NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Dupilumab for treating severe asthma [ID1213]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Dupilumab for treating severe asthma [ID1213]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website:

1. **Company submission summary** from Sanofi

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submission** from:
   a. Asthma UK
   b. British Thoracic Society
   c. Royal College of Physicians

4. **Expert personal perspectives** from:
   a. Andrew Menzies-Gow – clinical expert, nominated by British Thoracic Society
   b. Ian Pavord – clinical expert, nominated by Sanofi
   c. Lottie Renwick – patient expert, nominated by Asthma UK
   d. Nicola Ridgway – patient expert, nominated by Asthma UK

5. **Evidence Review Group report** prepared by Southampton Health Technology Assessment centre (SHTAC)

6. **Evidence Review Group report – factual accuracy check**

7. **Technical Report**

8. **Technical engagement response from company**
   a. Response form
   b. Additional Analysis Appendix

9. **Technical engagement responses from consultees and commentators:**
   a. Asthma UK
   b. Association of Respiratory Nurse Specialists
   c. British Thoracic Society – Endorsed by Royal College of Physicians
   d. AstraZeneca
   e. GlaxoSmithKline
   f. Novartis Pharmaceuticals UK Ltd

10. Evidence Review Group critique of company response to technical engagement prepared by SHTAC

11. Evidence Review Group critique of company response - addendum

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Dupilumab for treating severe asthma

Document A

Company evidence submission summary for committee

Sanofi confirm that all information in the submission summary is an accurate summary or replication of evidence in the main submission and accompanying appendices and that wherever possible a cross reference to the original source is provided.

12th August 2019

File name	Version	Contains confidential information	Date
ID1213_12August2019 _DocumentA_CIC	**1**	**Yes**	**12 August 2019**

Contents

Tables and figures

Submission summary

A.1 Health condition

Asthma is a chronic, heterogeneous, reversible airway disease, influenced by both genetic and environmental factors. It is estimated that around 8% of the UK population aged 12 and over have asthma, approximately 8 million people in the UK (1-6). Of these, 8.3% have severe asthma. The UK has one of the worst asthma death rates in Europe, almost 50% higher than the average death rate for the EU. Approximately three people in the UK die from an asthma exacerbation every day, with 1,320 people reported as dying from asthma in 2017 (7).

In practice, people with severe asthma may find themselves physically limited, may work less or withdraw socially, which in turn affects mental well-being (8). Patients with severe asthma do not respond to usual controller therapies, have an impaired quality of life due to breathlessness, night-time awakenings, wheezing and coughing. Despite high-dose inhaled corticosteroids (ICS) or maintenance oral corticosteroids (mOCS), people with uncontrolled severe asthma are 3.2 times more likely to have an exacerbation compared to patients with controlled asthma, leading to higher OCS use, attending Accident and Emergency (A&E) or being hospitalised (9).

A recent UK study on asthma control demonstrated that patients with severe asthma (on Step 4 or 5 of the British Thoracic Society [BTS]/Scottish Intercollegiate Guidelines Network [SIGN] guideline for the management of asthma 2014 treatment guidelines) had the highest levels of uncontrolled asthma (10). Another UK multi-site observational study estimated that patients with severe refractory asthma taking mOCS cost the National Health Service (NHS) 43% more than those not on mOCS, driven mostly by OCS-emergent adverse events (11). The same study found that patients who had two or more severe exacerbations were approximately 31% more costly than those with fewer than two exacerbations. (B, Table 4) (12-16).

The clinical manifestation of severe uncontrolled asthma is understood to be the result of Type 2 inflammation, an underlying type of inflammation driven by the products of two immune cells; T-helper 2 cells (Th2), and Innate lymphoid cells-subtype2 (ILC2). Severe uncontrolled asthma driven by Type 2 inflammation (T2i) arises due to an allergic sensitisation of the airways, leading to an inflammatory response and is characterised by the secretion of pro-inflammatory cytokines, including interleukin (IL)-4 and IL-13 (17).

Biomarkers of Type 2 inflammation such as blood eosinophils (EOS), fractional exhaled nitric oxide (FeNO) and immunoglobulin E (IgE) levels have a positive independent correlation with severe asthma exacerbations and lung function decline (18-22), tests for which are available in routine clinical practice at severe asthma centres in the UK (23-26).

The Global Initiative for Asthma (GINA 2019) guidelines define severe asthma with Type 2 inflammation as (27):

- Blood EOS ≥150 µl and/or
- Exhaled Nitric Oxide (FeNO) ≥20 ppb and/or
- Sputum EOS ≥2% and/or
- Asthma is clinically allergen-driven and/or
- Need for maintenance OCS

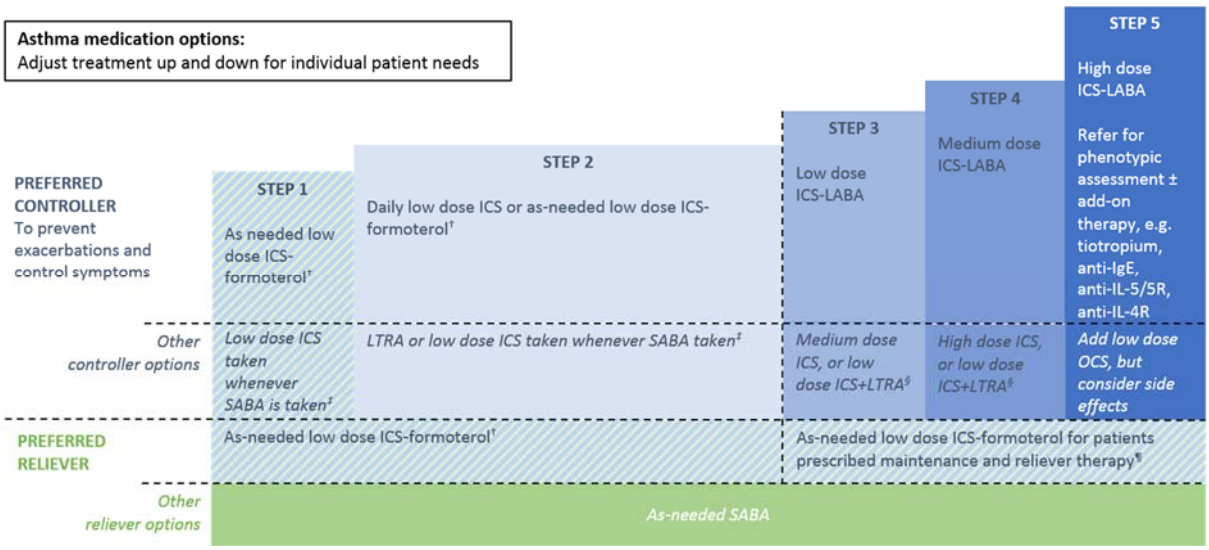
A.2 Clinical pathway of care

For patients with severe uncontrolled asthma, combination inhalers delivering medium or high dose ICS and LABA are the current standard of care. Additional controller medications (leukotriene receptor antagonist [LTRA], theophylline, OCS etc) may also be used as required (28, 29). Patients maximised on ICS still often demonstrate elevated Type 2 immune biomarkers such as EOS and FeNO and/or induced sputum, indicating significant residual T2i. The benefit of adding LABA beyond their bronchodilator effects is limited, and modest further reductions in severe exacerbations by approximately 20% are not accompanied by further reductions in serious asthma outcomes such as hospitalisations (30, 31).

Biologic therapies have been introduced as treatment options for specific phenotypes of severe asthma in the UK. Omalizumab is an anti-IgE therapy recommended for patients aged 6 and over for treating severe persistent IgE-mediated allergic asthma (32). Therapies for severe eosinophilic asthma, defined as EOS≥ 300, which target the IL-5 pathway (benralizumab, reslizumab and mepolizumab) have also recently been recommended by NICE (33-35).

For severe uncontrolled patients with type 2 inflammation without hypereosinophilia (defined by GINA as EOS≥150 and/or raised FeNO≥20ppb) treatment options are limited to further steroids, whether they be ICS or OCS, which may not mitigate symptoms (97). These patients therefore remain symptomatic and at risk of further morbidity and mortality.

Figure 1: Stepwise approach to asthma treatment as per GINA 2019 guidelines



Abbreviations: HDM, house dust mite; ICS, inhaled corticosteroids; Ig, immunoglobulin; IL, interleukin; OCS, oral corticosteroids; R, receptor; LABA, long-acting β2-agonist; LTRA, leukotriene receptor antagonist; SABA, short-acting β2-agonist; SLIT, sublingual allergy immunotherapy.
† Off-label, data only with budesonide-formoterol (bud-form); ‡ Off-label, separate or combination ICS and SABA inhalers; § Consider adding HDM SLIT for sensitised patients with allergic rhinitis and FEV_1 >70% predicted; ¶ Low dose ICS-form is the reliever for patients prescribed bud-form maintenance and reliever therapy.
Source: Adapted from GINA global strategy for asthma management and prevention, 2019 (36).

A.3 Equality considerations

No issues concerning equality were identified in the NICE scope or decision problem.

A.4 The technology

In May 2019, dupilumab received EMA marketing authorisation for adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment. Consistent with this licence, it is assumed that all patient populations discussed are treated with high dose ICS and another controller therapy.

A NICE recommendation is sought for patients with severe asthma driven by Type 2 inflammation defined as **EOS≥150 and/or FeNO≥25 and ≥3 exacerbations in the previous 12 months.**

Table 1 Technology being appraised – (Document B.1.2. - Page 23)

UK approved name and brand name	Dupilumab - Dupixent®
Mechanism of action	Dupilumab is a novel recombinant human IgG4 monoclonal antibody that inhibits IL-4 and IL-13 signalling. IL-4 and IL-13 act as major drivers of Type 2 inflammation by activating multiple cell types. Blocking the IL-4/IL-13 pathway in asthma patients with dupilumab decreases many of these markers of Type 2 inflammation, including IgE, periostin, and multiple proinflammatory cytokines and chemokines (e.g. eotaxin, TARC), as well as FeNO, a marker of lung inflammation.
Marketing authorisation/CE mark status	Dupilumab received marketing authorisation for severe asthma from the European Medicines Agency on 6 May 2019: Dupixent® is indicated in adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with Type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO (see section 5.1of the dupilumab SmPC), who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment.
Indications and any restriction(s) as described in the summary of product characteristics	Section 5.1 of the dupilumab SmPC states, 'Asthma treatment guidelines define Type 2 inflammation as eosinophilia ≥ 150 cells/mcL and/or FeNO ≥ 25 ppb.' Dupilumab is recommended for adults and adolescents 12 years of age and older.
Method of administration and dosage	The SmPC states: The recommended dose of dupilumab for adults and adolescents (12 years of age and older) is: • For patients with severe asthma and who are on oral corticosteroids or for patients with severe asthma and co-morbid moderate-to-severe atopic dermatitis, an initial dose of 600 mg (two 300 mg injections), followed by 300 mg every other week administered as subcutaneous injection. • For all other patients, an initial dose of 400 mg (two 200 mg injections), followed by 200 mg every other week administered as subcutaneous injection. Patients receiving concomitant oral corticosteroids may reduce their steroid dose once clinical improvement with dupilumab has occurred (see section 5.1). Steroid reductions should be accomplished gradually. The need for continued therapy should be considered at least on an annual basis as determined by physician assessment of the patient's level of asthma control.

<table>
<tr><td></td><td>Administration:
• Dupilumab (Dupixent®) is administered every other week by SC injection into the upper arm, thigh, or abdomen (except for the peri-umbilicus).</td></tr>
<tr><td>Additional tests or investigations</td><td>Blood eosinophil (EOS) and/or Fractional exhaled nitric oxide (FeNO) will be required to determine patient eligibility for dupilumab. Both these tests are used in routine clinical practice in centres where these patients would be initiating treatment and therefore do not constitute additional cost or burden to the system.</td></tr>
<tr><td>List price and average cost of a course of treatment</td><td>The list price for dupilumab (Dupixent®) per annum is £16,500. The list price acquisition cost per pack of 2 syringes is presented below:

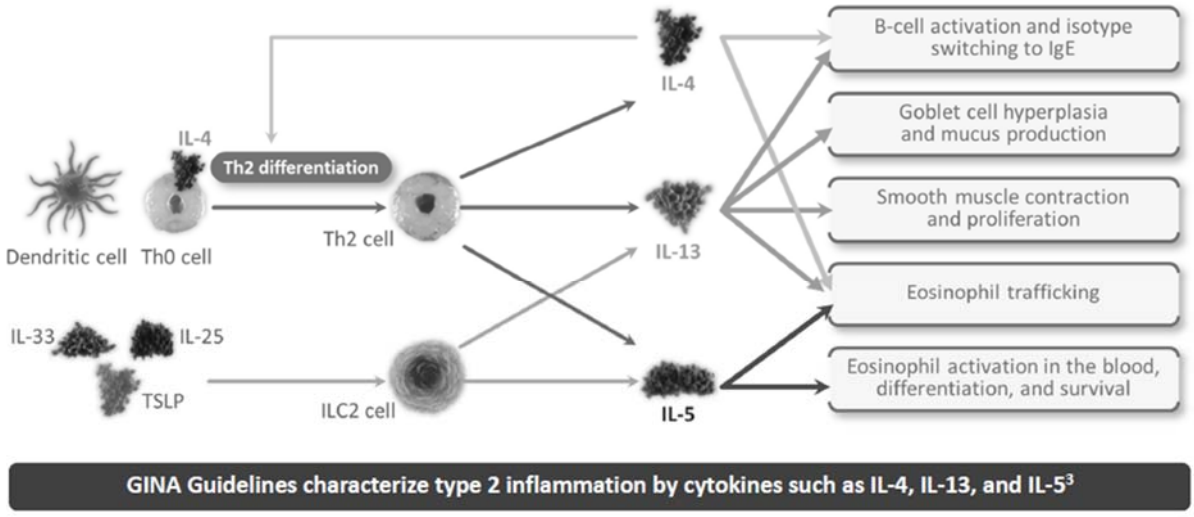
Table 2: Medicine acquisition cost at list price for dupilumab (Dupixent®)
<table><tr><th>Medicine</th><th>Formulation</th><th>Dose</th><th>List price per pack</th></tr><tr><td>Dupilumab (Dupixent®)</td><td>300 mg per 2 ml (150 mg/ml).</td><td>Patients with comorbid moderate-to-severe AD or maintenance mOCS</td><td>Per pack of 2 x 300 mg syringes: £1,264.89</td></tr><tr><td>Dupilumab (Dupixent®)</td><td>200 mg per 1.14 ml SC injection (175 mg/ml)</td><td>Patients on high dose inhaled corticosteroids (ICS) only</td><td>Per pack of 2 x 200 mg syringes: £1,264.89</td></tr></table>BNF January 2019, Dupilumab, https://www.medicinescomplete.com/#/content/bnf/_942227893</td></tr>
<tr><td>Patient access scheme (if applicable)</td><td>A Patient Access Scheme is available for the 300 mg in Atopic Dermatitis which will also apply to both doses (200 mg and 300 mg) for Severe Asthma driven by Type 2 inflammation.
The cost per pack of 2 x 200 mg or 2 x 300 mg is [redacted], which corresponds to [redacted] per annum.</td></tr>
</table>

Severe Asthma and Type 2 inflammation

Severe asthma driven by T2i results from allergic sensitisation of airway epithelium and the inflammatory response caused by infiltration of activated mast cells, EOS and basophils (6), and is characterised by the secretion of cytokines, including IL-4, IL-5, and IL-13 (17). Whereas IL-5 targets EOS and is concerned with eosinophil function and trafficking, IL-4 and IL-13 have both distinct and overlapping roles in T2i asthma pathogenesis (24, 37). IL-4 acts as an upstream cytokine of Type 2 effector cytokines and is essential in the development of Type 2 T-helper cells (Th2 cells) and subsequent T2i (38) (B, Figure 2, p. 29). Interleukin-4 also induces switching of B cells to plasma cells that produce IgE, a cytokine which activates mast cells, leading to classic symptoms of allergy through mast cell degranulation and the secretion of histamine (39). Interleukin-13 has various effector roles including goblet cell differentiation, excess mucin production by activating goblet cells, fibroblast activation, and airway hyper responsiveness, and stimulating IgE production from activated B cells (40). Interleukin-13 also activates the enzyme *inducible nitric oxide synthase* (iNOS), which is responsible for generating nitric oxide from airway epithelium, leading to elevated FeNO (29, 41, 42). Interleukin-4 and IL-13 are also involved in the recruitment of EOS into the airways. (Figure 2) (43, 44). Eosinophils release pro-inflammatory mediators that contribute to

epithelial damage, airway hyper-responsiveness, mucus hypersecretion and airway remodelling (28, 45, 46).

Figure 2: IL-4, IL-13, and IL-5 are Type 2 Cytokines with unique and overlapping roles, driving Type 2 inflammation. Source: (24, 47, 48)

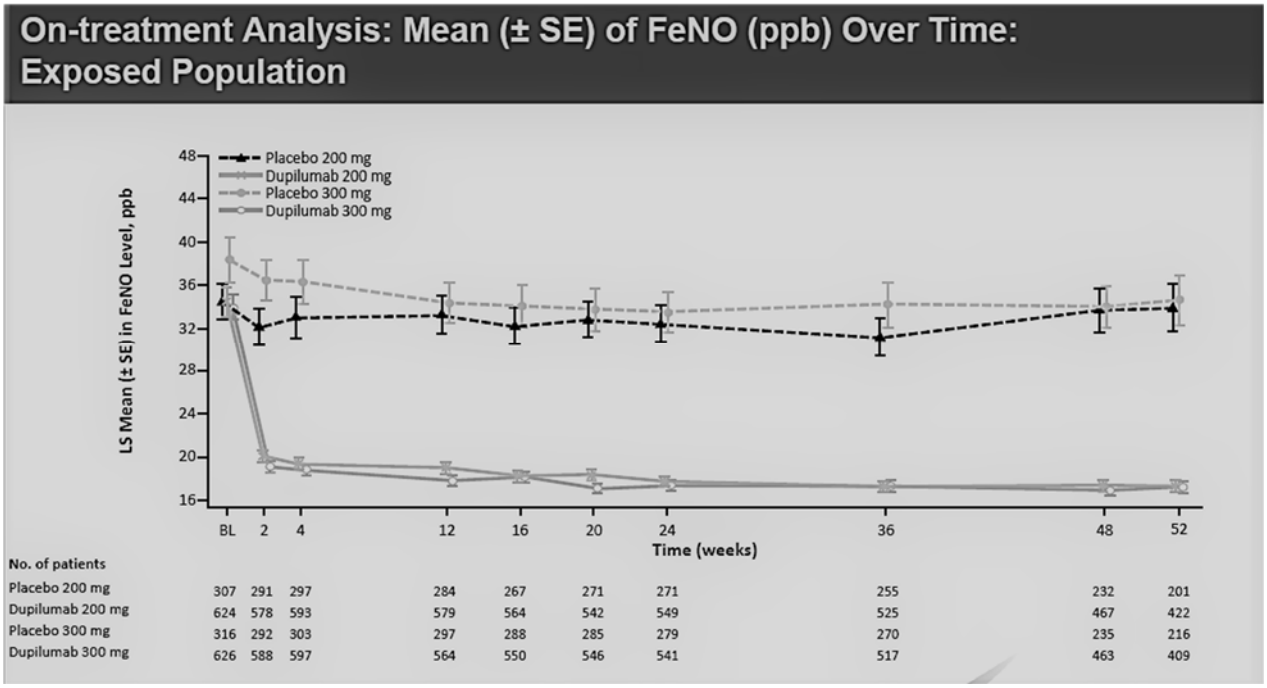


GINA Guidelines characterize type 2 inflammation by cytokines such as IL-4, IL-13, and IL-5[3]

IgE=immunoglobulin E; IL=interleukin; ILC2=group 2 innate lymphoid cell; Th2=type 2 helper; TSLP=thymic stromal lymphopoietin.

The impact of dupilumab on FeNO and EOS are essential elements of the pivotal trials due to the unique MOA of dupilumab compared to anti-IL5 monoclonal antibodies or omalizumab. In a literature review it was demonstrated that anti-IL5s do not have an impact upon FeNO levels but do drastically reduce EOS levels during therapy. Conversely dupilumab has a dramatic and consistent impact upon FeNO levels (Figure 3). Although higher baseline EOS levels correlated with increased efficacy of dupilumab in our trials, levels of EOS are not affected by treatment. This unique effect arising from a fundamentally different MOA corresponds with the definition of type 2 inflammatory asthma as defined within the licensed indication and recently updated GINA guidelines (2019).

Figure 3: Mean (+/-SE) of FeNO (ppb) Over Time: Exposed Population



A.5 Decision problem and NICE reference case

The submission supports the technology's marketing authorisation for patients with severe uncontrolled asthma driven by Type 2 inflammation defined by raised EOS and/or FeNO (EOS≥150 and/or FeNO≥25). The market authorisation was based upon FeNO effectiveness demonstrated within the clinical trials for dupilumab, namely >25 ppb, rather than >20 ppb as per the GINA guidelines. This submission also includes a requirement of ≥3 exacerbations in the previous 12 months, aligning with UK clinical practice and referral criteria to severe asthma centres where add-on biologics are prescribed.

The company submission is consistent with the final NICE scope and the NICE reference case. However, the final NICE scope referenced moderate or high dose ICS whilst the marketing authorisation for Dupilumab is as an add-on treatment for patients with severe asthma driven by Type 2 inflammation on high dose ICS. The company submission reflects the final European marketing authorisation granted on the 6th May 2019.

Table 3: The decision problem (Document B1.1 Page 18)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People 12 years and older with severe asthma inadequately controlled with optimised standard therapy (including moderate or high dose inhaled corticosteroid, and either long-acting beta-2 agonist, leukotriene receptor antagonist, slow-release theophylline or long-acting muscarinic agent)	Patients with severe asthma on high dose ICS with EOS ≥150/µl and/or FeNO ≥25 ppb in line with the marketing authorisation and ≥3 exacerbations based upon UK clinical practice	The submitted population is consistent with the licensed indication and is aligned with the most recently available clinical guidelines.(27)
Intervention	Dupilumab as an add-on to optimised standard therapy.	As per scope	N/A
Comparator(s)	For people with severe asthma for whom currently available biologics are not indicated and suitable: Optimised standard therapy including treatment with or without oral corticosteroids for people with eosinophilic asthma (subject to NICE guidance). For people with severe asthma for whom biologics are indicated and suitable: • Reslizumab in combination with optimised standard therapy including treatment with or without oral corticosteroids for people with eosinophilic asthma (in accordance with NICE recommendations) • Mepolizumab in combination with optimised standard therapy including treatment with or without oral corticosteroids for people with eosinophilic asthma	The company submission will compare cost-effectiveness of dupilumab compared with SoC. As agreed in the decision problem, in this population, SoC is considered the most appropriate comparator. For completeness, exploratory pairwise analyses will be conducted vs available anti-IL-5 biologics in their recommended sub-populations as additional scenario analyses. As agreed at the decision problem, comparison with omalizumab is not considered feasible due to differences in trial design and licence.	Dupilumab is the first treatment indicated for severe asthma with Type 2 inflammation defined by raised EOS and/or raised FeNO. Available biologic therapies are either for severe eosinophilic asthma (mepolizumab, reslizumab, benralizumab – anti-IL-5) or severe allergic asthma (omalizumab – anti-IgE) so differ to the patient population considered.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	(in accordance with NICE recommendations) • Benralizumab in combination with optimised standard therapy including treatment with or without oral corticosteroids for people with eosinophilic asthma (in accordance with NICE recommendations) • Omalizumab in combination with optimised standard therapy including treatment with or without oral corticosteroids for people with allergic IgE-mediated asthma (in accordance with NICE recommendations)		
Outcomes	The outcome measures to be considered include: • Objective measures of lung function (e.g. FEV_1, PEF) • Asthma control • Incidence of clinically significant exacerbations, including those which require unscheduled contact with healthcare professionals or hospitalisation • Use of oral corticosteroids • Mortality • Adverse effects of treatment • Health-related quality of life	As per scope	N/A

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account.	The economic analysis is conducted in agreement with the NICE reference case.	N/A

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Subgroups to be considered	If the evidence allows the following subgroups of people will be considered: • People who require maintenance oral corticosteroid treatment compared with people who are not steroid dependant • People with eosinophilic asthma • People with allergic IgE-mediated asthma	The primary economic analysis is for patients with severe asthma driven by T2i defined by raised blood EOS (≥150/μL) and/or raised FeNO (≥25 ppb) and ≥3 exacerbations vs SoC. Cost-effectiveness results for patients with severe asthma driven by T2i defined by raised blood EOS (≥150/μL) and/or raised FeNO (≥25 ppb), and either ≥3 exacerbations or mOCS vs SoC are also presented. Exploratory pairwise analyses will also be conducted, where feasible. Specifically, for severe eosinophilic asthma the following analyses are considered: • vs mepolizumab in its recommended population • vs benralizumab in its recommended population • vs reslizumab in its recommended population	Comparison of dupilumab vs omalizumab was considered out of scope: dupilumab is licensed for patients with raised EOS and/or raised FeNO. Omalizumab is recommended for allergic IgE-mediated asthma. (32)
Special considerations including issues related to equity or equality	None	N/A	N/A

Abbreviations: CUA, cost utility analysis; EOS, eosinophils; EQ-5D, EuroQol-5 dimensions; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; HRQoL, health-related quality of life; ICS, inhaled corticosteroids; LABA, long-acting beta agonist; LTRA, leukotriene receptor antagonist; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OCS, oral corticosteroids; PEF, peak expiratory flow; ppb, parts per billion; QALY, quality-adjusted life year; RCT, randomised controlled trial; SoC, standard of care; T2i, Type 2 inflammation.

Positioning of dupilumab

FeNO is currently used as a measure of adherence in severe asthma clinics in the UK and also measures airway inflammation driven by type 2 cytokines (23-26). The production of

nitric oxide (NO) is driven by the Type 2 cytokines IL-4 and IL-13 (Figure 2). Recent UK observational studies have shown that FeNO is correlated with risk of asthma exacerbations, and changes in lung function (18-22). The importance of FeNO as a biomarker in type 2 inflammation is outlined in the updated GINA guidelines (27).

Serum eosinophil count is measured as a blood test and is now considered routine UK practice (49-51). There is ongoing debate regarding the relative predictability of exacerbations from sputum EOS versus serum levels (52-54). Eosinophils are recognised as central effector cells in the inflamed airways, and play key role in airway remodelling, hyperresponsiveness and mucus secretions mediated by the IL-5 cytokine.

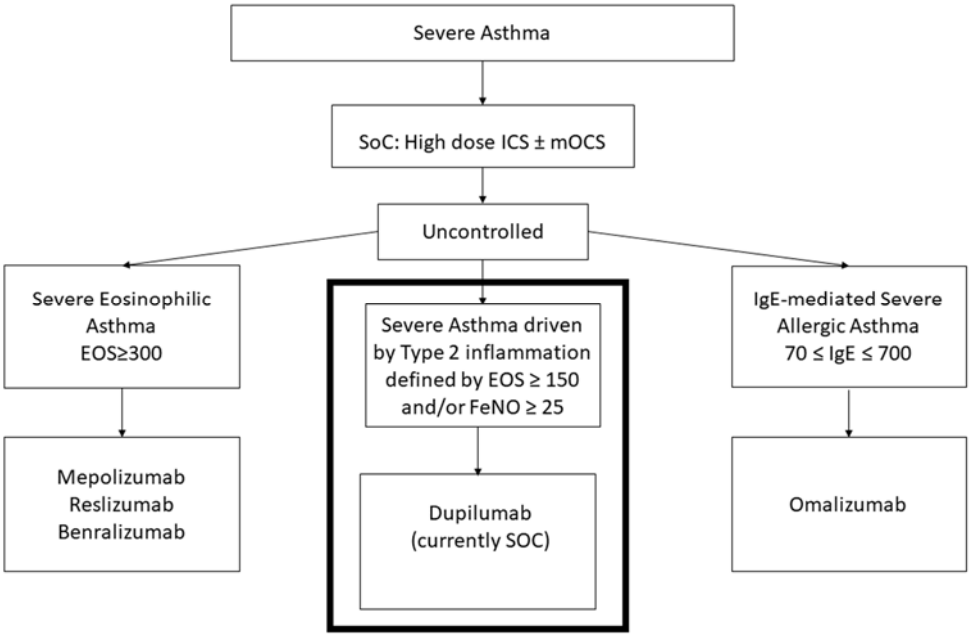
Dupilumab is indicated in adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with T2i characterised by raised blood EOS and/or raised FeNO, who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment.

Detailed recommendations for the use of this product are described in the updated SmPC, which are published in the revised European public assessment report (EPAR) (Appendix C). In line with its licensed indication, clinical guidelines and clinical practice in the UK, for severe asthma patients with T2i, dupilumab would be used for patients under specialist care who have been referred to severe asthma centres.

Patients are referred to severe asthma centres if they continue to have severe asthma exacerbations despite maximum corticosteroid therapy. In previous technology appraisals in severe asthma, exacerbation history of >=3 is required for treatment with biologic therapy. Patients with severe eosinophilic asthma as defined as EOS>300 are appropriate for anti-IL-5 therapy as recommended by NICE. Patients with allergic IgE mediated asthma as defined by IgE 70-700 are appropriate for an anti-IgE therapy as recommended by NICE.

Dupilumab is therefore the only biologic treatment indicated for patients with severe asthma driven by T2i defined as raised EOS and/or raised FeNO without hypereosinophilia, currently receiving standard of care (SoC) defined as high dose ICS, with or without OCS.

Figure 4: Position of dupilumab in treatment pathway



A.6 Clinical effectiveness evidence

A systematic literature review (SLR) was conducted to identify, appraise and synthesise the clinical trial evidence on the efficacy and safety of biologic therapies in persistent, uncontrolled asthma in adults and adolescents (aged ≥12 years). The search strategies are broad encompassing all possible treatments of relevance at the time the strategy was developed (2017), including ICS/LABA terms. However, the populations, interventions, comparators, outcomes, study design (PICOS) selection criteria applied, focused on a list of treatments of interest for the NICE submission (biologics/OCS/bronchial thermoplasty [BT]). Studies were screened for inclusion or exclusion in the SLR based on the populations, interventions, comparators, outcomes, study design, and timeframe (PICOS-T) criteria presented in (B, Table 9). Full details of the methodology used for the SLR including the search strategy, database search and selection criteria are provided in Appendix D.

The SLR identified 18 publications reporting on five trials[1] for dupilumab. Two trials were Phase II (one Phase IIa, one Phase IIb), two were Phase III. Additionally, one on-going open-label extension (OLE) (Section B, Table 10) was manually retrieved. This submission presents data from the Phase IIb and Phase III studies. A list of the relevant clinical studies is provided in (Section B, Table 11). DRI12544 could not be used to inform the economic model due to inherent differences in trial design (see table below). However, data are used for adjustment of post-trial exacerbation rates, and therefore efficacy and safety data are presented in this section. TRAVERSE is an on-going open label extension study, therefore final data is not available for inclusion either in the model, or to be presented in this section (baseline data are presented in Appendix L).

[1] One additional clinical study report (CSR) for LIBERTY ASTHMA TRAVERSE was not identified in the SLR as trial results have not yet been published; baseline characteristics are presented in Appendix.

Table 4 Clinical effectiveness evidence

Study	DRI12544 (55)	QUEST (56)	VENTURE (57)
Study design	Phase 2b, 24-week randomised, double blind, placebo-controlled, dose-ranging study N=769 Randomly assigned 1:1:1:1:1 ratio to receive subcutaneous dupilumab 200 mg or 300 mg every 2 weeks or every 4 weeks, or placebo	Phase 3, 52-week randomised, double blind, placebo-controlled, parallel group study N= 1902 Randomly assigned 2:2:1:1 ratio to receive add-on subcutaneous dupilumab at a dose of 200 or 300 mg every 2 weeks or matched-volume placebos	Phase 3, 24-week randomised, double blind, placebo-controlled, parallel group study N= 210 Randomly assigned 1:1 ratio to receive add-on subcutaneous dupilumab 300mg every 2 weeks or placebo
Population	Patients aged ≥18 with moderate-to-severe uncontrolled asthma	Patients aged ≥12 years with uncontrolled moderate-severe asthma (on a stable medium-high dose ICS plus 1–2 of the following controller medications; LABA, LAMA, LTRA, methylxanthines)	Patients aged ≥12 years with severe steroid-dependent asthma (regular prescribed systemic corticosteroids, treatment with high dose ICS plus second controller [LABA or LTRA])
Intervention(s)	Dupilumab 200 mg SC Q2W† Dupilumab 300 mg SC Q2W‡ Dupilumab 200 mg SC Q4W† Dupilumab 300 mg SC Q4W‡	Dupilumab 200 mg SC Q2W† Dupilumab 300 mg SC Q2W‡	Dupilumab 300 mg Q2W‡
Comparator(s)	Placebo + SoC	Placebo + SoC	Placebo + SoC
Indicate if trial supports application for marketing authorisation	Yes	Yes	Yes
Indicate if trial used in the economic model	No	Yes	Yes
Rationale if trial not used in model	- Difference in definition of “moderate exacerbation”	N/A	N/A

Study	DRI12544 (55)	QUEST (56)	VENTURE (57)
	- Definition of "severe exacerbation" had fewer constraints than QUEST - Protocol for timing of severe exacerbations did not match QUEST protocol		
Primary endpoint(s):	Change from baseline at Week 12 in FEV1	Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period Absolute change from baseline in pre-bronchodilator FEV1 at Week 12	Percentage reduction of OCS dose at Week 24 compare d with the baseline dose, while maintaining asthma control
Reported outcomes specified in the decision problem¶	Objective measures of lung function (**FEV_1**, PEF) Incidence of clinically significant exacerbations, including those which require unscheduled contact with healthcare professionals or hospitalisation (**severe exacerbation events**, LOAC events) Asthma control (**ACQ-5** score, LOAC events, asthma symptom scores; nocturnal awakening, number of inhalations/day of salbutamol/levosalbutamol) HRQoL (**AQLQ**, EQ-5D-3L, HADS, SNOT-22)Adverse effects of treatment (AE, vital signs, physical examination, ECG, clinical laboratory tests)	Objective measures of lung function (**FEV_1**, PEF, FVC, Incidence of clinically significant exacerbations, including those which require unscheduled contact with healthcare professionals or hospitalisation (LOAC, **severe exacerbation events**) Asthma control (**ACQ-5** [adults], ACQ-7 [adolescents], use of daily puffs of rescue medication, LOAC events, symptom score [eDiary]) HRQoL (**AQLQ[s],** RQLQ[s]+12, EQ-5D-5L, HADS, SNOT-22)Adverse effects of treatment (AE, vital signs, physical examination, ECG, clinical laboratory tests)	Objective measures of lung function (**FEV_1**, PEF, $FEF_{25–75\%}$) Incidence of clinically significant exacerbations, including those which require unscheduled contact with healthcare professionals or hospitalisation (**severe exacerbation events**, exacerbations requiring hospitalisation/ER visit) Use of OCS (**reduction in OCS dose**) Asthma control (**ACQ-5**, symptom score [eDiary], use of rescue medication) HRQoL (**AQLQ**, SNOT-22, HADS, EQ-5D-5L)Adverse effects of treatment (AE, vital signs, ECG, clinical laboratory tests)
All other reported outcomes	Health Resource Use	Health Resource Use	Health Resource Use

Study	DRI12544 (55)	QUEST (56)	VENTURE (57)

Abbreviations: AE, adverse events; ACQ; asthma control questionnaire; AQLQ, asthma quality of life questionnaire; AQLQ(S), asthma quality of life questionnaire with standardised activities; CS, corticosteroid; ECG, electrocardiogram; EOS, eosinophils; EQ-5D-3L, EuroQol-5 dimensions 3-levels; EQ-5D-5L, EuroQol 5-dimensions 5-levels; ER, emergency room; FEF, forced expiratory flow; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HADS, hospital anxiety and depression scale; HRQoL, health-related quality of life; HRU, healthcare resource utilisation; ICS, inhaled corticosteroids; LABA, long-acting beta-agonists; LAMA, long-acting muscarinic antagonists; LOAC, loss of asthma control; LTRA, leukotriene receptor antagonists; N/A, not applicable; OCS, oral corticosteroids; Q2W, every 2 weeks; Q4w, every 4 weeks; RQLQ(S)+12, standardised rhino conjunctivitis quality of life questionnaire ages 12+; SC, subcutaneous; SNOT-22, sino-nasal outcome test; TEAE, treatment-emergent adverse events. † 400 mg loading dose of dupilumab on Day 1; ‡ 600 mg loading dose of dupilumab on Day 1; § For patients from VENTURE parent study; ¶ Note: Outcomes included in the economic model are highlighted in bold.

A.7 Key results of the clinical effectiveness evidence

Dupilumab significantly improved outcomes for patients with T2i severe asthma across all Phase II and III trials, compared with standard of care (SOC). A summary of key outcomes relevant to economic modelling for each trial is presented below.

- In adult and adolescent patients aged 12 and over, dupilumab 200 mg significantly increased lung function, compared with SOC (LS mean difference of +0.31 L and +0.32 L vs. 0.12 and 0.18 at 12 weeks, p<0.001 for all comparisons with SOC), and achieved clinical significance (MCID 0.23 L). (58)
- In the licensed populations, patients had a reduced annualised rate of severe asthma exacerbations: 0.269 to 0.456 vs. 0.871 to 1.597, p<0.0001 in dupilumab 200 mg; and 0.897 vs. 0.269, p=0.0002 in dupilumab 300 mg for patients on maintenance OCS.
- Patients treated with dupilumab in addition to maintenance OCS had a greater decrease in OCS dose compared to patients on SOC (73.85% vs 45.28% (p<0.0001))
- Patients treated with dupilumab were significantly more likely to discontinue oral steroid use altogether, with an adjusted probability of achieving discontinuation of 0.25 vs. 0.48 (placebo vs. dupilumab, respectively, p= 0.0015 at Week 24).
- The effect of dupilumab on lung function in patients on high dose ICS was rapid and apparent within 2 weeks of the first administration of dupilumab.
- Patients on dupilumab had a greater increase of Exhaled Nitric Oxide (FeNO) compared to patients on placebo only (see Figure 23 in section B2.6.2 Page 106)
- Adverse drug reactions were generally mild and moderate in intensity.
- Dupilumab was generally well tolerated in all trials, and the incidence of TEAEs was well balanced across treatment groups.
- The Periodic Benefit-Risk Evaluation Report includes 7,781 patients exposed to dupilumab (including across the Atopic Dermatitis indication). No actions were taken for safety reasons during the period covered by the report.

Severe Asthma Exacerbations

Severe exacerbations are defined as episodes in which patients required OCS for at least three days, an A&E visit or hospitalisation, and have been shown to correlate with higher FeNO and a decrease in lung function. (21, 59). Reduction in severe asthma exacerbations are measured in all three pivotal dupilumab trials and is a co-primary outcome in QUEST and collected in VENTURE. In QUEST, dupilumab 200 mg reduced the rate of severe asthma exacerbations vs SOC. Results are summarized in the table below in the ITT and by Type 2 inflammation biomarker subgroups where available. For patients on high dose ICS only, data from DRI and QUEST are used in patients with EOS>=150 and/or FeNO>=25 and >= 3 exacerbations; for patients on maintenance OCS, data from VENTURE are used for the EOS>=150 or FeNO>=25 population.

Table 5: Severe Asthma Exacerbations

	QUEST		VENTURE	
	Placebo	**Dupilumab 200mg Q2W**	**Placebo**	**Dupilumab 300mg Q2W**
ITT				
N=	317	631	107	103
Adjusted annualised severe exacerbation event rate Estimate[a] (95% CI)	0.871 (0.724, 1.048)	0.456 (0.389, 0.534)	1.597 (1.248, 2.043)	0.649 (0.442, 0.955)
RR[a] vs matching placebo (95% CI)	-	0.523 (0.413, 0.662)	-	0.407 (0.263, 0.630)
p value[a] vs matching placebo	-	<0.0001	-	<0.0001
Risk difference[b] vs matching placebo	-	-0.416 (-0.588, -0.243)		–0.947 (–1.393, –0.501)
EOS≥150 OR FeNO≥25 and ≥ 3 exacerbations or mOCS*				
n=	126	223	74	78
Adjusted annualised severe exacerbation event rate Estimate[a] (95% CI)	2.185 (1.401, 3.408)	0.659 (0.423, 1.027)	1.421 (0.978, 2.064)	0.600 (0.362, 0.994)
RR[a] vs matching placebo (95% CI)		0.301 (0.168, 0.540)		0.422 (0.255, 0.701)
p value[a] vs matching placebo		<.0001		0.0010
Risk difference[b] vs matching placebo		-1.526 (-2.501, -0.551)		-0.821 (-1.326, -0.316)

ITT: Intention-to-Treat; RR: Relative Risk; CI: Confidence Intervals:

[a] 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, with the four treatment groups, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level and number of severe exacerbation events within 1 year prior to the study as covariates, and log-transformed standardized observation duration as an offset variable.

[a] VENTURE: Derived using negative binomial model with the total number of events onset from randomization up to Visit 11 (Week 24) or last contact date (whichever comes earlier) as the response variable, the treatment groups, baseline optimized OCS dose strata, regions, number of the events within 1 year prior to the study, and baseline eosinophil level subgroups (<0.15, ≥0.15 Giga/L) as covariates, and log-transformed treatment duration as an offset variable.

[b] Derived using delta method

Forced Expiratory Volume (FEV1)

In the QUEST ITT population, dupilumab 200 mg significantly improved pre-bronchodilator (BD) FEV_1 from baseline to Week 12 compared with matching placebo treatment (LS mean 0.32 L vs 0.34 L for dupilumab 200 mg and placebo respectively).

OCS Reduction

The mean percent reduction from baseline in OCS dose at Week 24 is greater in the dupilumab group (LS mean 70.09 mg/day) compared with the placebo group (LS mean 41.85 mg/day). There is a significant difference in the LS mean change from baseline for

dupilumab vs placebo at Week 24 vs placebo of 28.24% (95% CI: 15.81, 40.67; p<0.0001). In the ITT population at Week 24, dupilumab significantly increased the odds of no longer requiring OCS at Week 24 by 2.74 times (95% CI: 1.47, 5.10; p=0.0015) compared with placebo.

Table 6: VENTURE primary efficacy endpoint – Percentage reduction of OCS dose (mg/day) at Week 24 (ITT Population)

OCS (mg/day)	Placebo (N=107)	Dupilumab 300 mg Q2W (N=103)
ITT		
N	106	101
Mean (SD) [a]	45.28 (50.73)	73.85 (39.78)
Median [b]	50.00	100.00
LS mean (SE) [b]	41.85 (4.57)	70.09 (4.90)
LS mean difference vs placebo (95% CI) [b]	-	28.24 (15.81, 40.67)
p value vs placebo [b]	-	<0.0001
EOS≥150 or FeNO≥25 and mOCS		
N	74	78
Mean (SD) [a]	45.60 (50.66)	75.42 (36.87)
Median†	50.00	100.00
LS mean (SE) [b]	42.38 (6.32)	73.37 (6.66
LS mean difference vs placebo (95% CI) [b]	-	30.99 (16.75, 45.23)
p value vs placebo [b]	-	<.0001

[a] Calculated from observed data only
[b] 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 level subgroups (<0.15, ≥0.15 Giga/L) as covariates. Missing data is imputed using the primary approach - pattern mixture model by multiple imputation (seed = 13691).

Mean percentage reduction of OCS use is higher in the treatment arm compared with placebo. Patients on dupilumab had a mean dose reduction of 75.42%, whereas patients on placebo reduced OCS by 45.60%.

A.8 Evidence synthesis

Dupilumab is the only biologic treatment indicated for patients with severe asthma driven by T2i defined as raised EOS and/or raised FeNO without hypereosinophilia, currently receiving standard of care (SoC) defined as high dose ICS, with or without OCS.

Patients with severe eosinophilic asthma as defined as EOS≥300 are appropriate for anti-IL-5 therapy as recommended by NICE. Patients with allergic IgE mediated asthma as defined by IgE 70-700 are appropriate for an anti-IgE therapy as recommended by NICE.

No evidence synthesis is necessary for standard of care as the base case comparator in this submission, or the economic model, as it was the comparator in the dupilumab clinical trial programme. For completeness, an indirect treatment comparison (ITC) was conducted for dupilumab versus recommended add-on biologic treatments for severe eosinophilic asthma (Appendix L).

A.9 Key clinical issues

The dupilumab clinical trial programme was developed to ensure efficacy of dupilumab could be determined with accuracy. However, clinical issues remain in all trials. Key clinical issues identified for the dupilumab clinical trials are:

- The phase 3 pivotal trial QUEST of 52 weeks is the only trial of sufficient duration to allow a full evaluation of the impact of dupilumab on annual rate of severe asthma exacerbations.
- DRI is recognised as a pivotal clinical trial for dupilumab. However, due to differences in protocol between DRI and QUEST that would require assumptions to overcome, it is considered less critical for the economic evaluation.
- The clinical trials, QUEST and VENTURE, are designed for patients on either ICS plus an additional controller or ICS plus an additional controller and maintenance OCS. A clinical trial design that included both these populations in the same trial would have provided an evidence base more aligned to the UK context.

A.10 Overview of the economic analysis

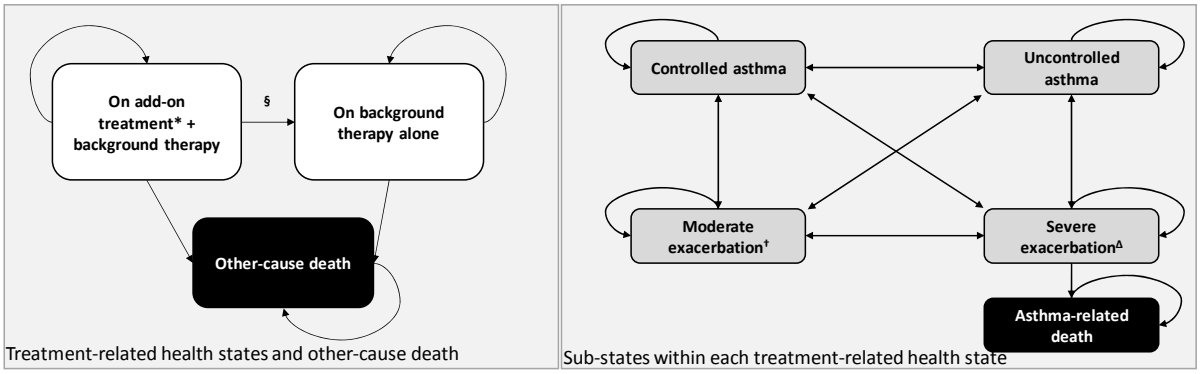
An SLR was conducted to identify economic analyses previously conducted in severe asthma.

A Markov cohort model was adopted to reflect both the chronic day-to-day asthma symptoms that patients with uncontrolled persistent asthma experience, which would influence their QoL, as well as the risk these patients may also experience intermittent asthma exacerbations that can vary in severity and in some instances, lead to death. The model structure was developed based on previous economic models for severe persistent asthma and suggestions by clinicians to make sure that the structure of the model was consistent with clinical practice.

Patients enter the model in an uncontrolled asthma health state, and transition between the “controlled asthma”, “moderate exacerbation” and “severe exacerbation” health states according to transition probabilities calculated from clinical trial data.

The length for a cycle in the model was four weeks. A lifetime horizon was considered most appropriate to capture the full benefits associated with the treatment, as treatment of uncontrolled persistent asthma is anticipated to continue over the whole life of the patient once diagnosed. This is consistent with NICE methodological guidelines. At 12 months, patients may discontinue treatment if they are non-responders; an annual discontinuation for any reason was included in the model consistent with data from the QUEST clinical trial.

Figure 5 Model diagram – Document B.3.2 - page 171)



A.11 Incorporating clinical evidence into the model

Transition probabilities

Estimation of transition probabilities were derived from pivotal trials QUEST and VENTURE by counting the number of patients in each health state every four weeks (consistent with the cycle length), with the frequency of transitions to other health states.

Separate transition probabilities were derived for the period before Week 12 and the period beyond week 12 for dupilumab, to reflect variation of transition probabilities over time. The rate of change in mean ACQ-7 (use to determine asthma control) was higher during the first 12 weeks compared with the rest of the trial period.

Due to small numbers, and in the absence of evidence to inform a variation in the risk of experiencing exacerbations over time it was assumed that the risk of experiencing severe exacerbations within each health state was independent of time from treatment initiation. In the case of the VENTURE trial, the risk of experiencing severe exacerbations appeared to be considerably higher in the period between 12–24 weeks as compared to 0–12 weeks. Since the trial was limited to 24 weeks, it was considered more appropriate to use transitions to the severe exacerbation state observed over the entire trial duration.

Transition probabilities for responders

Within the QUEST analyses, patients on dupilumab demonstrated a rapid increase in asthma control during the first 12 weeks on treatment. Transition probabilities for responders (>52 weeks, see A.11.4) were therefore based on observed data for the period beyond week 12, as a conservative approach. Transitions between controlled states for VENTURE analyses were based on observations between 12-24 weeks and adjusted as outlined above. However, transition probabilities to or between exacerbation states for responders were obtained from the entire treatment period due to the small event numbers: only five transitions from the severe exacerbation state are observed.

Asthma Control Questionnaire (ACQ)

The Asthma Control Questionnaire (ACQ) is a validated, widely-used questionnaire developed to measure asthma control, based on asthma symptoms in clinical practice. The questionnaire

was administered to all patients in the dupilumab trials and was used in the economic model to distinguish between controlled patients (ACQ<1.5) and uncontrolled patients (ACQ≥1.5). Level of asthma control is linked to the risk of asthma exacerbation and health-related QoL and was therefore anticipated to influence utility estimates as well as transition probabilities to exacerbation states. In the pivotal QUEST trial, the ACQ-7 score was recorded every four weeks (fortnightly in the first 12 weeks), which, along with data collected in the trial on the two types of exacerbation events, allowed determining the probabilities of staying in the same control-based health state or to move to any of the three other live states between two given model cycles.

Continuation Criteria

At 12 months, patients were assessed to determine response to treatment. Treatment response was confirmed if patients achieved at least 50% reduction in severe asthma exacerbations, or at least 50% decrease in OCS dose. Patients who did not respond stopped add-on therapy and were attributed the same costs and utilities as patients on SoC alone.

Maintenance OCS use

Patients with severe uncontrolled asthma may require regular use of oral corticosteroids. Side-effects from frequent use of oral OCS use can lead to the development of chronic conditions such as weight gain, diabetes, cataracts and osteoporosis, resulting in higher health care resource use and costs. Therefore, reducing OCS use as maintenance treatment is a major objective for new therapies and has been addressed in the previous technology appraisals for severe asthma.

The impact of reducing OCS use was captured in the model in the following ways:

- Impact on HRQoL (less disutility for AEs related to OCS)
- Impact on resource use (expected reduction in costs associated with treating AEs related to OCS)
- Impact on drug acquisition costs for OCS

Asthma related Mortality

Patients with severe asthma are at increased mortality risk compared to the general population. Nonetheless, asthma-related mortality is a rare event and given the rarity of occurrence in the clinical trials, UK specific real-world data is considered the most appropriate source of this data. As seen in the model structure, it was assumed that asthma-related mortality could only occur from a severe asthma exacerbation, and the probability of the exacerbation leading to fatality was dependent on the location of treatment of the exacerbation (i.e. a severe exacerbation requiring hospitalisation had a higher probability of death than a severe exacerbation treated with OCS only). This is consistent with the previous technology appraisals for severe asthma.

Key model assumptions and inputs

The economic model reflects how therapies for severe asthma driven by Type 2 inflammation benefit patients in the UK. All economic models require assumptions, and it is important to ensure these are captured and the uncertainty measured. The table below summarises key model assumptions and inputs in the base case.

