96 to 5.63; 0.0057)	52
QUEST 300 mg	66.12 (17.71)	12.11 (0.70)	448	65.62 (18.44)	9.43 (0.95)	238	2.68 (0.40 to 4.96; 0.0213)	52
VENTURE	63.29 (17.23)	10.22 (1.60)	98	64.21 (18.15)	4.43 (1.50)	100	5.78 (1.67 to 9.90; 0.0061)	24
DRI12544 200 mg	NR	NR		NR	NR		NA	24
DRI12544 300 mg	NR	NR		NR	NR		NA	24

CI = confidence interval; EQ VAS = EuroQol Visual Analogue Scale; LSM = least squares mean; NA = not applicable; NR = not reported; SD = standard deviation; SE = standard error.

Source: Clinical Study Report for QUEST,[1] VENTURE,[2] DRI12544.[3]

Pulmonary Function

For pre-bronchodilator FEV_1, in QUEST the difference between dupilumab 200 mg and placebo at 12 weeks was 0.14 L (95% CI, 0.08 to 0.19; P < 0.0001), and between dupilumab 300 mg and placebo was 0.13 L (95% CI, 0.08 to 0.18; P < 0.0001). In VENTURE, the difference between dupilumab and placebo at 24 weeks was 0.22 L (95% CI, 0.09 to 0.34) and in DRI12544 the difference between dupilumab 200 mg and placebo at 12 weeks was 0.20 L (95% CI, 0.11 to 0.28; P < 0.0001) and the difference between dupilumab 300 mg and placebo was 0.16 L (95% CI, 0.08 to 0.25; P = 0.0002). Results for this outcome in VENTURE were tested outside of the statistical hierarchy, and thus these results should be considered as supportive evidence that dupilumab is effective. The MPPI for FEV_1 is 0.23 L and is lower in older patients (0.17 L) than in younger patients (0.28 L).

In QUEST, for morning PEF, the LSM difference between dupilumab 200 mg and placebo was 26.62 L/minute (95% CI, 17.20 to 36.04) and between dupilumab 300 mg and placebo was 13.31 L/minute (95% CI, 3.94 to 22.67). In VENTURE, the difference between dupilumab and placebo at 24 weeks was 32.64 L/minute (95% CI, 16.03 to 49.24) and in DRI12544 the difference between dupilumab 200 mg and placebo was 18.15 L/minute (95% CI, 3.80 to 32.50) and between dupilumab 300 mg and placebo was 15.09 L/minute (95% CI, 0.92 to 29.25). Results for this outcome were tested outside of the statistical hierarchy, and thus these results should be considered as supportive evidence that dupilumab is effective. The MPPI has been reported to be 18.8 L/minute in 1 study, and 25 L/minute for MID has been used previously in clinical trials.

In QUEST, for evening PEF, the LSM difference between dupilumab 200 mg placebo was 23.51 L/minute (95% CI, 14.04 to 32.99) and between dupilumab 300 mg and placebo was 10.90 L/minute (95% CI, 1.47 to 20.32). In VENTURE, the difference between dupilumab and placebo at 24 weeks was 26.86 L/minute (95% CI, 10.35 to 43.38), and in DRI12544 the difference between dupilumab 200 mg and placebo was 24.41 L/minute (95% CI, 9.63 to 39.19) and between dupilumab 300 mg and placebo was 15.17 L/minute (95% CI, 0.59 to 29.76). Results

Table 23: Pre-Bronchodilator FEV_1, Change From Baseline

	Dupilumab			Placebo				
Study	Baseline, L, mean (SD)	Change, L, LSM (SE)	N	Baseline, L, mean (SD)	Change, L, LSM (SE)	N	Between-group LSM difference, L (95% CI; P value)	Follow up (weeks)
QUEST 200 mg	1.78 (0.62)	0.32 (0.02)	611	1.76 (0.61)	0.18 (0.02)	307	0.14 (0.08 to 0.19; < 0.0001)	12
QUEST 300 mg	1.78 (0.60)	0.34 (0.02)	610	1.75 (0.57)	0.21 (0.02)	313	0.13 (0.08 to 0.18; < 0.0001)	12
VENTURE	1.53 (0.53)	0.22 (0.05)	97	1.63 (0.61)	0.01 (0.05)	104	0.22 (0.09 to 0.34)	24
DRI12544 200 mg	1.79 (0.52)	0.31 (0.03)	136	1.82 (0.55)	0.12 (0.03)	129	0.20 (0.11 to 0.28; < 0.0001)	12
DRI12544 300 mg	1.85 (0.53)	0.28 (0.03)	146	1.82 (0.55)	0.12 (0.03)	129	0.16 (0.08 to 0.25; 0.0002)	12

CI = confidence interval; FEV_1 = forced expiratory volume in the first second; LSM = least squares mean; SD = standard deviation; SE = standard error.

Note: QUEST: Derived from mixed-effect model with repeated measures, with change from baseline in pre-bronchodilator FEV_1 values up to week 12 as the response variable, and treatment, age, sex, baseline height, region (pooled country), baseline eosinophil strata, baseline inhaled corticosteroid dose level, visit, treatment-by-visit interaction, baseline pre-bronchodilator FEV_1 value, and baseline-by-visit interaction as covariates.

Source: Clinical Study Report for QUEST,[1] VENTURE,[2] DRI12544.[3]

for this outcome were tested outside of the statistical hierarchy, and thus these results should be considered as supportive evidence that dupilumab is effective. The MPPI has been reported to be 18.8 L/minute in 1 study, and 25 L/minute for MID has been used previously in clinical trials.

Symptoms

ACQ-5 was reduced (improved) from baseline to week 24 in each of the dupilumab and placebo groups across the studies. In QUEST, the LSM difference between dupilumab 200 mg and placebo was −0.35 (95% CI, −0.48 to −0.21) and between dupilumab 300 mg and placebo was −0.19 (95% CI, −0.32 to −0.05). In VENTURE, the LSM difference between dupilumab and placebo after 24 weeks was −0.47 (95% CI, −0.76 to −0.18) and in DRI12544 for low-dose dupilumab versus placebo was −0.35 (95% CI, −0.57 to −0.14) and for high-dose dupilumab versus placebo was −0.31 (95% CI, −0.52 to −0.09). Responder analyses were also reported for the ACQ-5 in QUEST and VENTURE, with responders defined as those achieving a reduction in ACQ-5 from baseline of at least 0.5 (the MID for the ACQ-5 is 0.5). In QUEST, 76.2% of patients in the dupilumab 200 mg group and 67.5% of patients in the placebo group were responders (RR = 1.55; 95% CI, 1.14 to 2.10). In the dupilumab 300 mg group, 73.3% of patients responded versus 65.7% of patients in the placebo group (RR = 1.43; 95% CI, 1.06 to 1.92). In VENTURE, 55.3% of patients in the dupilumab 300 mg group were responders versus 46.7% of patients in the placebo group (RR = 1.67; 95% CI, 0.92 to 3.03). Results for all of these outcomes were tested outside of the statistical hierarchy.

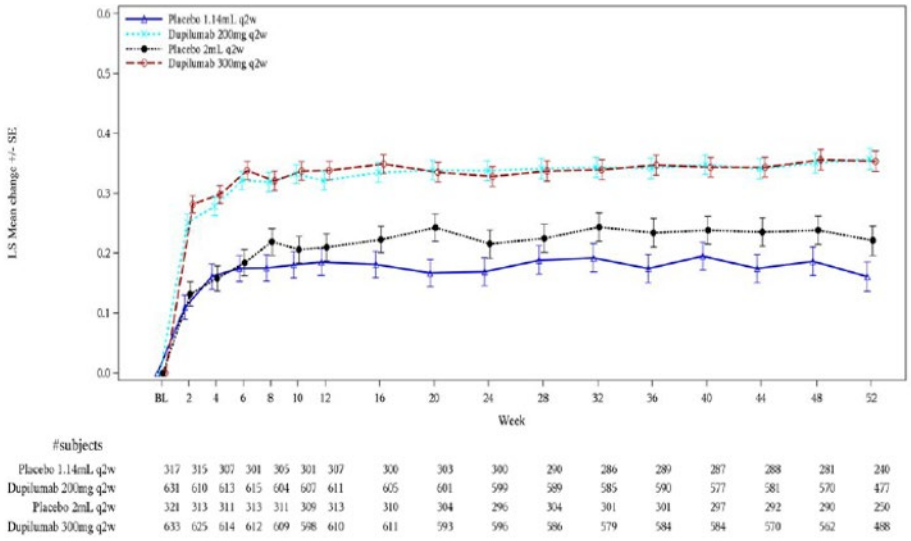
Asthma Symptom–Free Days and Nights

Not assessed.

Nocturnal Awakenings

The average number of nocturnal awakenings decreased from baseline in each of the dupilumab and placebo groups. In QUEST, after 52 weeks the LSM difference between

Figure 2: Pre-Bronchodilator FEV_1, Change From Baseline Over 52 Weeks in QUEST



Source: Clinical Study Report for QUEST [1]

Table 24: Morning PEF, Change From Baseline

Study	Dupilumab			Placebo				
	Baseline, L/min, mean (SD)	Change, L/min, LSM (SE)	N	Baseline, L/min, mean (SD)	Change, L/min, LSM (SE)	N	Between group LSM difference, L/min, (95% CI; P value)	Follow up (weeks)
QUEST 200 mg	281.37 (112.13)	28.97 (2.82)	544	286.84 (111.72)	2.35 (3.94)	270	26.62 (17.20 to 36.04; < 0.0001)	52
QUEST 300 mg	294.55 (115.93)	26.00 (2.82)	529	281.27 (107.57)	12.69 (3.91)	282	13.31 (3.94 to 22.67; 0.0054)	52
VENTURE	236.57 (100.21)	30.80 (6.17)	98	240.60 (115.50)	−1.84 (5.97)	105	32.64 (16.03 to 49.24; 0.0001)	24
DRI12544 200 mg	303.32 (117.60)	18.96 (5.26)	136	305.56 (112.09)	0.81 (5.14)	132	18.15 (3.80 to 32.50; 0.0132)	24
DRI12544 300 mg	300.50 (112.74)	15.90 (5.12)	145		0.81 (5.14)	132	15.09 (0.92 to 29.25; 0.0368)	24

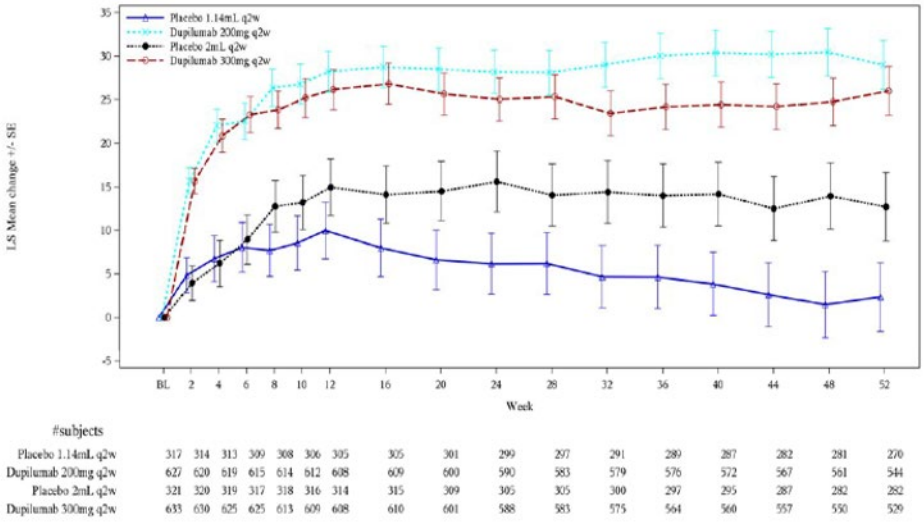
CI = confidence interval; LSM = least squares mean; PEF = peak expiratory flow; SD = standard deviation; SE = standard error.

Note: QUEST: Derived from mixed-effect model with repeated measures, with change from baseline in morning PEF values (periodical average) up to week 52 as the response variable, and treatment, age, sex, baseline height, region (pooled country), baseline eosinophil strata, baseline inhaled corticosteroid dose level, visit, treatment-by-visit interaction, baseline morning PEF value, and baseline-by-visit interaction as covariates.

Source: Clinical Study Report for QUEST,[1] VENTURE,[2] DRI12544.[3]

dupilumab 200 mg and placebo was −0.05 (95% CI, −0.13 to 0.02) and between dupilumab 300 mg and placebo was −0.11 (95% CI, −0.18 to −0.03). In VENTURE, after 24 weeks the LSM difference between dupilumab and placebo was −0.10 (95% CI, −0.32 to 0.12) and in DRI12544 after 24 weeks the LSM difference between dupilumab 200 mg and placebo was −0.06 (95% CI, −0.17 to 0.06) and between dupilumab 300 mg and placebo was −0.07 (95% CI, −0.19 to 0.05). These outcomes were outside of the statistical hierarchy in all studies.

Figure 3: Morning Peak Expiratory Flow From QUEST



Source: Clinical Study Report for QUEST [1]

Table 25: Evening PEF, Change From Baseline

Study	Dupilumab			Placebo				
	Baseline, L/min, mean (SD)	Change, L/min, LSM (SE)	N	Baseline, L/min, mean (SD)	Change, L/min, LSM (SE)	N	Between-group LSM difference, L/min (95% CI; P value)	Follow up (weeks)
QUEST 200 mg	293.55 (115.34)	17.50 (2.84)	526	306.93 (116.37)	−6.01 (3.96)	269	23.51 (14.04 to 32.99; < 0.0001)	52
QUEST 300 mg	306.93 (116.37)	15.34 (2.84)	523	294.75 (109.17)	4.44 (3.95)	268	10.90 (1.47 to 20.32; 0.0235)	52
VENTURE	251.79 (109.15)	21.40 (6.20)	99	256.12 (117.92)	−5.47 (5.98)	104	26.86 (10.35 to 43.38; 0.0016)	24
DRI12544 200 mg	315.06 (119.77)	15.45 (5.41)	136	320.52 (125.51)	−8.96 (5.30)	132	24.41 (9.63 to 39.19; 0.0012)	24
DRI12544 300 mg	315.64 (115.98)	6.21 (5.28)	145		−8.96 (5.30)	132	15.17 (0.59 to 29.76; 0.0415)	24

CI = confidence interval; LSM = least squares mean; PEF = peak expiratory flow; SD = standard deviation; SE = standard error.

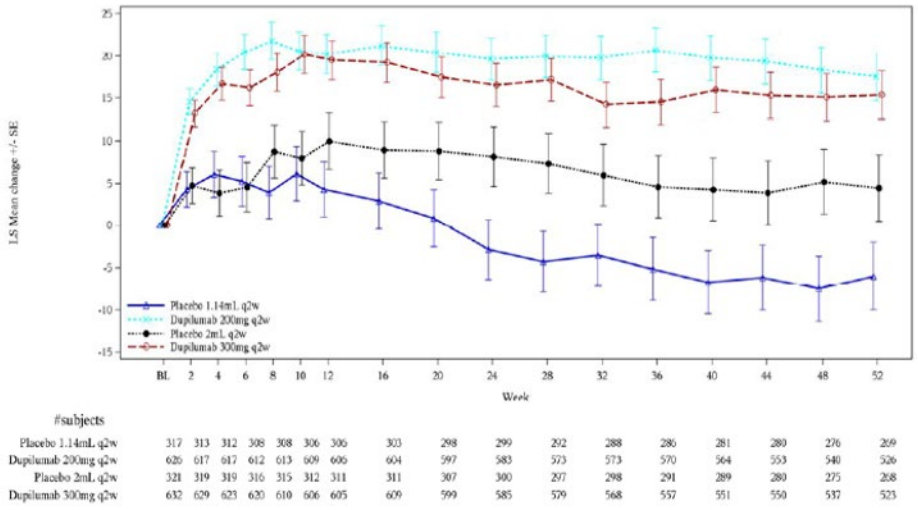
Note: QUEST: Derived from mixed-effect model with repeated measures, with change from baseline in evening PEF values (periodical average) up to week 52 as the response variable, and treatment, age, sex, baseline height, region (pooled country), baseline eosinophil strata, baseline inhaled corticosteroid dose level, visit, treatment-by-visit interaction, baseline evening PEF value, and baseline-by-visit interaction as covariates.

Source: Clinical Study Report for QUEST,[1] VENTURE,[2] DRI12544.[3]

Use of Rescue Inhalers

The use of rescue inhalers was reduced from baseline in both dupilumab and placebo groups in each of the studies. After 52 weeks in QUEST, the LSM difference between dupilumab 200 mg and placebo was −0.35 puffs/day (95% CI, −0.71 to 0.00) and between dupilumab 300 mg and placebo was −0.28 puffs/day (95% CI, −0.63 to 0.07). In VENTURE, after 24 weeks the LSM difference between dupilumab and placebo was −0.28 puffs/day (95% CI, −1.03 to 0.47), and in DRI12544 after 24 weeks the LSM difference between dupilumab 200 mg and placebo

Figure 4: Evening Peak Expiratory Flow in QUEST



Source: Clinical Study Report for QUEST.[1]

Table 26: ACQ-5, Change From Baseline

Study	Dupilumab			Placebo				
	Baseline, mean (SD)	Change, LSM (SE)	N	Baseline, mean (SD)	Change, LSM (SE)	N	Between-group LSM difference (95% CI; P value)	Follow up (weeks)
QUEST 200 mg	2.76 (0.80)	−1.44 (0.04)	590	2.71 (0.73)	−1.10 (0.06)	296	−0.35 (−0.48 to −0.21; < 0.0001)	24
QUEST 300 mg	2.77 (0.76)	−1.40 (0.04)	585	2.77 (0.77)	−1.21 (0.06)	297	−0.19 (−0.32 to −0.05; 0.0069)	24
VENTURE	2.42 (1.24)	−1.05 (0.11)	96	2.58 (1.09)	−0.58 (0.11)	99	−0.47 (−0.76 to −0.18)	24
DRI12544 200 mg	2.73 (0.82)	−1.49 (0.08)	143	2.69 (0.80)	−1.14 (0.08)	127	−0.35 (−0.57 to −0.14; 0.0015)	24
DRI12544 300 mg	2.80 (0.83)	−1.45 (0.08)	145	2.69 (0.80)	−1.14 (0.08)	127	−0.31 (−0.52 to −0.09; 0.0049)	24

ACQ-5 = Asthma Control Questionnaire, 5-item; CI = confidence interval; LSM = least squares mean; SD = standard deviation; SE = standard error.

Note: QUEST: LSM difference (ACQ-5) derived from a mixed-effect model with repeated measures, with change from baseline in ACQ-5 up to week 24 as the response variable, and treatment, age, region (pooled country), baseline eosinophil strata, baseline inhaled corticosteroid dose level, visit, treatment-by-visit interaction, baseline ACQ-5, and baseline-by-visit interaction as covariates.

Source: Clinical Study Report for QUEST,[1] VENTURE,[2] DRI12544.[3]

was −0.43 puffs/day (95% CI, −1.19 to 0.32) and between dupilumab 300 mg and placebo was −0.45 puffs/day (95% CI, −1.19 to 0.30). These outcomes were outside of the statistical hierarchy in all studies.

Table 27: Nocturnal Awakenings, Change From Baseline

	Dupilumab			Placebo				
Study	Baseline, mean (SD)	Change, LSM (SE)	N	Baseline, mean (SD)	Change, LSM (SE)	N	Between-group LSM difference (95% CI; P value)	Follow up (weeks)
QUEST 200 mg	0.56 (0.94)	−0.33 (0.02)	553	0.52 (0.61)	−0.27 (0.03)	275	−0.05 (−0.13 to 0.02; 0.1666)	52
QUEST 300 mg	0.54 (0.87)	−0.38 (0.02)	540	0.50 (0.81)	−0.27 (0.03)	286	−0.11 (−0.18 to −0.03; 0.0070)	52
VENTURE	0.89 (1.41)	−0.39 (0.08)	99	0.75 (1.07)	−0.28 (0.08)	106	−0.10 (−0.32 to 0.12)	24
DRI12544 200 mg	0.61 (1.12)	−0.35 (0.04)	136	0.46 (0.64)	−0.29 (0.04)	132	−0.06 (−0.17 to 0.06; 0.3663)	24
DRI12544 300 mg	0.55 (0.78)	−0.36 (0.04)	145	0.46 (0.64)	−0.29 (0.04)	132	−0.07 (−0.19 to 0.05; 0.2636)	24

CI = confidence interval; LSM = least squares mean; SD = standard deviation; SE = standard error.

Note: QUEST: Derived from a mixed-effect model with repeated measures, with change from baseline in number of nocturnal awakenings per night (periodical average) up to week 52 as the response variable, and treatment, age, region (pooled country), baseline eosinophil strata, baseline inhaled corticosteroid dose level, visit, treatment-by-visit interaction, baseline number of nocturnal awakenings per night, and baseline-by-visit interaction as covariates.

Source: Clinical Study Report for QUEST,[1] VENTURE,[2] DRI12544.[3]

Table 28: Rescue Inhaler Use, Change From Baseline

	Dupilumab			Placebo				
Study	Baseline, puffs/day, mean (SD)	Change, puffs/day, LSM (SE)	N	Baseline, puffs/day, mean (SD)	Change, puffs/day, LSM (SE)	N	Between-group LSM difference, puffs/day (95% CI; P value)	Follow up (weeks)
QUEST 200 mg	3.45 (4.23)	−1.30 (0.11)	522	3.15 (3.55)	−0.95 (0.15)	270	−0.35 (−0.71 to −0.00; 0.0493)	52
QUEST 300 mg	3.14 (3.48)	−1.36 (0.11)	521	3.13 (4.04)	−1.08 (0.15)	265	−0.28 (−0.63 to 0.07; 0.1158)	52
VENTURE	4.29 (4.33)	−1.56 (0.28)	98	4.94 (6.65)	−1.28 (0.27)	105	−0.28 (−1.03 to 0.47)	24
DRI12544 200 mg	2.98 (2.74)	−0.77 (3.43)	135	2.72 (2.73)	−0.25 (2.76)	132	−0.43 (−1.19 to 0.32; 0.2600)	24
DRI12544 300 mg	3.25 (3.15)	−0.83 (3.80)	144	2.72 (2.73)	−0.25 (2.76)	132	−0.45 (−1.19 to 0.30; 0.2413)	24

CI = confidence interval; LSM = least squares mean; SD = standard deviation; SE = standard error.

Source: Clinical Study Report for QUEST,[1] VENTURE,[2] DRI12544.[3]

Symptoms of Sinusitis and/or Atopic Dermatitis

SNOT-22 was assessed in patients with bilateral nasal polyposis and/or chronic rhinosinusitis in each of the included studies. After 52 weeks in QUEST, the LSM difference between dupilumab 200 mg and placebo was −11.88 (95% CI, −17.59 to −6.18) and between dupilumab 300 mg and placebo was −10.32 (95% CI, −15.77 to −4.87). In VENTURE, at week 24 the LSM difference between dupilumab and placebo was −7.95 (95% CI, −15.91 to 0.02), and in DRI12544 after 24 weeks the LSM difference between dupilumab 200 mg and placebo was −3.36 (95% CI, −7.04 to 0.32) and between dupilumab 300 mg and placebo was −6.42 (95% CI, −10.07 to −2.77). The differences between dupilumab and placebo in QUEST met the MID for SNOT-22, which is considered to be 8.9, or within the range of 8.3 to 17.5. Results for SNOT-22 were tested outside of the statistical hierarchy.

Table 29: SNOT-22, Change From Baseline

	Dupilumab			Placebo				
Study	Baseline, mean (SD)	Change, LSM (SE)	N	Baseline, mean (SD)	Change, LSM (SE)	N	Between-group LSM difference (95% CI; P value)	Follow up (weeks)
QUEST 200 mg	41.30 (17.98)	−16.35 (1.65)	89	44.77 (19.75)	−4.47 (2.44)	42	−11.88 (−17.59 to −6.18; < 0.0001)	52
QUEST 300 mg	42.76 (18.02)	−17.86 (1.72)	85	43.81 (19.28)	−7.54 (2.23)	49	−10.32 (−15.77 to −4.87; 0.0002)	52
VENTURE	43.55 (19.46)	−10.93 (3.29)	27	41.15 (22.39)	−2.98 (2.49)	37	−7.95 (−15.91 to 0.02; 0.0505)	24
DRI12544 200 mg	35.53 (18.72)	−10.53 (1.34)	131	35.11 (20.71)	−7.16 (1.36)	137	−3.36 (−7.04 to 0.32; 0.0733)	24
DRI12544 300 mg	36.39 (18.89)	−13.58 (1.31)	125		−7.16 (1.36)	137	−6.42 (−10.07 to −2.77; 0.0006)	24

CI = confidence interval; LSM = least squares mean; SD = standard deviation; SE = standard error; SNOT-22 = Sino-Nasal Outcomes Test, 22 items.

Note: QUEST: Derived from a mixed-effect model with repeated measures, with change from baseline in SNOT-22 total score up to week 52 as the response variable, and treatment, age, region (pooled country), baseline eosinophil strata, baseline inhaled corticosteroid dose level, visit, treatment-by-visit interaction, baseline SNOT-22 total score, and baseline-by-visit interaction as covariates.

Source: Clinical Study Report for QUEST,[1] VENTURE,[2] DRI12544.[3]

Table 30: RQLQ Overall Score, Change From Baseline

	Dupilumab			Placebo				
Study	Baseline, mean (SD)	Change, LSM (SE)	N	Baseline, mean (SD)	Change, LSM (SE)	N	Between-group LSM difference (95% CI; P value)	Follow up (weeks)
QUEST 200 mg	2.01 (1.16)	−0.84 (0.05)	263	1.95 (1.02)	−0.42 (0.08)	129	−0.42 (−0.61 to −0.24; < 0.0001)	52
QUEST 300 mg	1.90 (1.12)	−0.83 (0.05)	274	1.95 (1.20)	−0.45 (0.07)	149	−0.39 (−0.56 to −0.21; < 0.0001)	52

CI = confidence interval; LSM = least squares mean; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; SD = standard deviation; SE = standard error.

Note: Derived from a mixed-effect model with repeated measures, with change from baseline in RQLQ overall score up to week 52 as the response variable, and treatment, age, region (pooled country), baseline eosinophil strata, baseline inhaled corticosteroid dose level, visit, treatment-by-visit interaction, baseline RQLQ overall score, and baseline-by visit interaction as covariates.

Source: Clinical Study Report for QUEST.[1]

The RQLQ score was only reported in the QUEST trial. The RQLQ scores decreased (improved) from baseline in both the dupilumab and placebo groups, with an LSM difference between dupilumab 200 mg and placebo of −0.42 (95% CI, −0.61 to −0.24) and between dupilumab 300 mg and placebo of −0.39 (95% CI, −0.56 to −0.21). The difference between the dupilumab and placebo groups does not meet the MID for the RQLQ of 0.5. Results for the RQLQ were tested outside of the statistical hierarchy.

Harms

Only those harms identified in the review protocol are reported in the following sections. See Table 31, Table 32, and Table 33 for detailed harms data.

Adverse Events

In QUEST, with dupilumab 200 mg, 80.5% of patients experienced an adverse event versus 82.1% in placebo, and with dupilumab 300 mg, 81.5% experienced an adverse event versus 84.1% with placebo (Table 31). In VENTURE, 62.1% of dupilumab patients and 64.5% of placebo patients had an adverse event (Table 32), and in DRI12544 80.4% of patients in the dupilumab 200 mg group, 77.6% of patients in the dupilumab 300 mg group, and 74.7% of patients in the placebo group had an adverse event (Table 33).

The most common adverse events in QUEST were viral upper respiratory tract infection (18.9% for dupilumab 200 mg versus 19.2% for placebo; 17.6% for dupilumab 300 mg versus 19.9% for placebo), upper respiratory tract infection (10.9% for dupilumab 200 mg versus 11.8% for placebo; 12.2% for dupilumab 300 mg versus 15.3% for placebo), and bronchitis (11.6% for dupilumab 200 mg versus 15.0% for placebo; 11.2% for dupilumab 300 mg versus 13.2% for placebo). The most common adverse events in VENTURE were viral upper respiratory tract infection (8.7% for dupilumab and 17.8% for placebo) and bronchitis (6.8% for dupilumab and 5.6% for placebo). In DRI12544, the most common adverse events were upper respiratory tract infection (14.9% for dupilumab 200 mg, 12.8% for dupilumab 300 mg, and 17.7% for placebo) and injection site erythema (14.2% for dupilumab 200 mg, 21.8% for dupilumab 300 mg, and 7.6% for placebo).

Serious Adverse Events

In QUEST, serious adverse events occurred in 7.8% of the dupilumab 200 mg group versus 8.3% of the placebo group, and in 8.7% of the dupilumab 300 mg group versus 8.4% of the placebo group after 52 weeks (Table 31). Asthma was the most common serious adverse event. In VENTURE, 8.7% of dupilumab patients and 5.6% of placebo patients had a serious adverse event (Table 32), and in DRI12544 6.8% of patients in the dupilumab 200 mg group and 8.3% of patients in the dupilumab 300 mg group, versus 5.7% of patients in the placebo group, had a serious adverse event through 24 weeks of treatment (Table 33).

Withdrawals Due to Adverse Events

In QUEST, treatment-emergent adverse events leading to study drug discontinuation occurred in 3.0% of patients in the dupilumab 200 mg group versus 6.1% in the placebo group, and 7.0% of patients in the dupilumab 300 mg group versus 3.1% in the placebo group (Table 31). In VENTURE, adverse events leading to permanent discontinuation of treatment occurred in 1.0% of patients in the dupilumab group and 3.7% of patients in the placebo group (Table 32). In DRI12544, treatment-emergent adverse events leading to treatment discontinuation occurred in 4.1% of patients in the dupilumab 200 mg group, 2.6% of patients in the 300 mg group, and 3.2% of patients in the placebo group (Table 33).

Notable Harms

Anaphylactic reactions occurred in 2 patients (0.3%) in the dupilumab 200 mg group, 1 patient (0.2%) in the dupilumab 300 mg group, and no patients in either of the placebo groups in QUEST. No patients in VENTURE had an anaphylactic reaction.

In QUEST, serious or severe infections occurred in 1.0% of patients in the dupilumab 200 mg group and 1.9% in the placebo group, and in 2.7% of patients in the dupilumab 300 mg group and 1.6% in the placebo group over 52 weeks. In VENTURE, serious or severe infections occurred in 1.9% of the dupilumab group and 0.9% of the placebo group, and in DRI12544 serious or adverse infections occurred in 1.4% of patients in the dupilumab 200 mg group, 3.8% of patients in the dupilumab 300 mg group, and 1.3% of patients in the placebo group. There were no patients with parasitic infections across 24 weeks in either VENTURE or DRI12544, and 1 patient in each of the dupilumab 300 mg and placebo groups in QUEST. In QUEST, opportunistic infections occurred in 0.2% of patients in the dupilumab 200 mg group versus 0.6% in the placebo group, and 0.2% of patients in the dupilumab 300 mg group versus 0.9% in the placebo group.

Critical Appraisal

Internal Validity

All included studies were double-blinded and took steps to maintain blinding through use of a matching placebo. For example, in QUEST, 2 different volumes of injection solution were used in vials, corresponding to the 2 different doses of dupilumab used in the study, and these were each matched to corresponding volumes of placebo injection, meaning that there were 2 different placebo groups in this study. This also meant that investigators and perhaps patients may have been able to determine whether they were in the high-dose or low-dose groups, in other words whether they were receiving 200 mg or 300 mg dupilumab or its matching placebo, although they would not have been able to determine whether they were on dupilumab or placebo. It is possible that this may have biased results if patients believed they were in the high-dose versus low-dose groups; however, the fact that they did not know whether they were on dupilumab or placebo would have mitigated the risk of bias.

Allocation concealment was facilitated through the randomization process by use of an interactive voice or web response system. There were numerically more injection site reactions in the dupilumab groups than in the placebo groups across the studies and, given that this may be an anticipated adverse effect of dupilumab, this might have unblinded the drug. This would be expected to have a greater impact on patient-reported efficacy outcomes such as health-related quality of life and symptoms, and it is possible that this may have biased results in favour of dupilumab for such outcomes if patients believed they were assigned to the treatment group rather than to the placebo group.

The sponsor controlled for multiplicity through the use of a hierarchical testing procedure. In studies such as QUEST and DRI12544, which tested more than 1 dose of dupilumab, the hierarchy first tested the higher dose of dupilumab before going on to test the lower dose, and thus in QUEST when the hierarchy failed early in testing at the higher dose of dupilumab, none of the subsequent outcomes for the high dose of dupilumab were multiplicity controlled; none of secondary outcomes at the lower dose were controlled for multiplicity. Additionally, the study protocol for QUEST states that each hypothesis will be formally tested only if the previous 1 is significant at the 5% level, yet testing continued and P values continued to be reported.

Dropout rates were relatively low across the included trials, with no clear numerical differences between groups. For some outcomes, such as key patient-reported outcomes like the AQLQ and ACQ-5, there appeared to be more missing data than would simply be

Table 31: Summary of Harms: QUEST

Characteristic	Dupilumab 200 mg q.2.w. N = 631	Placebo N = 317	Dupilumab 300 mg q.2.w. N = 633	Placebo N = 321
Patients with an AE, n (%)	508 (80.5)	257 (82.1)	515 (81.5)	270 (84.1)
Specific AE (≥ 5% of patients), n (%)				
Viral upper respiratory tract infection	119 (18.9)	60 (19.2)	111 (17.6)	64 (19.9)
Upper respiratory tract infection	69 (10.9)	37 (11.8)	77 (12.2)	49 (15.3)
Bronchitis	73 (11.6)	47 (15.0)	71 (11.2)	42 (13.1)
Influenza	36 (5.7)	29 (9.3)	38 (6.0)	22 (6.9)
Sinusitis	36 (5.7)	27 (8.6)	26 (4.1)	29 (9.0)
Urinary tract infection	17 (2.7)	17 (5.4)	19 (3.0)	12 (3.7)
Headache	46 (7.3)	26 (8.3)	40 (6.3)	25 (7.8)
Allergic rhinitis	21 (3.3)	16 (5.1)	18 (2.8)	15 (4.7)
Back pain	30 (4.8)	16 (5.1)	25 (4.0)	7 (2.2)
Injection site erythema	76 (12.0)	13 (4.2)	98 (15.5)	22 (6.9)
Injection site edema	23 (3.6)	2 (0.6)	40 (6.3)	5 (1.6)
Accidental overdose of study drug	33 (5.2)	16 (5.1)	33 (5.2)	16 (5.0)
Patients with a serious AE, n (%)	**49 (7.8)**	**26 (8.3)**	**55 (8.7)**	**27 (8.4)**
Asthma	11 (1.7)	10 (3.2)	6 (0.9)	4 (1.2)
Pneumonia	0	0	4 (0.6)	2 (0.6)
Patients with a TEAE leading to death	1 (0.2)	3 (1.0)	4 (0.6)	0
Patients with a TEAE leading to study drug discontinuation, n (%)	**19 (3.0)**	**19 (6.1)**	**44 (7.0)**	**10 (3.1)**
Notable harms, n (%)				
Anaphylactic reactions	2 (0.3)	0	1 (0.2)	0
Hypersensitivity	18 (2.9)	7 (2.2)	22 (3.5)	11 (3.4)
Serious/severe injection site reactions	2 (0.3)	0	8 (1.3)	0
Infection (serious/severe)	6 (1.0)	6 (1.9)	17 (2.7)	5 (1.6)
Parasitic infections	0	0	1 (0.2)	1 (0.3)
Opportunistic infections	1 (0.2)	2 (0.6)	1 (0.2)	3 (0.9)
Eye disorders	20 (3.2)	11 (3.5)	25 (4.0)	14 (4.0)

AE = adverse event; q.2.w = every 2 weeks; TEAE = treatment-emergent adverse event.

Source: Clinical Study Report for QUEST.[1]

Table 32: Summary of Harms: VENTURE

Characteristic	Dupilumab 300 mg q.2.w. N = 103	Placebo N = 107
AEs		
Patients with an AE, n (%)	64 (62.1)	69 (64.5)
Specific AE, > 5% of patients in either group, n (%)		
Viral upper respiratory tract infection	9 (8.7)	19 (17.8)
Bronchitis	7 (6.8)	6 (5.6)
Sinusitis	7 (6.8)	4 (3.7)
Influenza	3 (2.9)	6 (5.6)
Eosinophilia	7 (6.8)	1 (0.9)
Eosinophil count increased	7 (6.8)	1 (0.9)
Patients with a serious AE, n (%)	9 (8.7)	6 (5.6)
Asthma	3 (2.9)	3 (2.8)
Eosinophilia	2 (1.9)	0
Pneumonia	1 (1.0)	0
Respiratory tract infection	1 (1.0)	0
Chylothorax	1 (1.0)	0
Pneumonia aspiration	1 (1.0)	0
Pneumothorax	1 (1.0)	0
Pulmonary mass	1 (1.0)	0
Acetabulum fracture	1 (1.0)	0
Foreign body aspiration	1 (1.0)	0
GI stromal tumour	0	1 (0.9)
Patients with an AE leading to permanent treatment discontinuation, n (%)	1 (1.0)	4 (3.7)
Specific AE, n (%)		
Arthralgia	1 (1.0)	0
GI stromal tumour	0	1 (0.9)
Eosinophilia	0	1 (0.9)
Adrenal insufficiency	0	1 (0.9)
Asthmatic crisis	0	1 (0.9)
Notable harms, n (%)		
Hypersensitivity	2 (1.9)	1 (0.9)
Severe/serious infection	2 (1.9)	1 (0.9)

Characteristic	Dupilumab 300 mg q.2.w. N = 103	Placebo N = 107
Parasitic infection	0	0
Opportunistic infection	0	0
Injection site reactions	9 (8.7)	4 (3.7)
Serious/severe injection site reactions	0	0
Anaphylactic reactions	0	0
Eye disorders	1 (1.0)	4 (3.7)

AE = adverse event; GI = gastrointestinal; q.2.w = every 2 weeks.

Source: Clinical Study Report for VENTURE.[2]

accounted for by withdrawals. For example, for AQLQ global scores, week 52 data appeared to be missing for between 10% and 15% of the original randomized population, despite the fact that study withdrawals were only between 4% and 7% and discontinuations of study treatment only occurred in 11% to 13% of patients across groups in the study. It is not clear why there were missing data, although this is not uncommon for patient-reported outcomes. There does not appear to be a clear imbalance in missing data between groups.

DRI12544 was originally designed as a dose-ranging study but was changed to a pivotal study after the interim analysis, based on feedback from regulatory agencies. At this point, controls for multiple comparisons were put in place. The concern with this approach is that the statistical hierarchy was determined after results had been seen. Additionally, perhaps due to the change in status to a pivotal study, the primary analysis population was changed from the high-eosinophil population to the intention-to-treat population. As a result, the primary outcome is reported differently in the Clinical Study Report than in the primary publication. It is also unclear why the annualized rate of severe exacerbation events was the first outcome tested in the statistical hierarchy when FEV_1 was the primary outcome of the trial.

External Validity

The clinical expert consulted by CADTH for this review believed that the demographics of patients in the included studies were consistent with the population that would be expected to use the drug. With respect to baseline disease characteristics, the clinical expert noted that patients exhibited airway reversibility at baseline, which is something most patients in practice would not have. These patients may therefore be more likely to respond to dupilumab (or placebo). The clinical expert also noted with respect to the VENTURE study that the percentage of those who have asthma with such severe disease and chronic use of OCSs, while still having an average of 2 exacerbations per year, would be very small. Across the studies, here was a relatively large number of patients were screened out, approximately 50% across studies, suggesting that the patients included in these studies may represent a relatively select population of patients with asthma.

None of the included studies had an active comparator; all compared dupilumab to placebo. Among the monoclonal antibodies, the most appropriate comparator would be an IL-5 inhibitor, and most of these were approved within the past few years, which might explain why no comparisons were made to 1 of these drugs. Nevertheless, this is a limitation when trying to assess the relative efficacy of dupilumab versus its most appropriate comparators.

Annualized severe asthma exacerbation rate was a primary outcome of QUEST, and reduction in OCS dose was the primary outcome of VENTURE; therefore, both pivotal phase III studies investigated outcomes that are of clinical importance to patients. Health-related quality of life was assessed using the disease-specific instrument the AQLQ, although because this was tested lower in the statistical hierarchy, the hierarchy had failed by the time AQLQ was to be tested. AQLQ was not part of the statistical hierarchy in VENTURE.

None of the included studies were of sufficient duration to assess the long-term efficacy and safety of dupilumab, a first-in-class drug. QUEST had the longest follow-up, at 52 weeks, while the other 2 included studies had a 24-week treatment period. There is an ongoing long-term

Table 33: Summary of Harms: DRI12544

Characteristic	Dupilumab 200 mg q.2.w. N = 148	Dupilumab 300 mg q.2.w. N = 156	Placebo N = 158
AEs			
Patients with an AE, n (%)	**119 (80.4)**	**121 (77.6)**	**118 (74.7)**
Specific AE, > 10% of patients in either group			
Bronchitis	11 (7.4)	19 (12.2)	16 (10.1)
Nasopharyngitis	15 (10.1)	16 (10.3)	15 (9.5)
Upper respiratory tract infection	22 (14.9)	20 (12.8)	28 (17.7)
Headache	17 (11.5)	17 (0.9)	20 (12.7)
Injection site erythema	21 (14.2)	34 (21.8)	12 (7.6)
Patients with a serious adverse event, n (%)	**10 (6.8)**	**13 (8.3)**	**9 (5.7)**
Asthma	5 (3.4)	1 (0.6)	4 (2.5)
Gastroenteritis	0	2 (1.3)	0
Deaths	0	2	0
TEAE leading to permanent treatment discontinuation, n (%)	**6 (4.1)**	**4 (2.6)**	**5 (3.2)**
Most common, > 1% in either group			
Injection site erythema	0	2 (1.3)	0
Injection site edema	0	2 (1.3)	0
Injection site pain	0	2 (1.3)	0
ALT increased	2 (1.4)	0	1 (0.6)
Notable harms, n (%)			
Serious or severe infections	2 (1.4)	7 (4.5)	2 (1.3)
Parasitic infections	0	0	0
Eye disorders	2 (1.4)	6 (3.8)	2 (1.3)
Injection site reactions	0	3 (1.9)	0

AE = adverse event; ALT = alanine aminotransferase; q.2.w = every 2 weeks; TEAE = treatment-emergent adverse event.
Source: Clinical Study Report for DRI12544.[3]

extension study (LTS12551), summarized in the "other evidence" section; however, this is an open-label study with no control group, and this limits any conclusions that can be drawn from these data.

Placebo responses were robust across the included studies, particularly for patient-reported outcomes such as the AQLQ and the ACQ-5, where improvements from baseline were consistently observed. This may suggest that patients benefited from the extra training and attention they received in a clinical trial and, thus, may be a generalizability issue. The clinical expert consulted by CADTH also believed that this robust placebo response may indicate that patients were undertreated going into the study.

Table 34 summarizes the generalizability of the evidence.

Indirect Evidence

Objectives and Methods for the Summary of Indirect Evidence

Due to the lack of direct evidence comparing dupilumab with other existing therapies as an add-on maintenance treatment in patients 12 years and older with severe asthma with a type 2 or eosinophilic phenotype or with OCS-dependent asthma, the sponsor submitted 2 ITCs.[4-6] In addition, CADTH conducted an independent literature search for published ITCs that compared dupilumab with other relevant comparators for the treatment of patients with a type 2 or eosinophilic phenotype or with OCS-dependent asthma. MEDLINE, Embase, and PubMed were searched, and 5 additional ITCs comparing these treatments were identified.[7-11] The objective of this section is to summarize and critically appraise the indirect evidence from the 2 sponsor-submitted ITCs and the 5 ITCs identified in the CADTH literature search. To align with the research protocol of this review, only information on population, intervention, comparator, outcome, and study (PICOS) of interest for this review are presented in this section.

Description of 2 Sponsor-Submitted Indirect Comparisons

The sponsor submitted 2 ITCs.[5,6] One was to identify, evaluate, and synthesize the empirical evidence on the clinical efficacy of dupilumab compared with other recommended biologics for the treatment of persistent, uncontrolled asthma (moderate to severe) in adults and adolescents 12 years and older.[5] The other ITC included OCS-dependent adults and adolescents 12 years and older.[6]

Systematic Literature Review

A search strategy was developed based on the PICOS criteria presented in Table 35 to identify relevant studies investigating the efficacy and safety of dupilumab with other existing treatments. The systematic literature search was performed in November 2017 and updated in March 2019.

The original search identified 6,646 publications for further screening. Following screening and a feasibility assessment, a total of 23 trials[1,32,49-69] were included in the ITC for uncontrolled persistent asthma, and 4 trials[53,70-72] were included in the ITC for OCS-dependent asthma.

Table 34: Assessment of Generalizability of Evidence for Dupilumab in Severe Asthma

Domain	Factor	Evidence	CADTH's assessment of generalizability
Population	Age	Two of the 3 included studies enrolled adolescents, and this age group is included in the indication for dupilumab.	Appropriate.
	Severity of asthma	VENTURE enrolled patients who were OCS-dependent and clearly had severe asthma. QUEST and DRI12544 enrolled patients with moderate-to-severe asthma, according to the investigators and sponsor.	There is some debate as to whether the populations in QUEST and DRI12544 were a mix of moderate-to-severe asthma or all had severe asthma. If a mix, then only a subset of patients from each study fit the indication for the drug. The clinical expert consulted by CADTH believed that if prescribing had been restricted to specialists (respirologists and allergists), this issue would have been mitigated.
	Sites	There were Canadian sites in QUEST and VENTURE.	Appropriate.
	FEV_1 reversibility	Patients exhibited airway reversibility at baseline.	This would not normally be seen in clinic. This may suggest populations that are more likely to be responsive to treatment, as their asthma is poorly or suboptimally controlled.
Intervention	Dupilumab 200 mg or 300 mg every 2 weeks	Both doses were studied in QUEST and DRI12544, while VENTURE focused on the 300 mg dose.	Consistent with the indication, those with OCS-dependent asthma were studied at the 300 mg dose.
	Co-interventions	Patients across all studies were receiving background therapy with moderate- to high-dose ICS with or without LABA and often a third controller.	Appeared to be receiving standard of care. The clinical expert noted that methylxanthines were used by some patients (< 5% in QUEST, as high as 12% in VENTURE). Methylxanthines are unlikely to be used in Canada.
	Background care	Placebo responses appeared robust across many outcomes, especially patient-reported outcomes such as ACQ-5 and AQLQ.	Strong responses in the placebo group may suggest that patients in the trial were benefiting from the additional training, support, and education typically seen in a clinical trial.
Comparator	Placebo	All studies were placebo controlled.	Lack of comparative evidence vs. other monoclonal antibodies is a limitation.

Domain	Factor	Evidence	CADTH's assessment of generalizability
Outcomes	See protocol	All major outcomes of interest were assessed. Health care resource use was assessed; however, these data were not reported, and the sponsor was unable to provide the data upon request. Health-related quality of life was assessed; however, it was lower on the statistical hierarchy, and the hierarchy had failed by the time testing reached that point. AQLQ and ACQ-5 were not controlled for multiplicity in VENTURE.	Lack of formal assessment of important patient-reported outcomes such as AQLQ and ACQ-5 is a limitation.
Setting	Canadian sites	There were Canadian sites in both QUEST and VENTURE.	

ACQ-5 = Asthma Control Questionnaire, 5-item; AQLQ = Asthma Quality of Life Questionnaire; FEV_1 = forced expiratory volume in the first second; ICS = inhaled corticosteroid; LABA = long-acting beta2-agonist; OCS = oral corticosteroid.

NMA Feasibility Assessment

To ensure that the assumptions inherent to ITCs were appropriate for any planned analyses, the clinical heterogeneity across all included studies was assessed. This was done by establishing a list of potential treatment effect modifiers (PICOS) (Table 36).

Methods of the Sponsor-Submitted ITCs

Based on the findings from the feasibility assessment, a full network Bayesian ITC was not recommended. Instead, as a base-case analysis — a series of pairwise Bucher ITCs comparing dupilumab with other biologics — was conducted, whereby subgroup data were generated by matching patient phenotypes for the dupilumab trials to relevant comparators.[4-6] For completeness, a full network Bayesian ITC was conducted as a sensitivity analysis only. However, the results of network Bayesian ITC were not provided in the sponsor's original ITC report, while the authors indicated that results of NMA were generally similar to those reported in the pairwise Bucher ITCs.[4-6]

In addition, various sensitivity analyses were conducted by excluding RCTs with fewer than 50 patients (Hoshino and Ohtawa [2012][66]) and excluding open-label trials (i.e., omalizumab trials EXALT,[68] QUALITX,[67] Hoshino and Ohtawa [2012],[66] Ayres et al. [2004],[64] and Niven et al. [2008][65]) from the base-case analysis for severe exacerbations and FEV_1.[5]

Statistical Approach

The Bucher method was selected as the base case since most networks were small (including only 3 to 4 studies) and star shaped (i.e., all trials have a placebo comparator). Base-case analyses were based on random effects models. A key assumption in Bucher indirect comparisons was that the relative effectiveness of a treatment is similar across all trials (homogeneity assumption). Analyses were carried out using the metaphor package in R 3.3.0.[73] Results of the Bucher ITCs are presented as a central estimate of the relative effect of interest (e.g., rate ratio, mean-median difference), along with 95% CIs.[4-6]

To ensure comparability, all estimated treatment rates were calculated starting with a set "anchor" rate, to which the previously estimated rate ratios (and their lower and upper 95% CI values) were applied. The anchor rate was calculated as the patient-year weighted average of the rates in the placebo arms across all trials (i.e., the absolute placebo effect),

Table 35: Original Study Selection Criteria and Methods for the Sponsor Submitted ITCs

Criteria	Description
Population	Adults (≥ 18 years) and adolescents (≥ 12 to 18 years) Patients with persistent or uncontrolled asthma, with medium- to high-dose ICS (plus LABA) as defined by 2017 GINA criteria Notes: • If ICS dose at inclusion was not reported, but study specified population as moderate-to-severe asthma, the study was included • OCS-dependent patients were included
Intervention	Biologics such as DUPI, BENR, RESL, MEPO, OMAL Medium- to high-dose ICS + LABA
Comparator	Any intervention of interest
Outcome	Asthma exacerbations, asthma symptoms and symptom score, assessment of steroid-sparing effect, rescue medication use, FEV_1, PEF, asthma control measures (ACQ-5, ACQ-6, ACQ-7), and AQLQ
Study design	RCTs (phase II, III, IV) including follow-up and extensions, subgroup analyses, post hoc analyses Randomized crossover trials Pooled analysis of RCTs or randomized crossover trials
Publication characteristics	Only English-language articles included
Exclusion criteria	Main exclusions: • Patients with acute asthma • Studies with LABA monotherapy • Journal articles and conference abstracts without English full text
Databases searched	Searches were conducted in November 2017 and updated in March 2019. MEDLINE (via Ovid), Embase (via Ovid), and Cochrane Library databases. This search also included conference proceedings (abstracts and/or posters) from 2015 to 2019 meetings.
Selection process	Two reviewers blindly and independently screened the titles and abstracts and assessed the full-text articles. Discrepancies were resolved by a third reviewer.
Data extraction process	Data were extracted by 1 reviewer and independently validated by a second reviewer. Extracted data were reviewed and validated for additional quality assurance.
Quality assessment	A risk-of-bias assessment was undertaken for the studies included in ITCs, in accordance with the "Quality assessment of the relevant RCTs," as described in the NICE single technology appraisal user guide for company evidence submission.[48]

ACQ = Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; BENR = benralizumab; DUPI = dupilumab; GINA = Global Initiative for Asthma; FEV_1 = forced expiratory volume in the first second; ICS = inhaled corticosteroid; ITC = indirect treatment comparison; LABA = long-acting beta2-agonist; MEPO = mepolizumab; NICE = National Institute for Health and Care Excellence; OCS = oral corticosteroid; OMAL = omalizumab; PEF = peak expiratory flow; RCT = randomized controlled trial; RESL = reslizumab.

Source: Sponsor-submitted network meta-analysis report.[4-6]

and the rate ratios for active treatments were applied to this anchor rate to calculate the expected treatment effect for each treatment of interest (i.e., the absolute arm-based treatment effect).[4-6]

In the Bucher ITC, statistical heterogeneity for a comparison was evaluated using the I^2 statistic. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity. Typically, I^2 values of 25%, 50%, and 75% were considered low, moderate, and high, respectively. A consistency assessment between direct and indirect sources of evidence was not applicable in the ITCs because there were no head-to-head comparisons between dupilumab and other comparators.[4-6]

Results of the Sponsor-Submitted ITCs

Summary of Included Studies

Twenty-three trials[1,32,49-69] were included in the ITC for uncontrolled persistent asthma. An overview of these trials is presented in Table 37. Four trials[53,70-72] were included in the ITC for OCS-dependent asthma. An overview of these trials is presented in Table 38.

Base-Case ITC

Pairwise Bucher ITCs were conducted as the base-case analysis. The analyses were performed using subgroups of patients from dupilumab trials who demonstrated patient baseline characteristics similar to those of the biologics of interest (i.e., mepolizumab, benralizumab, reslizumab, and omalizumab) for each comparator trial of interest (Table 39).

Base-case analyses for the OCS-dependent trials were conducted for subgroups of patients from the dupilumab trials whose characteristics matched the patient phenotypes of the approved US or global subgroups for each comparator trial of interest across relevant outcomes (Table 40). Of note, analyses comparing dupilumab with reslizumab were based on data collected from www.ClinicalTrials.gov (trial identifier NCT02501629), a non-peer-reviewed source.

Assessment of Risk of Bias of Included Trials

A risk-of-bias assessment was undertaken for the studies included in the ITC, in accordance with the "Quality assessment of the relevant RCTs," as described in the NICE single technology appraisal user guide for company evidence submission.[48] The results of the risk-of-bias assessment were not provided in the ITC reports.[4-6]

Table 36: Characteristics of Potential Treatment Effect Modifiers

Category	Modifiers
Population	Age, biomarkers (EOS and IgE levels), FEV_1, FeNO, exacerbation history, ICS dose
Treatment	Interventions: dosing, frequency of administration, treatment duration, concomitant therapies (LABA + ICS, OCS use at baseline)
Outcomes	Outcomes: definition, criteria, and method of evaluation; time points of assessment; baseline risk (i.e., observed placebo effect); correlation between baseline risk and relative effects
Study design	Treatment phases, follow-up period and timing of assessment, study recruitment period, sample size, patient ethnicity or study location, quality of the included studies

EOS = eosinophil; FeNO = fractional exhaled nitric oxide; FEV_1 = forced expiratory volume in the first second; ICS = inhaled corticosteroid; IgE = immunoglobin E; LABA = long-acting beta2-agonist; OCS = oral corticosteroid.

Source: Sponsor-submitted network meta-analysis report.[4,5]

Table 37: Overview of Included Studies in ITC for Uncontrolled Persistent Asthma

Study name, author, year	Dosage of interest	Treatment duration	N (ITT)	N included in ITC	Exacerbations[a]	Age, mean
DUPI (2 trials)						
QUEST (CSR data)[1]	200 mg, q.2.w. 300 mg, q.2.w.	52 weeks	1,902	MEPO-like: 406 (21.3%) RESL-like: 556 (29.2%) BENR-like: 439 (23.1%) OMAL-like: 762 (40.0%) Full ITT scenario: 1,902	≥ 1	MEPO-like: 49.6 RESL-like: 49.8 BENR-like: 47.9 OMAL-like: 45.6 Full ITT: 48.0
DRI12544, Wenzel et al. (2016), CSR data[32]	300 mg, q.2.w.	24 weeks	All Tx arms: 776 Tx arms of interest: 465	MEPO-like: 112 (24.1%) RESL-like: 128 (27.5%) BENR-like: 100 (21.5%) OMAL-like: 210 (45.2%) Full ITT scenario: 465[b]	≥ 1	MEPO-like: 51.0 RESL-like: 48.1 BENR-like: 48.4 OMAL-like: 47.4 Full ITT: 49.0
MEPO (3 trials)						
MUSCA, Chupp et al. (2017)[50]	100 mg, q.2.w.	20 weeks	551	551	≥ 2	51.0
MENSA, Ortega et al. (2014)[51]	75 mg, q.2.w. 100 mg, q.2.w.	32 weeks	576	576	≥ 2	50.0
DREAM, Pavord et al. (2012)[49]	75 mg, q.4.w.	52 weeks	All Tx arms: 621 Tx arms of interest: 308	308[b]	≥ 2	48.3
RESL (5 trials)						
BREATH (study 3,082), Castro et al. (2015)[53]	3 mg/kg, q.4.w.	52 weeks	489	489	≥ 1	48.5

Study name, author, year	Dosage of interest	Treatment duration	N (ITT)	N included in ITC	Exacerbations[a]	Age, mean
BREATH (study 3,083), Castro et al. (2015)[53]	3 mg/kg, q.4.w.	52 weeks	464	464	≥ 1	48.0
BREATH (study 3,084), Corren et al. (2016)[55]	3 mg/kg, q.4.w.	16 weeks	496	496	NR	45.0
BREATH (study 3,081), Bjermer et al. (2016)[52]	3 mg/kg, q.4.w.	16 weeks	All Tx arms: 315 Tx arms of interest: 211	211[b]	NR	43.6
Castro et al. (2011)[56]	3 mg/kg, q.4.w.	12 weeks	106	106	NR	45.4
BENR (3 trials)						
SIROCCO, Bleecker et al. (2016) (high ICS)[57]	30 mg, q.4.w., q.8.w.	48 weeks	All Tx arms: 1,204 Tx arms of interest: 805	805[b]	≥ 2	49.0
SIROCCO, Bleecker et al. (2016) (high ICS ≥ 300 EOS subgroup)[57]	30 mg, q.4.w., q.8.w.	48 weeks	All Tx arms: 1,204 Tx arms of interest: 805 Patients with 300 EOS and high-dose ICS: 534	534[b]	≥ 2	48.1
CALIMA, FitzGerald et al. (2016)[58]	30 mg, q.4.w., q.8.w.	56 weeks	All Tx arms: 1,306 Tx arms of interest: 881	881[b]	≥ 2	49.2
CALIMA, FitzGerald et al. (2016) (≥ 300 EOS subgroup)[58]	30 mg, q.4.w., q.8.w.	56 weeks	All Tx arms: 728 Tx arms of interest: 487	487[b]	≥ 2	49.0
OMAL (10 trials)						
EXTRA, Hanania et al. (2013)[54]	150 mg to 375 mg	48 weeks	848	848	≥ 1	44.5
INNOVATE, Humbert et al. (2005)[59]	150 mg to 375 mg	28 weeks	482	482	≥ 2	43.4

Study name, author, year	Dosage of interest	Treatment duration	N (ITT)	N included in ITC	Exacerbations[a]	Age, mean
Study 008, Busse et al. (2001)[60]	150 mg to 375 mg	28 weeks	525	525	NR	39.2
Ohta et al.[c] (2009)[61]	150 mg to 75 mg	16 weeks	315	315	NR	49.0
Li et al. [c] (2016)[62]	150 mg to 300 mg/220 mg to 375 mg	16 days (median)	609	609	≥ 2	46.5
SOLAR, Vignola et al. (2004)[63]	150 mg to 375 mg	28 weeks	405	405	NR	38.4
Ayres et al. (2004)[64]/ Niven et al. (2008) (OL)[65]	150 mg to 375 mg	12 months	312	312	≥ 1	38.1 (median)
Hoshino and Ohtawa[c] (2012), (OL)[66]	150 mg to 300 mg, q.4.w. or 225 mg to 375 mg, q.2.w.	16 weeks	30	30	NR	54.9
QUALITX, Rubin et al. (2012) (OL)[67]	150 mg to 375 mg	20 weeks	116	116	NR	44.3
EXALT, Bousquet et al. (2011) (OL)[68]	75 mg to 300 mg, q.4.w. or 225 mg to 375 mg, q.2.w.	32 weeks	400	400	≥ 2	45.7
Bardelas et al. (2012)[69]	150 to 300 mg, q.4.w. or 225 to 375 mg, q.2.w.	24 weeks	271	271	NR	41.3

BENR = benralizumab; CSR = Clinical Study Report; DUPI = dupilumab; EOS = eosinophil; ICS = inhaled corticosteroid; ITC = indirect treatment comparison; ITT = intention to treat; MEPO = mepolizumab; NR = not reported; OL = open label; OMAL = omalizumab; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; q.8.w. = every 8 weeks; RESL = reslizumab; Tx = treatment.

[a]Exacerbations in previous year.

[b]Not all treatment arms were included, as not all dosages or routes of administration were approved or recommended.

[c]Studies conducted in Asian countries.

Source: Sponsor-submitted network meta-analysis report.[4,5]

Results

The key findings of the ITCs are presented in Table 41 for the patient population of uncontrolled persistent asthma and in Table 42 for OCS-dependent asthma.

ITC Results for Uncontrolled Persistent Asthma

Dupilumab Versus Mepolizumab: For the dupilumab 200 mg regimen, the ITC results showed that dupilumab 200 mg was associated with a statistically significantly lower annual severe asthma exacerbation rate than mepolizumab (rate ratio = 0.68; 95% CI, 0.50 to 0.93). No statistically significant between-group difference was found in terms of changes from baseline in FEV_1, ACQ, or AQLQ.

In the dupilumab 300 mg group, no statistically significant between-group difference (dupilumab versus mepolizumab) was found in terms of severe asthma exacerbation or in the changes from baseline in FEV_1, ACQ, or AQLQ.

Dupilumab Versus Reslizumab: For the dupilumab 200 mg regimen, the ITC results showed that dupilumab 200 mg was associated with a statistically significantly lower annual severe asthma exacerbation than reslizumab (rate ratio = 0.58; 95% CI, 0.43 to 0.80). No statistically significant between-group difference was found in terms of changes from baseline in FEV_1, ACQ, or AQLQ.

In the dupilumab 300 mg group, dupilumab showed a statistically significantly larger improvement in FEV_1 from baseline to week 24 than reslizumab: mean treatment group difference (L) = 0.14 (95% CI, 0.02 to 0.25). No statistically significant between-group

Table 38: Overview of Included Studies in ITC for Patients with OCS-Dependent Asthma

Study name, author, year	Dosage of interest	Treatment duration	N (ITT)	N included in ITC	Exacerbations[a]	Age, mean
DUPI						
VENTURE, CSR data[53]	300 mg, q.2.w.	24 weeks	210	210	NR	51.3
MEPO						
SIRIUS, Bel et al. (2014)[70]	100 mg, SC, q.4.w.	20 weeks	135	135	NR	50.0
BENR						
ZONDA, Nair et al. (2017)[71]	30 mg, q.4.w., q.8.w.	28 weeks	All Tx arms: 220 Tx arms of interest: 148	148[b]	≥ 1	51.4
RESL						
NCT02501629[72]	110 mg, q.4.w.	24 weeks	177	177	NR	54.3

BENR = benralizumab; CSR = Clinical Study Report; DUPI = dupilumab; ITC = indirect treatment comparison; ITT = intention to treat; MEPO = mepolizumab; NR = not reported; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; q.8.w. = every 8 weeks; RESL = reslizumab; SC = subcutaneous; Tx = treatment.

[a]Exacerbations in previous year.

[b]Not all treatment arms were included, as not all dosages or routes of administration were approved or recommended.

Source: Sponsor-submitted network meta-analysis report.[4,6]

Table 39: Dupilumab Comparator-Like Subgroup Population Included in ITCs for Uncontrolled Persistent Asthma

DUPI population/ subgroups	Trial	N (% of ITT)	ICS + LABA baseline concentration (per day)	EOS level at baseline (cells/µL)	IgE/allergens	Exacerbations[a]	Age, years
DUPI, ITT	QUEST, DRI12544	1,902 (100%) 465 (100%)	Medium/high	Not required	NA	≥ 1	≥ 12[b]
Anti-IL-5 comparators							
MEPO-like subgroup	QUEST, DRI	406 (21.3%) 112 (24.1%)	High	EOS ≥ 150	NA	≥ 2	≥ 12[b]
RESL-like subgroup	QUEST, DRI	556 (29.2%) 128 (27.5%)	Medium/high	EOS ≥ 400	NA	≥ 1	≥ 18
BENR-like subgroup	QUEST, DRI	439 (23.1%) 100 (21.5%)	Medium/high	EOS ≥ 300	NA	≥ 2	≥ 12[b]
Anti-IgE comparators							
OMAL-like subgroup[c]	QUEST, DRI	300 (15.8%) 133 (28.6%)	Medium/high	NA	30 IU/mL ≤ IgE ≤ 700 IU/mL and at least 1 perennial allergen positive ≥ 0.35 IU/mL at baseline among 9 perennial allergens[d]	Not required	≥ 12[b]
OMAL-like EOS subgroup[c]	QUEST, DRI	300 (15.8%) 133 (28.6%)	Medium/high	EOS ≥ 300	30 IU/mL ≤ IgE ≤ 700 IU/mL and at least 1 perennial allergen positive ≥ 0.35 IU/mL) at baseline among 9 perennial allergens[d]	Not required	≥ 12[b]
Allergic subgroup[e]	QUEST, DRI	459 (24.1%) 183 (39.4%)	Medium/high	NA	IgE ≥ 30 IU/mL and at least 1 perennial allergen positive (≥ 0.35 IU/mL) at baseline among 9 perennial allergens[d]	Not required	≥ 12[b]

DUPI population/ subgroups	Trial	N (% of ITT)	ICS + LABA baseline concentration (per day)	EOS level at baseline (cells/µL)	IgE/allergens	Exacerbations[a]	Age, years
Allergic EOS subgroup[e]	QUEST, DRI	459 (24.1%) 183 (39.4%)	Medium/high	EOS ≥ 300	IgE ≥ 30 IU/mL and at least 1 perennial allergen positive (≥ 0.35 IU/mL) at baseline among 9 perennial allergens[d]	Not required	≥ 12[b]

BENR = benralizumab; DUPI = dupilumab; EOS = eosinophil; ICS = inhaled corticosteroid; IgE = immunoglobulin E; IL = interleukin; ITT = intention to treat; LABA = long-acting beta2-agonist; MEPO = mepolizumab; NA = not available; OMAL = omalizumab; RESL = reslizumab.

[a]Exacerbations in previous year.

[b]DRI recruited patients 18 years or older.

[c]Despite an attempt to align patients from the dupilumab trials with those in the omalizumab trials, some differences remained. Allergic skin tests were not performed in the dupilumab trials, but a positive skin test was required for entry into the omalizumab trials. Patients were included in the omalizumab-like subgroups if they had baseline total IgE levels between 30 IU/mL and ≤ 700 IU/mL and at least 1 antigen-specific IgE for perennial allergens with levels greater than or equal to 0.35 IU/mL. Dupilumab trials recruited patients with at least 1 exacerbation in the prior year.

[d]*Alternaria tenuis/alternata* IgE; *Cladosporium herbarum/hormodendrum* IgE; *Aspergillus fumigatus* IgE; Cat dander IgE; *Dermatophagoides farinae* IgE; *Dermatophagoides pteronyssinus* IgE; Dog dander IgE; German cockroach IgE; and Oriental cockroach IgE.

[e]Given that omalizumab trials included an upper limit on IgE (which is inconsistent with clinical practice on defining allergic asthma), a subgroup was defined based on an allergic asthma phenotype. Patients from the dupilumab trials were included in the allergic asthma subgroup if they had baseline total IgE greater than or equal to 30 IU/mL (without the upper limit) and at least 1 antigen-specific IgE for perennial allergens with levels greater than or equal to 0.35 IU/mL. Dupilumab trials recruited patients with at least 1 exacerbation in the prior year.

Source: Sponsor-submitted network meta-analysis report.[4,5]

difference was found in terms of severe asthma exacerbation or in change from baseline in ACQ or AQLQ between dupilumab and reslizumab.

Dupilumab Versus Benralizumab: For the dupilumab 200 mg regimen, the ITC results showed that dupilumab 200 mg was associated with a statistically significantly lower rate of severe asthma exacerbation than benralizumab (rate ratio = 0.46; 95% CI, 0.32 to 0.66). Dupilumab also showed a statistically significantly larger improvement in FEV_1 at week 24 than benralizumab (mean between-group difference of changes from baseline = 0.15; 95% CI,

Table 40: DUPI Comparator-Like Subgroups Population Included in ITC for OCS-Dependent Asthma

Trials	ICS + LABA baseline	EOS level at baseline, cells/µL	Exacerbations[a]	Age, years
MEPO-like subgroup				
SIRIUS, ITT (MEPO) Bel et al. (2014)[70]	High-dose ICS ≥ 880 mcg/day (ICS ≥ 440 mcg/day for patients aged > 18 years) fluticasone propionate or equivalent daily and an additional controller	> 150 between visit 1 and visit 3 and ≥ 300 in previous 12 months before visit 3 or baseline	NA	≥ 12
VENTURE (DUPI) MEPO-like subgroup CSR data[51]	High	≥ 150	NA	≥ 12[b]
BENR-like subgroup				
ZONDA, ITT (BENR) Nair et al. (2017)[71]	Medium- to high-dose ICS + LABA therapy for at least 12 months before enrolment and treated with high-dose ICS + LABA therapy for at least 6 months before enrolment	≥ 150[c] (85% patients with EOS ≥ 300)	≥ 1	18 to 75
VENTURE (DUPI), BENR-like subgroup, CSR data[51]	High	≥ 300	≥ 1	≥ 18
RESL-like subgroup				
NCT02501629, ITT (RESL)[72]	High-dose ICS ≥ 880 mcg/day (ICS at least medium dose for patients aged > 18 years) of inhaled fluticasone propionate or equivalent daily and another controller for at least 6 months before the screening visit	≥ 300	NA	≥ 12[d]
VENTURE (DUPI) RESL-like subgroup, CSR data[51]	High	≥ 150	NA	≥ 12[e]

BENR = benralizumab; CSR = Clinical Study Report, DUPI = dupilumab; EOS = eosinophil; ICS = inhaled corticosteroid; IgE = immunoglobulin E; ITT = intention to treat; LABA = long-acting beta2-agonist; MEPO = mepolizumab; NA = not available; OCS = oral corticosteroid; OMA = omalizumab; RESL = reslizumab.

[a]Exacerbations in previous year.

[b]Only 1 patient (1.6%) in the placebo arm was less than 18 years of age.

[c]In ZONDA, more than 85% of patients across all arms had EOS levels greater than 300 cells/µL at baseline.

[d]Only 1 patient (0.6%) in the placebo arm was less than 18 years of age.

[e]Only 1 patient (2.9%) in the placebo arm was less than 18 years of age.

Source: Sponsor-submitted network meta-analysis report.[4,6]

0.03 to 0.27). No statistically significant between-group differences were found in terms of changes from baseline in ACQ or AQLQ.

In the dupilumab 300 mg regimen, the ITC results showed that dupilumab 300 mg was associated with a statistically significantly lower rate of severe asthma exacerbation than benralizumab (rate ratio = 0.45; 95% CI, 0.30 to 0.65). Dupilumab also showed a statistically significantly larger improvement in FEV_1 at week 12 than benralizumab (mean between-group difference = 0.13; 95% CI, 0.00 to 0.26). No statistically significant between-group differences were found in terms of changes from baseline for ACQ or AQLQ.

Dupilumab Versus Omalizumab: For the dupilumab 200 mg regimen, the ITC results showed that dupilumab 200 mg was associated with a statistically significantly larger improvement of FEV_1 at week 12 than omalizumab (mean between-group difference = 0.11; 95% CI, 0.01 to 0.21) in the allergic asthma subgroup. No statistically significant between-group differences were found in the allergic asthma subgroup in terms of rate of annual severe exacerbation or in changes from baseline in ACQ or AQLQ.

For the dupilumab 300 mg regimen, dupilumab showed a statistically significantly larger improvement of FEV_1 at week 12 in the omalizumab-like subgroup than in the omalizumab group (mean between-group difference of changes from baseline, dupilumab versus omalizumab = 0.16; 95% CI, 0.05 to 0.27).

The ITC results also showed that dupilumab 300 mg in the allergic asthma subgroup was associated with a statistically significant lower rate of severe asthma exacerbation than omalizumab (rate ratio = 0.67; 95% CI, 0.47 to 0.96). In addition, dupilumab 300 mg in the allergic asthma subgroup showed a statistically significantly larger improvement of FEV_1 at week 12 than omalizumab (mean between-group difference = 0.13; 95% CI, 0.03 to 0.23). Furthermore, in the allergic asthma eosinophilic subgroup, dupilumab 300 mg was associated with a statistically significantly lower rate of severe asthma exacerbations than omalizumab (rate ratio = 0.60; 95% CI, 0.37 to 0.99). Dupilumab 300 mg in the allergic asthma eosinophilic subgroup also showed a statistically significantly larger improvement in percentage of predicted FEV_1 at week 24 and 52 than omalizumab, with a mean between-group difference of 4.21 (95% CI, 0.23 to 8.18) at week 24 and of 7.94 (95% CI, 3.48 to 12.40) at week 52. No statistically significant between-group differences were found in terms of changes from baseline in ACQ or AQLQ (see Table 41).