Table 7 Key model assumptions and inputs – (Document B3.6.3 page 228)

Model input and cross reference	Source/assumption	Justification	Section in Document B
Asthma-related mortality	Mortality calculations are based on Watson et al, and adjusted based on Roberts et al.	The committee's preferred assumption from the most recent severe eosinophilic asthma appraisal is considered a conservative approach	B3.3.10
Setting of asthma exacerbations	Setting of treatment severe exacerbations is informed by UK-specific published data	Using UK-specific data from a published observational study is considered to be more representative of UK clinical practice and therefore more appropriate for the base case	B3.3.9
Post-trial exacerbation rates	Severe asthma exacerbations increase after the clinical trial period.	It has been shown the recent severe exacerbations in the strongest predictor of future asthma exacerbations. All patients were required to have a period of ~7 weeks without an exacerbation to be included in QUEST, therefore excluding some of the most severe patients. It is assumed that the UK real-world would not require such a restriction, therefore assuming all patients would have a higher exacerbation risk. This is in line with a previously accepted assumption, where post-trial exacerbation rates for all patients were assumed to increase by 1.432	B3.3.3.

A.12 Base-case Incremental Cost-Effectiveness Results (Document B.3.7)

In the base case for patients with severe asthma driven by Type 2 inflammation defined by EOS≥150 and/or FeNO≥25 and ≥3 exacerbations, the ICER of dupilumab compared to patients on SoC is £ 28,087/QALY.

Table 8: Cost-effectiveness of patients with severe asthma driven by Type 2 inflammation defined as EOS≥150 and/or FeNO≥25 or ≥3 exacerbations (ICS only) – (Document B3.7.2 – Page 232)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Standard of care	[redacted]	[redacted]	[redacted]				
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£ 28,087

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

A.13 Deterministic sensitivity analysis – (Document B3.8 Page 233)

A probabilistic sensitivity analysis (PSA) was performed using a second-order Monte Carlo simulation. In this analysis, each parameter subject to parameter uncertainty was assigned a probability distribution, and cost-effectiveness results associated with the simultaneous selection of random values from the distribution of each of these parameters were generated. This process was repeated for 3,000 iterations and results of the PSA plotted on the cost-effectiveness plane (or scatter plot) and were used to calculate cost-effectiveness acceptability curves (CEACs), highlighting the probability of cost-effectiveness over various willingness to pay thresholds.

The model is most sensitive to the proportion of severe exacerbations that are either self-managed or a GP visit, and is also sensitive to the fatality rate of severe exacerbations requiring treatment at A & E. This is in line with expectation, as seen in previous technology appraisals for severe asthma.

These results also show that the relative effect of experiencing a severe exacerbation beyond the trial impacts the results. However, an increase in severe exacerbations beyond the trial end has been shown to occur, as reported in a published Open Label Extension for severe eosinophilic asthma and used in a previous technology appraisal.

A.14 Probabilistic sensitivity analysis

The probabilistic ICER for patients with severe uncontrolled asthma driven by Type 2 inflammation defined by EOS ≥ 150 and/or FeNO ≥ 25 and ≥ 3 severe exacerbations in the previous is £28, 466.

Figure 6: Scatterplot of probabilistic results EOS≥150 and/or FeNO≥25 and ≥3 exacerbations vs. SOC – (Document B.3.8.1.2 page [234])

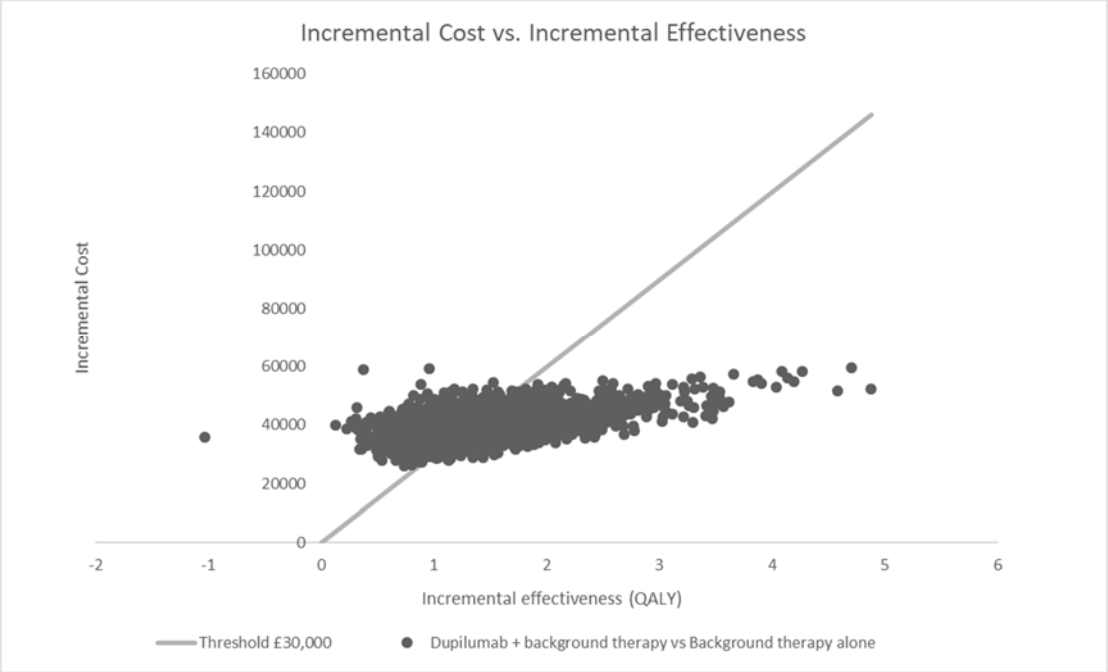


Table 9: Base case cost-effectiveness results for patients with EOS ≥ 150 and/or FeNO ≥ 25 and ≥ 3 exacerbations (Probabilistic) – (Document B3.8.1.2 Page 235)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs baseline (£/QALY)
SoC	[redacted]	[redacted]	[redacted]				
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£ 28,466

A.15 Key sensitivity and scenario analyses

Sensitivity and scenario analyses are conducted to determine which variables most influence the outcomes of the economic model. This helps understand parameter uncertainty and assess the influence of patient heterogeneity. Results of the sensitivity and scenario analyses that have the most impact on results are shown in the following tables.

Table 10: Key scenario analyses EOS≥150 and/or FeNO≥25 and r ≥3 exacerbations vs. SOC B3.8.1.3 (page 236)

Scenario	Scenario detail	Impact on base-case ICER
Base-case		£ 28,087
Discount rate for health effects 1.5 percent	Discount rates reduced to 1.5%	£ 21,446
Severe exacerbations after trial period: Increase risk based on severe exacerbations prior to enrolment	Severe exacerbations were adjusted to reflect pre-trial rates Severe exacerbations were adjusted to reflect pre-trial rates	£ 23,538
Post-acute hospitalization costs for severe exacerbations	Costs were adjusted to reflect an increase in health care resource use after discharge from hospital, based on PSSRU (60)	£ 23,742
Time horizon 10 years	Time horizon is 10 years	£ 46,645
Time horizon 5 years	Time horizon is 5 years	£ 62,536
Asthma-related mortality set to 0	Mortality set to 0 in the model	£ 71,950

A.16 Subgroup analysis: EOS ≥150 and/or FeNO ≥25 and ≥3 exacerbations or mOCS

Table 11: Cost-effectiveness summary results: Dupilumab vs SoC in EOS ≥150 and/or FeNO ≥25, and either ≥3 exacerbations or mOCS – B3.9 (page 237)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs baseline (£/QALY)
SoC	[redacted]	[redacted]	[redacted]				
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£ 35,486

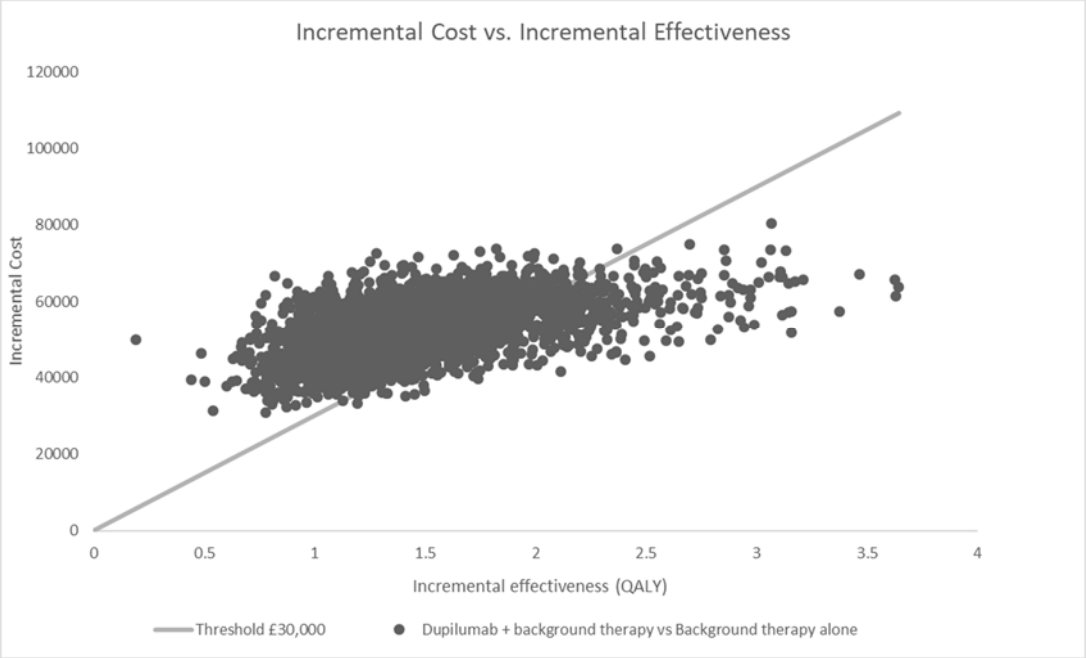
Abbreviations: EOS, eosinophils; FeNO, fractional exhaled nitric oxide; ICER, incremental cost-effectiveness ratio; LY, life year; mOCS, maintenance oral corticosteroids; QALY, quality-adjusted life year; SoC, standard of care.

Deterministic Sensitivity Analyses

Deterministic Sensitivity Analyses of dupilumab vs. SoC in EOS ≥ 150 and/or FeNO ≥ 25, and either ≥ 3 exacerbations or mOCS in document B3.9.1 (page 238) demonstrate that cost-effectiveness of dupilumab is sensitive to the proportion of patients on dupilumab having an exacerbation requiring a GP visit, or self-managed and the relative effect of experiencing an exacerbation after the clinical trial period.

Probabilistic Sensitivity Analyses

Table 12: Scatter plot: Dupilumab vs SoC in EOS ≥150 and/or FeNO ≥25, and either ≥3 exacerbations or mOCS - B3.9.2 (page 238)



Abbreviations: EOS, eosinophils; FeNO, fractional exhaled nitric oxide; mOCS, maintenance oral corticosteroids; QALY, quality-adjusted life years; SoC, standard of care.

Table 13: Base case cost-effectiveness results for patients with EOS ≥ 150 and/or FeNO ≥ 25 and ≥ 3 exacerbations (Probabilistic) - B3.9.1 (page 239)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs baseline (£/QALY)
SoC	[redacted]	[redacted]	[redacted]				
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£ 36,096

The probabilistic ICER for patients with severe uncontrolled asthma driven by Type 2 inflammation defined by EOS ≥ 150 and/or FeNO ≥ 25, and either ≥ 3 severe exacerbations in the previous 12 months or mOCS is £ 36,096.

A.17 Innovation

Dupilumab has a novel mechanism of action via inhibition of the IL-4 and IL-13 pathways. Current biologics for severe asthma target either IL-5 or IgE and are only suitable for patients with a specific phenotype of asthma; high EOS or IgE, respectively. Due to the distinct IL-4 and IL-13 pathways, dupilumab targets a different patient population compared to current biologic therapies (24, 37).

In the UK, in addition to severe asthma, dupilumab is indicated for the treatment of moderate-severe AD (63), offering a treatment option for both AD and severe asthma patients. Furthermore, due to the nature of atopic disease mediated by T2i, e.g. AD, allergic nasal polyps, and eosinophilic oesophagitis, and the cross over between these populations,

dupilumab will have an additional effect within a population of patients with Type 2 comorbidities (24, 61, 62).

Dupilumab has demonstrated significant improvements in multiple markers of asthma disease severity and QoL, with reductions in exacerbations, improved QoL scores and lung function as well as reducing OCS use (61, 64). As a result of these demonstrated improvements, a shift in management away from long-term high-dose OCS use in patients with severe asthma with T2i is anticipated. GINA highlight the high priority of strategies that reduce OCS use (27). Chronic OCS treatment is associated with side effects including muscle weakening, formation of cataracts, central nervous system disorders, and osteoporosis (65-68).

A.18 Budget impact

Table 14 Budget impact – Budget Impact Model (pages 12 and 15)

	2020	2021	2022	2023	2024	Cross reference
Number of people in England who would have treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Budget Impact Model
Average treatment cost per person – prevalent population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Budget Impact Model
Average treatment cost per person – prevalent population - Incident population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Budget Impact Model
Estimated annual budget impact on the NHS in England	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Budget Impact Model

A.19 Interpretation and conclusions of the evidence

Clinical Effectiveness and Safety

Dupilumab is the only treatment licensed for patients with severe asthma driven by Type 2 inflammation defined by raised EOS and/or raised FeNO. Throughout the clinical development programme of three pivotal clinical trials, dupilumab was shown to be effective

in severe asthma driven by Type 2 inflammation defined by EOS≥150 and/or FeNO≥25 and ≥3 exacerbations. Dupilumab significantly reduced severe asthma exacerbations and chronic use of OCS while increasing lung function and improving patient HRQoL and asthma control. Across all indications, after a cumulative exposure to dupilumab estimated to be 38,816 patient years, it is considered that dupilumab offers a favourable risk-benefit balance.

Economic Analysis

A lifetime, 5-state Markov model is designed to capture the health states of severe asthma driven by Type 2 inflammation, defined by level of asthma control and exacerbation severity. Dupilumab incremental cost-effectiveness ratios for patients with severe asthma driven by Type 2 inflammation defined by EOS ≥ 150 and/or FeNO ≥ 25 and ≥ 3 exacerbations is £ 28,087/QALY versus SOC of high dose ICS and £ 35,486 versus standard of care, encompassing high dose ICS or maintenance OCS.

Conclusion

Dupilumab is a clinically and cost-effective intervention for patients with GINA-defined severe asthma driven by Type 2 inflammation defined by EOS≥150 and/or FeNO≥25 and ≥3 exacerbations or maintenance OCS.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Dupilumab for treating severe asthma [ID1213]

Clarification questions

August 2019

File name	Version	Contains confidential information	Date
	1.0	Yes	17th September 2019

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Marketing authorisation and decision problem population

A1. Priority question: **The company states in the introduction to CS Appendix P "omalizumab is considered out of scope, as allergic asthma, defined by IgE, is not considered to be part of the EMA licence for dupilumab. Additionally, any comparison would be unreliable, due to the inherent differences between the dupilumab and omalizumab clinical trial protocols." Please would the company elaborate on this by answering the following questions:**

a) **Where in the regulatory documents does it state that the population eligible for omalizumab is ruled out of the indication for dupilumab? The GINA 2019 description of severe asthma driven by type 2 inflammation (CS B.1.3.3.2) lists "Asthma is clinically allergy-driven" as one of the criteria defining type 2 inflammation when a patient is taking high-dose inhaled corticosteroids (ICS) or daily oral corticosteroids (OCS). Additionally, the SmPC (5.1 Pharmacodynamic properties) indicates that dupilumab does decrease total IgE and allergen specific IgE. Baseline total IgE in the DRI12544 RCT (Wenzel 2016, appendix to the published paper) lies within the range shown in CS Figure 5 for IgE-mediated severe allergic asthma.**

Omalizumab and dupilumab have different licences as they have differing modes of action.

Omalizumab is an anti-IgE monoclonal antibody and therefore it's indication states treatment "should only be considered for patients with convincing IgE (immunoglobulin E) mediated asthma." (1) In omalizumab trials, as well as in the SmPC, evidence of a perennial aeroallergen is required (2, 3).

Dupilumab is an anti-IL-4/13 antibody licenced for severe asthma with Type 2 inflammation defined by raised EOS and/or FeNO. Dupilumab has no specific indication statement for IgE-mediated asthma. In contrast to FeNO and EOS, IgE was not a pre-specified subgroup in QUEST. Additionally, IgE has not been shown to be a predictor of response to dupilumab.

In the phase 3 QUEST trial, a pharmacodynamic endpoint for IgE was assessed and a reduction of IgE was observed for patients on treatment however, a consistent reduction in the rate of severe asthma exacerbations with dupilumab versus placebo was observed irrespective of IgE.

Severe allergic asthma is not solely defined by IgE but includes the patient's history (seasonality, particular triggers), confirmation of aero-allergens and other clinical parameters. Dupilumab may be suitable for severe allergic asthma per the GINA guidelines if they have raised EOS and/or raised FeNO as stated in the dupilumab licence. Some patients with Type 2 inflammation defined by raised EOS and/or FeNO may have IgE-mediated asthma but it is expected that those patients with convincing IgE-mediated severe asthma would be treated with the targeted anti-IgE antibody, omalizumab.

b) What are the specific differences in the dupilumab and omalizumab clinical trial protocols that makes any comparison with omalizumab unreliable?

Differences in definitions of asthma exacerbations and the populations included in clinical trials make an indirect treatment comparison between dupilumab and omalizumab highly unreliable.

In omalizumab trials, a positive skin test was required for entry into the omalizumab trials but allergic skin tests were neither required nor performed in the dupilumab trials.

A summary of the inclusion criteria for QUEST (dupilumab) and INNOVATE (omalizumab) are shown in Table 1.

Table 1: QUEST and INNOVATE inclusion criteria

QUEST (4)	INNOVATE (5)
• Existing treatment with medium to high dose ICS (≥250 mcg of fluticasone propionate twice daily or equipotent ICS daily dosage to a maximum of 2000 mcg/day of fluticasone propionate or equivalent) in combination with a second controller (eg, LABA, LTRA) for at least 3 months with a stable dose ≥1 month prior to Visit 1. • Pre-bronchodilator forced expiratory volume (FEV1) ≤ 80% of predicted normal for adults and ≤ 90% of predicted normal for adolescents at Visits 1 and 2, prior to randomization. • Asthma Control Questionnaire 5-question version (ACQ-5) score ≥1.5 at Visits 1 and 2, prior to randomization. • Reversibility of at least 12% and 200 mL in FEV1 after the administration of 200 to 400 mcg albuterol/salbutamol or levalbuterol/levosalbutamol (2 to 4 inhalations of albuterol/salbutamol or levalbuterol/levosalbutamol, or of a nebulized solution of albuterol/salbutamol or levalbuterol/levosalbutamol • Must have experienced, within 1 year prior to Visit 1, any of the following events: - Treatment with a systemic steroid (oral or parenteral) for worsening asthma at least once. - Hospitalization or emergency medical care visit for worsening asthma.	• Positive skin prick test to ≥1 perennial aeroallergen, to which they were likely to be exposed during the study, and total serum IgE level of ≥30 to ≤700 IU/ml. • Severe persistent asthma requiring regular treatment with >1000 µg/day BDP or equivalent and LABA (GINA step 4 treatment). • Forced expiratory volume in 1 s (FEV1) ≥40 to <80% of predicted normal value and continuing asthma symptoms. • FEV1 reversibility ≥12% from baseline within 30 min of inhaled (up to 400 µg) or nebulized (up to 5 mg) salbutamol. • Despite high-dose ICS and LABA use at least two asthma exacerbations requiring systemic corticosteroids, or one severe exacerbation [peak expiratory flow (PEF)/FEV1 <60% of personal best, requiring systemic corticosteroids] resulting in hospitalization or emergency room treatment, in the past 12 months. • Additional asthma medications, taken regularly from >4 weeks prior to randomization were permitted, including theophyllines, oral β2-agonists and antileukotrienes. • Maintenance oral corticosteroids (maximum 20 mg/day) were permitted providing at least one of the exacerbations in the previous 12 months had occurred while on this therapy.

Dupilumab trials were designed to include patients with moderate-to-severe asthma, irrespective of known asthma biomarkers (EOS, FeNO or IgE) and may therefore include patients eligible for omalizumab based on IgE. It is expected that patients with convincing IgE-mediated asthma would be treated with an anti-IgE antibody.

Definitions of exacerbations in the omalizumab trials could not be reconciled with the data available from the dupilumab trials. Specifically:

- Timing of exacerbation
- Clinical definition of exacerbation
- Treatment required for exacerbation

A side-by-side comparison of definitions used in clinical trials is shown in

Table 2.

c) What proportion of the dupilumab trial populations would meet the eligibility criteria for omalizumab?

Skin prick test positivity to a perennial aeroallergen was required to determine patients eligible for omalizumab in omalizumab trials. However, patients in the dupilumab trials were not given this test. Therefore, it is not possible to determine with certainty the proportion of patients eligible for omalizumab in the UK. However, 2.5% of patients from QUEST across all arms met the omalizumab NICE criteria (>=12 years, high ICS, at least 1 perennial allergen positive (>=0.35 IU/mL) among 9 perennial allergens, >=30>= IgE =<700 and >=4 severe exacerbations in the previous 12 months).

Table 2: Outcome Definitions: Severe Exacerbations

Trial Name	Definition of Exacerbations	Hospitalization Component	ER Component	OCS Component	Exacerbation Reporting Time Points	Definition Similarity/Inclusion in Network
Dupilumab						
QUEST, CSR data(6)	A severe exacerbation event was defined as a deterioration of asthma requiring either the use of systemic corticosteroids for ≥3 days or hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids.	Yes	ER visit	Systemic use for ≥3 days	Annualized rate (52-week follow-up)	Yes/yes
DRI, Wenzel et al 2016/CSR(7)	A severe exacerbation event was defined as a deterioration of asthma requiring either the use of systemic corticosteroids for ≥3 days or hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids.	Yes	ER visit	Systemic use for ≥3 days	Annualized rate (24-week follow-up)	Yes/yes
Omalizumab						
EXALT OL, Bousquet et al 2011(8)	Worsening of asthma requiring treatment with rescue systemic [oral or intravenous] corticosteroids)	No	No	Treatment with rescue systemic [oral or intravenous] corticosteroids)	Rate (32-weeks)	No/No [sensitivity analysis only – open label trial]
EXTRA, Hanania et al 2013[4]	An exacerbation with worsening asthma symptoms requiring treatment with systemic corticosteroids for ≥3 days; for patients receiving long-term OCS, an exacerbation was a ≥20 mg in the average daily dose of oral	No	No	Systemic use for ≥3 days or ≥20 mg increase in the average daily dose of oral prednisone (or	Rate [HR; p-values] (48-week)	No/No [exploratory analysis only]

	prednisone (or a comparable dose of another systemic corticosteroid).			a comparable dose of another systemic corticosteroid)		
INNOVATE, Humbert et al 2005(5)	A severe exacerbation was defined as PEF or FEV_1 <60% of personal best, requiring treatment with systemic corticosteroids. The study's primary efficacy variable was clinically significant exacerbations, which was defined as worsening of asthma symptoms requiring treatment with systemic corticosteroids.	No	No	Systemic use	Rate (28 weeks)	No/no [exploratory analysis only]

A2. Priority question: What proportion of the DRI12544 population of relevance to this STA (i.e. dupilumab 200mg Q2W and placebo arm) meet the criteria for the decision problem population? Why were these patients not included in the post-hoc analysis of dupilumab in the agreed decision problem population (CS B.2.7.2).

In DRI12544, 158 patients were on placebo, 150 patients were on dupilumab 200 mg Q2W. Of these, 24 (15.2%) and 22 (14.7%) respectively, had EOS≥150 and/or FeNO ≥ 25 and ≥ 3 exacerbations.

The economic model utilized data from QUEST and VENTURE as the pivotal phase III trials. DRI was not included in the economic model as pooling data between QUEST and DRI to derive transition probabilities and utilities would be challenged by:

- Different follow-up periods:
    - QUEST evaluated patients over 52 weeks whilst DRI evaluated patients over 24 weeks. With a cycle length of 4 weeks each patient enrolled in QUEST would contribute to a maximum of 13 transitions whilst a patient enrolled in DRI would contribute to a maximum of 6 possible transitions.
- Inconsistent outcomes:
    - QUEST defined loss of asthma control (LOAC) which was used to determine the occurrence of moderate exacerbations (calculated from LOAC events by excluding severe exacerbations) as:
        1. Increase in ICS dose ≥4 times than the dose at Visit 2;
        2. ≥ 6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol in a 24-hour period (compared to baseline) on 2 consecutive days;
        3. ≥20% decrease in pre-bronchodilator forced expiratory volume in one second (FEV_1) compared with baseline
        4. A decrease in AM or PM peak flow of 30% or more on two consecutive days of treatment, based on the defined stability limit. The treatment period stability limit is defined as the

respective mean AM or PM peak expiratory flow (PEF) obtained over the last seven days prior to randomisation (Day 1)

5. Use of systemic corticosteroids for ≥3 days; or- Hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids (severe exacerbations- excluded from calculation of moderate exacerbations)
    - In DRI only 1, and 2 were used to define LOAC. Therefore, moderate exacerbations using consistent definitions could not be captured in the model by pooling DRI and QUEST.

- ACQ-7 was not collected in DRI, only ACQ-5. As the model aimed to capture the full benefits associated with treatment, use of ACQ-7 was preferred since the 7th item includes lung function.
- DRI collected EQ-5D-3L whilst QUEST collected EQ-5D-5L

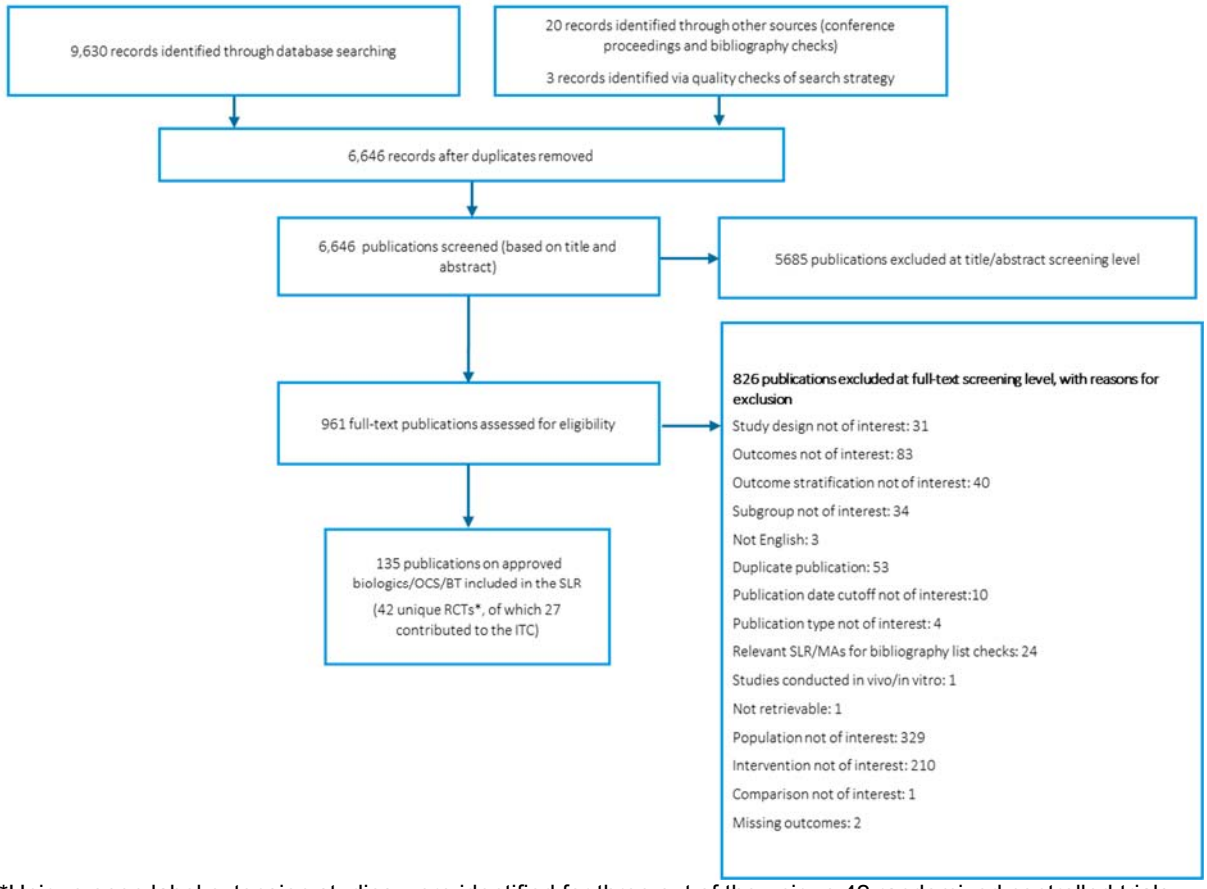
- In addition to the above, additional assumptions would be necessary with regards to deriving transition probabilities in the placebo arm, since DRI didn't include a placebo arm for q2w 200mg.

Systematic review methodology

A3. The eligibility criteria for the systematic review (CS Table 7) indicate that only biologics approved by regulatory authorities were eligible for inclusion. Why then does CS Figure 6 (PRISMA flow diagram for the systematic review) show 34 publications on unapproved/unlicensed biologics shown as part of the 169 publications in the systematic review?

The PRISMA diagram shows studies of unapproved therapies in the "excluded at full-text" box in the diagram. The submitted PRISMA was taken from a draft report.

Figure 1. Updated PRISMA flow diagram



*Unique open label extension studies were identified for three out of the unique 42 randomized controlled trials (reported across 10 publications out of the 135 included in this systematic literature review)
Abbreviations: BT = bronchial thermoplasty; ITC = indirect treatment comparison; MA = meta-analysis; OCS = oral corticosteroid; RCT = randomized controlled trial; SLR = systematic literature review

A4. Please would the company confirm whether or not the SLR described in B.2.1 is identical to the SLR described in appendix N.2.1.

The SLR presented in B.2.1. is identical to the SLR described in the N.2.1. The search retrieved 135 publications on 42 unique trials, of which dupilumab (four trials), mepolizumab (six trials), omalizumab (17 trials), reslizumab (six trials), benralizumab (five trials), bronchial thermoplasty (three trials), and OCS (prednisone; one trial).

16 trials were excluded during the feasibility assessment for the indirect treatment comparison (ITC), due to dose not being approved (7); treatment not of interest (4); patient population outliers (2); and outcomes of interest for ITC not being reported (3).

26 trials remained, which were stratified based on OCS dependence. Of the 23 uncontrolled persistent asthma trials, evidence of interest was available for two

dupilumab trials, three mepolizumab trials, five reslizumab trials, two benralizumab trials, and [redacted] omalizumab trials, shown in Table 84 in Appendix N.

For the OCS-dependent asthma trials, one trial for each of the following biologics was available: dupilumab, benralizumab, and mepolizumab.

One OCS-dependent reslizumab trial published on clinicaltrials.gov only (NCT02501629) (9) was found only after the SLR was conducted, and was not published in a journal. However, an exploratory ITC was conducted, confusion in reporting of 26 or 27 trials included in quantitative analysis.

One additional dupilumab open-label trial, TRAVERSE, was also not reported in the literature (the study is on-going) and was therefore manually added; hence, Figure 6 of B.2.1.2. in the main CS includes 27 trials included in the ITC and one additional trial.

A5. Appendix D.1.3. Is this table of quality assessments based on 71 references reporting on the 74 RCTs identified as shown in CS Figure 6 (42 unique RCTs on approved biologics/OCS/BT included in the SLR plus 32 unique RCTs on unapproved /unlicensed biologics)?

74 unique RCTs were identified based on 72 references. A draft version of the quality assessment was mistakenly included in the submission. Chanez (10) was retrieved and assessed for final quality assessment, which is included below.

Additionally, two publications, Hanania (11) and Panettieri (12) reported two studies each (LUTE and VERSE, and STRATOS 1 and 2, respectively).

The risk of bias was assessed in all publications included in the SLR (see Figure 2 and Figure 3). Most of the studies included in the evidence base were well designed. Eight studies (20%) were considered to have a low risk of bias based on study design, conduct, and analysis, including two dupilumab RCTs, one omalizumab RCT, one benralizumab RCT, one mepolizumab, and three reslizumab RCTs (Figure 2). Eight studies (20%) were considered to have a high risk of bias, including four omalizumab RCTs, one benralizumab RCT, and three bronchial thermoplasty trials

(Figure 2). High risk of bias was attributed to lack of masking of treatment status and outcome assessment and attrition bias (Figure 3). Twenty-six studies had moderate risk of bias, mostly due to inadequate allocation concealment and masking of treatment status and outcome assessment (Figure 3).

Figure 2. Distribution of the Risk of Bias across Included Studies

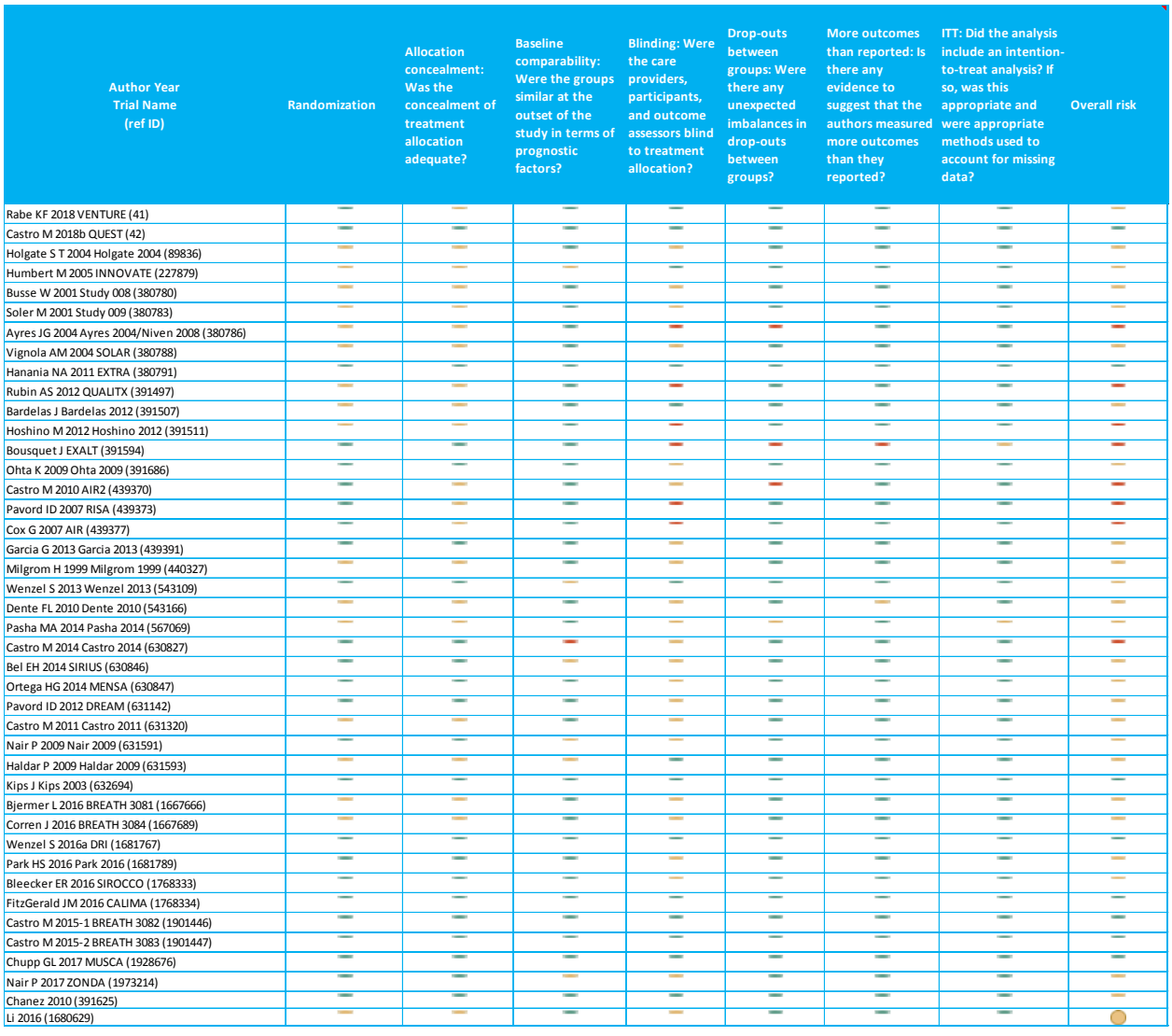
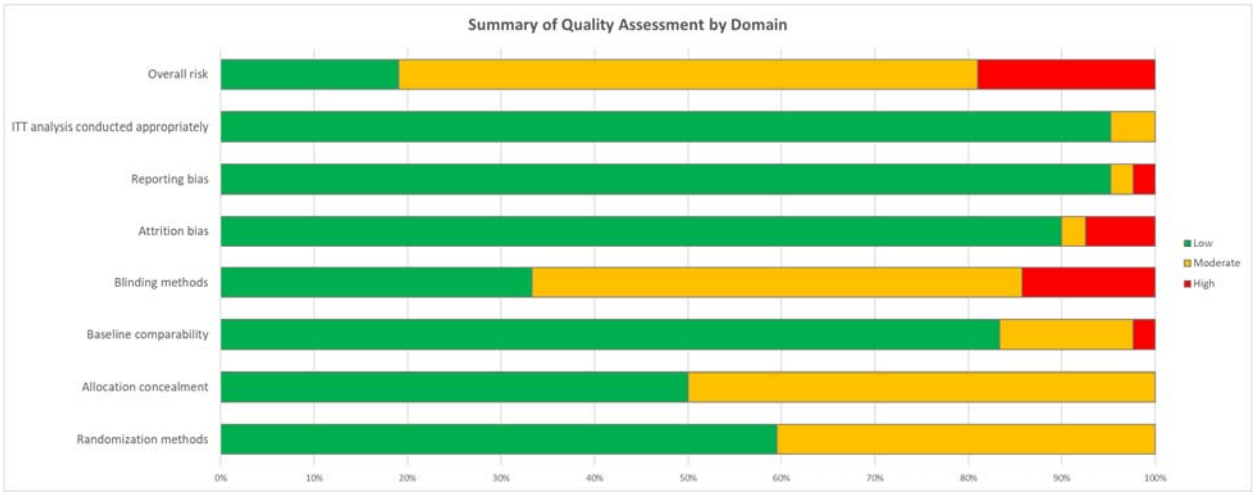


Figure 3. Quality Assessment for the Identified RCTs (Qualitative Summary)



A6. CS Figure 6: Was the 1 trial identified by hand searching the TRAVERSE OLE or NCT02501629 (Reslizumab, mentioned in N.3.1)? Was NCT02501692 subject to quality assessment and if so, where is this reported?

The additional trial identified in Figure 6 of the CS refers to TRAVERSE OLE (see question A3 above. The study is on-going and therefore not published. It was manually retrieved and included for completeness, however it was not included in quantitative outcomes analysis (ITC or pooling) nor assessed for quality as it is not published.

Outcome definitions

A7. The footnotes to CS Table 10 include outcome definitions. Please would the company confirm that any patient needing to use systemic corticosteroids for 3 or more days or who required hospitalisation or an A&E visit because of asthma requiring corticosteroids would meet the criteria for experiencing a loss of asthma control event and the criteria for a severe exacerbation.

A loss of asthma control (LOAC) event during the study (QUEST- EFC 13579) is 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 FEV1 compared with baseline; Increase in ICS dose ≥4 times than the dose at Visit 2; A decrease in AM or PM peak flow of 30% or more on 2 consecutive days of treatment, based on the defined stability limit. The Treatment Period stability limit is defined as the respective mean AM or PM PEF obtained over the last 7 days prior to randomization (Day1);
- Severe exacerbation event

In the model, moderate exacerbations exclude severe exacerbations to avoid double-counting.

A8. More extensive EQ-5D results are reported for DRI2544 and QUEST (CS Figures 11, 20) than for VENTURE (CS Table 31). Please provide all available EQ-5D results for these trials.

EQ-5D results are presented in the Appendices.

A9. Please provide references for the sources of the MCIDs for the patient-reported outcomes (ACQ-5, AQLQ, RQLQ, HADS, SNOT-22) reported for the QUEST trial in Appendix L. Please confirm whether the reported MCID for ACQ-5 as used in QUEST is the same as the MCID for ACQ-7.

ACQ

Juniper (13) et al. and Juniper et al. (14) investigated the interpretation of ACQ scores by deriving estimates of minimal important difference (MID), defined as clinically important changes over time (i.e., difference over time). Using estimates from a geometric mean regression model (in which ACQ change scores were predicted from Mini AQLQ change scores) conducted with data collected with adults aged 18 to 81 years with asthma, Juniper (13) reported an MID of approximately 0.50 for both the ACQ-7 and ACQ-5 (geometric mean values of 0.46 for the ACQ-7 and 0.52 for the ACQ-5). Juniper (14) confirmed this threshold of 0.50 with data collected from a sample of patients aged 6 to 16 years, using a similar geometric mean regression model.

Nguyen (15) used a combination of anchor- and distribution-based approaches to recommend an MID of 0.40 in a sample of patients with asthma aged 6 to 17 years. Individual estimates for patients aged 12 to 17 years ranged from 0.35 (distribution based) to 0.54 (anchor based).

Overall, these findings suggest that the recommended threshold of 0.50 for important change is an appropriate threshold to define an improvement in ACQ-7 and ACQ-5 scores in the dupilumab clinical trials.

AQLQ

According to the developers, the AQLQ was designed to be "sensitive to small within-subject changes over time and therefore appropriate for capturing the effect of an intervention in a clinical trial" (16) [p. 832]. Using data collected in an 8-week study of 37 patients with asthma aged 16 to 60 years (16), Juniper et al. (17) computed thresholds to establish meaningful change (referred to as the MID) in the AQLQ overall, activity limitations, symptoms, and emotional function scores (a threshold for the environmental exposure domain was not computed).(17) Specifically, four Global Ratings of Change items (i.e., activity limitations, symptoms, emotions, and overall quality of life) ranging from –7 (a very great deal worse) to 7 (a very great deal better) were used as anchor measures for the changes in the corresponding AQLQ score. Patients were grouped based on the magnitude of their global score (i.e., no change [0 or 1], minimal change [2 or 3], moderate change [4 or 5], and large change [6 or 7]), and the mean change in the corresponding AQLQ scale was computed per global-based subgroup. This anchorbased approach yielded a minimal important AQLQ change close to 0.50 for all scales (0.47 [activity], 0.49 [symptoms], 0.58 [emotional], and 0.52 [overall]).

Based on the above evidence, 0.50 is considered an appropriate threshold to define an improvement in AQLQ(S) scores.

RQLQ

A clinically important change on the RQLQ total was estimated using an anchor-based approach in 60 patients with moderate to severe rhinoconjunctivitis. (18) A mean RQLQ total change score of 0.57 was reported for those patients who had a change of –3, –2, 2, or 3 points on a global rating of change (15-point scale, where

+7 = a very great deal better, 0 = no change, and –7 = a very great deal worse). The

authors recommended that score changes of approximately 0.5 on the RQLQ can be

considered clinically important.

A similar anchor-based approach was subsequently used to estimate an MID for the RQLQ(S) using data from 83 patients with current symptoms of rhinoconjunctivitis. A mean change of 0.48 was reported for the RQLQ(S) total for those patients who had a change of –3, –2, 2, or 3 points on the global rating of change, providing further support for the 0.5 threshold for a clinically important change. (19)

From the evidence presented, 0.50 is considered an appropriate threshold to define an improvement in RQLQ(S)+12 scores.

SNOT-22

The MID on the SNOT-22 (defined by the authors as the

change in scores that a group of patients can detect as a real improvement) was investigated by evaluating SNOT-22 change scores in relation to a global rating of change (5-point scale:

1 = ‘much better’, 2 = ‘a little better’, 3 = ‘about the same’, 4 = ‘a little worse’, and

5 = much worse’) 3 months after surgery to treat CRS with or without nasal polyposis.

The authors calculated the MID as being 8.9, based on the difference in mean change scores for patients who reported their symptoms to be ‘a little better’ (9.5) and those who reported their symptoms were ‘about the same’ (0.6). Thus, a change score of 8.9 points or above reflects a meaningful improvement for patients. (20)

HADS

As described in the previous section, it was confirmed that the HADS performs well as a screening tool for identification of anxiety disorders and depression and provided evidence that the optimal balance between sensitivity and specificity for HADS as a screening instrument was achieved at a cut-off score of 8 or more for both the anxiety and the depression subscales (Bjelland et al., 2002). Accordingly, a score of 8 or more on the HADS anxiety or the HADS depression subscale is considered to be indicative of anxiety or depression, respectively.

A10. Please provide a description of the scale and MCID for the utility index AQL-5D (as referred to in CS Table 61).

AQL-5D is a 5-dimension, 5-level health state classification system, derived from the Asthma Quality of Life Questionnaire (AQLQ).

The AQLQ is a 32-item instrument that was designed to assess HRQOL in patients with asthma. It comprises of a series of questions across 4 domains: symptoms (12 items), activity limitations (11 items), emotional function (5 items), and environmental stimuli (4 items). For each item, the respondent is asked to choose from a series of 7 levels, ranging from extreme problems (level 1) to no problems (level 7). The overall score is derived from the mean across all 32 items, and each domain score is derived from the mean of the items comprising the domain. Total and domain scores range from 1 to 7, with higher scores denoting better HRQOL. This potentially generates too many states for valuation and states that would be too large for valuation using choice-based preference elicitation techniques. The AQLQ cannot be used in economic evaluation as its scoring is not preference-based. The MCID reported for AQLQ is 0.5.

AQL-5D, which is derived from the Asthma Quality of Life Questionnaire (AQLQ), is a preference-based measure for asthma. This measure enables AQLQ data to be used to generate utility values for use in economic evaluation.(21) Rasch models were applied to samples of responders to the AQLQ with the aim of selecting a number of items for a preference-based utility measure (AQL-5D).(22) Selection of items for the evaluation survey was supported with classical psychometric criteria for item selection (feasibility, internal consistency, floor and ceiling effects, and responsiveness). The five dimensions of AQL-5D are: concern about asthma, shortness of breath, weather and pollution stimuli, sleep impact and activity limitations. Each of these dimensions has 5 levels of severity, which ranges from 1 (no problem) to 5 (extreme problem). The classification system overall describes 3125 states. The AQL-5D scale ranges from 0 (dead) to 1 (full health). All AQLQ health states which contain the five items can be mapped on to the newly defined AQL-5D.

In the valuation study, 98 health states were selected out of the 3,125 possible health states defined by the classification. (21) These health states were valued by a sample of 307 members of the UK general population using time-trade-off. Models were estimated to predict all possible 3,125 health states.

A11. **HRQoL and asthma control results are reported for ITT analyses but there are missing data (e.g. for EQ-5D in CS Figures 11 and 20; ACQ-5 in CS Figure 10; ACQ-7 in CS Figure 19; and for a range of HRQoL instruments and ACQ versions in Appendix L). Please explain the data imputations/assumptions used in each analysis to achieve the ITT population.**

No data imputations were used. At each timepoint, only available data were used to determine the HRQoL and asthma control results.

A12. **For the analyses of ACQ and AQLQ the table footnotes are worded slightly differently, making it not fully clear whether the same covariates and stratification factors were applied in the analyses in each of the three trials (e.g. Appendix Tables 57, 67, 70 for AQLQ; Appendix Tables 53, 65 for ACQ). Please clarify whether the analyses were the same in each trial and, if not, why.**

The following covariates were used for the 3 studies:

treatment groups, regions, baseline EOS level subgroups (study-dependent categories), visits, treatment-by-visit interaction, baseline ACQ or AQLQ value, baseline-by-visit interaction

The following study-dependent covariates were added:

<u>QUEST:</u>

Baseline ICS dose (stratification factor)

Age, since Quest included 5.6% adolescent patients; in the other studies, age was not added as a covariate since there were 1.4% adolescents included in Venture and no adolescents in DRI)

VENTURE:

Baseline optimised OCS dose (stratification factor)

In the MMRM, an unstructured correlation matrix was used to model the within-patient errors in the 3 studies.

Indirect treatment comparison – Bucher methodology

A13. Priority question: Subgroup dupilumab data were generated by matching dupilumab patient data to the patient phenotypes for the approved US/global labels of the comparator biologics. Please would the company comment on how similar the patients included in the trials of comparator biologics were to the relevant US/global labels (i.e. how similar were the patients in the mepolizumab trials to the US/global mepolizumab label?).

The US/global labels for each comparator of interest were used initially to identify the patient phenotypes that were important to match. However, labels alone did not serve the basis for the dupilumab subgroups selected, rather the patients (inclusion criteria and baseline values) in the registrational trials were matched as closely as possible.

The US labels are consistent for all comparators of interest, indicating each biologic of interest as add-on maintenance treatment for patients with severe asthma with an eosinophilic phenotype. The mepolizumab and benralizumab labels require patients to be 12 years and older, while the reslizumab label requires patients to be 18 years and older. We therefore used these age thresholds as criteria for the dupilumab subgroups. Since eosinophilic phenotype is not defined in the labels, the criteria in the comparator trials was used to match dupilumab patients as closely as possible. Comparisons to mepolizumab were limited by the fact that the mepolizumab trials included patients with baseline EOS ≥150 cells/μL or EOS ≥300 cells in the prior year, while the dupilumab trials did not select patients on the basis of EOS status, nor did they collect data on EOS levels in the prior year. Furthermore, the mepolizumab trials included patients who were receiving maintenance OCS, which was not permitted in the dupilumab trials. Given these differences, it was not

possible to create dupilumab subgroups that fully aligned with the populations assessed in the mepolizumab trials.

A14. Bucher and Bayesian ITCs (Appendix N.2.3). The final sentence of Appendix N section 2.3 appears to indicate that Bayesian analyses were conducted but the ERG has not found any methodological details or results reported. Please confirm that no Bayesian pairwise or network ITC results are reported in the company's submission or used in the economic model.

That is correct. The Bayesian analyses are not presented nor used in the economic model.

A15. Priority question: Appendix N.6 appears to provide the reported study data for severe exacerbations (e.g. Table 91) which was used for each of the ITCs (e.g. Figure 35). Please would the company explain the reason for the slight differences that can be observed between the reported individual study data and the individual study outcomes reported in the corresponding figures.

Arm-level data was used instead of contrast-level data, because of the desire to be consistent in analysis strategy across subgroups/outcomes (not all of which reported contrast-level results). While point estimates match, we are aware there are sometimes slight discrepancies in 95% interval width, with contrast data usually having slightly narrower intervals. Thus, the results we provide are sometimes conservative with regards to conclusions of statistical significance (as with contrast-level data, the intervals would probably be very slightly narrower).

A16. Priority question: In several of the tables in Appendix N (e.g. Appendix N Tables 94, 97, 101) a footnote states "person years were calculated for all trials, except the dupilumab trials". Please clarify this statement and provide calculations. For clarity, please present the number of events in the ITC inputs tables (i.e. Tables 91, 92, 94, 95, 97, 101, 105). Please also explain why a logistic regression approach was preferred over a Poisson regression to account for different length of follow-up.

When necessary (i.e., for the non-dupilumab trials), person-years were estimated as the # years of follow-up multiplied by the # of patients analysed for efficacy. All rates of severe exacerbations used were as reported by the literature (most using Poisson or Negative Binomial models). We have updated the tables to include # of events, when reported (unfortunately, most non-dupilumab studies did not report # of

events). Poisson or negative binomial regressions were used by Regeneron/Sanofi to estimate the (adjusted) arm-level annualized rates, and a Poisson model was used to estimate the variance for each contrast between rates. The ITC is not based on a logistic regression approach.

Tables 91, 92, 94, 95, 97, 101, 105 have been modified to include number of events, below.