Patients With Moderate-to-Severe OCS-Dependent Asthma: Children and Adults 12 Years and Older: No statistically significant treatment group differences were found between dupilumab 300 mg and mepolizumab or between dupilumab 300 mg and mepolizumab in terms of reducing the dose of OCS, reducing the rate of annual exacerbations, or improving FEV_1, ACQ, or AQLQ. No base-case analysis was done to compare dupilumab with reslizumab in the OCS-dependent population (Table 42).

Critical Appraisal of the Sponsor-Submitted ITCs

Several limitations of these ITCs are discussed in this section. An important limitation of both sponsor-submitted ITCs is the use of subgroups from the dupilumab studies to conduct the analyses. The use of subgroups resulted in reduced sample sizes when compared to the original trial populations, and the generalizability of the results relative to the original trial populations is unclear. In addition, results across the different biologic agents cannot be compared because the dupilumab subgroup varied based on the comparator. Lastly,

Table 41: Primary Results Summary in Uncontrolled Persistent Asthma: Patients 12 Years and Older

Comparison	ASE[a] (rate ratio)	FEV_1 CFB at 12 weeks, L, MD (95% CI)	FEV_1 CFB at 24 weeks, L, MD (95% CI)	Predicted FEV_1 CFB at 24 weeks, %, MD (95% CI)	Predicted FEV_1 CFB at 52 weeks, %, MD (95% CI)	ACQ-5[a] CFB at 24 weeks, MD (95% CI)	ACQ-6[a] CFB at 24 weeks, MD (95% CI)	ACQ-6[a] CFB at 52 weeks, MD (95% CI)	AQLQ[b] CFB at 24 weeks, MD (95% CI)
Dupilumab 200 mg q.2.w. vs.									
Anti-IL-5 comparators									
MEPO-like subgroup vs. MEPO	**0.68 (0.50 to 0.93)**	0.06 (−0.10 to 0.22)	0.09 (−0.03 to 0.21)	1.43 (−2.51 to 5.37)	NA	−0.24 (−0.86 to 0.38)	−0.26 (−0.63 to 0.11)	−0.16 (−0.57 to 0.25)	NA
RESL-like subgroup vs. RESL	**0.58 (0.43 to 0.80)**	0.07 (−0.05 to 0.18)	*0.15 (0.04 to 0.27)*	NA	NA	NA	NA	NA	0.26 (−0.24 to 0.76)
BENR-like subgroup vs. BENR	**0.46 (0.32 to 0.66)**	0.12 (−0.01 to 0.25)	**0.15 (0.03 to 0.27)**	NA	NA	NA	NA	−0.16 (−0.45 to 0.13)	NA
Anti-IgE comparators									
OMAL-like subgroup vs. OMAL	0.76 (0.35 to 1.68)[c]	0.05 (−0.05 to 0.16)	0.03 (−0.08 to 0.14)	NA	NA	NA	NA	NA	−0.18 (−0.42 to 0.07)
OMAL-like eosinophilic subgroup vs. OMAL	0.86 (0.49 to 1.51)[c]	NA	NA	1.63 (−2.76 to 6.03)	5.51 (0.53 to 10.49)	NA	NA	NA	NA
Allergic asthma subgroup vs. OMAL	0.80 (0.61 to 1.05)	**0.11 (0.01 to 0.21)**	0.07 (−0.02 to 0.16)	NA	NA	NA	NA	NA	−0.20 (−0.41 to 0.01)
Allergic asthma eosinophilic subgroup vs. OMAL	0.68 (0.42 to 1.10)[c]	NA	NA	3.51 (−0.89 to 7.91)	8.84 (4.55 to 13.13)	NA	NA	NA	NA
Dupilumab 300 mg q.2.w. vs.									
Anti-IL-5 comparators									
MEPO-like subgroup vs. MEPO	0.79 (0.58 to 1.09)	0.10 (−0.05 to 0.26)	0.10 (−0.07 to 0.27)	1.97 (−1.89 to 5.83)	NA	−0.05 (−0.63 to 0.54)	−0.10 (−0.47 to 0.27)	−0.15 (−0.54 to 0.24)	NA

Comparison	ASE[a] (rate ratio)	FEV_1 CFB at 12 weeks, L, MD (95% CI)	FEV_1 CFB at 24 weeks, L, MD (95% CI)	Predicted FEV_1 CFB at 24 weeks, %, MD (95% CI)	Predicted FEV_1 CFB at 52 weeks, %, MD (95% CI)	ACQ-5[a] CFB at 24 weeks, MD (95% CI)	ACQ-6[a] CFB at 24 weeks, MD (95% CI)	ACQ-6[a] CFB at 52 weeks, MD (95% CI)	AQLQ[b] CFB at 24 weeks, MD (95% CI)
RESL-like subgroup vs. RESL	0.45 (0.13 to 1.58)	0.10 (−0.02 to 0.21)	**0.14 (0.02 to 0.25)**	NA	NA	NA	NA	NA	0.30 (−0.21 to 0.81)
BENR-like subgroup vs. BENR	**0.45 (0.30 to 0.65)**	**0.13 (0.00 to 0.26)**	0.08 (−0.07 to 0.24)	NA	NA	NA	NA	−0.23 (−0.52 to 0.06)	NA
Anti-IgE comparators									
OMAL-like subgroup vs. OMAL	0.77 (0.46 to 1.29)[c]	**0.16 (0.05 to 0.27)**	0.09 (−0.02 to 0.20)	NA	NA	NA	NA	NA	−0.06 (−0.42 to 0.31)
OMAL-like eosinophilic subgroup vs. OMAL	0.61 (0.35 to 1.09)[c]	NA	NA	4.32 (−0.14 to 8.79)	8.41 (3.18 to 13.64)	NA	NA	NA	NA
Allergic asthma subgroup vs. OMAL	**0.67 (0.47 to 0.96)**[c]	**0.13 (0.03 to 0.23)**	0.07 (−0.02 to 0.17)	NA	NA	NA	NA	NA	−0.10 (−0.41 to 0.22)
Allergic asthma eosinophilic subgroup vs. OMAL	0.60 (0.37 to 0.99)[c]	NA	NA	**4.21 (0.23 to 8.18)**	**7.94 (3.48 to 12.40)**	NA	NA	NA	NA

ACQ = Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; ASE = annualized severe exacerbations; BENR = benralizumab; CFB = change from baseline; CI = confidence interval; FEV_1 = forced expiratory volume in the first second; IgE = immunoglobin E; IL = interleukin; MD = mean difference; MEPO = mepolizumab; NA = not available; OMAL = omalizumab; q.2.w. = every 2 weeks; RESL = reslizumab; vs. = versus .

[a]Lower scores indicate better asthma control.

[b]Higher scores indicate better health-related quality of life.

[c]Exploratory analysis given inconsistent definition of severe exacerbations in the dupilumab vs. OMAL trials. Analyses were conducted using data on the number of severe exacerbations that occurred during the 24-week study period or last dose date plus 14 days, whichever was later, regardless of whether patients were on or off treatment.

Source: Sponsor-submitted network meta-analysis report.[4,5]

despite matching specific populations, important differences remained in the distributions of potential treatment effect modifiers (e.g., severity of the included patients).

ITCs for the Uncontrolled Persistent Asthma Population

Even though various subgroup data were generated from the QUEST[1] and DRI12544[3] trials to better align the baseline patient characteristics with the corresponding comparator trials, some differences in patient populations remained. For example, most comparator trials included some patients on maintenance OCS, which was not permitted in the dupilumab trials.

The mepolizumab trials included patients with baseline eosinophils greater than or equal to 150 cells/µL or greater than or equal to 300 cells/µL in the prior year, while the dupilumab trials did not select patients based on eosinophil status, nor did they collect data on eosinophil levels in the prior year. Subgroup data were available from the MENSA trial for mepolizumab,[51] which excluded patients on OCS and those with fewer than 4 prior exacerbations. However, given the further reduction in the sample size for both dupilumab subgroups and MENSA, a large degree of uncertainty in estimates would be expected in any analyses on this small subgroup.

In the omalizumab trials, the definition of severe exacerbations varied across uncontrolled persistent asthma trials, with most differences concerning the duration of increased OCS use and the requirement of hospitalization or emergency department visit.

Seasonality might also be associated with a subtle modulation of lung function tests. Asthma exacerbations likely differ slightly across seasons. Given the seasonality of asthma symptoms and the potential impact that the timing of assessment could also have on exacerbation rates, data with regard to season of assessment were sought. None of the

Table 42: Primary Results Summary (Bucher ITCs) for OCS-Dependent Asthma: Patients 12 Years and Older

Comparison	Reduction in OCS dose < 5 mg/day, OR (95% CI)	Reduction in OCS dose ≥ 50%, OR (95% CI)	100% reduction in OCS dose, OR (95% CI)	FEV_1 CFB at 12 weeks, L, MD (95% CI)	FEV_1 CFB at 24 weeks, L, MD (95% CI)	ACQ-5[a] CFB at 24 weeks, MD (95% CI)	ACQ-6[a] CFB at 24 weeks, MD (95% CI)	AQLQ[b] CFB at 24 weeks, MD (95% CI)	ASE (rate ratio)
Dupilumab 300 mg q.2.w. vs.									
MEPO-like subgroup vs. MEPO	1.50 (0.54 to 4.14)	1.80 (0.62 to 5.21)	1.16 (0.31 to 4.44)	NA	0.17 (−0.05 to 0.39)	0.06 (−0.51 to 0.63)	NA	NA	0.67 (0.36 to 1.28)
BENR-like subgroup vs. BENR	1.95 (0.51 to 7.38)	1.15 (0.30 to 4.45)	0.98 (0.21 to 4.59)	−0.01 (−0.27 to 0.25)	0.18 (−0.09 to 0.45)	NA	−0.32 (−1.15 to 0.51)	0.28 (−0.52 to 1.08)	0.86 (0.35 to 2.13)

ACQ = Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; ASE = annualized severe exacerbations; BENR = benralizumab; CFB = change from baseline; CI = confidence interval; FEV_1 = forced expiratory volume in the first second; ITC = indirect treatment comparison; MD = mean difference; MEPO = mepolizumab; NA = not available; OCS = oral corticosteroid; OR = odds ratio; q.2.w. = every 2 weeks; vs. = versus .

[a]Lower scores indicate better asthma control.

[b]Higher scores indicate better health-related quality of life.

Source: Sponsor-submitted network meta-analysis report.[4,6]

included trials assessed exacerbation outcomes by season of assessment, and data around recruitment and follow-up were variable.

Not all studies reported rate ratios or the mean difference of changes from baseline; therefore, analyses were conducted using arm-level data. For severe exacerbations, the number of patient-years was calculated for comparator trials, since no such information was reported. In addition, arm-level analyses conducted for each study were generally based on the raw reported rates and were not adjusted in any way. Due to these important methodological differences, there were discrepancies between the calculated results (which used arm-level data and estimated patient-years, and were unadjusted) and the reported results from some of the included trials.

There were some variations in terms of the outcome estimation time points across trials and differences in the study design (e.g., randomization versus partial randomization, blind versus open label, parallel versus cross over). Given the limited data available per analysis, it was not possible to perform a meta-regression to account for those differences, such as variation in the time points or patient characteristics.

Due to these differences across the trials, it was not possible to create dupilumab subgroups that fully aligned with the populations assessed in the comparator trials. Using the various dupilumab subgroup data in the ITCs resulted in a small number of patients in the subgroups; therefore, the results of the analysis were associated with uncertainty due to the small evidence base.

Furthermore, safety outcomes were not assessed in the ITCs due to variation in terms of follow-up duration, with inconsistent definitions of adverse events across included trials.

ITCs for the OCS-Dependent Asthma Population

The heterogeneity across the trials and the ITC only included 1 relatively small- to modest-sized study each for mepolizumab and benralizumab; therefore, it is uncertain whether the findings from the ITCs can be generalized to the overall OCS-dependent asthma population.

In addition, no ITCs were performed that compared dupilumab with reslizumab or with omalizumab in this population.

Overall, there is considerable uncertainty in the findings of the 2 sponsor-submitted ITCs.

Summary

In the absence of direct evidence comparing dupilumab with other existing therapies as an add-on maintenance treatment in patients 12 years and older with severe asthma with a type 2 or eosinophilic phenotype or with OCS-dependent asthma, the sponsor submitted 2 Bucher ITCs.[4-6] One was for patients with uncontrolled persistent severe asthma; the other was for patients with OCS-dependent asthma in children 12 years and older and in adults.

For patients with uncontrolled persistent asthma: For dupilumab 200 mg, the results of the ITC showed that dupilumab 200 mg was associated with a statistically significantly lower rate of severe asthma exacerbation than mepolizumab, benralizumab, and reslizumab. Dupilumab 200 mg statistically significantly improved the FEV_1 at week 24 compared with reslizumab. Dupilumab 200 mg also showed a statistically significant improvement in FEV_1 at week 12 compared with omalizumab in the patients with allergic asthma subgroup. The ITC showed that dupilumab 300 mg was associated with a statistically significantly lower rate of severe

asthma exacerbations than benralizumab and than omalizumab in the allergic asthma subgroup and the allergic eosinophilic asthma subgroup. Dupilumab 300 mg also statistically significantly improved the FEV_1 at week 24 compared with reslizumab and with benralizumab at 12 weeks. Dupilumab also showed a statistically significantly improved FEV_1 at week 12 compared with the overall omalizumab group and when compared with omalizumab in the patients with allergic asthma subgroup. No statistically significant differences were identified between dupilumab and mepolizumab, benralizumab, reslizumab, and omalizumab in terms of ACQ and AQLQ scores.

For patients with OCS-dependent asthma: In children and adults 12 years and older, no statistically significant difference was found between dupilumab and the other recommended biologics in terms of reducing the dose of OCS, reducing the rate of annual exacerbations, or improving FEV_1, ACQ, or AQLQ.

However, due to various methodological limitations, no robust conclusions can be drawn about the comparative clinical efficacy of dupilumab versus mepolizumab, benralizumab, reslizumab, and omalizumab in the treatment of patients with uncontrolled persistent or OCS-dependent asthma. The clinical expert CADTH consulted for this review also expressed concerns about the credibility of the findings due to the methodological limitations.

Description of 5 ITCs Identified by CADTH Literature Search

A total of 510 citations were identified in the literature search. Following screening of titles and abstracts, 505 citations were excluded and 5 potentially relevant reports from the electronic search were retrieved for full-text review. All 5 ITCs[7-11] were identified to be relevant to this review and were included in this ITC summary. Only PICOS of interest for this review are reported in this section.

Methods of the 5 ITCs Identified by CADTH

The key characteristics of the 5 ITCs identified by CADTH are presented in Table 43.

Ando et al. (2020)[7] conducted an ITC using a Bayesian approach to assess the comparative efficacy and safety of dupilumab and benralizumab in patients with inadequately controlled asthma. The primary efficacy end point was the annual exacerbation rate; the secondary outcomes included FEV_1, AQLQ, and adverse events.

Bourdin et al. (2020)[8] performed an anchored MAIC to assess the efficacy of dupilumab and benralizumab in the treatment of patients with asthma who were receiving OCS. The outcomes included OCS dosage reduction, OCS elimination, and annual asthma exacerbation rate reduction.

Ramonell and Iftikhar (2020)[9] conducted an NMA using a frequentist approach to examine the efficacy of dupilumab compared with benralizumab, mepolizumab, and reslizumab in the treatment of patients with severe eosinophilic asthma (defined in this NMA as an absolute eosinophil count ≥ 250 cells/μL). The outcome was the annual asthma exacerbation rate reduction.

Edris et al. (2019)[10] performed an NMA using a Bayesian approach to evaluate the efficacy of dupilumab compared with benralizumab, mepolizumab, and reslizumab in the treatment of patients with type 2 inflammation asthma. The outcome reported was asthma exacerbations.

Iftikhar et al. (2018)[11] conducted an NMA using a frequentist approach to examine the efficacy of dupilumab compared with benralizumab, mepolizumab, and reslizumab in the treatment of patients with eosinophilic asthma. The outcomes were FEV_1, ACQ, and AQLQ.

The risk of bias of the included studies was assessed in Ando et al. (2020)[7] and Edris et al. (2019)[10]; the publication bias was assessed in the ITCs by Iftikhar et al. (2018)[11] and Ramonell and Iftikhar (2020).[9] The ITC by Bourdin et al.[8] was a MAIC. The included studies in each of the 5 ITCs entirely or partially overlapped the studies included in the sponsor's ITCs or overlapped 1 of the other 5 ITCs.

Results

The key findings of the 5 ITCs identified by CADTH are presented in Table 44.

In the treatment of patients with inadequately controlled asthma, Ando et al. (2020)[7] reported that the annual exacerbation rate was lower in the dupilumab group than in the benralizumab group in the subgroups with a blood eosinophil count of 150 to 299 cells/μL and greater than or equal to 300 cells/μL, which had dupilumab versus benralizumab rate ratios of 0.51 (95% credible interval [CrI] 0.29 to 0.92) and 0.58 (95% CrI, 0.39 to 0.84), respectively. However, there was no difference in the annual exacerbation rate between dupilumab and benralizumab in overall patient population or in the subgroup with a blood eosinophil count of less than 150 cells/μL (Table 44). There was no difference observed in terms of FEV_1, AQLQ, and any adverse events between the dupilumab and benralizumab groups.

In the treatment of patients with asthma who were receiving OCS, the MAIC by Bourdin et al. (2020)[8] demonstrated that there was no statistically significant difference between dupilumab and benralizumab in terms of OCS dosage reduction, OCS elimination, and annual asthma exacerbation rate reduction.

In the treatment of patients with severe eosinophilic asthma (defined as and absolute eosinophil count greater than or equal to 250 cells/μL), in terms of asthma exacerbations, the NMA by Ramonell and Iftikhar (2020)[9] showed that dupilumab was associated with a statistically significantly larger reduction than benralizumab (rate ratio = −0.97; 95% CI, −1.39 to −0.56). However, there was no statistically significant treatment group difference with dupilumab compared to mepolizumab or reslizumab.

In the treatment of patients with severe eosinophilic asthma, in terms of asthma exacerbations, Edris et al. (2019)[10] reported that there was no treatment group difference when comparing dupilumab with benralizumab, mepolizumab, or reslizumab in the treatment of patients with type 2 inflammation asthma.

Iftikhar et al. (2018)[11] found that there was no statistically significant treatment group difference when comparing dupilumab with benralizumab, mepolizumab, or reslizumab in terms of FEV_1, ACQ, or AQLQ in the treatment of patients with eosinophilic asthma.

Critical Appraisal of the 5 ITCs Identified by CADTH

The key limitations of the 5 ITCs identified by CADTH are presented in Table 45.

Compared with the sponsor-submitted ITCs, the scope of the 5 ITCs identified by the CADTH literature search were narrower; that is, they were focused on some particular asthma populations, and fewer comparators and fewer outcomes were assessed. Overall, heterogeneity across studies was an important limitation for all 5 ITCs. In addition, in

Table 43: Five ITCs Identified by CADTH

First author, publication year,	Study design	Patient characteristics	Comparisons	Outcomes
Ando et al. (2020)[7]	SR/ITC (Bayesian) N = 3 RCTs[23,57,58] Literature search period: from 1946 to April 2019. Note: Of the 3 studies: • Two studies[57,58] overlapped with the studies included in the sponsor-submitted ITC[5] • One study[23] overlapped with the Ramonell and Iftikhar (2020)[9] ITC and the Edris et al. (2019)[10] ITC	Patients with inadequately controlled asthma	DUPI vs. BENR	AER FEV_1 AQLQ AEs
Bourdin et al. (2020)[8]	SR/MAIC N = 2 RCTs[28,71] Literature search: August 2016 Note: Of the 2 studies: • One study[71] overlapped with the studies included in the sponsor-submitted ITC[6] • One study[28] overlapped with studies included in the Ramonell and Iftikhar (2020)[9] ITC	Patients with asthma receiving OCS	BENR vs. DUPI	OCS reduction Annual rate of clinically significant exacerbations
Ramonell and Iftikhar (2020)[9]	SR/NMA (frequentist) N = 8 RCTs[23,28,32,50,51,53,58,74] Literature search period: from inception to July 2019 Note: Of the 8 studies: • Five studies[50-53,58] overlapped with the studies included in the sponsor-submitted ITC[5] • One study[23] overlapped with the Ando et al. (2020)[7] ITC and the Edris et al. (2019)[10] ITC • One study[28] overlapped with studies included in the Bourdin et al. (2020)[8] ITC • One study[74] overlapped with the studies included in the Iftikhar et al. (2018)[11] ITC	Patients with severe eosinophilic asthma (defined in this meta-analysis as absolute eosinophil count ≥ 250 cells/μL)	DUPI vs. BENR DUPI vs. MEPO DUPI vs. RESL	Acute exacerbations

First author, publication year,	Study design	Patient characteristics	Comparisons	Outcomes
Edris et al.[a] (2019)[10]	SR/NMA (Bayesian) N = 9 RCTs[23,49,51,53,57,58,75-77] Literature search period: 2005 to 2018 Note: Of the 9 studies: • Five studies[49,51,53,57,58] overlapped with the studies included in the sponsor-submitted ITC[5] • One study[23] overlapped with the Ramonell and Iftikhar (2020)[9] ITC and the Ando et al. (2020)[7] ITC • Three studies[75-77] overlapped with the studies included in the Iftikhar et al. (2018)[11] ITC	Patient with type 2 inflammation asthma	DUPI vs. BENR DUPI vs. MEPO DUPI vs. RESL	Risk of exacerbations
Iftikhar et al.[a] (2018)[11]	SR/NMA (frequentist) N = 20 RCTs[57,58,71,75-78,32,74,49-51,79-81,52,53,55,56,70] Literature search period: from inception to December 2017 Note: Of the 20 studies: • Eleven studies[32,49-53,55-58,71] overlapped with the studies included in the sponsor-submitted ITCs[5,6] • One study[74] overlapped with the studies included in the Ramonell and Iftikhar (2020)[9] ITC • Three studies[75-77] overlapped with the studies included in the Edris et al. (2019)[10] ITC	Patient with eosinophilic asthma	DUPI vs. BENR DUPI vs. MEPO DUPI vs. RESL	FEV_1 ACQ AQLQ

ACQ = Asthma Control Questionnaire; AE = adverse event; AER = annual exacerbation rate; AQLQ = Asthma Quality of Life Questionnaire; BENR = benralizumab; DUPI = dupilumab; FEV_1 = forced expiratory volume in the first second; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison; MEPO = mepolizumab; NMA = network meta-analysis; OCS = oral corticosteroid; RCT = randomized controlled trial; RESL = reslizumab; SR = systematic review; vs. = versus .

Note: Only populations, interventions, comparators, outcomes, and studies relevant to this review were presented in this summary. Only results of ITCs were reported.

[a]Tezepelumab, tralokinumab, and lebrikizumab are not marketed in Canada. Therefore, relevant data on tezepelumab, tralokinumab, and lebrikizumab are not reported in this review.

Source: Five ITCs.[7-11]

the MAIC by Bourdin et al. (2020),[8] not all effect factors could be matched and adjusted. Therefore, the findings derived from the 5 ITCs should be interpreted with caution.

Summary of 5 ITCs Identified by CADTH

Five ITCs that indirectly compared dupilumab with benralizumab, mepolizumab, and reslizumab were identified by CADTH.

In the ITC by Ando et al. (2020),[7] dupilumab was associated with a lower rate of annual exacerbations than benralizumab in patients with inadequately controlled asthma and higher blood eosinophil counts (≥ 150 cells/μL). In the MAIC by Bourdin et al. (2020),[8] benralizumab was similar to dupilumab for OCS dosage reduction, OCS elimination, and annual exacerbation rate reduction. In the NMA by Edris et al. (2019)[10] and the ITC by Ramonell and

Table 44: Summary of Findings of 5 ITCs Identified by CADTH

Comparison	AER	FEV_1 CFB, L, MD (95% CI)	ACQ[a] CFB, MD (95% CI)	AQLQ CFB, MD (95% CI)	OCS reduction, %	AE, OR (95%CrI)
Ando et al. (2020)[7]						
DUPI 300 mg q.2.w. vs. BENR 30 mg q.8.w.	Rate ratio, 95% CrI Overall population 0.83 (0.62 to −1.09) Subgroup with a blood eosinophil count of ≥ 300 cells/µL **0.58 (0.39 to 0.84)** Subgroup with blood eosinophil count of > 150 cells/µL but < 300 cells/µL **0.51 (0.29 to 0.92)** Subgroup eosinophil count of < 150 cells/µL 1.57 (0.73 to 2.82)	Overall population 0.032 (−0.047 to 0.111) Subgroup with a blood eosinophil count of ≥ 300 cells/µL 0.106 (−0.007 to 0.218)	NR	Overall population 0.041 (−0.145 to 0.227) Subgroup with a blood eosinophil count of ≥ 300 cells/µL 0.042 (−0.220 to 0.304)	NR	Any AEs OR (95%CrI) 1.023 (0.688 to 1.526) SAEs OR (95%CrI) 1.319 (0.768 to 2.265)
Bourdin et al. (2020)[8]						
BENR q.8.w. vs. DUPI q.2.w. at 24 weeks	After matching Rate ratio (95% CI; P value) 0.50 (0.20 to 1.28; 0.15)	NR	NR	NR	After matching, OCS, % reduction, between group MD (95% CI; P value) −0.71 (−20.56 to 19.15; 0.94) OCS, % elimination: OR (95% CI; P value) 2.26 (0.52 to 9.84; 0.28)	NR

Comparison	AER	FEV_1 CFB, L, MD (95% CI)	ACQ[a] CFB, MD (95% CI)	AQLQ CFB, MD (95% CI)	OCS reduction, %	AE, OR (95%CrI)
Ramonell and Iftikhar (2020)[9]						
DUPI vs. BENR	Rate ratio (95% CI) **−0.97 (−1.39 to −0.56)[b]**	NR	NR	NR	NR	NR
DUPI vs. MEPO	Rate ratio (95% CI) −0.16 (−0.76 to 0.44)	NR	NR	NR	NR	NR
DUPI vs. RESL	Rate ratio (95% CI) −0.19 (−0.91 to 0.53)	NR	NR	NR	NR	NR
Edris et al. (2019)[10]						
DUPI vs. BENR	Rate ratio (95% CI) −0.439 (−2.07 to 1.12)	NR	NR	NR	NR	NR
DUPI vs. MEPO	Rate ratio (95% CI) −0.472 (−2.33 to 1.53)	NR	NR	NR	NR	NR
DUPI vs. RESL	Rate ratio (95% CI) −0.347 (−2.43 to 1.74)	NR	NR	NR	NR	NR
Iftikhar et al. (2018)[11]						
DUPI vs. BENR	NR	0.03 (−0.05 to 0.12)	−0.02 (−0.24 to 0.18)	0.03 (−0.22 to 0.29)	NR	NR
DUPI vs. MEPO	NR	0.06 (−0.03 to 0.16)	0.11 (−0.1 to 0.34)	0.02 (−0.27 to 0.32)	NR	NR
DUPI vs. RESL	NR	0.02 (−0.06 to 0.11)	−0.04 (−0.28 to 0.18)	0.03 (−0.24 to 0.31)	NR	NR

ACQ = Asthma Control Questionnaire; AE = adverse event; AER = annual exacerbation rate; AQLQ = Asthma Quality of Life Questionnaire; BENR = benralizumab; CFB = change from baseline; CI = confidence interval; CrI = credible

interval; DUPI = dupilumab; FEV_1 = forced expiratory volume in the first second; ITC = indirect treatment comparison; MD = mean difference; MEPO = mepolizumab; NR = not reported; OCS = oral corticosteroid; OR = odds ratio; q.2.w. = every 2 weeks; q.8.w. = every 8 weeks; RESL = reslizumab; SAE = serious adverse event; vs. = versus .

[a]ACQ not specified as ACQ-5, ACQ-6, or ACQ-7.

[b]Indicated between differences in log rate ratio of asthma exacerbations.

Source: Five ITCs.[7-11]

Iftikhar (2020),[9] as well as the NMA by Iftikhar et al. (2018),[11] no differences were reported between dupilumab and benralizumab, mepolizumab, or reslizumab for rate of annual exacerbation, change in FEV_1, change in ACQ, and change in AQLQ.

However, due to various methodological limitations of the 5 ITCs identified by CADTH, no robust conclusions can be drawn about the clinical efficacy of dupilumab compared with benralizumab, mepolizumab, or reslizumab in the treatment of uncontrolled asthma, severe type 2 inflammation asthma, and severe eosinophilic asthma.

Other Relevant Evidence

This section includes 1 study (Study LTS12551)[12] provided in the sponsor's submission. Study LTS12551 was an ongoing study. The study started August 5, 2014. The cut-off date for this interim report was July 29, 2017.[12] The purpose of the study was to evaluate the long-term safety and tolerability of dupilumab 300 mg every 2 weeks as well as the maintenance of efficacy in patients with asthma who participated in a previous dupilumab asthma study.

Methods

Study LTS12551 was an open-label extension study to evaluate the long-term safety and tolerability of dupilumab in patients with asthma who participated in 1 of the 4 previous dupilumab asthma clinical studies (QUEST,[1] VENTURE,[2] DRI12544,[3] and EXPEDITION [PDY14192]).[4,12] The EXPEDITION trial was an exploratory, randomized, double-blind, placebo-controlled study of the effects of dupilumab 300 mg every 2 weeks, subcutaneously, for 12

Table 45: Key Limitations of the 5 ITCs Identified by CADTH

First author, publication year,	Main limitations
Ando et al. (2020)[7]	Heterogeneity between studies in terms of the severity of the included patients.
Bourdin et al. (2020)[8]	The trials varied in defining which patients were eligible for OCS elimination. This component could not be adjusted with MAIC methodology, so the results should be interpreted with caution. Not all patient characteristics were accounted for in the matching process (e.g., which patients were eligible for OCS elimination varied between the 2 included studies). Effective sample size was reduced from the original trial populations. The optimization and OCS-tapering schemes also differed between included studies.
Ramonell and Iftikhar (2020)[9]	The definition of eosinophilic asthma for this study was lowered to include patients with peripheral eosinophilia ≥ 250 cells/μL to allow inclusion of a relatively bigger study population, although more consensus definitions seem to include an eosinophil blood count of ≥ 300 cells/μL. Another limitation of this meta-analysis is that it did not capture all the currently available biologics, including omalizumab.
Edris et al. (2019)[10]	Mepolizumab, benralizumab, and reslizumab trials mostly included subjects based on previous exacerbations and high number of eosinophils. However, the trials evaluating dupilumab selected subjects based only on previous exacerbations. This review primarily points out the major findings owing to difficulties comparing different trials with identical biologics, or comparing between different biologics. This is caused by diversity in administered doses, routes of administration, inclusion criteria, and primary outcomes.
Iftikhar et al. (2018)[11]	Focused on eosinophilic asthma only.

ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison; OCS = oral corticosteroid.
Sources: Five ITCs.[7-11]

weeks on the airway inflammation of adults with uncontrolled persistent asthma.[4,12] The EXPEDITION trial was not a pivotal study and is not included in this submission.

Findings

A total of 1,315 patients (69.1%) from QUEST, 534 (68.6%) from DRI12544, and 139 (66.2%) from VENTURE were enrolled in Study LTS1255. Information about patients from EXPEDITION (PDY14192) was not provided in the Clinical Study Report.[12]

Harms

Overall, the most frequent treatment-emergent adverse events were upper respiratory tract infections, such as viral upper respiratory tract infection (12.4%), bronchitis (7.9%), and upper respiratory tract infection (7.6%). Eosinophilia adverse events in this open-label extension study were observed with rates of 3.1% to 3.6% among patients enrolled from DRI12544, 0.1% to 0.9% among patients enrolled from QUEST, and 4.4% among patients enrolled from VENTURE. The incidence of these events was generally lower than in the parent studies. It was noted that most treatment-emergent adverse events of eosinophilia were laboratory findings without any associated symptoms. Most of the cases were of mild and moderate intensity and did not require corrective treatment or treatment interruption.

The most frequently reported treatment-emergent serious adverse events were asthma and pneumonia.

No patients discontinued dupilumab due to serious adverse events or adverse events.

Three patients, all of them enrolled from DRI12544 and previously treated with dupilumab in this study, experienced treatment-emergent adverse events leading to death.

In the 70 adolescent patients who participated in the study, the safety profile of dupilumab was similar to that observed in the overall population, and no new safety signals were identified in this population.

Efficacy

The findings of the study indicated that dupilumab 300 mg every 2 weeks in patients with asthma maintained a low event rate of severe asthma exacerbation (i.e., the unadjusted annualized event rate of severe asthma exacerbation was 0.347), a reduction of rescue inhaler use, and improved FEV_1, ACQ-5, and AQLQ when compared to the baseline of the parent studies.

Overall, 83.4% of patients enrolled from studies DRI12544 and QUEST who participated in the study had no asthma exacerbation over a mean exposure to dupilumab of 634 and 140 days, respectively. The unadjusted annualized event rate in the overall population was 0.347. The low asthma exacerbation event rate was maintained throughout the study duration.

A mean FEV_1 improvement of greater than or equal to 0.30 L from baseline of the parent study was observed from week 2 of the open-label extension study, and the improvement was sustained up to week 96 for patients enrolled from DRI12544 and up to week 24 (i.e., the last time point with a sufficient number of patients with available data) for patients enrolled from QUEST.

The authors concluded that long-term treatment of adult and adolescent asthma patients with dupilumab 300 mg every 2 weeks was generally well tolerated, with a long-term safety

profile similar to that observed in the respective parent studies. It was also suggested that long-term treatment with dupilumab 300 mg every 2 weeks was associated with sustained clinical benefits for adult and adolescent patients with asthma who had previously participated in controlled dupilumab clinical trials.

Limitations

The limitations of this study were its open-label design and the use of a single arm without a control group. In addition, this was an interim analysis, and subgroup efficacy results for patients from VENTURE were not well reported. Furthermore, no subgroup data for patients from EXPEDITION (PDY14192) were provided in the Clinical Study Report. Lastly, all patients in the LTS1255 study received dupilumab 300 mg. As a result, it is unclear if the efficacy and safety results of this study apply to the 200 mg dose of dupilumab.

Discussion

Summary of Available Evidence

Three double-blind randomized controlled trials were included in this review. QUEST (N = 1,902) and DRI12544 (N = 465) were conducted in patients with moderate-to-severe asthma, and VENTURE (N = 210) featured patients with severe asthma, who despite persistent use of OCSs were still having severe exacerbations at least once per year. QUEST compared 2 dosages of dupilumab (200 mg every 2 weeks and 300 mg every 2 weeks) to matched placebo over 52 weeks, while DRI124544 was a dose-ranging study that compared dupilumab 200 mg every 2 weeks or every 4 weeks and dupilumab 300 mg every 2 weeks or every 4 weeks to placebo, over 24 weeks. VENTURE compared dupilumab 300 mg every 2 weeks to placebo over 24 weeks. The co-primary outcome of QUEST was annualized rate of severe exacerbations and change from baseline to week 12 in pre-bronchodilator FEV_1, while the primary outcome of VENTURE was the percent reduction in OCS dose by week 24.

Indirect evidence comparing the efficacy of dupilumab to other monoclonal antibodies for asthma was available from 2 sponsor-submitted ITCs as well as 5 published ITCs; however, a variety of methodological issues limit any conclusions that can be drawn from these data. With respect to other relevant studies, longer term data evaluating the efficacy and safety of dupilumab 300 mg were available from the open-label extension study, LTS12551, which continued to follow patients from QUEST, VENTURE, and DRI12544. The findings of this study are limited by the open-label design and lack of control group.

Interpretation of Results

Efficacy

The sponsor has proposed reimbursement criteria in addition to the indication for dupilumab. First, the sponsor suggests that all patients should have had 2 or more clinically significant asthma exacerbations in the past year, and this is consistent with the average number of asthma exacerbations within the previous year seen across the studies, although there is no pre-planned subgroup data from the included studies that focus on these patients. The sponsor published a post hoc subgroup analysis that focused on response in patients with 2 or more severe asthma exacerbations in the past year; however, such analyses need to be interpreted with caution.[30] Some of their proposals, such as the requirement for reaching

a certain threshold for FeNO and the requirement for clinically allergen-driven asthma are impractical, as FeNO is not routinely measured in clinical practice according to the clinical expert consulted by CADTH. The requirement for clinically allergen-driven asthma relates to the GINA guidelines, which describe a list of characteristics that might indicate type 2 inflammation that is refractory. There was no pre-planned subgroup that focused on this subpopulation in the included studies. The sponsor did publish a post hoc subgroup analysis using what it described as a common definition of allergic asthma used in the US (total serum IgE ≥ 30 IU/mL and ≥ 1 perennial aeroallergen specific IgE ≥ 0.35 kU/L at baseline). The findings of this subgroup analysis may suggest that dupilumab has efficacy in this subpopulation; however, these results should be interpreted with caution, given the potential for bias with such analyses.[82] Patients with blood eosinophils of at least 150/µL was another suggested criterion, and this, along with other cut-offs for eosinophils were pre-specified subgroups in all the studies, were part of the primary analysis in DRI12544, and were multiplicity controlled in QUEST. The findings from these subgroup analyses indicate that patients with higher eosinophil counts appear to derive greater benefit from dupilumab, at least with respect to annualized exacerbation rates, and that for patients with lower eosinophil counts (< 300 cells/µL or < 150 cells/µL), there was no difference in annualized exacerbation rates between dupilumab and placebo. These findings, along with the fact that GINA uses 150 cells/µL as a cut-off for refractory type 2 inflammation, suggest that it may indeed be prudent to limit the use of dupilumab to those with eosinophil counts of at least 150 cells/µL, although different provinces may report lab values with less acuity than others, and the clinical expert consulted by CADTH thought 200 cells/µL might be a reasonable cut-off for labs that only report round numbers (i.e., 100 cells/µL, 200 cells/µL, 300 cells/µL). Another suggested criterion was to limit use to those with OCS-dependent asthma. Data for this subgroup are found in the VENTURE trial.

VENTURE enrolled patients who were still having exacerbations despite treatment with high-dose ICS and chronic use of OCSs, labelled as patients with severe asthma. The primary and key secondary outcomes of this study all focused on reducing the use of OCS while maintaining asthma control, and dupilumab appears to have achieved these goals, allowing a larger percentage of dupilumab patients to reduce their OCS dose by 50% or more and allowing a larger percentage of dupilumab patients to stop OCSs altogether when compared to placebo. Dupilumab also allowed patients to reduce their OCS dose by 2.8 mg/day over placebo, from a baseline of 11 mg daily, and the clinical expert consulted on this review believed this to be a clinically significant reduction in dose. There are numerous well-documented toxicities associated with the chronic use of systemic corticosteroids, including osteoporosis and increased fracture risk, and thus reducing corticosteroid exposure is desirable. According to the clinical expert consulted by CADTH on this review, only a relatively small percentage of patients would have asthma severe enough to require long-term OCSs.

With the addition of dupilumab, an IL-4 and IL-13 inhibitor, there are now 3 classes of monoclonal antibodies approved for use, typically in severe asthma. Currently, no studies directly compare any of these drugs, and thus any comparisons of the efficacy and safety of the various monoclonal antibodies for asthma must come from indirect comparisons. CADTH reviewed 2 sponsor-submitted ITCs as well as 5 ITCs in the literature[5-11]; however, methodological limitations associated with each of these studies preclude any definitive conclusions being drawn about the efficacy and safety of dupilumab versus other monoclonal antibodies for asthma, although the submitted ITCs currently provide the best available comparative clinical efficacy of dupilumab versus benralizumab, mepolizumab, and omalizumab. There is also no evidence with respect to sequencing, as there were few or no

patients in the included trials who had previous exposure to other monoclonal antibodies. It is therefore not known, for example, whether a patient who did not respond to an IL-5 inhibitor would be more or less likely to respond to dupilumab, or vice versa.

Dupilumab is indicated for use in patients with severe asthma despite the fact that only 1 of the 3 pivotal trials (VENTURE) focused exclusively on this population. Based on the Health Canada reviewers report, it appears that the sponsor's initial application was for an indication in moderate-to-severe asthma.[27] Health Canada argued, however, that the indication should actually be for severe asthma, with 2 key reasons being that most of the currently approved monoclonal antibodies for asthma are indicated for severe asthma and that the populations of QUEST and DRI12544 were actually consistent with that of severe asthma, rather than a mix of moderate-to-severe asthma. Health Canada also noted that the GINA guidelines recommend use of dupilumab in patients with severe asthma. Health Canada noted that patients with moderate asthma are considered to be at GINA step 3, where patients are expected to experience asthma control with low-dose ICS, while patients with severe asthma (GINA steps 4 to 5) are those who require medium- to high-dose ICS, in addition to other controllers and/or systemic corticosteroids to maintain control of their asthma (or remain uncontrolled despite these therapies). Therefore, since most patients were on medium- to high-dose ICS in QUEST and DRI12544, Health Canada considered these to be patients with severe asthma. The sponsor countered that patients in these studies were on medium to high doses of ICS and, thus, should be considered to have moderate-to-severe asthma. Based on the high placebo response seen in the studies, patients may have also been undertreated according to the clinical expert consulted by CADTH on this review; in other words, many of the patients should have been on high-dose ICS, although this cannot be confirmed without access to patient-level data.

Asthma clearly has an important impact on health-related quality of life, and this is clear from the patient input provided to CADTH. The disease-specific AQLQ was used to assess improvements in health-related quality of life in the included studies. In VENTURE, AQLQ was not controlled for multiplicity, and in QUEST, the results are unclear due to early failure of the statistical hierarchy, making it difficult to draw definitive conclusions about the impact of dupilumab on health-related quality of life. In DRI12544, the late changes made to the study design as a result of change in status to a pivotal trial also confound interpretation of results, including health-related quality of life and symptoms. However, the overall differences between dupilumab and placebo for AQLQ global scores did not meet the MID of 0.5 in any of the studies, although the changes from baseline met the MID of 0.5 in all 3 studies. Part of the reason for this may have been a robust placebo response that was not only evident in assessment of AQLQ but across a number of other outcomes including nighttime awakenings, use of rescue inhalers, and tests of pulmonary function. These large placebo responses were also seen with the ACQ-5, a validated instrument used to assess asthma symptom control. The ACQ-5 had the same issue as the AQLQ with respect to lack of control for multiplicity, and the differences between dupilumab and placebo also failed to meet the MID threshold of 0.5. Thus, 1 cannot conclude that dupilumab improves health-related quality of life or asthma symptoms, despite improvements in risk of exacerbations, pulmonary function, and — in VENTURE — reduced need for OCS. Asthma symptoms and health-related quality of life are clearly of importance to patients who have asthma, based on their input to CADTH.

Harms

There was no clear or consistent indication of serious safety or tolerability issues with dupilumab in the included studies. The product monograph for dupilumab notes hypersensitivity reactions, helminth infections, eye disorders (conjunctivitis and keratitis), and eosinophilia as notable harms. Hypersensitivity reactions are an issue common to all monoclonal antibodies, although there was no indication of an increased risk of hypersensitivity reactions with dupilumab versus placebo. Helminth infections were identified as a concern from the clinical trials investigating dupilumab for atopic dermatitis, and though the mechanism has not been established, the theory is that immune suppression creates an environment where helminth infections may develop. Conjunctivitis and keratitis were also observations from the clinical trials of dupilumab for other indications, namely atopic dermatitis. Longer term follow-up data from the extension, LTS12551, did not reveal any new safety issues or any increased risk of existing safety issues from those seen in the parent trials; however, these findings are limited by the lack of control group.

Conclusions

Three sponsor-funded, multinational, double-blind randomized controlled trials were included in this review. Both the 200 mg and 300 mg doses of dupilumab, every 2 weeks, reduced the annualized rate of severe exacerbations compared to placebo. In a population with severe OCS-dependent asthma, dupilumab 300 mg every 2 weeks reduced the daily OCS dose requirements versus placebo, a clinically significant reduction according to the clinical expert, and this is important given the serious adverse effects associated with this class of drugs. Dupilumab also improved FEV_1 versus placebo. However, although numerical improvements in health-related quality of life and symptoms were reported, the between-group differences were not controlled for multiple comparisons, and the difference between the dupilumab and placebo groups did not exceed the MID. There was no indication of any clear or consistent differences in serious harms or tolerability issues between dupilumab and placebo. Findings from several ITCs, both sponsor submitted and published, were inconclusive with respect to the relative efficacy of dupilumab to other monoclonal antibodies due to methodological issues associated with each. A longer term extension study did not identify any new safety issues and appeared to suggest that efficacy results are durable, including reduction in risk of severe exacerbations; however, the lack of control group limits any conclusions that can be drawn from these data.

References

1. Clinical Study Report: EFC13579. A randomized, double blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab in patients with persistent asthma [internal sponsor's report]. Mississauga (ON): Sanofi Genzyme; 2017 Dec 4.
2. Clinical Study Report: EFC13691. A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of dupilumab in patients with severe steroid dependent asthma [internal sponsor's report]. Mississauga (ON): Sanofi Genzyme; 2017 Dec 13.
3. Clinical Study Report: DRI12544. A randomized, double-blind, placebo-controlled, dose-ranging study to evaluate dupilumab in patients with moderate to severe uncontrolled asthma [internal sponsor's report]. Mississauga (ON): Sanofi Genzyme; 2016 Feb 24.
4. Drug Reimbursement Review sponsor submission: Dupixent (dupilumab), 200 mg and 300 mg solution for subcutaneous injection [internal sponsor's package]. Mississauga (ON): Sanofi Genzyme; 2020 Nov 26.
5. Comparative efficacy of dupilumab vs. approved biologic therapies for uncontrolled and persistent asthma [internal sponsor's report] In: *Drug Reimbursement Review sponsor submission: Dupixent (dupilumab), 200 mg and 300 mg solution for subcutaneous injection.* Mississauga (ON): Sanofi Genzyme; 2020 Nov 26.
6. Comparative efficacy of dupilumab vs. approved biologic therapies for OCS-dependent asthma population [internal sponsor's report] In: *Drug Reimbursement Review sponsor submission: Dupixent (dupilumab), 200 mg and 300 mg solution for subcutaneous injection.* . Mississauga (ON): Sanofi Genzyme; 2020 Nov 26.
7. Ando K, Tanaka A, Sagara H. Comparative efficacy and safety of dupilumab and benralizumab in patients with inadequately controlled asthma: a systematic review. *Int J Mol Sci.* 2020;21(3):30. PubMed
8. Bourdin A, Husereau D, Molinari N, et al. Matching-adjusted comparison of oral corticosteroid reduction in asthma: systematic review of biologics. *Clin Exp Allergy.* 2020;50(4):442-452. PubMed
9. Ramonell RP, Iftikhar IH. Effect of anti-IL5, anti-IL5R, anti-IL13 therapy on asthma exacerbations: a network meta-analysis. *Lung.* 2020;198(1):95-103. PubMed
10. Edris A, De Feyter S, Maes T, Joos G, Lahousse L. Monoclonal antibodies in type 2 asthma: a systematic review and network meta-analysis. *Respir Res.* 2019;20(1):179. PubMed
11. Iftikhar IH, Schimmel M, Bender W, Swenson C, Amrol D. Comparative efficacy of anti IL-4, IL-5 and IL-13 drugs for treatment of eosinophilic asthma: a network meta-analysis. *Lung.* 2018;196(5):517-530. PubMed
12. Clinical Study Report: LTS12551. Open–label extension study to evaluate the long-term safety and tolerability of dupilumab in patients with asthma who participated in a previous dupilumab asthma clinical study [CONFIDENTIAL internal sponsor's report]. Mississauga (ON): Sanofi Genzyme; 2017 Dec 5.
13. Asthma statistics Ottawa (ON): Statistics Canada; 2014.
14. Global strategy for asthma management and prevention. Fontana (WI): Global Initiative for Asthma; 2020: www.ginasthma.org. Accessed 2021 Feb 10.
15. e-CPS. Ottawa (ON): Canadian Pharmacists Association 2020.
16. Bateman ED, Reddel HK, O'Byrne PM, et al. As-needed budesonide-formoterol versus maintenance budesonide in mild asthma. *N Engl J Med.* 2018;378(20):1877-1887. PubMed
17. Normansell R, Kew KM, Stovold E. Interventions to improve adherence to inhaled steroids for asthma. *Cochrane Database Syst Rev.* 2017;4:CD012226. PubMed
18. FitzGerald JM, Lemiere C, Lougheed MD, et al. Recognition and management of severe asthma: a Canadian Thoracic Society position statement. *Can J Respir Crit Care Sleep Med* 2017;1(4):199-221.
19. Lougheed MD, Lemiere C, Dell SD, et al. Canadian Thoracic Society Asthma Management Continuum--2010 consensus summary for children six years of age and over, and adults. *Can Respir J.* 2010;17(1):15-24. PubMed
20. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 guideline statement. *J Clin Epidemiol.* 2016;75:40-46. PubMed
21. Grey matters: a practical tool for searching health-related grey literature. Ottawa (ON): CADTH; 2019: https://www.cadth.ca/grey-matters. Accessed 2020 Dec 11.
22. Castro M, Rabe KF, Corren J, et al. Dupilumab improves lung function in patients with uncontrolled, moderate-to-severe asthma. *ERJ Open Res.* 2020;6(1). PubMed
23. Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med.* 2018;378(26):2486-2496. PubMed
24. Busse WW, Maspero JF, Rabe KF, et al. Liberty Asthma QUEST: phase 3 randomized, double-blind, placebo-controlled, parallel-group study to evaluate dupilumab efficacy/safety in patients with uncontrolled, moderate-to-severe asthma. *Adv Ther.* 2018;35(5):737-748. PubMed
25. Center for Drug Evaluation Research. Medical review(s). *Dupixent (dupilumab) injection. Company: Regeneron Pharmaceuticals, Inc. Application No.:761055. Approval date: 03/28/2017 (FDA approval package)*. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2017: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761055Orig1s000MedR.pdf. Accessed 2020 Dec 11.
26. Center for Drug Evaluation Research. Statistical review(s). *Dupixent (dupilumab) injection. Company: Regeneron Pharmaceuticals, Inc. Application No.:761055. Approval date: 03/28/2017 (FDA approval package)*. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2017: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761055Orig1s000StatR.pdf. Accessed 2020 Dec 11.
27. Health Canada reviewer's report: Dupixent (dupilumab) [internal sponsor's report]. Mississauga (ON): Sanofi Genzyme; 2020 Nov 12.

28. Rabe K, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med.* 2018;378(26):2475-2485. PubMed

29. Corren J, Castro M, Chanez P, et al. Dupilumab improves symptoms, quality of life, and productivity in uncontrolled persistent asthma. *Ann Allergy Asthma Immunol.* 2019;122(1):41-49.e42. PubMed

30. Corren J, Castro M, Ford LB, et al. Dupilumab improves asthma outcomes irrespective of frequency of previous asthma exacerbation history. *Ann Allergy Asthma Immunol.* 2019;123(2):222-224.e221. PubMed

31. Weinstein SF, Katial R, Jayawardena S, et al. Efficacy and safety of dupilumab in perennial allergic rhinitis and comorbid asthma. *J Allergy Clin Immunol.* 2018;142(1):171-177.e171. PubMed

32. 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 beta2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet.* 2016;388(10039):31-44. PubMed

33. Santanello NC, Zhang J, Seidenberg B, Reiss TF, Barber BL. What are minimal important changes for asthma measures in a clinical trial? *Eur Respir J.* 1999;14(1):23-27. PubMed

34. Szentes BL, Schultz K, Nowak D, Schuler M, Schwarzkopf L. How does the EQ-5D-5L perform in asthma patients compared with an asthma-specific quality of life questionnaire? *BMC Pulm Med.* 2020;20(1):168. PubMed

35. Jones PW. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. *Eur Respir J.* 2002;19(3):398-404. PubMed

36. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific quality of life questionnaire. *J Clin Epidemiol* 1994;47(1):81-88. PubMed

37. Juniper EF, Svensson K, Mörk AC, Ståhl E. Modification of the asthma quality of life questionnaire (standardised) for patients 12 years and older. *Health Qual Life Outcomes.* 2005;16(3):58. PubMed

38. Wyrwich KW, Ireland AM, Navaratnam P, Nolte H, Gates DF Jr. Validation of the AQLQ12+ among adolescents and adults with persistent asthma. *Qual Life Res.* 2011;20(6):903-912. PubMed

39. Wyrwich KW, Khan SA, Navaratnam P, Nolte H, Gates DF Jr. Validation and agreement across four versions of the asthma control questionnaire in patients with persistent asthma. *Respir Med.* 2011;105(5):698-712. PubMed

40. Sinnot PL, Joyce VR, Barnett PG. Guidebook: preference measurement in economic analysis. Menlo Park (CA): Health Economics Resource Center (HERC); 2007: https://www.herc.research.va.gov/files/BOOK_419.pdf. Accessed 2021 Feb 4.

41. McClure NS, Sayah FA, Xie F, Luo N, Johnson JA. Instrument-defined estimates of the minimally important difference for EQ-5D-5L index scores. *Value Health.* 2017;20(4):644-650. PubMed

42. Barnes PJ, Casale TB, Dahl R, Pavord ID, Wechsler ME. The Asthma Control Questionnaire as a clinical trial endpoint: past experience and recommendations for future use. *Allergy.* 2014;69(9):1119-1140. PubMed

43. Jia CE, Zhang HP, Lv Y, et al. The Asthma Control Test and Asthma Control Questionnaire for assessing asthma control: systematic review and meta-analysis. *J Allergy Clin Immunol.* 2013;131(3):695-703. PubMed

44. Juniper EF, Svensson K, Mörk AC, E. S. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respir Med.* 2005;99(5):553-558. PubMed

45. Hopkins C, Gillett S, Slack R, Lund VJ, Browne JP. Psychometric validity of the 22-item Sinonasal Outcome Test *Clin Otolaryngol.* 2009;34(5):447-454. PubMed

46. Phillips KM, Hoehle LP, Caradonna DS, Gray ST, Sedaghat AR. Minimal clinically important difference for the 22-item Sinonasal Outcome Test in medically managed patients with chronic rhinosinusitis. *Clin Otolaryngol* 2018;43(5):1328-1334. PubMed

47. Juniper EF, Thompson AK, Ferrie PJ, Roberts JN. Validation of the standardized version of the Rhinoconjunctivitis Quality of Life Questionnaire. *J Allergy Clin Immunol.* 1999;104(2 Pt 1):364-369. PubMed

48. National Institute for Health and Care Excellence. Single technology appraisal: User guide for company evidence submission template. *(Process and methods PMG24)* 2017; https://www.nice.org.uk/process/pmg24/chapter/instructions-for-companies. Accessed 2021 Apr 2.

49. Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial *Lancet.* 2012;380(9842):651-659. PubMed

50. Chupp GL, Bradford ES, Albers FC, et al. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. *Lancet Respir Med.* 2017;5(5):390-400. PubMed

51. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med.* 2014;371(13):1198-1207. PubMed

52. Bjermer L, Lemiere C, Maspero J, Weiss S, Zangrilli J, Germinaro M. Reslizumab for inadequately controlled asthma with elevated blood eosinophil levels: a randomized phase 3 study. *Chest.* 2016;150 (4):789-798. PubMed

53. Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med.* 2015;3(5):355-366. PubMed

54. Hanania NA, Wenzel S, Rosén K, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. *Am J Respir Crit Care Med.* 2013;187(8):804-811. PubMed

55. Corren J, Weinstein S, Janka L, Zangrilli J, Garin M. Phase 3 study of reslizumab in patients with poorly controlled asthma: effects across a broad range of eosinophil counts. *Chest.* 2016;150(4):799-810. PubMed

56. Castro M, Mathur S, Hargreave F, et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. *Am J Respir Crit Care Med.* 2011;184(10):1125-1132. PubMed

57. Bleecker ER, FitzGerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting beta2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet.* 2016;388(10056):2115-2127. PubMed

58. FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor alpha monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet.* 2016;388(10056):2128-2141. PubMed

59. Humbert M, Beasley R, Ayres J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy.* 2005;60(3):309-316. PubMed

60. Busse W, Corren J, Lanier BQ, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol.* 2001;108(2):184-190. PubMed

61. Ohta K, Miyamoto T, Amagasaki T, Yamamoto M, 1304 Study Group. Efficacy and safety of omalizumab in an Asian population with moderate-to-severe persistent asthma. *Respirology.* 2009;14(8):1156-1165. PubMed

62. Li J, Kang J, Wang C, et al. Omalizumab improves quality of life and asthma control in chinese patients with moderate to severe asthma: a randomized phase III study. *Allergy Asthma Immunol Res.* 2016;8(4):319-328. PubMed

63. Vignola AM, Humbert M, Bousquet J, et al. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR *Allergy.* 2004;59(7):709-717. PubMed

64. Ayres JG, Higgins B, Chilvers ER, Ayre G, Blogg M, Fox H. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with poorly controlled (moderate-to-severe) allergic asthma. *Allergy.* 2004;59(7):701-708. PubMed

65. Niven R, Chung KF, Panahloo Z, Blogg M, Ayre G. Effectiveness of omalizumab in patients with inadequately controlled severe persistent allergic asthma: an open-label study. *Respir Med.* 2008;102(10):1371-1378. PubMed

66. Hoshino M, Ohtawa J. Effects of adding omalizumab, an anti-immunoglobulin E antibody, on airway wall thickening in asthma. *Respiration.* 2012;83(6):520-528. PubMed

67. Rubin AS, Souza-Machado A, Andradre-Lima M, Ferreira F, Honda A, Matozo TM. Effect of omalizumab as add-on therapy on asthma-related quality of life in severe allergic asthma: a Brazilian study (QUALITX). *J Asthma.* 2012;49(3):288-293. PubMed

68. Bousquet J, Siergiejko Z, Swiebocka E, et al. Persistency of response to omalizumab therapy in severe allergic (IgE-mediated) asthma. *Allergy.* 2011;66(5):671-678. PubMed

69. Bardelas J, M. F, Kianifard F, Meng X. A 26-week, randomized, double-blind, placebo-controlled, multicenter study to evaluate the effect of omalizumab on asthma control in patients with persistent allergic asthma. *J Asthma.* 2012;49(2):144-152. PubMed

70. Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med.* 2014;371(13):1189-1197. PubMed

71. Nair P, Wenzel S, Rabe KF, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. *N Engl J Med.* 2017;376(25):2448-2458. PubMed

72. Teva Branded Pharmaceutical Products R&D Inc. NCT02501629: An efficacy and safety study of reslizumab subcutaneous in patients with oral corticosteroid dependent asthma and elevated blood eosinophils. *ClinicalTrials.gov.* . Bethesda (MD): U.S. National Library of Medicine; 2015: https://clinicaltrials.gov/ct2/show/NCT02501629. Accessed 2021 Apr 5.

73. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Softw.* 2010;36(3).

74. 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. PubMed

75. Park HS, Kim MK, Imai N, et al. A phase 2a study of benralizumab for patients with eosinophilic asthma in South Korea and Japan. *Int Arch Allergy Immunol.* 2016;169(3):135-145. PubMed

76. Nowak RM, Parker JM, Silverman RA, et al. A randomized trial of benralizumab, an antiinterleukin 5 receptor alpha monoclonal antibody, after acute asthma. *Am J Emerg Med.* 2015;33 (1):14-20. PubMed

77. Castro M, Wenzel SE, Bleecker ER, et al. Benralizumab, an anti-interleukin 5 receptor alpha monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. *Lancet Respir Med.* 2014;2(11):879-890. PubMed

78. Ferguson GT, FitzGerald JM, Bleecker ER, et al. Benralizumab for patients with mild to moderate, persistent asthma (BISE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med.* 2017;5(7):568–576. PubMed

79. Flood-Page P, Swenson C, Faiferman I, et al. A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma. *Am J Respir Crit Care Med.* 2007;176(11):1062–1071. PubMed

80. Haldar P, Brightling CE, Hargadon B, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med.* 2009;360(10):973–984. PubMed

81. Nair P, Pizzichini MM, Kjarsgaard M, et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med.* 2009;360(10):985–993. PubMed

82. Corren J, Castro M, O'Riordan T, et al. Dupilumab efficacy in patients with uncontrolled, moderate-to-severe allergic asthma. *J Allergy Clin Immunol Pract.* 2020;8(2):516-526. PubMed

83. Carranza RJ, Edwards L, Lincourt W, Dorinsky P, ZuWallack RL. The relationship between health-related quality of life, lung function and daily symptoms in patients with persistent asthma. *Respir Med.* 2004;98(12):1157-1165. PubMed

84. Voorend-van BS, Vaessen-Verberne AA, Landstra AM, et al. Monitoring childhood asthma: web-based diaries and the asthma control test. *J Allergy Clin Immunol.* 2014;133(6):1599-1605. PubMed

85. Ehrs PO, Aberg H, Larsson K. Quality of life in primary care asthma. *Respir Med.* 2001;95(1):22-30. PubMed

86. Moy ML, Israel E, Weiss ST, et al. Clinical predictors of health-related quality of life depend on asthma severity. *Am J Respir Crit Care Med.* 2001;163(4):924-929. PubMed

87. Enright PL, Beck KC, Sherrill DL. Repeatability of spirometry in 18,000 adult patients. *Am J Respir Crit Care Med* 2004;169(2):235-238. PubMed

88. Ulrik CS, Postma DS, Backer V. Recognition of asthma in adolescents and young adults: which objective measure is best? *J Asthma.* 2005;42(7):549-554. PubMed

89. Drazen JM, Israel E, Boushey HA, et al. Comparison of regularly scheduled with as-needed use of albuterol in mild asthma. *Acad Emerg Med.* 1996;335(12):841-847. PubMed

90. Boushey HA, Sorkness CA, King TS, et al. Daily versus as-needed corticosteroids for mild persistent asthma. *N Engl J Med.* 2005;352(15):1519-1528. PubMed

91. Karras DJ, Sammon ME, Terregino CA, Lopez BL, Griswold SK, Arnold GK. Clinically meaningful changes in quantitative measures of asthma severity. *Acad Emerg Med.* 2000;7(4):327-334. PubMed

92. Juniper EF, Guyatt GH, Ferrie PJ, Griffith LE. Measuring quality of life in asthma. *Am Rev Respir Dis* 1993;147(4):832-838. PubMed

93. Juniper EF, Buist AS, Cox FM, Ferrie PJ, King DR. Validation of a standardized version of the asthma quality of life questionnaire *Chest.* 1999;115(5):1265-1270. PubMed

94. Gimena Hernandez H, Pont À, Garin O, et al. AB022. Validity of the five-level new version of the EQ-5D in asthma patients. *J Thorac Dis.* 2016;8(Suppl 5).

95. Crossman-Barnes CJ, Sach T, Wilson A, Barton G. The construct validity and responsiveness of the EQ-5D-5L, AQL-5D and a bespoke TTO in acute asthmatics. *Qual Life Res* 2020;29(3):619-627. PubMed

96. Brooks R. EuroQol: the current state of play. *Health Policy.* 1996;37(1):53-72. PubMed

97. EuroQol Group. EuroQol - a new facility for the measurement of health-related quality of life. *Health Policy.* 1990;16(3):199-208. PubMed

98. Juniper EF, Chauhan A, Neville E, et al. Clinicians tend to overestimate improvements in asthma control: an unexpected observation. *Prim Care Respir J.* 2004;13(4):181-184. PubMed

99. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999;14(4):902-907. PubMed

100. Juniper EF, O'Byrne PM, Roberts JN. Measuring asthma control in group studies: do we need airway calibre and rescue beta2-agonist use? *Respir Med* 2001;95(5):319-323. PubMed

101. Farhood Z, Schlosser RJ, Pearse ME, Storck KA, Nguyen SA, Soler ZM. Twenty-two-item Sino-Nasal Outcome Test in a control population: a cross-sectional study and systematic review. *Int Forum Allergy Rhinol.* 2016;6(3):271-277. PubMed

102. Marambaia PP, Lima MG, Santos KP, Gomes Ade M, de Sousa MM, Marques ME. Evaluation of the quality of life of patients with chronic rhinosinusitis by means of the SNOT-22 questionnaire. *Braz J Otorhinolaryngol.* 2013;79(1):54-58. PubMed

103. Feng AL, Wesely NC, Hoehle LP, et al. A validated model for the 22-item sino-nasal outcome test subdomain structure in chronic rhinosinusitis. *Int Forum Allergy Rhinol.* 2017;7(12):1140-1148. PubMed

104. Juniper EF, Guyatt GH, Griffith LE, Ferrie PJ. Interpretation of rhinoconjunctivitis quality of life questionnaire data. *J Allergy Clin Immunol.* 1996;98(4):843-845. PubMed

105. Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. *Clin Exp Allergy.* 1991;21(1):77-83. PubMed

106. Stavem K, Erikssen J, Boe J. Performance of a short lung-specific health status measure in outpatients with chronic obstructive pulmonary disease. *Respir Med.* 1999;93(7):467-475. PubMed

107. van Dalen C, Harding E, Parkin J, Cheng S, Pearce N, Douwes J. Suitability of forced expiratory volume in 1 second/forced vital capacity vs percentage of predicted forced expiratory volume in 1 second for the classification of asthma severity in adolescents. *Arch Pediatr Adolesc Med.* 2008;162(12):1169-1174. PubMed

108. Committee for Medicinal Products for Human Use. Guideline on the clinical investigation of medicinal products for the treatment of asthma. *(European public assessment report)*. Amsterdam (NL): European Medicines Agency; 2015: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-asthma_en.pdf. Accessed 2021 Apr 2.

109. Yawn BP. Factors accounting for asthma variability: achieving optimal symptom control for individual patients. *Prim Care Respir J.* 2008;17(3):138-147. PubMed

110. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): guidelines for the diagnosis and management of asthma-summary report 2007. *J Allergy Clin Immunol.* 2007;120(5 (Suppl)):S94-138. PubMed

111. Corre KA, Rothstein RJ. Assessing severity of adult asthma and need for hospitalization. *Ann Emerg Med.* 1985;14(1):45-52. PubMed

112. Quanjer PH, Lebowitz MD, Gregg I, Miller MR, Pedersen OF. Peak expiratory flow: conclusions and recommendations of a Working Party of the European Respiratory Society. *Eur Respir J.* 1997;*Suppl*(24):25-85.

113. Tepper RS, Wise RS, Covar R, et al. Asthma outcomes: pulmonary physiology. *Allergy Clin Immunol* 2012;129(3 Suppl):S65-S87. PubMed

114. Dekker FW, Schrier AC, Sterk PJ, Dijkman JH. Validity of peak expiratory flow measurement in assessing reversibility of airflow obstruction. *Thorax.* 1992;47(3):162-166. PubMed

115. Williams AE, Agier L, Wiklund I, Frith L, Gul N, E J. Transcultural and measurement evaluation of the asthma quality-of-life questionnaire. *Health Outcomes Res Med.* 2010;1(2):e69-79.

116. Szentes BL, Schultz K, Nowak D, Schuler M, Schwarzkopf L. How does the EQ-5D-5L perform in asthma patients compared with an asthma-specific quality of life questionnaire? *BMC Pulm Med.* 2020;20(1):168. PubMed

117. EQ-5D-5L user guide: basic information on how to use the EQ-5D-5L instrument Rotterdam (NL): EQ-5D; 2015.

118. *2014 Alberta population norms for EQ-5D-5L.* Calgary (AB): Health Quality Council of Alberta; 2014.

119. Sastre J, Olaguibel J, Vega JM, Del Pozo V, Picado C, Lopez Viña A. Cut-off points for defining asthma control in three versions of the Asthma Control Questionnaire. *J Asthma.* 2009;47(8):865-870. PubMed

120. Juniper EF, Bousquet J, Abetz L, Bateman ED, Committee G. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. *Respir Med.* 2006;100(4):616-621. PubMed

121. Bateman ED, Esser D, Chirila C, et al. Magnitude of effect of asthma treatments on Asthma Quality of Life Questionnaire and Asthma Control Questionnaire scores: systematic review and network meta-analysis. *J Allergy Clin Immunol.* 2015;136(4):914-922. PubMed

122. Halbert RJ, Tinkelman DG, Globe DR, SL. L. Measuring asthma control is the first step to patient management: a literature review. *J Asthma* 2009;46(7):659-664. PubMed

123. Reeve BB, Wyrwich KW, Wu AW, et al. ISOQOL recommends minimum standards for patient-reported outcome measures used in patient-centered outcomes and comparative effectiveness research. *Qual Life Res.* 2013;22(8):1889-1905. PubMed

124. Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the Mini Asthma Quality of Life Questionnaire. *Eur Respir J* 1999;14(1):32-38. PubMed

125. Juniper EF SE, O'Byrne PM. Minimal important difference for the asthma control questionnaire. *Am J Respir Crit Care Med.* 2001;164(642 (A)).

126. Juniper EF, Gruffydd-Jones K, Ward S, Svensson K. Asthma Control Questionnaire in children: validation, measurement properties, interpretation. *Eur Respir J* 2010;36(6):1410-1416. PubMed

127. Nguyen JM, Holbrook JT, Wei CY, et al. Validation and psychometric properties of the Asthma Control Questionnaire among children. *J Allergy Clin Immunol.* 2014;133(1):91-97. PubMed

128. Calderon MA, Casale TB, Demoly P. Validation of patient-reported outcomes for clinical trials in allergic rhinitis: a systematic review. *J Allergy Clin Immunol Pract.* 2019;7(5):1450-1461.e1456. PubMed

129. Schwanke T, Carragee E, Bremberg M, Reisacher WR. Quality-of-life outcomes in patients who underwent subcutaneous immunotherapy and sublingual immunotherapy in a real-world clinical setting. *Am J Rhinol Allergy.* 2017;31(5):310-316. PubMed

130. Demoly P, Bousquet PJ, Mesbah K, Bousquet J, Devillier P. Visual analogue scale in patients treated for allergic rhinitis: an observational prospective study in primary care: asthma and rhinitis. *Clin Exp Allergy.* 2013;43(8):881-888. PubMed

131. Wasserfallen JB, Gold K, Schulman KA, Baraniuk JN. Development and validation of a rhinoconjunctivitis and asthma symptom score for use as an outcome measure in clinical trials. *J Allergy Clin Immunol* 1997;100(1):16-22. PubMed

132. Barnes ML, Vaidyanathan S, Williamson PA, Lipworth BJ. The minimal clinically important difference in allergic rhinitis. *Clin Exp Allergy* 2010;40(2):242-250. PubMed

133. Juniper EF, Thompson AK, Ferrie PJ, Roberts JN. Development and validation of the mini Rhinoconjunctivitis Quality of Life Questionnaire. *Clin Exp Allergy.* 2000;30(1):132-140. PubMed

Appendix 1: Literature Search Strategy

Clinical Literature Search	
Overview	
Interface:	Ovid
Databases:	MEDLINE All (1946-present) Embase (1974-present) **Note:** Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	December 23, 2020
Alerts:	Biweekly search updates until project completion
Study types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts: excluded
Syntax Guide	
/	At the end of a phrase, searches the phrase as a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
MeSH	Medical Subject Heading
exp	Explode a subject heading
.ti	Title
.ab	Abstract
.dq	Candidate term word (Embase)
.ot	Original title
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.mp	Mapped term
.rn	Registry number
.yr	Publication year
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

Clinical Literature Search	
Multi-Database Strategy	
Line # Search Strategy 1. (dupilumab* or dupixent* or regn668 or regn 668 or sar231893 or sar 231893 or 420K487FSG).ti,ab,kf,ot,hw,rn,nm 2. exp Asthma/ 3. (asthma* or antiasthma* or wheez*).ti,ab,kf. 4. (bronchospas* or bronchiospas* or (bronch* adj2 spas*)).ti,ab,kf.. 5. or/2-4 6. 1 and 6 7. 6 use medall 8. *dupilumab/ 9. (dupilumab* or dupixent* or regn668 or regn 668 or sar231893 or sar 231893).ti,ab,kw,dq.	10. 8 or 9 11. exp Asthma/ 12. (asthma* or antiasthma* or wheez*).ti,ab,kw,dq. 13. (bronchospas* or bronchiospas* or (bronch* adj2 spas*)).ti,ab,kw,dq. 14. or/11-13 15. 10 and 14 16. 15 use oemezd 17. 16 not (conference review or conference abstract).pt. 18. 7 or 17 19. remove duplicates from 18
Clinical Trials Registries	
ClinicalTrials.gov	Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials. [Search -- Studies with results dupilumab OR Dupixent AND asthma]
WHO ICTRP	International Clinical Trials Registry Platform, produced by the WHO. Targeted search used to capture registered clinical trials. [Search terms -- dupilumab OR Dupixent AND asthma]
Health Canada's Clinical Trials Database	Produced by Health Canada. Targeted search used to capture registered clinical trials. [Search terms -- dupilumab OR Dupixent AND asthma]
EU Clinical Trials Register	European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials. [Search terms -- dupilumab OR Dupixent AND asthma]

Grey Literature

Search dates: December 15-17, 2020

Keywords: dupilumab, Dupixent, asthma

Limits: None

Updated: Search updated before the completion of stakeholder feedback period

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals

- Advisories and Warnings
- Drug Class Reviews
- Clinical Trials Registries
- Databases (free)
- Health Statistics
- Internet Search.