Table 3: Mepolizumab-like label (mepolizumab 75 mg scenario analysis): Reported study data for severe exacerbations (uncontrolled persistent asthma trials)

Trial	Treatment	Follow-up (weeks)	Person-years	N	# events	Rate (95% CI)	RR (95% CI)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

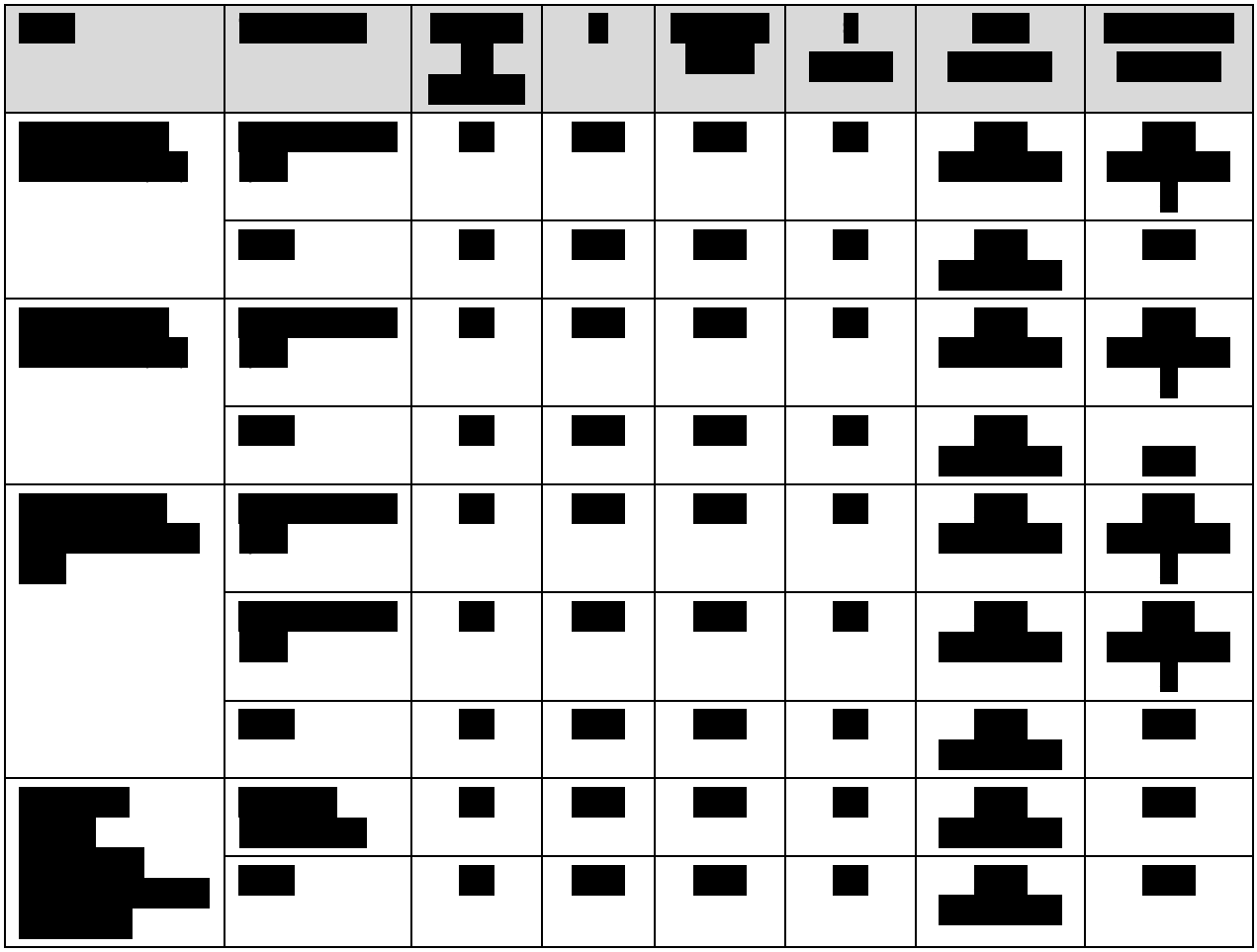
Abbreviations: CI, confidence interval; CSR, clinical study report; DUPI, dupilumab; EOS, eosinophil; MEPO, mepolizumab; NR, not reported; PBO, placebo; q2w, every two weeks; q4w, every four weeks; RR, rate ratio; SC, subcutaneous.
Note: Person-years were calculated for all trials, except the dupilumab trials.

Table 4: Mepolizumab-like subgroup: Reported study data for severe exacerbations

Trial	Treatment	Follow-up (weeks)	N	Person-years	# events	Rate (95% CI)	Rate Ratio (95% CI)*
QUEST 300, CSR DUPI data (27)	300 mg q2w	52	32	27.9	22	0.71 (0.39, 1.29)	0.37 (0.16, 0.82)
	PBO	52	24	20.7	48	1.95 (1.05, 3.59)	ref
QUEST 200, CSR data (27)	DUPI 200 mg q2w	52	30	29.7	22	0.69 (0.37, 1.30)	0.28 (0.13, 0.62)
	PBO	52	22	21	58	2.48 (1.37, 4.48)	ref
DRI, CSR data (23)	DUPI 300 mg q2w	24	14	5.7	3	0.60 (0.15, 2.42)	0.28 (0.07, 1.16)
	DUPI 200 mg q2w	24	9	4.1	2	0.41 (0.07, 2.53)	0.19 (0.03, 1.19)
	PBO	24	15	6.8	7	2.14 (0.86, 5.29)	ref
MENSA, NICE Committee Report (28)	MEPO 100 mg q4w SC	32	54	NR	NR	1.22 (NR, NR)	0.39 (0.23, 0.67) †
	MEPO 75 mg q4w IV	32	48	NR	NR	1.20 (NR, NR)	0.39 (0.22, 0.68) †
	PBO	32	45	NR	NR	3.10 (NR, NR)	ref

Abbreviations: CI, confidence interval; CSR, clinical study report; DUPI, dupilumab; IV, intravenous; MEPO, mepolizumab; NICE, National Institute for Health and Care Excellence; NR, not reported; PBO, placebo; q2w, every 2 weeks; q4w, every 4 weeks; SC, subcutaneous.
*The estimates of RRs, adjusted for patient-level covariates fitting negative binomial models in all studies, were analysed; † Pooled estimates of mepolizumab 100 mg vs. placebo and mepolizumab 75 mg vs placebo obtained assuming correlation of 0.5 between them.

Table 5: Reslizumab-like label: Reported study data for severe exacerbations (uncontrolled persistent asthma trials)



Abbreviations: CI, confidence interval; CSR, clinical study report; DUPI, dupilumab; NR, not reported; PBO, placebo; q2w, every 2 weeks; q4w, every 4 weeks; RESLI, reslizumab.
*RRs presented by study were adjusted for patient-level covariates in a negative binomial model; *Castro 2015 reported pooled patients baseline and outcome for two BREATH trials, which were used in the ITC as one data input.
Note: Person-years were calculated for all trials, except the dupilumab trials.

Table 6. Reslizumab-like subgroup: Reported study data for severe exacerbations

Trial	Treatment	Follow-up (weeks)	N	Person-years	# events	Rate (95% CI)	Rate ratio (95% CI)*
QUEST 300, CSR data (27)	DUPI 300 mg q2w	52	55	50	13	0.29 (0.16, 0.51)	0.21 (0.10, 0.43)
	PBO	52	30	29.3	20	1.37 (0.86, 2.18)	ref
QUEST 200, CSR data a (4)	DUPI 200 mg q2w	52	43	41.4	10	0.31 (0.17, 0.58)	0.16 (0.08, 0.34)
	PBO	52	33	32.3	21	1.89 (1.25, 2.87)	ref
DRI, CSR data (23)	DUPI 300 mg q2w	24	13	5.2	2	0.33 (0.06, 1.87)	0.14 (0.02, 0.89)

Trial	Treatment	Follow-up (weeks)	N	Person-years	# events	Rate (95% CI)	Rate ratio (95% CI)*
	DUPI 200 mg q2w	24	15	6.5	8	1.17 (0.38, 3.66)	0.50 (0.14, 1.75)
	PBO	24	14	6.3	15	2.34 (0.96, 5.68)	ref
BREATH, Poster (30)	RESLI 3.0 mg/kg q4w IV	52	67	NR	NR	1.21 (NR, NR)	0.33 (0.22, 0.49)
	PBO	52	91	NR	NR	3.71 (NR, NR)	ref

Abbreviations: CI, confidence interval; CSR, clinical study report; DUPI, dupilumab; IV, intravenous; NR, not reported; PBO, placebo; q2w, every 2 weeks; q4w, every 4 weeks; RESLI, reslizumab; ref, reference.
*The estimates of RRs, adjusted for patient-level covariates fitting negative binomial models in all studies, were analysed.

Table 7. Benralizumab-like label: Reported study data for severe exacerbations (uncontrolled persistent asthma trials)

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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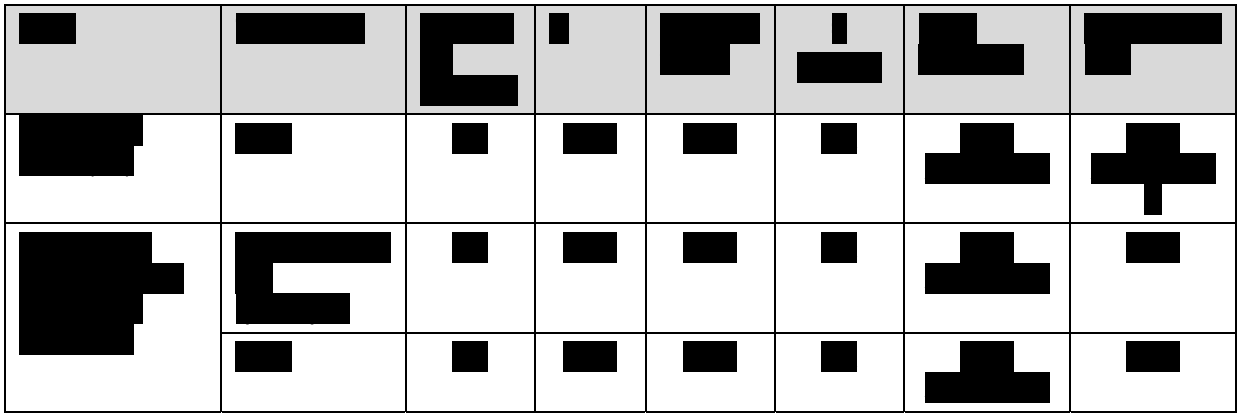


Abbreviations: BENRA, benralizumab; CI, confidence interval; CSR, clinical study report; DUPI, dupilumab; ICS, inhaled corticosteroid; NR, not reported; PBO, placebo; q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; RR, rate ratio.
*RRs presented by study were adjusted for patient-level covariates in a negative binomial model; ** Data from SIROCCO(31) and CALIMA(32) were not available for the full ITT population; therefore, data for a subgroup of patients with baseline EOS ≥300 were included.
Note: Person-years were calculated for all trials, except the dupilumab trials.

Table 8: Mepolizumab-like Subgroup: Reported Study Data for Severe Exacerbations on the Treatment Period (OCS-dependent Asthma Trials)

Trial	Treatment	Follow-up (weeks)	N	Person-years	# events	Rate (95% CI)	RR (95% CI)
SIRIUS, Bel 2014 (33)	MEPO 100 mg q4w	24	66	31.8	NR	1.44 (NR)	0.68 (0.47, 0.99)
	PBO	24	69	30.5	NR	2.12 (NR)	ref
VENTURE, CSR data (34)	DUPI 300 mg q2w	24	71	32.5	21	0.68 (0.44, 1.04)	0.46 (0.27, 0.78)
	PBO	24	61	28.1	41	1.48 (1.1, 2.10)	ref

Abbreviations: CI, confidence interval; CSR, clinical study report; DUPI, dupilumab; MEPO, mepolizumab; NR, not reported; PBO, placebo; q2w, every 2 weeks; q4w, every 4 weeks; RR, rate ratio.
*RRs presented by study were adjusted for patient-level covariates in a negative binomial model.
Person-years were calculated for all trials, except the dupilumab trials.

Table 9: Benralizumab-like subgroup: Reported study data for severe exacerbations on the treatment period (OCS-dependent asthma trials)

Trial	Treatment	Follow-up (weeks)	N	Person-years	# events	Rate (95% CI)	RR (95% CI)
ZONDA, Nair 2017 (35)	BENRA 30 mg q4w>q8w	28	73	39.3	NR	0.54 (0.34, 0.88)	0.30 (0.17, 0.53)
	PBO	28	75	40.4	NR	1.83 (1.33, 2.50)	ref
VENTURE, CSR data (36)	DUPI 300 mg q2w	24	30	13.5	6	0.61 (0.28, 1.34)	0.25 (0.11, 0.60)

	PBO	24	27	12.4	26	2.41 (1.54, 3.78)	ref

Abbreviations: BENRA, benralizumab; CI, confidence interval; CSR, clinical study report; DUPI, dupilumab; NR, not reported; PBO, placebo; q2w, every 2 weeks; q4w, every 4 weeks; q8w, every 8 weeks; RR, rate ratio.
*RRs presented by study were adjusted for patient-level covariates in a negative binomial model.
Note: Person-years were calculated for all trials, except the dupilumab trials.

A17. The footnote to Appendix N Table 94 states that data from two BREATH studies were pooled as one. Please confirm it was not possible to include BREATH 3082 and BREATH 3083 as separate studies and meta-analyse prior to inclusion in the Bucher ITC.

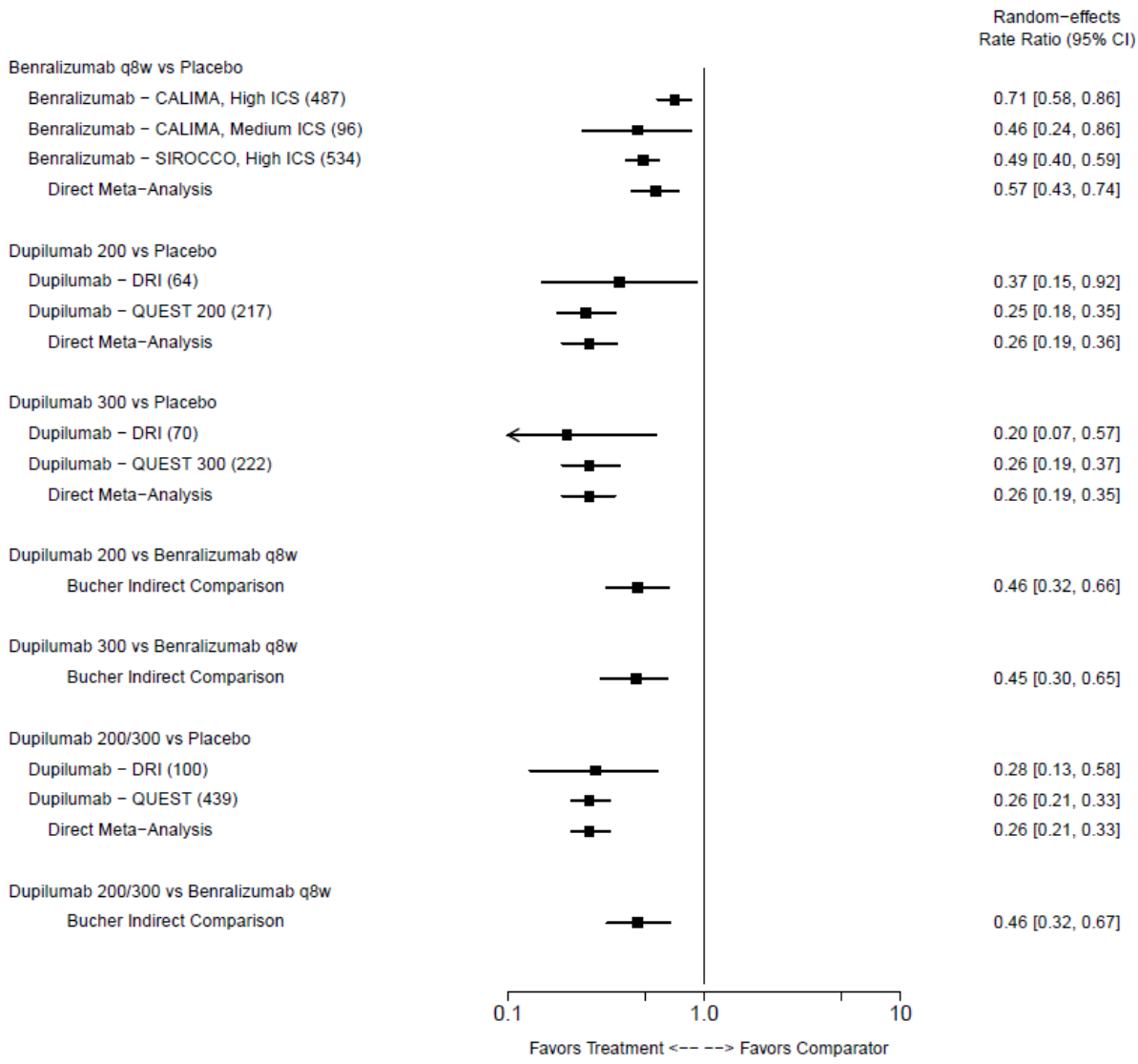
Pooled results from two BREATH programs were used only for the comparison with reslizumab on severe exacerbations, as separate data were not available for this outcome. For FEV1 and other outcomes, separate data were available and used.

A18. Priority question: Please provide R code for the Bucher ITCs

The code is provided in a separate confidential file.

A19. Appendix N 6.5.1 Please present the forest plot for the dupilumab vs benralizumab ITC

Figure 4: Benralizumab-like Label: Forest Plot of Bucher RE ITC Results for Severe Exacerbations (Uncontrolled Persistent Asthma Trials)



A20. Appendix N.2.3.1.2 states that the I^2 statistic would be used to evaluate statistical heterogeneity but I^2 values are not reported although heterogeneity is alluded to in the text (e.g. last paragraph of N.6.2 states “there were signs of heterogeneity between results for QUEST and DRI”). Please report the I^2 statistics for each of the analyses.

Table 10: I2 Statistics for heterogeneity testing

Comparator	Outcome	Time	Comparison	k	Q.pval	I2
Mepolizumab	SevExacerb	Annualized	Mepo vs Placebo	3	0.48369	0
			Dupi 200 vs Placebo	2	0.42646	0
	FEV1	12wk	Dupi 200 vs Placebo	2	0.45418	0
	FEV1	24wk	Dupi 200 vs Placebo	2	0.51593	0
	ACQ5	24wk	Mepo vs Placebo	2	0.80652	0
			Dupi 200 vs Placebo	2	0.04965	74
Reslizumab	SevExacerb	Annualized	Dupi 200 vs Placebo	2	0.8845	0
	FEV1	12wk	Resli q4w vs Placebo	5	0.22506	30.1
			Dupi 200 vs Placebo	2	1	0
	FEV1	24wk	Resli q4w vs Placebo	2	0.37665	0
			Dupi 200 vs Placebo	2	0.70292	0
	AQLQ	24wk	Resli q4w vs Placebo	2	0.8198	0
			Dupi 200 vs Placebo	2	0.06857	69.9
Benralizumab	SevExacerb	Annualized	Benra q8w vs Placebo	3	0.02019	66.6
			Dupi 200 vs Placebo	2	0.41281	0
	FEV1	12wk	Benra q8w vs Placebo	2	0.65946	0
			Dupi 200 vs Placebo	2	0.82589	0
	FEV1	24wk	Benra q8w vs Placebo	2	0.86378	0
			Dupi 200 vs Placebo	2	0.81749	0
	ACQ6	24wk	Benra q8w vs Placebo	2	0.741	0

Indirect treatment comparison – MAIC methodology

A21. Were Simulated Treatment Comparisons considered as an alternative to MAIC?

Methods of indirect treatment comparison of existing severe asthma biologics were discussed in detail during the benralizumab NICE appraisal. To determine the most appropriate methodology to compare technologies for the dupilumab submission, independent expert advice was sought from [redacted], the summary of which is reported here:

"Since in each case IPD would be available for the dupilumab study then a MAIC or STC could be conducted for each to ensure that any indirect treatment effect estimate took account for differences in the patient populations in the two trials which went into the MAIC/STC [1]. However, there are also a number of considerations which need to be taken into account. Firstly is the degree to which a MAIC/STC could allow for trial-to-trial differences – this is driven via the information available on the trials only reporting summary aggregate results, i.e. the inclusion/exclusion criteria and baseline population data (assuming that such information is readily available in the IPD for the dupilumab studies). Both MAIC and STC approaches

also assume that any observed differences between the trials can be explained by the covariates available, i.e. they break randomisation (also termed *unanchored*) unlike the NMA meta-regression techniques described above. A further consideration is the choice between MAIC and STC, though whilst from a methodological perspective both approaches should yield similar results there is empirical evidence that both NICE Appraisal Committees and ERGs are unfamiliar with STC and favour MAIC [5]. […]

On balance, for this particular decision problem, and without further evidence (i.e. regarding an expanded network of evidence), it is my opinion that a MAIC approach would be more likely to be accepted. In fact, it is one of the most clear cut examples I have encountered of where a MAIC approach *is* the preferred option."

A22. Priority question: Please explain the function of the data filters applied to the dupilumab data (Appendix O Table 106 and 107). How were these filters chosen and what was their relationship to the effect modifiers? E.g. For mepolizumab the data filters were medium/high ICS (not in the KOL set of effect modifiers) and number of exacerbations in the past year ≥2 (exacerbations is in the KOL set of effect modifiers).

The data filters applied to the dupilumab trials are separate to the set of effect modifiers, and are based on the comparator trials' patient inclusion/exclusion criteria. In comparison to comparator trials, dupilumab trials recruited a broader patient population with no biomarker requirement, patients aged 12 and over and ≥ 1 severe asthma exacerbations in the previous 12 months. These filters are applied to include dupilumab patients in the MAIC who may have been eligible for inclusion in the comparator clinical trials focusing on ICS/LABA level, blood EOS level, number of prior exacerbations in the past year and age. Please note that although ICS/LABA and age were not confirmed as effect modifiers by clinical experts, it was decided to focus the indirect comparisons on populations with similar population characteristics with respect to these factors to increase comparability between study populations. In most cases these criteria could be fully matched, however, in some cases only similar criteria could be used. For example, patients in the MENSA and MUSCA ITT populations (mepolizumab) could either have baseline blood EOS ≥150 cells/µl or blood EOS in the last 12 months ≥300 cells/µl. Since data on blood EOS in the last

12 months were not reported in the QUEST and DRI trials (dupilumab), the MAIC analyses in these populations matched the proportion of patients with baseline blood EOS ≥150 cells/µl without excluding patients with EOS <150 cells/µl from the analyses.

As this initial filtering step matched populations with respect to the minimum blood EOS levels and the minimum number of exacerbations in the past year, both Bucher ITCs and MAICs were adjusted to some extent for population differences between trials. Then, in addition to matching the general profiles of the comparator populations, the MAIC further adjusted dupilumab populations for potential differences in as many as possible attributes of the distributions (e.g. mean, SD, medians, proportion of patients above certain thresholds) of effect modifiers validated by the KOL (blood EOS level, number of prior exacerbations in the past year, FeNO and presence of nasal polyps).

Additional information has been included in Tables 106 and 107 of Appendix O to report the population characteristics of the comparator trials to facilitate comparison with the data used from the dupilumab trials.

Table 11: Dupilumab and comparator trial data included in the primary MAIC analyses in uncontrolled persistent asthma

	Comparator data			Dupilumab data after filtering						MAIC analyses
Population/ subgroup	**Available data**	**Treatment Sample size**	**Placebo sample size**	**Filters applied to dupilumab data**	**IPLD**	**dupilumab dose**	**dupilumab sample size before matching**	**Placebo dose**	**Placebo sample size before matching**	**Primary outcomes**
Mepolizumab										
MENSA (ITT)	- Medium or High ICS/LABA below 18 years and High/LABA over 18 years - Baseline blood EOS ≥150 cells/µL or blood EOS ≥300 cells/µL in past year - Number of exacerbations in the past year ≥2 - Age≥12	194	191	- Medium or High ICS/LABA below 18 years and High/LABA over 18 years - Number of exacerbations in the past year ≥2	Pooled DRI† and QUEST	200 mg	223	2.0 mL in DRI and 1.4 mL in QUEST	150	Exacerbations, CFB in FEV_1 24W
DREAM (ITT)	- High ICS/LABA - Raised peripheral blood EOS (≥300 cells/µL), sputum EOS (≥3%), exhaled nitric oxide (≥50 ppb) or prompt	153	155	- High ICS/LABA - Number of exacerbations in the past year ≥2	Pooled DRI† and QUEST	200 mg	213	2.0 mL in DRI and 1.4 mL in QUEST	142	Exacerbations, CFB in FEV_1 12W, 24W

	Comparator data			Dupilumab data after filtering						MAIC analyses
	deterioration of asthma control following a ≥25% reduction - Number of exacerbations in the past year ≥2 -Age≥12 and Age≤74									
MUSCA (ITT)	- Medium or High ICS/LABA below 18 years and High ICS/LABA over 18 years - Baseline blood EOS ≥150 cells/µL or blood EOS ≥300 cells/µL in past year - Number of exacerbations in the past year ≥2 - Age≥12	274	277	- Medium or High ICS/LABA below 18 years and High ICS/LABA over 18 years - Number of exacerbations in the past year ≥2	Pooled DRI† and QUEST	200 mg	223	2.0 mL in DRI and 1.4 mL in QUEST	150	Exacerbations, CFB in FEV_1 12W, 24W
Benralizumab										
CALIMA (EOS ≥300)	- High ICS/LABA - Baseline blood EOS level ≥300 cells/µl - Number of	239	248	- High ICS/LABA - Baseline blood EOS level ≥300 cells/µl - Number of	Pooled DRI† and QUEST	200 mg	101	2.0 mL in DRI and 1.4 mL in QUEST	68	Exacerbations, CFB in FEV_1 12W, 24W

	Comparator data			Dupilumab data after filtering						MAIC analyses
	exacerbations in the past year ≥2 - Age≥12			exacerbations in the past year ≥2						
SIROCCO (EOS ≥300)	- High ICS/LABA - Baseline blood EOS level ≥300 cells/µl - Number of exacerbations in the past year ≥2 - Age≥12	267	267	- High ICS/LABA - Baseline blood EOS level ≥300 cells/µl - Number of exacerbations in the past year ≥2	Pooled DRI† and QUEST	200 mg	101	2.0 mL in DRI and 1.4 mL in QUEST	68	Exacerbations, CFB in FEV_1 12W, 24W
Reslizumab										
BREATH 82-83 (ITT)	- Medium or High ICS/LABA - Baseline blood EOS level ≥400 cells/µl - Number of exacerbations in the past year ≥1 - Age≥12	477	476	- Medium or High ICS/LABA - Baseline blood EOS level ≥400 cells/µl - Number of exacerbations in the past year ≥1	Pooled DRI† and QUEST	200 mg	238	2.0 mL in DRI and 1.4 mL in QUEST	156	Exacerbations, CFB in FEV_1 12W, 24W

Table 12: Dupilumab and comparator trial data included in the primary MAIC analyses in OCS-dependent asthma

	Comparator data			Dupilumab data after filtering						MAIC analyses
Population/ subgroup	Available data	Comparator drug sample size	Placebo sample size	Filters applied to dupilumab data	IPLD	dupilumab dose	dupilumab sample size before matching	Placebo dose	Placebo sample size before matching	Primary outcomes
Mepolizumab										
SIRIUS (ITT)	- High ICS/LABA - Baseline blood EOS ≥150 cells/µL or blood EOS ≥300 cells/µL in past year - Age ≥12	69	66	-High ICS/LABA	VENTURE	300 mg	103	2.0 mL	107	≥50% and 100% OCS dose reduction, CFB in FEV_1 24W
Benralizumab										
ZONDA (ITT)	- Medium/high ICS/LABA	73	75	-High ICS/LABA - Baseline blood EOS	VENTURE	300 mg	64	2.0 mL	56	≥50% and 100% OCS dose reduction,

	- Baseline blood EOS ≥150 cells/µL - Number of exacerbations in the past year ≥1 - Age ≥18			≥150 cells/µl - Number of exacerbations in the past year ≥1 - Age ≥18						CFB in FEV_1 24W

Abbreviations: CFB, change from baseline; EOS, eosinophil; FEV_1 = forced expiratory volume in 1 second; ICS, inhaled corticosteroids; IPLD, individual patient level data; ITT, intention to treat; LABA, long-acting beta-agonist; MAIC, matching-adjusted indirect comparison; OCS, oral corticosteroids

A23. Priority question: Please provide post-match patient characteristics for each of the MAIC analyses. Did matching work?

Post-match patient characteristics are provided in a separate Appendix. In all MAIC analyses, the matching was successful. Specifically, the algorithm converged resulting in identical post-matching characteristics between the dupilumab and comparator trials with respect to the selected matching factors.

A24. Priority question: Please provide the Stata, R, and SAS code used for the MAIC ITCs.

The key parts of the programming code that were used to conduct the MAIC/Bucher ITCs are provided as attachments:

- [redacted] Macro to prepare data and execute R code for matching.do
- [redacted] macro for MAIC based on adjusted relative efficacy.R
- [redacted] macro for deriving balancing weights.R

A25. Priority question: Please clarify the "seasonality adjustment" made to the DRI trial (described in Appendix O.3 Methods) and provide calculations.

To adjust for the potential bias incurred by merging QUEST with DRI due to differences in the coverage of calendar months in each trial, seasonality was adjusted for by including $S(t)$ in the linear combination of the regression model as follows: $S(t) = s_1 \sin\left(\frac{2\pi t}{12}\right) + s_2 \cos\left(\frac{2\pi t}{12}\right)$,

where s_1, s_2 are regression coefficients and $t = 1, \ldots, 12$ is calendar month at randomisation.

Additionally, in line with the guidelines by NICE DSU study was included as an additional explanatory variable to account for the clustering of patients within each study. (37)

Statistical methods of the MAIC Analyses, which include the adjustment for seasonality, are shown in the Appendix.

A26. Priority question: Please provide further detail on the matching in the MAIC. Were the placebo arms also matched or was matching done to the pooled arms? If possible, please provide the pre- and post-match characteristics for the placebo arms.

To provide fair comparisons, the matching process in the MAIC analyses was carried out separately for active treatments and placebo arms to ensure that any potential imbalance in baseline characteristics between the treatment arms of a comparator trial due to an unsuccessful randomisation would be mimicked in the weighted data of the dupilumab trials.

The post-match patient characteristics for the full list of available factors are provided for both active treatment and placebo arms in the appendices.

A27. Priority question: Please clarify the process of matching with the KOL set of effect modifiers. Taking the dupilumab vs mepolizumab comparison as an example, Appendix O.3.2.1.1 Table 109 shows the distribution of effect modifiers in the dupilumab and mepolizumab trials active arms. It is clear that not all effect modifiers are reported by all trials (e.g. no FeNO at baseline for MENSA or MUSCA trials) and yet Appendix O.5.1.1.1 shows the effective sample sizes achieved after matching populations on the KOL set of effect modifiers.

The process of matching started with investigating the potential imbalances in all available baseline characteristics, and in particular, effect modifiers. The distribution of the effect modifiers was compared separately across the active arms (dupilumab vs. comparator treatment) and across the control arms (placebo in dupilumab trial vs. placebo in comparator trial). The comparisons across the active arms are presented in Section O.3.2.

Then, balancing weights were derived separately for active treatments and placebo arms so that the reweighted profile of the dupilumab cohort and placebo cohort of the dupilumab trials matched the target active and placebo profile reported in comparator populations with respect to the set of effect modifiers validated by KOLs. When the models producing the balancing weights failed to converge, or the estimated effective sample size was very small, simpler models adjusting on fewer statistics for each effect modifier (e.g., adjusting for means only vs. adjusting for both

means and standard deviations) were investigated. The priority over multiple statistics for a given effect modifier is described below:

1. Adjustment for all statistics was carried out if possible (e.g., mean, standard deviation [SD], median, proportion of patients with values above a certain threshold).
2. If adjustment for all available statistics was not possible, then effort was made to adjust for the largest set of variables giving highest priority to means.
3. If both geometric and arithmetic means were reported, preference was given to the geometric mean.
4. Having ensured that adjustment for means was feasible, higher priority was given for adjustment on SD than medians.

The statistical methods and MAIC matching models are provided in the Appendices.

A28. Priority question: Please provide a histogram of weights for each MAIC

The histograms of balancing weights for each MAIC are provided as Excel files in the appendices.

A29. **Please check the cross referencing in Appendix O.4 and correct if necessary. In two of the subsections for the comparator drugs (O.4.1.1.1 and 0.4.1.1.2) the text states that the MAICs were conducted "by matching the dupilumab data described in Table 114" but Table 114 does not contain any dupilumab data (it is the summary MAIC results for the comparisons with the three comparators).**

Table 114 should not contain dupilumab data. Table 114 shows the data filters applied to the dupilumab trials for the severe asthma trials and OCS-sparing trials to "match" the inclusion criteria for the comparator trials.

Subgroup analyses

A30. CS B.2.7.1 states that subgroup analyses for other endpoints and subgroups for DRI12544, QUEST and VENTURE are presented in Appendix E. Appendix E refers the reader to the CSRs. Please supply the CSRs for DRI12544, QUEST and VENTURE.

The CSRs of DRI12544, QUEST and VENTURE are attached separately.

A31. For all subgroup analyses in QUEST, VENTURE and DRI2544 (i.e. those reported under CS section B.2.6.1.2 by EOS levels, high ICS dose subgroup, and all subgroups referenced to Appendix E):

(a) Please clarify whether the subgroup analyses were pre-specified or post hoc

The list of pre-specified subgroups for the primary endpoints are shown in ***Table 13*** for the QUEST, VENTURE and DRI clinical trials.

Table 13: Trial pre-specified analyses

DRI	QUEST	VENTURE
Age group: Classification 1: [18-65, [65-75[, ≥75 years; Classification 2: [18-65[, ≥65 years	Gender (Male, Female)	Baseline optimized OCS dose strata (≤10mg/day, >10mg/day),
Gender (Male, Female)	Region (Asia: Japan, South Korea and Taiwan; Latin America: Argentina, Brazil, Colombia, Chile and Mexico; East Europe: Hungary, Poland, Russia, Turkey and Ukraine; Western Countries: Australia , Canada, France, Germany, Italy, South Africa, Spain, United Kingdom and USA)	Age group (<40, ≥40 years),
Region (Asia: Japan and South Korea; Latin America: Argentina, Mexico and Chile; East Europe: Poland, Russia, Turkey and Ukraine; Western Countries: USA, South Africa, France, Italy, Spain, New Zealand and Australia)	Territory (North America: Canada and USA; European Union: France, Germany, Hungary, Italy, Poland, Spain and United Kingdom; Rest of World: Argentina, Australia, Brazil, Colombia, Chile, Japan, Mexico, Russia, South Africa, South Korea, Taiwan, Turkey and Ukraine)	Gender (Male, Female),
Race (Caucasian/White, Black, Asian/Oriental, all the other)	Ethnicity (Hispanic, non-Hispanic)	Region (East Europe: Hungary, Poland, Romania, Russia, and Ukraine; Latin America: Argentina, Brazil, Colombia, Chile, and Mexico; Western Countries: Belgium, Canada, Israel, Italy, Netherlands, Spain, and USA)
Background ICS/LABA dose levels at randomization (medium, high)	Baseline blood eosinophil level (≥ 0.3 Giga/L, <0.3 Giga/L; ≥ 0.15 Giga/L, < 0.15 Giga/L)	Race (Caucasian/White, the others)
Baseline FEV1 (≤ median, > median)	Background ICS dose levels at randomization (medium, high)	Baseline pre-BD FEV1 (≤ 1.75L, > 1.75L)
ACQ-5 (≤2, >2)	Background controller type at randomization (ICS and LABA only, ICS and LABA and	baseline predicted FEV1 % (<60%, ≥60%)
Number of asthma events prior to the study (1,>1): asthma exacerbation during 1 year prior to visit 1 defined as any treatment with 1 systemic (oral or parenteral) steroid bursts or more for worsening asthma or hospitalization or an emergency/urgent medical care visit for worsening asthma	Anti-leukotrienes only, Other; ICS, LABA and any third controller, Other)	ACQ-5 (≤ 2, >2),
Baseline weight (≤ 90, > 90 kg)	Baseline FEV1 (≤ 1.75, > 1.75 L)	Weight (< 70, ≥ 70 - < 90, ≥ 90 kg)

BMI (< 30, ≥ 30 kg/m2) Smoking history (Former, Never)	ACQ-5 (≤ 2, >2) Number of severe asthma exacerbation prior to the study as defined in Section 2.1.1 (1,>1) Baseline weight (< 70, ≥ 70 - < 90, ≥ 90 kg; <60, ≥ 60 kg) Baseline BMI (< 25, 25- <30, ≥ 30 kg/m2) Smoking history (Former, Never) Atopic medical condition (Yes, No) Age of onset of asthma (<18, 18-40, >40 years) Baseline predicted FEV1% (<60%, 60%-90%) Baseline periostin(NG/ML) (< median, ≥ median) Baseline fractional exhaled nitric oxide (FeNO) (< 25, ≥25- < 50, ≥50 ppb)	BMI (<25, ≥25 - <30, ≥ 30 kg/m2) Smoking history (Former, Never) Ongoing atopic medical history (Yes, No) Age of onset of asthma (<18, 18-40, >40 years) Number of severe asthma exacerbation within1 year before Visit 1 (≤1,>1) Baseline eosinophil level subgrouping 1 (<0.15 Giga/L or ≥0.15 Giga/L) Baseline eosinophil level subgrouping 2 (<0.3 Giga/L or ≥0.3 Giga/L)

(b) Please confirm whether the statistical power was assessed for subgroup comparisons

Subgroup analyses were not powered, and statistical power was not assessed.

Section B: Clarification on cost-effectiveness data

Population characteristics

B1. Baseline characteristics for trial participants in the base case (QUEST EOS≥150 or FeNO≥25 and ≥3 exacerbations) and scenario (VENTURE EOS≥150 or FeNO≥25 and mOCS) subgroups are provided in Tables 32 and 33 (B.2.7.2.2). Please provide the same information for subgroups in the exploratory analyses in Appendix P:

- QUEST EOS≥300 or FeNO≥25 and ≥4 exacerbations
- QUEST EOS≥400 or FeNO≥25 and ≥3 exacerbations
- VENTURE EOS≥300 and mOCS

Participant characteristics for subgroups included in exploratory analyses are presented in **Error! Reference source not found.** among a population with EOS≥300 or FeNO ≥25 and ≥4 exacerbations, ***Table 14*** among a population with EOS≥400 or FeNO ≥25 and ≥3 exacerbations and ***Table 15*** among a population with EOS ≥ and mOCS.

[redacted]

[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]	[redacted]	
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

Transition probabilities

B2. Priority question: **The model uses time-dependent probabilities for the transitions between the 'Controlled' and 'Uncontrolled' health states (B.3.3.2 and M.1.1). However, on inspection of Table 73 (Appendix M), the transition probabilities between 'Controlled' and 'Uncontrolled' appear similar for the 0-**

12 week and 12-52 week periods in both QUEST treatment groups; time differences may be due to chance. Similarly, it is not evident that the VENTURE control transition probabilities for the 0-12 and 12-24 week periods differ (Appendix M Table 74). The only evidence cited in the submission for time-dependent rates of control is the rate of change in mean ACQ-7 in the QUEST ITT population (CS Figure 19). Please provide statistical evidence comparing rates of 'control' (ACQ < 1.5 and no exacerbation) before and after 12 weeks from the QUEST and VENTURE trials.

Transition probabilities were analysed for the period prior to the first 12 weeks and the period thereafter, as transition probabilities between control states were hypothesized to differ over time a priori, based on evidence on the change in ACQ on a continuous scale. This was considered to be conservative. The Fisher's exact test was used retrospectively, to determine whether the probability of transitioning to the 'Controlled Asthma' state differed in the first 12 weeks of treatment compared to the period beyond 12 weeks.

In the ICS population (QUEST), transition probabilities to the 'Controlled Asthma' health state from each of the four health states included in the model did not differ significantly between 0-12 weeks and 12-52 weeks (***Table 16***). Whilst transition probabilities from individual health states did not differ between the two periods, the overall probability (i.e. from any health state) of transitioning to the 'Controlled Asthma' health state was significantly higher in the period between 12-52 weeks compared to the first 12 weeks among patients treated with dupilumab.

Table 16. Fisher's exact test – Transition probabilities before and after 12 weeks of treatment; ICS population (QUEST) EOS ≥150 OR FeNO ≥25 and ≥3 severe exacerbations

Treatment	Transition probability to 'Controlled Asthma' health state from:	0-12 weeks			12-52 weeks			P-Value
		%	n	N	%	n	N	Two-tailed
Placebo	From any health state	21.70%	23	106	29.14%	95	326	0.1672
	Controlled Asthma	73.33%	11	15	70.21%	66	94	1.0000
	Uncontrolled asthma	14.49%	10	69	11.94%	16	134	0.6595
	Moderate exacerbation	9.09%	1	11	3.13%	1	32	0.4507
	Severe exacerbation	9.09%	1	11	18.18%	12	66	0.6785
Dupilumab	From any health state	32.45%	61	188	47.37%	288	608	**0.0003**
	Controlled Asthma	69.23%	27	39	77.82%	221	284	0.2309
	Uncontrolled asthma	20.18%	23	114	16.74%	36	215	0.4530

	Moderate exacerbation	34.62%	9	26	23.08%	18	78	0.3027
	Severe exacerbation	22.22%	2	9	41.94%	13	31	0.4401
Dupilumab responders	From any health state	36.77%	57	155	52.00%	263	505	**0.0009**
	Controlled Asthma	72.22%	26	36	79.92%	209	261	0.2722
	Uncontrolled asthma	22.34%	21	94	17.93%	29	160	0.5187
	Moderate exacerbation	37.50%	9	24	27.08%	19	71	0.2888
	Severe exacerbation	100.00%	1	1	46.75%	6	13	1.0000

In the mOCS population (VENTURE), the transition probability to the 'Controlled Asthma' health state from the 'Controlled Asthma' health state was significantly lower in the subsequent 12 weeks, compared to the first 12 weeks, among placebo treated patients (29.41% versus 66.67%) (***Table 17***). Among patients treated with dupilumab, the transition probability to the 'Controlled Asthma' state from the 'Uncontrolled Asthma' state was significantly lower in the subsequent 12 weeks, compared to the first 12 weeks.

Table 17. Fisher's exact test – Transition probabilities before and after 12 weeks of treatment; mOCS population (VENTURE) EOS ≥150 OR FeNO ≥25 and mOCS

Treatment	Transition probability to 'Controlled Asthma' health state from:	0-12 weeks			12-24 weeks			P-Value
		%	n	N	%	n	N	Two-tailed
Placebo	Any health state	18.47%	41	222	18.14%	39	215	1.0000
	Controlled Asthma	66.67%	24	36	29.41%	15	51	**0.0009**
	Uncontrolled asthma	6.40%	11	172	10.37%	14	135	0.2152
	Severe exacerbation	42.86%	6	14	34.48%	10	29	0.7388
Dupilumab	From any health state	40.69%	94	231	42.53%	94	221	0.7035
	Controlled Asthma	91.30%	63	69	82.11%	78	95	0.1134
	Uncontrolled asthma	19.61%	30	153	9.48%	11	116	**0.0258**
	Severe exacerbation	11.11%	1	9	50.00%	5	10	0.1409
Dupilumab responders	From any health state	43.90%	90	205	46.23%	92	199	0.6893
	Controlled Asthma	92.54%	62	67	83.70%	77	92	0.1451
	Uncontrolled asthma	20.15%	27	134	10.78%	11	102	0.0729
	Severe exacerbation	25.00%	1	4	80.00%	4	5	0.2063

Since most transition probabilities were not significantly different in the first 12 weeks compared to subsequent weeks of treatment, an argument could be made to use transition probabilities derived over the entire duration of the trial, to reduce uncertainty. Nonetheless, given that some transition probabilities were significantly different, alongside evidence that the trends in change in ACQ (as a continuous outcome) varied over time, it was considered more conservative to use time-dependent transition probabilities to model changes in asthma control.

To examine the influence of this uncertainty, an option has been included in the model to utilize transition probabilities derived over the entire trial duration. Results across these scenarios are displayed in ***Table 18***. As indicated below, use of transition probabilities derived over the entire trial duration improves the ICERs, indicating that the adopted base case is conservative.

Table 18. Scenario Analysis – Time-dependency of transition probabilities

Population	Scenario	Incremental Costs	Incremental QALYs	ICER
ICS population (QUEST) EOS ≥150 OR FeNO ≥25 and ≥3 severe exacerbation	Base Case	[redacted]	[redacted]	£ 28,087
	Transition probabilities derived based on 0-52 weeks for all patients treated with placebo, dupilumab and dupilumab responders	[redacted]	[redacted]	£ 27,229
EOS ≥150 OR FeNO ≥25, and either ≥3 severe exacerbations or mOCS	Base Case	[redacted]	[redacted]	£ 35,486
	Transition probabilities derived based on 0-52 weeks for all patients treated with placebo, dupilumab and dupilumab responders	[redacted]	[redacted]	£ 33,117

B3. Priority question: **Please provide transition probabilities and event counts calculated over the whole trial period for end of trial responders:**

- **QUEST ITT population and model subgroups: please provide data for the 0-52 week period in the same format as for the 12-52 week period (cells E151 to L184 in the 'Data Dupi 200 – Clinical Trials' sheet in the model).**

- **VENTURE ITT population and model subgroups: please provide data for the 0-24 week period in the same format as for the 12-24 week period (cells E141 to T169 in the 'Data OCS – Clinical Trials' sheet in the submitted model).**

Transition probabilities among responders over the entire trial duration in the target population are displayed in Table 19. Data for the ITT population are displayed in Table 20 whilst data for all subgroups considered have been included in the model. An option has been incorporated in the model to utilize data over the entire trial duration for responders. Scenario analysis (as indicated in the response above) show that use of data over the entire trial duration for responders did not alter conclusions. In these scenarios, ICERs were lower.

Table 19. Transition Probabilities (Event Counts) for Dupilumab Responders over whole trial period; EOS ≥150 OR FeNO ≥25 and ≥3 severe exacerbations or mOCS

	Controlled Asthma	Uncontrolled Asthma	Moderate Exacerbation	Severe Exacerbation
ICS population (QUEST) EOS ≥150 OR FeNO ≥25 and ≥3 severe exacerbations				
Controlled Asthma	79.46% (236)	11.11% (33)	7.74% (23)	1.68% (5)
Uncontrolled Asthma	20.08% (51)	62.99% (160)	13.78% (35)	3.15% (8)
Moderate Exacerbation	27.37% (26)	31.58% (30)	40% (38)	1.05% (1)
Severe Exacerbation	50% (7)	35.71% (5)	14.29% (2)	0% (0)
mOCS population (VENTURE) EOS ≥150 OR FeNO ≥25 and mOCS				
Controlled Asthma	87.42% (139)	9.43% (15)	0% (0)	3.14% (5)
Uncontrolled Asthma	16.1% (38)	81.36% (192)	0% (0)	2.54% (6)
Severe Exacerbation	55.56% (5)	44.44% (4)	0% (0)	0% (0)

Table 20. Transition Probabilities (Event Counts) for Dupilumab Responders in the ITT population

	Controlled Asthma	Uncontrolled Asthma	Moderate Exacerbation	Severe Exacerbation
0-12 weeks				
Controlled Asthma	85.07% (302)	8.45% (30)	5.92% (21)	0.56% (2)
Uncontrolled Asthma	26.41% (248)	61.77% (580)	11.29% (106)	0.53% (5)
Moderate Exacerbation	25.4% (32)	38.89% (49)	35.71% (45)	0% (0)
Severe Exacerbation	100% (4)	0% (0)	0% (0)	0% (0)
12-52 weeks				
Controlled Asthma	83.83% (2012)	10.75% (258)	4.88% (117)	0.54% (13)
Uncontrolled Asthma	19.33% (293)	70.12% (1063)	9.89% (150)	0.66% (10)
Moderate Exacerbation	25.22% (116)	35.22% (162)	39.13% (180)	0.43% (2)
Severe Exacerbation	42.86% (12)	39.29% (11)	14.29% (4)	3.57% (1)
0-52 weeks				
Controlled Asthma	83.99% (2314)	10.45% (288)	5.01% (138)	0.54% (15)
Uncontrolled Asthma	22.04% (541)	66.92% (1643)	10.43% (256)	0.61% (15)
Moderate Exacerbation	25.26% (148)	36.01% (211)	38.4% (225)	0.34% (2)
Severe Exacerbation	50% (16)	34.38% (11)	12.5% (4)	3.13% (1)

B4. Priority question: **The explanation of how the background exacerbation rate is adjusted for trial exclusion criteria is difficult to follow (M.2.1). Please state the source of data in Table 75 and provide the number of observations at baseline and end of trial for each category of days since last severe exacerbation. And please provide detailed calculations to explain how the final multiplier of [redacted] was derived.**

The numbers of observations at baseline and at end of trial for each category of days since last severe exacerbation (DSLSE) are provided in Table 21. When evaluating the distribution of DSLSE at baseline (i.e. with exclusion criteria), 35.33% (N=153) of patients had a severe exacerbation in the preceding 90 days. When evaluating the distribution of DSLSE at the end of the trial, among a cohort who experienced ≥3 severe exacerbations during the trial (i.e. proxy for elimination of exclusion criteria), [redacted] of patients had a severe exacerbation in the preceding 90 days.

Table 21: Potential impact of exclusion criteria on severe exacerbation rate

	Patients with ≥3 severe exacerbations in preceding year	
Days since last severe exacerbation	**% baseline**	**% at end of trial**
Number of patients	433	[redacted]
0-30	0.00% (0)	[redacted]
30-60	4.62% (20)	[redacted]
60-90	30.72% (133)	[redacted]
90-120	15.94% (69)	[redacted]
120-150	17.78% (77)	[redacted]
150-180	10.62% (46)	[redacted]
180+	20.32% (88)	[redacted]

These estimates were used alongside estimates from the Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study, which suggest that recent severe asthma exacerbations are a strong independent factor predicting future exacerbations (38). In that study, the odds of experiencing a future severe exacerbation were significantly higher (odds ratio [OR] 2.99 [2.57-3.47]) among patients with a recent severe exacerbation (i.e. steroid burst in preceding 3 months) after adjusting for other risk factors.(38)

Specifically, in the model, the odds ratio of experiencing a severe exacerbation at baseline, as compared to a cohort with no recent severe exacerbation (i.e. a cohort of patients for whom the last severe exacerbation was more than 90 days ago) was estimated as:

$$OR_{Baseline} = 2.99 \times 35.33\% + 1 \times (1 - 35.33\%) = 1.703$$

The odds ratio of experiencing a severe exacerbation when eliminating exclusion criteria (i.e. proxied by using the distribution of DSLSE at trial end), as compared to a cohort with no recent severe exacerbation was estimated as:

[redacted]

The ratio of the two estimates was then assumed to reflect the increase in the risk of severe exacerbation that would have been observed, had exclusion criteria been relaxed.

[redacted]

This estimate does not include any adjustment to account for the protocol definition that an exacerbation must be separated by 28 days or more from the previous event in order to be defined as a separate exacerbation. If so, this would have results in at least a [redacted] increase in exacerbations rates. Therefore, this multiplier is a conservative estimate.

B5. Priority question: **Please provide further information about the binomial regression used to calculate the multipliers for small subgroups in QUEST (P.1.1 Table 123). For each of the four subgroups, please state: the number of people; the number of outcome events; and mean values for covariates. Please also provide diagnostic statistics regarding the model fit and validity.**

The total number of patients, numbers of moderate and severe exacerbation events, numbers of patients achieving response by treatment (dupilumab and placebo) and number of severe exacerbations in the preceding year are displayed in ***Table 22*** below. The binomial regression is based on EOS ≥ 150 to increase sample size.

The same data using patients who achieved response with dupilumab are displayed in ***Table 23***. Mean values for covariates and diagnostic statistics are provided in the appendix.