Appendix 2: Excluded Studies

Note that this appendix has not been copy-edited.

Table 46: Excluded Studies

Reference	Reason for exclusion
Merman 2019	Review
Wechsler 2013	Review
Svenningsen 2019	Case report
Rabe 2020	Post hoc analysis
Corren 2019	Post hoc analysis
Busse 2020	Subgroup not of interest
Bourdin 2020	Subgroup not of interest
Maspero 2020	Subgroup not of interest

Appendix 3: Detailed Outcome Data

Note that this appendix has not been copy-edited.

Table 47: Subgroup Data From QUEST

Characteristic	Dupilumab 200 mg q.2.w. N = 631	Placebo N = 317	Dupilumab 300 mg q.2.w. N = 633	Placebo N = 321
Annualized rate of severe exacerbation events				
Baseline eosinophils, cells/µL				
≥ 150 cells/µL	N = 437	N = 232	N = 452	N = 237
Adjusted annualized exacerbation rate, estimate [95% CI]	0.445 [0.368, 0.538]	1.007 [0.814, 1.245]	0.434 [0.359, 0.525]	1.081 [0.879, 1.329]
RR vs. placebo [95% CI]	0.442 [0.337, 0.581], P < 0.0001		0.402 [0.307, 0.526], P < 0.0001	
RD vs. placebo [95% CI]	−0.561 [-0.785, −0.338]		−0.647 [-0.879, −0.415]	
≥ 300 cells/µL	N = 264	N = 148	N = 277	N = 142
Adjusted annualized exacerbation rate, estimate [95% CI]	0.370 [0.289, 0.475]	1.081 [0.846, 1.382]	0.403 [0.317, 0.512]	1.236 [0.972, 1.571]
RR vs. placebo [95% CI]	0.342 [0.244, 0.480], P < 0.0001		0.326 [0.234, 0.454], P < 0.0001	
RD vs. placebo [95% CI]	−0.711 [-0.987, −0.436]		−0.833 [-1.140, −0.525]	
< 300 cells/µL	N = 366	N = 169	N = 356	N = 178
Adjusted annualized exacerbation rate, estimate [95% CI]	0.512 [0.418, 0.628]	0.675 [0.515, 0.884]	0.610 [0.502, 0.742]	0.732 [0.562, 0.954]
RR vs. placebo [95% CI]	0.759 [0.548, 1.052], P = 0.0975		0.834 [0.608, 1.144], P = 0.2599	
RD vs. placebo [95% CI]	−0.163 [-0.366, 0.041]		−0.122 [-0.341, 0.098]	
Baseline eosinophils, cells/µL				
< 150 cells/µL				
Adjusted annualized exacerbation rate, estimate [95% CI]	0.472 [0.358, 0.623]	0.511 [0.346, 0.755]	0.737 [0.575, 0.946]	0.642 [0.445, 0.927]
RR vs. placebo [95% CI]	0.925 [0.580, 1.474]		1.149 [0.747, 1.767]	
RD vs. placebo [95% CI]	−0.039 [-0.271, 0.194]		0.095 [-0.194, 0.385]	
150 to < 300 cells/µL				
Adjusted annualized exacerbation rate, estimate [95% CI]	0.559 [0.416, 0.751]	0.867 [0.592, 1.271]	0.471 [0.347, 0.638]	0.844 [0.578, 1.234]
RR vs. placebo [95% CI]	0.644 [0.407, 1.019]		0.557 [0.350, 0.888]	
RD vs. placebo [95% CI]	−0.308 [-0.663, 0.046]		−0.374 [-0.713, −0.034]	
300 to < 500 cells/µL				

Characteristic	Dupilumab 200 mg q.2.w. N = 631	Placebo N = 317	Dupilumab 300 mg q.2.w. N = 633	Placebo N = 321
Adjusted annualized exacerbation rate, estimate [95% CI]	0.398 [0.269, 0.587]	0.801 [0.532, 1.208]	0.445 [0.314, 0.631]	1.215 [0.844, 1.751]
RR vs. placebo [95% CI]	0.496 [0.294, 0.839]		0.366 [0.225, 0.596]	
RD vs. placebo [95% CI]	−0.404 [-0.747, −0.060]		−0.770 [-1.230, −0.310]	
500 cells/µL	N = 145	N = 76	N = 141	N = 74
Adjusted annualized exacerbation rate, estimate [95% CI]	0.341 [0.245, 0.474]	1.333 [0.982, 1.810]	0.358 [0.257, 0.498]	1.246 [0.911, 1.705]
RR vs. placebo [95% CI]	0.256 [0.164, 0.398]		0.287 [0.184, 0.449]	
RD vs. placebo [95% CI]	−0.993 [-1.412, −0.574]		−0.888 [-1.292, −0.485]	
P value for interaction	P = 0.0014		P = 0.0002	
Number of severe exacerbations before study				
1 or less				
RR vs. placebo [95% CI]	0.771 [0.525, 1.134]		0.656 [0.452, 0.951]	
> 1				
RR vs. placebo [95% CI]	0.412 [0.305, 0.557]		0.471 [[0.353, 0.629]	

CI = confidence interval; RD = risk difference; RR = relative risk

Derived using binomial model with the total number of events onset from randomization up to visit 18 or last contact data (whichever comes earlier) as the response variable, with the 4 treatment groups, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level and number of severe exacerbation events within 1 year before the study as covariates, and log-transformed standardized observation duration as an offset variable

Source: Clinical Study Report for QUEST[1]

Table 48: Subgroup Data From VENTURE

Characteristic	Dupilumab 300 mg q.2.w. N = 103	Placebo N = 107
Primary outcome		
Percent reduction in OCS dose, mg/day, at week 24		
Baseline eosinophils (Cells/µL) group 1		
< 150	N = 21	N = 37
Mean (SD)	62.82 (52.29)	40.23 (53.06)
LSM (SE) [a]	63.77 (11.14)	36.87 (8.60)
LS MD [95% CI] vs. placebo[a]	26.89 [-0.73, 54.52]	
≥ 150	N = 80	N = 69
Mean (SD)	76.75 (35.63)	47.99 (49.61)
LSM (SE) [a]	75.91 (4.76)	46.51 (5.21)
LS MD [95% CI] vs. placebo[a]	29.39 [15.67, 43.12]	
P value for interaction[b]	P = 0.7081	
Baseline eosinophils (Cells/µL) group 2		
< 300	N = 54	N = 65
Mean (SD)	67.87 (43.74)	46.05 (50.17)
LSM (SE) [a]	66.31 (6.47)	44.98 (6.00)
LS MD [95% CI] vs. placebo[a]	21.33 [3.90, 38.75]	
≥ 300	N = 47	N = 41
Mean (SD)	80.73 (33.83)	44.05 (6.77)
LSM (SE) [a]	79.54 (6.36)	42.71 (6.77)
LS MD [95% CI] vs. placebo[a]	36.83 [18.94, 54.71]	
P value for interaction[b]	P = 0.2382	

ACQ-5 = Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; CI = confidence interval; ICS = inhaled corticosteroid; LS = least square; LSM = least square mean; MD = mean difference; q.2.w. = every 2 weeks; RR = relative risk; SD = standard deviation; SE = standard error;

[a]Derived from combining results from analyzing multiple imputed data using an ANCOVA model by Rubin's rule. The model includes the percentage reduction of OCS dose at week 24 as the response variable and the treatment groups, optimized OCS dose at baseline, regions, and baseline eosinophil subgroups (< 150, 150 cells/µL) as covariates. Imputed data were generated from the primary missing data handling approach – pattern mixture model by multiple imputation.

[b]Derived from combining results of analyzing subgroup-by-treatment interaction based on multiple imputed data using an ANCOVA model by Rubin's rule. The model includes the percentage reduction of OCS dose at week 24 as the response variable and the treatment groups, optimized OCS dose at baseline, regions, and baseline eosinophil subgroups (< 150, 150 cells/µL), the subgroups (if different than the aforementioned covariates) and subgroup-by-treatment interaction as covariates.

Source: Clinical Study Report for VENTURE[2]

Table 49: Subgroup Data From DRI12544

Characteristic	Dupilumab 200 mg q.2.w. N = 150	Dupilumab 300 mg q.2.w. N = 157	Placebo N = 158
Change from baseline to week 12 in FEV_1			
Patients with baseline eosinophils < 300 cells/μL	N = 79	N = 87	N = 71
Mean (SD) change	0.23 (0.33)	0.19 (0.31)	0.09 (0.36)
LSM (SE) [a]	0.25 (0.04)	0.22 (0.04)	0.10 (0.04)
LSM difference [95% CI] [a]	0.15 [0.04, 0.25], P = 0.0057	0.12 [001, 0.22], P = 0.0262	
Patients with high eosinophils (HEos)			
Mean (SD) baseline FEV_1	1.80 (0.52) N = 65	1.77 (0.50) N = 64	1.86 (0.68) N = 68
Mean (SD) change from baseline to week 12 in FEV_1	0.45 (0.40) N = 57	0.36 (0.46) N = 59	0.18 (0.38) N = 58
LSM (SE) change from baseline to week 12	0.43 (0.05)	0.39 (0.05)	0.18 (0.05)
LSM difference [95% CI] vs. placebo	0.26 [0.11, 0.40], P = 0.0008	0.21 [0.06, 0.36], P = 0.0063	

[a]Derived from MMRM model with change in FEV_1 (L) from baseline to week 12 as dependent variables, factors (fixed effects) for treatment, baseline eosinophil strata, pooled countries/regions, visit, treatment-by-visit interaction, FEV_1 (L) baseline value and baseline-by-visit interaction as covariates, unstructured correlation matrix.

Table 50: Detailed Efficacy Outcome Data From QUEST

Outcomes	Dupilumab 200 mg q.2.w. N = 631	Placebo N = 317	Dupilumab 300 mg q.2.w. N = 633	Placebo N = 321
Deaths	1 (0.2)	3 (1.0)	4 (0.6)	0
Primary outcomes				
Patients with 1 severe exacerbation event, n (%)	184 (29.2)	134 (42.3)	202 (31.9)	139 (43.3)
Unadjusted Annualized rate of severe exacerbation events	0.481	0.980	0.560	1.092
Number of severe exacerbation events				
0	447 (70.8)	183 (57.7)	431 (68.1)	182 (56.7)
1	111 (17.6)	62 (19.6)	121 (19.1)	54 (16.8)
2	44 (7.0)	31 (9.8)	43 (6.8)	34 (10.6)
3	23 (3.6)	19 (6.0)	24 (3.8)	26 (8.1)
≥ 4	6 (1.0)	22 (6.9)	14 (2.2)	25 (7.8)
Adjusted annualized rate of severe exacerbation events, estimate [95% CI]	0.456 [0.389, 0.534]	0.871 [0.724, 1.048]	0.524 [0.450, 0.611]	0.970 [0.810, 1.160]
RR vs. placebo [95% CI]	0.523 [0.413, 0.662], P < 0.0001		0.540 [0.430, 0.680], P < 0.0001	
Risk difference vs. placebo [95% CI]	−0.416 [-0.588, −0.243]		−0.446 [-0.633, −0.258]	
Secondary outcomes				
Annualized rate of severe exacerbations resulting in hospitalizations or ED visits				
Estimate [95% CI]	0.043 [0.027, 0.068]	0.081 [0.049, 0.135]	0.025 [0.014, 0.043]	0.034 [0.017, 0.066]
RR vs. placebo [95% CI]	0.531 [0.275, 1.026], P = 0.0598		0.736 [0.319, 1.695], P = 0.4711	
Adjusted annualized rate of severe exacerbations resulting in hospitalizations				
Estimate [95% CI]	0.024 [0.013, 0.044]	0.051 [0.027, 0.099]	0.011 [0.005, 0.025]	0.017 [0.007, 0.042]
RR vs. placebo [95% CI]	0.468 [0.196, 1.118], P = 0.0874		0.653 [0.199, 2.144], P = 0.4824	
Change from baseline in pre-bronchodilator FEV_1 (L), week 12				
Mean (SD) baseline	1.78 (0.62)	1.76 (0.61)	1.78 (0.60)	1.75 (0.57)
LSM (SE) change from baseline at week 12	0.32 (0.02)	0.18 (0.02)	0.34 (0.02)	0.21 (0.02)
LSM difference vs. placebo [95% CI]	0.14 [0.08, 0.19], P < 0.0001		0.13 [0.08, 0.18], P < 0.0001	
Percent change from baseline to week 12, mean (SD)	18.74 (30.86) N = 611	10.16 (23.88) N = 307	20.89 (34.14) N = 610	11.87 (26.40) N = 313
LSM (SE)	21.34 (1.13)	12.11 (1.56)	23.08 (1.13)	13.67 (1.56)
LSM difference vs.` placebo [95% CI]	9.23 [5.54, 12.92], P < 0.0001		9.41 [5.74, 13.07], P < 0.0001	

Outcomes	Dupilumab 200 mg q.2.w. N = 631	Placebo N = 317	Dupilumab 300 mg q.2.w. N = 633	Placebo N = 321
AQLQ global score				
Mean (SD) baseline	4.31 (1.08) N = 591	4.26 (1.02) N = 299	4.28 (1.05) N = 603	4.30 (1.03) N = 314
Mean (SD) change from baseline to week 24	1.13 (1.14) N = 560	0.95 (1.03) N = 281	1.17 (1.11) N = 569	1.02 (1.10) N = 295
LSM (SE) change from baseline to week 24	1.14 (0.04)	0.94 (0.06)	1.15 (0.04)	1.00 (0.06)
LSM difference [95% CI] vs. placebo	0.20 [0.06, 0.34], P = 0.0039		0.15 [0.01, 0.28], P = 0.0298	
AQLQ symptoms score				
Mean (SD) baseline	4.24 (1.11) N = 591	4.20 (1.07) N = 299	4.18 (1.10) N = 603	4.21 (1.05) N = 314
Mean (SD) change from baseline to week 24	1.25 (1.23) N = 281	0.97 (1.11) N = 281	1.28 (1.23) N = 569	1.06 (1.20) N = 295
LSM (SE) change from baseline to week 24	1.28 (0.05)	0.99 (0.06)	1.27 (0.04)	1.05 (0.06)
LSM difference [95% CI] vs.vplacebo	0.30 [0.15, 0.44], P = 0.0001		0.22 [0.07, 0.37], P = 0.0031	
AQLQ emotional score				
Mean (SD) baseline	4.24 (1.46) N = 591	4.18 (1.39) N = 299	4.21 (1.41) N = 603	4.19 (1.39) N = 314
Mean (SD) change from baseline to week 24	1.24 (1.44) N = 560	1.07 (1.28) N = 281	1.35 (1.40) N = 569	1.20 (1.42) N = 295
LSM (SE) change from baseline to week 24	1.26 (0.05)	1.06 (0.07)	1.33 (0.05)	1.17 (0.07)
LSM difference [95% CI] vs. placebo	0.20 [0.03, 0.36], P = 0.0192		0.17 [0.01, 0.33], P = 0.0415	
AQLQ environmental stimuli score				
Mean (SD) baseline	4.31 (1.41) N = 591	4.26 (1.35) N = 299	4.34 (1.38) N = 603	4.33 (1.32) N = 314
Mean (SD) change from baseline to week 24	0.98 (1.34) N = 560	0.92 (1.31) N = 281	1.01 (1.36) N = 569	0.91 (1.28) N = 295
LSM (SE) change from baseline to week 24	0.99 (0.05)	0.90 (0.07)	1.00 (0.05)	0.91 (0.07)
LSM difference [95% CI] vs. placebo	0.09 [-0.07, 0.25], P = 0.2678		0.09 [-0.07, 0.25], P = 0.2593	
AQLQ activity limitation score				
Mean (SD) baseline	4.42 (1.13) N = 591	4.36 (1.06) N = 299	4.41 (1.07) N = 603	4.46 (1.09) N = 314
Mean (SD) change from baseline to week 24	1.01 (1.17) N = 560	0.89 (1.08) N = 281	1.02 (1.12) N = 569	0.93 (1.11) N = 295
LSM (SE) change from baseline to week 24	1.00 (0.04)	0.85 (0.06)	1.00 (0.04)	0.92 (0.06)

Outcomes	Dupilumab 200 mg q.2.w. N = 631	Placebo N = 317	Dupilumab 300 mg q.2.w. N = 633	Placebo N = 321
LSM difference [95% CI] vs. placebo	0.14 [0.00, 0.29], P = 0.0454		0.08 [-0.06, 0.22], P = 0.2486	
EQ-5D-5L single index score				
Mean (SD) baseline	0.74 (0.19) N = 584	0.74 (0.18) N = 293	0.74 (0.19) N = 594	0.74 (0.19) N = 309
Mean change from baseline to week 52	0.10 (0.19) N = 457	0.07 (0.20) N = 220	0.10 (0.20) N = 448	0.08 (0.19) N = 238
LSM (SE) change from baseline to week 52	0.10 (0.01)	0.07 (0.01)	0.10 (0.01)	0.09 (0.01)
LSM difference [95% CI] vs. placebo	0.03 [0.01, 0.06], P = 0.0133		0.01 [-0.01, 0.04], P = 0.2896	
EQ VAS				
Mean (SD) baseline	65.32 (17.62) N = 584	66.03 (16.16) N = 293	66.12 (17.71) N = 594	65.62 (18.44) N = 309
Mean (SD) change from baseline to week 52	12.98 (18.71) N = 457	8.35 (18.51) N = 220	11.90 (19.60) N = 448	9.52 (20.81) N = 238
LSM (SE) change from baseline to week 52	12.37 (0.70)	9.07 (0.99)	12.11 (0.70)	9.43 (0.95)
LSM difference [95% CI] vs. placebo	3.30 [0.96, 5.63], P = 0.0057		2.68 [0.40, 4.96], P = 0.0213	
ACQ-5 score				
ACQ-5 score, mean (SD) baseline	2.76 (0.80)	2.71 (0.73)	2.77 (0.76)	2.77 (0.77)
ACQ-5 score, mean (SD) change from baseline to week 24	−1.43 (1.05) N = 590	−1.06 (1.01) N = 296	−1.38 (1.10) N = 585	−1.19 (1.10) N = 297
LSM (SE) change from baseline to week 24	−1.44 (0.04)	−1.10 (0.06)	−1.40 (0.04)	−1.21 (0.06)
LSM difference vs. placebo [95% CI]	−0.35 [-0.48, −0.21], P < 0.0001		−0.19 [-0.32, −0.05], P = 0.0069	

ACQ-5 = Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; CI = confidence interval; ICS = inhaled corticosteroid; LS = least square; LSM = least square mean; MD = mean difference; q.2.w. = every 2 weeks; RR = relative risk; SD = standard deviation; SE = standard error.

RR derived using negative binomial model with the total number of events onset from randomization up until visit 18 or last contact date (whichever comes earlier) as the response variable, with the 4 treatment groups, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level, and number of events within 1 year before the study as covariates, and log-transformed standardized observation duration as offset variable.

LSM difference (AQLQ) derived from a MMRM model with change from baseline up to week 24 as the response variable, and treatment, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level, visit, treatment-by-visit interaction, baseline score and baseline-by-visit interaction as covariates.

LSM difference (ACQ-5) derived from a MMRM model with change from baseline in ACQ-5 up to week 24 as the response variable, and treatment, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level, visit, treatment-by-visit interaction, baseline ACQ-5 and baseline-by-visit interaction as covariates.

Derived from MMRM model with change from baseline in EQ-5D-5L single index score up to week 52 at the response variable, and treatment, age, region (pooled country) baseline eosinophil strata, baseline ICS dose level, visit, treatment-by-visit interaction, baseline EQ-5D-5L single index score and baseline-by-visit interaction as covariates.

Table 51: Detailed Efficacy Outcome Data From VENTURE

Outcome	Dupilumab 300 mg q.2.w. N = 103	Placebo N = 107
Primary outcome		
Percent reduction in OCS dose, mg/day, at week 24		
Mean (SD) baseline	10.75 (5.90)	11.75 (6.31)
Mean (SD) percent reduction from baseline, week 24	73.85 (39.78)	45.28 (50.73)
LSM (SE) percent reduction from baseline to week 24	70.09 (4.90)	41.85 (4.57)
LSM difference [95% CI] vs. placebo	28.24 [15.81, 40.67], P < 0.0001	
Secondary outcomes		
Patients with 50% reduction in OCS dose, week 24	81.0%	53.3%
Adjusted probability of achieving the reduction, estimate [95% CI]	0.80 [0.70, 0.87]	0.50 [0.40, 0.61]
OR vs placebo [95% CI]	3.98 [2.06, 7.67], P < 0.0001	
Absolute reduction in OCS dose (mg/day) at week 24		
Mean (SD) change from baseline to week 24	7.66 (6.10) N = 101	5.45 (6.80) N = 106
LSM (SE) change from baseline to week 24	7.58 (0.58)	4.77 (0.54)
[a] LSM difference [95% CI] between groups	2.81 [1.33, 4.29], P = 0.0002	
Other efficacy		
Annualized rate of severe exacerbations over 24 weeks		
Adjusted estimate [95% CI]	0.649 [0.442, 0.0955]	1.597 [1.248, 2.043]
RR vs. placebo [95% CI]	0.407 [0.263, 0.630], P < 0.0001	
Risk difference [95% CI]	−0.947 [-1.393, −0.501]	
Annualized rate of severe exacerbations requiring hospitalizations or ED visits over 24 weeks		
Patients with an event, n (%)	4 (3.9)	8 (7.5)
Unadjusted annualized event rate	0.125	0.201
Adjusted annualized event rate, estimate [95% CI]	0.114 [0.040, 0.328]	0.198 [0.086, 0.457]
RR vs. placebo [95% CI]	0.577 [0.161, 2.071], P = 0.3972	
RD vs. placebo [95% CI]	−0.084 [-0.279, 0.111]	
Change from baseline to week 24 in pre-bronchodilator FEV_1		
Mean (SD) baseline pre-bronchodilator FEV_1, L	1.53 (0.53) N = 103	1.63 (0.61) N = 107

Outcome	Dupilumab 300 mg q.2.w. N = 103	Placebo N = 107
Mean (SD) change from baseline in pre-bronchodilator FEV_1	0.29 (0.46) N = 97	0.0 (0.51) N = 104
LSM (SE) change from baseline	0.22 (0.05)	0.01 (0.05)
LSM difference between groups [95% CI]	0.22 [0.09, 0.34]	
Mean (SD) percent change from baseline in pre-bronchodilator FEV_1, week 24	24.84 (40.31)	3.67 (31.14)
LSM (SE) percent change from baseline in pre-bronchodilator FEV_1, week 24	19.90 (3.48)	4.77 (3.30)
LSM difference [95% CI] between groups	15.13 [6.12, 24.15]	
Mean change from baseline in post-bronchodilator FEV_1, week 24		
Mean (SD) baseline FEV_1, L	1.83 (0.60) N = 102	1.89 (0.73) N = 105
Mean (SD) change from baseline in post-bronchodilator FEV_1, L	0.17 (0.39) N = 92	−0.04 (0.44) N = 100
LSM (SE)	0.13 (0.04)	−0.06 (0.04)
LSM difference [95% CI] vs. placebo	0.19 [0.08, 0.30]	
Mean (SD) percent change from baseline in post-bronchodilator FEV_1	13.33 (32.42)	0.36 (21.91)
LSM (SE)	9.92 (2.80)	−0.95 (2.64)
LSM difference [95% CI] vs. placebo	10.87 [3.72, 18.02]	
PEF, A.M., mean (SD) baseline, L/min	236.57 (100.21) N = 103	240.60 (115.50) N = 106
Mean (SD) change to week 24	34.88 (66.00) N = 98	−0.99 (60.27) N = 105
LSM (SE)	30.80 (6.17)	−1.84 (5.97)
LSM difference [95% CI] vs. placebo	32.64 [16.03, 49.24], P = 0.0001	
PEF, P.M., mean (SD) baseline, L/min	251.79 (109.15) N = 103	256.12 (117.92) N = 106
Mean (SD) change to week 24	23.51 (67.66) N = 99	−4.84 (59.28) N = 104
LSM (SE)	21.40 (6.20)	−5.47 (5.98)
LSM difference [95% CI] vs. placebo	26.86 [10.35, 43.38], P = 0.0016	
ACQ-5 score		
Mean (SD) baseline	2.42 (1.24) N = 102	2.58 (1.09) N = 107
Mean (SD) change from baseline to week 24	−0.94 (1.22) N = 96	−0.57 (1.19) N = 99

Outcome	Dupilumab 300 mg q.2.w. N = 103	Placebo N = 107
LSM (SE) change from baseline to week 24	−1.05 (0.11)	−0.58 (0.11)
LSM difference [95% CI] vs. placebo	−0.47 [-0.76, −0.18]	
AQLQ global score		
Mean (SD) baseline	4.38 (1.24) N = 105	4.31 (1.12) N = 107
Mean (SD) change from baseline to week 24	0.94 (1.17)	0.56 (0.97)
LSM (SE) change from baseline to week 24	0.89 (0.10)	0.54 (0.10)
LSM difference [95% CI] between groups	0.35 [0.09, 0.62]	
Nocturnal awakenings/night, mean (SD) baseline	0.89 (1.41) N = 103	0.75 (1.07) N = 107
Mean (SD) change from baseline to week 24	−0.45 (1.37) N = 99	−0.28 (0.08) N = 106
LSM (SE)	−0.39 (0.08)	−0.28 (0.08)
LSM difference [95% CI] vs. placebo	−0.10 [-0.32, 0.12]	
SNOT-22, mean (SD) baseline	43.35 (19.46) N = 31	41.15 (22.39) N = 39
Mean (SD) change from baseline to week 24	−14.56 (15.89) N = 27	−2.46 (19.11) N = 37
LSM (SE) change from baseline	−10.93 (3.29)	−2.98 (2.49)
LSM difference [95% CI] vs. placebo	−7.95 [-15.91, 0.02], P = 0.0505	
Number of reliever puffs, mean (SD) baseline	4.29 (4.33) N = 103	4.94 (6.65) N = 107
Mean (SD) change from baseline to week 24	−1.50 (3.36) N = 98	−1.45 (3.85) N = 105
LSM (SE) change to week 24	−1.56 (0.28)	−1.28 (0.27)
LSM difference [95% CI]	−0.28 [-1.03, 0.47]	
EQ-5D-5L		
Mean (SD) baseline single index score	0.74 (0.18) N = 103	0.72 (0.19) N = 107
Mean (SD) change from baseline to week 24	0.05 (0.18) N = 98	0.05 (0.18) N = 100
LSM (SE) change from baseline to week 24	0.06 (0.02)	0.04 (0.02)
LSM difference [95% CI] vs. placebo	0.01 [-0.03, 0.06], P = 0.5518	
EQ-5D VAS		

Outcome	Dupilumab 300 mg q.2.w. N = 103	Placebo N = 107
Mean (SD) baseline	63.29 (17.23) N = 103	64.21 (18.15) N = 107
Mean (SD) change from baseline to week 24	11.06 (17.60) N = 98	4.16 (16.74) N = 100
LSM (SE) change from baseline to week 24	10.22 (1.60)	4.43 (1.50)
LSM difference [95 CI] vs. placebo	5.78 [1.67, 9.90], P = 0.0061	

ACQ-5 = Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; A.M. = morning; CI = confidence interval; ICS = inhaled corticosteroid; LSM = least square mean; PEF = peak expiratory flow; P.M. = afternoon/evening; q.2.w. = every 2 weeks; RR = relative risk; SD = standard deviation; SE = standard error; SNOT-22 = Sino-nasal outcomes test

[a]Derived by combining results from analyzing multiple imputed data using an ANCOVA model by Rubin's rule. The model includes the percentage reduction of OCS dose at week 24 as the response variable, and the treatment groups, optimized OCS dose at baseline, regions, and baseline eosinophil level subgroups, (< 150, ≥ 150 cells/μL) as covariates. Missing data are imputed using the primary approach – pattern mixture model by multiple imputation.

Derived by combining results from analyzing multiple imputed data using a logistic regression model by Rubin's rule. The logistic regression model used the binary status of whether or not a patient achieved the 50% dose reduction criterion as the response variable, and treatment groups, optimized OCS dose at baseline, regions, and baseline eosinophil level subgroups (< 150, ≥ 150 cells/μL) as covariates.

Derived using negative binomial model with the total number of events onset from randomization up to week 24 or last contact date (whichever comes earlier) as the response variable, the treatment groups, baseline optimized OCS dose strata, regions, number of events within 1 year before the study, and baseline eosinophil level subgroups (< 150, ≥ 150 cells/μL) as covariates, and long-transformed treatment duration as an offset variable.

Derived from MMRM model with change from baseline in SNOT-22 global score as response variables and the treatment groups, baseline optimized OCS dose strata, regions, baseline eosinophil level subgroup (< 150 cells/μL, ≥ 150 cells/μL), visits, treatment-by-visit interaction, baseline SNOT-22 global score, and baseline-by-visit interaction as covariates.

Table 52: Detailed Efficacy Outcome Data From DRI12544

Outcome	Dupilumab 200 mg q.2.w. N = 150	Dupilumab 300 mg q.2.w. N = 157	Placebo N = 158
Change from baseline in FEV_1, L			
Mean (SD) baseline	1.79 (0.52) N = 150	1.85 (0.53) N = 157	1.82 (0.55) N = 158
Mean (SD) change from baseline to week 12	0.32 (0.38) N = 136	0.26 (0.39) N = 146	0.13 (0.37) N = 129
LSM (SE) change from baseline to week 12	0.31 (0.03)	0.28 (0.03)	0.12 (0.03)
LSM difference [95% CI]	0.20 [0.11, 0.28], P < 0.0001	0.16 [0.08, 0.25], P = 0.0002	
Mean (SD) percent change from baseline to week 12 in FEV_1	19.15 (23.53) N = 136	16.64 (27.78) N = 146	7.04 (19.26) N = 129
LSM (SE) percent change from baseline	18.00 (1.89)	17.75 (1.84)	6.06 (1.89)
LSM difference [95% CI] vs. placebo	11.94 [6.77, 17.11], P < 0.0001	11.69 [6.59, 16.80], P < 0.0001	
Mean (SD) percent change from baseline to week 24/EOT in FEV_1	18.20 (23.07) N = 135	16.95 (26.23) N = 143	
LSM (SE) change from baseline	16.62 (1.88)	17.34 (1.83)	7.01 (1.87)
LSM difference [95% CI] vs. placebo	9.60 [4.47, 14.74], P = 0.0003	10.33 [5.26, 15.40] P < 0.0001	
PEF, A.M., L/minute, Mean (SD) baseline	303.32 (117.60)	300.50 (112.74)	305.56 (122.09)
Mean (SD) change from baseline to week 24	22.39 (73.31) N = 136	17.80 (64.89) N = 145	4.22 (62.30) N = 132
LSM (SE) change from baseline to week 24	18.96 (5.26)	15.90 (5.12)	0.81 (5.14)
LSM difference [95% CI]	18.15 [3.80, 32.50], P = 0.0132	15.09 [0.92, 29.25] P = 0.0368	
PEF, P.M., L/min, Mean (SD) baseline	315.06 (119.77) N = 150	315.64 (115.98) N = 157	320.52 (125.51) N = 158
Mean (SD) change from baseline to week 24	18.72 (76.66) N = 136	8.46 (67.56) N = 145	−6.61 (63.26) N = 132
LSM (SE) change from baseline to week 24	15.45 (5.41)	6.21 (5.28)	−8.96 (5.30)
LSM difference [95% CI]	24.41 [9.63, 39.19], P = 0.0012	15.17 [0.59, 29.76] P = 0.0415	
Annualized rate of severe exacerbations			
Patients with 1 severe exacerbation event, n (%)	13 (8.8)	17 (10.9)	41 (25.9)

Outcome	Dupilumab 200 mg q.2.w. N = 150	Dupilumab 300 mg q.2.w. N = 157	Placebo N = 158
Unadjusted annualized severe exacerbation rate	0.305	0.332	1.073
Adjusted annualized severe exacerbation rate, estimate [95% CI]	0.269 [0.157, 0.461]	0.265 [0.157, 0.445]	0.897 [0.619, 1.300]
RR [95% CI] vs. placebo	0.300 [0.159, 0.565], P = 0.0002	0.295 [0.159, 0.546], P = 0.0001	
AQLQ overall score, mean baseline (SD)	4.03 (1.15) N = 148	3.91 (1.13) N = 153	4.12 (1.10) N = 156
Mean (SD) change from baseline to week 24	1.25 (1.21) N = 132	1.36 (1.23) N = 141	0.90 (1.09) N = 127
LSM (SE) change from baseline to week 24	1.20 (0.09)	1.24 (0.08)	0.88 (0.09)
LSM difference [95% CI]	0.31 [0.08, 0.55], P = 0.0090	0.36 [0.12, 0.59], P = 0.0027	
Use of rescue medication			
Use of reliever medication for symptom relief, mean (SD) baseline, puffs/day	2.98 (2.74) N = 150	3.25 (3.15) N = 157	2.72 (2.73) N = 158
Mean (SD) change from baseline to week 24	2.11 (3.86) N = 135	2.42 (4.10) N = 144	2.47 (3.28) N = 132
LSM (SE) change from baseline to week 24	−0.77 (3.43)	−0.83 (3.80)	−0.25 (2.76)
LSM difference [95% CI]	−0.43 [-1.19, 0.32], P = 0.2600	−0.45 [-1.19, 0.30], P = 0.2413	
Nocturnal awakenings, mean (SD) baseline	0.61 (1.12) N = 150	0.55 (0.78) N = 157	0.46 (0.64) N = 158
Mean (SD) change from baseline to week 24	−0.41 (1.18) N = 136	−0.34 (0.60) N = 145	−0.21 (0.57) N = 132
LSM (SE) change from baseline to week 24	−0.35 (0.04)	−0.36 (0.04)	−0.29 (0.04)
LSM difference [95% CI]	−0.06 [-0.17, 0.06], P = 0.3663	−0.07 [-0.19, 0.05], P = 0.2636	
SNOT-22, mean (SD) baseline	35.53 (18.72) N = 148	36.39 (18.89) N = 157	35.11 (20.71) N = 156
Mean (SD) change from baseline to week 24	−10.58 (19.01) N = 131	−13.85 (17.88) N = 137	−7.05 (18.74) N = 125
LSM (SE) change from baseline to week 24	−10.53 (1.34)	−13.58 (1.31)	−7.16 (1.36)
LSM difference [95% CI]	−3.36 [-7.04, 0.32], P = 0.0733	−6.42 [-10.07, −2.77], P = 0.0006	

Outcome	Dupilumab 200 mg q.2.w. N = 150	Dupilumab 300 mg q.2.w. N = 157	Placebo N = 158
ACQ-5 score, mean (SD) baseline	2.73 (0.82) N = 150	2.80 (0.83) N = 157	2.69 (0.80) N = 158
Mean (SD) change from baseline to week 24	−1.50 (1.00) N = 143	−1.51 (1.18) N = 145	−1.13 (1.01) N = 127
LSM (SE) change from baseline to week 24	−1.49 (0.08)	−1.45 (0.08)	−1.14 (0.08)
LSM difference [95% CI]	−0.35 [-0.57, −0.14], P = 0.0015	−0.31 [-0.52, −0.09], P = 0.0049	
EQ-5D-3L single index utility score mean (SD) baseline	0.80 (0.19) N = 147	0.78 (0.19) N = 155	0.78 (0.20) N = 158
Mean (SD) change from baseline to week 24	0.05 (0.21) N = 131	0.09 (0.19) N = 139	0.05 (0.19) N = 127
LSM (SE) change from baseline to week 24	0.06 (0.01)	0.09 (0.01)	0.06 (0.01)
LSM difference [95% CI] vs. placebo	0.00 [-0.04, 0.04], P = 0.9299	0.03 [-0.01, 0.07], P = 0.1316	

ACQ-5 = Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; A.M. = morning; CI = confidence interval; ICS = inhaled corticosteroid; LSM = least square mean; PEF = peak expiratory flow; P.M. = afternoon/evening; q.2.w. = every 2 weeks; RR = relative risk; SD = standard deviation; SE = standard error; SNOT-22 = Sino-nasal outcomes test

Derived from MMRM model with change in FEV_1 (L) from baseline to week 12 as dependent variables, factors (fixed effects) for treatment, pooled countries/regions, visit, treatment-by-visit interaction, FEV_1 (L) baseline value and baseline-by-visit interaction as covariates, unstructured correlation matrix. FEV_1 collected from systemic corticosteroid start date to systemic corticosteroid end date + 30 days for each severe exacerbation episode are excluded

Derived from MMRM model with change in A.M. PEF (L/min) from baseline to week 24 as dependent variables, factors (fixed effects) for treatment, baseline eosinophil strata, pooled countries/regions, visit, treatment-by-visit interaction, A.M. PEF (L/min) baseline value and baseline-by-visit interaction as covariates, unstructured correlation matrix.