Table 22: Number of patients and number of outcome events by severe exacerbations in preceding year; All patients with high dose ICS and EOS≥150

Number of severe exacerbations in preceding year	**1**		**2**		**3**		**>=4**	
Treatment	**Placebo**	**Dupilumab**	**Placebo**	**Dupilumab**	**Placebo**	**Dupilumab**	**Placebo**	**Dupilumab**
Total number of patients	49	98	41	65	14	30	22	30
Total patient-years followed	46.6	89.9	36.6	63.6	11.3	27.8	21.2	30
Total number of severe exacerbations events	33	49	53	30	20	20	57	22
Unadjusted annualized rate of severe exacerbations events	0.709	0.545	1.448	0.472	1.777	0.719	2.689	0.734
Adjusted annualized rate of severe exacerbation events	0.693	0.561	1.301	0.443	1.701	0.652	2.473	0.707
Total number of moderate exacerbations events	102	137	74	70	4	45	40	61
Unadjusted annualized rate of moderate exacerbations events	2.19	1.525	2.021	1.1	0.355	1.618	1.887	2.034
Adjusted annualized rate of moderate exacerbation events	2.349	1.46	1.815	1.04	0.439	1.328	1.777	1.986

Total number of responders	NA	67	NA	49	NA	23	NA	26
Unadjusted response rate	NA	68.37	NA	75.38	NA	76.67	NA	86.67
Adjusted response rate	NA	66.77	NA	83.7	NA	87.15	NA	87.18

Table 23: Number of patients and number of outcome events by severe exacerbations in preceding year; Patients with high dose ICS and EOS≥150; Dupilumab responders versus placebo

Number of severe exacerbations in preceding year	**1**		**2**		**3**		**>=4**	
Treatment	**Placebo**	**Dupilumab**	**Placebo**	**Dupilumab**	**Placebo**	**Dupilumab**	**Placebo**	**Dupilumab**
Total number of patients	49	67	41	49	14	23	22	26
Total patient-years followed	46.6	61.7	36.6	47.9	11.3	21.2	21.2	26
Total number of severe exacerbations events	33	0	53	4	20	4	57	10
Unadjusted annualized rate of severe exacerbations events	0.709	0	1.448	0.083	1.777	0.188	2.689	0.384
Adjusted annualized rate of severe exacerbation events	0.668	0	1.337	0.08	1.651	0.179	2.47	0.355
Total number of moderate exacerbations events	102	93	74	48	4	38	40	57
Unadjusted annualized rate of moderate exacerbations events	2.19	1.508	2.021	1.002	0.355	1.789	1.887	2.19
Adjusted annualized rate of moderate exacerbation events	2.352	1.511	1.853	0.978	0.448	1.506	1.804	2.192

Utilities

B6. Priority question: Please provide the number of observations used to estimate the 'controlled asthma' and 'uncontrolled asthma' utility values in CS Tables 60 and 61.

Utility values for the "controlled asthma" and "uncontrolled asthma" health states for the target populations, alongside the number of observations, are presented in *Table 24* below. As indicated in the CS, utilities were derived based on data combined across all arms. Due to the limited number of observations in the severe exacerbation state within the target populations, disutilities associated with exacerbations were based on the ITT population.

Table 24: Trial-based utilities for patients with EOS ≥150 OR FeNO ≥25, and either ≥3 severe exacerbations or mOCS

Population	Health State	EQ-5D			AQL-5D		
		N	Mean	SE	N	Mean	SE
ICS population (QUEST) EOS ≥150 OR FeNO ≥25 and ≥3 severe exacerbations	Controlled asthma	329*	0.906	0.0068	331*	0.943	0.0035
	Uncontrolled asthma	327*	0.735	0.0110	328*	0.801	0.0064
mOCS population (VENTURE) **EOS ≥150 OR FeNO ≥25 and mOCS**	Controlled asthma	95	0.890	0.016	95	0.937	0.007
	Uncontrolled asthma	173	0.713	0.014	173	0.780	0.009

*Fewer EQ-5D observations were available compared to the number of observations on AQLQ

B7. Priority question: **Please provide the CCC disease classification code in Sullivan et al. 2011 for the following disutilities from mOCS-related AEs (CS Table 68): Severe infections; Affective disorders; Cardiovascular events.**

For completeness, the ICD codes used to identify the disutilities associated with each adverse event are provided in Table 25 below. Disutilities associated with herpes zoster and severe infections were sourced from Sullivan 2017.(39) The remaining disutilities were sourced from Sullivan 2011.(40) Where multiple ICD codes were considered relevant, a weighted average disutility was estimates based on the number of observations reported for each ICD code in the source study.

Table 25: Disutilities from mOCS-related AEs

Adverse event	Code	N	Disutility of Condition
Bone-related conditions(40)	ICD-9 733 Oth Bone & Cartilage Dis	2,089	-0.0363
Severe infections(39)	ICD-9 486 pneumonia, organism nos	1,235	-0.0320
Herpes Zoster(39)	ICD-9 486 pneumonia, organism nos	1,235	-0.0320
Hypertension(40)	ICD-9 401 Essential Hypertension	14,766	-0.0460
Diabetes Mellitus(40)	ICD-9 250 Diabetes Mellitus	5,791	-0.0714
Glaucoma(40)	ICD-9 365 Glaucoma	1,290	-0.0385
Cataract(40)	ICD-9 366 Cataract	1,661	-0.0334
Peptic Ulcer(40)	ICD-9 531 Gastric Ulcer	510	-0.0569
	ICD-9 535 Gastritis And Duodenitis	481	-0.0439
	ICD-9 537 Oth Gastroduodenal Dis	795	-0.0684
	Weighted average of codes 531, 535 and 537	1,786	-0.0585
Chronic Kidney Disease(40)	ICD-9 586 Renal Failure Nos	194	-0.1104
Affective disorders(40)	ICD-9 296 Affective Psychoses	527	-0.1269
	ICD-9 311 Depressive Disorder Nec	6,530	-0.1123
	Weighted average of codes 296 and 311	7,057	-0.1134
Cardiovascular events(40)	ICD-9 410 Acute Myocardial Infarct	496	-0.0626

	ICD-9 412 Old Myocardial Infarct	123	-0.0368
	ICD-9 428 Heart Failure	590	-0.1167
	ICD-9 436 Cva	691	-0.1171
	Weighted average of codes 410, 412, 428 and 436	1,900	-0.0976

Abbreviations: ICD: International Classification of Diseases

B8. Priority question: **Please give the correct source for the disutilities in CS Table 68 (Table gives source as Sullivan et al. 2017 whilst model gives source as Lloyd et al. 2007). Please list any assumptions that have been made.**

In both the model and the CS Table 68, the source for disutilities for mOCS related AEs is listed as Sullivan et al. 2017(39) and Sullivan et al. 2011.[40] Lloyd et al. 2007 was used and listed as a source for estimates of disutilities related to exacerbation events. The assumptions that have been made with regards to ICD codes for mOCS related AEs are provided above. No disutility was identified for herpes zoster, therefore the disutility was assumed to be equivalent to that associated with other infections. The zoster quality of life study (ZQOL) conducted in the UK reported EQ-5D values of 0.65 at initial visit and 0.66 at follow-up (7–14 days after)(41). However, the age-matched population norm reported was 0.78 and a disutility of -0.12 appeared high in comparison with the disutility values for the other AEs, therefore adopting this assumption was considered more conservative.

B9. Priority question: **Please provide a list of serious adverse events of grade 3-4 that occurred in the VENTURE and QUEST trials, with the incidence rate by treatment arm.**

Severe adverse events were not graded in the CSRs, so additional data have been requested from biostatistics and will be sent as an addendum tomorrow morning 18th September 2019.

Resources and costs

B10. Priority question: Please explain how the resource use for OCS per mg and emergency room attendance were estimated in CS Table 81.

The rescue OCS use in terms of total mg associated with treatment of severe exacerbation (in the various treatment settings), as well as the resource use in terms of emergency room attendances among patients hospitalised for severe exacerbation, were taken directly from CS for TA431, Table 123. The number of emergency room attendances for severe exacerbations requiring an A&E visit (but no hospitalisation) was assumed to be 1.

Table 123: Resource utilisation per exacerbation type (taken from DREAM and MENSA)

Resource	Type of exacerbation		
	OCS	ED	Hosp
Telephone call	0.554	0.258	0.708
Home day visit	0.018	0.000	0.047
Home night visit	0.004	0.000	0.000
Practice Visit	0.523	0.344	0.500
Outpatient attendance	0.072	0.118	0.066
Rescue OCS - total mg	350.0	491.1	758.7
Emergency room attendances	-	1.129	0.623
Hospitalisation	-	-	1.000

B11. Priority question: The costs reported in CS Table 83 for mOCS-related AEs unit costs do not match those used in the model for most of the AEs. Please confirm whether those reported in CS Table 83 or used in the model are correct.

The costs reported for mOCS-related AEs are correct in the model, but incorrect in CS Table 83. Corrections are included in *Table 26*.

Table 26: mOCS-related AEs: unit costs

AE	Acute/Initial Cost*			Long-term Cost (per Cycle)		Source
	Mean	SE	Unit	Mean	SE	
Bone-related conditions	£ 3,420.69	£ 684.14	First-year costs converted to a one-off cost‡	£ 8.93	£ 1.79	Davis et al, 2015 (42); weighted average of hip, vertebrae, proximal humerus and wrist fractures
Severe infections	£ 2,851.03	£ 570.21	Per episode	£ 0.00	£ 0.00	2019/20 National Tariff Payment System (43); admitted patient care and outpatient procedure prices; combined day case / ordinary elective spell; weighted average¶ across the following currency codes: Bronchopneumonia DZ23H-DZ23N; Atypical or viral pneumonia DZ11K-DZ11V; Sepsis WJ06A-WJ06J; Kidney or Urinary tract infection LA04H-LA04S; Tuberculosis DZ51Z, DZ14F-DZ14J
Herpes zoster	£ 143.91	£ 28.78	Per episode	£ 0.00	£ 0.00	Gauthier et al, 2009 (44); cost per herpes zoster episode
Hypertension	£ 17.25	£ 3.45	Annual cost converted to per cycle§	£ 17.25	£ 3.45	Sheppard et al, 2014 (45); total cost of treatment in patients with uncomplicated hypertension Stage 1, aged ≥55 years, requiring three different drugs and GP management
Diabetes mellitus	£ 235.75	£ 47.15	Annual cost converted to per cycle§	£ 235.75	£ 47.15	Hex et al, 2012 (46); total cost of Type 2 diabetes divided by total number of cases

AE	Acute/Initial Cost*			Long-term Cost (per Cycle)		Source
	Mean	SE	Unit	Mean	SE	
Glaucoma	£ 122.99†	£ 24.60	Annual cost converted to per cycle§	£ 122.99	£ 24.60	Pezzullo et al, 2018 (47); total health care system cost in the UK (excluding R&D and capital and administration) multiplied by share of costs due to glaucoma, divided by number of glaucoma cases
Cataracts	£ 135.30†	£ 27.06	Annual cost converted to per cycle§	£ 135.30	£ 27.06	Pezzullo et al, 2018 (47); total health care system cost in the UK (excluding R&D and capital and administration) multiplied by share of costs due to cataract, divided by number of cataract cases
Peptic ulcer	£ 1,132.77	£ 226.55	Per episode	£ 0.00	£ 0.00	2019/20 National Tariff Payment System (43); admitted patient care and outpatient procedure prices; combined day case / ordinary elective spell; weighted average¶ across the following currency codes: Gastrointestinal infections FD01A-FD01J; Gastrointestinal bleed FD03A-FD03H
Chronic kidney disease	£ 47.00	£ 9.40	Annual cost converted to per cycle§	£ 47.00	£ 9.40	Kerr et al, 2012 (48); primary care tests, prescription, transplant and dialysis costs divided by the number of cases
Affective disorders	£ 149.40	£ 29.88	Annual cost converted to per cycle§	£ 149.40	£ 29.88	McCrone et al, 2008 (49); weighted average of depression, anxiety disorder and bipolar disorder

AE	Acute/Initial Cost*			Long-term Cost (per Cycle)		Source
	Mean	SE	Unit	Mean	SE	
Cardiovascular events	£ 3,796.65	£ 759.33	Per episode	£ 211.19	£ 14.25	Cost of acute event: 2019/20 National Tariff Payment System (43); admitted patient care and outpatient procedure prices; combined day case / ordinary elective spell; weighted average¶ across the following currency codes: Stroke AA35A-AA35F; Cerebrovascular accident, Nervous System Infections or Encephalopathy AA22C-AA22G; Myocardial Infarction EB10A-EB10E; Long-term cost: Luengo-Fernandez et al. 2012 (50); annual costs of stroke and Alva et al. 2015 (51); annual costs of myocardial infarction. Weighted average¶ of annual costs for stroke and for myocardial infarction (based on activity for currency codes for Stroke AA35A-AA35F and Myocardial Infarction EB10A-EB10E)

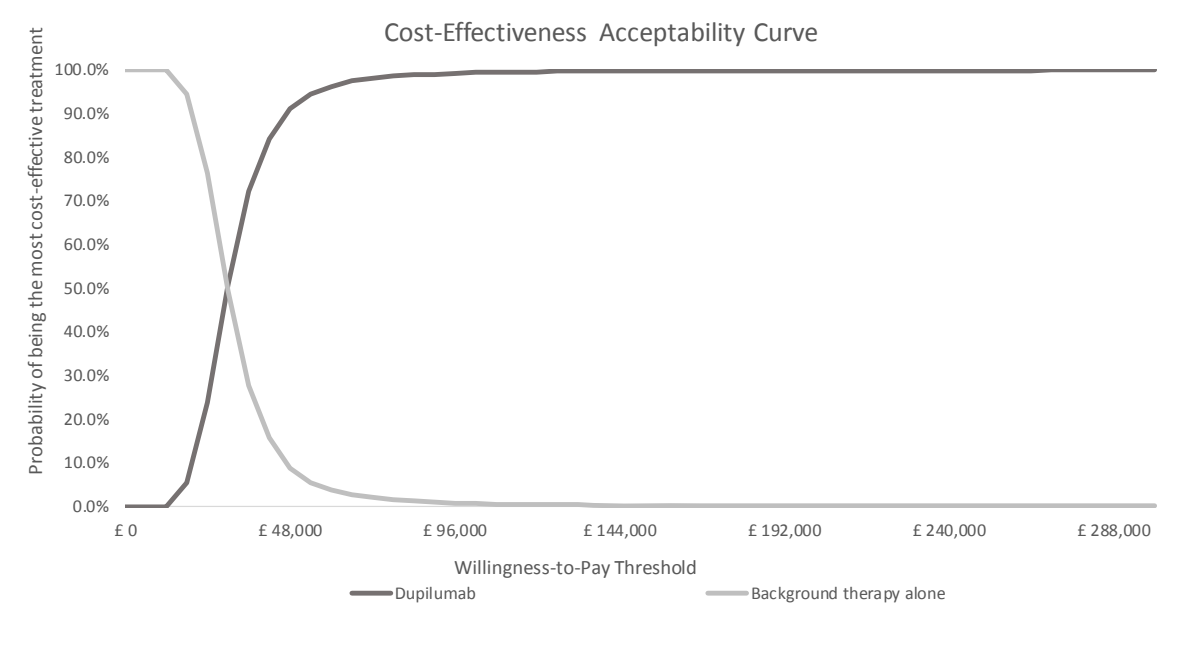
Abbreviations: AE, adverse event; CI, confidence interval; mOCS, maintenance oral corticosteroid; NA, not applicable; NHS, National Health Service; SE, standard error. §The cost for the acute phase is applied as a one-off cost to incident patients in the model, in a single cycle;; ‡ The one-off acute cost for bone-related conditions is calculated based on the first-year costs and on the annual cost in subsequent years reported in the source, as: One-off acute cost = First-year costs – (Annual cost in subsequent years/ Number of Cycles per Year)*(Number of Cycles per Year – 1); ¶ Weights from NHS reference costs 2017/18 (52); Total HRG's; § Using the formula: Cost per Cycle = Cost per Year/Number of Cycles per Year.

Model results

B12. The base case CEAC (B.3.8.1.2 Figure 39) is not consistent with the results presented in Table 90: the CEAC curves cross at less than £10,000 per QALY willingness-to-pay, but the ICER is over £28,000. Please provide the correct CEAC for this analysis.

The x axis in Figure 39 provided in the submission is incorrectly labelled. A corrected CEAC is provided in ***Figure 5*** below.

Figure 5: Cost-effectiveness Acceptability Curve. Probability of dupilumab being the most-effective treatment in patients with EOS ≥ 150 and/or FeNO ≥ 25 and ≥ 3 exacerbations



B13. The tornado diagram for EOS≥150 or FeNO≥25 and mOCS subgroup (B.3.9.1 Table 93) differs from that produced by the 'Run DSA' macro in the submitted model. Please would you confirm which is correct.

The tornado diagram in the model provides results of the 20 most influential parameters on the ICER, whilst the one included in the submission is limited to the 10 most influential parameters. The results are otherwise identical.

Section C: Textual clarification and additional points

Minor textual clarification

C1. CS B.1.3.1.2 The text that reads “BTS 2019 guidelines define asthma as” should presumably read “BTS 2019 guidelines define severe asthma as” to match the definition that follows “two or more severe asthma exacerbations a year or persistent symptoms with SABA use more than twice a week despite specialist-level therapy”.

Yes, the correct phrase should read “severe asthma”.

C2. Appendix O tables 109, 110, 111, 112, 113: In the footnotes NA is stated to be an abbreviation for ‘not applicable’. Should this read not available (or alternatively, not stated)?

Indeed, this has been a typo. In Table 109, 110, 111, 112, and 113 of Appendix O, NA should be interpreted as "not available”.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Dupilumab for treating severe asthma [ID1213]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Asthma UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who	Asthma UK is a membership-based charity with a current membership of approximately 5,200.There are currently 5.4 million people receiving treatment for asthma in the UK, including 1.1 million children, all of whom can access Asthma UK's website and helpline services. Our strategy for 2017 - 2020, has two overarching goals: to stop asthma attacks and cure asthma. We continue to track the four most important overall outcome measures for people with asthma (asthma attacks, asthma deaths, access to the basic

funds it). How many members does it have?	elements of care and emergency hospital admissions) and continue to work to drive improvements in care for all people with asthma. In March 2019, the Trustees agreed to cease its corporate membership programme with pharmaceutical companies with immediate effect. Asthma UK will no longer partner with pharmaceutical companies or accept any financial (or non-financial) incentives. Asthma UK has always adhered to the principles outlined in its partnership policy and will not partner with any third party that would compromise the independent status of Asthma UK or conflict with its strategic aims.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Information about the experiences of patients and carers living with asthma is gathered regularly through our helpline and social media interactions with people with asthma, Asthma UK also conducts annual patient surveys and we recently held a face to face workshop for patients living with severe asthma.
Living with the condition	
6. What is it like to live with the condition? What do carers	Asthma is one of the most prevalent long-term conditions in the UK, with 5.4 million people currently receiving treatment for the condition. On average, 3 people die from an asthma attack in the UK every day[1] and 1,320 people died from asthma in England and Wales in 2017 [2]. Severe asthma affects nearly

[1] Asthma UK, Asthma Facts and Statistics, accessed at: https://www.asthma.org.uk/about/media/facts-and-statistics/ (July 2019)
[2] Office for National Statistics, Deaths Registered in England and Wales 2017. Accessed at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsregistrationsummarytables/2017, (July 2019).

experience when caring for someone with the condition?	3.6% of people with asthma – which equates to around 173,000 people in England and Wales.[3] The National Review of Asthma Deaths highlighted that almost 40% of asthma deaths were patients who had severe asthma.[4] If approved, dupilumab would be the fifth biologic drug available for people with severe asthma in England and Wales that helps reduce asthma exacerbations without the need for continual use of oral corticosteroids (OCS)– the only other treatment available to people with severe asthma. However, most of the severe asthma population do not qualify for the four biologic drugs currently available, due their strict eligibility criteria[5]. Dupilumab, though, holds the potential to serve a far larger cohort of the severe asthma population, and could go a long way in addressing this large unmet need. Severe asthma does not respond well to standard treatments and requires more intensive therapies with significant side effects to control symptoms and prevent attacks, hospitalisations and deaths. People with severe asthma fall outside the robust evidence-base that informs most asthma care, requiring specialist treatment and pathways. There is no dedicated NICE guideline for treating severe asthma. Ongoing severe symptoms and a complex medicines regime are often accompanied by frequent hospital admissions for many people with severe asthma. Numerous hospital admissions can lead to further social isolation and economic disadvantage, as well as high costs for the NHS.[6] As such, people with uncontrolled severe asthma cost four times as much to treat as the average patient.[7] What is more,

[3] Hekking P, et al, 'The prevalence of severe refractory asthma', The Journal of Allergy and Clinical Immunology, 135(4), (2015)
[4] Royal College of Physicians, 2014, 'Why asthma still kills: the National Review of Asthma Deaths (NRAD)', accessed at https://www.rcplondon.ac.uk/file/868/download?token=JQzyNWUs
[5] Albers FC, Gunsoy NB, Hartmann CEA, Mehta RA, Starkie Camejo H, 'P16 Implications of nice guidance in England and Wales on eligibility for treatment with mepolizumab and omalizumab – an ideal study analysis', (2017)
[6] D'Amato, Gennaro, et al., "Treating severe allergic asthma with anti-IgE monoclonal antibody (Omalizumab): a review." *Multidisciplinary respiratory medicine* 9.1 (2014): 23.
[7] Marjan Kerkhof et al., 'Healthcare Resource Use and Costs of Severe, Uncontrolled Eosinophilic Asthma in the UK General Population', Thorax (2017), https://doi.org/10.1136/thoraxjnl-2017-210531

	people with severe asthma remain symptomatic on high doses of treatment. However, a lack of referrals to a specialist for an assessment often leads to patients being left on continuous courses of oral steroids.[8] Experiences of people living with severe asthma "Life with severe asthma is limiting. There's no spontaneity because everything I do is timed by when I need to use my nebulisers... I have a wide range of triggers – dust mites, tree moulds, pollen, temperature changes, exercise, smoke, and rapeseed …[therefore] whenever I go out I need to make sure I take my asthma medicines half an hour beforehand." Julia, 29 years old[9] "I was diagnosed with severe asthma after several years of struggling to keep my symptoms under control. I was using my reliever inhaler more than usual, despite taking my preventer as prescribed, having frequent asthma attacks and taking courses of steroids several times a year. In 10 months alone, I had 12 emergency hospital admissions and was seeing my GP at least once a week for a nebuliser." Callie-Anne, 31 years old[10]
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Side effects from existing treatments The existing treatments for severe asthma are extremely limited. Patients predominantly rely on OCS to control their symptoms, which can cause toxic and debilitating side effects, particularly when taken for long periods, which in cases of severe asthma, they often are. A survey into the side effects of OCS used by people with asthma was conducted by Asthma UK in 2017. Various side effects were reported, including 56% reporting weight gain; 37% felt more anxious and 33% reported aching and cramping muscles and joints.[11] NHS England reports that the side-effects of maintenance OCS, which "will affect the majority of patients with severe asthma" include diabetes,

[8] Asthma UK, 'Slipping through the net: The reality facing patients with difficult and severe asthma', (2018), Accessed at: https://www.asthma.org.uk/globalassets/get-involved/external-affairs-campaigns/publications/severe-asthma-report/auk-severe-asthma-gh-final.pdf p.8
[9] Asthma UK, https://www.asthma.org.uk/advice/severe-asthma/your-stories-severe-asthma/julia-kerr/ (accessed: 12/02/19)
[10] Asthma UK, https://www.asthma.org.uk/advice/severe-asthma/your-stories-severe-asthma/sex-and-romance-callie-anne/ (accessed: 12/02/2019)
[11] Broadbent C, Pfeffer P, Steed L, Walker S, 'Patient-reported side effects of oral corticosteroids', (2018) European Respiratory Journal 2018 52: PA3144

	hypertension, cataracts, osteoporosis, glaucoma, skin disease, reflux oesophagitis, non-alcoholic fatty liver disease and obesity.[12] Likewise, a study by Sweeney et al. which presents data from two large severe asthma populations (the Optimum Patient Care Research Database and the British Thoracic Difficult Asthma Registry), showed that OCS use results in a higher prevalence of comorbidities, including type II diabetes, hypertension and osteoporosis.[13] In effect, with the exception of biologic drugs, therapeutic options are limited for patients with severe asthma whose symptoms cannot be controlled with the available treatments such as high dose inhaled or OCS. <u>Impact on everyday life</u> Dupilumab has the potential to reduce the need for use of OCS and its subsequent side effects for those with severe asthma, which should be factored into any calculations made to determine dupilumab's incremental cost-effectiveness ratio. The side effects and ineffectiveness of OCS in reducing severe asthma symptoms in patients can also contribute to an increased rate of sickness absence for people with asthma. Asthma UK found that even across the far broader asthma population as a whole, 20% of people aged 0-59 miss 1-4 days of work or education a year due to their asthma, whilst 19% miss 10 or more days.[14] Given the uncontrolled and life limiting nature of severe asthma, people with severe asthma who are not in receipt of a biologic drug, tend to suffer more frequent exacerbations in their condition and thus have frequent trips to hospital and time off work. Despite people with severe asthma adhering to their recommended asthma treatment, including OCS, symptoms can persist, and asthma can remain uncontrolled, putting people at risk of potentially life-threatening asthma attacks.[15] The wider impact that asthma can have on life includes depression, anxiety and fear of social rejection or loss of employment.[16] It is likely that this impact will be even greater for those with severe asthma. <u>Experiences of people living with severe asthma</u>

	The introduction of biologics to treat asthma has proved to be life-transforming for people with severe asthma who are eligible for them. For example, Jane, who was diagnosed with severe eosinophilic asthma and started taking mepolizumab (another biologic treatment for severe asthma) said, "Two weeks after my first injection I could climb hills in the Peak District. After just three injections, instead of contemplating taking early retirement from the midwifery job I love, I'm actually thinking about increasing the number of hours I do. This treatment has really transformed my life." Jenny was diagnosed with severe asthma and treated with omalizumab after suffering from a sudden severe asthma attack whilst on holiday and ended up in hospital for 10 days. "Since having monthly Xolair injections to reduce my allergic response, at least I'm able to go outside in summer now."[17] Lehanne's life has been devastated by her severe asthma. "Being on high doses of corticosteroids for such a long time has led to all sorts of health problems from their side effects including bone damage. I've had a hip replacement and surgery on my neck because my bones have weakened and I also live in constant pain from problems with my lower back. I am on regular nebulisers and cannot leave the house without my portable nebuliser. Daily, I take home infusions of Bricanyl and every five weeks I'm admitted to the Royal Brompton hospital for ten days treatment of intravenous infusion of aminophylline, hydrocortisone and physiotherapy."[18] Sadly, Lehanne, like many people with severe asthma, does not currently qualify for the biologics currently available. As Lehanne reflects, "life is an endless stream of good periods interspersed with episodes of deterioration which end with me being admitted to hospital. I spent last Christmas in hospital being intubated because I couldn't breathe. My husband is very

[12] NHS England, Specialised Respiratory Services (adult) – Severe Asthma, Service Specification: 170002/S. Accessed at: https://www.england.nhs.uk/wp-content/uploads/2017/04/specialised-respiratory-services-adult-severe-asthma.pdf, July 2019.
[13] Sweeney J, Patterson CC, Menzies-Gow A, Niven RM et al. 'Comorbidity in severe asthma requiring systemic corticosteroid therapy: cross-sectional data from the Optimum Patient Care Research Database and the British Thoracic Difficult Asthma Registry'. Thorax 2016; 71:339-346 https://thorax.bmj.com/content/71/4/339
[14] Asthma UK, 'Annual Asthma Survey 2016 report', 2017, p.31, Accessed at: https://www.asthma.org.uk/share/?rid=6770
[15] Asthma UK, 'Severe Asthma: the unmet need and the global change', (2017), Accessed at: https://www.asthma.org.uk/globalassets/get-involved/external-affairs-campaigns/publications/severe-asthma-report/auk_severeasthma_2017.pdf p.8
[16] Ahmad, Sohail, and Nahlah Elkudssiah Ismail. 'Stigma in the lives of asthma patients: a review from the literature.' International Journal of Pharmacy and Pharmaceutical Sciences 7, no. 7 (2015): 40-46.
[17] Asthma UK, 'How I cope with severe asthma', accessed at: https://www.asthma.org.uk/advice/severe-asthma/your-stories-severe-asthma/how-i-cope-with-severe-asthma/
[18] Asthma UK, 'Press release: New generation asthma drug gets approval for NHS use', accessed at: https://www.asthma.org.uk/about/media/news/new-generation-asthma-drug-gets-approval-for-nhs-use/, (2017)

	understanding and does his best to help, but it's stressful and difficult for both of us. I'm desperate for new treatments as are so many of us who live with severe asthma. I really hope the new drugs becoming available will make a difference to our lives." [19]
8. Is there an unmet need for patients with this condition?	There is a large unmet need for effective treatments for people with severe asthma, primarily around access to existing biologic drugs. The IDEAL study (Identification and Description of Severe Asthma Patients in a Cross-Sectional Study) aimed to define the proportion of severe asthma patients in England and Wales who are eligible for biologic therapy in accordance with NICE guidance and found that only 13% were eligible for mepolizumab and 27% were eligible for omalizumab. Furthermore, even amongst those eligible, some weren't in receipt of a biologic, emphasising the vast unmet need within this patient group.[20] Although existing biologics can reduce asthma attacks by >50%, their potential is limited in that they are only made available to specific sub-populations.[2122] Mepolizumab, for example, is only available to patients who have had a blood eosinophil count of 300 cells/microlitre or more in the previous 12 months and have had 4 or more asthma exacerbations needing systemic corticosteroids in the previous 12 months, or who have had continuous OCS of at least the equivalent of prednisolone 5 mg per day over the previous 6 months.[23] Because dupilumab's licensing authorisation makes it suitable for a far larger population than all other biologics that have come before it, this drug offers the opportunity to greatly reduce the number of patients currently taking OCS who currently have no hope of an alternative. A further example of this is the age at which patients can qualify for existing biologics. Mepolizumab, reslizumab and benralizumab are all only available for adults whereas dupilumab has been certified for use in patients aged 12 years and over, thereby fulfilling a large unmet need in the severe asthma population, particularly the 12-18 age group. It should be born in mind that in 2017 there were 35 asthma-

[19] Ibid
[20] Albers FC, Gunsoy NB, Hartmann CEA, Mehta RA, Starkie Camejo H, 'P16 Implications of nice guidance in England and Wales on eligibility for treatment with mepolizumab and omalizumab – an ideal study analysis', (2017)
[21] Fasenra, 'considering fasenra', accessed at: https://www.fasenra.com/eosinophilic-asthma-treatment.html, accessed on 16/07/2019
[22] American Academy of allergy asthma and immunology, 'Mepolizumab: sustained safety and efficacy in severe eosinophilic asthma', accessed at:https://www.aaaai.org/global/latest-research-summaries/Current-JACI-Research/mepolizumab, (2018)
[23] NICE, 'Mepolizumab for treating severe refractory eosinophilic asthma', accessed at: https://www.nice.org.uk/guidance/TA431/chapter/1-Recommendations

	related deaths in people under 25 in England and Wales [24] while 17 children under 15 years died from asthma in the England and Wales in 2017 [25]. The National Review of Asthma Deaths (2014) found that of the155 patients who died for whom severity could be estimated, 61 (around 40%) appeared to have severe asthma [26]. Although we welcomed the approval of benralizumab earlier in 2019, we were disappointed that it was only approved for sub-populations already eligible for mepolizumab and reslizumab. Dupilumab may offer new hope for those people with severe asthma that are not eligible for any other biologic, especially young people under 18.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Dupilumab offers people with severe asthma the opportunity to control their symptoms and live a life unhindered by their condition. This medication could greatly reduce the dependency of patients on their family and/or carer(s). Biologics have proven to reduce emergency admissions and cases of asthma attacks for those with severe asthma, which would also reduce the emotional and psychological impact of caring for someone with severe asthma.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Anecdotal evidence from patients indicates some wariness towards the method of drug delivery, with some patients claiming they would prefer inhaled or oral methods of drug delivery, instead of an injection. The frequent visits to hospital that patients and their carers have to undertake whilst in receipt of a biologic drug can also be disruptive and costly.

[24] Office for National Statistics, Deaths Registered in England and Wales 2017. Accessed at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsregistrationsummarytables/2017, July 2019
[25] Ibid
[26] Royal College of Physicians, 'Why Asthma Still Kills, National Review of Asthma Deaths', (2014). Accessed at: https://www.asthma.org.uk/globalassets/campaigns/nrad-full-report.pdf, July 2019.

	Patients can also sometimes be concerned about how they will respond to the drug, both through fear of potential side effects and the unknown effectiveness of the drug on their condition.[27] However, there is no evidence to suggest this has resulted in a patient declining treatment and is merely noted to make known the concerns of patients in receipt of a monoclonal antibody to treat their asthma.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	NA
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No

[27] We have conducted qualitative research with people with severe asthma and reflected their concerns in this submission. Reference currently unavailable.

Other issues	
13. Are there any other issues that you would like the committee to consider?	As a point of reference, please find below the bibliography for the evidence used for this response Bibliography Ahmad, Sohail, and Nahlah Elkudssiah Ismail. 'Stigma in the lives of asthma patients: a review from the literature.' International Journal of Pharmacy and Pharmaceutical Sciences 7, no. 7 (2015) Albers FC, Gunsoy NB, Hartmann CEA, Mehta RA, Starkie Camejo H, 'P16 Implications of nice guidance in england and wales on eligibility for treatment with mepolizumab and omalizumab – an ideal study analysis', (2017) Asthma UK, 'Annual Asthma Survey 2016 report', (2017) Asthma UK, 'How I cope with severe asthma', accessed at: https://www.asthma.org.uk/advice/severe-asthma/your-stories-severe-asthma/how-i-cope-with-severe-asthma/ Asthma UK, 'Press release: New generation asthma drug gets approval for NHS use', accessed at: https://www.asthma.org.uk/about/media/news/new-generation-asthma-drug-gets-approval-for-nhs-use/, Asthma UK, 'Severe Asthma: the unmet need and the global change', (2017), Accessed at: https://www.asthma.org.uk/globalassets/get-involved/external-affairs-campaigns/publications/severe-asthma-report/auk_severeasthma_2017.pdf Asthma UK, 'Slipping through the net: The reality facing patients with difficult and severe asthma', (2018), Accessed at: https://www.asthma.org.uk/globalassets/get-involved/external-affairs-campaigns/publications/severe-asthma-report/auk-severe-asthma-gh-final.pdf Asthma UK, https://www.asthma.org.uk/advice/severe-asthma/your-stories-severe-asthma/julia-kerr/ (accessed: 12/07/19) Asthma UK, https://www.asthma.org.uk/advice/severe-asthma/your-stories-severe-asthma/sex-and-romance-callie-anne/ (accessed: 12/07/2019)

Asthma UK, https://www.asthma.org.uk/advice/inhalers-medicines-treatments/steroids/ (accessed 12/07/2019)

Bajorek, Hind & Bevan (2016) 'The Work Foundation: The Impact of long term conditions on employment and the wide UK economy'

Broadbent C, Pfeffer P, Steed L, Walker S, 'Patient-reported side effects of oral corticosteroids', (2018) European Respiratory Journal 2018 52:PA3144

D'Amato, Gennaro, et al., "Treating severe allergic asthma with anti-IgE monoclonal antibody (Omalizumab): a review." Multidisciplinary respiratory medicine 9.1 (2014)

Hekking P, Wener R, Amelink M, Zwinderman A, Bouvy M, Bel E., 'The prevalence of severe refractory asthma', The Journal of Allergy and Clinical Immunology, 135(4), (2015)

Marjan Kerkhof et al., 'Healthcare Resource Use and Costs of Severe, Uncontrolled Eosinophilic Asthma in the UK General Population', Thorax (2017), https://doi.org/10.1136/thoraxjnl-2017-210531

NICE, 'Mepolizumab for treating severe refractory eosinophilic asthma', accessed at: https://www.nice.org.uk/guidance/TA431/chapter/1-Recommendations

Royal College of Physicians, 2014, 'Why asthma still kills: the National Review of Asthma Deaths (NRAD)', accessed at https://www.rcplondon.ac.uk/file/868/download?token=JQzyNWUs

Sweeney J, Patterson CC, Menzies-Gow A, Niven RM et al. 'Comorbidity in severe asthma requiring systemic corticosteroid therapy: cross-sectional data from the Optimum Patient Care Research Database and the British Thoracic Difficult Asthma Registry'. Thorax 2016; 71:339-346 https://thorax.bmj.com/content/71/4/339

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Severe asthma affects nearly 3.6% of people with asthma (roughly 173,000 adults in England and Wales), who might benefit from being prescribed dupilumab.

- At present, existing biologics approved for use by NICE only serve a small proportion of the total number of those with severe asthma, leaving the majority of patients with severe asthma reliant on OCS to control their asthma.[28]
- People with severe asthma do not generally respond to standard inhaled asthma treatment and require more intensive treatments to control their asthma symptoms, prevent asthma attacks, hospitalisations and deaths.
- There is a substantial unmet need for people with severe asthma in the treatment options available to them: they have to rely largely on high doses of OCS drugs to control their symptoms. Patients may have to have multiple rounds of OCS, which, if taken over a longer period of time, are known to have severe adverse side effects[29]
- Even when taking oral steroids, some patients' severe asthma remains poorly controlled, and therefore dupilumab could provide an alternative option for people with severe asthma who do not respond well to existing treatment options.

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[28] Albers FC, Gunsoy NB, Hartmann CEA, Mehta RA, Starkie Camejo H, 'P16 Implications of nice guidance in England and Wales on eligibility for treatment with mepolizumab and omalizumab – an ideal study analysis', (2017)

[29] Asthma UK, https://www.asthma.org.uk/advice/inhalers-medicines-treatments/steroids/ (accessed 12/02/2019)

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Dupilumab for treating severe asthma [ID1213]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**British Thoracic Society**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The British Thoracic Society (BTS) is the professional society for respiratory medicine and related health care professions. The Society exists to improve standards of care for people who have respiratory diseases and to support and develop those who provide that care. It is a registered charity and a company limited by guarantee.

5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**None**
Topic specific questions	
6. Are eosinophil and/or FeNo levels routinely used as clinical criteria for treating people with Type II asthma in NHS practice? And if so, what is the threshold for initiating treatment for each?	Blood eosinophils and FeNO are routinely used in all severe asthma centres in the NHS. Blood eosinophil cut offs of either 300 (mepolizumab or benralizumab) or 400 (reslizumab or benralizumab) are used when prescribing anti-eosinophilic biologics according to their relevant NICE HTAs. Expert consensus on T2 asthma would suggest that a cut off above or equal to 150 eosinophils and/or 25ppb for FeNO are indicative of ongoing type 2 inflammation in people with severe asthma receiving high dose inhaled corticosteroids. At present we would not initiate any treatment based on FeNO levels alone.
7. How is adequate response to treatment defined in this population?	With all biologics treatment response should be assessed at 6 months (GINA pocket handbook on severe asthma 2019) and a decision to continue or switch to an alternative is based on a combination of exacerbation frequency, FEV1, PROM e.g. ACQ-6 and decreased oral steroid (OCS) burden. Response should then be reassessed after 12 months and then on an annual basis.
The aim of treatment for this condition	
8. What is the main aim of treatment? (For example, to stop progression, to improve	1. Decrease exacerbation frequency 2. Minimise oral steroid exposure 3. Improve quality of life 4. Improve or prevent decline in lung function

mobility, to cure the condition, or prevent progression or disability.)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	1. 50% decreased in exacerbation frequency 2. Clinically meaningful decrease in OCS burden 3. MCID improvement in PROM, e.g. 0.5 improvement in ACQ-6 4. 100ml improvement in FEV1
10. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, there remains a significant unmet need. Current biologics treat approximately 50%-60% of patients with severe asthma and up to 30% fail a trial of anti-eosinophilic therapy. Better treatment of co-morbidities, e.g. nasal polyps is also required.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	At NHS England commissioned severe asthma centres
• Are any clinical guidelines used in the	BTS/SIGN Guideline for the management of asthma July 2019. GINA 2019 severe asthma pocket book

treatment of the condition, and if so, which?	
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes, through commissioned centres with an ongoing NHS Improving Value Project, GIRFT and NHS E CQUIN helping to standardise care.
• What impact would the technology have on the current pathway of care?	It will allow the first in class anti-IL-4/13 biologic to treat relevant patients
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, it will be prescribed via biologic MDTs at commissioned severe asthma centres
• How does healthcare resource use differ between the technology and current care?	No difference

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Tertiary specialist clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None, facilities, etc are already in place
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	No evidence to support this at present
• Do you expect the technology to increase health-related quality of life more than current care?	Yes, as will also treat co-morbidities

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	It will be more effective in people with T2 high severe asthma
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	The same as current biologics

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Will need a minimum of a 12 month stopping rule as for other biologics
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Yes, see above answers

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	No safety signal of concern from the phase III pivotal studies
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Exacerbations, FEV1, PROMs and OCS sparing were all measured in the trial programme
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Not applicable
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator	No

treatment(s) since the publication of NICE technology appraisal guidance [TA565]?	
23. How do data on real-world experience compare with the trial data?	Too early to comment
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
24b. Consider whether these issues are different from issues with current care and why.	
Key messages	

25. In up to 5 bullet points, please summarise the key messages of your submission.

- First in class biologic targeting IL-4/13
- Appropriate phase III programme with correct outcomes measured
- Will benefit people with severe asthma that fail trials of currently available biologics
- Will be first line for some patients with mixed T2 high disease, i.e. FeNO and eos high
-

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Dupilumab for treating severe asthma [ID1213]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Royal College of Physicians**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	
5b. Do you have any direct or indirect links with, or funding	

from, the tobacco industry?	
Topic specific questions	
6. Are eosinophil and/or FeNo levels routinely used as clinical criteria for treating people with Type II asthma in NHS practice? And if so, what is the threshold for initiating treatment for each?	Both measurements are used routinely in severe asthma centres where this technology would be initiated and administered. All patients attending a severe asthma centre would have blood eosinophil counts and FeNO measured
7. How is adequate response to treatment defined in this population?	A reduction in exacerbation frequency for example by a halving of OCS courses, reduced burden of maintenance OCS, improved quality of life using standard instruments such as AQLQ
The aim of treatment for this condition	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or	To reduce exacerbation frequency, OCS use and hospital admissions and improve quality of life for asthma sufferers

disability.)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Halving of exacerbation frequency and OCS use OR significant QOL improvement OR clinically significant reduction in maintenance OCS eg 50-100% reduction. Associated improvements in comorbidities eg atopic eczema and nasal polyp recurrence should also be considered
10. In your view, is there an unmet need for patients and healthcare professionals in this condition?	The UK continues to have unacceptably high asthma death rates and hospital admissions with considerable regional variation despite current biologic therapies. Dupilumab offers a potential alternative with effects on some commonly occurring co-morbidities.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	GINA step 5 with frequent or maintenance OCS or with currently approved anti-IgE or anti IL5 biologics.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	BTS, NICE and GINA (most up to date)

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The introduction of NHSE commissioned severe asthma centres has led to standardisation of pathways and treatments.
• What impact would the technology have on the current pathway of care?	Likely to replace use of other biologics and reduce OCS use. However this technology requires an injection every two weeks and therefore may generate considerable capacity issues compared to other biologics which are generally administered every 4-8 weeks and also lead to increased administration costs
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	This is a new treatment with a novel mode of action and its place in therapy will evolve over time. However likely to be used in a similar manner to current biologics and because of frequency of dosing home therapy may be preferred in patients able to comply and self-administer
• How does healthcare resource use differ between the technology and current care?	Two weekly administration and possibly home therapy will be a challenge
• In what clinical setting should the technology be used? (For example, primary or secondary	Specialist centres - NHSE commissioned – will bear overall responsibility for initiation and continuation of therapy

care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Most already in place however a shift to home therapy and more frequent dosing will incur changes in practice and requirements for increased capacity for administration. In addition a significant proportion of patients in atopic dermatitis studies developed conjunctivitis requiring ophthalmologic review. It remains to be seen if this also occurs when dupilumab is used in asthma
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Likely to be similar to current biologics although different mode of action may widen response-population eg those asthma patients with fungal sensitisation or severe nasal polyps or atopic dermatitis
• Do you expect the technology to increase length of life more than current care?	No evidence for this
• Do you expect the technology to increase health-related quality of life more than current care?	Possibly – but depends on which study is used to compare effects
14. Are there any groups of people for whom the technology would be more or	This technology is for type 2 asthma with either an allergic or eosinophilic phenotype and those with comorbidities as stated above. The advantage of this technology is that FeNO can be used to closely monitor response

less effective (or appropriate) than the general population?	
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Two weekly administration is more frequent than most current biologics and therefore home therapy will need to be considered and patients monitored in a different way with a focus on remote monitoring. Compliance with home therapy may become a concern and will be difficult to assess posing different challenges compared to home therapies self-administered for physically disabling conditions such as arthritis or IBD. Novel methods assessing compliance may be required to minimise wastage and a certain degree of wastage should perhaps be factored into an economic analysis
16. Will any rules (informal or formal) be used to start or stop treatment with the technology?	Treatment will be for T2 asthma and it is then for NOCE to determine severity at which economically viable to initiate therapy. However, likely similar threshold to other biologics depending on acquisition cost

Do these include any additional testing?	
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Improvements in comorbidities
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Innovative mode of action is likely to deliver different benefits to other biologics particularly wrt to co-morbidities
• Is the technology a 'step-change' in the management of the	Perhaps with regard to con-morbidities but for asthma unlikely

condition?	
• Does the use of the technology address any particular unmet need of the patient population?	Nasal polyps and atopic dermatitis
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Conjunctivitis and keratitis remains potential concerns and will need to be monitored post market. There may be some interactions with live vaccine administrations and it remains unclear whether treatment results in increased susceptibility to helminth infections
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Generally yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they	Yes measured ie OCS use, exacerbation frequency, spirometry, QOL

measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Conjunctitis, keratitis, pregnancy related effects, live vaccine interactions, helminth infections
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA565]?	

23. How do data on real-world experience compare with the trial data?	
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	no
24b. Consider whether these issues are different from issues with current care and why.	
Key messages	

25. In up to 5 bullet points, please summarise the key messages of your submission.

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Thank you for your time.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Dupilumab for treating severe asthma [ID1213]

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About you	
1. Your name	**Andrew Menzies-Gow**
2. Name of organisation	**Royal Brompton Hospital**

3. Job title or position	**Director of the Lung Division**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **x**☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**x**☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Prevent exacerbations, minimise OCS exposure, improve quality of life and asthma control.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	50% decrease in AER, clinically significant decrease in OCS exposure, MCID improvement in PROM, e.g. ACQ-6, AQLQ, MCID improvement in FEV1
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, not all people with severe asthma respond to the currently available biologics
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	At commissioned severe asthma centres
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	GINA pocketbook for severe asthma.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes, there is a service specification developed by the Adult Specialised Respiratory CRG for NHS E Further detail is being produced as part of an NHS Improving Value Project commissioned by the CRG
• What impact would the technology have on the current pathway of care?	Additional option for treatment of people with severe asthma driven by Type 2 inflammation
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, there are already 4 biologics with NICE HTA for severe asthma

• How does healthcare resource use differ between the technology and current care?	There is no difference, see above
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Commissioned severe asthma centres
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, this biologic has a different MOA to currently available treatment options and published studies suggest that it is also beneficial in certain co-morbidities such as atopic dermatitis and nasal polyps
• Do you expect the technology to increase length of life more than current care?	No

• Do you expect the technology to increase health-related quality of life more than current care?	I would need to see the economic modelling to be able to answer this question
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	More effective in people with Type 2 inflammation measured by a combination of blood eosinophils and FeNO
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	It will be the same as other biologics, i.e. initial subcutaneous injection at the specialist centre followed by home administration via an autoinjector.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes We are building in 6 month review of all biologic responses into the biologic choice guideline being developed by the NHS Improving Value collaborative.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No, as long as the true impact of cumulative OCS exposure is included in the QALY calculation.
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	Yes This drug has a different MOA to the other biologics that are currently available

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes, this is the first biologic to target the IL-4 and 13 pathways.
• Does the use of the technology address any particular unmet need of the patient population?	Yes, it is a valuable treatment option in people with Type 2 inflammation that fail to respond to other classes of biologic
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	From my reading of the phase III pivotal studies the overall side effect profile is similar to other licensed biologics for severe asthma.
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	AER, OCS exposure, which were the primary outcomes for the phase III pivotal studies
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	NA
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to my knowledge
20. Are you aware of any relevant evidence that might	No

not be found by a systematic review of the trial evidence?	
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	No
22. How do data on real-world experience compare with the trial data?	Not yet available
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

23b. Consider whether these issues are different from issues with current care and why.	
Key messages	
24. In up to 5 bullet points, please summarise the key messages of your statement. • This is the first in its class of biologic for severe asthma • Dupilumab is an important addition, as significant numbers of people with severe asthma do not respond to the first class of biologic which they are treated with • The phase III pivotal programme has demonstrated a positive impact on the most clinically relevant outcomes for people with severe asthma •	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Dupilumab for treating severe asthma [ID1213]

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Ian D Pavord**
2. Name of organisation	**University of Oxford**

3. Job title or position	**Professor of Respiratory Medicine**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	• To reduce attacks of severe type-2 asthma (i.e. eosinophilic asthma) • To enable safe oral corticosteroid (OCS) withdrawal in patients with severe asthma on regular OCS • To improve lung function and symptoms in patients with severe type-2 asthma • To improve comorbid chronic rhinosinusitis and nasal polyposis and atopic dermatitis in patients with severe type-2 asthma
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A reduction of asthma attacks of around 20% ; a doubling in the proportion of patients able to lower OCS dose; a >100 ml improvement in FEV1; and a 0.5 point improvement in Asthma Control Questionnaire (ACQ) score are regarded as clinically important. Dupilumab achieves a 50-60% reduction in exacerbations, triples the likelihood of OCS dose reduction, improves FEV1 by 200-300 ml and increases ACQ by around 0.5 points. Importantly these beneficial effects are very closely related to the patient's exhaled nitric oxide (FeNO) and blood eosinophil count. High FeNO and blood eosinophil count are independently associated with a 2-3 fold increased risk of asthma attacks. This excess risk is completely reversed by Dupilumab so that in this subgroup (representing about half of the severe asthma population) the benefits of Dupilumab are greater (i.e. 70% reduction in frequency of asthma attacks). FeNO is particularly predictive of efficacy of Dupilumab and blood eosinophils for anti-IL-5 (i.e. Mepolizumab, benralizumab). Biomarker profiles may be used to match patient to biologic in the future. This close relationship between treatment response and an easily measured biomarker is a very important feature of Dupilumab and the anti-IL-5 biologics in use in severe asthma.

9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, in two main groups: 1. In patients who have an inadequate response to Omalizumab and/or anti-IL-5 and have a raised FeNO I would say that Dupilumab would be the obvious biologic to swap to; 2. Dupilumab is the obvious first choice in patients with severe type-2 asthma with comorbid nasal disease or atopic dermatitis because of the much greater efficacy of Dupilumab against the comorbid conditions than anti-IL-5 and Omalizumab
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Well standardised care pathways delivered through a network of severe asthma centres. The UK has an enviable track record of using biologics in airways disease economically and effectively. For example, the use of Omalizumab in the UK is 10% of the use in France.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	ATS/ERS severe asthma guidelines have just been updated and there was a 2018 GINA severe asthma guideline. The UK community largely adhere to these guidelines with some minor changes. For example, we are much more careful about ensuring optimum adherence with inhaled treatment prior to escalation to biologics.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes, well defined. The beneficial effects of Dupilumab and anti-IL-5 are very closely related to the patient's exhaled nitric oxide (FeNO) and blood eosinophil count. This is widely accepted.

• What impact would the technology have on the current pathway of care?	Dupilumab will fill an important gap in patients not responding well to anti-IL-5 who have the right pattern of airway inflammation. It would be an attractive first line biologic in patients with relevant comorbidities.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, this will integrate very well with existing care pathways in severe asthma. Biologics have had a major positive impact in severe asthma (for example regular OCS are now almost never used to treat the conditions whereas in 2010 they were the most common therapeutic intervention). The severe asthma community would welcome the opportunity to use an agent with a different mechanism of inhibition of type-2 inflammation than anti-IL-5. The impressive efficacy of Dupilumab against common co-morbidities seen in patients with severe type-2 asthma is important.
• How does healthcare resource use differ between the technology and current care?	Dupilumab has a distinct mechanism of action and is likely to help a different sub-group of patients with severe type-2 asthma. It is the obvious swap biologic in patients not doing well on Omalizumab or anti-IL-5
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics. There is an established network of severe asthma centres.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Drug cost. No additional investment
12. Do you expect the technology to provide clinically	Yes, the impact of biologics in severe asthma has been huge. Regular use of OCS has been largely confined to the history books, thankfully.

meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	Unknown but likely. Life expectancy in severe asthma is modestly reduced as a result of asthma related factors and comorbidities.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes. Important increased in Asthma Related QOL have been documented in phase 3 trials
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients with high exhaled nitric oxide and blood eosinophils respond particularly well
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare	No difference. Treatment is usually self-administered after appropriate training

professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Usually a go no-go decision will be made after 6-12 months, depending on what the main goal of treatment was.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the	Yes. Reduction in OCS related morbidity. Health gains from increasing activity and fitness.

quality-adjusted life year (QALY) calculation?	
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Highly innovative
• Is the technology a 'step-change' in the management of the condition?	Yes. See above
• Does the use of the technology address any particular unmet need of the patient population?	Recurrent asthma attacks and the need for O regular OCS. Poor lung function and asthma symptoms.
18. How do any side effects or adverse effects of the technology affect the	No

management of the condition and the patient's quality of life?	
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes. QUEST included some UK patients
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	50-70% reduction in exacerbations depending on biomarker profile; 200-300 ml improvement in FEV1; tripling of the chance of OCS reduction (see above)
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	NA
• Are there any adverse effects that were not apparent in clinical trials	None. Treatment associated eosinophilia is an anticipated effect of blocking IL-4 &13

but have come to light subsequently?	
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	An ITC analysis vs other biologics is in press with Resp med and has been presented as an abstract.
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	No
22. How do data on real-world experience compare with the trial data?	NA
Equality	
23a. Are there any potential equality issues that should be	No

taken into account when considering this treatment?	
23b. Consider whether these issues are different from issues with current care and why.	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your statement.

- The most effective biologic yet assessed in terms of reductions in asthma attacks, improvement in lung function and reduction in comorbidities commonly seen in severe type-2 asthma
- Important OCS sparing effect
- Safe
- Beneficial effects are very closely associated with raised values of two readily available biomarkers: FeNO and blood eosinophils
- Mechanism is distinct from other available biologics, making this the most logical swap biologic in patients not responding well to anti-IL-5 or Omalizumab

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient expert statement

Dupilumab for treating severe asthma [ID1213]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Charlotte Renwick**
2. Are you (please tick all that apply):	☐ a patient with the condition? ☐ a carer of a patient with the condition? X a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	Asthma UK
4. Did your nominating organisation submit a submission?	**X** yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**X** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☐ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: **X** I am drawing on others' experiences. Please specify how this information was gathered: We have recently conducted qualitative interviews with people with severe asthma who are being treated with biologics.
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	As highlighted in Asthma UK's submission, having severe asthma is very disruptive with regular hospital admissions and courses of oral steroids. Our recent qualitative research (not yet published), has highlighted that the consequences of this can be isolation and loneliness as well as fear and anxiety- it is much more than just the hospital visits and asthma symptoms. "But, obviously, I spent all the time in hospital. The first few times you get admitted, everybody comes to see you. But then, it gets a little bit boring and out of the way. So, friendships drift off and fall into a bit of isolation, really." (Participant 2)

	"I just wish I had been put on this biologic a lot sooner. Because the period I was suffering, you can't explain it in words. It was really, really hard for me. It was just so depressing that sometimes you think your life is just not worth living anymore." (Participant 1) "They were just saying to my husband well, we've tried everything and she's not responding. And all I could remember was the clock on the wall and I was just staring at the clock, thinking that when am I going to stop breathing because it's getting too painful, I just can't carry on anymore. And that experience, I think, is still stuck with me every time I can't breathe. It just brings all that back to me. And I think that's part of my panic and I just start breathing, getting anxiety." (Participant 1) We also found that severe asthma can have a huge impact on work or school. For example: "Yes, and the worst thing was trying to get used to it, from being such an active person and working fulltime, it was just trying to get used to it because I just couldn't work. For quite a long time, I just couldn't work" (Participant 1) "I've been off work, most of the time this year because of my asthma. I've literally had no life, really. And then when I was in Year 11, my school attendance was 43%." (Participant 5) "And then I knew it was serious when I retired from my job at the age of 30, because I was spending more time as a patient than I was as a nurse." (Participant 6) We also know from these interviews severe asthma can create a huge burden on family members. For example: "I think it was a big relief [the severe asthma diagnosis] for my parents as well, because I think they felt the burden as well. Because they had to stop work to look after me. So, obviously, they had the financial burden. I think that they felt that they were labelled as well, because I was still poorly despite them helping me administer my medication and things. Even though it was asthma, it was a separate asthma conditions, I think they felt quite relieved as well" (Participant 2).

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	Covered in Asthma UK's submission
10. Is there an unmet need for patients with this condition?	Covered in Asthma UK's submission
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	Covered in Asthma UK's submission
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	Covered in Asthma UK's submission

Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Covered in Asthma UK's submission
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Covered in Asthma UK's submission
Other issues	
15. Are there any other issues that you would like the committee to consider?	Covered in Asthma UK's submission

Key messages

16. In up to 5 bullet points, please summarise the key messages of your statement:

- The impact of severe asthma is so much more than asthma attacks and hospital admissions. It can have devastating consequences on someone's wellbeing with patients feeling isolated, lonely and scared.

Covered by Asthma UK's submission

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Patient expert statement

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Nicola Ridgway**
2. Are you (please tick all that apply):	☒ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	Asthma UK
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☒ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	To summarise my experiences over the last few years, living with asthma has been truly awful. It's impacted every area of my life from work to social-life. I feel I have wasted away so much time stuck at home or in hospital unwell and I have become scared that I may not survive some of the attacks. I am lucky in that I have continued to work but I switched my job to be home-based so I can still work but retain flexibility for treatments and being unwell so much. I have struggled to keep work going when my asthma is so uncontrolled and have had to turn down promotions and make life choices based on my asthma and current state of health. I haven't been able to progress in my career as I would have liked and had a lot of time off work. It has made working very difficult. I was diagnosed as asthmatic at 5 years old and I was brought up to believe that asthma should not dictate my life choices and wouldn't stop me doing anything I wanted. I had a couple of asthma exacerbations most years growing-up, but these were easily controlled with prednisolone and nebulisers.

	Unfortunately, as I got older my asthma deteriorated and it has taken over every aspect of my life. My asthma was very uncontrolled and I had frequent exacerbations. I was on and off steroids every 4-6 weeks and spending all my time in A&E, walk-in centres or my GP surgery. I couldn't ever make any plans as I was unwell so often and my breathing was always deteriorating rapidly. Although always under consultant care, it took a long time for anyone to realise what was going on, how severe it had gotten and to try to put a plan in place. My consultant at the time was unsure what to do with me and wondered about discharging me back to primary care, even though I had only recently been discharged from hospital with pneumonia and still had no control. I managed to find a different consultant, whom was fantastic and immediately suspected I had severe eosinophilic asthma. He took me under his care and my treatment pathway was changed to reflect the new diagnosis. When well, my lung function can be very good but I deteriorate quickly and frequently. I suffer a lot of breathlessness and become house-bound. Once formally diagnosed with eosinophilic asthma, I was put forward for Omalizumab injections. Although these helped a little, I was still living with a lot of asthma symptoms (exacerbations, breathlessness, night waking) and struggling day-to-day so I started on maintenance prednisolone. This is something I have always tried to avoid due to side-effects (impacts on bone, mood, weight and sleep) but I was left with no choice and just wanted some control. This was back in 2017 and I have remained on steroids ever since. After a year on Omalizumab my consultant suggested we try Mepolizumb as it should suppress my eosinophils and hopefully help with asthma control. I had heard Mepoliuzumab had been incredibly effective for eosinophilic asthmatics so was really hopeful. Unfortunately, despite being on it for 18months, it didn't help and I was unable to wean off steroids due to continued exacerbations. I had a particularly bad exacerbation in December 2018 and ended up in resus on Christmas Day. Unfortunately, I didn't respond to the usual treatment medications (magnesium etc) and it took a long time to stabilise me. I stayed on supplementary oxygen and was bed-bound for 7 days and in hospital for 11 days. I missed all of the Christmas and New Year period. Even after being discharged, I continued to be unwell and my respiratory system seemed hyper-sensitive and 'twitchy'. It was a very scary time for both me and my family. My family had to rush to be at my bedside and once I was finally able to get out of bed, I had to rely on my partner to wash and care for me. During my time on Mepolizumab, my FENO readings remained high so my consultant suggested I may be better suited to Dupilumab as it had been shown to improve FENO readings whilst still suppressing eosinophils. Unfortunately, as this isn't yet licensed I had to wait until December 2019 when my consultant

	eventually secured access through a compassionate use programme. The period waiting to try Dupilumab was so difficult as I felt my life was on hold. I couldn't plan to do anything as I was continuously having exacerbations and had no control over my asthma. I spent many appointments crying to my asthma nurses and consultant as I felt scared, lost and exhausted. Since starting Dupilumab in December I have seen a dramatic improvement, very quickly. It is still early days, but I have already been able to wean my steroids down. I am now able to exercise daily (something I've been unable to do for years), have lost weight and feel healthier and fitter. Finally, I feel excited and able to plan for my future. Asthma has unfortunately taken over so many years of my life and I began to feel defined by it. Finally, I feel like I am getting my life back due to Dupilumab.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	I have been lucky to try a range of treatments but it's difficult to have felt like I've 'lost' years of my life when treatments haven't worked and I've waited a long time for the right treatment to be available. The care I have received from my current consultant and respiratory team is absolutely incredible. I feel very well supported and cared for.
10. Is there an unmet need for patients with this condition?	I believe there is a desperate need for anyone not responding to other medications or ineligible for other biologics to get more support. So many of us waste valuable time with a reduced quality of life due to asthma.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	It gives asthmatics their life back. My family and friends know I am safe and well and don't have to waste time worrying about me. My parents have made frequent emergency plan trips across the world and cancelled holidays to dash to care for me in the past. My parents and partner no longer feel like my carers. I feel well for the first time in years. I am finally able to walk around and exercise which also has huge mental health and wellbeing benefits beyond asthma. Being well enough to come off steroids and

	avoiding the side effects they cause such as weight gain, osteoporosis, diabetes, insomnia etc has been my main goal.
B	
12. What do patients or carers think are the disadvantages of the technology?	It's a time commitment to attend hospital every other week for injections but this is such a small price to pay for being well.
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Severe asthmatics with high FENO.
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	N/A

Other issues	
15. Are there any other issues that you would like the committee to consider?	

Key messages

16. In up to 5 bullet points, please summarise the key messages of your statement:

- Severe impact of asthma on my everyday life and deteriorating quality of life prior to Dupilumab
- Frequent severe exacerbations and high dose steroids.
- Mine and my partner's lives were on hold as I kept getting so unwell.
- Dupilumab has changed everything for me so far. I finally feel like myself again
- Able to wean off steroids as a result of Dupilumab – something I was unable to do with the last 2 biologic treatments

Thank you for your time.

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Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

Dupilumab for treating severe asthma

Produced by Southampton Health Technology Assessments Centre

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Declared competing interests of the authors

None

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Joanne Lord critically appraised the health economic systematic review, critically appraised the economic evaluation and drafted the report. Neelam Kalita critically appraised the

health economic systematic review, critically appraised the economic evaluation and drafted the report. Geoff Frampton critically appraised the clinical effectiveness systematic review and drafted the report. David Scott critically appraised the indirect treatment comparisons and drafted the report, Joanna Picot critically appraised the clinical effectiveness systematic review, critically appraised the indirect treatment comparisons, drafted the report, project managed the review and is the project guarantor.

Word count: 57,467

[redacted]

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LIST OF ABBREVIATIONS

ACQ	Asthma Control Questionnaire
ACT	Asthma Control Test
AE	Adverse event
AESI	Adverse events of special interest
AIC	Academic in confidence
ANCOVA	Analysis of covariance
AQLQ	Asthma Quality of Life Questionnaire
ATS	American Thoracic Society
BD	Bronchodilator
BMI	Body mass index
BNF	British National Formulary
BTS	British Thoracic Society
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curves
CFB	Change from baseline
CI	Confidence interval
CIC	Commercial in confidence
CRD	Centre for Reviews and Dissemination
CSR	Clinical study report
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EMA	European Medicines Agency
EOS	Eosinophil
EQ-5D-5L	European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels
ERG	Evidence Review Group
ERS	European Respiratory Society
$FEF_{25–75\%}$	Forced expiratory flow at 25–75% forced vital capacity
FeNO	Fractional concentration of exhaled nitric oxide
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GINA	Global Initiative for Asthma
GP	General practitioner
HADS	Hospital Anxiety and Depression Scale
HCRU	Healthcare resource use
HES	Hospital Episode Statistics
HR	Hazard ratio

HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ICS	Inhaled corticosteroids
ICU	Intensive care unit
IgE	Immunoglobulin E
IL5	Interleukin 5
ITC	Indirect treatment comparison
ITT	Intent to treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
KM	Kaplan-Meier
KOL	Key opinion leader
LABA	Long-acting beta agonists
LAMA	Long-acting muscarinic receptor antagonists
LOAC	Loss of asthma control
LOCF	Last observation carried forward
LS	Least squares
LTRA	Leukotriene receptor antagonists
LY	Life year
MAIC	Matching-adjusted indirect comparisons
MCID	Minimal clinically important difference
MCS	Mental component summary
MMRM	Mixed-effect model with repeated measures
mOCS	Maintenance oral corticosteroids
N/A	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reported
OCS	Oral corticosteroid
OLE	Open-label extension
OR	Odds ratio
PAS	Patient access scheme
PCS	Physical component summary
PEF	Peak expiratory flow
PMM-MI	Pattern mixture modelling-multiple imputation
ppb	Parts per billion
PPSRU	Personal Social Services Research Unit

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
Q2W	Every 2 weeks
Q4W	Every 4 weeks
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RR	Relative risk/risk ratio
SABA	Short-acting $beta_2$-agonist
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean
SF	Short form
SIGN	Scottish Intercollegiate Guidelines Network
SmPC	Summary of product characteristics
SNOT-22	22-item sino-nasal outcome test
SoC	Standard of care
T2i	Type 2 inflammation
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TSLSE	Time since last severe exacerbation
UK	United Kingdom
US	United States
USD	United States dollars
VAS	Visual analogue scale

SUMMARY

Scope of the company submission

The company's decision problem is broadly in line with the NICE scope but considers a more restricted population (due to the marketing authorisation for dupilumab and UK clinical practice). The company also omit a comparison with omalizumab because (i) dupilumab does not have a specific indication statement for IgE-mediated asthma; (ii) IgE has not been shown to be a predictor or response to dupilumab and (iii) the company believe that patients with convincing IgE-mediated severe asthma would be treated with omalizumab. The ERG agrees with this decision.

The company's decision problem population is:

> "Patients with severe asthma on high dose ICS with EOS ≥150/μl and/or FeNO ≥25 ppb in line with the marketing authorisation and ≥3 exacerbations based upon UK clinical practice"

This is a more restricted population than that specified in the NICE scope because it limits the population to those with blood eosinophils (EOS) ≥150/μl and/or fraction of exhaled nitric oxide (FeNO) ≥25 ppb to be consistent with the licensed indication. It further limits the population to people who have experienced at least three exacerbations in the past 12 months because this is the group of patients who are referred to severe asthma centres in the UK.

The intervention is dupilumab, as an add-on to optimised standard therapy. Dupilumab is a monoclonal antibody (a type of biological therapy) that inhibits IL-4 and IL-13 signalling which are drivers of type 2 inflammation. Type 2 inflammation drives one sub-type of severe asthma which is characterised by criteria that include (but are not limited to) blood EOS ≥150 μl and/or FeNO ≥20 ppb. The ERG notes that company's decision problem specifies a higher FeNO threshold (FeNO ≥25 ppb) than is included as part of the definition of severe asthma driven by Type 2 inflammation given in the GINA guidelines[1] (FeNO ≥20 ppb).

The company's primary chosen comparator is standard care (defined as high dose inhaled corticosteroids (ICS), with or without oral corticosteroids (OCS). The company make the case that people with severe asthma with the features of Type 2 inflammation (defined by raised EOS and/or raised FeNO) are currently receiving standard care as they are not eligible for other biological therapies that target the IL-5 pathway which drives other sub-types of severe asthma. There is some overlap between the different subtypes of severe

asthma so the company conducts some exploratory pairwise analyses versus the available anti-IL5 biologics (reslizumab, mepolizumab and benralizumab).

The outcomes in the company's submission are consistent with the NICE scope.

Summary of submitted clinical effectiveness evidence

Five trials of dupilumab were identified by a broad systematic literature review that underpinned the clinical effectiveness section of the CS.

- 1x phase IIa RCT (referred to as a proof of concept study, not discussed in the CS)
- 1x phase IIb RCT, DRI12544
- 2x phase III placebo-controlled RCTs, Liberty Asthma QUEST and Liberty Asthma VENTURE (referred to throughout this report as QUEST and VENTURE, respectively).
- 1x single-arm open label extension (OLE) study, TRAVERSE, which is ongoing (no outcome data available).

The clinical evidence is drawn from three placebo controlled RCTs: DRI12544, QUEST and VENTURE. DRI12544 was a five arm RCT with two arms relevant to this STA, QUEST was a four arm RCT with two arms relevant to this STA, and VENTURE was two arm RCT with both arms relevant. The company's pivotal clinical trials enrolled a broader population than the company's decision problem population (Table 1). The CS reviews the three RCTs and presents results for the whole trial populations. Results for one outcome (annualised rate of severe exacerbations) are provided for the QUEST and VENTURE trials for the subgroup of patients matching the decision problem population.

The participants in the DRI12544 and QUEST RCTs were receiving moderate or high dose ICS as their existing background treatment but were not receiving treatment with oral corticosteroids whereas those in the VENTURE RCT had steroid-dependent severe asthma, i.e. they were receiving treatment with oral corticosteroids in addition to treatment with high dose inhaled corticosteroids and a second controller medication.

Table 1 Summary of the three RCTs contributing clinical evidence in the CS

RCT	**DRI12544**		**QUEST**		**VENTURE**	
Patient group	Adults (≥18 years) with moderate-to-severe asthma		Adults and adolescents (≥12 years) with uncontrolled moderate-to-severe asthma		Adults and adolescents (≥12 years) with steroid-dependent severe asthma	
Existing background treatment	Moderate or high dose ICS/LABA		medium-high dose ICS plus second/third controller (LABA,LTRA)		regular prescribed systemic CS, treatment with high dose ICS plus second controller (LABA or LTRA)	
Relevant RCT arms	SC Dup 200 mg Q2W	PBO	SC Dup 200mg Q2W	PBO	SC Dup 300mg Q2W	PBO
No. of patients (ITT population)	150	158	631	317	103	107
Decision problem population, n (% of ITT)	22 (14.7%)	24 (15.2%)	64 (10.1%)	37 (11.7%)	78 (75.7%)	74 (69.2%)

Dup, Dupilumab; ITT, intention to treat; No., Number; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; SC, subcutaneous

The CS presents the clinical effectiveness evidence in the following locations:

- Results from the ITT populations of the three dupilumab RCTs and the one outcome for the subgroup matching the decision problem (two RCTs) in CS Document B
- Results from Bucher ITCs and matching adjusted indirect comparisons (MAIC) for comparisons with reslizumab, mepolizumab and benralizumab in CS Appendices N and O

Results from the three dupilumab RCTs

All three trials reported the annualised rate of severe exacerbations. This was one of the two co-primary outcomes of the QUEST RCT, a secondary outcome of the DRI12544 RCT and an 'other' outcome of the VENTURE RCT. This was also the only outcome reported for the post-hoc subgroups of QUEST and VENTURE that reflected the decision problem population definition. Dupilumab reduced the rates of severe exacerbations in the ITT populations of all three trials. Dupilumab also reduced the rates of severe exacerbations in the post-hoc subgroups of QUEST and VENTURE that reflected the decision problem

population (QUEST: [redacted], 95% CI [redacted] lower rate of severe exacerbations in the dupilumab group, p<0.0001; VENTURE: [redacted], 95% CI [redacted] lower rate of severe exacerbations in the dupilumab group in comparison to the placebo group, p<0.0010). The time to the first severe exacerbation event was also significantly delayed in the two trials (QUEST and VENTURE) that reported this outcome.

Change from baseline in FEV_1 was also reported in all three trials and was the primary outcome for the DRI12544 RCT and a co-primary outcome in the QUEST RCT. In the DRI12544 and QUEST RCTs improvements in FEV_1 at 12 weeks occurred in dupilumab and placebo arms but the increase was greater in the dupilumab arms and exceeded the minimal clinically important difference. The improvement in FEV1 in the dupilumab arm in comparison to the placebo arm was sustained in both trials throughout the trial period (24 weeks for DRI12544 and 52 weeks for QUEST). In the VENTURE trial FEV1 increased from baseline in the dupilumab arm but not in the placebo arm. At 24 weeks, the mean difference between the arms in change from baseline was statistically significant.

The primary outcome for the VENTURE trial, which enrolled participants who were receiving treatment with OCS, was the reduction in OCS dose at week 24. A greater reduction in OCS dose was reported for the dupilumab arm than for the placebo arm (mean reduction 73.85 mg/day vs 45.28 mg/day in the placebo arm). The LS mean difference versus placebo was 28.24 mg (95% CI 15.81 to 40.67, p<0.0001). Secondary outcomes in the VENTURE trial also related to reductions in OCS use at week 24 (probability of patients achieving ≥50% reduction in OCS dose, probability of patients achieving reduction in OCS dose to <5mg/day, proportion of patients no longer requiring OCS) all showed a statistically significant effect in favour of dupilumab.

Asthma control was measured in all three trials by the asthma control questionnaire (either ACQ-5 or ACQ-7). This is a patient-reported measure and a reduction in ACQ score indicates an improvement in asthma control. The least squares (LS) mean difference in the reduction in the dupilumab arm versus the placebo arm at 12 weeks (DRI12544, ACQ-5) or at 24 and 52 weeks (QUEST, ACQ-7) was in favour of dupilumab and statistically significant in both trials. In the VENTURE trial a greater improvement in asthma control (measured by the ACQ-7) was observed in the dupilumab group in comparison to the placebo group but no p-value was reported.

Loss of asthma control (which was defined slightly differently in the DRI12544 and QUEST trials) was an outcome that was used in calculating the moderate exacerbation health state

in the economic model. In both trials the adjusted LOAC event rate was lower in the dupilumab arm than the placebo arm. This outcome was not measured for the VENTURE trial.

Other outcomes reported in the CS (reduced FeNO levels in all three trials and morning and evening PEF for the QUEST trial only) were also in favour of dupilumab.

Subgroup analyses of the primary outcomes for QUEST based on baseline EOS, baseline FeNO and baseline ICS provided some evidence that people with lower baseline blood eosinophil levels, and lower baseline FeNO levels obtained less benefit from dupilumab than people with higher levels of EOS and FeNO. Subgroup results for people receiving high dose ICS at baseline were consistent with those of the ITT population.

Health related quality of life was measured using the EQ-5D-3L (DRI12544) or EQ-5D-5L (QUEST and VENNTURE). Aside from statistically significant differences in the change from baseline scores at weeks 24 and 52 in the QUEST trial (but not at weeks 12 or 36) no significant differences in the change from baseline EQ-5D scores were observed.

Subgroup analyses of the primary outcome for VENTURE based on baseline EOS and baseline FeNO provided some evidence that a reduction in OCS dose at week 24 (whilst maintaining asthma control) was achieved by all participants.

Adverse events are presented for all three trials, also including data from the trial study arms that were not relevant to this STA. The company do not indicate what the overall exposure was to dupilumab in the trials. Treatment-emergent adverse events were experienced by participants in the dupilumab and placebo arms of all three trials to a similar degree. The proportion of treatment-emergent serious adverse events ranged from 4.0% to 10.2% and the ERG calculated that the proportions of participants experiencing serious events was similar in dupilumab and placebo treated patients (less than 8%). No deaths were attributed to dupilumab.

Indirect treatment comparisons

No head-to-head comparisons of dupilumab versus reslizumab, mepolizumab or benralizumab were identified by the company and the available evidence precluded an NMA. Therefore “exploratory pairwise analyses” by two indirect treatment comparison (ITC) methods [Bucher ITC and matching adjusted indirect comparisons (MAIC)] were conducted. The purpose of the MAIC was to compliment the findings from Bucher

analysis. ITC results were reported in the CS for the outcomes of:

- The rate of severe exacerbations (uncontrolled asthma population and OCS dependent asthma population
- Reduction in OCS dose <5mg/day; reduction in OCS dose ≥50%; 100% reduction in OCS dose (in the OCS dependent asthma population)

The Bucher ITC results for rate of severe exacerbations, and 100% reduction in OCS dose informed exploratory cost-effectiveness analyses. The MAIC results were used in a scenario analysis.

Bucher ITC methods

For the Bucher ITCs subgroup dupilumab data were generated, breaking randomisation. The dupilumab subgroups were created because of heterogeneity between the dupilumab trial data and the comparator trial data and they were obtained by matching individual patient data from the dupilumab trials to:

- the inclusion criteria and baseline values of the patients in the registrational trials for the US/global label of each comparator IL-5 biologic.
- A comparator subgroup that was more closely aligned with, but not identical to, the population described in NICE guidance as eligble for treatment with that comparator. This was only possible when such a comparator subgroup was available.

Thus none of the dupilumab subgroups formed for Bucher ITCs precisely matched the populations of patients who would be eligible for comparator treatment as per NICE guidance on reslizumab, mepolizumab and benralizumab.

Once the subgroup dupilumab data had been generated by the matching process pairwise Bucher ITCs were conducted in two steps:

1. Where there were multiple trials (or for dupilumab, the subgroups from trials) for the same comparison, data were pooled using classical (frequentist) random-effects meta-analysis.

2. The pooled estimates (or study level data if no pooling was needed) for each biologic versus placebo were used to derive the pairwise Bucher ITC estimates for dupilumab versus each of the IL-5 biologics.

MAIC methods

The MAICs were conducted following the methods provided in the NICE Decision Support Unit (DSU) technical support document[2] and Signorovitch et al, 2012[3]. Patient level data from the DRI12544 and QUEST RCTs were pooled to increase the sample size and

diversity in the index patient population. DRI12544 trial was subject to a seasonality adjustment because of its shorter length (24 weeks in DRI12544 and 52 weeks in QUEST). The pooled data were then filtered using data filters to include dupilumab patients in the MAIC who may have been eligible for inclusion in the comparator clinical trials based on ICS/LABA level, blood EOS level, number of prior exacerbations in the past year and age.

Four important treatment effect modifiers were identified: blood EOS level, number of exacerbations, nasal polyps and fractional nitric oxide concentration in exhaled breath. The filtered dupilumab pooled population and the comparator populations were then matched on the agreed set of effect modifiers. However, for some trials matching was on fewer than the four factors due to data limitations. Where there were multiple RCTs for each comparator, the matching was conducted for each comparator RCT separately then results were pooled. This is an approach the ERG believes is flawed. After matching the effective sample sizes seemed reasonable in most cases. The Company reported that matching was successful but the ERG observed that in some mepolizumab analyses small proportions of patients attracted disproportionately high weights and thus relatively few patients would drive the results.

Indirect treatment comparison results

There are limitations to both the Bucher ITC and MAIC methods so the results should be interpreted cautiously. However the ERG is mindful that these ITC approaches, even though limited by the available data, are likely to be the best currently available option to enable comparisons between dupilumab and other IL-5 biologics in the NICE scope.

<u>Bucher ITC results</u>

The outcomes were numerically consistently in favour of dupilumab, however, the confidence intervals frequently crossed or reached the line of no effect. Therefore the majority of results would not be considered statistically significantly in favour of dupilumab. The exceptions were that in dupilumab subgroups matched to the comparator labels, dupilumab led to fewer severe exacerbations in the uncontrolled persistent asthma population than either benralizumab (rate ratio [redacted] or reslizumab (rate ratio [redacted].

<u>MAIC results</u>

MAIC results were similar to the Bucher ITC results although for some comparisons and outcomes the numerical result was not in favour of dupilumab (and was not statistically significant).

Summary of submitted cost effectiveness evidence

The CS includes:

- A systematic review of published economic evaluations for moderate to severe asthma.
- A description of the company's de novo model developed to assess the cost-effectiveness of dupilumab in its licensed indication as add-on therapy for adults and adolescents with severe asthma.

Review of published economic analyses

The company conducted a search to identify studies assessing the cost, healthcare use and cost-effectiveness of interventions for the treatment of moderate-to-severe asthma. The company identified 29 economic evaluations of treatments for severe uncontrolled asthma. Of these, 15 studies included treatments identified in the NICE decision problem. Five of these studies were UK based, of which three informed previous NICE TAs (TA479, TA431, and TA565). One of the included studies assessed the cost-effectiveness of dupilumab as an add-on therapy in adults and children aged ≥ 6 years with moderate-to-severe uncontrolled asthma with evidence of T2i. This US based study[4] developed a Markov model for a lifetime horizon from the perspective of healthcare sector and reported the ICERs for dupilumab + standard care versus standard care of $351,000 per QALY.

Description of the company's economic model

The company developed a model to assess the cost-effectiveness of dupilumab compared with background therapy (standard care) alone. The Markov model contains four live health states: controlled asthma, uncontrolled asthma, moderate exacerbation and severe exacerbation. In addition, the model includes states for asthma-related deaths and death from other causes; and for patients who enter the model taking maintenance oral corticosteroids (OCS), the proportions of patients who change to a lower dose (< 5mg per day) or who stop OCS use are estimated. The model uses a lifetime horizon (up to a maximum age of 100 years). Costs and QALYs are discounted at an annual rate of 3.5%.

The cohort enters the model in the uncontrolled asthma health state. At each four-week cycle, people in the live health states may remain in the same health state, transition to one of the other three live health states or die from asthma-related or other causes. Rates of movement between the live states are regulated by a transition probability matrix and mortality rates are applied for asthma and other deaths. Transition probabilities between health states are derived from the observed data for the relevant populations from the

QUEST and VENTURE clinical trials for dupilumab and standard care. These probabilities are adjusted for other biologic comparators (mepolizumab, reslizumab and benralizumab) using relative treatment effects estimated from the Bucher ITC comparisons (and from the MAICs in scenario analysis). Relative treatment effects are only available for severe exacerbations, OCS dose reduction and withdrawal. Other outcomes (incidence of moderate exacerbations and changes in asthma control) are assumed the same for dupilumab and other biologic comparators.

For the add-on treatments, the model includes a response assessment at 52 weeks, at which time non-responders stop the add-on and continue on standard care alone. Responders continue add-on treatment but may subsequently stop as a constant long-term risk of discontinuation is applied after 52 weeks to reflect 'natural attrition'. No residual effect of treatment is assumed after discontinuation.

The model accumulates costs associated with drug acquisition, administration and monitoring as well as routine care and management by health state and treatment for OCS-related adverse events. QALYs are estimated by applying utilities to time spent in the controlled and uncontrolled asthma health states and disutilities for moderate and severe exacerbations and for OCS-related adverse events. Base case utility estimates were taken from an analysis of EQ-5D data from the QUEST and VENTURE trials, supplemented with estimates from the literature. The model does not include any cost or disutility for adverse events associated with the biologic or other medications.

The company's cost-effectiveness results

The submission reports four sets of cost-effectiveness results, defined by patient subgroup and included comparators:

- *Base case analysis*: dupilumab versus standard care only for people with EOS ≥ 150 or FeNO ≥ 25 and at least 3 exacerbations in the previous year.
- *Mixed scenario*: dupilumab versus standard care only for people with EOS ≥ 150 or FeNO ≥ 25 and at least 3 exacerbations in the previous year or on maintenance OCS.
- *Mepolizumab eligible subgroup*: duplilumab versus mepolizumab, benralizumab or standard care for people with EOS ≥ 300 and at least 4 exacerbations in the previous year or on maintenance OCS.

- *Reslizumab eligible subgroup*: duplilumab versus reslizumab, benralizumab or standard care for people with EOS ≥ 400 and at least 3 exacerbations in the previous year

The company urge caution in drawing conclusions from the results for the latter two, 'exploratory' analyses, as these are based on comparative effectiveness estimates for the biologic treatments from the Bucher ITC analyses, which have limitations.

Results for the four analyses are shown in the following tables. These include a confidential PAS discount price for dupilumab. The company also included an assumed price reduction of [redacted] for mepolizumab, reslizumab and benralizumab. This does not represent the true price of these drugs to the NHS. We report results including agreed confidential PAS discounts for all comparators in a confidential addendum to this report.

Table 2 Deterministic results: company base case EOS≥150 or FeNO≥25 and ≥3 exacerbations in previous year (non-mOCS), with discounted price for dupilumab

Technology	Cost	QALYs	ICER (£/QALY)
Standard care	[redacted]	[redacted]	Reference
Dupilumab	[redacted]	[redacted]	£28,087

Source: CS Table 89

Table 3 Deterministic results: company EOS≥150 or FeNO≥25 and ≥3 exacerbations in previous year or mOCS (41.7%), discounted price for dupilumab

Technology	Cost	QALYs	ICER (£/QALY)
Standard care	[redacted]	[redacted]	Reference
Dupilumab	[redacted]	[redacted]	£ 35,486

Source: CS Table 92

Table 4 Deterministic results: company EOS ≥300 and ≥4 exacerbations or mOCS (41.7%), confidential discounted price for dupilumab and assumed [redacted] discount for mepolizumab and benralizumab

Technology	Cost	QALY	ICER (£/QALY) incremental analysis	ICER (£/QALY) Dupilumab vs. comparator
Standard care	[redacted]	[redacted]	-	£29,215
Mepolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab	[redacted]	[redacted]	£ 29,215	Reference
Benralizumab	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS Table 143

Table 5 Deterministic results: company EOS ≥400 and ≥3 exacerbations in previous year, discount for dupilumab and assumed reduction of [redacted] for other biologics

Technology	Cost	QALY	ICER (£/QALY) incremental analysis	ICER (£/QALY) Dupilumab vs. comparator
Standard care	[redacted]	[redacted]	Reference	£23,923
Dupilumab	[redacted]	[redacted]	£ 23,923	Reference
Benralizumab	[redacted]	[redacted]	[redacted]	[redacted]
Reslizumab	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS Table 148

The company draw the following conclusions:

- Dupilumab is a cost-effective addition to standard treatment for people with severe asthma driven by Type 2 inflammation, defined by EOS≥150 or FeNO and at least 3 exacerbations in the previous year and not on maintenance oral corticosteroids.
- It “may be considered cost-effective” compared with standard care in a mixed population.
- Cost-effectiveness results compared with other biologics is presented for information purposes only and should be interpreted with caution.
- The cost-effectiveness of dupilumab is most sensitive to the proportions of severe exacerbations that are fatal and parameters that influence the long-term incidence of severe exacerbations.

- However, "*it has been demonstrated that the trial design is likely to reflect lower rates of exacerbations, in addition to excluding patients most likely to exacerbate. Therefore, an increase in exacerbation rates could be anticipated in the real world.*" (CS B.3.11.1)

Commentary on the robustness of submitted evidence

Strengths

Clinical effectiveness

The company conducted a systematic review for relevant trials the ERG believes all the relevant evidence for dupilumab has been identified. The trials of dupilumab are of good quality.

Cost effectiveness

The structure of the economic model is appropriate, accurately implemented and similar to other models developed to inform NICE technology appraisals for severe asthma. The transition probabilities between the model health states during the trial period were estimated appropriately from individual patient data from the QUEST and VENTURE clinical trials. Outcomes related to OCS use were appropriately modelled, including the impact of dose reduction and withdrawal estimated from the VENTURE trial, and the model included estimates of the cost and QALY loss associated with OCS related adverse events. Utility values were estimated from trial EQ-5D-5L data, appropriately valued using the crosswalk procedure with UK tariff. Cost assumptions were mostly appropriate. The company report a good range of scenarios, illustrating the impact of alternative data sources or assumptions on model results.

Weaknesses and areas of uncertainty

Clinical effectiveness

The included dupilumab trials enrolled a wider population group that that specified by the NICE scope and the company's own decision problem. In the DRI12544 and QUEST trials a minority of the ITT population match the decision problem population (14.9% and 10.7% respectively); in VENTURE more than two thirds (72%) of the ITT population match the decision problem population. The only outcome reported for the subgroup of trial participants who match the company's decision problem was the adjusted annualised rate of severe exacerbation events.

The anti-IL5 biologics are a relevant comparator to dupilumab for an overlap population of patients with the features of type 2 inflammation and eosinophilic asthma but no head-to-head evidence was available. Therefore an ITC approach was needed to compare dupilumab with reslizumab, mepolizumab and benralizumab. However heterogeneity between the dupilumab and comparator trials (which is not fully described or tabulated in the CS) led the company to select subgroups of their trial data for their Bucher ITCs in an effort to more closely match the comparator data. Use of subgroups breaks randomisation in the dupilumab trials. Furthermore none of the dupilumab subgroups created precisely match the populations of patients who would be eligible for comparator treatment as per NICE guidance on reslizumab, mepolizumab and benralizumab. MAICs were conducted to compliment the findings from Bucher analyses but not all treatment effect modifiers could be matched on and each comparator trial was matched to in turn (when there were multiple trials for a comparator) with the results then pooled. Therefore there are limitations to the Bucher ITC and MAIC approaches which mean the findings are unlikely to be robust.

Cost effectiveness

The ERG considers that there are four main weaknesses of the company's economic evaluation. Firstly, we understand that asthma-related mortality estimated in the company's base case analysis is unrealistically high: with an mean initial age of 47, 20% are estimated to have died within 10 years. We are satisfied that the base case inputs for severe exacerbation fatality by age and location of treatment are appropriate, as they match values accepted by the committee in a recent NICE appraisal (TA565). However, the assumed proportions of severe exacerbations treated in A&E (7.8%) or hospital (18.7%) are higher than in previous appraisals or the dupilumab clinical trials.

Secondly, there is considerable uncertainty over the long-term rates of severe exacerbations. The company applies a multiplier of [redacted] to increase the rate after the trial period. This is intended to adjust for the exclusion of people with a recent exacerbation from the clinical trials, which the company leads to an underestimate of rates for the relevant population. However, the question of why exacerbation rates during clinical trials tend to be lower than previous rates for patients randomised to both active and placebo treatments, and whether and how this should be corrected for, is controversial. NICE guidance for benralizumab and reslizumab (TA565 and TA479) was based on observed trial data only (with no assumed long-term increase), while the guidance for mepolizumab used a lower multiplier (1.35).

The third main weakness relates to the definition of the population in the company's base case analysis. This is EOS≥150 or FeNO≥25 and at least 3 exacerbations in the previous year. However, this population includes patients who meet criteria for access to other biologic treatments and who are at higher risk of exacerbations and uncontrolled asthma. Pooling these higher-risk subgroups with lower-risk subgroups who are not currently eligible for biologic treatment will give an unrealistic estimate of cost-effectiveness. The TA565 committee concluded that cost-effectiveness estimates for such a mixed population were not suitable for decision making. A similar issue arises for mixed population of people taking and not taking maintenance oral corticosteroids, although the company does not use this approach in their base case.

The final main weakness of the submitted model relates to limitations in the estimates of relative effectiveness for dupilumab compared with other biologics. As discussed above, the robustness of both Bucher ITC and MAIC analyses is questionable. This means that it is difficult to draw meaningful conclusions about the cost-effectiveness of dupilumab compared with other biologics in overlap populations who might receive either treatment.

Summary of additional work undertaken by the ERG

The ERG conducted four additional scenario analyses to assess the robustness of the company's base case analysis.

- Utility for controlled asthma limited to the age-related general population mean
- Discontinuation of add-on biologic treatments at the same rate as observed in the clinical trial before the 12 month response assessment as well as after
- NHS Reference costs as source for unit cost estimates for A&E attendances and hospitalisation for severe exacerbation
- No self-administration of subcutaneous injections

The company's results were generally robust to these assumptions, across all four patient patient subgroups (base case, mixed mOCS/ non mOCS, mepolizumab eligible and reslizumab eligible).

ERG base case and scenarios

We included five changes to the company base case in our preferred analysis:

1) No adjustment to severe exacerbation rates after the trial period
2) Distribution of treatment settings for severe exacerbations based on trial data
3) Utility for controlled asthma limited to the age-related general population mean
4) Discontinuation of add-on biologic treatments at the same rate as observed in the clinical trial before the 12 month response assessment as well as after
5) NHS Reference costs as source for unit cost estimates for A&E attendances and hospitalisation for severe exacerbation

The first two changes led to a sizeable increase in the estimated ICERs. The cap on utility led to a modest increase and the impact of the discontinuation and cost changes were negligible The results from this ERG base case are shown in Table 6.

Table 6 Deterministic results: ERG base case EOS≥150 or FeNO≥25 and ≥3 exacerbations in previous year (non-mOCS), with discounted price for dupilumab

Technology	Cost	QALYs	ICER (£/QALY)
Standard care	[redacted]	[redacted]	
Dupilumab	[redacted]	[redacted]	£55,348

This estimate remained above £30,000 per QALY gained across a range of scenarios, including use of the company's base case multiplier for the long-term rate of severe exacerbations ([redacted]) which reduced the ICER to £37,533.

The company's results for the mixed population are sensitive to the proportion of patients taking mOCS at baseline. The company's base case ICER increases from £28,087 with no mOCS patients; to £31,682 with 20% mOCS; £35,486 with 41.7% mOCS; and £45,240 with 100% mOCS.

We also considered cost-effectiveness in subgroup for whom standard care is the only treatment option. We approximated this by taking a weighted difference between results for the company's target population (EOS≥150 or FeNO≥25 and ≥3 prior exacerbations) and a subgroup who meet NICE criteria for access to either mepolizumab or reslizumab. In both cases, the ICERs increase when patients who would be eligible for other biologics are excluded. This is not surprising, given that biologic treatment is estimated to be more cost-effective for people with more 'severe' asthma (as indicated by higher EOS levels or more prior exacerbations).

Results of the ERG base case and scenarios for the subgroups of patients who are eligible for treatment with other biologics, which include confidential PAS discounts for other comparators as well as dupilumab, are presented in a confidential addendum to this report.

1 Introduction to ERG Report

This report is a critique of the company's submission (CS) to NICE from Sanofi on the clinical effectiveness and cost effectiveness of dupilumab for treating severe asthma. It identifies the strengths and weakness of the CS. Clinical experts were consulted to advise the evidence review group (ERG) and to help inform this review.

Clarification on some aspects of the CS was requested from the company by the ERG via NICE on 28th August 2019. A response from the company via NICE was received by the ERG on 24th September 2019 and this can be seen in the NICE committee papers for this appraisal. CSRs for two of the included studies were not accessible to the ERG when originally received but accessible versions were provided on request.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

The CS provides an overview of asthma, including severe asthma, in CS B.1.3.1. The definitions of severe asthma in the British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) guidelines, the Global Initiative for Asthma (GINA) guidelines and the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines are slightly different (Table 7 below). The CS definition of severe uncontrolled asthma is based on previous severe asthma health technology appraisals (not further specified in the CS) that describe a cohort of patients who are referred to severe asthma centres. The CS definition of severe asthma is therefore relevant to UK practice and is the one used in this report.

Table 7 Definition of severe uncontrolled asthma in the CS and definitions of severe asthma in different guidelines

CS	Severe uncontrolled asthma is defined in the CS as ≥3 severe asthma exacerbations in the previous 12 months whilst on concomitant high dose inhaled corticosteroid (ICS) and/or oral corticosteroid (OCS).
BTS/SIGN[5]	Two or more severe asthma attacks a year or persistent symptoms with short-acting beta$_2$-agonist (SABA) use more than twice a week despite specialist-level therapy.

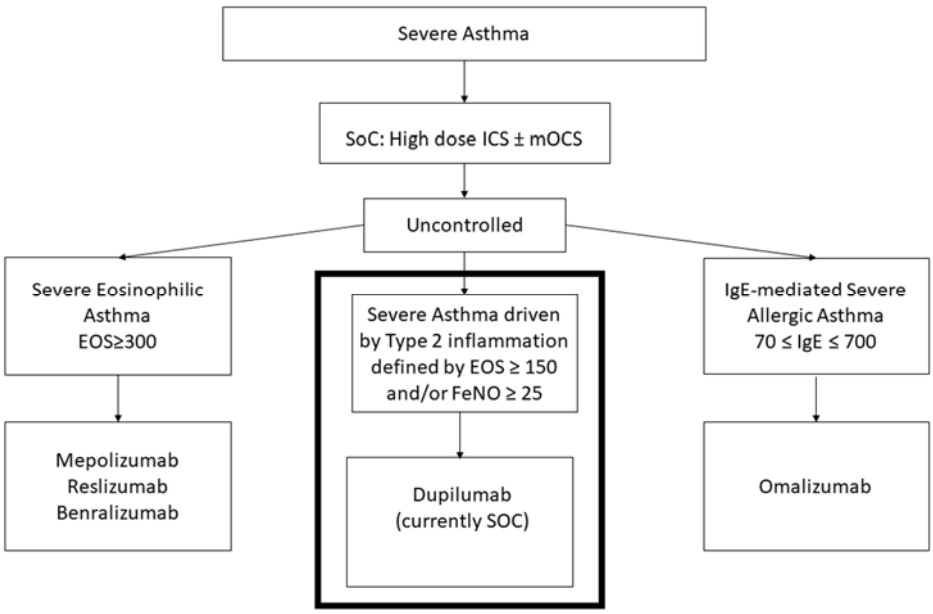
GINA[1]	Asthma that is uncontrolled despite adherence with maximal optimized therapy and treatment of contributory factors, or that worsens when high dose treatment is decreased
ATS/ERS[6]	Patients are defined as having severe asthma if they experience any of the following criteria: Poor symptom control: Asthma Control Questionnaire (ACQ) consistently ≥1.5 or Asthma Control Test (ACT) <20 (or "not well controlled" by National Asthma Education and Prevention Program [NAEPP] or GINA guidelines) Frequent severe exacerbations: ≥2 bursts of systemic corticosteroids (≥3 days each) in the previous year Serious exacerbations: ≥1 hospitalisation, intensive care unit (ICU) stay, or mechanical ventilation in the previous year Airflow limitation: Forced expiratory volume in 1 second (FEV1) <80% of predicted value, in the presence of reduced FEV1/forced vital capacity [FVC] ratio (defined as less than the lower limit) following a withhold of both short- and long-acting bronchodilators (BD).

In addition to defining severe uncontrolled asthma the CS also describes the different subtypes of severe asthma, focussing on severe eosinophilic asthma, severe asthma driven by Type 2 inflammation and immunoglobulin E (IgE) mediated severe allergic asthma. Determining the subtype of severe asthma that a patient has is important in guiding treatment decisions. The subtype of severe asthma also has an important influence on the comparisons made and analyses presented in the CS. In CS Figure 5 (reproduced below as Figure 1) these subtypes of severe asthma are implied to be mutually exclusive but this is a simplification. The ERG sought expert clinical advice regarding any potential overlap between these subgroups of patients. The clinicians were in agreement that in reality there would be overlap between the different subtypes of asthma and the groups are not as distinct as the company implies in their figure. The clinicians had differing views regarding the extent to which the different subtypes of asthma might overlap. One described the overlap as minimal and the other suggested that at least 75% of patients with "EOS >150 and/or FeNO>25" would meet the criteria of one of the other two groups, highlighting one French study[7] in which 50% of patients treated with omalizumab had a blood eosinophil count of over 300. In Figure 1, the company defines severe asthma driven by Type 2 inflammation by blood eosinophils (EOS) ≥ 150 cells/μl and/or fractional concentration of exhaled nitric oxide (FeNO) ≥25 parts per billion (ppb). The ERG notes that this is a more restricted definition than the GINA guidelines[1] which

specify that severe asthma driven by Type 2 inflammation is indicated when any of the following criteria are met:

- Blood EOS ≥150 µl and/or
- FeNO ≥20 ppb and/or
- Sputum EOS ≥2% and/or
- Asthma is clinically allergen-driven and/or
- Need for maintenance oral corticosteroids

The company's definition of asthma driven by Type 2 inflammation therefore rests solely on the first two items in the GINA list (with the threshold for FeNO being slightly higher at 25 ppb versus 20 ppb in the GINA list). It does not depend on the presence of sputum EOS ≥2%, asthma that is clinically allergen-driven or asthma with a need for maintenance oral corticosteroids.



Source: reproduction of CS Figure 5

Figure 1 Position of dupilumab in the treatment pathway

2.2 Critique of company's overview of current service provision

The CS describes the clinical pathway of care in CS B.1.3.3 and explains that biologic therapies have been introduced for some of the specific subtypes of severe asthma, as shown in Figure 1. In England omalizumab (TA278[8]), reslizumab (TA479[9]), mepolizumab (TA431[10]) and benralizumab (TA565[11]) are recommended by NICE for patients who meet specific criteria as shown in Table 8. The only treatment option for patients with severe asthma who do not meet the criteria for treatment with omalizumab, reslizumab,

mepolizumab or benralizumab has been high dose ICS with or without oral corticosteroids (i.e. standard of care; SoC). The company state that the unmet need addressed by dupilumab is people with severe uncontrolled asthma with type 2 inflammation (characterised by EOS ≥ 150 and FENO ≥ 25ppb) and without hypereosinophilia.

Table 8 NICE recommended therapies for severe asthma subtypes

Treatment options	NICE recommended population
Asthma sub-type: Severe eosinophilic asthma	
Reslizumab	adults with severe eosinophilic asthma that is inadequately controlled despite maintenance therapy with high-dose inhaled corticosteroids plus another drug, only if: • the blood eosinophil count has been recorded as 400 cells/μl or more • the person has had 3 or more severe asthma exacerbations needing systemic corticosteroids in the past 12 months
Mepolizumab	adults with severe refractory eosinophilic asthma, only if: the blood eosinophil count is 300 cells/μl or more in the previous 12 months and • the person has agreed to and followed the optimised standard treatment plan and • has had 4 or more asthma exacerbations needing systemic corticosteroids in the previous 12 months or • has had continuous oral corticosteroids of at least the equivalent of prednisolone 5 mg per day over the previous 6 months
Benralizumab	adults with severe eosinophilic asthma that is inadequately controlled despite maintenance therapy with high-dose inhaled corticosteroids and long-acting beta-agonists, only if: • the person has agreed to and followed the optimised standard treatment plan and • the blood eosinophil count has been recorded as 300 cells/μl or more and the person has had 4 or more exacerbations needing systemic corticosteroids in the previous 12 months, or has had continuous oral corticosteroids of at least the equivalent of prednisolone 5 mg per day over the previous 6 months (that is, the person is eligible for mepolizumab) or

	• the blood eosinophil count has been recorded as 400 cells/μl or more with 3 or more exacerbations needing systemic corticosteroids in the past 12 months (that is, the person is eligible for reslizumab)
Asthma sub-type: IgE-mediated severe allergic asthma	
Omalizumab	for treating severe persistent confirmed allergic IgE-mediated asthma as an add-on to optimised standard therapy in people aged 6 years and older: • who need continuous or frequent treatment with oral corticosteroids (defined as 4 or more courses in the previous year)

2.3 Critique of company's definition of decision problem

Population

The NICE scope specifies the population of interest as:
"People 12 years and older with severe asthma inadequately controlled with optimised standard therapy (including moderate or high dose inhaled corticosteroid, and either long-acting beta-2 agonist, leukotriene receptor antagonist, slow-release theophylline or long-acting muscarinic agent)".

In contrast, the population described by the company's decision problem is "Patients with severe asthma on high dose ICS with EOS ≥150/μl and/or FeNO ≥25 ppb in line with the marketing authorisation and ≥3 exacerbations based upon UK clinical practice" (CS Table 1). This population is appropriate for the NHS and the clinicians the ERG contacted agreed that these patients could be identified in clinical practice because both EOS and FeNO are routinely measured in specialist asthma clinics. This population is also in line with the licensed indication for dupilumab which is: "adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood EOS and/or raised FeNO, who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment" (CS Table 2).