Derived from MMRM model with change in AQLQ global score from baseline to week 24 as dependent variables, factors (fixed effects) for treatment, baseline eosinophil strata, pooled countries/regions, visit, treatment-by-visit interaction, AQLQ global score baseline value and baseline-by-visit interaction as covariates, unstructured correlation matrix

Derived from MMRM model with change in number of inhalations/day of salbutamol or levosalbutamol for symptom relief from baseline to week 24 as dependent variables, factors (fixed effects) for treatment, baseline eosinophil strata, pooled countries/regions, visit, treatment-by-visit interaction, number of inhalations/day of salbutamol and levosalbutamol baseline value and baseline-by-visit interaction as covariates, unstructured correlation matrix

Derived from MMRM model with change in SNOT-22 total score from baseline to week 24 as dependent variables, factors (fixed effects) for treatment, baseline eosinophil strata, pooled countries/regions, visit, treatment-by-visit interaction, SNOT-22 total score baseline value and baseline-by-visit interaction as covariates, unstructured correlation matrix

Derived from MMRM model with change in EQ-5D-3L single index utility score from baseline to week 12 as dependent variables, factors (fixed effects) for treatment, baseline eosinophil strata, pooled countries/regions, visit, treatment-by-visit interaction, EQ-5D-3L single utility score baseline value and baseline-by-visit interaction as covariates, unstructured correlation matrix

Appendix 4: Description and Appraisal of Outcome Measures

Note that this appendix has not been copy-edited.

Aim

To describe the following outcome measures summarized in Table 53 and review their measurement properties including validity, reliability, responsiveness to change, and clinical relevance (i.e., MID).

Table 53: Outcome Measures Included in Each Study

Outcome measure	QUEST[1]	VENTURE[2]	DRI12544[3]
FEV_1	Primary	Other	Primary
PEF	Other secondary	Other	Secondary
AQLQ	Other secondary	Other	Secondary
EQ-5D-5L(Including EQ-5D-5L VAS)	Other secondary	Other	NR
EQ-5D- 3L	NR	NR	Secondary
ACQ-5	Other secondary	Other	Secondary
SNOT-22	Other secondary	Other	Secondary
RQLQ(S)	Other secondary	NR	NR

ACQ - 5 = Asthma Control Questionnaire - 5; ACQ - 7 = Asthma Control Questionnaire - 7; AQLQ = Asthma Quality of Life Questionnaire; EQ-5D- 3L = EuroQol 5-dimensions 3-levels questionnaire; EQ-5D-5L = EuroQol 5-dimensions 5-levels questionnaire; FEV_1 = forced expiratory volume in 1 second; NR = not reported; PEF = peak expiratory flow; RQLQ(S) = Standardized Rhinoconjunctivitis Quality of Life Questionnaire ; SNOT-22 = 22-item Sino-Nasal Outcome Test.

Source: Clinical Study Reports for QUEST,[1] VENTURE[2] and DRI12544.[3]

Findings

Table 54: Summary of Outcome Measures and Their Measurement Properties

Measure	Type	Conclusions about measurement properties	MID
FEV_1	FEV_1 is the volume of air that can be forcibly expired in 1 second after a full inspiration.	Validity: Weak to strong correlations between the FEV_1 and various measures of clinical status (such as patient-reported symptoms), and health-related quality of life measures (such as the AQLQ, the EQ VAS, and the Juniper AQLQ) support the presence of construct validity of the FEV_1.[83-86] Reliability: FEV_1 values demonstrated high within-session repeatability, with 90% of 18,526 patients able to reproduce FEV_1 within 120 mL.[87]	The MPPI for FEV_1 is 230 mL or a 10.38% change from baseline.[33]

Measure	Type	Conclusions about measurement properties	MID
PEF	PEF is the maximum flow achieved during an expiration delivered with maximal force starting from the level of maximal lung inflation.	There is minimal evidence supporting the construct validity of the PEF, through a moderate strength correlation with the FEV_1.[88] No evidence was identified regarding the reliability or the responsiveness of the PEF.	An MID of 25 L/min has been used in clinical trials previously.[89,90] The MPPI for PEF was 18.8 L/min or a 5.39% change from baseline.[91] In patients with acute asthma exacerbations presenting to the ER a % predicted PEF of 12% has been identified as the MID.[91]
AQLQ	AQLQ is a patient-reported assessment of functional impairments experienced by patients with asthma. It includes 32 questions grouped into 4 domains: (1) symptoms, (2) activity limitations, (3) emotional function, and (4) environmental stimuli. Each question is scored on a 7-point Likert scale, which ranges from 7 (no impairment) to 1 (severe impairment). The overall score is calculated as the mean of all questions, and the 4 domain scores are the means of the scores for the questions in the respective domains.	Validity: Known-groups validity was established through large Cohen d values in patients with different levels of asthma severity.[34] Moderate to strong Spearman's rank correlations with a variety of measures of health status indicate adequate longitudinal and cross-sectional validity.[92] Reliability: Test-retest and internal consistency reliability was adequate with ICC > 0.7 and Cronbach alpha > 0.7 in 2 independent publications.[34,92] Responsiveness: The AQLQ is responsive to within-subject,[93] between-group, and to within-group changes in asthma severity.[92] Moreover, the AQLQ is responsive to between-group changes when groups are divided on a 3-point change in the ACT (the MID of the ACT).[34]	The MID for the AQLQ has been determined to be a cut point of 0.5, with publications reporting values such as 0.67,[34] 0.52,[35] and a range of 0.42-0.58 for the AQLQ domains.[36-39]
EQ-5D-5L	EQ-5D-5L is a general, non–disease-specific health-related quality-of-life questionnaire.	Validity: Known-groups validity was present when the ACQ-5 was used to classify patients in terms of asthma severity,[94] but was not present when PEF values were used to classify patients into categories of varying asthma severity.[95] Convergent validity was established through moderate to strong Spearman's rank correlations with the Asthma Quality of Life Utility Index.[95] Reliability: No evidence of reliability was identified. Responsiveness: The EQ-5D-5L was able to effectively discriminate between patient-reported improvement or deterioration in asthma.[95] The EQ VAS records the respondent's self-rated health on a vertical VAS where the end points are labelled 0 ("the worst health you can imagine") and 100 ("the best health you can imagine").	MID of 0.056 for general use in the Canadian population.[41] There was no MID established in a population of patients with asthma.

Measure	Type	Conclusions about measurement properties	MID
EQ-5D-3L	A generic preference-based HRQoL instrument that has been applied to a wide range of health conditions and treatments	The validation of EQ-5D-3L available across countries around the world and in various conditions.[96,97]	MID: 0.033 to 0.074[40]; Unknown for asthma population
ACQ-7	Patient-reported tool to assess asthma control. It comprises the following 7 questions, of which the mean of the results is the overall score ranging from 0 for well-controlled asthma to 6 for extremely poorly controlled asthma: • Daytime symptoms • Nighttime awakening/ symptoms • Activity limitation • Rescue treatment requirements (use of SABA) • Lung Function (FEV_1) • Shortness of breath • Wheezing	Validity: Studies support the presence of longitudinal, cross-sectional, and construct validity of the ACQ-7 through correlations with a variety of measures of health status.[39,98,99] Known-groups validity was established by significantly different ($P < 0.001$) ACQ-7 scores in patient groups split by presence of and lack of nighttime awakenings and rescue medication use.[39] Reliability: Test-retest and internal consistency reliability was adequate with ICC > 0.7 and Cronbach alpha > 0.7 in 3 independent publications.[39,98,99] Responsiveness: The ACQ-7 was able to distinguish between adults with stable and unstable asthma in 2 independent publications ($P < 0.001$).[98,99]	The ACQ MID has been well established and accepted as 0.5 points for within person change.[42,4344]
ACQ-5/ ACQ-6	Shortened version of ACQ-7 by excluding rescue use of SABA and FEV_1. Including: • -Daytime symptoms • -Nighttime awakening/ symptoms • -Activity limitation • -Shortness of breath • -Wheezing[42,44]	• ACQ-5 and ACQ-6 had strong associations with the AQLQ (Pearson correlation coefficients ranging from 0.77 to 0.85)[100] • Test-retest reliability (ICCs of 0.89 to 0.90).[100] • Responsiveness in patients with unstable asthma for the shortened versions were similar to that for the full version.[100]	• 0.5,[44]

Measure	Type	Conclusions about measurement properties	MID
SNOT-22	SNOT-22 is a disease-specific, commonly used health-related quality-of-life outcome measure for chronic rhinosinusitis(CRS).[101,102] The SNOT-22 includes 22 questions which reflect nasal, sleep, ear/facial discomfort and emotional symptoms.(Philips 2018 ref 10,11)[45,46,103]	Validity: Compared to global QoL question, the mean SNOT-22 score increased significantly, in terms of overall effect (P < 0.0001), from excellent overall QoL to poor QoL.[45] Reliability: The Cronbach alpha scores for the SNOT-22 were 0.91.[45] The test-retest reliability coefficient was 0.93.[45] Responsiveness: SNOT-22 was able to effectively discriminate the scores before and after surgery(P < 0.0001,t = 39.94). The overall effect size in all patients was 0.81. In chronic rhinosinusitis patients with polyps the effect size was 0.90, while in those without polyps it was 0.63.[45]	MID: 8.9[45] MID: ranged from 8.3 to 17.5 depending on the methods used.[46]
RQLQ(s)	Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) was specific self-administered questionnaire to measure the QoL that for adults with allergic rhinitis and rhinoconjunctivitis.[104-106,47] It contains 28 questions in 7 domains.	Validity: correlation with index values of health status, such as the SF-36 was strong for RQLQ(S).[47] Reliability: For RQLQ(s), the overall concordance was high (ICC = 0.996) in patients whose rhinoconjunctivitis was stable. Reliability was high (ICC = 0.97). Cronbach Alpha was 0.93.[47] Responsiveness RQLQ(s) were able to detect within-subject changes in all domains (P < 0.001) between those patients who remained stable over 5 weeks period and those whose rhinoconjunctivitis changed (P < 0.005).[47]	0.5[47,104]

ACQ - 5 = Asthma Control Questionnaire - 5; ACQ - 7 = Asthma Control Questionnaire - 7; AQLQ = Asthma Quality of Life Questionnaire; EQ-5D- 3L = EuroQol 5-dimensions 3-levels questionnaire; EQ-5D-5L = EuroQol 5-dimensions 5-levels questionnaire; FEV_1 = forced expiratory volume in 1 second; NR = not reported; MPPI = minimal patient perceivable improvement; PEF = peak expiratory flow; RQLQ(S) = Standardized Rhinoconjunctivitis Quality of Life Questionnaire ; SNOT-22 = 22-item Sino-Nasal Outcome Test.

Forced Expiratory Volume in One Second (FEV_1)

Forced expiratory volume in 1 second (FEV_1) is the maximal amount of air forcefully exhaled in 1 second. The measured volume can be converted to a percentage of predicted normal value, which is adjusted based on height, weight, and race. The percentage of predicted FEV_1 is 1 of the most commonly reported pulmonary function tests.[107] Moreover, trough FEV_1 and pre-dose FEV_1 are also used as clinical measures of lung function, where trough FEV_1 is defined as the mean of the 2 FEV_1 values measured at 23 hours 15 minutes and 23 hours 45 minutes after the evening treatment dose is taken, and pre-dose FEV_1 is defined as the mean of the 2 FEV_1 values measured 45 minutes and 15 minutes before the evening dose. The EMA considers pre-bronchodilator FEV_1 as the most suitable measure of asthma control as it changes with acute fluctuations in airway limitation.[108]

Clinically, the percentage of predicted FEV_1 appears to be a valid marker for the degree of airway obstruction with asthma and other respiratory conditions. Together with measures of asthma symptoms and use of inhaled short-acting beta-agonists, FEV_1 is used to classify the severity of asthma.[109,110] However, the extent to which FEV_1 values are associated with health-related quality of life is uncertain, as researchers have reported variable correlations among adults and children with asthma, ranging from no association to strong associations.[83-86] Conversely, FEV_1 values appear to correlate well with certain clinical outcomes, such as the likelihood of

hospitalization.[111] Furthermore, FEV_1 values demonstrated high within-session repeatability. In a study of 18,526 adult patients, of whom 11% gave a history of physician-diagnosed asthma, 90% were able to reproduce FEV_1 within 120 mL.[87]

There appears to be limited published evidence relating to a MID for FEV_1 among adult patients with asthma. In 1 study of 281 adult patients with mild to moderate asthma symptoms (baseline mean FEV_1: 2.30 L/s [standard deviation of 0.66 L/s]), the authors calculated the MPPI for FEV_1 as the mean change in FEV_1 in patients rating themselves as "a little better" (n = 86) on the global rating of change in asthma.[33] Across all patients, the MPPI for FEV_1 was 230 mL or a 10.38% change from baseline. Males and females showed similar MPPI values, but older patients had a lower MPPI (170 mL) than younger ones (280 mL) for FEV_1.[33]

Peak Expiratory Flow (PEF)

PEF, sometimes referred to as PEF rate, is defined as "the maximum flow achieved during an expiration delivered with maximal force starting from the level of maximal lung inflation."[112] Electronic peak flow metres automatically store and download measurements as needed, circumventing the need for patients to manually record PEF values in diaries. PEF is usually expressed in units of L per minute (L/min) and sometimes as a percentage of the predicted normal value or as a change from baseline average values.[113] The EMA considers PEF (along with FEV_1) a valid spirometric evaluation for anti-asthmatic drugs.[108] PEF values appear to discriminate between patients with reversible and irreversible airflow obstruction.[114] PEF values also appear to be a valid clinical marker of airway responsiveness and asthma severity.[113] In addition, they seem to correlate well with other measures of lung function, including FEV_1,[88] although evidence that directly links PEF with health-related quality of life is lacking. Some trialists have used a value of 25 L/min as an MID for PEF values among patients with asthma.[89,90] However, no research seems to support the use of this MID. In 1 study of 281 adult patients with mild to moderate asthma symptoms, researchers calculated the MPPI for PEF as the mean change in PEF in patients rating themselves as "a little better" (n = 86) on the global rating of change in asthma. The MPPI for PEF was 18.8 L/min, or a 5.39% change from baseline, with no differences in MPPI values by gender or age.[33] In another study, researchers noted a predicted PEF of about 12% to be a minimal clinically significant improvement among patients presenting to the emergency department with acute asthma exacerbation.[91]

Asthma Quality of Life Questionnaire (AQLQ)

AQLQ is a patient-reported, disease-specific, health-related quality-of-life measure that was developed to evaluate asthma in the clinical trial setting.[115] The AQLQ includes 32 questions grouped into 4 domains: (1) symptoms, (2) activity limitations, (3) emotional function, and (4) environmental stimuli. Each question is scored on a 7-point scale, which ranges from 7 (no impairment) to 1 (severe impairment). The overall score is calculated as the mean of all questions, and the 4 domain scores are the means of the scores for the questions in the respective domains. Patients recall their relevant experiences during the previous 2 weeks. The EMA recommends the use of patient-reported outcomes in clinical trials which assess health-related quality of life, such as the validated AQLQ.[108] The AQLQ showed no evidence for a floor or a ceiling effect.[34]

Validity

The AQLQ was assessed 3 months apart in a group of patients defined as having "well-controlled asthma" and having "not well-controlled asthma" to evaluate known-groups validity. The AQLQ showed the best discriminatory power when compared to the EQ-5D as evaluated through large Cohen d values, indicating that the AQLQ was able to distinguish between clinical groups with different asthma severities.[34] Cross-sectional validity, evaluated at a point in time, and longitudinal validity, evaluated over time, was evaluated in a cohort of patients with symptomatic asthma (N = 39) with Spearman's rank correlations. The change in the AQLQ domains showed none to strong correlations with measure of clinical status such as the % predicted FEV_1 (r = 0.27 to 0.43), asthma control, asthma global ratings of change (r = 0.52 to r = 0.82), the Sickness Impact Profile (r = 0 to r = 0.24), and the Rand General Health Survey (r = 0.3 to r = 0.51) indicating presence of longitudinal construct validity. With regards to cross-sectional validity, the AQLQ domains displayed a strong Spearman's rank correlation coefficient with asthma control (r = 0.31 to r = 0.69), and there were no relationships with the other measures of clinical status outlined above.[92]

Reliability

Test-retest reliability was evaluated 4 weeks apart in 2 separate studies with patients whose asthma was deemed as stable for 4 weeks, evaluated by the investigators. In both studies the intraclass correlation coefficient (ICC) > 0.7 indicating that the AQLQ displayed test-retest reliability.[34,92]

Responsiveness

The AQLQ was responsive to within-subject changes both in patients whose asthma was stable and whose asthma changed (responsiveness indices of 1.35 for the AQLQ).[93] The AQLQ was also responsive to changes between groups with stable and with worsened asthma (P < 0.001), and to changes within-groups (P < 0.001).[92] In a publication by Szentes et al., when the patients were divided by those which had a 3-point change in the asthma control test (MID of the asthma control test) and those that did not, the AQLQ was highly responsive, explaining 0.63 of the variance.[34]

Clinical Relevance

The MID for the AQLQ has been determined to be a cut point of 0.5, with publications reporting values such as 0.67,[116] 0.52,[35] and a range of 0.42 to 0.58 for the AQLQ domains.[36-39]

EuroQol 5-Dimensions 5-Levels Questionnaire (EQ-5D-5L)

EQ-5D is a generic quality-of-life instrument developed by the EuroQol Group.[117] It may be applied to a wide range of health conditions and treatments.[117] As a generic measure of HRQoL that can capture the net effect of treatment benefits and harms, the EQ-5D provides valuable information from a patient perspective. In addition to this purpose, the EQ-5D is used in clinical trials to obtain utility weights for economic models.[118] The EQ-5D-5L consists of the EQ-5D descriptive system and the EQ visual analogue scale. The descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, each with 5 levels: a level 1 response represents "no problems," level 2 "slight problems," level 3 "moderate problems," level 4 "severe problems," and level 5 "extreme problems" or "unable to perform," which is the worst response in the dimension. Respondents are asked to choose the level that reflects their health state for each of the 5 dimensions. In total, there are 3,125 possible unique health states defined by the EQ-5D-5L, with 11111 and 55555 representing the best and worst health states. The numerical values assigned to levels 1 to 5 for each dimension reflect rank order categories of function. In terms of measurement properties, these are ordinal data; they do not have interval properties and therefore should not be summed or averaged to, for example, produce an individual dimension "score." Results from the EQ-5D-5L descriptive system can be converted into a single index score using a scoring algorithm taking the local patient and population preferences into account. Therefore, the index score is a country-specific value and a major feature of the EQ-5D instrument.[118] The range of index scores will differ according to the scoring algorithm used; however, in all scoring algorithms of the EQ-5D-5L, a score of 0 represents the health state "dead" and 1.0 reflects "perfect health." Negative scores are also possible for those health states that society (not the individual patient) considers to be "worse than dead."

The EQ VAS records the respondent's self-rated health on a vertical VAS where the end points are labelled 0 ("the worst health you can imagine") and 100 ("the best health you can imagine"). The respondents are asked to mark an X on the point of the VAS that best represents their health on that day. The EQ-5D index and VAS scores can be summarized and analyzed as continuous data.[117,118] Hence, the EQ-5D produces 3 types of data for each respondent:

- a profile indicating the extent of problems on each of the 5 dimensions represented by a 5-digit descriptor, such as 11121 or 21143
- a population preference-weighted health index score based on the descriptive system
- a self-reported assessment of health status based on the EQ VAS.

The EQ-5D-5L has been validated in terms of feasibility, ceiling effects, discriminatory power, and convergent validity in a diverse patient population from 6 countries with chronic conditions (including patients with asthma or chronic obstructive pulmonary disease).[117] MID estimates for the index score in the general Canadian population were generated by simulating the effects of single level transitions in each dimension.[41] The results yielded MIDs with a summarized mean of 0.056 (SD = 0.011), and a summarized median of 0.056 (interquartile range, 0.049 to 0.063).[41] In a European cohort of 316 patients with asthma aged 12 to 40 years, construct validity was established using the known-groups method in groups with good, intermediate, and bad asthma control defined by the ACQ-5.[94] The EQ-5D-5L index score was significantly different between the groups with good control (mean [95% CI] = 0.91 [0.89 to 0.93]), intermediate control (mean [95% CI] = 0.84 [0.81 to 0.87]), and poor control (mean [95% CI] = 0.73 [0.69 to 0.78]).[94] Convergent validity was established in a prospective observational cohort study (N = 121) with asthma patients. The EQ-5D-5L displayed moderate to strong Spearman's rank correlations with the Asthma Quality of Life Utility Index. Within the same study, there was no evidence of known-groups validity identified when patients were classified in categories of asthma severity based on PEF values.[95] When the authors evaluated responsiveness by asking patients "Compared to your asthma state when you were in hospital approximately 4

weeks ago, how would you rate your asthma now?", the EQ-5D-5L displayed large standardized response means for the good and poor groups (0.95, −1.03 respectively), and 0.75 for the very good, and 0.303 for the moderate response options.[95] No information was found on the reliability or MID of the EQ-5D-5L in an asthma population.

EuroQol 5-Dimensions 3-Levels Questionnaire (EQ-5D-3L)

The EuroQoL-5 Dimensions 3 Levels (EQ-5D-3L) is a generic preference-based HRQoL instrument that has been applied to a wide range of health conditions and treatments.[96,97] The first of 2 parts of the EQ-5D-3L is a descriptive system that classifies respondents (aged ≥ 12 years) into 1 of 243 distinct health states. The descriptive system consists of the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 possible levels (1, 2, or 3) representing "no problems," "some problems," and "extreme problems," respectively. Respondents are asked to choose 1 level that reflects their own health state for each of the 5 dimensions. A scoring function can be used to assign a value (EQ- 5D-3L index score) to self-reported health states from a set of population-based preference weights.[96,97] The second part is a vertical, calibrated 20 cm visual analogue scale (EQ VAS) that has end points labelled 0 and 100, with respective anchors of "worst imaginable health state" and "best imaginable health state," respectively. Respondents are asked to rate their own health by drawing a line from an anchor box to the point on the EQ VAS which best represents their own health on that day. Hence, the EQ-5D-3L produces 3 types of data for each respondent:

- A profile indicating the extent of problems on each of the 5 dimensions represented by a 5-digit descriptor, such as 11121, 33211, and so forth
- A population preference-weighted health index score based on the descriptive system
- A self-reported current health status based on the EQ VAS that is used to assess the overall health of the respondent rather than selected dimensions of individuals" health

The EQ-5D-3L index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The lowest possible overall score (corresponding to severe problems on all 5 attributes) varies depending on the utility function that is applied to the descriptive system (e.g., −0.59 for the UK algorithm and −0.109 for the US algorithm). Scores less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health," respectively.

EQ-5D-3L has been extensively validated across countries around the world and in various conditions. However, the EQ-5D-3L has not been validated in patient with asthma specifically, therefore its validity, reliability, and responsiveness to change have not been evaluated in the patient population of interest. No information on the validity of EQ-5D-3L and MID was found for asthma populations. The MID for the EQ-5D3L ranges from 0.033 to 0.074.[40]

Asthma Control Questionnaire-7 (ACQ-7)

The ACQ, also termed the ACQ-7, was developed to evaluate asthma control in patients with asthma and is 1 of the most commonly used instruments measuring asthma control.[42,119] The questionnaire comprises 7 questions, the responses of which are scored on a 7-point scale. Questions regarding 6 aspects of the patient's previous week's experiences are answered by the patient and include questions on activity limitation, nocturnal waking, shortness of breath, wheezing, symptoms on waking, and the use of short-acting Beta2-agonist.[119] In addition, the seventh item includes calculations performed by clinical staff with regard to pre-bronchodilator FEV_1 or PEF (% predicted).[42,119] The ACQ score is calculated as the mean of the 7 questions (as all questions are equally weighted), with scores at zero meaning the patient has asthma which is well controlled and those at 6 means the patient has asthma which is extremely poorly controlled.[42,98,119] The ACQ is used extensively in clinical trials to measure clinically meaningful change in asthma control.[42]

Validity

Evidence for longitudinal and cross-sectional construct validity has been observed by correlations between the ACQ and other asthma health status measures in 2 separate studies.[98,99] The ACQ showed variable evidence for presence of construct validity; with a strong Pearson correlation coefficients for the AQLQ for patients 12 years or older (r = - 0.77), strong correlation with shortened versions of the ACQ (r > 0.9), and weak correlation morning or evening (r = - 0.16 and r = - 0.15, respectively).[39] In the same study, the ACQ scores were significantly different (P < 0.001) between 4 pre-established patient groups (those with nighttime awakenings compared to those with no nighttime awakenings; those with daytime use of SABAs compared to those with no daytime SABA use; those with nighttime

SABA use compared to those with no nighttime SABA use; and those with any use of SABAs compared to those with no SABA use), indicating that the ACQ is able to distinguish between clinical groups with different levels of asthma severity, and thus, the presence of known-groups validity.[39]

Reliability

The ACQ is a multidimensional and standardized tool[43] that has high test-retest reliability in 3 separate publications. In 2 studies published by Juniper et al., the authors reported an ICC of 0.90 in both studies.[98,99] Furthermore, test-retest (ICC > 0.7) and internal consistency (Cronbach alpha > 0.7) reliability was present when patients with stable persistent asthma were evaluated 4 weeks apart in 2 clinical trials.[39]

Responsiveness

Responsiveness of the ACQ has been evaluated in a number of studies.[39,98,99] Overall, the ACQ was responsive to change in studies published by Juniper et al. as the ACQ scores were significantly different ($P < 0.001$) between adults with stable and unstable asthma.[98,99] To further evaluate the responsiveness of the ACQ, the change in ACQ score from baseline to 26 weeks was evaluated with a Pearson correlation coefficient to the change in AQLQ-S + 12, and the % predicted FEV_1 in 2 separate clinical trials. Responders were identified with the previously established ACQ cut point of 1.0 to distinguish between "well-controlled" versus "not well-controlled asthma."[120] Overall, the change in ACQ correlated well with the change in the AQLQ-S + 12 (Pearson correlation coefficient 0.74 to 0.78), but did not correlate with the change in % predicted FEV_1 (Pearson correlation coefficient 0.01 to 0.03).[39]

Clinical Relevance

The ACQ MID has been well established and accepted as 0.5 points for within person change.[42,43] However, Bateman et al. questioned its use as a measure between groups or between patients, further speculating that patient-reported outcomes should be presented as a responder rate comparison or a net treatment benefit analysis.[121] In addition, a score of 1.5 on the ACQ is the most appropriate discriminator for "well-controlled" and " not well-controlled" asthma patients.[122]

Asthma Control Questionnaire-5 and −6 (ACQ-5, ACQ-6)

The ACQ also exists in abbreviated versions with the ACQ-5 focusing only on the symptoms (exclusion of the FEV_1 and bronchodilator use) while the ACQ-6 includes everything except the FEV_1 item.[42,44]

Validation and agreement across the shortened versions of the ACQ (ACQ-5 and ACQ-6) has also been investigated.[39,44,100] In a re-analysis of the aforementioned ACQ-7 validation study, all 3 shortened versions of the ACQ had strong associations with the AQLQ (Pearson correlation coefficients ranging from 0.77 to 0.85) and acceptable test-retest reliability (ICCs of 0.89 to 0.90).[100] Responsiveness in patients with unstable asthma for the shortened versions were similar to that for the full version.[100] These findings were corroborated by 2 subsequent validation studies which were based on samples from a 26-week randomized controlled trial (RCT, N = 552) and a post hoc analysis of 2 large RCTs (N = 737 and N = 772).[39,44] In the 26-week RCT in 552 adults with asthma requiring inhaled steroids, the ACQ-6 omitting the FEV_1 item had acceptable (≥ 0.7,[123]) internal consistency reliability (Cronbach alpha = 0.98), acceptable test-retest reliability (ICC = 0.82), and a strong positive association with the mini AQLQ (Pearson correlation coefficient = 0.76).[44] The MIDs for all versions of the ACQ were found by regressing the changes in ACQ score on changes in mini AQLQ score using a geometric mean regression model.[44] Using an MCID of 0.5 for the mini AQLQ, the results indicated an MID of approximately 0.5 for all versions of the ACQ.[44] However, it is not clear how the MCID for the mini AQLQ was determined.[124] A separate study determined the MID for the ACQ-7 to be 0.53 using an anchor-based approach with a global rating, though the conference abstract in which it is cited was not available at the time of this review.[125] Studies in pediatric patients with asthma have found an MID of 0.63 for the ACQ-6 using an anchor-based approach with global rating of change[126] an MID of 0.375 for the ACQ-7 using a distribution-based approach,[127] and MCIDs ranging from 0.4 to 0.5 for the ACQ-7 using an anchor-based approach.[127]

Twenty-two-item Sino-Nasal Outcome Test (SNOT-22)

The 22-item Sino-Nasal Outcome Test (SNOT-22) is a validated, disease-specific, self-administered questionnaire that is used to assess the health-related quality of life (QoL) of patients with chronic rhinosinusitis.[45] SNOT-22 consists of 22 items, which include nasal symptoms, sleep, ear/facial discomfort, and emotional symptoms. Each question score range from 0 to 5. The lower score indicates a better health-related quality of life, i.e., "0" means no problem at all, and "5" means the worst possible problem.[45] SNOT-22 total scores

range from 0 to 110. Psychometric properties have been reported for the SNOT-22 total score.[45] The SNOT-22 has been widely used in clinical practice and in research.[101,102]

Validity

Validation of SNOT-22 was performed by Hopkins et al.[45] } The study was conducted in 3,128 adult patients undergoing sino-nasal surgery. Patients" response to the global QoL question was compared with the SNOT-22 score. The results showed that the mean SNOT-22 score increased statistically significantly in terms of overall effect (P < 0.0001) from excellent overall QoL to poor QoL.[45]

Reliability

In patients after sino-nasal surgery, the Cronbach alpha score for the SNOT-22 were 0.9, which showed a high internal consistency.[45] In patients awaiting surgery for nasal surgery, the test-retest reliability coefficient was 0.93, which indicated a high reliability. The SNOT-22 was able to discriminate between patients with chronic rhinosinusitis and healthy people (P < 0.0001, t = 85.3).

Responsiveness

Responsiveness was assessed by examining SNOT-22 scores before and after sino-nasal surgery by measuring the effect size (the mean change score divided by baseline standard deviation). It was reported that a statistically significant (P < 0.0001,t = 39.94) decrease in patient-reported SNOT-22 scores 3 months after surgery. At 3-months the overall effect size in all patients was 0.81, which was considered large. In chronic rhinosinusitis patients with polyps the effect size was 0.90, while in those without polyps it was 0.63.[45]

Clinical Relevance

The MID for the SNOT-22 has been estimated to be 8.9.[45] However, in a study by Phillips et al.,[46] the MID of SNOT-22 in the patients with chronic rhinosinusitis ranged from 8.3 to 17.5 depending on the method used. The author suggested a 12 as the MID of SNOT-22 for medically managed patients with chronic rhinosinusitis.[46]

Standardized Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ(s))

The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) was developed to measure the health-related quality of life for adults with rhinoconjunctivitis.[104-106] The RQLQ is an allergic rhinitis specific, self-administered questionnaire.[47,128] It contains 28 questions in 7 domains. These domains include activity limitation (3 questions), sleep problems (3 questions), nose symptoms (4 questions), eye symptoms (4 questions), non-nose/eye symptoms (7 questions), practical problems (3 questions) and emotional function (4 questions). The score ranged from 0 (not troubled/none of the time) to 6 (extremely troubled/all of the time). The overall RQLQ score is the mean of all 28 responses, and the individual domain scores are the means of the questions in each domain – both range from 0 to 6. A lower score for each question indicates a better health-related quality of life.[47] Juniper, et al.[47] developed a standardized version of the RQLQ, the RQLQ(S) in 1999. The RQLQ(s) assessed the activities most frequently selected by patients and formulated 3 generic questions. RQLQ(s) has been widely used in clinical trials and research.[128-130]

Validity

The RQLQ has been validated in adult patients with seasonal and perennial rhinoconjunctivitis.[131] The RQLQ(s) has been validated in a study by Juniper (1999)[47] in a 5-week observational study in 100 adults with symptomatic rhinoconjunctivitis. Patients completed the RQLQ(S), RQLQ and other measures of health status at baseline and 1 and 5 weeks. The findings showed that the construct validity (i.e., correlation with other index values of health status, such as the SF-36) was strong for both the RQLQ(S) and the RQLQ.

Reliability

The reliability was estimated in a group of patients with stable rhinoconjunctivitis. Test-retest reliability has been estimated as the within-subject SD and related to the overall SD as an ICC. For RQLQ(s), the result showed that the overall concordance was high (intraclass correlation coefficient = 0.996). In patients whose rhinoconjunctivitis was stable between clinic visits, reliability was high for both instruments and almost identical (ICC = 0.97). Cronbach Alpha was 0.93 for RQLQ(s) and 0.92 for RQLQ respectively, which indicated a high internal consistency.[47]

Responsiveness

The responsiveness was examined whether the RQLQ(s) could detect change by use of a paired t-test in a group of patients who had a change in their rhinoconjunctivitis between weeks 1 and 5 (i.e., either improved or deteriorated by a score of 2 or greater on the global rating). In addition, it was also assessed whether the RQLQ(s) could detect a difference between patients who changed and patients who remained stable by use of an unpaired t-test. Both the RQLQ and RQLQ(s) were able to detect within-subject changes in all domains ($P < 0.001$) between those patients who remained stable over 5-week period and those whose rhinoconjunctivitis changed ($n = 83$) ($P < 0.005$).[47] Furthermore, a responsiveness index was calculated. Differences in responsiveness index values were tested with paired t-tests. It was reported a similar responsiveness index values both for the activity domains (RQLQ(s) = 0.82, RQLQ = 0.80, P = 0.73) and overall health-related quality of life (RQLQ(s) = 0.75, RQLQ = 0.76, P = 0.76).[47]

Clinical Relevance

The MID of RQLQ(s) was estimated as 0.48 ± 0.93, which is similar to MID of RQLQ (0.49 ± 0.96).[47] It has been well accepted and established as 0.5 for the overall or individual domain scores.[104]

Other versions of the RQLQ (including electronic, mini, adolescent and pediatric specific versions) have been developed and validated. The MID values range from 0.4 to 0.7.[132,133]

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Abbreviations

ACQ	Asthma Control Questionnaire
BIA	budget impact analysis
FEV_1	forced expiratory volume in the first second
ICER	incremental cost-effectiveness ratio
ICS	inhaled corticosteroid
LABA	long-acting beta2-agonist
LAMA	long-acting muscarinic antagonist
LTRA	leukotriene receptor antagonist
OCS	oral corticosteroid
QALY	quality-adjusted life-year
WTP	willingness to pay

Executive Summary

The executive summary comprises 2 tables (Table 1 and Table 2) and conclusions.

Conclusions

Dupilumab reduces severe asthma exacerbations compared to background therapy alone, although the effects of dupilumab on health-related quality of life are uncertain. The comparative effects of dupilumab relative to other biologic treatments for severe asthma are highly uncertain owing to a lack of direct comparative evidence and limitations within the sponsor's indirect treatment comparisons.

CADTH undertook reanalyses to address limitations in the sponsor's submission, including aligning the relative risk of severe asthma exacerbations with the QUEST trial data, removing the risk of mortality with a severe exacerbation, removing response assessment at 52 weeks, and fixing programming errors in the model. CADTH reanalyses focused on patients with type 2 or eosinophilic asthma, which is in line with the Health Canada indication and may include a proportion of patients with oral corticosteroid (OCS)–dependent asthma. CADTH was unable to address the lack of head-to-head comparative clinical data, uncertainty regarding

Table 1: Submitted for Review

Item	Description
Drug product	Dupilumab (Dupixent), solution for subcutaneous injection (200 mg per 1.14 mL pre-filled syringe [175 mg/mL]; 300 mg per 2 mL pre-filled syringe [150 mg/mL])
Submitted price	Dupilumab 200 mg, 300 mg: $960 per pre-filled syringe
Indication	Indicated as add-on maintenance treatment in patients aged 12 years and older with severe asthma with a type 2/eosinophilic phenotype or oral corticosteroid–dependent asthma
Health Canada approval status	NOC
Health Canada review pathway	Standard
NOC date	November 12, 2020
Reimbursement request	For patients with type 2 or eosinophilic asthma characterized by the following: • 2 or more clinically significant asthma exacerbations in the last 12 months and ◦ Blood eosinophils ≥ 150 µL, or ◦ FeNO ≥ 25 ppb, or ◦ Treatment with maintenance oral corticosteroids, or ◦ Clinically allergen-driven asthma.
Sponsor	Sanofi Genzyme
Submission history	Previously reviewed: Yes Indication: Atopic dermatitis Recommendation date: June 27, 2018 Recommendation: Do not reimburse

FeNO = fractional exhaled nitric oxide; NOC = Notice of Compliance; ppb = parts per billion.

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Patients with severe asthma with a type 2 or eosinophilic phenotype or with OCS dependency
Treatment	Dupilumab + background therapy
Comparator	Background therapy (consisting of ICS, ICS + LABA, LABA, LTRA, LAMA, theophylline, prednisolone)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs, number of exacerbations
Time horizon	Lifetime (up to patient age 100 years)
Key data source	QUEST trial, VENTURE trial
Submitted results	Base case: type 2 or eosinophilic phenotype: • ICER = $125,305 per QALY (incremental costs: $182,434; incremental QALYs: 1.46) Scenario analysis: OCS-dependent asthma: • ICER = $139,397 per QALY (incremental costs: $337,177; incremental QALYs: 2.42)
Key limitations	• The sponsor's 5-substate economic model lacks face validity. Asthma control, defined using ACQ-5, was dichotomized (controlled vs. uncontrolled), with a threshold of 1.5 used to classify patients as controlled or uncontrolled. This dichotomization implies that a patient whose ACQ score improved by as little as 0.01 (i.e., from 1.50 to 1.49) would be considered to have controlled asthma and would receive the utility benefit for the controlled health state (0.906) instead of that for the uncontrolled health state (0.769). • The number of exacerbations predicted by the sponsor's model is not aligned with clinical trial evidence. Both the 5- and 4-substate models overestimate the number of severe exacerbations in the background therapy arm during the trial period. • The comparative clinical efficacy of dupilumab relative to other biologic treatments for severe asthma is highly uncertain. There is no direct head-to-head evidence comparing dupilumab and other biologics, and there is substantial uncertainty in the results of the sponsor's indirect treatment comparisons. • There is limited evidence about the duration of the treatment effect. The sponsor assumed that the clinical effects of dupilumab on asthma exacerbations observed in 52-week trials would be maintained for approximately 50 years. • The assumption of increased mortality with a severe asthma exacerbation in the model implies a significant survival benefit with dupilumab that has not been shown in clinical trials. • The model structure does not adequately reflect the management of asthma in clinical practice. The sponsor assumed that treatment response would be assessed after 52 weeks, with response defined as an improved exacerbation risk (reduced annualized rate of severe asthma exacerbation events of at least 50%, decreased OCS use, or both), and nonresponders were assumed to discontinue dupilumab and receive background therapy alone. In practice, initial treatment response would be assessed earlier (e.g., after 2 to 3 months) on the basis of ACQ score and lung function (i.e., FEV_1). Patients with an inadequate treatment response would likely be switched to an alternative biologic, not to background therapy alone.

Component	Description
	• The sponsor's model employed poor modelling practices, was unnecessarily complex, and lacked transparency, preventing CADTH from fully validating the model and its findings. CADTH identified some errors in the model coding. • The cost-effectiveness of dupilumab among adolescents is uncertain. The sponsor's analyses were based on clinical trials which predominantly enrolled adult patients. • The cost-effectiveness of the 300 mg strength of dupilumab in patients with type 2 or eosinophilic phenotype asthma is unknown. The sponsor's submitted analysis of dupilumab in patients with type 2 or eosinophilic asthma incorporated data based solely on the 200 mg arm of the QUEST trial.
CADTH reanalysis results	• In the CADTH reanalysis, the relative risk of severe asthma exacerbations was aligned with the QUEST trial, the risk of mortality with a severe exacerbation was removed, response assessment at 52 weeks was removed, programming errors were fixed, and the population was aligned with the QUEST trial (i.e., patients with type 2 or eosinophilic asthma). CADTH was unable to address the lack of head-to-head comparative clinical data vs. biologics, uncertainty regarding long-term clinical effectiveness, lack of data related to the 300 mg strength, and lack of data for adolescents for dupilumab. • Based on CADTH reanalyses, dupilumab plus background therapy remained more costly and more effective than background therapy alone: ICER = $721,678 per QALY (incremental costs = $188,483; incremental QALYs = 0.26). A price reduction of 93% would be required for dupilumab to be considered at a WTP threshold of $50,000 per QALY. Cost-effectiveness relative to other biologics and in the adolescent population could not be determined.

ACQ = Asthma Control Questionnaire; FEV_1 = forced expiratory volume in the first second; ICER = incremental cost-effectiveness ratio; ICS = inhaled corticosteroid; LABA = long-acting beta2-agonist, LAMA = long-acting muscarinic antagonist; LTRA = leukotriene receptor antagonist; LY = life-year; OCS = oral corticosteroid; QALY = quality-adjusted life-year; WTP = willingness to pay.

long-term clinical effectiveness, lack of data related to the 300 mg strength, and lack of data for adolescents.

In the CADTH base case, dupilumab plus background therapy was more effective and more costly than background therapy alone (incremental costs = $188,483; incremental quality-adjusted life-years [QALYs] = 0.26). Dupilumab is not cost-effective compared to background therapy at a willingness-to-pay (WTP) threshold of $50,000 (incremental cost-effectiveness ratio [ICER] = $721,678 per QALY). The key driver of the ICER is the cost of dupilumab acquisition, and a 93% price reduction would be required for it to be considered optimal at a WTP threshold of $50,000. This price reduction is likely conservative given that the cost-effectiveness is reliant on maintaining long-term treatment benefit. Without long-term sustained asthma control, the ICER goes beyond $4 million per QALY. There is no clinical evidence to support a price premium for dupilumab above other biologics.

Stakeholder Input Relevant to the Economic Review

This section is a summary of the feedback received from the patient groups, registered clinicians, and drug plans that participated in the CADTH review process.

Patient group input from the British Columbia Lung Association and Lung Groups and the Lung Health Foundation indicated that the goal of asthma therapy is to relieve symptoms, prolong life, reduce disability, stabilize lung function, and slow disease progression. Patients who provided input had experience with short-acting beta2-agonists, inhaled corticosteroids (ICSs), ICS plus long-acting beta2-agonists (LABAs), ICS plus long-acting muscarinic

antagonist (LAMA) combination inhalers, and OCSs. Current treatments were described as providing some relief for fatigue, shortness of breath, wheezing, cough, and reduced energy but not an improved ability to exercise. Described side effects of current treatments included voice hoarseness, dry mouth, appetite loss, impact on mood, and difficulty sleeping. Side effects were reported to be particularly common with OCS and included obesity, diabetes, osteoporosis, cataracts, hypertension, and adrenal suppression, as well as psychological side effects (e.g., depression, anxiety). The patient groups reported a desire for treatments that go beyond symptom relief to improve overall lung function, as well as strategies to minimize the need for OCS. Patient feedback from those with dupilumab experience indicated that reactions at the injection site were common but minor and that blood eosinophilia may affect some patients.

Clinician input was received from the Family Physician Airways Group of Canada. Severe asthma was described as affecting less than 10% of patients with asthma. The group noted that a biologic treatment may be considered when treatment with ICSs, LAMAs, LABAs, and leukotriene receptor antagonists (LTRAs) is insufficient, pending a review of the diagnosis for accuracy, adherence, device technique, and comorbidities. Clinician input noted that the goal of treatment is to improve asthma control, prevent exacerbations, improve lung function, and allow patients to reduce or stop the use of OCS. Input from the clinician group noted that dupilumab may be the preferred biologic for patients with atopic dermatitis and nasal polyps and may reduce costs related to the treatment of rhinitis, dermatitis, and nasal polyps.

Drug plan input received for this review noted that there is a lack of comparative evidence between dupilumab and other currently available biologic treatments for asthma (i.e., benralizumab, mepolizumab, reslizumab, omalizumab). The plans noted that the pivotal trials for dupilumab enrolled patients with moderate-to-severe asthma, with no minimum threshold for baseline blood eosinophil count or other specific biomarker thresholds required for inclusion. The potential for off-label use in patients with moderate asthma was noted.

Several of these concerns were addressed in the sponsor's model:

- Clinical effectiveness was based on the rate of asthma exacerbations, with those who experienced a severe exacerbation were assumed to have lower health-related quality of life for the duration of the exacerbation. The sponsor assumed that moderate exacerbations would not affect patients' quality of life.
- Adverse events were incorporated for OCSs.

CADTH was unable to address the following concerns raised from stakeholder input owing to structural or data limitations:

- Lack of comparative evidence between dupilumab and other currently available biologic treatments for severe asthma
- Improvements in lung function
- Adverse events related to dupilumab or background therapy
- Costs related to rhinitis, dermatitis, or nasal polyps

Economic Review

The current review is for dupilumab (Dupixent) as add-on maintenance treatment in patients 12 years and older with severe asthma with a type 2 or eosinophilic phenotype or with OCS-dependent asthma.

Economic Evaluation

Summary of Sponsor's Economic Evaluation

Overview

The sponsor submitted a cost-utility analysis of dupilumab plus background therapy compared with background therapy alone in patients with (i) a type 2 or eosinophilic phenotype or (ii) OCS-dependent asthma.[1] The modelled population is consistent with the reimbursement request. The composition of background therapy reflected a basket of treatments including ICS, ICS + LABA combination inhalers, LAMAs, LTRAs, and theophylline. The cost-effectiveness of dupilumab relative to other monoclonal antibodies (mepolizumab, reslizumab, benralizumab, omalizumab) was assessed in scenario analyses.

Two strengths of dupilumab are available (200 mg/1.14 mL [175 mg/mL] and 300 mg/2 mL [150 mg/mL]) in pre-filled syringes for self-administration.[2] The recommended dosage for dupilumab is 200 mg (patients with severe asthma with a type 2 or eosinophilic phenotype) or 300 mg (OCS-dependent asthma or comorbid moderate-to-severe atopic dermatitis or severe chronic rhinosinusitis with nasal polyposis) every 2 weeks.[2] The annual cost of dupilumab (for both strengths) is $24,949 (initial year: $25,909) based on a unit cost of $959.60 per syringe. The annual cost of background therapy was calculated by the sponsor to be $10,098 per patient.

The clinical outcomes were QALYs, life-years, and asthma exacerbations (moderate, severe). The sponsor adopted a lifetime horizon (defined by the sponsor as 100 years minus the starting age of the cohort) using 4-week cycles and undertook the analysis from the perspective of the publicly funded health care payer. Costs and clinical outcomes were discounted at a rate of 1.5% per year.

Model Structure

The sponsor submitted 2 Markov models (5-substate model and 4-substate model) (Appendix 3).[1] In the sponsor's submission, the 5-substate model was used for analyses involving type 2 or eosinophilic patients, while the 4-substate model was used for analyses in the OCS-dependent subgroup. The 5-substate model includes 2 asthma control–based states (uncontrolled asthma and controlled asthma), as well as 2 exacerbation states (moderate exacerbations and severe exacerbations). The asthma control health states were defined based on Asthma Control Questionnaire (ACQ) scores (controlled asthma: ACQ score < 1.5 and no moderate or severe exacerbations; uncontrolled asthma: ACQ score ≥ 1.5 and no moderate or severe exacerbations). The 4-substate model comprises health states related to "no exacerbations" (i.e., no moderate or severe exacerbations), "moderate exacerbations," and "severe exacerbations," with no further breakdown by asthma control. Both models included a death state. In both models, patients in the severe exacerbation state were at risk of asthma-related mortality, while patients in all states were at risk of all-cause mortality.

Patients entered the model either on-treatment (dupilumab plus background therapy) or off-treatment (background therapy alone). Over time, patients who started on dupilumab

would discontinue and move to background therapy alone. In the 5-substate model, patients started in the uncontrolled asthma substate. In the 4-substate model, they started in the no exacerbation substate. Movement between states was defined by a set of transition probabilities that varied depending on what treatment the patient was receiving and over time (< 12 weeks, 12 to 52 weeks, > 52 weeks).[1]

Model Inputs

The baseline patient characteristics in the sponsor's model were aligned with the QUEST trial (mean age 47.98 years; 60.75% female; mean number of severe exacerbations in the past 12 months: 3.15). Clinical efficacy (i.e., probability of transition between health states) was based on the 52-week period of the QUEST trial or the 24-week period of the VENTURE trial. QUEST was a phase III, multi-centre, randomized, placebo-controlled trial that compared 2 dosages of dupilumab (200 mg every 2 weeks; 300 mg every 2 weeks) to placebo and enrolled participants (≥ 12 years) with all the following characteristics:

- Taking medium- or high-dose ICS in combination with 1 or 2 additional controllers (e.g., LABA, LTRA)
- Registering pre-bronchodilator forced expiratory volume in the first second (FEV_1) less than or equal to 80% of the predicted normal for adults (adolescents: ≤ 90%),
- Having an ACQ-5 score greater than or equal to 1.5
- Being treated with a systemic steroid (oral or parenteral) for worsening asthma or experiencing hospitalization or emergency medical care visit for worsening asthma at least once within the previous year

VENTURE was a phase III, multi-centre randomized controlled trial that compared 300 mg dupilumab every 2 weeks to placebo among participants (≥ 12 years) with severe asthma who were taking systemic corticosteroids for up to 6 months (5 mg/day to 35 mg/day prednisone or prednisolone) and high-dose ICS with 2 or 3 additional controllers (e.g., LABA, LTRA), and who had FEV_1 less than or equal to 80% of the predicted normal for adults (adolescents: ≤ 90%) and positive methacholine challenge. Transition between health states was based on a count of patients in each health state in QUEST and VENTURE every 4 weeks, along with the frequency of transition to other health states in the model.

Patients were assumed to remain on treatment for the first 52 weeks in the model, at which time treatment response was assessed. Treatment response was defined as an improved exacerbation risk (reduced annualized rate of severe asthma exacerbation events > 50%) or decreased OCS use (≥ 50% reduction in OCS dose for patients taking OCS at model start). The proportion of responders was based on the QUEST and VENTURE trials. Treatment responders were assumed to continue to receive dupilumab, while nonresponders were assumed to continue on background therapy alone. Treatment effect was assumed to be maintained over the model time horizon. Long-term discontinuation was based on the QUEST and VENTURE trials for the type 2 or eosinophilic and the OCS-dependent subgroups, respectively, and was assumed to occur at a constant rate regardless of health state.

Moderate exacerbations in the sponsor's model were defined per the QUEST trial (at least 1 of the following: ≥ 6 additional reliever puffs of salbutamol-albuterol or levosalbutamol-levalbuterol in a 24-hour period on 2 consecutive days; ≥ 20% decrease in pre-bronchodilator FEV_1 compared with baseline; increase in ICS dose ≥ 4 times the dose at visit 2; decrease in morning or evening peak flow of ≥ 30% on 2 consecutive days). Severe exacerbations were defined as the use of systemic corticosteroids for 3 days or more, admission to hospital, or

an emergency department visit because of asthma requiring systemic corticosteroids. The proportion of severe exacerbations managed by office visit, emergency department visit, or admission to hospital varied by type 2 or eosinophilic (office visits: 93.34%; emergency department visits: 3.00%; hospitalization: 3.66%) and OCS-dependent (office visits: 85.32%; emergency department visits: 6.42%; hospitalization: 8.26%) subgroups on the basis of post hoc analyses of the QUEST and VENTURE trials. The risk of asthma-related mortality among those with a severe exacerbation varied by age and whether the exacerbation resulted in an office visit, an emergency department visit, or a hospital admission.[3] Annual mortality rates for other-cause death were based on general population life tables,[4] after the exclusion of asthma-related deaths.

Utility values were estimated for the controlled asthma, uncontrolled asthma, moderate exacerbation, and severe exacerbation health states in the 5-substate model. In the 4-substate model, the same utilities were applied to moderate and severe exacerbations, but a separate utility estimate was generated for the no exacerbation health state, which included all levels of asthma control. In the 4-substate model, a utility benefit was applied to patients receiving dupilumab to account for improvement in asthma control. Utilities for the asthma control health states were based on EuroQol 5-Dimensions 5-Levels questionnaire (EQ-5D) data from the QUEST and VENTURE trials, mapped to the EuroQol 5-Dimensions 3-Levels questionnaire.[5] Disutilities for moderate and severe exacerbations were derived from EQ-5D data from the QUEST trial and were assumed to be experienced for the duration of an exacerbation, which was dependent on the treatment received. Disutilities were applied for OCS-related adverse events only.[6]

The economic model included drug costs, disease management costs, and exacerbation-related costs to the health care system (i.e., office visits, emergency department visits, admission to hospital). Disease management costs included outpatient visits to a family physician or specialist and spirometry testing. The price of dupilumab was based on the sponsor's submitted price,[1] while the prices of background therapy drugs were obtained from the Ontario Drug Benefit Formulary.[7] For scenario analyses, the cost of mepolizumab, benralizumab, and omalizumab was obtained from the Ontario Drug Benefit Exceptional Access Program,[8] while the cost of reslizumab was obtained from the sponsor's submission to CADTH.[9] It was assumed that there would be no administration costs for background therapy, and biologics were assumed to be self-administered, with the exception of reslizumab.

Summary of Sponsor's Economic Evaluation Results

The sponsor's cost-effectiveness analysis was based on 4,000 probabilistic iterations, for which findings are presented below. Additional details pertaining to the sponsor's submission are available in Appendix 3.

Base-Case Results

The sponsor's base-case results for type 2 or eosinophilic asthma are shown in Table 3. The addition of dupilumab to background therapy was associated with incremental costs of $182,434 compared with background therapy alone over the lifetime horizon. The addition of dupilumab was associated with a gain of 1.46 QALYs over the same period, resulting in an ICER of $125,305 per QALY gained. At a WTP threshold of $50,000 per QALY, dupilumab has a 3% probability of being cost-effective.

Sensitivity and Scenario Analysis Results

The sponsor conducted a scenario analysis involving patients who are OCS dependent. This analysis found that the incremental costs and QALYs were higher in this subgroup, leading to a slightly higher ICER of $139,397 per QALY.

The sponsor conducted several other sensitivity and scenario analyses — adopting a societal perspective (i.e., including productivity costs); varying the time horizon; varying the discount rate (0%, 3%); varying the proportion of patients with OCS dependence — none of which significantly changed the model conclusions. Across various subgroups based on different blood eosinophil counts, the ICER for dupilumab compared to background therapy ranged from $120,847 to $449,736 per QALY.

The sponsor conducted several scenario analyses to explore the cost-effectiveness of dupilumab compared to other biologic treatments for severe asthma in subgroups aligned with the various reimbursement criteria; these analyses were informed by indirect treatment comparisons conducted by the sponsor. The cost-effectiveness of dupilumab relative to other biologics varied from being dominant (providing more QALYs at a lower cost versus mepolizumab and benralizumab) to being more costly and more effective ($127,681 per QALY versus reslizumab).

CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations to the sponsor's analysis that have notable implications for the economic analysis:

- **The sponsor-submitted 5-substate pharmacoeconomic model lacks face validity.** The sponsor submitted 2 pharmacoeconomic models (5-substate and 4-substate, as described in the Model Structure section), with the 5-substate model used to assess the cost-effectiveness of dupilumab among patients with a type 2 or eosinophilic phenotype. The controlled and uncontrolled asthma health states in the 5-substate model were defined based on ACQ score, with a threshold of 1.5 used to classify patients as controlled or uncontrolled (controlled: ACQ score < 1.5; uncontrolled: ACQ score ≥ 1.5). This dichotomization lacks face validity, as it implies that a patient whose ACQ score improved by as little as 0.01 (i.e., from 1.50 to 1.49) would be considered to have controlled asthma and would receive the utility benefit for the controlled state (0.906) instead of that for the uncontrolled state (0.769). CADTH recognizes that an ACQ score of 1.5 is a commonly used threshold in clinical trials; however, the Global Initiative for Asthma guidelines[10] consider an ACQ score of 0.75 to 1.5 to represent a grey zone between well-controlled and uncontrolled asthma. As noted in the CADTH Clinical Review, health-related quality of life (assessed via ACQ-5 and the Asthma Quality of Life Questionnaire) was improved

Table 3: Summary of the Sponsor's Economic Evaluation Results: Type 2 or Eosinophilic Asthma

Drug	Total costs, $	Incremental costs, $	Total QALYs	Incremental QALYs	ICER vs. background therapy, $/QALY
Background therapy	74,096	Ref.	16.64	Ref.	Ref.
Dupilumab + background therapy	256,531	182,434	18.09	1.46	125,305

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; Ref. = reference.

Source: Sponsor's pharmacoeconomic submission.[1]

from baseline in QUEST and VENTURE; however, the minimum clinically important difference was not met for either instrument, and the results were tested outside of the statistical hierarchy.

  - CADTH reanalyses used the sponsor-provided 4-substate model, which includes health states based on asthma exacerbations (no exacerbations, moderate exacerbations, and severe exacerbations) and does not include health states related to overall asthma control. A scenario analysis was conducted that assumed the only benefit from dupilumab would come from a reduction in exacerbations, removing the utility benefit derived from improvements in asthma control.

- **The number of exacerbations predicted by the model is not aligned with clinical trial evidence.** Both the 4-substate and 5-substate models overestimated the number of severe exacerbations in the background therapy group during the clinical trial period relative to the clinical data from the QUEST trial. For example, the 4-substate model predicts 0.47 and 1.89 severe exacerbations during the trial period, while — as noted in the CADTH Clinical Review — the annualized rate of severe exacerbations observed in the QUEST trial over the 52-week treatment period was 0.456 with dupilumab and 0.871 with placebo.
  - As noted later in this section, CADTH was unable to fully validate the programming of the sponsor's model owing to the poor modelling practices employed, and, as such, relied on the face validity of the model (i.e., consistency between the number of predicted exacerbations in the trial period and observed in the QUEST clinical trial). To reconcile the clinical trial data with the model, CADTH applied the trial-based relative risk of exacerbations to the transition probabilities calculated for the dupilumab arm.
- **Increased mortality was assumed during severe asthma exacerbation.** The sponsor assumed an increased risk of asthma-related death when patients had a severe exacerbation, and the risk varied by age group and treatment setting (i.e., hospital, emergency department, office). This implies a survival benefit with dupilumab treatment, which has not been shown in clinical trials. As noted in previous CADTH reviews[11] and by the clinical expert consulted for this review, asthma-related mortality is rare and often linked to non-treatment-specific causes such as adherence and incorrect management. Likewise, the clinical expert noted that the assumption of a 2.05% mortality rate among patients with a severe exacerbation who visit an emergency department is not reflective of Canadian patients. Finally, the model results lacked face validity when it came to asthma deaths. In the background therapy alone arm, the model predicted that 37% of patients would die from an exacerbation-related death.
  - The predicted survival benefit with dupilumab compared with background therapy is highly uncertain and is not supported by clinical trial data. This mortality benefit was removed in CADTH reanalyses, consistent with previous CADTH reviews.[11]
- **The model structure does not adequately reflect the management of asthma in clinical practice.** In the sponsor's model, response to treatment is assessed at 52 weeks, with treatment response defined as an improved exacerbation risk (reduced annualized rate of severe asthma exacerbation events > 50%), decreased OCS use (≥ 50% reduction in OCS dose for patients taking OCS at model start), or decreased OCS use and exacerbation rate.[1] The clinical expert consulted by CADTH for this review, as well as in prior CADTH reviews,[11] indicated that response to biologic treatment is usually assessed in clinical practice at an earlier time point on the basis of improved ACQ score and lung function (i.e., FEV_1) from a baseline assessment. Treatment response is not typically assessed in terms of exacerbation risk, as exacerbations may be infrequent and may be influenced by factors other than asthma control (e.g., influenza, pneumonia).

The sponsor assumed that patients with no treatment response at 52 weeks would receive background therapy alone for the remainder of the time horizon; however, the clinical expert consulted by CADTH indicated that patients with an inadequate treatment response would be switched to an alternative biologic, not moved to background therapy alone. Further, it is likely that a proportion of patients who improve but not to the extent of the response criteria would continue to receive their current biologic treatment.

  - In CADTH reanalyses, treatment response assessment at 52 weeks was disabled, such that patients discontinued treatment based only on the constant long-term discontinuation rate, as derived from the trial data.

- **Poor modelling practices were employed.** The model was unnecessarily complex and lacked transparency. First, the sponsor used numerous IFERROR statements in its model. IFERROR statements lead to situations in which the parameter value is overwritten with an alternative value without alerting the user to the automatized overwriting. The systematic use of IFERROR statements makes thorough auditing of the sponsor's model impossible, as it remains unclear whether the model is running inappropriately by overriding errors. Best programming practices are such that any errors alert the user to a specific error. Second, the model repeated the same information numerous times, making it unclear what values were being used to derive model estimates. As noted previously, the results of the sponsor's submitted model lacked face validity, which CADTH was unable to fully address owing to the complex coding of the model. CADTH also noted that the probabilistic results of the 4-substate model were implausible as dupilumab produced zero QALYs.
  - CADTH is concerned about the validity of the model and notes that the results presented should be treated with a degree of caution. Errors relating to the probabilistic analysis were corrected.
- **Comparative clinical efficacy versus biologics is highly uncertain.** There have been no head-to-head trials of dupilumab and other biologic treatments for asthma (i.e., omalizumab, mepolizumab, reslizumab, benralizumab). The sponsor conducted indirect treatment comparisons to provide comparative clinical effectiveness data (i.e., the proportion of patients achieving a treatment response) for scenario analyses. The CADTH Clinical Review raised several concerns regarding the interpretation of the findings of the indirect treatment comparisons, including between-trial differences in clinical populations, outcome definitions, and the timing of outcome assessment, as well as discrepancies between the calculated results and the reported trial results. As such, no robust conclusions can be drawn about the comparative clinical efficacy of dupilumab versus other currently available biologic treatments. The clinical expert CADTH consulted for this review also expressed concerns about the credibility of the findings due to the methodological limitations.
  - CADTH was unable to address this limitation owing to a lack of direct evidence and limitations with the sponsor's indirect treatment comparisons. The cost-effectiveness of dupilumab relative to other biologic treatments indicated for type 2 or eosinophilic asthma (Table 8) is unknown.
- **Long-term clinical effectiveness is uncertain.** In the sponsor's pharmacoeconomic submission, the effects of dupilumab were considered to be consistent over the lifetime analysis horizon (approximately 50 years). The potential waning of treatment effect over time was not considered in the sponsor's model. The sponsor assumed that the rate of severe exacerbations would be higher after the duration of the clinical trials owing to "potential improved monitoring in a clinical trial setting and inclusion criteria resulting in a lower severe exacerbation rate as compared to what would be expected in the real-world."[1] The sponsor based this increase on mepolizumab[12]; however, it is unknown whether

long-term response to dupilumab is equal to that of mepolizumab. Additionally, patients who experience an increase in exacerbations would likely try different biologics, meaning that differences captured at the end of the trial would likely not be permanent for the rest of the patient's life.

    - CADTH was unable to address this limitation owing to the structure of the sponsor's economic model and a lack of long-term data for dupilumab effectiveness.

- **The cost-effectiveness of dupilumab among adolescents is uncertain.** Dupilumab is indicated for patients 12 years and older; however, the sponsor's pharmacoeconomic submission was based on the QUEST and VENTURE trials, which had mean ages of 48 and 51 years, respectively, and enrolled relatively few participants aged 12 to 17 years (QUEST: 5.6%; VENTURE: 1.4%). As noted by the clinical expert consulted by CADTH, health care use by those with severe asthma exacerbations may differ between adolescents and adults. Further, the sponsor's model assumed a starting age of 46 to 48 years, and no analyses were provided in an adolescent population.

    - CADTH was unable to address this limitation owing to a lack of data on the effectiveness and health care resource use among adolescents. The cost-effectiveness of dupilumab among adolescents is thus unknown.

Additional limitations were identified but were not considered to be key limitations:

- **The cost-effectiveness of 300 mg dupilumab is uncertain.** The sponsor's submitted economic analysis of dupilumab incorporated data from the 200 mg arm of the QUEST trial. The 200 mg dose is recommended for patients with severe asthma with a type 2 or eosinophilic phenotype, while the 300 mg dose is recommended for patients with OCS-dependent asthma or with comorbid moderate-to-severe atopic dermatitis or severe chronic rhinosinusitis with nasal polyposis.[2] Chronic rhinosinusitis and nasal polyposis are common among patients with severe asthma, affecting 23.1% of participants in QUEST at baseline.[13] The clinical expert consulted by CADTH noted that patients with severe asthma and these comorbidities may try dupilumab before other biologics owing to the approved indication for these comorbidities.

    - CADTH was unable to address this limitation owing to a lack of supplied data for the 300 mg dupilumab dose. The submitted cost of both dupilumab doses is the same; however, potential differences in effectiveness could result in a difference in cost-effectiveness.

- **The duration of exacerbations across treatments is uncertain.** In the sponsor's model, the duration of an exacerbation, and hence the duration of the associated quality of life decrement, was assumed to differ between dupilumab and background therapy. The sponsor states that these assumptions were based on post hoc data analysis from the QUEST trial. These data are not reported in the Clinical Study Report. Therefore, CADTH could not verify that the duration of exacerbation differed between dupilumab and background therapy. It was further unclear how the duration of exacerbation was measured or defined in the QUEST trial.

    - In a CADTH scenario analysis, the duration of exacerbations was assumed to be equal across treatment groups.

Additionally, several key assumptions were made by the sponsor and have been appraised by CADTH (see Table 4).

CADTH Reanalyses of the Economic Evaluation

Several limitations with the sponsor's submission could not be adequately addressed (i.e., lack of head-to-head comparative clinical data, uncertainty regarding long-term clinical effectiveness, lack of data related to the 300 mg strength, lack of data for adolescents). Further, CADTH could not fully validate the sponsor's model owing to a lack of transparency and poor modelling practices employed. CADTH undertook a stepped reanalysis using the 4-substate model: aligning the relative risk of severe asthma exacerbations with the QUEST trial, assuming no mortality benefit associated with dupilumab, and removing the response assessment at 52 weeks. CADTH reanalyses were conducted for type 2 or eosinophilic phenotypic asthma.

The CADTH base case was derived by making changes in model parameter values and assumptions in consultation with a clinical expert. Table 5 details each change made to derive the CADTH reanalyses, which were conducted in a stepwise approach to the sponsor's base case to highlight the impact of each change. The summary results of the CADTH reanalyses are presented in Table 6 (disaggregated results are presented in Appendix 4, Table 12).

In CADTH's reanalyses, dupilumab was associated with higher costs (incremental: $188,483) and higher QALYs (incremental: 0.26) than background therapy over a lifetime horizon (approximately 52 years). The ICER for dupilumab versus background therapy was $721,678 per QALY. There is a 0% probability that dupilumab is optimal compared to background therapy at a WTP threshold of $50,000 per QALY. The results were primarily driven by drug acquisition costs associated with dupilumab (Appendix 4, Table 12). Compared to background therapy, approximately 12% of the incremental benefit (i.e., QALYs) observed with dupilumab was acquired from the observed trial period, and the remaining 88% benefit was obtained over the extrapolated period.

Table 4: Key Assumptions of the Submitted Economic Evaluation

Sponsor's key assumption	CADTH comment
Patients enrolled in QUEST and VENTURE were assumed to be representative of patients in Canada who would be eligible for dupilumab.	Reasonable. The clinical expert consulted by CADTH indicated that the study populations are generally representative of patients with type 2 or eosinophilic asthma, although patients in clinical practice may show less FEV_1 reversibility.
Health state utility values were mapped from EQ-5D-5L to EQ-5D-3L.	Uncertain. The sponsor unnecessarily mapped utility values from EQ-5D-5L (captured as part of QUEST) to the EQ-5D-3L via a mapping function.[5] Mapping utility values introduces uncertainty.
Adverse events related only to OCS treatment were included.	Reasonable. Adverse events other than those related to OCS were not considered in the sponsor's model (no justification provided). As noted in the CADTH Clinical Review, serious adverse events were infrequent in the QUEST trial. Costs related to adverse events could have been included for completeness; however, this is unlikely to influence model results.
Health care resource use was based on a survey of 15 health care providers in the UK.[14]	Uncertain. The clinical expert consulted by CADTH indicated that the health care resource use estimates incorporated in the sponsor's model may not reflect Canadian asthma management.

EQ-5D-3L = EuroQol 5-Dimensions 3-Levels questionnaire; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; FEV_1 = forced expiratory volume in the first second; OCS = oral corticosteroid.

Scenario Analysis Results

Several scenario and sensitivity analyses were conducted on the CADTH base case. These scenario analyses explored the impact of the duration of asthma exacerbations and the

Table 5: CADTH Revisions to the Submitted Economic Evaluation

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Edits to sponsor's base case		
Errors relating to the probabilistic analysis were corrected.	—	—
Model choice	5-substate model	4-substate model
Changes to derive the CADTH base case		
1. Number of severe exacerbations (transition probabilities)	The number of severe exacerbations predicted by the model was not aligned with the annualized rate of severe exacerbations from QUEST.	The model was set to "use relative risk versus all patients in ITT population." The relative risk of severe exacerbations observed in QUEST (200 mg dupilumab vs. placebo: 0.523) was applied, such that the number of predicted severe exacerbations during the trial period was aligned with the annualized rate of severe exacerbations reported for QUEST.
2. Asthma-related mortality	A mortality benefit associated with dupilumab was assumed.	No mortality benefit associated with dupilumab was assumed.
3. Response assessment	Treatment response assessed at 52 weeks.	No response assessment at 52 weeks.

CADTH reanalyses (1 + 2 + 3)

ITT = intention to treat.

Table 6: Summary of the Stepped Analysis of the CADTH Reanalysis Results

Stepped analysis	Drug	Total costs, $	Total QALYs	ICER, $/QALYs
Sponsor's base case	Background therapy	74,096	16.64	Ref.
	Dupilumab + background therapy	256,531	18.09	125,305
Sponsor's base case (using the 4-substate model)	Background therapy	67,733	16.79	Ref.
	Dupilumab + background therapy	248,588	18.19	128,444
CADTH reanalysis 1	Background therapy	63,756	18.94	Ref.
	Dupilumab + background therapy	245,347	19.70	237,315
CADTH reanalysis 2	Background therapy	83,202	20.43	Ref.
	Dupilumab + background therapy	261,047	20.84	428,632
CADTH reanalysis 3	Background therapy	67,733	16.79	Ref.
	Dupilumab + background therapy	250,748	17.97	154,072
CADTH base case (reanalysis 1 + 2 + 3)	Background therapy	70,741	20.74	Ref.
	Dupilumab + background therapy	259,008	21.00	721,678

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; Ref. = reference.

Note: The reanalysis is based on the publicly available prices of the comparator treatments.

impact of asthma control benefit on the results. Assuming that exacerbation duration was equal in both treatments made dupilumab slightly less cost-effective. Assuming no long-term health-related quality of life benefit, outside of reducing exacerbations, made dupilumab significantly less cost-effective and increased the ICER to $4,169,776. This shows that the assumption of a long-term, sustained benefit to asthma control has a significant influence on the cost-effectiveness of dupilumab and that the CADTH base case is likely optimistic in the absence of any treatment waning. Among patients with OCS-dependent asthma, the ICER for dupilumab versus background therapy is $425,333. However, due to unclear modelling, this result is highly uncertain and should be interpreted with caution.