In comparison to the NICE scope, the company's decision problem population is a more restricted population because it is limited to those with blood eosinophils (EOS) ≥150/μl and/or fraction of exhaled nitric oxide (FeNO) ≥25 ppb to be consistent with the licensed indication. It further limits the population to people who have experienced at least 3

exacerbations in the past 12 months because it is this group of patients who are referred to severe asthma centres in the UK.

Intervention

The intervention in the company's decision problem is dupilumab as an add-on to optimised standard therapy (CS Table 1). No dose is given in the decision problem but the dosing regimens described in the SmPC are described in CS Table 2. The dose given differs depending on whether the patient (12 years of age and older) is on oral corticosteroids or not.

For patients with severe asthma (as defined in the SmPC) an initial dose of 400 mg (two 200 mg injections), followed by 200 mg is given every other week, administered by subcutaneous injection. For patients with severe asthma and who are on oral corticosteroids, an initial dose of 600 mg (two 300 mg injections), followed by 300 mg every other week is administered by subcutaneous injection. This dosing also applies to patients with comorbid moderate-to-severe atopic dermatitis.

Comparators

The comparator in the company's decision problem is standard of care (SoC) defined as high dose ICS, with or without OCS. However, due to the overlap between the subgroups of severe asthma types the company also presents exploratory pair-wise analyses against the anti-IL5 biologics reslizumab, mepolizumab and benralizumab. The company does not include omalizumab as a comparator because they considered it out of scope for the following reasons: dupilumab does not have a specific indication statement for IgE-mediated asthma; IgE has not been shown to be a predictor or response to dupilumab; the company believe that patients with convincing IgE-mediated severe asthma (even if they may also have indicators of type 2 inflammation defined by raised EOS and/or FeNO) would be treated with omalizumab (clarification question A1). The ERG agrees that because of the reasons stated, and because of differences between the dupilumab and omalizumab clinical trials, a comparison with omalizumab would have been unreliable.

Outcomes

The outcomes listed in the company's decision problem match those in the NICE scope and they are appropriate and clinically meaningful.

Other relevant factors

The NICE scope indicated that if the evidence allows the following subgroups of people will be considered:

- People who require maintenance oral corticosteroid treatment compared with people who are not steroid dependant
- People with eosinophilic asthma
- People with allergic IgE- mediated asthma

The company's decision problem does not specify any subgroups; however, the ERG notes that:

- The clinical evidence includes populations who require maintenance oral corticosteroid treatment and those who are not steroid dependent.
- exploratory pairwise economic analyses supported by exploratory indirect treatment comparisons (ITCs) are presented for populations with severe eosinophilic asthma meeting the criteria for treatment with either mepolizumab, reslizumab or benralizumab.

No issues related to equity or equality are noted in the NICE scope or decision problem.

Summary: The company's decision problem is broadly in line with the NICE scope but considers a more restricted population (due to the marketing authorisation for dupilumab and UK clinical practice) and omits a comparison with omalizumab.

3 CLINICAL EFFECTIVENESS

3.1 Critique of company's approach to systematic review

3.1.1 Description of company's search strategy

The CS details the following literature searches:

- Clinical effectiveness, 1980-June 2017, updated twice to cover June 2017-November 2017 and August 2017-March 25th 2019
- HRQoL and utility of patients with moderate-to-severe asthma, 2004-March 15th 2019
- Cost and healthcare resource use (HCRU), 2014-March 15th 2019
- Economic evaluations related to available treatment options, 2009-March 15th 2019

The search strategy for the clinical effectiveness SLR is detailed in Appendix D of the CS. Relevant databases were searched and the strategies are clearly reproduced with the number of hits returned per line, including for each of the two updates. The combinations of subject headings and free text terms are appropriate to the PICO-T and each one is helpfully annotated to show groups of terms and how they are combined. The company included handsearching of recent conference proceedings (2015-2018) for the American Thoracic Society (ATS) conference and the European Academy of Allergy & Clinical Immunology (EAACI) congress. The search process was adapted to include handsearching where the conferences were not indexed in Embase. In addition, the bibliographies of relevant SLRs identified across the electronic database searches were screened by the company to check for any additional relevant references.

The Cochrane Central Register of Controlled Trials was searched by the company, however it is not reported that any further trials databases were searched, and ongoing trials do not appear to have been reported. The ERG searched ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) trial databases and found no further clinical trials of relevance to this STA.

The ERG updated the search to cover the 6 months since March 2019 by carrying out a search of the same databases and focusing on the dupilumab search terms only (12 publications identified). As the 2019 conferences were held in May 2019 and June 2019 for each organisation respectively, which was after the company's latest search update in March 2019, the ERG included handsearching of the conference proceedings in their update. No further relevant studies were found from the ERGs update search or handsearching.

The cost effectiveness SLR strategies are described collectively in Appendix G, with PRISMA flow diagrams presented for the HRQoL and HCRU searches in Appendices H and I respectively.

The databases searched by the company were Embase, Medline, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, National Health Service Economic Evaluation Database (NHS EED) and EconLit, all of which are appropriate and adequate. In addition, published SLRs were identified in the searches via the Cochrane Library and the above databases. The reference lists of these reviews were scrutinised as a supplemental source to identify relevant publications. The company's searches are current to 15 March 2019, so the ERG carried out brief searches on Medline

and EMBASE, using the same terms, to update the searches to September 2019. No further relevant studies were found.

The grey literature search was comprehensive, including searching several relevant conferences. As for the cost effectiveness SLR, the search process was adapted to include handsearching where the conferences were not indexed in EMBASE. This was then supplemented by searching directly on the websites for all conferences to ensure that all relevant material was identified. Additional searches were carried out on the websites of other key organisations.

The documentation of the search strategies in Tables 10-13 show that, for each search, all the databases were interrogated in one search strategy in OVID. Reporting would be more transparent if the databases that the search strategies represented were mentioned in the table captions. Tables 12 and 13 (documenting the economic evaluations related to available treatment options search) are the same strategies with different captions which makes the submission somewhat unclear. By searching all the databases at the same time, it is not clear that if where the thesaurus terms differ between databases that they have been automatically mapped and included, e.g. they have only documented searching for the heading beclomethasone/ (MeSH) and not for beclametasone/ (EMTREE). However, the free text terms used in the search are comprehensive for all comparators and so the ERG is confident that relevant studies have not been missed.

Overall, the searches are thorough and well-constructed, and captured all the relevant studies.

3.1.2 Statement of the inclusion/exclusion criteria used in the study selection.

The inclusion and exclusion criteria for the systematic review of clinical effectiveness are reported in CS Table 7. These criteria are wider than the NICE scope and the company's decision problem in the following two respects:

- population criteria allow for inclusion of persistent uncontrolled asthma which is stated to include moderate asthma and moderate-to-severe asthma whereas the NICE scope and the company's decision problem focus on severe asthma only (in line with the marketing authorisation for dupilumab)
- intervention criteria allow the inclusion of bronchial thermoplasty which is not included in either the NICE scope or the company's decision problem.

The results of the literature search and inclusion / exclusion screening process are illustrated in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow-diagram (updated version, Figure 1, provided in response to clarification A3).

3.1.3 Identified studies

A total of five trials for dupilumab were included:

- 1x phase IIa RCT (referred to as a proof of concept study, not discussed in the CS or this ERG report)
- 1x phase IIb RCT, DRI12544 (five-arm dose ranging trial with one active and one placebo arm relevant to the current appraisal included in this ERG report)
- 2x phase III placebo-controlled RCTs, Liberty Asthma QUEST (two active arms and two placebo arms with one active arm and one placebo arm relevant to the current appraisal) and Liberty Asthma VENTURE (2-arms both relevant to this appraisal). These two studies are referred to throughout this report as QUEST and VENTURE and both are included in this ERG report.
- 1x single-arm open label extension (OLE) study, TRAVERSE (also see section 3.1.3.4), which is ongoing (no outcome data available; CS Table 8 says "*not expected to have results until 2020, interim results were identified by hand searching CSRs*", but only baseline characteristics are presented in CS Appendix L).

3.1.3.1 Key features of the DRI12544, QUEST and VENTURE RCTs

The clinical evidence presented in the CS is drawn from three RCTs: DRI12544, QUEST and VENTURE which were all sponsored by the company. As indicated above, not all the trial arms from DRI12544 and QUEST are relevant to the decision problem, because they were for doses and /or dosing schedules that are not in line with the SmPC. These irrelevant arms are not included in the CS (aside from in CS Appendix L) and are not mentioned further in this ERG report. A summary of the three RCTs is provided in Table 9. The participants in the DRI12544 and QUEST RCTs were receiving moderate or high dose ICS but were not receiving treatment with oral corticosteroids whereas those in the VENTURE RCT had steroid-dependent severe asthma, i.e. they were receiving treatment with oral corticosteroids in addition to treatment with high dose inhaled corticosteroids and a second controller medication. Therefore the placebo arms in the DRI12544 and QUEST

RCTs, which received background therapy of moderate or high dose ICS, did not match the comparator in the company's decision problem, SoC, which was defined as high dose ICS, with or without OCS. The placebo arms in the VENTURE study did match the SoC definition because all patients received high dose ICS as part of the background therapy in the placebo arm. In line with the SmPC the relevant dose of dupilumab (administered as subcutaneous injection) for the DRI12544 and QUEST RCT populations is 200 mg given every other week after the initial dose of 400 mg (two 200 mg injections). For the VENTURE population it is 300 mg every other week after the initial dose of 600 mg (two 300 mg injections). The two patient groups represented by i) DRI12544 and QUEST and ii) VENTURE, are subgroups identified in the NICE scope (people who are not steroid dependent and people who require maintenance oral corticosteroid treatment respectively).

Table 9 Summary of the three RCTs contributing clinical evidence in the CS

RCT	DRI12544		QUEST		VENTURE	
Patient group	Adults (≥18 years) with uncontrolled moderate-to-severe asthma		Adults and adolescents (≥12 years) with uncontrolled moderate-to-severe asthma		Adults and adolescents (≥12 years) with steroid-dependent severe asthma	
Existing treatment	Moderate or high dose ICS/LABA		medium-high dose ICS plus second/third controller (LABA,LTRA)		regular prescribed systemic CS, treatment with high dose ICS plus second controller (LABA or LTRA)	
RCT arms	SC Dup 200 mg Q2W	PBO[a] 2.0 ml	SC Dup 200mg Q2W	PBO[a] 1.14 ml	SC Dup 300mg Q2W	PBO[a] 2.0 ml
No. of patients	150	158	631	317	103	107
Relevant to STA	YES	YES	YES	YES	YES	YES

Dup – Dupilumab; No. – Number; PBO – placebo; Q2W – every 2 weeks; Q42 – every 4 weeks; SC – subcutaneous

[a] Placebos in all trials were matched volume placebos

DRI12544 (CS Tables 8 to 10)

This phase IIb dose ranging trial randomised 776 adults (aged ≥18 years) with a diagnosis of moderate-to-severe asthma to five arms in a 1:1:1:1:1 ratio: subcutaneous (SC) dupilumab 200mg every two weeks (Q2W); SC dupilumab 200mg every 4 weeks (Q4W); SC dupilumab 300mg Q2W; SC dupilumab 300mg (Q4W); and placebo. All the interventions were received in addition to existing treatment with moderate or high dose ICS/LABA. Patients received treatment for 24 weeks at 174 centres in 15 countries (these did not include the UK). For the purposes of this STA two trial arms are relevant: SC dupilumab 200mg Q2W and placebo. It was not clear what proportion of the enrolled participants meet the company's decision problem population definition (i.e. patients with severe asthma on high dose ICS with EOS ≥ 150/ul and/or FeNO ≥25ppb and ≥3 exacerbations in the previous 12 months) so the ERG asked the company to clarify this (clarification question A2). In response the company confirmed that 22/150 (14.7%) of patients in the dupilumab arm and 24/158 (15.2%) in the placebo arm met the decision problem population definition. The primary outcome for the trial was change from baseline at week 12 in FEV1. Secondary outcomes included annualised rates of loss of asthma control (LOAC), severe exacerbation events, time to LOAC, and time to severe exacerbation.

QUEST (CS Tables 8 to 10)

The QUEST phase III RCT randomised 1,902 adults and adolescents (aged ≥12 years) with uncontrolled moderate-to-severe asthma to four arms in a 2:2:1:1 ratio: SC dupilumab 200mg Q2W; SC dupilumab 300mg Q2W, and two matched-volume placebos (1.4 ml placebo for the 200 mg dupilumab arm; 2.0 ml placebo for the 300mg duplimab arm). For the purposes of this STA two trial arms are relevant: the SC dupilumab 200mg Q2W arm and its corresponding 1.4 ml placebo arm. In both arms dupilumab or placebo was received in addition to existing treatment with moderate or high dose ICS/LABA. Patients received treatment for 52 weeks at 331 centres in 22 countries. Six trial sites were in the UK and 13 UK patients were enrolled. Information reported in CS Table 32 indicates that 64 of the 631 patients in the SC dupilumab 200 Q2W arm (10.1%) and 37 of the 317 patients in the corresponding placebo arm (11.7%) meet the company's population decision problem definition (i.e. patients with severe asthma on high dose ICS with EOS ≥ 150/ul or FeNO ≥25ppb and ≥3 exacerbations in the previous 12 months). The trial had two co-primary outcomes: annualised rate of severe exacerbation events during the 52-week placebo-controlled treatment period, and absolute change from baseline in pre-bronchodilator FEV_1 at week 12. The percentage change from baseline in pre-

bronchodilator FEV1 at week 12 is stated to be a key secondary efficacy endpoint. A range of other outcomes is also reported.

VENTURE (CS Tables 8 to 10 and the published paper[12])

VENTURE randomised 210 adults and adolescents (aged ≥12 years) with steroid-dependent severe asthma to one of two arms (1:1): SC dupilumab 300mg Q2W or a matched-volume placebo for 24 weeks. In both arms patients also received regular prescribed systemic CS, treatment with high dose ICS plus second controller (LABA or LTRA). The treatment period had three phases: a four week induction phase in which patients received their randomised treatment and remained on their optimised dose of oral corticosteroid and other baseline medications; a 16 week oral corticosteroid reduction phase during which a pre-determined schedule was followed to down-titrate oral corticosteroid dose; and a four week maintenance phase when patients received the oral corticosteroid dose that was established at week 20. Patients were recruited from 68 centres in 17 countries. Information reported in CS Table 33 indicates that 78 of the 103 patients in the SC dupilumab 300 Q2W arm (75.7%) and 74 of the 107 patients in the corresponding placebo arm (69.2%) meet the company's decision problem definition (patients with severe asthma on high dose ICS with EOS ≥ 150/ul or FeNO ≥25ppb). The primary endpoint for the trial was the percentage reduction in the oral corticosteroid dose at week 24 whilst maintaining asthma control. The key secondary endpoints were the proportion of patients achieving a reduction ≥50% in oral corticosteroid dose at week 24 whilst maintaining asthma control and the proportion of patients achieving a reduction of OCS dose to <5 mg/day at Week 24. A range of other outcomes were also reported, including some related to reduction of oral corticosteroid dose, exacerbations, FEV_1, and asthma control.

3.1.3.2 The decision problem population

As noted above, for all of the included trials the intention to treat (ITT) population includes a wider group of patients than that specified by the NICE scope and the company's decision problem as summarised in Table 10. In the DRI12544 and QUEST trials (participants not in receipt of maintenance OCS) a minority of the ITT population match the decision problem population criteria (14.9% across the two relevant arms of DRI12544 and 10.7% in the two relevant arms of QUEST). In the VENTURE RCT (participants receiving maintenance OCS) more than two thirds of the ITT population match the decision problem population criteria (72.4%).

Table 10 Number of participants in each trial matching the decision problem population

RCT	DRI12544		QUEST		VENTURE	
Trial arm	Dupilumab 200mg Q2W	Placebo	Dupilumab 200mg Q2W	Placebo	Dupilumab 300mg Q2W	Placebo
ITT population	150	158	631	317	103	107
Decision problem population,[a] n (% of ITT)	22 [b] (14.7%)	24 [b] (15.2%)	64 (10.1%)	37 (11.7%)	78 (75.7%)	74 (69.2%)

[a] The decision problem population is EOS ≥150 OR FeNO ≥25 AND ≥3 exacerbations.

[b] From clarification question response A2

3.1.3.3 Baseline characteristics in the ITT populations of the DRI12544, QUEST and VENTURE RCTs

A summary of patient baseline demographic characteristics in the ITT populations is provided in Table 11, a summary of patient baseline clinical characteristics is provided in Table 12, and the baseline optimised daily oral corticosteroid dose in the VENTURE trial (the only trial in which patients received oral corticosteroids) is provided in Table 13 (CS Tables 12 and 13 provide more detail on baseline demographic characteristics). For each of the three included trials the CS comments that patients' demographic and baseline characteristics were generally similar between the treatment arms. Although this is the case for most characteristics, the ERG notes that:

DRI12544

Comparing the two arms of relevance to this STA (dupilumab 200mg Q2W and placebo):

- There was a higher proportion of participants aged 65 years or over in the dupilumab group (13% [20/150] versus 8% [13/158] in the placebo group)
- A smaller proportion experienced 4 or more exacerbations in the past year in the dupilumab group (8.7% versus 15.8% in the placebo group).

VENTURE

There was a lower proportion of participants aged 65 years or over in the dupilumab group (11% [11/103] versus 16% [17/107] in the placebo group)

There was a higher mean and median baseline blood EOS count (GIGA/L) in the dupilumab group (mean (SD) 0.37 (0.32) and median 0.28 versus mean (SD) 0.33 (0.30) and median 0.24 in the placebo group).

Clinical advice to the ERG was that none of these differences were likely to affect outcomes.

Table 11 Baseline demographic characteristics of the clinical trials

Baseline demographic characteristic	DRI12544		QUEST		VENTURE	
	Dupilumab 200 mg Q2W	Placebo	Dupilumab 200 mg Q2W	Placebo 1.4 ml	Dupilumab 300 mg Q2W	Placebo
	N=150	N=158	N=631	N=317	N=103	N=107
Age, years, mean (SD)	51.0 (13.4)	49.0 (12.7)	47.9 (15.3)	48.2 (15.6)	51.9 (12.5)	50.7 (12.8)
<18 years, %	N/A	N/A	5.4	6.6	1.0	1.9
18-64 years, %	86.7	91.8	81.1	79.8	88.3	82.2
≥65 years, % [a]	13.3	8.2	13.5	13.6	10.7	15.9
Sex, female, %	64.0	65.8	61.3	62.5	60.2	60.7
Race, %						
Caucasian/White	76.0	75.3	80.8	83.6	94.2	93.5
Black/African descent	6.0	5.7	5.2	4.4	3.9	0.9
Asian/Oriental	16.7	15.8	12.4	10.4	0	1.9
Other [a]	1.3	3.2	1.6	1.6	1.9	3.7
Weight, kg, mean (SD)	80.66 (18.34)	78.70 (18.08)	79.6 (19.0)	81.2 (21.7)	78.7 (16.9)	82.6 (19.7)
BMI, kg/m^2, mean (SD)	29.72 (5.87)	29.15 (6.39)	29.1 (6.5)	29.8 (7.3)	28.9 (5.9)	29.8 (6.0)
Geographical region						
Asia, %	14.7	13.9	10.1	10.1	0	0
Latin America, %	20.0	20.3	27.9	28.4	28.2	26.2
East Europe, %	26.7	26.6	25.0	24.9	39.8	46.7
Western countries, % [b]	38.7	39.2	36.9	36.6	32.0	27.1

Source: CS Tables 12 and 13
BMI, body mass index; N/A, not applicable (by the inclusion criteria participants in DRI12544 had to be 18 years or older); Q2W, every 2 weeks;
[a] Percentages calculated by the ERG from the sum of other groups
[b] Western countries include (depending on the trial) Australia, Canada, US, Israel, South Africa and/or western European countries

Table 12 Baseline clinical characteristics of the clinical trials

Baseline clinical characteristic	DRI12544		QUEST		VENTURE	
	Dupilumab 200 mg Q2W	Placebo	Dupilumab 200 mg Q2W	Placebo 1.4 ml	Dupilumab 300 mg Q2W	Placebo
	N=150	N=158	N=631	N=317	N=103	N=107
ACQ-7 score, mean (SD)	2.73 (0.82)[a]	2.69 (0.80)[a]	2.86 (0.71)	2.84 (0.65)	2.70 (0.98)	2.81 (1.00)
AQLQ global score, mean (SD)	4.03 (1.15)	4.12 (1.10)	4.31 (1.08)	4.26 (1.02)	4.38 (1.24)	4.31 (1.12)
Number of asthma exacerbations[b] in the past year (%)						
Mean (SD)	1.85 (1.43)	2.27 (2.25)	2.07 (2.66)	2.07 (1.58)	2.01 (2.08)	2.17 (2.24)
1, %	58.0	50.0	53.9	47.3	28.2	29.0
2, %	18.0	22.2	25.8	28.7	23.3	25.2
3, %	15.3	12.0	10.1	12.3	11.7	15.9
≥4, %	8.7	15.8	10.1	11.7	16.5	13.1
Number of asthma exacerbations[b] requiring hospitalisation/urgent medical care in the past year						
Mean (SD)	0.57 (0.91)	0.65 (1.37)	0.69 (1.41)	0.62 (1.15)	1.04 (1.83)	1.00 (1.40)
ICS/LABA controller medication						
High,[c] %	52.1 n=144 [d]	49.7 n=155 [d]	50.2	54.3	100	100
Blood eosinophil count (10^9/L)						
Mean (SD)	0.36 (0.35)	0.34 (0.30)	0.35 (0.35)[g]	0.37 (0.34)	0.37 (0.32)	0.33 (0.30)
≥0.15–<0.3,[e] %	34.0	32.9	30.6[g]	26.8	21.4	35.5
≥0.15–<0.3,[f] %	22.7	24.1	27.5[g]	26.5	32.0	26.2
≥0.3, %	43.3	43.0	41.9[g]	46.7	46.6	38.3
FeNO (ppb)	**n=136**	**n=144**	**n=624**	**n=311**	**n=101**	**n=103**
Mean (SD)	39.25 (36.67)	38.95 (34.79)	34.45 (34.91)	34.47 (28.54)	35.55 (28.34)	39.62 (34.12)
Median	29.00	28.00	23.00	26.00	28.00	29.00

Source: CS Tables 12 and 13

ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroids; LABA, long-acting β2-agnoists; OCS, oral corticosteroid; Q2W, every 2 weeks;

[a] The DRI12544 RCT used the ACQ-5 not the ACQ-7

[b] Asthma exacerbation prior to the trial was defined in all three studies as ”severe asthma exacerbation”: a deterioration of asthma that results in emergency treatment, hospitalisation due to asthma, or treatment with systemic steroids at least twice their current dose for at least 3 days.

[c] Participants in the DRI12544 and QUEST trials had to be receiving medium-to-high-dose inhaled glucocorticoid to be eligible for the trial [DRI12544 ≥250 µg fluticasone propionate (FP), or equivalent inhaled corticosteroids, twice daily; QUEST ≥500 µg total daily dose FP or equipotent equivalent]. High and medium doses not defined. All participants in the VENTURE trial were receiving high dose inhaled glucocorticoid (>500 µg total daily dose FP or equivalent). The company’s definition of standard care is high dose ICS, with or without OCS

[d] Sample size not reported; deduced by ERG from n and %
[e] In DRI12544 the cutoff was <0.2 (<0.15 in the other trials)
[f] In DRI12544 the cutoff was 0.2-0.299 (≥0.15–<0.3 in the other trials)
[g] Based on data from n=360 patients

Table 13 Baseline optimised daily oral corticosteroid dose (mg/day) in the VENTURE RCT

Optimised daily oral corticosteroid dose (mg/day)	VENTURE	
	Dupilumab 300 mg Q2W	**Placebo**
	N=103	**N=107**
Mean (SD)	10.75 (5.90)	11.75 (6.31)
Median	10.00	10.00
≤5, %	24.3	16.8
>5–≤10, %	42.7	44.9
>10–≤15, %	18.4	22.4
>15–≤25, %	12.6	13.1
>25, %	1.9	2.8

Source: CS Table 13

The CS also presents summary baseline characteristics for the decision problem subgroups of QUEST and VENTURE (CS Table 32 and 33). These are similar to those of the ITT population.

3.1.3.4 Ongoing studies

The CS reports that an open label extension study, TRAVERSE (single-arm, dupilumab 300mg Q2W; N=1,844), is ongoing and not expected to have results until 2020 (CS section B.2.2 and CS Table 8). The TRAVERSE study (NCT02134028) includes participants who have participated in the following dupilumab studies in people with asthma:

- Phase II randomised trial (PDY14192).
- DRI12544
- QUEST (EFC13579)
- VENTURE (EFC13691)

The ERG is not aware of any additional studies of dupilumab that have been completed or are in progress.

3.1.4 Description and critique of the approach to validity assessment

The CS assessed the trials using the NICE criteria for RCTs. The ERG has independently assessed the trials using the same criteria and judgements differ only for two items in the VENTURE trial assessment. These two items are that:

i) the ERG believes the concealment of treatment allocation was adequate (CS assessed as 'unclear')

and

ii) the ERG finds that there is evidence that more outcomes were measured in VENTURE than are reported which puts this trial at potential risk of reporting bias (CS reported that there was no evidence that more outcomes were measured than reported).

The CS and ERG assessments are compared in Table 14.

Table 14 Company and ERG assessment of trial quality

		DRI12544	QUEST	VENTURE
1. Was randomisation carried out appropriately?	CS:	Yes	Yes	Yes
	ERG:	Yes	Yes	Yes
2. Was concealment of treatment allocation adequate?	CS:	Yes	Yes	Unclear
	ERG:	Yes	Yes	Yes
3. Were groups similar at outset in terms of prognostic factors?	CS:	Yes	Yes	Yes
	ERG:	Yes	Yes	Yes
Comment: Overall the 2 groups appear well balanced (cross refer back to Table 6 and 7). Clinical advice to the ERG was that the small (5-10 percentage point) differences between arms for some items (summarised in section 3.1.3.3) are unlikely to have had an impact on treatment outcomes.				
4. Were care providers, participants and outcome assessors blind to treatment allocation?	CS:	Yes	Yes	Yes
	ERG:	Yes	Yes	Yes
5. Were there any unexpected imbalances in drop-outs between groups?	CS:	No	No	No
	ERG:	No	No	No
6. Is there any evidence that authors measured more outcomes than reported?	CS:	No	No	No
	ERG:	No	No	Yes

Comment: For DRI12544 and QUEST the appendix to the published paper lists additional secondary endpoints that were measured but not reported. However, these are reported in Appendix L or the CS. For VENTURE the publication appendix states several "other efficacy" outcomes (CFB in: PEF, FEF25%-75% (Forced expiratory flow at 25–75% forced vital capacity), symptom score & nocturnal awakening, use of rescue medication, airway hyper-responsiveness [selected sites only]) were measured. Results for these are not reported in the publication, CS, or CS Appendix L (PEF and FEF25%-75% are very briefly summarised for subgroup analyses only in a narrative statement in CS section B.2.7.1.3). The trial publication states that ACQ-5 was used, but CS Table 31 reports ACQ-7 results rather than ACQ-5.				
7. Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	CS:	Yes	Yes	Yes
	ERG:	Yes (primary outcome only)	Yes (primary outcome only)	Yes (primary outcome only)
Comment: although the primary analyses were not ITT, sensitivity analyses were conducted in which missing data were imputed and we judged that these were appropriate for protecting ITT				

ERG conclusion: The CS reports an appropriate assessment of trial quality (risks of bias) for the DRI12544, QUEST and VENTURE RCTs. For the DRI12544 and QUEST RCTS we agree with the company's assessment and find that these trials are at low risks of performance, detection, selection, reporting and attrition biases for the primary outcomes. For VENTURE we believe there are low risks of performance, detection, selection and attrition biases for the primary outcome but there is a potential risk of reporting bias.

3.1.5 Description and critique of company's outcome selection

The outcomes specified in the decision problem are those detailed in the NICE scope: objective measures of lung function, asthma control, incidence of clinically significant exacerbations, use of oral corticosteroids, mortality, adverse effects of treatment and health related quality of life (HRQoL).

In addition to the outcomes listed in the NICE scope, the CS reports the change from baseline in FeNO. CS Appendix L contains additional secondary outcomes that were not included in CS Document B. Outcomes that are reported only in CS Appendix L have not been included in this ERG report.

Lung function

The CS reports analyses of change from baseline in the following lung function outcomes measured by spirometry:

FEV1: the volume of air expelled in the first second of a forced expiration. (DRI12544, QUEST and VENTURE RCTs).

Morning and evening peak expiratory flow: the greatest rate of airflow that can be obtained during a forced exhalation (CS Tables 9 and 10 state that PEF was measured in DRI12544 and VENTURE, but results are reported in the CS and trial publications for QUEST only).

Other lung function outcomes: CS Tables 9 and 10 report that forced vital capacity (FVC) and forced expiratory flow at 25–75% of FVC (FEF25%-75%) were measured in QUEST and VENTURE. However, results are reported in the CS only for FVC in VENTURE (a brief narrative statement in CS section B.2.7.1.3 mentions FEF25%-75% in VENTURE, but only for subgroup analyses, and with no quantitative data or source provided).

Asthma control

Asthma control was assessed using the change from baseline in the Asthma Control Questionnaire (ACQ) score. The DRI12544 RCT used the ACQ-5 and the QUEST RCT used the ACQ-7. The VENTURE paper and supplementary appendix refer only to the ACQ-5 but the CS reports ACQ-7 instead of ACQ-5 results. The ACQ is a validated and widely used instrument and the full version has seven questions. The shorter ACQ-5 version contains five symptom questions but omits two questions on rescue bronchodilator use and FEV1% of predicted normal (as these measurements are not always available).[13] Each question is answered on a 7-point scale with a possible score ranging from 0–6. The total score is the mean of all responses so for both the ACQ-5 and the ACQ-7 the score can range from 0 (totally controlled asthma) to 6 (severely uncontrolled asthma). The minimum clinically important difference for the ACQ is regarded as a change of score ≥0.5.[14] The cut-off points on the ACQ-7 that best confidently differentiate between 'well-controlled' and 'not well-controlled' asthma are 0.75 (negative predictive value=0.85) for well-controlled asthma and 1.50 (positive predictive value=0.88) for inadequately controlled asthma.[14]

Loss of asthma control (LOAC) events were reported by the DRI12544 and QUEST RCTs but the definition of an LOAC event differs between the trials (response to clarification A2). Loss of asthma control was defined in the trials as shown in Table 15.

Table 15 Comparison of the LOAC definitions in the DRI12544 and QUEST RCTs

DRI12544	QUEST
A LOAC event is defined as any of the following: • ≥6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol in a 24 hour period (compared with baseline) on 2 consecutive days • increase in ICS ≥4 times the dose at Visit 2 • use or systemic CS for ≥3 days • hospitalisation or A&E visit because of asthma requiring corticosteroid	A LOAC event is defined as any of the following: • ≥6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol in a 24-hour period (compared with baseline) on 2 consecutive days; • ≥20% decrease in pre-bronchodilator FEV_1 compared with baseline; • Increase in ICS dose ≥4 times than the dose at Visit 2 • A decrease in AM or PM PEF of 30% or more on 2 consecutive days of treatment, based on the defined stability limit. The Treatment Period stability limit is defined as the respective mean AM or PM PEF obtained over the last 7 days prior to Day 1(randomization). • Severe exacerbation event
Source: CS Table 10 footnotes	Source: QUEST trial protocol (available with trial publication) and response to clarification questions A2 and A7

Exacerbations

The NICE scope specifies “Incidence of clinically significant exacerbations, including those which require unscheduled contact with healthcare professionals or hospitalisation”. “Severe exacerbation events” were reported by all three of the included RCTs. A severe exacerbation event was defined as the use of systemic corticosteroids for ≥3 days (for VENTURE, at least double the dose currently used), or hospitalisation or A&E visit because of asthma requiring systemic corticosteroids (CS Table 10 footnote).

The ERG notes that for the DRI12544 and QUEST RCTs there is overlap in the definitions of loss of asthma control events and severe exacerbations. Participants in DRI12544 would meet the criteria for both a LOAC event and a severe exacerbation if they i) needed

to use systemic corticosteroids for 3 or more days or ii) required hospitalisation or an A&E visit because of asthma requiring corticosteroids. Participants in QUEST with a severe exacerbation event would automatically meet the criteria for a LOAC event.

HRQoL

In the CS health-related quality of life (HRQoL) is reported using either the EQ-5D-3L (DRI12544 RCT) or the EQ-5D-5L (QUEST and VENTURE). The EQ-5D is used to describe and value health across five dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression. Respondents rate their health on that day for each dimension. For each dimension the EQ-5D-3L has three levels of severity whereas the EQ-5D-5L has five levels of severity. The five-digit health state profile obtained from the EQ-5D can be converted into a single index value using one of the standard EQ-5D value sets (for either the 5L or 3L versions of the EQ-5D).

The CS also indicates that the three dupilumab RCTs also used the Asthma Quality of Life Questionnaire (AQLQ)[15] to assess HRQoL and these results are presented in CS Appendix L.

Use of oral corticosteroids

VENTURE was the only trial to enrol patients on oral corticosteroids at baseline and hence was the only trial reporting on changes in use of oral corticosteroids during the trial period.

Mortality and adverse effects of treatment

Safety evidence, including deaths, is reported using data from the three RCTs included in the CS. The CS also reports a very brief overview of the safety of dupilumab when used in atopic dermatitis (CS section B.2.10.2).

FeNO

The fraction of exhaled nitric oxide was reported as a "pharmacodynamics endpoint" for all three dupilumab trials. The clinicians that the ERG consulted confirmed that FeNO is routinely measured in patients with severe asthma. The clinicians agreed that a FeNO measurement of 25 ppb or more was likely to be driven by type 2 inflammation, with a higher FeNO (40 ppb or more for one clinician and over 50 ppb for the second clinician) would be highly likely driven by type 2 inflammation.

ERG conclusion: The outcomes presented in the CS are appropriate for the evaluation of severe asthma and are consistent with the NICE scope.

3.1.6 Description and critique of the company's approach to trial statistics

Analysis populations in the clinical trials

The CS reports results from the intent-to-treat (ITT) analysis (i.e. in which all randomised patients were analysed) for the primary outcome of all three trials (for FEV1 sensitivity analyses were conducted in which missing data were imputed and we judged that these were appropriate for protecting ITT). For the VENTURE RCT only, analysis of the proportion of patients no longer requiring OCS at Week 24 while maintaining asthma control (a secondary outcome), was restricted to patients in the ITT population whose optimised OCS dose at baseline was ≤30 mg/day. This was because it was not possible for patients starting with 35mg/day at baseline to achieve complete (100%) reduction in OCS dose at week 24 (CS B.2.4.1.3). Other secondary outcomes from the trials were not ITT.

A safety population was defined which included all patients who received at least one dose, or part of a dose, and patients were analysed according to the treatment they received. In the QUEST trial, non-randomised patients who received dupilumab were also included in the safety population but the CS does not indicate how many such patients there were (no non-randomised patients were treated in the DRI12544 RCT and such patients are not mentioned in the definition of the safety population for the VENTURE trial). The ERG notes that the number of trial participants analysed for safety was either the same, or slightly less than the number of participants randomised to a trial arm.

Statistical analysis approaches in the clinical trials

The CS provides an overview of the statistical methods used to analyse the primary outcomes in the three dupilumab trials in CS Table 14, with additional details for primary and secondary outcomes provided in CS section B.2.4.2. The ERG has drawn together this information to provide an overview of the statistical approaches employed (Table 16).

The ERG notes that the DRI12544 trial publication[16] and the clinical study report (CSR)[17] state that the primary analysis was for the change from baseline in FEV1 at week 12 in participants with ≥300 eosinophils per µL at baseline. However, the CS states that the primary analysis for DRI12544 was for the ITT population (CS section B.2.6.1) with CS section B.2.4.1.1 stating that the ITT population was considered the primary population for evaluation based on feedback received from the European Medicines Agency (EMA).

Table 16 Overview of statistical approaches in the trials of dupilumab

	DRI 12544	QUEST		VENTURE
		Co-primary outcomes		
Primary outcome	Change from baseline at Week 12 in FEV1	Annualised rate of severe exacerbation events during the 52-week placebo-controlled treatment period	Absolute change from baseline in pre-bronchodilator FEV1 at week 12	Percentage reduction in the oral corticosteroid dose at week 24 whilst maintaining asthma control
Summary of primary outcome analysis	MMRM approach	Negative binomial regression model	MMRM approach	ANCOVA model
Statistical power for comparison of dupilumab vs placebo	Based on the comparison between dupilumab doses vs placebo with regard to the primary endpoint in the patient subgroup with eosinophil counts of ≥300 per µL	Based on a comparison between dupilumab 300 mg and placebo with regard to the two primary endpoints		Based on the comparison between dupilumab doses vs placebo with regard to the primary endpoint and the key secondary endpoint (proportion of patients achieving a reduction ≥50% in oral corticosteroid dose at week 24 whilst maintaining asthma control)
	60 patients per group in the high blood eosinophils group would provide 83% power to detect a difference of 0.2 L between the highest dupilumab dose and placebo groups in the	≥1,638 patients provide 99% power to detect a 55% relative risk reduction in annualised rate of severe exacerbations	≥1,638 patients provide 98% power to detect a treatment difference of 0.15 L in the change of FEV1 from baseline at Week 12.	With 90 randomised patients per group, the trial had 94% power to detect a treatment difference of 27%

	change in FEV1 from baseline to Week 12.			
Multiple testing accounted for?	A step-down procedure was used to strongly control the overall type I error rate for testing multiple doses against placebo. An unlicenced dose, 300mg Q4W) had priority in the sequence.	A hierarchical testing procedure was applied at a 2-sided 5% significance level to mitigate the risk of Type I error for the primary analyses (two primary endpoints and for the whole trial two dupilumab doses. The unlicenced dose, dupilumab 300mg, had priority in the sequence).		If the primary endpoint met the significance level, secondary endpoints were tested at a 2-sided 5% significance level in a hierarchical order.
Missing data imputation for the primary outcome	No imputation was conducted for the MMRM model. Sensitivity analyses were conducted but the descriptions of these are inconsistent in different parts of the CS. CS Table 14 states that an ANCOVA model, based on last observation carried forward (LOCF), was used as a sensitivity analysis.	For each patient with missing data for severe exacerbation events, individual monthly event probability was estimated (how the probability was estimated is not reported).	For patients who discontinued trial medication before Week 12, additional off-study treatment pre-BD FEV1 values measured up to Week 12 were included in the primary analysis.	If patients had permanently discontinued trial medication but returned for all remaining trial visits, the data collected after treatment discontinuation were used in the primary analysis. For patients who discontinued the trial the primary missing data handling approach was PMM-MI

ANCOVA: analysis of covariance; BD: bronchodilator; LOCF: last observation carried forward; MMRM: mixed-effects model with repeated measures; PMM-MI: pattern mixture model-multiple imputation.

Each RCT was adequately statistically powered to detect the specified difference in the primary outcome (Table 16). The RCTs adjusted for testing multiple doses (DRI12544 and QUEST), co-primary endpoints (QUEST) and secondary outcomes (VENTURE).

The CS reports adjusted analyses for all outcomes. For outcomes derived from an MMRM model (change from baseline in: FEV1, asthma control questionnaire scores, EQ-5D), a core set of covariates were used in analyses for the three trials. This core set was: treatment groups, regions, baseline EOS level subgroups (study-dependent categories), visits, treatment-by-visit interaction, baseline outcome value, baseline-by-visit interaction. The core set was supplemented with trial specific covariates for some outcomes (FEV1: QUEST - age, sex, baseline height, baseline ICS dose level; VENTURE - age, sex, baseline height, baseline OCS dose strata; ACQ or AQLQ: QUEST – baseline ICS dose, age; VENTURE – baseline optimised OCS dose; EQ-5D: VENTURE – baseline optimised OCS dose strata). For outcomes derived from a negative binomial regression model the parameters are summarised in Table 17.

Table 17 Features of the negative binomial regression models used to derive the adjusted annualised severe exacerbation event rate in the trials

	DRI12544	QUEST	VENTURE
Response variable	number of severe exacerbation events	total number of events onset from randomisation up to Visit 18 or last contact date (whichever came earlier)	total number of events onset from randomisation up to Visit 11 (Week 24) or last contact date (whichever comes earlier)
Covariates	treatment, baseline EOS strata, pooled countries/regions and number of asthma event prior to the study	the four treatment groups, age, region (pooled country), baseline EOS strata, baseline ICS dose level and number of severe exacerbation events within 1 year prior to the study	treatment groups, baseline optimised OCS dose strata, regions, number of the events within 1 year prior to the study, and baseline EOS level subgroups (<0.15, ≥0.15 Giga/L)
Offset variable	log-transformed standardised duration	log-transformed standardised observation duration	log-transformed treatment duration

In the VENTURE trial the statistical methods for the outcomes related to reductions in OCS dose are summarised in Table 18.

Table 18 Summary of the statistical methods for outcomes related to reduction in OCS dose

Outcome	Method (source: footnotes to the relevant CS outcome tables)
Mean and median percentage reduction in OCS dose from baseline	Calculated from observed data only
Percentage reduction in OCS dose from baseline: LS mean, LS mean difference vs placebo & p-value	Derived from combining results from analysing 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, optimised OCS dose at baseline, regions, and baseline EOS level subgroups (<0.15, ≥0.15 Giga/L) as covariates. Missing data is imputed using the primary approach – pattern mixture model by multiple imputation (seed=13691).
Patients achieving a reduction of ≥50% in OCS dose at Week 24	Percentage with the answer 'yes' calculated based on imputed data where the missing data are imputed from the primary missing data handling approach for the primary efficacy endpoint. The adjusted probability of achieving the reduction was derived from combining results from analysing multiple imputed data using a logistic regression model by Rubin's rule. The logistic regression model uses the binary status of whether or not a patient achieved the outcome as the response variable, and treatment groups, optimised OCS dose at baseline, regions, and baseline EOS level subgroups (<0.15, ≥0.15 Giga/L) as covariates.
Patients achieving a reduction of OCS dose to <5 mg/day at Week 24	
Patients no longer requiring OCS at Week 24	

ERG Conclusion: Overall the statistical approaches appear generally reasonable.

Proportion of missing data

Methods for handling missing primary outcome data have been summarised above (Table 16). Table 19 below provides an overview of the actual proportion of missing data for selected outcomes. For FEV1, although the primary analyses were not ITT, sensitivity analyses were conducted in which missing data were imputed and we judged that these were appropriate for protecting ITT.

Table 19 Percent (n/N) of missing outcome data in the trials (difference between the number of patients analysed and the number randomised)

Outcome (change from baseline)	DRI12544		QUEST		VENTURE	
	Dupilumab	Placebo	Dupilumab	Placebo	Dupilumab	Placebo
	N=150	N=158	N=631	N=317	N=103	N=107
FEV1 to wk 12	9.3% a (14/150)	18.4% a (29/158)	NR	NR	NR	NR
Pre-BD FEV1 To wk 12	NR	NR	3.2% a (20/631)	3.2% a (10/317)	NR	NR
Pre-BD FEV1 To wk 24	NR	NR	NR	NR	5.8% (6/103)	2.8% (3/107)
ACQ-5 to wk 12	10.7% (16/150)	18.4% (29/158)	NR	NR	NR	NR
ACQ-5 to wk 24	10.7% (16/150)	19.6% (31/158)	NR	NR	NR	NR
ACQ-7 to wk 24	NR	NR	6.5% (41/631)	6.6% (21/317)	15.5% (16/103)	18.7% (20/107)
ACQ-7 to wk 52	NR	NR	25.5% (161/631)	25.6% (81/317)	NR	NR
AQLQ to wk 12	9.3% (14/150b)	14.6% (23/158b)	NR	NR	NR	NR
AQLQ to wk 24	10.7% (16/150b)	18.4% (29/158b)	11.3% (71/631)	11.4% (36/317)	4.9% (5/103)	6.5% (7/107)
EQ-5D to wk 12	12.0% (18/150b)	16.5% (26/158)	10.1% (64/631b)	11.7% (37/317b)	NR	NR
EQ-5D to wk 24	12.7% (19/150b)	19.6% (31/158)	12.5% (79/631b)	13.2% (42/317b)	4.9% (5/103)	6.5% (7/107)
EQ-5D to wk 52	NR	NR	27.6% (174/631b)	30.6% (97/317b)	NR	NR
Data sources	CS Table 16 (FEV1) CS Table 18 (ACQ-5) CS Appx Table 57 (AQLQ) CS Figure 11 (EQ-5D-3L)		CS Table 22 (FEV1) CS Table 26 (ACQ-7) CS Appx Table 67 (AQLQ) CS Figure 20 (EQ-5D-5L)		CS Appx Table 70 (FEV1, AQLQ) CS Table 31 (ACQ-7, EQ-5D-5L)	

Appx: appendix; NR: not reported; wk: week
[a] Primary analysis; sensitivity analyses were also conducted accounting for these missing data
[b] There were also missing data at baseline for this outcome

Reporting of analyses

Results of the statistical analyses are reported clearly in the CS, including the number and proportion of patients where appropriate; point estimates [mean, least squares (LS) mean, probability, annualised rate]; variance estimates (SD, SE or 95% confidence interval; CI) except no confidence interval around the LS mean difference versus placebo for PEF; and effect estimates (relative risk, odds ratio, risk difference, or LS mean difference).

3.1.7 Description and critique of the company's approach to the evidence synthesis

The company's evidence synthesis presented in CS Document B is a description of the clinical evidence from the three individual RCTs of dupilumab versus placebo (CS section

B.2.6). No meta-analyses of ITT data from the dupilumab versus placebo RCTs are presented in CS B.2.8. The company have conducted some Bucher adjusted indirect treatment comparisons (ITCs) and matching adjusted indirect comparisons (MAICs) which are described in this section of our report.

3.1.7.1 Rationale for ITCs and MAICs

Dupilumab is the only biologic treatment indicated for patients with severe asthma driven by type 2 inflammation characterised by raised blood eosinophils and /or raised FeNO, who are inadequately controlled with high dose inhaled corticosteroid plus another medicinal product for maintenance treatment.

The ERG notes that whilst a lower limit of eosinophils (blood eosinophils ≥150/µl) forms part of the population defined in the company's decision problem, no upper boundary to the number of eosinophils is provided so the population may include a proportion of patients with the features of type 2 inflammation and eosinophilic asthma. Patients with severe eosinophilic asthma (EOS ≥ 300/µl) may be eligible for treatment with one of available anti-IL5 biologics (reslizumab, mepolizumab and benralizumab). These anti-IL5 biologics are therefore a relevant comparator to dupilumab for the overlap population of patients with severe asthma that has the features of type 2 inflammation and eosinophilic asthma. A comparison of dupilumab versus the anti-IL5 biologics is within the NICE scope. The company identified no head-to-head comparisons of dupilumab against reslizumab, mepolizumab and benralizumab. Furthermore, "*heterogeneity in both clinical … and methodological factors*" precluded an NMA including all comparators. Therefore, a series of indirect treatment comparisons (ITCs), described as "*exploratory pairwise analyses*" were undertaken for dupilumab versus each of these three available anti-IL5 biologics in their recommended populations using two different methods:
(i) adjusted indirect comparisons according to the method proposed by Bucher[18]
and
(ii) matching adjusted indirect comparisons (MAIC). The CS states that the purpose of the MAIC was to complement the Bucher adjusted indirect comparison.
The methods and results of the Bucher adjusted indirect comparisons are presented in Appendix N (not Appendix M as stated in some places in the CS) and the methods and results of the MAIC are presented in Appendix O.

Omalizumab, which is indicated in allergic (IgE-mediated) asthma was not included in an indirect comparison with dupilumab. In response to clarification question A1(b & c) the

company stated that 2.5% of the QUEST trial population met the NICE criteria for treatment with omalizumab and that it was expected that any patient with convincing IgE mediated asthma would be treated with an anti-IgE antibody. The ERG agrees that a comparison with omalizumab would have been unreliable.

3.1.7.2 Identification, selection and feasibility assessment of studies for ITC and MAIC

The company conducted a systematic review to identify evidence for the ITCs (Appendix N.2.1). This was confirmed to be the same review presented in CS B.2.1 (clarification question A4). The SLR identified 42 unique RCTs that met the inclusion criteria.

The company also report data extraction, risk of bias assessment, and an initial 'feasibility assessment' to ascertain i) whether there was a connected network for the treatments and outcomes of interest, and ii) whether there were differences in study, patient or outcome characteristics across comparisons that were likely modifiers of the relative treatment effects (Table 20).

Table 20 Identification, selection and feasibility assessment of studies included in ITCs

Process element	Strengths	Limitations
Searches (CS Appendix N.2)	Overall search strategy appears appropriate. Number of references identified clearly reported	
Eligibility screening (eligibility criteria in CS Appendix Table 82)	Eligibility criteria appear mostly appropriate. Process followed good practice (blinded independent investigators). PRISMA flow chart reported with number of studies and reasons for exclusion (CS Appendix Figure 33)	CSRs for two of the included studies were not accessible to the ERG until five working days before submission of the ERG report due to password protection
Data extraction (CS Appendix section N.2.1.3)	Pilot-tested process, checked by a second reviewer	
Risk of bias assessment	Followed standard NICE criteria.	Not reported whether checked by a second reviewer.

(CS Appendix section N.2.1.3)		
Feasibility assessment process (CS Appendix N.2.2)	The general approach appears reasonable: the company considered whether connected networks could be formed, and whether the studies were heterogeneous regarding effect modifiers and placebo effects. A list of potential effect modifiers is provided (CS Appendix Table 83). The effect modifiers were identified through a review of subgroup analyses from included RCTs, validated by clinical opinion, but no details are reported. The ERG consulted with two independent clinicians who agreed with the choice of treatment effect modifiers.	List of effect modifiers includes some factors such as sample size and outcomes that are not strictly effect modifiers. Very limited study characteristics are provided (CS Appendix Table 84) – only age, prior exacerbations, treatment duration and intervention dosage from the list of effect modifiers. The time points at which outcomes were measured differed across the dupilumab and comparator trials. The CS does not provide a comprehensive overview of the time points for outcomes that were recorded in all the trials contributing data to ITCs. However, the overall treatment duration of the trials is reported in CS Appendix N Table 84 and this ranged from 12 weeks to 56 weeks. CS Table 85 narratively summarises some aspects of study heterogeneity and implies that additional data on ICS dose, EOS level, FEV1, baseline LABA, baseline ICS, ACQ score and AQLQ score were available but these have not been provided in the CS. The ERG therefore cannot check whether the company's conclusions on homogeneity and heterogeneity in CS Appendix Table 85 are appropriate.

Of the 42 unique RCTs meeting the inclusion criteria of the SLR, 16 were excluded during the feasibility assessment for the reasons reported in CS Appendix N Figure 33 and CS Appendix N.3.3. Thus 26 RCTs plus an additional reslizumab trial published in clinicaltrials.gov remained for inclusion in ITCs. However, a subsequent filter was applied to limit the interventions to the four interventions considered relevant to the decision

problem and this left 16 RCTs to be included (Table 21). The trials were stratified, depending on whether or not the participants were dependent on oral corticosteroids, forming two population groups: an uncontrolled persistent asthma population (where outcomes focus on exacerbation reduction) and an oral-corticosteroid dependent asthma population (where outcomes focus on OCS-sparing).