A price reduction analysis was performed based on the sponsor's and CADTH's reanalysis. Results presented in Table 7 indicate that a price reduction of 93% is required to make dupilumab cost-effective compared to background therapy.

Issues for Consideration

- There may be an indication creep with dupilumab used in patients with less severe asthma who have comorbid atopic dermatitis and/or chronic rhinosinusitis or nasal polyposis. The clinical expert consulted by CADTH indicated that dupilumab may be considered in practice for patients with moderate uncontrolled asthma in the presence of these comorbidities.
- Other biologic treatments with a less frequent administration schedule (e.g., benralizumab) may be preferred by patients over dupilumab.

Overall Conclusions

Dupilumab may reduce asthma exacerbations compared to background therapy alone, although the effects of dupilumab on health-related quality of life are uncertain. The comparative effects of dupilumab relative to other biologic treatments for severe asthma

Table 7: CADTH Price Reduction Analyses

Price reduction	ICER for dupilumab plus background therapy vs. background therapy, $/QALY	
	Sponsor base case	CADTH reanalysis
No price reduction	125,305	716,601
10%	113,057	644,364
20%	98,838	572,131
30%	86,220	499,897
40%	73,603	427,663
50%	60,985	355,430
60%	**48,367**	283,196
70%	NA	210,963
80%	NA	138,729
90%	NA	66,495
93%	NA	**44,825**

ICER = incremental cost-effectiveness ratio; NA = not applicable; QALY = quality-adjusted life-year.
Note: The reanalysis is based on the publicly available prices of the comparator treatments.

are highly uncertain owing to a lack of direct comparative evidence and limitations within the sponsor's indirect treatment comparisons.

CADTH undertook reanalyses to address limitations in the sponsor's submission, including aligning the relative risk of severe asthma exacerbations with the QUEST trial, removing the risk of mortality with a severe exacerbation, removing response assessment at 52 weeks, and fixing programming errors in the model. CADTH reanalyses focused on patients with type 2 or eosinophilic asthma, which is in line with the Health Canada indication and may include a proportion of patients with OCS-dependent asthma. CADTH was unable to address the lack of head-to-head comparative clinical data, uncertainty regarding long-term clinical effectiveness, lack of data related to the 300 mg strength, and lack of data for adolescents.

In the CADTH base case, dupilumab plus background therapy was more effective and more costly than background therapy alone (incremental costs = $188,483; incremental QALYs = 0.26). Dupilumab is not cost-effective compared to background therapy at a WTP threshold of $50,000 (ICER = $721,678 per QALY). The key driver of the ICER is the cost of dupilumab acquisition, and a 93% price reduction would be required for it to be considered optimal at a WTP threshold of $50,000.

There remains some degree of uncertainty in the CADTH reanalysis. Scenario analysis shows that cost-effectiveness is highly sensitive to the assumption of long-term sustained utility improvement due to improvement in asthma control. The cost-effectiveness of dupilumab relative to currently available biologic treatments for severe asthma is unknown owing to a lack of comparative evidence. There is no clinical evidence to support a price premium for dupilumab above other biologics.

References

1. Pharmacoeconomic evaluation [internal sponsor's report]. In: *Drug Reimbursement Review sponsor submission: Dupixent (dupilumab), 200 mg and 300 mg solution for subcutaneous injection.* Mississauga (ON): Sanofi Genzyme; 2020 Nov 26.
2. Dupixent (dupilumab injection): solution for subcutaneous injection, 300 mg single-use syringe (300 mg/2 mL), 200 mg single-use syringe (200 mg/1.14 mL) [product monograph]. Laval (QC): Sanofi-aventis Canada Inc; 2020 Nov 12.
3. National Institute for Health and Care Excellence. Benralizumab for treating severe eosinophilic asthma *(Single technology appraisal ID1129)* 2018; https://www.nice.org.uk/guidance/ta565/evidence/final-appraisal-determination-committee-papers-pdf-6715489647. Accessed 2021 Feb 9.
4. Table: 13-10-0114-01. Life expectancy and other elements of the life table, Canada, all provinces except Prince Edward Island. Ottawa (ON): Statistics Canada; 2020: https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310011401. Accessed 2021 Apr 2.
5. van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health.* 2012;15(5):708-715. PubMed
6. Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. *Med Decis Making.* 2011;31(6):800-804. PubMed
7. Ontario Ministry of Health, Ontario Ministry of Long-Term Care. Ontario drug benefit formulary/comparative drug index. 2020; https://www.formulary.health.gov.on.ca/formulary/. Accessed 2021 Feb 23.
8. Exceptional Access Program (EAP). Toronto (ON): Ontario Ministry of Health; Ontario Ministry of Long-Term Care; 2020: https://www.health.gov.on.ca/en/pro/programs/drugs/odbf/odbf_except_access.aspx. Accessed 2021 Feb 23.
9. CADTH Canadian Drug Expert Committee (CDEC) final recommendation: reslizumab (Cinqair-Teva Canada Innovation). Ottawa (ON): CADTH; 2019: https://www.cadth.ca/sites/default/files/cdr/complete/sf0591-cinqair-cdec-rec-march-29-19.pdf. Accessed 2021 Feb 16.
10. Global strategy for asthma management and prevention. Fontana (WI): Global Initiative for Asthma; 2020: https://ginasthma.org/wp-content/uploads/2020/06/GINA-2020-report_20_06_04-1-wms.pdf. Accessed 2021 Feb 16.
11. CADTH common drug review pharmacoeconomic report: benralizumab (Fasenra). Ottawa (ON): CADTH; 2018: https://cadth.ca/sites/default/files/cdr/pharmacoeconomic/SR0561_Fasenra_PE_Report.pdf. Accessed 2021 Apr 5.
12. CADTH common drug review pharmacoeconomic report: mepolizumab (Nucala). Ottawa (ON): CADTH; 2016: https://www.cadth.ca/sites/default/files/cdr/pharmacoeconomic/SR0461_Nucala_PE_Report_e.pdf. Accessed 2021 Feb 24.
13. Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med.* 2018;378(26):2486-2496. PubMed
14. Willson J, Bateman ED, Pavord I, Lloyd A, Krivasi T, Esser D. Cost effectiveness of tiotropium in patients with asthma poorly controlled on inhaled glucocorticosteroids and long-acting beta-agonists. *Appl Health Econ Health Policy.* 2014;12(4):447-459. PubMed
15. Drug Reimbursement Review sponsor submission: Dupixent (dupilumab), 200 mg and 300 mg solution for subcutaneous injection [internal sponsor's package]. Mississauga (ON): Sanofi Genzyme; 2020 Nov 26.
16. DeltaPA. [Ottawa (ON)]: IQVIA; 2020: https://www.iqvia.com/. Accessed 2021 Jan 6.
17. Saskatchewan Drug Plan: search formulary. 2020; https://formulary.drugplan.ehealthsask.ca/SearchFormulary. Accessed 2021 Feb 23.
18. Alberta Health Care Insurance Plan: medical price list as of 31 March 2020. Edmonton (AB): Government of Alberta; 2020: https://open.alberta.ca/dataset/30add047-29c2-4fc7-83b5-a8ab78605cdd/resource/48d0dd0b-bb33-478d-a85c-85a86d4555ad/download/health-somb-medical-price-list-2020-03.pdf. Accessed 2021 Feb 23.
19. CADTH drug reimbursement review pharmacoeconomic review report: indacaterol/mometasone furoate (Atectura Breezehaler). Ottawa (ON): CADTH; 2021: https://www.cadth.ca/sites/default/files/cdr/pharmacoeconomic/sr0646-atectura-breezhaler-pharmacoeconomic-review-report.pdf. Accessed 2021 Feb 17.
20. CADTH drug reimbursement review pharmacoeconomic report: indacaterol acetate-glycopyrronium bromide-mometasone furoate (Enerzair Breezhaler). Ottawa (ON): CADTH; 2021: https://cadth.ca/sites/default/files/cdr/pharmacoeconomic/sr0645-enerzair-breezhaler-pharmaceconomic-review-report.pdf. Accessed 2021 Feb 17.
21. Budget Impact Analysis [internal sponsor's report]. In: *Drug Reimbursement Review sponsor submission:Dupixent (dupilumab), 200 mg and 300 mg solution for subcutaneous injection.* Mississauga (ON): Sanofi Genzyme; 2020 Nov 26.
22. *Table: 17-10-0057-01 (formerly CANSIM 052-0005). Projected population, by projection scenario, ageand sex, as of July 1 (x 1,000).* Ottawa (ON): Statistics Canada; 2020.
23. Fast facts about asthma. Ottawa (ON): Public Health Agency Canada; 2011: https://www.phac-aspc.gc.ca/cd-mc/crd-mrc/assets/pdf/asthma_fs_asthme-eng.pdf. Accessed 2021 Apr 2.
24. FitzGerald JM, Lemiere C, Lougheed MD, et al. Recognition and management of severe asthma: a Canadian Thoracic Society position statement. *Can J Respir Criti Care Sleep Med.* 2017;1(4):199-221.
25. *Table: 13-10-0392-01 (formerly CANSIM 102-0551). Deaths and age-specific mortality rates,by selected grouped causes.* Ottawa (ON): Statistics Canada; 2020.

Appendix 1: Cost Comparison Table

Note that this appendix has been formatted for accessibility but has not been copy-edited.

The comparators presented in Table 8 have been deemed to be appropriate based on feedback from clinical expert(s). Comparators may be recommended (appropriate) practice or actual practice. Existing Product Listing Agreements are not reflected in the table and as such, the table may not represent the actual costs to public drug plans.

Table 8: CADTH Cost Comparison Table of Biologics for Severe Eosinophilic Asthma

Treatment	Strength	Form	Price	Recommended dosage	Daily cost ($)	Annual cost ($)
Dupilumab (Dupixent)	200 mg 300 mg	Pre-filled syringe for SC injection	959.5950[a]	Initial dose of 400 mg or 600 mg, followed by 200 or 300 mg every 2 weeks	68.35	Year 1: 25,909 Year 2 +: 24,949
Biologics						
Benralizumab (Fasenra)	30 mg/mL	Pre-filled syringe for SC injection	3,876.9200	30 mg every 4 weeks for first 3 doses, then once every 8 weeks	84.97	Year 1: 31,015 Year 2 +: 25,200
Mepolizumab (Nucala)	100 mg/mL	Vial of powder for SC injection	1938.4600	100 mg every 4 weeks	69.23	25,269
		Pre-filled syringe for SC injection				
		Pre-filled autoinjector for SC injection				
Omalizumab (Xolair)	150 mg	Vial of powder for SC injection	635.2000[b]	150 to 375 mg every 2 or 4 wk[c,d]	22.69 to 136.11	8,280 to 49,682
	75 mg	Pre-filled syringe for SC injection	274.1800		39.17 to 97.92	14,297 to 35,741
	150 mg		628.7400		22.46 to 134.73	8,196 to 49,176
Reslizumab (Cinqair)	10 mg/mL	Vial of solution for IV infusion	640.0000[e]	3 mg/kg every 4 weeks	22.86 to 91.43[f]	8,349 to 33,394[f]

SC = subcutaneous.

Note: All prices are from the Ontario Exceptional Access Program Formulary[8] (accessed February 2021), unless otherwise indicated, and do not include dispensing fees.

[a]Based on sponsor's submission.[15]

[b]Price obtained from Delta PA Database.[16]

[c]Assumes wastage.

[d]Dosing is dependent upon body weight and baseline IgE and can range from 150 mg to 300 mg when dosed every 4 weeks, and 225 mg to 375 mg when dosed every 2 weeks.

[e]Price obtained from CDEC Recommendation for reslizumab.[9]

[f]Assumed weight range 30 kg to 120 kg.

Table 9: CDR Cost Comparison Table of Other Medications for Asthma

Drug/Comparator	Strength	Dosage form	Price ($)	Recommended dosage		Daily drug cost ($)	Annual drug cost ($)
Inhaled corticosteroids							
Beclomethasone dipropionate (QVAR)	50 mcg 100 mcg	MDI (200 doses)	36.0400 71.8700	50 to 400 mcg twice daily		0.36 to 2.87	131 to 1,049
Budesonide (Pulmicort Turbuhaler)	100 mcg 200 mcg 400 mcg	MDPI (200 doses)	33.5900 68.7000 100.2900	200 to 400 mcg twice daily		0.67 to 1.00	245 to 366
Ciclesonide (Alvesco)	100 mcg 200 mcg	MDI (120 doses)	46.9200 77.6400	100 to 800 mcg twice daily		0.39 to 2.59	142 to 945
Fluticasone furoate (Arnuity Ellipta)	100 mcg 200 mcg	MDPI (30 doses)	40.1000 80.2000	100 or 200 mcg once daily		1.34 2.67	487 976
Fluticasone propionate (Flovent Diskus)	100 mcg 250 mcg 500 mcg	MDPI (60 doses)	26.1000[a] 45.0200 70.0300	100 to 500 mcg twice daily		0.87 to 2.33	318 to 852
Fluticasone propionate (Flovent HFA)	50 mcg 125 mcg 250 mcg	MDI (120 doses)	26.1000 45.0200 90.0400	100 to 500 mcg twice daily		0.87 to 3.00	317 to 1,095
Mometasone furoate (Asmanex Twisthaler)	100 mcg 200 mcg 400 mcg	MDPI (60 doses)	74.8800[b] 39.2280 78.4380	200 or 400 mcg once daily		0.65 to 2.50	239 to 1,822
ICS/LABA combinations							
Indacaterol acetate/ mometasone furoate (Atectura Breezhaler)	150/80 mcg 150/160 mcg 150/320 mcg	Inhalation powder hard capsules (30 doses)	58.0800[c]	One capsule for inhalation daily		1.9360	707
Budesonide/ formoterol fumarate dihydrate (Symbicort Turbuhaler)	100/6 mcg 200/6 mcg	MDPI (120 dose pack)	69.5400 90.3600	Low	100/6 mcg, 2 inhalations twice daily	2.32	846
				Med	200/6 mcg, 2 to 4 inhalations daily	1.51 to 3.01	550 to 1,099
				High	200/6 mcg, > 4 inhalations daily[d]	> 3.01	> 1,099

Drug/Comparator	Strength	Dosage form	Price ($)	Recommended dosage		Daily drug cost ($)	Annual drug cost ($)
Fluticasone propionate/ salmeterol (Advair)	125/25 mcg 250/25 mcg	MDI (120 pack)	105.0700 149.1600	Low	125/25 mcg, 1 inhalation twice daily	1.75	639
				Med	125/25 mcg, 2 inhalations twice daily	3.50	1,278
				High	250/25 mcg, 2 inhalations twice daily	4.97	1,815
Fluticasone propionate/ salmeterol (Advair Diskus, generic)	100/50 mcg 250/50 mcg 500/50 mcg	MDPI (60 doses)	42.4050 50.7600 72.0600	Low	100/50 mcg, 1 inhalation twice daily	1.41	516
				Med	250/50 mcg, 1 inhalation twice daily	1.69	618
				High	500/50 mcg, 1 inhalation twice daily	2.40	877
Fluticasone furoate/vilanterol (Breo Ellipta)	100/25 mcg 200/25 mcg	MDPI (30 doses)	86.6300 135.6900	Low	NA	NA	NA
				Med	100/25 mcg, 1 inhalation once daily	2.89	1,054
				High	200/25 mcg, 1 inhalation once daily	4.52	1,651
Mometasone furoate/formoterol fumarate dihydrate (Zenhale)	100/5 mcg 200/5 mcg	MDI (120 doses)	98.8440 119.7720	Low	NA	NA	NA
				Med	100/5 mcg, 2 inhalations twice daily	3.29	1,203
				High	200/5 mcg, 2 inhalations twice daily	3.99	1,457
Long-acting beta$_2$-adrenergic agonists (LABA)							
Salmeterol xinafoate (Serevent Diskhaler)	50 mcg	Dry powder inhaler (60 doses)	62.1300	50 mcg twice daily		2.07	756
Formoterol fumarate (Foradil)	12 mcg	Dry powder capsules for inhalation (60 doses)	53.6700	12 mcg twice daily		1.79	653

Drug/Comparator	Strength	Dosage form	Price ($)	Recommended dosage	Daily drug cost ($)	Annual drug cost ($)
Formoterol fumarate dehydrate (Oxeze Turbuhaler)	6 mcg 12 mcg	MDPI (60 doses)	33.6500 44.8000	6 to 12 mcg twice daily	1.12 to 1.49	409 to 545
ICS/LABA/LAMA combinations						
Indacaterol/ glycopyrronium/ mometasone furoate (Enerzair Breezhaler)	150/50/160 mcg	Inhalation powder hard capsules (30 doses)	102.82[e]	One capsule inhaled daily	3.43	1,251
Leukotriene receptor antagonists (LTRA)						
Montelukast (Singulair, generics)	4 mg 5 mg 10 mg	Chew Tablet Chew Tablet Tablet	0.2758 0.3082[a] 0.4231[a]	Age 6-14: 5 mg daily Age 15 +: 10 mg daily	0.42 to 0.62	124 to 225
Long-acting muscarinic antagonists (LAMA)						
Tiotropium (Spiriva Respimat)	2.5 mcg	Solution for inhalation (60 doses)	54.2607	2 inhalations once daily	1.81	660
Oral corticosteroids						
Prednisone (generic)	1 mg 5 mg 50 mg	Tablet	0.1166[a] 0.0220 0.1735	5 to 60 mg daily	0.02 to 0.17	8 to 71

[a]Price obtained from Saskatchewan Online Formulary Database.[17]

[b]Price obtained from Alberta Online Formulary Database.[18]

[c]Based on sponsor's CDR submission for indacaterol acetate/mometasone furoate.[19]

[d]Based on clinical expert feedback.

[e]Based on sponsor's CDR submission for indacaterol acetate/glycopyrronium/mometasone furoate.[20]

Appendix 2: Submission Quality

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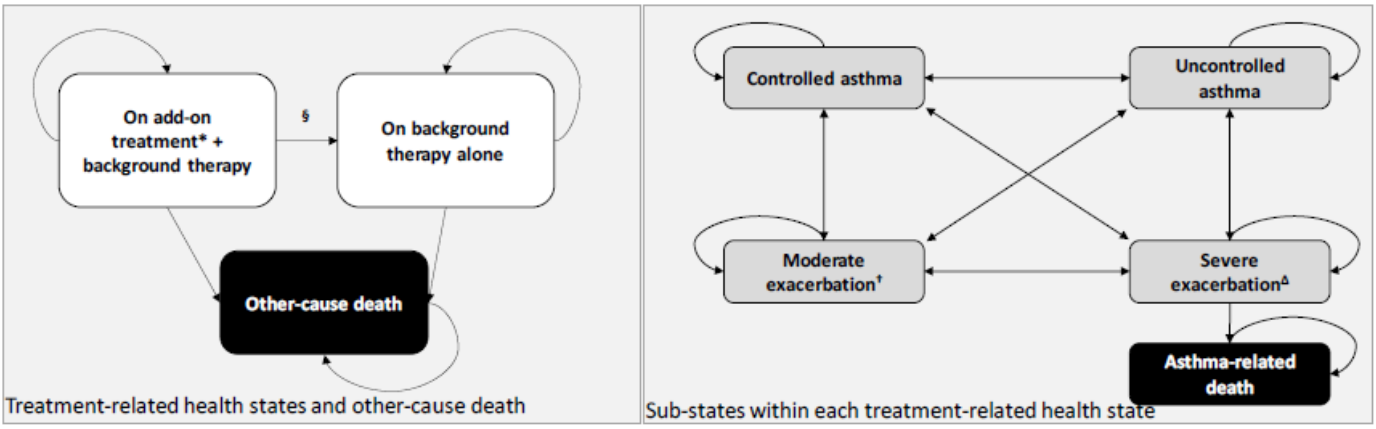
Table 10: Submission Quality

Description	Yes/No	Comments
Population is relevant, with no critical intervention missing, and no relevant outcome missing	No	Cost-effectiveness is assessed relative to background therapy; cost-effectiveness relative to other biologic treatments is unknown.
Model has been adequately programmed and has sufficient face validity	No	Poor modelling practices were employed (see main text), including incorrect programming of the 4-substate probabilistic model.
Model structure is adequate for decision problem	No	The sponsor's 4- and 5-substate models lacked face validity compared with the QUEST clinical trial results. Owing to the poor modelling practices, CADTH was unable to fully validate the sponsor's model.
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis)	Yes	No comment
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem	Yes	No comment
The submission was well organized and complete; the information was easy to locate (clear and transparent reporting; technical documentation available in enough details)	No	The model was unnecessarily complex, and the report lacked transparency. The utility mapping function was not well described. Inconsistencies were noted between the stated source of data and the referenced trial (e.g., Table 37 notes that the source of utilities and disutilities was the QUEST trial; however, the cited reference corresponds to the "LIBERTY ASTHMA VENTURE trial.")

Appendix 3: Additional Information on the Submitted Economic Evaluation

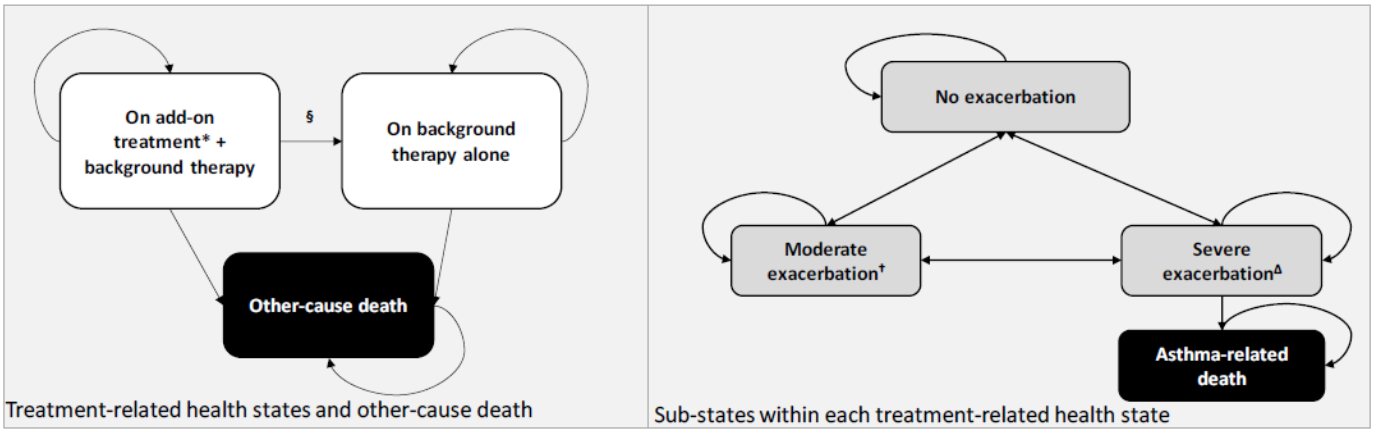
Note that this appendix has been formatted for accessibility but has not been copy-edited.

Figure 1: Model Structure — Five Substate Model



Source: Sponsor's pharmacoeconomic submission.[1]

Figure 2: Model Structure — Four Substate Model



Source: Sponsor's pharmacoeconomic submission.[1]

Detailed Results of the Sponsor's Base Case

Table 11: Disaggregated Summary of Sponsor's Economic Evaluation Results — Type 2/ Eosinophilic Phenotypic Asthma

Drug	Dupilumab plus background therapy	Background therapy
Discounted LYs		
Total	23.93	22.55

Drug	Dupilumab plus background therapy	Background therapy
Discounted QALYs		
Total	18.09	16.64
Trial Period	0.77	0.74
Extrapolation Period	17.32	15.88
Discounted Exacerbations		
Total	122.14	135.28
Moderate	50.29	46.07
Trial Period	1.67	1.48
Extrapolation Period	48.62	44.60
Severe Exacerbations	72.33	88.78
Trial Period	0.51	1.90
Extrapolation Period	71.82	86.89
Discounted Costs ($)		
Total	256,531	74,096
Drug Acquisition	220,385	74,096
Dupilumab	185,608	0
Background Treatment	34,777	32,775
Disease Management	12,426	12,483
Exacerbation Costs	23,720	28,839
ICER ($/QALY)	139,397	

Source: Sponsor's pharmacoeconomic submission.[1]

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

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Detailed Results of CADTH Base Case

Table 12: Disaggregated Summary of CADTH's Economic Evaluation Results

Drug	Dupilumab plus background therapy	Background therapy
Discounted LYs		
Total	27.68	27.68
Discounted QALYs		
Total	21.00	20.74
Trial Period	0.77	0.75
Extrapolation Period	20.23	20.00
Exacerbations		
Total (All Exacerbations)	101.59	108.70
Moderate	60.17	62.38
Trial Period	1.30	1.51
Extrapolation Period	58.87	60.87
Severe	41.42	46.33
Trial Period	0.48	0.87
Extrapolation Period	40.93	45.45
Discounted Costs ($)		
Total	259,008	70,525
Drug Acquisition		
Dupilumab	189,993	0
Background Treatment	40,288	40,288
Disease Management	12,158	11,886
Exacerbation Costs	16,569	18,352
ICER ($/QALY)	721,678	

ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year.
Note: Reanalyses are based on publicly available prices of the comparator treatments.

Scenario Analyses

Table 13: CADTH Scenario Analyses

Scenario	CADTH base case	CADTH scenario
1. Duration of exacerbations	The duration of exacerbations was treatment specific.	The duration of exacerbations was assumed to be equal regardless of treatment received.
2. Utility benefit associated with asthma control	Assumed utility benefit associated with asthma control, maintained for full time horizon	Assumed no utility benefit associated with improvement in dupilumab asthma control
3. OCS-dependent asthma	Type 2 or eosinophilic asthma	OCS-dependent asthma patients, informed by the VENTURE trial

OCS = oral corticosteroid.

[a]Defined as an improved exacerbation risk (reduced annualized rate of severe asthma exacerbation events > 50%), decreased OCS use (≥ 50% reduction in OCS dose; for patients taking OCS at model start), or decreased OCS use or exacerbation rate.[1]

Table 14: Summary of CADTH's Scenario Analyses Results

Drug	Total costs ($)	Total QALYs	ICER ($/QALY)
Scenario 1: Equal exacerbation duration across treatments			
Background therapy	70,122	20.74	Ref.
Dupilumab + background therapy	256,330	21.00	737,807
Scenario 2: Remove long-term utility benefit			
Background therapy	70,122	20.74	Ref.
Dupilumab + background therapy	256,330	20.79	4,169,776
Scenario 3: OCS-dependent asthma			
Background therapy	124,404	15.15	Ref.
Dupilumab + background therapy	473,740	15.97	425,533

ICER = incremental cost-effectiveness ratio; LY = life-year; OCS = oral corticosteroid; QALY = quality-adjusted life-year; Ref. = reference.

Note: Reanalyses are based on publicly available prices of the comparator treatments.

Appendix 5: Submitted BIA and CADTH Appraisal

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Table 15: CADTH Summary Findings from the Sponsor's Budget Impact Analysis

Key Take-Aways of the BIA
• CADTH identified the following key limitations with the sponsor's analysis: ◦ The number of patients eligible for dupilumab is uncertain. The sponsor assumed that severe asthma affects 5% of patients with diagnosed asthma; however, estimates from the Canadian Thoracic Society and clinical expert input suggest that this could be up to 10%. Further, clinicians may consider dupilumab for patients with moderate asthma and comorbid atopic dermatitis or chronic rhinosinusitis. ◦ The sponsor's submission did not differentiate between incident and prevalent use of biologic treatments. The clinical expert consulted by CADTH indicated that market uptake may not be equal between groups. Prevalent users of biologic treatment whose asthma is well controlled are unlikely to switch to dupilumab; however, new biologic users with comorbid atopic dermatitis or chronic rhinosinusitis or prevalent users with these comorbidities may be more likely to initiate dupilumab. ◦ Uptake of dupilumab was assumed to be [redacted]% in the first year, |% in the second year, and |% in the third year. The clinical expert consulted by CADTH indicated this is likely an overestimate, owing to the number of currently available biologic treatments for severe asthma. It is further uncertain whether dupilumab would equally displace existing biologic treatments. ◦ The sponsor assumed market uptake would come solely at the expense of other biologics. The clinical expert consulted by CADTH noted that some patients who currently do not receive a biologic may be placed on dupilumab if approved. The budget impact of this was not explored by the sponsor. • Owing to the high degree of uncertainty around these model parameters, CADTH did not reanalyze the sponsor's BIA submission. The budget impact of dupilumab will be dependent on the size of the eligible population, how many patients switch to dupilumab, and from what comparator.

Summary of Sponsor's BIA

The submitted budget impact analysis (BIA)[21] assessed the introduction of dupilumab as an add-on maintenance treatment in patients aged 12 years and older with severe asthma with a type 2 or eosinophilic phenotype or OCS-dependent asthma. Comparator treatments were those considered by the sponsor to be replaced by the introduction of dupilumab (omalizumab, reslizumab, mepolizumab, benralizumab). The BIA was undertaken from the perspective of the Canadian public drug plans over a 3-year time horizon, and the sponsor's pan-Canadian estimates reflect the aggregated results from provincial budgets (excluding Quebec), as well as the Non-Insured Health Benefits Program. Key inputs to the BIA are documented in Table 16.

The sponsor estimated the current population using an epidemiologic approach, with the estimated prevalence of asthma (8.40%) used to estimate the total number eligible patients. The sponsor assumed that 5% of patients with a confirmed diagnosis of asthma would have severe asthma and that 100% of those would be eligible for a biologic, although [redacted]% would receive a biologic. The sponsor further assumed that 79% of patients would be eligible for public drug plan coverage.

The sponsor's submission considered a reference scenario in which patients received a biologic (omalizumab, reslizumab, mepolizumab, benralizumab) and a new-drug scenario in which dupilumab was reimbursed. The cost of dupilumab was based on the sponsors submitted price ($959.59 per syringe; annual cost per patient including markup and dispensing fees: $28,832 in the first year, $27,764 in subsequent years). Drug costs for omalizumab, benralizumab, and mepolizumab were obtained from the provincial formularies, while the cost for reslizumab was obtained from the CADTH reslizumab CDR submission.[9] Administration fees were included for reslizumab. The cost of background therapy was assumed to be equal across treatments and in both scenarios and was excluded from the analysis. The uptake of dupilumab was assumed to be [redacted]% in Year 1, [redacted]% in Year 2, and [redacted]% in Year 3. Dispensing fees and mark-ups were included in the sponsor's base-case analysis.

Table 16: Summary of Key Model Parameters

Parameter	Sponsor's estimate
Target population	
Proportion of Canadian population aged ≥ 12 years	86%[22]
Asthma prevalence	8.40%[23]
Severe asthma	5%[24]
Proportion of eligible patients who receive biologic treatment	[redacted]%[a]
Population growth	1.40% per year[25]
Number of eligible patients (Y1/ Y2/ Y3)	12,989 / 13,171 / 13,355
Market uptake (3 years)	
Uptake (reference scenario)	
Dupilumab	0% / 0% / 0%
Comparators	Jurisdiction-specific[b]
Uptake (new-drug scenario)	
Dupilumab	[redacted]
Comparators	Jurisdiction-specific[c]
Annual cost of treatment (per patient)[d,e]	
Dupilumab	Year 1: $27,702; Year 2 +: $26,676
Omalizumab	$26,374
Reslizumab[f]	$35,392
Mepolizumab	$26,827
Benralizumab	Year 1: $32,947; Year 2 +: $26,769

Y = year.

[a]Sponsor assumption based on internal data.

[b]Projected market uptake for each biologic comparator in the reference scenario was based on jurisdiction-specific internal sponsor market research.

[c]Dupilumab was assumed to have the same impact on all current available treatment (same displacement).

[d]Includes markup and dispensing fees.

[e]Annual cost varies by jurisdiction; based on Ontario, unless otherwise stated.

[f]Reslizumab was assumed to capture 0% of market share in both the reference and new-drug scenario.

Summary of the Sponsor's BIA Results

The estimated budget from the drug plan perspective of reimbursing dupilumab for the treatment of type 2 or eosinophilic severe asthma is expected to be $88,336 in Year 1, $134,359 in Year 2, and $170,299 in Year 3, with a 3-year budget impact of $392,994.

In the sponsor's scenario analyses, increasing several parameters (i.e., proportion of patients with severe asthma, proportion of patients with severe asthma eligible for or who receive biologic treatment) resulted in increased costs to the drug plans over 3 years by 20%.

CADTH Appraisal of the Sponsor's BIA

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the results of the BIA:

- **Uncertainty regarding the number of patients eligible to receive dupilumab.** In deriving the target population, the sponsor assumed that 5% of patients with a confirmed diagnosis of asthma would have severe asthma. The clinical expert consulted by CADTH indicated severe asthma may affect up to 10% of patients with severe asthma; this is supported by estimates from the Canadian Thoracic Society.[24]

The sponsor assumed that the number of eligible patients with severe asthma eligible for a biologic would not be affected by the reimbursement of dupilumab. The clinical expert consulted by CADTH indicated that the number of patients with type 2 severe asthma who should be receiving biologic treatment is not likely to change with the reimbursement of dupilumab; however, the clinical expert indicated that clinicians may consider dupilumab for patients with moderate asthma and comorbid atopic dermatitis and/or rhinosinusitis, owing to dupilumab's Health Canada–approved indication for atopic dermatitis (patients aged 12 years and older) and chronic rhinosinusitis with nasal polyposis (adults).[2] These comorbidities are commonly co-occurring: in the QUEST trial, 23.1% of patients had nasal polyposis or chronic rhinosinusitis at baseline.

  - The number of patients who would be considered for dupilumab is uncertain. This could have an important effect on the budget impact of reimbursing dupilumab.
- **Uncertainty about the uptake of dupilumab among incident versus prevalent biologic users.** The sponsor's BIA did not distinguish between patients who were initiating a biologic for the first time (incident use) and those who were uncontrolled on current biologic treatment (prevalent use). The clinical expert consulted by CADTH indicated that there would likely be differential uptake of dupilumab between incident and prevalent users. Among prevalent users, it unlikely that patients whose asthma is well controlled on their current biologic would switch to dupilumab, with the exception of those with comorbidities (e.g., chronic rhinosinusitis, atopic dermatitis) who may be more likely to switch to dupilumab. The clinical expert indicated that, for those initiating a biologic for the first time, the decision between biologics may be influenced by the presence of comorbidities.
  - The number of patients receiving dupilumab may be lower than the sponsor's analysis suggests if there is reduced uptake from patients currently on another biologic.
- **Uncertainty regarding the uptake of dupilumab and displacement of existing biologic treatments.** The market uptake of dupilumab was assumed to be [redacted]% in year 1, |% in year 2, and |% in year 3, based on the sponsor's internal assumptions. The sponsor further assumed that dupilumab would equally displace currently available biologic treatments. The clinical expert consulted by CADTH indicated that, because there are multiple biologic treatments available, an assumption of capturing |% of the market by year 3 is likely overestimated. The validity of the assumption of equal displacement of currently available treatments is uncertain, given the availability of multiple biologic treatments for asthma.
  - The number of patients receiving dupilumab may be lower than the sponsor's analysis suggests if there is reduced uptake among all asthma patients.
- **Uncertainty regarding the size of the biologic market.** The sponsor assumed market uptake would come solely at the expense of other biologics. The clinical expert consulted by CADTH noted that some patients who currently do not receive a biologic may be placed on dupilumab if approved. The budget impact of this was not explored by the sponsor.
  - If patients currently not on a biologic are placed on dupilumab then this will significantly increase the budget impact as the cost of background therapy alone is considerably less expensive than biologic therapies.
- **Uncertainty about the market share of comparator treatments.** The sponsor estimated the comparator market shares on the basis of "internal Sanofi Genzyme market research."[21] The proportion of patients who currently receive each biologic comparator could not be validated by CADTH.

Additional limitations were identified, but were not considered to be key limitations.

- **The sponsor's model does not provide disaggregated drug costs and dispensing fees/markup costs.** In the sponsor's BIA, dispensing fees/markup costs were incorporated, and the disaggregated costs drug are not reported or calculable using the sponsor's model.

CADTH Reanalyses of the BIA

CADTH did not undertake reanalysis of the sponsor's BIA, owing to the high degree of uncertainty around key model parameters, including the size of the eligible population. Owing to this uncertainty, as well as the additional limitations described above, the impact of reimbursing dupilumab to the drug plans is uncertain.