Table 21 RCT evidence included in the indirect comparisons

	Uncontrolled persistent asthma population	**OCS-dependent asthma population**
Dupilumab	2 trials: QUEST and DRI12544	1 trial: VENTURE
Mepolizumab	3 trials: MUSCA, MENSA and DREAM	1 trial: SIRIUS
Reslizumab	5 trials: 4 BREATH studies (3082, 3083, 3084, 3081) and Castro 2011	1 trial: ZONDA
Benralizumab	2 trials: SIROCCO, CALIMA	1 trial: NCT02501629

All the RCTs that were identified for inclusion in ITC were assessed using the criteria suggested by NICE for critical appraisal. The results of these assessments are reported in Appendix D.1.3 (alongside those of all the other RCTs identified by the company's systematic literature review). These judgements did not inform trial eligibility decisions for the ITC. The company's critical appraisal judgements for the RCTs that contributed data to at least one ITC are reproduced in Appendix 8.1 Table 107. We conducted our own assessment for the dupilumab trials (see section 3.1.4) and for the comparators we referred to previous ERG assessments conducted for NICE appraisals where these were undertaken. Overall our judgement and the ERGs' judgements from other NICE appraisal were in broad agreement with the company's judgements, apart from whether a true ITT analysis had been conducted. For some of the trials ERG judgements from other NICE appraisals were that the key analyses were modified ITT analyses. As we don't know if the modified ITT populations were very similar to the full ITT populations or not, this is a source of uncertainty.

Following the feasibility assessment summarised above and selection of the 16 RCTs available to include in an ITC the company argued that heterogeneity "precluded the confident application of an ITC in which all comparator interventions could be assessed simultaneously". A full network meta analysis was therefore not recommended. Instead the company undertook pairwise ITCs using two methods (Bucher method and MAIC) which are described in more detail below in section 3.1.7.3 and section 3.1.7.4 respectively.

ERG conclusion: Parts of the evidence identification process were well conducted, although the ERG also has some concerns (Table 20). A key issue is that the company's assessment of study heterogeneity is not transparent. The company appear to have considered several factors (potential effect modifiers and/or prognostic variables) for which they have provided no quantitative data, and therefore we cannot confirm whether the company's judgements relating to study heterogeneity (CS Appendix N Table 85) are appropriate.

3.1.7.3 Adjusted pair-wise Bucher ITCs

The approach for the Bucher ITC[18] is summarised in Appendix N section 2.3.

3.1.7.3.1 Generation of dupilumab subgroups

As described above (3.1.7.1) the anti-IL5 biologics are a relevant comparator to dupilumab for an overlap population of patients with the features of type 2 inflammation and eosinophilic asthma. Therefore the pairwise Bucher ITCs were conducted using subgroups of the dupilumab trial populations. The CS labels for these subgroups are open to mis-interpretation and therefore we have used an alternative naming convention in our report as shown below in Table 22.

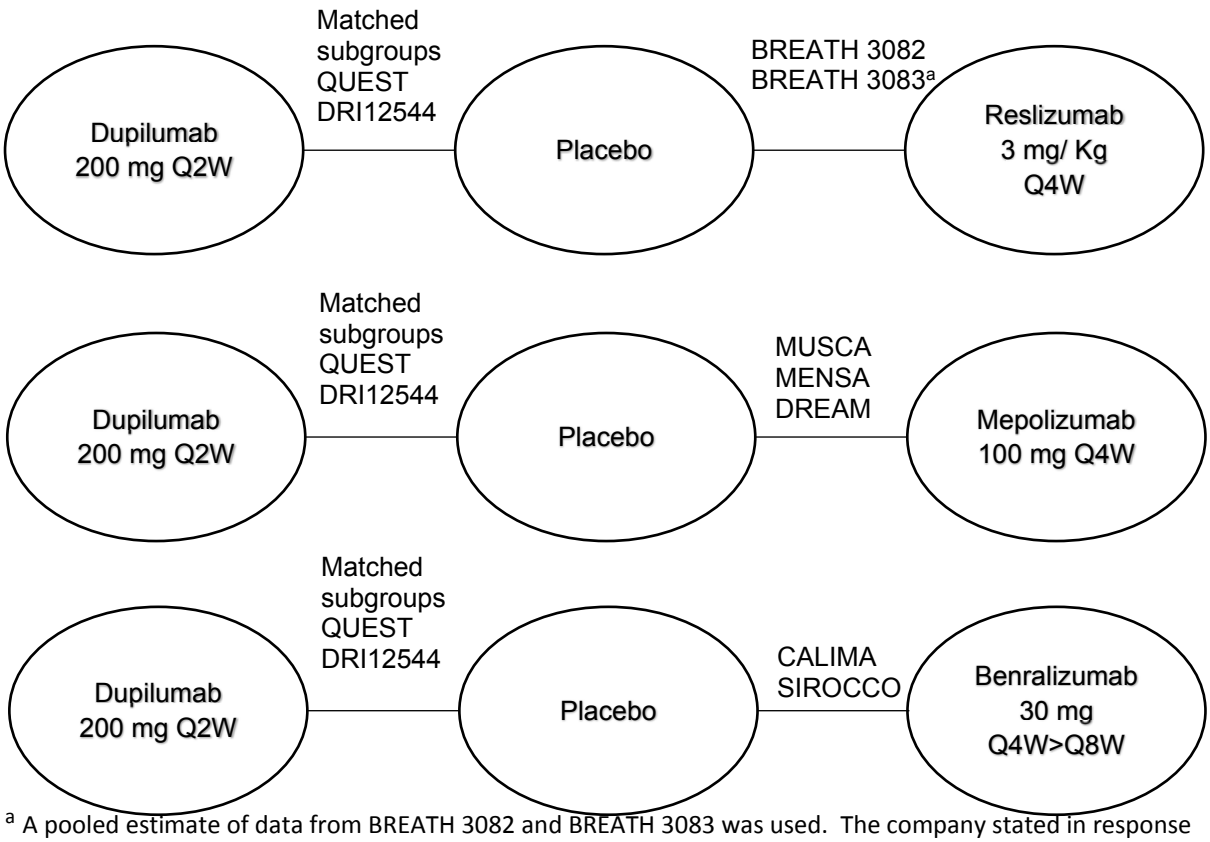
Table 22 Descriptors for the dupilumab trial subgroups formed for the Bucher ITCs

Company dupilumab subgroup descriptors	Feature of subgroup	ERG dupilumab subgroup descriptors
Reslizumab- like label	The US/global labels for each comparator of interest were used to identify the patient phenotypes that were important to match. Then the inclusion criteria and baseline values of the patients in the registrational trials were matched as closely as possible. The subgroups of patients from the dupilumab trials should therefore demonstrate patient baseline characteristics similar to those of the approved US/global labels for each comparator of	Subgroup matched to reslizumab label
Mepolizumab-like label		Subgroup matched to mepolizumab label
Benralizumab-like label		Subgroup matched to

	interest.(CS N.4.1.1 and clarification question A13)	benralizumab label
Reslizumab-like subgroup in NICE population	A subgroup from a combined analysis of two reslizumab RCTs (BREATH 3082 &3083) and a subgroup from a single mepolizumab RCT (MENSA) were identified. The patients in these RCT subgroups are more similar to, but not an exact match with, patients described in NICE guidance for reslizumab and mepolizumab than the patients in the ITT reslizumab and mepolizumab trial populations. Dupilumab patient subgroups were formed using the same inclusion criteria as the comparator subgroups.	Subgroup matched to NICE-like reslizumab subgroup
Mepolizumab NICE population		Subgroup matched to NICE-like mepolizumab subgroup

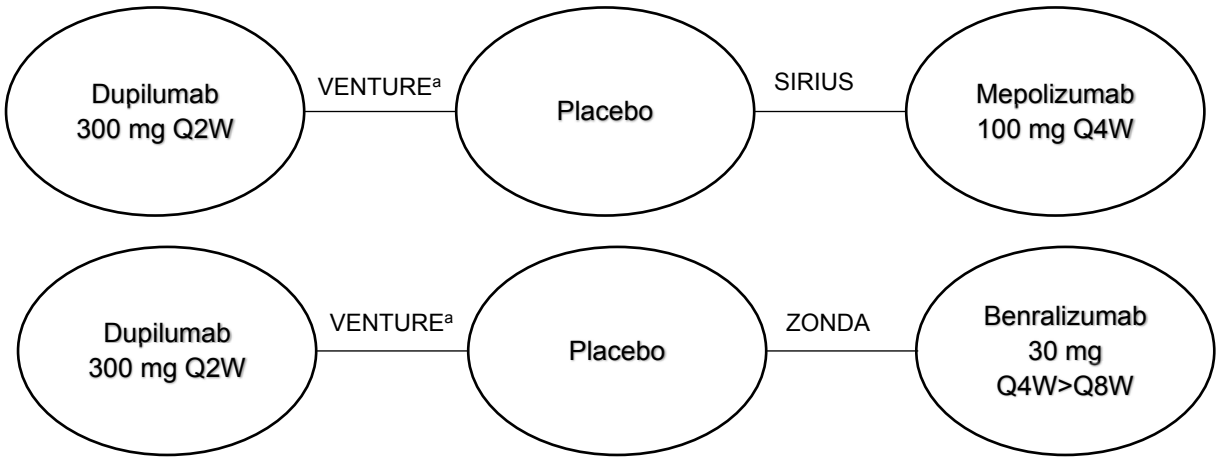
A series of pairwise indirect comparisons via the common placebo comparator were undertaken for subgroups of dupilumab patients matched against each of the comparator US/global labels in the uncontrolled persistent asthma population as shown in Figure 2.

A series of pairwise indirect comparisons via the common placebo comparator were also undertaken for the VENTURE ITT population and for the subgroup of dupilumab patients matched against each of the comparator US/global labels in the oral corticosteroid dependent asthma population as shown in Figure 3



[a] A pooled estimate of data from BREATH 3082 and BREATH 3083 was used. The company stated in response to clarification question A17 that separate data were unavailable. Three other trials identified, BREATH 3081, BREATH 3084 and Castro 2011, did not contain data that could be included in the ITC.

Figure 2 ITC comparisons for uncontrolled persistent asthma population



[a] ITCs were conducted using subgroup data for VENTURE matched to the comparator population and using ITT VENTURE data.

Figure 3 ITC comparisons for the oral corticosteroid dependent asthma population

The subgroup dupilumab data used in the Bucher ITCs were generated by matching dupilumab individual patient data (IPD) from the DRI12544, QUEST and VENTURE RCTs to the patient phenotypes for each of the "approved US/global labels" of the comparator biologics "where data was available". It is unclear whether these labels fully matched the comparator trial populations (clarification question A13). The response to clarification question A13 also notes that eosinophilic phenotype was used to match patients albeit it was not defined in the US labels and the company concede that "it was not possible to create dupilumab subgroups that fully aligned with the populations assessed in the mepolizumab trials" (response to clarification question A13). Nevertheless, in creating these subgroups, trial randomisation was effectively broken and a distinct subgroup of dupilumab patients were used for each Bucher adjusted pairwise ITC analysis. The results of this matching are shown in CS Appendix N Table 86 and Table 87 reproduced below as Table 23 and Table 24 respectively. In the OCS dependent asthma population, the company believe that the differences between the VENTURE dupilumab trial and the comparator biologic trials are small. Therefore, ITC analyses were conducted using both matched and ITT data in this population.

Table 23 Criteria applied to the dupilumab trials (QUEST; DRI12544) to derive comparator-matched subgroups for uncontrolled persistent asthma comparator biologics

Dupilumab population/ subgroups	Trial	N (% of ITT population)	ICS/LABA baseline concentration (per day)	EOS level at baseline (cells/µL)	Previous exacerbations (prior year)	Age (years)
ITT	QUEST	1,902 (100%)	Medium/High	Not required	≥1	≥12†
	DRI12544	465 (100%)				
Subgroup matched to mepolizumab label	QUEST	406 (21.3%)	High	EOS ≥150	≥2	≥12†
	DRI12544	112 (24.1%)				
Subgroup matched to reslizumab label	QUEST	556 (29.2%)	Medium/High	EOS ≥400	≥1	≥18
	DRI12544	128 (27.5%)				
	QUEST	439 (23.1%)	Medium/High		≥2	≥12[a]

Subgroup matched to benralizumab label	DRI12544	100 (21.5%)		EOS ≥300		

Source: CS Appendix N Table 86
BENRA, benralizumab; DUPI, dupilumab; EOS, eosinophil; ICS, inhaled corticosteroid; IgE, immunoglobulin E; ITT, intention to treat; LABA, long-acting beta-agonist; MEPO, mepolizumab; NA, not available; RESLI, reslizumab.
[a] DRI recruited patients ≥18 years old.

Table 24 Criteria applied to the dupilumab trial (VENTURE) to derive comparator-matched subgroups for OCS-dependent comparator biologics

Dupilumab population	Trial	N (% of ITT population)	ICS/ LABA baseline	EOS level at baseline (cells/μL)	Previous exacerbations (prior year)	Age (years)
ITT	VENTURE	210 (100%)	High	NA	NA	≥12
Subgroup matched to mepolizumab label	VENTURE	132 (62.9%)	High	≥150	NA	≥12[a]
Subgroup matched to benralizumab label	VENTURE	57 (27.1%)	High	≥300	≥1	≥18

Source CS Appendix N Table 87
EOS, eosinophil; ICS, inhaled corticosteroid; IgE, immunoglobulin E; ITT, intention to treat; LABA, long-acting beta-agonist; OCS, oral corticosteroid.
[a] Only one patient (1.6%) in the placebo arm was less than 18 years of age.

There are some differences between the uncontrolled persistent asthma and OCS-dependent asthma sub-populations described by the US/global label for the comparator anti-IL5 biologics and the population described by the company's decision problem. There are also some differences between the US global labels and the NICE guidance for the anti-IL5 biologics as can be seen in Table 25 and Table 26. This means that the patients from the dupilumab trials who have been matched to the US/global label for the comparator drugs could include patients who are not included in the company's decision problem and patients who would not be eligible for the comparator drugs according to NICE guidance recommendations. Conversely, in some cases patients included in the company's decision problem or covered by NICE guidance are not included in the US/global label.

Table 25 Uncontrolled persistent asthma subgroup: Differences between the US/global label and the decision problem and NICE guidance defined populations

	Differences versus the decision problem population	Differences versus anti-IL5 biologic NICE guidance
US/global label for mepolizumab	Decision problem does not include: people with 2 previous exacerbations	NICE guidance does not include: Adolescents (12-17 years) people with EOS 150-299 cells/ul people with 2 exacerbations people with 3 previous exacerbations
US/global label for reslizumab	Decision problem does not include: people receiving medium ICS/LABA people with 1 previous exacerbation people with 2 previous exacerbations US/global label does not include: those aged 12-18 years whereas the decision problem population is ≥12 years EOS 150-399 cells/ul whereas the decision problem includes EOS ≥150 cells/ul	NICE guidance does not include: people receiving medium ICS/LABA people with 1 exacerbation people with 2 previous exacerbations
US/global label for benralizumab	Decision problem does not include: people receiving medium ICS/LABA people with 2 previous exacerbations US/global label does not include: EOS 150-299 cells/ul whereas the decision problem includes EOS ≥150 cells/ul	NICE guidance does not include: Adolescents (12-17 years) people receiving medium ICS/LABA people with EOS at baseline of 300-399 cells/ul and 2 or 3 previous exacerbations people with EOS at baseline of ≥400 and 2 previous exacerbations

Table 26 OCS-dependent asthma subgroup: Differences between the US/global label and the decision problem and NICE guidance defined populations

	Not matching the decision problem population	Not eligible for anti-IL5 biologic according to NICE guidance
US/global label for mepolizumab	Decision problem does not include: people with 1 previous exacerbation people with 2 previous exacerbations	NICE guidance does not include: Adolescents (12-17 years) people with EOS 150-299 cells/ul
US/global label for benralizumab	Decision problem does not include: people with 2 previous exacerbations US/global label does not include: EOS 150-299 cells/ul whereas the decision problem includes EOS ≥150	US/global label does not include: People with no previous exacerbations whereas NICE guidance does not specify a threshold number of previous exacerbations.

In addition to matching the DRI12544 and QUEST dupilumab trials (uncontrolled persistent asthma) to the US/global labels the company also matched these trials against comparator subgroups that were more closely aligned to, but not an exact match with, populations described by NICE guidance as eligible for treatment with reslizumab or mepolizumab. The comparator subgroup data were obtained either from the NICE appraisal committee papers (mepolizumab), or a published source (reslizumab) for the subgroups described in Table 27. Although not explicitly stated in the CS the ERG presumes that the company were not able to identify and subgroup data for benralizumab that was a closer match to NICE guidance. The results of this matching are shown below in Table 28.

Table 27 ITCs conducted for dupilumab subgroups matched to NICE-like comparator subgroups

Comparison	Subgroup population	Available outcome data
Mepolizumab 100 mg vs placebo 75 mg vs placebo	2 or 3 exacerbations in the prior year and not dependent on modified OCS	severe exacerbations (52 weeks) forced expiratory volume in one second (FEV1) at 32 weeks Asthma Control Questionnaire (ACQ-5) at 32 weeks
Reslizumab 3.0 mg/kg q4w IV vs placebo	≥3 severe exacerbations in the prior year	severe exacerbations (52 weeks) FEV1 at 16 weeks FEV1 at 24 weeks ACQ-7 at 52 weeks AQLQ at 52 weeks

Table 28 Results of matching the dupilumab trials to the NICE-like comparator subgroups

RCT	DRI12544		QUEST	
	SC Dup 200 mg Q2W	PBO	SC Dup 200mg Q2W	PBO
No. of patients (ITT population)	150	158	631	317
Matched to NICE-like mepolizumab MENSA trial subgroup	9 (6%)	15 (9.5%)	30 (4.8%)	22 (6.9%)
Subgroup matched to NICE-like reslizumab BREATH trials subgroup	15 (10%)	14 (8.9%)	43 (6.8%)	33 (10.4%)

3.1.7.3.1 Statistical methods for the Bucher ITC

After the subgroup dupilumab data both had been generated by the matching process (to either the US/global comparator labels or the NICE-like comparator subgroups) the pairwise Bucher ITCs[18] were conducted in two steps:

1. Where there were multiple trials (or for dupilumab, subgroups from trials) for the same comparison e.g. dupilumab versus placebo, data were pooled using classical (frequentist) random-effects meta-analysis.
2. The pooled estimates (or study level data if no pooling was needed) for each biologic versus placebo were used to derive the pairwise Bucher ITC estimates for dupilumab versus each of the IL-5 biologics.

For the uncontrolled persistent asthma population random-effects models were used as the base-case if pooled estimates had been generated by meta-analysis at Step 1 for a biologic versus placebo comparison included in the ITC. Fixed-effect models were used if no meta-analysis had been required prior to the ITC and when a random-effects model had been used in the base-case. For the OCS-dependent population fixed-effect models were used due to the limited number of trials.

In the analyses for the uncontrolled persistent asthma population, the four-arm QUEST trial (which had two different placebo arms) was treated as two separate trials:

- dupilumab 200 mg q2w vs placebo 200 mg q2w
- dupilumab 300 mg q2w vs placebo 300 mg q2w

For this appraisal and the economic model only the dupilumab 200 mg q2w vs placebo 200 mg q2w results are relevant but Appendix N also reports for the 300mg dupilumab dose.

The rationale for the choice of outcome measures is not described. In both the uncontrolled persistent asthma population and the OCS dependent asthma population, ITCs were conducted (where data were available) for the outcomes of:

- severe asthma exacerbations
- FEV1
- asthma control questionnaire (ACQ)
- and asthma quality of life questionnaire (AQLQ).

For the OCS dependent asthma population ITCs were also conducted for the outcomes of:

- reduction in OCS dose <5mg/day
- reduction in OCS dose≥50%
- 100% reduction in OCS dose.

In Appendix N the CS only reports the results for severe asthma exacerbations [which inform exploratory pairwise cost effectiveness analyses (CS Appendix P)], and the results

on steroid sparing for the OCS dependent asthma population (results for 100% reduction from OCS and reduction to a daily dose <5mg inform the economic model).

The RCTs which were included in each indirect comparison and for each of the outcomes reported in Appendix N are shown in Appendix 8.1 Table 108. A description of the locations of the data used for each ITC is also reported in Appendix 8.1.

CS Appendix N Table 85 indicates that that for both the uncontrolled persistent asthma trials and the OCS-dependent asthma trials ITCs on severe exacerbations would be based on the annualised rate of severe exacerbations. Basing the ITCs for severe exacerbations on an annualised rate allowed comparison of trials with different treatment durations. The Company response to clarification question A16 provided further detail on the annualised rate calculations and it appears the method used was appropriate. For OCS sparing in the OCS-dependent asthma population (which is the other outcome of relevance to the economic model) analyses were based on the numbers of patients achieving the outcome at the end of the trial.

The Bucher methodology is correctly described (section N2.3.1.1). Analyses were conducted using the metaphor package in R 3.3.0 software. The ERG asked the company to supply the R programming code for the Bucher ITCs (clarification question A18). The company supplied the code, which is complex for a simple Bucher calculation, but this was not executable (without a data file) so we have been unable to test or validate it.

ITC results for severe asthma exacerbations are reported as rate ratios and these relative efficacy estimates are used in the exploratory cost-effectiveness analyses (CS Appendix P Table 126). ITC results for steroid sparing in the OCS dependent population are reported as odds ratios with reduction in OCS dose <5 mg/day and 100% reduction in OCS dose used in the exploratory cost-effectiveness analyses (CS Appendix P Table 127).

For binary outcomes (e.g. steroid sparing) the inverse-variance weighted pooled risk difference (RD) and relative risk were also reportedly calculated but these results were not reported in the CS.

An alternative approach to the method described above, which could have been taken where there were multiple trials for the same comparison, would have been to undertake an NMA in place of Step 1 [pooling using classical (frequentist) random-effects meta-analysis] and then using the pooled result in the Bucher ITC. However, the ERG would have

expected this to give similar results. The option of using Bayesian analyses in a full NMA is also discussed by the company in section N2.3 but the company argued this approach is more complex and random effects could be influenced by choice of prior. The ERG agrees that the approach is more complex relatively speaking but it is still not difficult nor more time consuming. The ERG also agrees that random effects could be influenced by choice of prior (if we use informative priors and if there is insufficient data to estimate between-study standard deviation) but fixed effects could have been used (depending on judgements regarding heterogeneity). There are several references to Bayesian analyses in the CS but none are reported. In response to clarification question A14 the company confirmed the Bayesian analyses are not reported nor used in the economic model.

3.1.7.3.2 Bucher ITC quality assessment

The ERG has assessed the methodological aspects of the Bucher indirect comparisons reported in the CS guided by the criteria suggested by Donegan et al.[19]

ITC method

The Bucher method is a valid method for ITC that preserves randomisation. However subgroup dupilumab data, generated by the matching processes described above which breaks randomisation, are used in all the indirect comparisons for the uncontrolled persistent asthma population. In the oral corticosteroid dependent population, ITT analyses were conducted as well as the analyses using matched data.

Similarity of treatment effects

The similarity of treatment effects (meaning that the included trials are similar for modifiers of relative treatment effect) is a key assumption underlying any ITC.[19] The company conducted a feasibility assessment (described in section 3.1.7.2 above) which included an examination of factors that would underpin the similarity of treatment effects. However, because this was not reported in sufficient detail we cannot confirm whether the company's conclusions are appropriate.

3.1.7.4 Statistical methods for the MAIC

In addition to the ITCs using the Bucher method the company also conducted analysis using matching adjusted indirect comparison (MAIC) methodology. The purpose of the MAIC was to compliment the findings from Bucher analysis. Whilst the Bucher approach created dupilumab subpopulations to attempt to match studies, the MAIC approach

balanced studies according to predefined treatment effect modifiers. However, the MAIC did not inform the base-case cost-effectiveness exploratory analyses instead the results are used in scenario analysis. Appendix Q states that for the exploratory cost-effectiveness analyses "*the indirect treatment comparison methodology ….was considered the most appropriate methodology, given the limitations of the MAIC*". Consequently, the ERG has briefly summarised the MAIC with cross referencing to CS Appendix O (with Appendix O.8 listing the limitations of the company's MAIC) which provides more details.

MAICs use individual patient data (IPD) from studies of one treatment (in this case the dupilumab RCTs) to match aggregate (summary) baseline statistics reported from trials of another treatment studies (in this case the anti-IL-5 biologic comparator studies). Because there is a common comparator arm in each trial (placebo in this case) the MAICs reported in the CS are said to be "anchored". MAIC is a form of propensity score weighting in which individuals in the IPD population (dupilumab) are weighted to balance the covariate distribution with that of the target aggregate population (anti-IL5 biologics), so that treatment outcomes can then be compared across balanced study populations.

The limitations to the MAIC approach are:

- The matching or adjustment will reduce the effective sample size (ESS) for the dupilumab study. This reduces statistical power.
- MAIC matches to the target (anti-IL5 biologic) study population rather than to an appropriate real-world population (so it is important that the IL5 studies adequately reflect severe asthma patients in the NHS).
- The method makes a fundamental assumption that all effect modifiers (and prognostic factors for "unanchored" comparisons) are accounted for in the covariates used in the MAIC. This is considered 'largely impossible' to meet, leading to an unknown amount of bias in the unanchored estimate.[2]

Another approach that could have been considered as an alternative to MAIC is a simulated treatment comparison (STC). In response to clarification question A21 the company favoured MAIC on advice from an independent methodological expert who advised that results using MAIC and STC should be similar but "Committees and ERGs are unfamiliar with STC". The company's independent methodological expert expressed a strong preference for MAIC in this circumstance in the absence of "further evidence (i.e. regarding an expanded network of evidence)". Hence it is unclear what data was shared

with the expert and it seems unlikely they were presented with the global network of evidence.

The company states that the MAICs were:

- conducted in accordance with the NICE Decision Support Unit (DSU) technical support document[2] and Signorovitch et al, 2012[3]
- underpinned by the same systematic literature review that informed the Bucher ITCs
- supplemented by information from a "targeted review" of grey literature. The CS states that the grey literature review provided additional detail on outcomes and baseline characteristics from reports or reviews published by regulatory agencies (e.g. European Medicines Agency, Food and Drug Administration and NICE)
- conducted using the same studies identified for the Bucher ITC, the same two populations groups (an uncontrolled persistent asthma population and an oral-corticosteroid dependent asthma population) and following the same feasibility assessment (which identified substantial differences in patient inclusion criteria and patient baseline characteristics, including effect modifiers, between the dupilumab and comparator trials).

MAICs in the uncontrolled persistent asthma population were conducted for the outcomes of severe asthma exacerbations and FEV1 (at 24 weeks and where data were available also at 12 weeks). For the OCS dependent asthma population MAICs were conducted for severe asthma exacerbations, reduction in OCS dose ≥50% and 100% reduction in OCS dose and FEV1 at 24 weeks. Only the results for severe asthma exacerbations and steroid sparing for the OCS dependent asthma population are presented in Appendix O.

Before the MAICs were undertaken the patient level data from the DRI12544 and QUEST RCTs were pooled. The CS states that this pooling was done to increase the sample size and diversity in the index patient population. However, because the two trials differed in length (24 weeks in DRI12544 and 52 weeks in QUEST) the DRI12544 trial was subject to a seasonality adjustment. The company provided details of their seasonality adjustment, including methods for their calculations, in response to Clarification question A25. The appears appropriate and to have followed the methodology described in Stolwijk et al.[20] The pooled DRI12544 and QUEST dupilumab data were then filtered as shown in CS Appendix O Table 106. The data filters were based on the comparator trials' patient inclusion/exclusion criteria (company response to Clarification question A22). The purpose

of the filters was to include dupilumab patients in the MAIC who may have been eligible for inclusion in the comparator clinical trials based on ICS/LABA level, blood EOS level, number of prior exacerbations in the past year and age. The company do not comment on whether there was any risk that the filtering process could have removed patients who could have been included in the matching. The ERG believes that providing the filtering only removed dupilumab patients who couldn't have been enrolled on the comparator trial, then the removed patients wouldn't have matched any of the comparator trial patients. After this initial filtering step the baseline distribution of effect modifiers in the dupilumab filtered data and the comparator trials was assessed.

Identification of treatment effect modifiers

For an anchored MAIC all treatment effect modifiers should be adjusted for to ensure balance and reduce bias. However, no purely prognostic variables should be adjusted otherwise standard error could be inflated due to over-matching.[2] The company state that their logistic propensity score model included all effect modifiers but not prognostic variables. To identify all the effect modifiers the company created a list of 16 potential adjustment factors (reported in CS Appendix O Table 108) which included those population characteristics reported in Table 83. Two clinical experts (the CS does not indicate whether these were independent experts) affirmed that four characteristics on the list were important treatment effect modifiers and there were no others to add. However, lack of reporting meant that some trials were matched on fewer than the four treatment effect modifiers. The four treatment effect modifiers indicated as being important were:

- Blood EOS level
- Number of exacerbations
- Nasal polyps
- Fractional nitric oxide concentration in exhaled breath.

The two clinicians consulted by the ERG agreed that these treatment effect modifiers were appropriate.

The distributions of effect modifiers in the filtered dupilumab data and comparator trials are presented in the following CS Tables with the observed between-trial differences in the treatment effect modifiers stated in the text following each table:

- Dupilumab and mepolizumab Appendix O Table 109 and Table 110
- Dupilumab and benralizumab Appendix O Table 111 and 112
- Dupliumab and reslizumab Appendix O Table 113

There are minor discrepancies between numbers of matched patients in the CS Appendix O Tables:

- Table 109 reports a sample size of 222 for the dupilumab patients pre-matching whilst table 106 reports 223 patients for the comparisons to MENSA and MUSCA and 213 patients to DREAM.
- Table 107 reports a sample size of 103 whereas Table 110 reports 102 patients
- Table 107 reports a sample size of 238 whereas Table 113 reports 237 patients

MAIC models

The filtered dupilumab pooled population and the comparator populations were matched on the agreed set of effect modifiers. It was unclear whether placebo arms were matched or if matching was done to pooled arms. In response to clarification question A26 asking about this, the company responded that matching was carried out separately for active and placebo arms. Tables of post-match baseline characteristics were presented for both active and placebo treatment in the clarification responses appendix. Matching was successful in terms of balancing patient populations according to choice of treatment effect modifiers (clarification response A23).

Where there were multiple RCTs for each comparator, the matching was conducted for each comparator RCT separately then results were pooled (e.g CS Tables 47, 55).

The analyses were conducted using STATA v14.2, R v3.4.2 and SAS v9.4. The code used was not provided so this was requested by the ERG and NICE (clarification question A24). Stata and R code were provided, SAS code was not. The key constituent parts of the code to perform the MAIC are consistent with the NICE DSU guidance on methods for population-adjusted indirect comparisons.[2] As the ERG does not have access to the dupilumab IPD it was not possible to validate the analyses.

After matching the filtered dupilumab population with the comparator trial populations sample sizes were further reduced. The effective sample sizes (ESS) after matching are available in Appendix O Tables 116 – 122. In most cases the ESS seems reasonable but there are some low ESS where the ESS for the post-match arms has decreased by more than 50% (for the exploratory population). The company did not provide the post-match patient characteristics for the MAIC analyses so these were requested (Clarification A23). The Company reported that matching was successful and that “identical post-matching characteristics between dupilumab and comparator trials were observed”. A histogram of

weights was also requested for each MAIC (Clarification A28). Small proportions of patients attracted disproportionately high weights in certain mepolizumab analyses and thus the results would be driven by these relatively few patients.

3.1.7.5 Summary of the company's ITCs

- The anti-IL5 biologics are a relevant comparator to dupilumab for an overlap population of patients with the features of type 2 inflammation and eosinophilic asthma.
- The company conducted a feasibility assessment before proceeding with the ITCs but the results of the feasibility assessment were not reported in detail. In particular the company did not provide tables of baseline characteristics for the comparator studies. The ERG is therefore unable to confirm whether the company's conclusions about the similarity of treatment effects are correct.
- Results for severe asthma exacerbations and the results on steroid sparing for the OCS dependent asthma population (results for 100% reduction from OCS and reduction to a daily dose <5mg) from the exploratory Bucher ITCs inform the company's exploratory cost-effectiveness analyses. The results of some MAIC analyses are used in a scenario analysis in the economic model.
- The company indicated that Bucher ITC results were preferred for the exploratory cost-effectiveness analyses because of the limitations of the MAIC. The limitations of the MAIC predominantly seem to stem from limitations in the matching process (summarised in CS Appendix O.8).

Bucher ITCs

- Subgroup dupilumab data were generated by using the US/global labels for each comparator of interest to identify the patient phenotypes that were important to match. Individual patient data for dupilumab were then matched to the inclusion criteria and baseline values of the patients in the registrational trials. These dupilumab population subgroups therefore differ from the company's decision problem population and the populations described by the NICE guidance recommendation for each of the comparators.
- For two of the three comparators, mepolizumab and reslizumab, the company was able to match to and compare dupilumab data against a comparator subgroup that better matched (but was not identical to) the NICE recommended populations.

- In creating subgroups randomisation was effectively broken and a different subgroups of dupilumab patients was used to compare against each comparator in each pairwise ITC.
- The ERG have not been able to test or validate the R programming code for the Bucher ITCs because it was not executable (without a data file).

MAICs

- The choice of treatment effect modifiers seems appropriate. However some trials were matched on fewer than the four treatment effect modifiers because the necessary information for some treatment effect modifiers was not reported.
- Pre-match "filtering" appears not to have removed any patients with potential for inclusion in matching
- The methods of the MAIC appear to have been properly applied and the matching (where it was possible) appears to have been successful.
- It is difficult to ascertain from the CS how similar the comparator study populations were to patients that would be treated in the NHS. Therefore how well the results of the MAICs represent severe asthma patients treated in the NHS is uncertain.

A summary of the Bucher ITC and MAIC approaches is provided in Table 29.

Table 29 Comparison of aspects of the Bucher ITC and MAIC approaches

	Bucher ITC approach	**MAIC approach**
Strengths (in relation to this appraisal)	Simple transparent methodology. Methodology followed appropriately. Use of annualised relapse rate adjusts for differences in follow-up between trials.	Robust methodology to adjust for differences between trials. Matching successful in terms of balancing patient populations according to choice of treatment effect modifiers albeit there remain imbalances of other non-treatment-effect modifiers.
Limitations (in relation to this appraisal)	Method itself cannot adjust for heterogeneity between trials. An investigation of heterogeneity between studies is not fully described nor tabulated. Instead the	Assumption underlying MAIC is that comparator population is the target real-world population. The choice of treatment effect modifiers to

	Company has selected subgroups of their trial data to "match" the licenses/registrational trials of comparators. Use of subgroups breaks the randomisation within the dupilumab trials. Random effects meta-analysis used by default for comparator trials regardless of reported I^2 thereby increasing uncertainty.	match on is limited to four but some trials matched on fewer than four factors. Where there were multiple trials for comparators, each trial was matched to in turn, then results were pooled. No adjustment for different lengths of follow-up between trials.
What would be the changes that would be necessary in the data to make this approach as robust as possible (and are these feasible)?	Unclear	Comparator populations' approximation to real world population. No pooling of matched studies across comparators.
Any other key issues?	Results used in economic model. Instead of conducting a "global" NMA comprising all comparators, the Company have conducted a series of ITCs each using different subgroups of the dupilumab IPD set. This precludes comparison across more than one treatment at a time. An NMA would have included the ITT population for dupilumab and comparator trials. Bayesian analyses reportedly conducted but not reported.	Included as a scenario in the economic model but cost-effectiveness results not reported in the CS. The MAIC scenario does not change conclusions from the company's exploratory comparisons with other biologics.

3.2 Summary statement of company's approach

The ERG's quality assessment of the CS review is summarised in Table 30.

Table 30 Quality assessment (CRD criteria) of CS review

CRD Quality Item: score Yes/ No/ Uncertain with comments	
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes. The CS reports inclusion and exclusion criteria for their clinical effectiveness review (CS Table 7). These criteria are wider than the NICE scope and the company's decision problem. The review also informed the NMAs and MAICs using the same eligibility criteria. The ERG agrees that the eligibility are generally appropriate.
2. Is there evidence of a substantial effort to search for all relevant research? Ie all studies identified	Yes. The company made a sufficient effort to search for all relevant research. Appropriate bibliographic databases were searched and the results were supplemented with the results of a trey literature search and hand searching recent conference proceedings. The ERG updated the searches and did not find anything additional to include. The ERG does not believe that any key trials or publications have been missed.
3. Is the validity of included studies adequately assessed?	Yes. The company assessed the validity of the included studies using NICE's criteria for RCTs. This included assessing studies included in the NMAs and MAICs. For the majority of decisions on the company's three dupilumab trials the ERG agrees with the company judgements (slight disagreements are noted in Section 3.1.4). For the comparator studies we referred to previous ERG assessments conducted for NICE appraisals and found that overall the ERGs' and company judgements were in agreement apart from determining whether a true ITT or a modified ITT analysis had been conducted for some trials.
4. Is sufficient detail of the individual studies presented?	Yes. Sufficient details were reported.
5. Are the primary studies summarised appropriately?	Yes. The included studies have been well summarised. The results reported appear accurate.

The ERG considers the systematic review processes followed good practice although it was not reported whether a second reviewer checked the validity assessments. The evidence presented for dupilumab however comes from trials with wider inclusion criteria than the decision problem. Only one outcome, annualised rate of severe exacerbations, was reported for the post-hoc subgroups of two of the three dupilumab RCTs that matched the decision problem population definition.

3.3 Summary of submitted evidence

In this section we present whole trial (i.e. ITT) population results for each outcome, firstly for people not receiving treatment with oral corticosteroids (the DRI12544 and QUEST RCTs), and then for people with steroid-dependent severe asthma (the VENTURE RCT). For all the trials the ITT population is broader than the decision problem population. For one outcome, the annualised rate of severe exacerbations, the CS reports results for post-hoc subgroup analyses on those participants in the QUEST and VENTURE trials who reflected the decision problem population:

- QUEST: EOS ≥150 or FeNO≥25 and ≥ 3 exacerbations
- VENTURE: EOS ≥150 or FeNO≥25, in patients receiving oral corticosteroids.

The results from these post-hoc subgroups are presented below alongside the ITT results for comparison. The company do not state why the post-hoc subgroup analyses for the decision problem population were only conducted for one outcome.

The CS does not report post-hoc analysis of a decision problem population subgroup for the DRI12544 trial (n= 46, approximately 15% of the ITT population). In response to clarification question A2, the company stated that this trial was not included in the economic model as there would be methodological difficulties in pooling data between QUEST and DRI12544 to derive transition probabilities.

3.3.1 Annualised rate of severe exacerbations

All three trials reported the annualised rate of severe exacerbations. This was one of the two co-primary outcomes of the QUEST RCT, a secondary outcome of the DRI12544 RCT and an 'other' outcome of the VENTURE RCT. This was also the only outcome reported for the post-hoc subgroups of QUEST and VENTURE that reflected the decision problem population definition.

DRI12544 and QUEST trials

In people with severe asthma who were not receiving treatment with oral corticosteroids the adjusted annualised rate of severe asthma exacerbations was lower among patients in the dupilumab 200mg Q2W arms than in the placebo arms of both DRI12544 and QUEST (Table 31). In the DRI12544 trial there was a 70% (95% CI 43.5% to 84.1%) lower rate of severe exacerbations than in the placebo group (p= 0.0002) whereas in the QUEST trial there was a 47.7% (95% CI 33.8% to 58.7%) lower rate of severe exacerbations in dupilumab group (p<0.0001). The unadjusted and adjusted annualised rates of severe

exacerbation events were similar in the QUEST trial (the unadjusted rate was not reported for DRI12544). In DRI12544 the mean annualised exacerbation rate for individual patients was just over 1 (SD 2.26) in the placebo group but this was only 0.3 (SD 1.19) in the dupilumab 200 mg Q2W group. In QUEST a smaller proportion of participants in the duplilumab group experienced at least 1 exacerbation event than in the placebo group (29.2% versus 42.3% respectively) (not reported for DRI12544).

In the QUEST trial decision problem population subgroup there was a [redacted] (95% CI [redacted]) lower rate of severe exacerbations in the dupilumab group in comparison to the placebo group (p<0.0001) (Table 31). The company also present the results of a dupilumab responder analysis, which included those patients in the dupilumab decision problem subgroup who experienced a reduction in annualised rate of severe asthma exacerbations of greater than 50% on the 52-week treatment period compared to the year prior to randomisation (the number of such patients is not reported). In this analysis, reported in CS Table 34, there was an [redacted] (95% CI [redacted]) lower rate of severe exacerbations in the dupilumab responders in comparison to all placebo group patients (p<0.0001).

Table 31 Severe exacerbations, ITT population

Outcome measure	DRI12544 On-treatment analysis		QUEST ITT population		QUEST decision problem population [a]	
	Dupilumab 200 mg Q2W	Placebo	Dupilumab 200 mg Q2W	Placebo	Dupilumab 200 mg Q2W	Placebo
	N=150	N=158	N=631	N=317	N=64	N=37
Adjusted annualised severe exacerbation event rate						
Estimate (95% CI)	0.269; (0.157, 0.461)	0.897 (0.619, 1.300)	0.456 (0.389, 0.534)	0.871 (0.724, 1.048)	[redacted]	[redacted]
Relative risk versus placebo (95% CI)	0.300 (0.159, 0.565); p=0.0002		0.523 (0.413, 0.662); p<0.0001		[redacted]; p<0.0001	
Risk difference vs placebo (95% CI)	-0.628[b] (NR)		–0.416 (–0.588, –0.243)		[redacted]	
Unadjusted annualised rate of severe exacerbation events[c]						
Estimate	NR	NR	0.481	0.980	[redacted]	[redacted]
Individual patient annualised severe exacerbation events rated						
n	148	158	NR	NR	NR	NR
Mean (SD)	0.30 (1.19)	1.07 (2.26)	NR	NR	NR	NR
Patients with ≥1 severe exacerbation event						
Mean (SD)	NR	NR	184 (29.2)	134 (42.3)	NR	NR
Number of severe exacerbation events, n (%)						
0	NR	NR	447 (70.8)	183 (57.7)	NR	NR
1	NR	NR	111 (17.6)	62 (19.6)	NR	NR
2	NR	NR	44 (7.0)	31 (9.8)	NR	NR
3	NR	NR	23 (3.6)	19 (6.0)	NR	NR
≥4	NR	NR	6 (1.0)	22 (6.9)	NR	NR

Source: CS Tables 17, 19, 34
NR not reported
[a] EOS ≥150 OR FeNO ≥25 AND ≥3 exacerbations.
[b] Calculated by ERG.
[c] The total number of events that occurred during the 52-week treatment period divided by the total number of patient-years followed in the 52-week treatment period.
[d] The number of severe exacerbation events for each patient divided by the number of years followed in the treatment period for that patient.

For the QUEST trial only the CS reports that dupilumab treatment did not have an effect on severe exacerbations resulting in hospitalisation of A&E visits (CS Table 24). Although the company note that the overall rate of events in the placebo groups was low no indication is given as to what a typical rate of events might be.

3.3.1.1 VENTURE trial

In the VENTURE trial population (people with asthma who were receiving treatment with oral corticosteroids) the adjusted annualised rate of severe asthma exacerbations was 59.3% (95% CI 37.0% to 73.7%) lower among patients in the dupilumab 300mg Q2W arm than in the placebo arm (Table 32).

In the VENTURE trial decision problem population subgroup there was a [redacted] (95% CI [redacted]) lower rate of severe exacerbations in the dupilumab group in comparison to the placebo group (p<0.0010) (Table 32). A responder analysis was conducted which included those dupilumab patients in the decision problem subgroup who reduced their OCS dose by 50% or more at week 12 or who had a reduction in the annualised rate of severe asthma exacerbation events over 50% on the 24-week treatment period compared to the year prior to randomisation (the number of such patients is not reported). In this analysis, reported in CS Table 35, there was a [redacted] (95% CI [redacted]) lower rate of severe exacerbations in the dupilumab responders in comparison to all patients in the placebo group (p=0.0002).

Table 32 Annualised rate of severe exacerbations

Outcome measure	ITT population		Decision problem population [a]	
	Dupilumab 300 mg Q2W	Placebo	Dupilumab 300 mg Q2W	Placebo
	N=103	N=107	N=78	N=74
Adjusted annualised rate of severe exacerbation events[b]				
Estimate (95% CI)	0.649 (0.442, 0.955)	1.597 (1.248, 2.043)	[redacted]	[redacted]
Risk ratio versus placebo (95% CI); p-value	0.407 (0.263, 0.630); p-value not reported		[redacted]; p=0.0010	
Risk difference versus placebo (95% CI)	–0.947 (–1.393, –0.501)		[redacted]	
Unadjusted annualised rate of severe exacerbation events at Week 52[c]				
Estimate	Not reported	Not reported	[redacted]	[redacted]

Source: CS Tables 31 and 35
[a] EOS ≥150 OR FeNO ≥25 AND mOCS
[b] Derived using negative binomial model with the total number of events onset from randomisation up to week 24 or last contact date (whichever comes earlier) as the response variable.
[c] The total number of events that occurred during the 24-week treatment period divided by the total number of patient-years followed in the 24-week treatment period.

The CS appendix (CS Appendix L. Table 70) shows that dupilumab treatment did not have a statistically significant effect on severe exacerbations resulting in hospitalisation of A&E visits.

3.3.2 Time to first severe exacerbation event

3.3.2.1 DRI12544 and QUEST trials

Time to the first severe exacerbation event is not reported in the CS for the DRI12544 trial but the published paper[16] states that dupilumab significantly delayed the time to first severe exacerbation. In the QUEST trial, the time to first severe exacerbation was also significantly delayed for the dupilumab 200mg Q2W group (HR = 0.611, p<0.001). The CS presents a Kaplan-Meier plot of time to asthma exacerbation in CS Figure 18.

3.3.2.2 VENTURE trial

The CS states that there was a significant delay in time to first severe exacerbation for the dupilumab group in the VENTURE trial in comparison to the placebo group. A hazard ratio is not report but the Kaplan-Meier plot is presented in CS Figure 26.

3.3.3 Change from baseline in FEV_1 at 12 weeks

Change from baseline in FEV_1 was reported in all three trials, but was reported as "FEV_1" in DRI12544 and as "pre-bronchodilator FEV_1" in QUEST and VENTURE. The ERG notes that the DRI12544 CSR states "Spirometry was to be performed between 6 and 10:30 AM after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for 6 hours and withholding the last dose of ICS/LABA for 12 hours and prior to administration of investigational product, if applicable" we therefore believe that the DRI12544 trial FEV_1 was also a "pre-bronchodilator FEV_1".

3.3.3.1 DRI12544 and QUEST trials

Change from baseline (CFB) in FEV1 at 12 weeks was the primary outcome in the DRI12544 trial and one of the two co-primary outcomes in the QUEST trial. Missing data (in DRI12544 9.3% in the dupilumab arm and 18.4% in the placebo arm; in QUEST approximately 3.2% in both the dupilumab and placebo arms) were not imputed in the primary analysis so therefore these results are not from ITT analyses. There was an

increase in FEV1 at 12 weeks in comparison to baseline in the placebo and dupilumab arms of both trials (Table 33). In asthma, an improvement in FEV1 of over 10% from baseline measurements is considered the minimal clinically important difference (MCID). This was achieved in the dupilumab arms but not the placebo arms (based on ERG calculations). The increase was greater in the dupilumab arms than in the placebo arms leading to least-squares mean differences of 0.20L and 0.14L in favour of dupilumab in the DRI12544 and QUEST trials respectively (p-value for the comparison against placebo 0.0001 in both trials).

Table 33 Change from baseline in FEV_1 at week 12 in DRI12544 and QUEST

	DRI12544: Change in FEV1		**QUEST: Change in pre-bronchodilator FEV1**	
FEV1 (L)	**Dupilumab 200 mg Q2W (N=150)**	**Placebo (N=158)**	**Dupilumab 200 mg Q2W (N=631)**	**Placebo (N=317)**
Baseline, n	150	158	631	317
Mean (SD)	1.79 (0.52)	1.82 (0.55)	1.78 (0.62)	1.76 (0.61)
Week 12, n	136	129	611	307
Mean (SD)	2.12 (0.68)	2.01 (0.69)	2.07 (0.76)	1.92 (0.70)
CFB primary analysis, n	136	129	611	307
Mean (SD)	-	-	0.28 (0.45)	0.15 (0.36)
LS mean (SE)	0.31 (0.03)	0.12 (0.03)	0.32 (0.02)	0.18 (0.02)
LS mean difference (95% CI)	0.20 (0.11, 0.28)		0.14 (0.08, 0.19)	
p value vs placebo	<0.0001		<0.0001	

Source: CS Tables 16 and 22
CFB: change from baseline; LS: least squares

The CS reports a number of sensitivity analyses conducted on the FEV_1 data from the DRI12544 trial (CS Table 16) which showed consistent results. The sensitivity analyses were conducted to test different methods of handling FEV_1 measurements confounded by the use of systemic corticosteroids during an asthma exacerbation episode, and different approaches to handling missing data.

The trial papers for the DRI12544[16] and QUEST[21] trials report the change in FEV_1 and the change in pre-bronchodilator FEV_1, respectively, to the end of the trial periods (24 weeks for DRI12544 and 52 weeks for QUEST) but the CS does not present or discuss these results. In both trials the improvement in FEV_1 in the dupilumab arm compared to placebo was sustained throughout the trial period.

3.3.3.2 VENTURE trial

Pre-bronchodilator FEV_1 in the VENTURE trial increased from baseline in the dupilumab arm but not in the placebo arm (Table 34). The mean difference between arms in the change from baseline at 24 weeks was statistically significant, being 0.22L in the dupilumab arm and close to zero in the placebo arm.

Table 34 Change from baseline in pre-bronchodilator FEV1 at week 24 in VENTURE

Outcome measure	**Dupilumab 300 mg Q2W (N=103)**	**Placebo (N=107)**
n	97	104
Mean (SD)	0.29 (0.46)	0.00 (0.51)
LS mean (SE)	0.22 (0.05)	0.01 (0.05)
LS mean difference from placebo (95% CI)	0.22 (0.09, 0.34)	
Source: CS Appendix Table 70 LS: least squares		

3.3.4 Reduction in OCS dose: VENTURE trial

Reduction in OCS dose at week 24 was the primary outcome in the VENTURE trial (participants in DRI12544 and QUEST were not on OCS at baseline and so OCS dose reduction outcomes are not relevant in these trials).

A reduction in OCS dose at week 24 was observed in the dupilumab and placebo arms of the VENTURE trial with a greater reduction in the dupilumab arm (mean reduction 73.85 mg/day vs 45.28 mg/day in the placebo arm). The LS mean difference versus placebo was 28.24 mg (95% CI 15.81 to 40.67, $p<0.0001$) (Table 35).

Table 35 Percentage reduction of OCS dose at Week 24 in VENTURE

OCS (mg/day)	Dupilumab 300 mg Q2W (N=103)	Placebo (N=107)
Baseline		
n	103	107
Mean (SD)	10.75 (5.90)	11.75 (6.31)
Week 24		
n	101	106
Mean (SD)	3.13 (5.44)	6.32 (6.75)
Percentage reduction from baseline		
n	101	106
Mean (SD)[a]	73.85 (39.78)	45.28 (50.73)
Median†	100.00	50.00
LS mean (SE)	70.09 (4.90)	41.85 (4.57)
LS mean difference vs placebo (95% CI)	28.24 (15.81, 40.67)	-
p value vs placebo	<0.0001	-

Source: CS Table 27
ANCOVA, analysis of covariance; CI, confidence interval; EOS, eosinophil; ITT, intent to treat; LS, least squares; OCS, oral corticosteroid; Q2W, every 2 weeks; SD, standard deviation; SE, standard error.
[a] Calculated from observed data only

The CS reports three further secondary outcomes regarding reductions in OCS use in the VENTURE trial (Table 36):

- Probability of patients achieving ≥50% reduction in OCS dose
- Probability of patients achieving reduction in OCS dose to <5mg/day
- Proportion of patients no longer requiring OCS

Results for these three outcomes related to reductions in OCS use at week 24 all show a statistically significant effect in favour of dupilumab (Table 36).

Table 36 Reduction in OCS use – other outcomes at week 24 in VENTURE

Outcome measure		Dupilumab 300 mg Q2W (N=103)	Placebo (N=107)
Patients achieving a reduction of ≥50% in OCS dose at Week 24			
Yes[a], %		81.0	53.3
Adjusted probability of achieving the reduction[b]	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 value vs placebo	<0.0001	
Patients achieving a reduction of OCS dose to <5 mg/day at Week 24			
Yes[a], %		72.9	37.4
Adjusted probability of achieving the reduction	Estimate (95% CI)	0.69 (0.58, 0.79)	0.33 (0.24, 0.44)
	OR vs placebo (95% CI)	4.48 (2.39, 8.39)	
	p value vs placebo	<0.0001	
Patients no longer requiring OCS at Week 24[b]			
Yes,[a] %		52.8	29.2
Adjusted probability of achieving the reduction	Estimate (95% CI)	0.48 (0.36, 0.59)	0.25 (0.17, 0.35)
	OR vs placebo (95% CI)	2.74 (1.47, 5.10)	
	p value vs placebo	0.0015	

Source: CS Tables 28 - 30
CI, confidence interval; EOS, eosinophil; OCS, oral corticosteroid; OR, odds ratio; Q2W, every 2 weeks.
[a] Calculated based on imputed data where the missing data are imputed from the primary missing data handling approach for the primary efficacy endpoint;. [b] Only the patients in the ITT population with a baseline optimised OCS dose ≤30mg/day were included in the analysis;

3.3.5 Asthma control

All three trials used an asthma control questionnaire (either the ACQ-5 or the ACQ-7) to measure the adequacy of asthma control. This is a patient-reported measure with a score ranging from 0 to 6 for both the ACQ-5 and the ACQ-7 (see section 0). The QUEST trial also reported on loss of asthma control (LOAC) events. The CS does not discuss the changes in ACQ scores in relation to the ACQ score cut-points for uncontrolled asthma (score ≥1.5) and well controlled asthma (score ≤0.75).

3.3.5.1 DRI12544 and QUEST trials

A reduction in ACQ score indicates improvement in asthma control, and the threshold for a minimal clinically important difference in the ACQ-5 and ACQ-7 is 0.5. The reduction in ACQ-5 score in the dupilumab and placebo arms of the DRI12544 trial exceeded this threshold and was greater in the dupilumab arm, with the difference between arms at 12

weeks being statistically significant (Table 37). In the QUEST trial the LS mean difference in the reduction in ACQ-7 score versus placebo was reported at week 24 and at week 52. At both time points the difference between the dupilumab and placebo arms was in favour of dupilumab and statistically significant.

The CS (CS p. 74) indicates that the ACQ-7 score was analysed separately for the adolescent patient population but these results are not reported in the CS. The ERG also notes that the QUEST publication[21] reports ACQ-5 data for 24 and 52 weeks but this is not mentioned in the CS.

Table 37 Change in asthma control questionnaire scores in DRI12544 and QUEST trials

Outcome measure	DRI12544: ACQ-5 score[a]		QUEST: ACQ-7 score	
	Dupilumab 200 mg Q2W (N=150)	Placebo (N=158)	Dupilumab 200 mg Q2W (N=631)	Placebo (N=317)
Baseline, n	150	158	631	317
Mean (SD)	2.73 (0.82)	2.69 (0.80)	2.86 (0.71)	2.84 (0.65)
Week 12, n	134	129	NR	NR
LS mean change from baseline (SE)	-1.35 (0.08)	-1.13 (0.08)	NR	NR
LS mean difference vs placebo (95% CI)[b]	–0.22 (–0.44, –0.01)		NR	
p value vs placebo	0.0398		NR	
Week 24, n	134	127	590	296
LS mean difference vs placebo (95% CI)	–0.35 (–0.57, –0.14)		–0.36 (–0.48, –0.24)	
p value vs placebo	0.0015		<0.0001	
Week 52, n	NA	NA	470	236
Mean	NA	NA	1.53	1.95
LS mean difference vs placebo (95% CI)	NA		–0.39 (–0.52, –0.27)	
p value vs placebo	NA		p<0.0001	

Source: CS Tables 13, 18 and 26 and CS section B.2.6.2.6 with additional data from the appendix to the published DRI12544 paper.[16]
ACQ, Asthma Control Questionnaire; NA, not applicable; NR, not reported; Q2W, every 2 weeks; SD, standard deviation; SE, standard error.
[a] ACQ-5 score collected from systemic corticosteroid start date to systemic corticosteroid end date +30 days for each exacerbation episode are excluded in order to reduce the confounding effect of systemic corticosteroids.

Loss of asthma control

Loss of asthma control (LOAC) (as defined above in section 3.1.5) was reported as a secondary outcome in DRI12544 (CS Appendix L.2.1.2.4) and QUEST (CS section

B.2.6.2.4) (Table 38). The CS states that LOAC event rates from QUEST were used in calculating the moderate exacerbation health state in the economic model (CS section B.3.2.2).

In both trials the adjusted LOAC event rate was lower in the dupilumab arm than the placebo arm. The annualised risk of loss of asthma control in the dupilumab group was 68.6% (95% CI 45.7% to 81.9%) lower in DRI12544 and 37.6% (95% CI 25.4% to 47.9%) lower in QUEST compared to the respective placebo group.

For DRI12544 the individual patient annualised LOAC events rate is also reported (CS Appendix Table 56). This rate was lower in the dupilumab 200mg Q2W arm (mean 0.38, SD 1.31, n=148) than in the placebo arm (mean 1.33, SD 2.51, n=158).

Table 38Annualised loss of asthma control event rates in DRI12544 and QUEST

Annualised rate of LOAC events	DRI12544		QUEST	
	Dupilumab 200 mg Q2W (N=150)	Placebo (N=158)	Dupilumab 200 mg Q2W (N=631)	Placebo (N=317)
Adjusted estimate (95% CI)	0.347 (0.217, 0.555)	1.107 (0.801, 1.530)	1.853 (1.654, 2.076)	2.972 (2.573, 3.432)
Relative risk vs placebo (95% CI)	0.314 (0.181, 0.543); <0.0001		0.624 (0.521, 0.746); p<0.0001	
Risk difference vs placebo (95% CI)	–0.76[a] (NR)		–1.119 (–1.586, –0.651)	

Source: CS Table 25 and CS Appendix Table 56
LOAC: loss of asthma control; NR: not reported
[a] calculated by ERG

3.3.5.2 VENTURE trial

At week 24 of the VENTURE trial there was a LS mean change in the ACQ-7 from baseline of -0.93 in the dupilumab group and -0.40 in the placebo group indicating a greater improvement in asthma control in the dupilumab group, with a mean difference relative to placebo of -0.53 (95% CI -0.80 to -0.25, no p-value reported).

Table 39 Change in ACQ-7 scores in the VENTURE trial

ACQ-7 global score	Dupilumab 300 mg Q2W (N=103)	Placebo (N=107)
Baseline, n	103	107
Mean (SD)	2.70 (0.98)	2.81 (1.00)
Week 24, n	87	87
CFB LS mean (SE)	–0.93 (0.10)	–0.40 (0.10)
CFB LS mean difference vs placebo (95% CI)	–0.53 (–0.80, –0.25)	

Source: CS Tables 13 and 31
CFB, change from baseline; LS, least squares; n, number; Q2W, every 2 weeks; SD, standard deviation; SE, standard error

Loss of asthma control

This outcome was not measured in the VENTURE trial.

3.3.6 Peak expiratory flow

Morning and evening PEF are reported in the CS for the QUEST trial only (Table 40). The CS reports baseline values and the difference in the change from baseline between the dupilumab and placebo arms but does not report the change from baseline per trial arm. The LS mean difference in the change from baseline favoured dupilumab over placebo, both for morning and evening PEF measurements. The CS reports the differences as being nominally statistically significant, although no confidence intervals are provided and there are some missing data that were not accounted for in the analyses.

Table 40 Mean difference between dupilumab and placebo in the change from baseline in morning and evening PEF at week 12 in QUEST

Outcome measure	Morning PEF		Evening PEF	
	Dupilumab 200 mg Q2W (N=631)	Placebo (N=317)	Dupilumab 200 mg Q2W (N=631)	Placebo (N=317)
Baseline, n	631	317	631	317
PEF, L/min, mean (SD)	281.37 (112.13)	286.84 (111.72)	293.55 (115.34)	298.31 (110.59)
CFB at week 12, n	608	305	606	306
LS mean difference vs placebo, L/min	18.24 (nominal p<0.0001)		15.92 (nominal p<0.0001)	

Sources: CS section B.2.6.2.8, CS Figures 21 and 22, and CS Appendix Table 44
CFB: Change from baseline; LS: least squares

Graphs presented in the CS show that the difference between dupilumab and placebo group PEF measurements observed at 12 weeks persisted through to the end of the trial at 52 weeks, both for morning PEF (CS Figure 21) and evening PEF (CS Figure 22).

3.3.7 Change from baseline in FeNO

FeNO is a biomarker of type-2 inflammation and the change from baseline in FeNO is reported in the CS for all three trials.

3.3.7.1 DRI12544 and QUEST trials

The CS presents figures showing the mean percent change in FeNO over time for the DRI12544 trial (CS Figure 12) and the mean FeNO as ppb over time for the QUEST trial (CS Figure 23). The published papers for these two trials provide additional numerical data, and these have been drawn together in Table 41 below.

A fall in FeNO levels in the dupilumab arms, but not in the placebo arms, of both trials had occurred by week 2 (CS Figure 12 and Figure 23). At week 12 the LS mean difference versus placebo was -35.60 (95% CI -54.63 to 16.57) in DRI12544. The LS mean difference versus placebo is not reported for the QUEST trial but the LS mean % change from baseline at 12 weeks in the dupilumab and placebo groups was -14.9 (SD 31.3) and -2.5 (SD 21.0) respectively (Table 41). The falls in FeNO were sustained to week 24 in DRI12544 and to week 24 and week 52 in QUEST. CS Figure 12 shows that after treatment stopped at 24 weeks in DRI12544 FeNO levels returned to baseline levels in the dupilumab arm at the post-treatment follow-ups (F1 to F4 in CS Figure 12).

Table 41 Change from baseline in FeNO (ppb) in DRI12544 and QUEST trials

Outcome measure	DRI12544		QUEST	
	DUP 200 mg Q2W (N=150)	Placebo (N=158)	DUP 200 mg Q2W (N=631)	Placebo (N=317)
Baseline, n	136	144	631	313
Mean (SD)	39.25 (36.67)	38.95 (34.78)	34.4 (34.9)	34.5 (28.7)
Week 12, n	117	131	579	284
LS mean % change from baseline	-24.02 (7.06[a])	11.58 (6.73[a])	-14.9 (SD 31.3)	-2.5 (SD 21.0)
LS mean difference vs placebo (95% CI)	-35.60 (-54.63 to -16.57)		NR	
p value vs placebo	0.0003		NR	
Week 24, n	114	120	542	271

Outcome measure	DRI12544		QUEST	
	DUP 200 mg Q2W (N=150)	Placebo (N=158)	DUP 200 mg Q2W (N=631)	Placebo (N=317)
LS mean % change from baseline	-21.86 (5.59[a])	10.91 (5.39[a])	-16.2 (SD 32.6)	-2.8 (SD 21.2)
LS mean difference vs placebo (95% CI)	-32.77 (-47.89 to -17.65)		NR	
p value vs placebo	<0.0001		NR	
Week 52, n	NA	NA	422	201
Mean	NA	NA	-16.0 (SD 27.1)	-2.1 (SD 20.2)
LS mean difference vs placebo (95% CI)	NA		NR	
p value vs placebo	NA		NR	

Sources: Appendices to the published DRI12544[16] and QUEST[21] published papers, CS Tables 12 and 13, CS Figure 23
[a] Published paper does not state if this is an SD or an SE
DUP: dupilumab; NA: not applicable; NR: not reported

3.3.7.2 VENTURE trial

For the VENTURE trial the CS presents a figure (CS Figure 27) showing the mean percent change in FeNO over time. The published paper for the VENTURE trial provides a numerical value for the mean change from baseline at week 24 (Table 42).

A similar pattern to that observed in DRI12544 and QUEST is reported for VENTURE. FeNO levels fell by week 2 in the dupilumab arm, but not the placebo arm (CS Figure 27). At week 24 the mean change from baseline was -17.3 (SE 27.9) in the dupilumab arm and 0.3 (SE 27.9) (Table 42).

Table 42 Change from baseline in FeNO in the VENTURE trial

	Dupilumab 300 mg Q2W (N=103)	Placebo (N=107)
Baseline, n	101	103
Mean (SD)	35.55 (28.34)	39.62 (34.12)
Week 24, n	88	87
Mean change from baseline (SE)	-17.3 (27.9)	0.3 (27.9)

Source: Appendix to the VENTURE trial published paper[12], CS Table 13 and CS Figure 27

3.3.8 Summary of Health related quality of life

The CS reports change from baseline in the EQ-5D-3L at weeks 12 and 24 for DRI12544 (CS Figure 11), change from baseline in the EQ-5D-5L at weeks 12, 24, 36 and 52 for QUEST (CS Figure 20) and the change from baseline in the EQ-5D-5L at week 24 for VENTURE (CS Table 31).

In response to Clarification question A8 the company provided all available EQ-5D results for these trials. The ERG has summarised these data for DRI12544 and QUEST in Table 43 and for VENTURE in Table 44.

Across the 24 week DRI12544 trial, no significant differences in the change from baseline EQ-5D scores were observed. In the 52 week QUEST trial no significant differences in the change from baseline EQ-5D scores were observed at weeks 12 or 36 whereas a statistically significant difference was observed at week 24 (p = 0.0412) and at week 52 (p=0.0133). In the QUEST trial the CS states that on the EQ-5D visual analogue scale (VAS) a difference was observed at weeks 12, 24 and 52. The ERG infers that no difference was observed at week 36.

Table 43 Change from baseline in EQ-5D single index utility scores in DRI12544 and QUEST trials

	DRI12544 trial: EQ-5D-3L		**QUEST trial: EQ-5D-5L**	
	Dupilumab 200 mg Q2W (N=150)	**Placebo (N=158)**	**Dupilumab 200 mg Q2W (N=631)**	**Placebo (N=317)**
Baseline, n	147	158	584	293
Mean (SD)	0.80 (0.19)	0.78 (0.20)	0.74 (0.19)	0.74 (0.18)
Week 12, n	132	132	567	280
LS mean change from baseline (SE)	0.09 (0.01)	0.05 (0.01)	0.09 (0.01)	0.08 (0.01)
LS mean diff vs placebo (95% CI)	0.03 (-0.01, 0.08)	-	0.01 (-0.01, 0.03)	-
p value vs placebo	0.0902	-	0.2673	-
Week 24, n	131	127	552	275
LS mean change from baseline (SE)	0.06 (0.01)	0.06 (0.01)	0.10 (0.01)	0.07 (0.01)
LS mean diff vs placebo (95% CI)	0.00 (-0.04, 0.04)	-	0.02 (0.00, 0.05)	

	DRI12544 trial: EQ-5D-3L		QUEST trial: EQ-5D-5L	
	Dupilumab 200 mg Q2W (N=150)	Placebo (N=158)	Dupilumab 200 mg Q2W (N=631)	Placebo (N=317)
p value vs placebo	0.9299	-	0.0412	
Week 36, n			548	264
LS mean change from baseline (SE)	N/A	N/A	0.10 (0.01)	0.08 (0.01)
LS mean diff vs matching placebo (95% CI)	N/A	-	0.02 (-0.01, 0.04)	
p value vs matching placebo	N/A	-	0.2131	
Week 52, n			457	220
LS mean change from baseline (SE)	N/A	N/A	0.10 (0.01)	0.07 (0.01)
LS mean diff vs matching placebo (95% CI)	N/A	-	0.03 (0.01, 0.06)	
p value vs matching placebo	N/A	-	0.0133	

Source: Clarification question A8

In the VENTURE RCT no differences were observed in the change in EQ-5D scores at week 12 or at week 14 (Table 44). The CS states that at Week 24 there was "*nominal significant improvement*" in the EQ VAS (p=0.0061).

Table 44 Change from baseline in EQ-5D single index utility scores in VENTURE

	VENTURE	
EQ-5D-5L single index score	**Dupilumab 300mg q2w (N=103)**	**Placebo (N= 107)**
Baseline, n	103	107
Mean (SD)	0.74 (0.18)	0.72 (0.19)
Week 12, n	98	105
LS Mean (SE)	0.04 (0.02)	0.04 (0.02)
LS Mean Diff vs. placebo (95% CI)[a]	0.01 (-0.04, 0.05)	
P-value vs. placebo[a]	0.7951	
Week 24, n	98	100
LS Mean (SE)	0.06 (0.02)	0.04 (0.02)
LS Mean Diff vs. placebo (95% CI)	0.01 (-0.03, 0.06)	
P-value vs. placebo	0.5518	

Source: Clarification question A8

3.3.9 Sub-group analyses results

This section reports on the pre-planned subgroup analyses conducted for DRI12544, QUEST and VENTURE, as reported in the CS (note that not all pre-planned subgroup analyses are presented in the CS). In addition to these pre-specified subgroup analyses, the company conducted post-hoc subgroup analyses based on a subset of patients in the QUEST and VENTURE trials who reflect the company's decision problem population. These post-hoc subgroups were used in the analyses of one outcome, the annualised rate of severe exacerbations, and are reported in section 3.3.1 above.

The company lists the pre-planned subgroups for each of the three included RCTs in CS Table 10. The relevant row of this table is reproduced below (Table 45).

Table 45 Pre-planned subgroups in the DRI12544, QUEST and VENTURE RCTs

<table>
<tr><th>DRI12544</th><th>QUEST</th><th>VENTURE</th></tr>
<tr><td rowspan="2">• Region
• Background ICS/LABA dose levels
• Baseline FEV1
• ACQ-5
• Number of asthma events prior to the study</td><td colspan="2">• Region
• Baseline EOS level Group 1 (<0.15 Giga/L or ≥0.15 Giga/L)
• Baseline EOS level Group 2 (<0.3 Giga/L or ≥0.3 Giga/L)
• ACQ-5 (≤2, >2)
• Baseline pre-BD FEV_1 (≤1.75, >1.75 L)
• Baseline predicted FEV_1% (<60%, 60–90%)
• Baseline weight
• Baseline BMI (<25, 25–<30, ≥30 kg/m^2)
• Smoking history (former, never)
• Age at onset of asthma (<18, 18–40, >40 years)
• Baseline FeNO (<25, ≥25–<50, ≥50 ppb)
• Atopic medical conditions (yes, no)
• Number of severe asthma exacerbations prior to the study</td></tr>
<tr><td>• Territory (North America, EU, rest of world)
• Background ICS dose level at randomisation (medium, high)
• Background controller at randomisation (ICS and LABA only, ICS and LABA and anti-leukotrienes only, Other; ICS, LABA and any third controller, Other)
• Baseline periostin (ng/mL) (<median, ≥median)</td><td>• Baseline optimised OCS dose strata (≤10 mg/day, >10 mg/day)</td></tr>
</table>

Subgroup analysis results are presented in CS section B.2.7. A narrative summary of the subgroup analysis for the primary outcome of DRI12544 (change from baseline at week 12 in FEV_1) is provided and numerical data are presented for the two co-primary outcomes of QUEST and the primary outcome of VENTURE for subgroups based on EOS and FeNO levels at baseline. Some secondary outcome results for subgroups of patients for baseline blood EOS and receipt of high dose ICS at baseline are reported within CS section B.2.6. The CS states that subgroup analyses for other outcomes and subgroups in all three included studies are presented in Appendix E. However, Appendix E directs the reader to the study CSRs, which were not included in the submission. Whilst the CSRs were subsequently provided by the company (Clarification question A30), only the CSR for DRI12544 was accessible, the CSRs for QUEST and VENTURE were password protected and accessible versions were not supplied in time for the ERG to take this information into consideration. Consequently the ERG has focused on the subgroup analyses for the primary outcome(s) of each study based on baseline EOS, baseline FeNO, baseline ICS. All subgroup analyses have smaller sample sizes than the ITT populations and this should be borne in mind when interpreting results.

3.3.9.1 DRI12544

A narrative summary of the subgroup analysis for the primary outcome of DRI12544 (change from baseline at week 12 in FEV_1) is provided. This states that "*generally consistent increases in FEV_1 from baseline at Week 12 with dupilumab vs placebo across a range of demographic and baseline characteristics*" but the CS does not present any numerical data.

3.3.9.2 QUEST

Subgroup analyses for the annualised rate of severe exacerbations (co-primary outcome) suggest there was less benefit from dupilumab compared to placebo, in participants with lower baseline blood eosinophil levels (EOS <0.3 G/L in group 1 and EOS <0.15 G/L in group 2) (relative risks 0.759 and 0.925 respectively) than for participants with higher EOS levels (EOS ≥0.3 in group 1 and EOS ≥ 0.15 in group 2) (relative risks of 0.342 and 0.442 respectively). For both the lower EOS subgroups, the 95% CI for the relative risk crosses 1, indicating no statistically significant effect (Table 46). A similar pattern is evident in the subgroup analyses of FeNO, with greater benefit of dupilumab being shown for participants with baseline FeNO levels above 25 ppb (which is indicative of type-2 inflammation).

For the other co-primary outcome, change from baseline in pre-bronchodilator FEV_1 at week 12, all subgroups experienced improvements but the observed improvements were greater in the subgroups of patients with higher baseline EOS levels or higher FeNO levels.

For the subgroup of patients receiving high dose ICS at baseline the CS states that the reduction in the annualised rate of severe exacerbations and the increase in pre-bronchodilator FEV1 from baseline to week 12 were consistent with the results observed for the ITT population (CS B.2.6.2.1).

Table 46 Summary of relative risks in the annualised rate of severe exacerbations and in change from baseline in pre-BD FEV1 at week 12 in subgroups of the QUEST RCT population

Outcome	**Subgroup**		**n**	**relative risk (95% CI)**
Co-primary outcome 1: annualised event rate of severe exacerbations	Baseline blood eosinophil group 1 (Giga/L)	<0.3	535	0.759 (0.548, 1.052)
		≥0.3	412	0.342 (0.244, 0.480) p<0.0001[a]
	Baseline blood eosinophil group 2 (Giga/L)	<0.15	278	0.925 (0.580, 1.474
		≥0.15	669	0.442 (0.337, 0.581) p<0.0001[a]
	CS Figure 29 header suggests data for alternative baseline EOS cut-off criteria subgroups are available. However, there appears to be an error because CS Figure 29 is a duplicate of CS Figure 28.			
	Baseline FeNO (ppb)	<25	474	0.752 (0.541, 1.046)
		≥25 to <50	271	0.386 (0.243, 0.616)
		≥50	190	0.308 (0.183, 0.519)
	ICS dose at baseline[b]	High	489	0.539 (0.400, 0.725) p<0.0001

Co-primary outcome 2: CFB in pre-BD FEV_1 (L) at week 12	Baseline blood eosinophil group 1 (Giga/L)	<0.3	517	0.08 (0.01, 0.15)
		≥0.3	400	0.21 (0.13, 0.29) p<0.0001[c]
	Baseline blood eosinophil group 2 (Giga/L)	<0.15	268	0.06 (-0.04, 0.15)
		≥0.15	649	0.17 (0.11, 0.23) p<0.0001[c]
	Baseline blood eosinophil, alternative cut offs	<0.15	268	0.06 (-0.04, 0.15)
		≥0.15 to <0.3	249	0.11 (0.01, 0.21)
		≥0.3 to <0.5	182	0.15 (0.03, 0.26)
		≥0.5	218	0.28 (0.17, 0.39)
	Baseline FeNO (ppb)	<25	460	0.05 (-0.02, 0.12)
		≥25 to <50	262	0.19 (0.09, 0.28)
		≥50	183	0.30 (0.17, 0.44)
	ICS dose at baseline[c]	High	477	0.13 (0.06, 0.21) p = 0.0003

Source: CS Figure 28 to Figure 33, CS Table 20, CS Table 21, CS Table 23
[a] From CS Table 20
[b] From CS Table 21
[c] From CS Table 23

3.3.9.3 VENTURE

In the VENTURE trial population, a reduction in OCS dose at week 24 in comparison to baseline (whilst maintaining asthma control) was achieved in all baseline blood EOS count subgroups and all baseline FeNO level subgroups (Table 47).

Table 47 Summary of treatment difference on percentage reduction of OCS dose (mg/day) at week 24 in subgroups of the VENTURE RCT population

Primary outcome	Subgroup		n	LS Mean difference (95% CI)
Treatment difference on percentage reduction of OCS dose (mg/day) at week 24	Baseline blood eosinophil group 1 (Giga/L)	<0.15	58	26.89 (-0.73, 54.52)
		≥0.15	149	29.39 (15.67, 43.12)
	Baseline blood eosinophil group 2 (Giga/L)	<0.3	119	21.33 (3.90, 38.75)
		≥0.3	88	39.83 (18.94,54.71)
	Baseline FeNO (ppb)	<25	89	17.27 (-3.62, 38.16)
		≥25 to <50	60	38.31 (14.84, 61.78)
		≥50	52	33.64 (13.67, 53.61)

Source: CS Figures 34 and 35

3.3.10 Bucher ITC results

3.3.10.1 Uncontrolled persistent asthma population severe exacerbations

Dupilumab versus mepolizumab

As described in section 3.1.7.3.1 of this report the first step of the Bucher ITCs, when there were multiple trials or trial subgroups, was to pool the data using a random effects meta-analysis. The meta-analysis results for the DRI12544 and QUEST trial subgroups matched to the mepolizumab label indicate a lower rate of severe exacerbations among patients in receipt of dupilumab 200mg versus placebo. Similarly the meta-analysis of the three mepolizumab versus placebo trials contributing data to the Bucher ITC demonstrates a lower rate of severe exacerbations among patients in receipt of mepolizumab in comparison to those receiving placebo. When dupilumab and mepolizumab were compared with each other in a Bucher indirect treatment comparison the result suggests that treatment with dupilumab 200mg leads to a lower rate of severe exacerbations than

with mepolizumab in people with uncontrolled persistent asthma (ITC rate ratio [redacted])

Table 48 Severe exacerbations: Bucher ITC results (Dupilumab subgroup matched to mepolizumab label)

Comparison	Trial or subgroup	Rate ratio (95% CI)	Meta-analysis rate ratio (95% CI)
Dupilumab 200mg vs placebo	DRI12544 subgroup (matched to mepolizumab label)	[redacted]	[redacted]
	QUEST subgroup (matched to mepolizumab label)	[redacted]	
Mepolizumab vs placebo	DREAM	[redacted]	[redacted]
	MENSA	[redacted]	
	MUSCA	[redacted]	
		Bucher ITC rate ratio (95% CI)	
Dupilumab vs mepolizumab		[redacted]	

Source: Figure 1 Sanofi factual accuracy check form. This replaces CS Appendix Figure 35, which was submitted by the company in error.

The company were also able to form subgroups of dupilumab patients from the DRI12544 and QUEST trials who were similar to a subgroup of the MENSA mepolizumab trial reported within a NICE committee report (report not referenced in the CS). The patients in these RCT subgroups are more similar to, but not an exact match with, patients described in NICE guidance for mepolizumab. The size of the subgroups was small (individual subgroup arms ranging from 9 to 54 patients as reported in CS Table 92). The Bucher ITC rate ratio for dupilumab vs mepolizumab was [redacted] (Table 49). The company state that this result suggests dupilumab "offered a similar or a slight statistically non-significant advantage over mepolizumab". However, due to the small numbers in the subgroups (Table 28) these results have low precision (as evidenced by the wide confidence intervals).

Table 49 Severe exacerbations: Bucher ITC results (dupilumab subgroup matched to mepolizumab NICE-like subgroup)

Comparison	Trial subgroup	Rate ratio (95% CI)	Meta-analysis rate ratio (95% CI)
Dupilumab 200mg vs placebo	DRI12544 subgroup (matched to MENSA NICE-like subgroup)	[redacted]	[redacted]
	QUEST subgroup (matched to MENSA NICE-like subgroup)	[redacted]	
Mepolizumab vs placebo	MENSA NICE-like subgroup	[redacted]	Not applicable
		Bucher ITC rate ratio (95% CI)	
Dupilumab vs mepolizumab		[redacted]	

Source: Appendix N Figure 36

Dupilumab versus benralizumab

Dupilumab and benralizumab treatment both resulted in fewer severe exacerbations than placebo and when dupilumab and benralizumab were compared in a Bucher ITC the result suggests that treatment with dupilumab 200mg led to a lower rate of severe exacerbations than benralizumab in people with uncontrolled persistent asthma (ITC rate ratio [redacted]) (Table 50).

Table 50 Severe exacerbations: Bucher ITC results (Dupilumab subgroup matched to benralizumab label)

Comparison	Trial or subgroup	Rate ratio (95% CI)	Meta-analysis rate ratio (95% CI)
Dupilumab 200mg vs placebo	DRI12544 subgroup (matched to benralizumab label)	[redacted]	[redacted]
	QUEST subgroup (matched to benralizumab label)	[redacted]	

Benralizumab vs placebo	CALIMA, High ICS	[redacted]	[redacted]
	CALIMA, medium ICS	[redacted]	
	SIROCCO, High ICS	[redacted]	
		Bucher ITC rate ratio (95% CI)	
Dupilumab vs benralizumab		[redacted]	

Source: Figure 4 in the response to clarification question A19

Dupilumab versus reslizumab

Pooled results from the two BREATH RCTs were used for the ITC comparison between dupilumab and reslizumab because separate data from the individual BREATH RCTs were not available (response to clarification question A17). The Bucher ITC suggests that treatment with dupilumab 200mg led to a lower rate of severe exacerbations than treatment with reslizumab in people with uncontrolled persistent asthma (ITC rate ratio [redacted]) (Table 51).

Table 51 Severe exacerbations: Bucher ITC results (Dupilumab subgroup matched to reslizumab label)

Comparison	Trial	Rate ratio (95% CI)	Meta-analysis rate ratio (95% CI)
Dupilumab 200mg vs placebo	DRI12544 subgroup (matched to reslizumab label)	[redacted]	[redacted]
	QUEST subgroup (matched to reslizumab label)	[redacted]	
Reslizumab vs placebo	BREATH (3082 &3083)	[redacted]	Not applicable
		Bucher ITC rate ratio (95% CI)	
Dupilumab vs reslizumab		[redacted]	

Source: CS Appendix N Figure 37

The company were able to form a subgroup of dupilumab patients who were similar to a subgroup of the pooled BREATH 3082 and 3083 RCTs that better matched patients

described by the NICE reslizumab guidance (patients experiencing at least 3 severe exacerbations a year). The size of the subgroups was small (Table 28). The Bucher ITC rate ratio for dupilumab vs reslizumab was [redacted](Table 52). The company state that this result suggests dupilumab "offered a similar or slight statistically non-significant advantage over reslizumab". However, due to the uncertainty caused by the small numbers in the subgroups (as evidenced by the wide confidence intervals), the ERG would be very cautious in generalising from this result.

Table 52 Severe exacerbations: Bucher ITC results (dupilumab subgroup matched to reslizumab NICE-like subgroup)

Comparison	Study	Study rate ratio (95% CI)	Meta-analysis rate ratio (95% CI)
Dupilumab 200mg vs placebo	DRI12544 subgroup (matched to BREATH NICE-like subgroup)	[redacted]	[redacted]
	QUEST subgroup (matched to BREATH NICE-like subgroup)	[redacted]	
Reslizumab vs placebo	BREATH (3082, 3083) NICE-like subgroup	[redacted]	N/A
		Bucher ITC rate ratio (95% CI)	
Dupilumab vs reslizumab		[redacted]	

Source: Appendix N Figure 38

3.3.10.2 OCS-dependent asthma population

For the OCS-dependent asthma population there was only a single dupilumab trial (VENTURE) and only single mepolizumab and benralizumab trials (SIRIUS and ZONDA respectively to include in the Bucher ITCs. For each ITC a dupilumab subgroup was formed by matching the patients in the dupilumab VENTURE trial to the mepolizumab (SIRIUS) or to the benralizumab (ZONDA) trial population characteristics.

3.3.10.2.1 Reduction in OCS dose <5mg/Day

Dupilumab versus mepolizumab

The Bucher ITC results favoured dupilumab 300mg suggesting that more people would achieve a reduction on OCS dose <5mg/day in comparison to mepolizumab, but this was not a statistically significant result (ITC odds ratio 1.50, 95% CI 0.54, 4.14) (Table 53).

Table 53 Reduction in OCS dose <5mg/Day: Bucher ITC results (Dupilumab subgroup matched to mepolizumab label)

Comparison	Trial or subgroup	Fixed-effect OR (95% CI)
Dupilumab 300mg vs placebo	VENTURE subgroup (matched to mepolizumab label)	3.71 (1.78, 7.74)
Mepolizumab vs placebo	SIRIUS	2.48 (1.23, 5.00)
		Bucher ITC OR (95% CI)
Dupilumab vs mepolizumab		1.50 (0.54, 4.14)

Source: CS Appendix N Figure 39

Dupilumab versus benralizumab

In a subgroup of the dupilumab VENTURE trial population formed by matching to the benralizumab US/global label there was a numerical, but not a statistically significant advantage over benralizumab (ITC OR 1.95 95% CI 0.51, 7.38) for the outcome of reduction in OCS dose to less than 5mg/day (Table 54).

Table 54 Reduction in OCS dose <5mg/Day: Bucher ITC results (Dupilumab subgroup matched to benralizumab label)

Comparison	Trial or subgroup	Fixed-effect odds ratio (95% CI)
Dupilumab 300mg vs placebo	VENTURE subgroup (matched to benralizumab label)	5.59 (1.77, 17.67)
Benralizumab vs placebo	ZONDA	2.87 (1.47, 5.60)

		Bucher ITC odds ratio (95% CI)
Dupilumab vs benralizumab		1.95 (0.51, 7.38)

Source: CS Appendix N Figure 43

3.3.10.2.2 Reduction in OCS dose ≥ 50%

Dupilumab versus mepolizumab

The Bucher ITC odds ratio (1.80, 95% CI 0.62, 5.21) favoured dupilumab 300mg in comparison to mepolizumab for the outcome of a reduction in OCS dose of 50% or more, but this was not a statistically significant result (Table 55).

Table 55 Reduction in OCS dose ≥50%: Bucher ITC results (Dupilumab subgroup matched to mepolizumab label)

Comparison	**Trial or subgroup**	**Fixed-effect odds ratio (95% CI)**
Dupilumab 300mg vs placebo	VENTURE subgroup (matched to mepolizumab label)	4.17 (1.88, 9.28)
Mepolizumab vs placebo	SIRIUS	2.31 (1.15, 4.64)
		Bucher ITC odds ratio (95% CI)
Dupilumab vs mepolizumab		1.80 (0.62, 5.21)

Source: CS Appendix N Figure 40

Dupilumab versus benralizumab

The Bucher ITC results for reduction on OCS dose of 50% or more favoured dupilumab 300mg in comparison to benralizumab, but this was not a statistically significant result (ITC odds ratio 1.15, 95% CI 0.30, 4.45) (Table 56).

Table 56 Reduction in OCS dose ≥50%: Bucher ITC results (Dupilumab subgroup matched to benralizumab label)

Comparison	Trial or subgroup	Fixed-effect odds ratio (95% CI)
Dupilumab 300mg vs placebo	VENTURE subgroup (matched to benralizumab label)	3.71 (1.15, 11.97)
Benralizumab vs placebo	ZONDA	3.22 (1.64, 6.32)
		Bucher ITC odds ratio (95% CI)
Dupilumab vs benralizumab		1.15 (0.30, 4.45)

Source: CS Appendix N Figure 44

3.3.10.2.3 Reduction in OCS dose 100%

Dupilumab versus mepolizumab

The result of the ITC for reduction in OCS dose of 100% offered a small numerical advantage to dupilumab over mepolizumab but the result is not statistically significant (ITC OR 1.16, 95% CI 0.31, 4.44) (Table 57).

Table 57 Reduction in OCS dose 100%: Bucher ITC results (Dupilumab subgroup matched to mepolizumab label)

Comparison	Trial or subgroup	Fixed-effect odds ratio (95% CI)
Dupilumab 300mg vs placebo	VENTURE subgroup (matched to mepolizumab label)	2.41 (1.18, 4.91)
Mepolizumab vs placebo	SIRIUS	2.07 (0.67, 6.41)
		Bucher ITC odds ratio (95% CI)
Dupilumab vs mepolizumab		1.16 (0.31, 4.44)

Source: CS Appendix N Figure 41

Dupilumab versus benralizumab

For the outcome of a 100% reduction in OCS dose the results of the Bucher ITC suggested that dupilumab 300mg and benralizumab demonstrate very similar efficacy (ITC OR 0.98 95% CI 0.21, 4.59) (Table 58).

Table 58 Reduction in OCS dose 100%: Bucher ITC results (Dupilumab subgroup matched to benralizumab label

Comparison	**Trial or subgroup**	**Fixed-effect odds ratio (95% CI)**
Dupilumab 300mg vs placebo	VENTURE subgroup (matched to benralizumab label)	4.57 (1.38, 15.11)
Benralizumab vs placebo	ZONDA	4.67 (1.76, 12.45)
		Bucher ITC odds ratio (95% CI)
Dupilumab vs benralizumab		0.98 (0.21, 4.59)

Source: CS Appendix N Figure 45

3.3.10.2.4 Severe exacerbations

Dupilumab versus mepolizumab

The Bucher ITC suggests there is no statistically significant difference between dupilumab and mepolizumab in terms of annualised severe exacerbation rates (ITC rate ratio 0.67, 95% CI 0.36, 1.28) (Table 59).

Table 59 Severe exacerbations on the treatment period: Bucher ITC results (Dupilumab subgroup matched to mepolizumab label)

Comparison	Trial or subgroup	Rate ratio (95% CI)
Dupilumab 300mg vs placebo	VENTURE subgroup (matched to mepolizumab label)	0.46 (0.27, 0.77)
Mepolizumab vs placebo	SIRIUS	0.68 (0.47, 0.99)

		Bucher ITC rate ratio (95% CI)
Dupilumab vs mepolizumab		0.67 (0.36, 1.28)

Source: CS Appendix N Figure 42

Dupilumab versus benralizumab

For the outcome of severe exacerbations, results from the ITC suggest that dupilumab 300mg does not have a statistically significant advantage over benralizumab (Bucher ITC rate ratio 0.86 95% CI 0.35, 2.13) (Table 60).

Table 60 Severe exacerbations on the treatment period: Bucher ITC results (Dupilumab subgroup matched to benralizumab label)

Comparison	Trial or subgroup	Rate ratio (95% CI)
Dupilumab 300mg vs placebo	VENTURE subgroup (matched to benralizumab label)	0.25 (0.12, 0.55)
Benralizumab vs placebo	ZONDA	0.30 (0.18, 0.48)
		Bucher ITC rate ratio (95% CI)
Dupilumab vs benralizumab		0.86 (0.35, 2.13)

Source: CS Appendix N Figure 46

3.3.11 MAIC results

As stated in section 3.1.7.1 the purpose of the MAICs was to compliment the findings from the Bucher ITCs. The results of the MAIC are not used in the basecase economic model but there is an option in the model settings to use data from the MAICs and the MAIC results were used in a scenario analysis. Consequently, we report summary results only. More detailed results (including details of the effective sample sizes after matching can be found in Appendix 8.2). For some analyses there was a low effective sample size and in others some effect modifiers had to be omitted from the model. These caveats need to be kept in mind and the results should be interpreted cautiously.

3.3.11.1 Uncontrolled persistent asthma population

In the uncontrolled persistent asthma population (DRI12544 and QUEST RCTs) the MAIC results for severe exacerbations were statistically in favour of dupilumab for the comparison against mepolizumab (ITT trial populations) and against benralizumab (rate ratios of 0.74, 95% CI 0.56 to 0.99 and 0.59, 95% CI 0.38 to 0.89 respectively). In the comparison against the mepolizumab MENSA trial subgroup and the comparison against reslizumab the rate ratios were numerically in favour of dupilumab but did not reach statistical significance.

Table 61 Uncontrolled persistent asthma population MAIC results: Severe exacerbations

MAIC comparison	Comparator trial(s)	Dupilumab vs comparator MAIC rate ratio (95%CI)
Dupilumab vs mepolizumab	MENSA (ITT)	[redacted]
	DREAM (ITT)	
	MUSCA (ITT)	
Dupilumab vs mepolizumab subgroup	MENSA (Subgroup) EOS ≥300 in past year and ≥4 exacerbations or mOCS	[redacted]
Dupilumab vs benralizumab	CALIMA (EOS ≥300)	[redacted]
	SIROCCO (EOS ≥300)	
Dupilumab vs reslizumab	BREATH 82-83	[redacted]

Source: CS Appendix O Figures 47, 48, 55, 59

3.3.11.2 OCS-dependent asthma population

In the OCS-dependent asthma population results for three outcomes, severe exacerbations, ≥50% reduction in OCS dose and 100% reduction in OCS dose are presented (Table 62 to Table 64). For all three of these outcomes when dupilumab was compared with the mepolizumab ITT population the result was numerically in favour of dupilumab but was not statistically significant. The comparison of dupilumab with the mepolizumab subgroup (EOS ≥300 in past year and ≥4 exacerbations or mOCS) was not statistically significant for any of the three outcomes and was numerically in favour of dupilumab for the outcomes of severe exacerbations and ≥50% reduction in OCS dose but was numerically in favour of the mepolizumab subgroup for the 100% reduction in OCS dose outcome.

In the MAICs comparing dupilumab against benralizumab none of the results were statistically significant. For the outcome of ≥50% reduction in OCS dose the results was numerically in favour of dupilumab but for the severe exacerbations and 100% reduction in OCS dose outcomes the result favoured benralizumab numerically.

Table 62 OCS-dependent asthma population MAIC results: Severe exacerbations

MAIC comparison	Comparator trial	Dupilumab vs comparator MAIC rate ratio (95%CI)
Dupilumab vs mepolizumab	SIRIUS ITT	0.48 (0.21, 1.1)
Dupilumab vs mepolizumab subgroup	SIRIUS subgroup EOS ≥300 in past year and ≥4 exacerbations or mOCS	0.56 (0.31, 1.01)
Dupilumab vs benralizumab	ZONDA ITT	1.52 (0.69, 3.36)

Source: CS Appendix O Figures 49, 52, 56

Table 63 OCS-dependent asthma population MAIC results: ≥50% reduction in OCS dose

MAIC comparison	Comparator trial	Dupilumab vs comparator MAIC odds ratio (95%CI)
Dupilumab vs mepolizumab	SIRIUS ITT	1.7 (0.53, 5.47)
Dupilumab vs mepolizumab subgroup	SIRIUS subgroup EOS ≥300 in past year and ≥4 exacerbations or mOCS	1.47 (0.43, 5.06)
Dupilumab vs benralizumab	ZONDA ITT	1.13 (0.33, 3.78)

Source: CS Appendix O Figures 50, 53, 57

Table 64 OCS-dependent asthma population MAIC results: 100% reduction in OCS dose

MAIC comparison	Comparator trial	Dupilumab vs comparator MAIC odds ratio (95%CI)
Dupilumab vs mepolizumab	SIRIUS ITT	1.36 (95% CI 0.3, 6.21)

Dupilumab vs mepolizumab subgroup	SIRIUS subgroup EOS ≥300 in past year and ≥4 exacerbations or mOCS	0.51 (95% CI 0.08, 3.34)
Dupilumab vs benralizumab	ZONDA ITT	0.93 (0.22, 4.02)

Source: CS Appendix O Figures 51, 54, 58

3.3.12 Summary of adverse events

Information on adverse events presented in the CS comes from the three included RCTs DRI12544, QUEST and VENTURE, including data from study arms that were not relevant to the current STA. The company do not indicate what the overall exposure to dupilumab was in the trials.

Treatment-emergent adverse events (TEAEs)

The proportion of participants with TEAEs was similar within each trial between participants receiving dupilumab (at any of the four doses used) and placebo (Table 65). In the DRI12544 and QUEST trials the proportion of participants with any TEAE ranged from 74.7% to 84.1% whereas in the VENTURE trial a smaller proportion experienced any TEAE (64.5% and 62.1% in the placebo and dupilumab arms respectively). The proportion of treatment-emergent serious adverse events ranged from 4.0% to 10.2% and overall, across all the study arms of the three RCTs the ERG estimates that 68/899 (7.56%) of placebo participants and 158/1977 (7.99%) of dupilumab participants experienced a treatment-emergent SAE. There were 10 deaths as a result of a TEAE, seven among dupilumab treated participants and three among placebo treated participants. None of the deaths were attributed to the investigational medicinal product. The proportion of participants who had to permanently discontinue treatment due to a TEAE ranged between 1% and 7% (the ERG calculates 4.23% across all the placebo treated participants and 4.60% across all the dupilumab treated participants).

Table 65 Summary of TEAEs in the DRI12544, QUEST and VENTURE RCTs

Trial	Trial arms	n (%)			
		Patients with any TEAE	Patients with any treatment-emergent SAE	Patients with any TEAE leading to death	Patients with any TEAE leading to permanent treatment discontinuation
DRI12544	Placebo (N=158)	118 (74.7)	9 (5.7)	0	5 (3.2)

	Dupilumab	200 mg Q4W (N=150)	113 (75.3)	6 (4.0)	0	7 (4.7)
		300 mg Q4W (N=157)	130 (82.8)	16 (10.2)	2 (1.3)	10 (6.4)
		200 mg Q2W (N=148)	119 (80.4)	10 (6.8)	0	6 (4.1)
		300 mg Q2W (N=156)	121 (77.6)	13 (8.3)	0	4 (2.6)
QUEST	1.14mL/200 mg Q2W	Placebo (N=313)	257 (82.1)	26 (8.3)	3 (1.0)	19 (6.1)
		Dupilumab (N=631)	508 (80.5)	49 (7.8)	1 (0.2)	19 (3.0)
	2 mL/300 mg Q2W	Placebo (N=321)	270 (84.1)	27 (8.4)	0	10 (3.1)
		Dupilumab (N=632)	515 (81.5)	55 (8.7)	4 (0.6)	44 (7.0)
VENTURE	Placebo (N=107)		69 (64.5)	6 (5.6)	0	4 (3.7)
	Dupilumab 300 mg Q2W (N=103)		64 (62.1)	9 (8.7)	0	1 (1.0)

Source: CS Table 37, Table 40 and Table 43
AE, adverse event; Q2W, every 2 weeks; Q4W, every 4 weeks; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

The TEAEs that occurred with a frequency of 5% of more in the DRI12544 and QUEST trials and a frequency of 2% or more in the VENTURE trial were reported. An overview of these events is reported in Table 66, with detail on the number of events and the types of event contributing to each class of event reported in the CS. Across all three trials the most common types of events were infections (42.1% to 67.6% across the four placebo arms, 40.8% to 59.7% across the seven dupilumab arms). Injection site reactions were another event that occurred in all trials. The CS highlights that in the DRI12544 trial, the two lower dupilumab dose groups (200mg and 300mg Q4weeks) had a similar frequency of injection site reactions to the placebo group, whereas the higher dose groups (200mg and 300mg Q2W, which are the doses relevant to this STA) had higher frequencies of injection site reactions than the placebo group.

Table 66 Number (%) of patients with TEAE(s) that occurred with a frequency ≥5% (DRI12544 and QUEST) or ≥2% (VENTURE) in any treatment arm by System Organ Class grouping (Safety Population)

	DRI12544					QUEST				VENTURE	
		Dupilumab				1.14mL/200 mg Q2W		2 mL/300 mg Q2W			
Primary System Organ Class Grouping, %	Placebo (N=158)	200 mg Q4W (N=150)	300 mg Q4W (N=157)	200 mg Q2W (N=148)	300 mg Q2W (N=156)	Placebo (N=313)	Dupilumab (N=631)	Placebo (N=321)	Dupilumab (N=632)	Placebo (N=107)	Dupilumab 300 mg Q2W (N=103)
Any class	74.7	75.3	82.8	80.4	77.6	82.1	80.5	84.1	81.5	64.5	62.1
Infections & infestations	53.2	56.0	59.2	52.0	54.5	63.9	57.7	67.6	59.7	42.1	40.8
Nervous system disorders	17.1	10.7	17.8	17.6	17.3	14.4	11.4	14.3	11.1	NR	NR
Blood & lymphatic system disorders	NR	NR	NR	NR	NR	NR	NR	NR	NR	0.9	9.7
Vascular disorders	NR	NR	NR	NR	NR	NR	NR	NR	NR	4.7	2.9
Respiratory, thoracic & mediastinal disorders	15.2	15.3	26.8	16.9	19.2	16.6	15.8	16.5	14.7	13.1	12.6
Gastrointestinal disorders	NR	NR	NR	NR	NR	NR	NR	NR	NR	8.4	8.7
Skin & subcutaneous tissue disorders	NR	NR	NR	NR	NR	NR	NR	NR	NR	3.7	9.7
Musculoskeletal & connective tissue disorders	13.9	15.3	14.6	14.2	20.5	16.3	14.7	15.9	15.7	12.1	13.6

	DRI12544					QUEST				VENTURE	
		Dupilumab				1.14mL/200 mg Q2W		2 mL/300 mg Q2W			
Primary System Organ Class Grouping, %	**Placebo (N=158)**	**200 mg Q4W (N=150)**	**300 mg Q4W (N=157)**	**200 mg Q2W (N=148)**	**300 mg Q2W (N=156)**	**Placebo (N=313)**	**Dupilumab (N=631)**	**Placebo (N=321)**	**Dupilumab (N=632)**	**Placebo (N=107)**	**Dupilumab 300 mg Q2W (N=103)**
General disorders & administration site conditions	19.0	16.7	16.6	22.3	30.1	11.2	19.3	15.3	23.9	10.3	10.7
Investigations	NR	NR	NR	NR	NR	NR	NR	NR	NR	3.7	10.7
Injury, poisoning & procedural complications	NR	NR	NR	NR	NR	14.7	13.9	13.1	17.1	13.1	9.7

Source: CS Table 38, Table 41, Table 44

Treatment-emergent serious adverse event (SAEs)

The company also report on treatment-emergent serious adverse event (SAEs) that occurred in the three included RCTs. A summary of the numbers and proportions of patients with treatment-emergent SAEs by System Organ Class groupings is presented below for DRI12544 and QUEST (data were not presented in this way for VENTURE) Table 67. Preferred Term information is reported in the CS.

The proportion of participants experiencing a treatment-emergent SAE was balanced between those receiving dupilumab and those receiving placebo (the ERG calculates 7.99% in dupilumab groups combined versus 7.56% in placebo groups combined). In all three trials the most frequent treatment-emergent SAE was asthma. In all cases the event was a severe asthma exacerbation that required hospitalisation (DRI12544: 1.6% in dupilumab groups vs 2.5% in the placebo group; QUEST: 1.7% in dupilumab 200 mg group and 0.9% in the dupilumab 300 mg group versus 3.2% and 1.2% in the corresponding placebo groups; VENTURE: 2.9% in the dupilumab group versus 2.8% in the placebo group).

In the QUEST RCT it was observed that there was an imbalance in the Cardiac Disorders System Organ Class group (dupilumab 200mg Q2W n=4, 300 mg Q2W n=10 versus zero in both the matching placebo groups). The CS notes that no imbalance in cardiac SAEs has been observed in any other dupilumab studies in either the asthma programme or the atopic dermatitis programmes. After a broad database search for cardiovascular events and a blinded adjudication analysis of potential cardiovascular events by three independent cardiologists it was concluded that the higher incidence rates in the 300mg Q2W group compared with the 200mg Q2W group were likely to be by chance. No cardiovascular SAEs were reported in the VENTURE RCT.

Table 67 Number (%) of patients with treatment-emergent SAEs by primary System Organ Class grouping in the DRI12544 and QUEST RCTs (Safety Population)

	DRI12544					QUEST			
		Dupilumab				1.14mL/200 mg Q2W		2 mL/300 mg Q2W	
Primary System Organ Class group, n (%)	Placebo (N=158)	200 mg Q4W (N=150)	300 mg Q4W (N=157)	200 mg Q2W (N=148)	300 mg Q2W (N=156)	Placebo (N=313)	Dupilumab (N=631)	Placebo (N=321)	Dupilumab (N=632)
Any class	9 (5.7)	6 (4.0)	16 (10.2)	10 (6.8)	13 (8.3)	26 (8.3)	49 (7.8)	27 (8.4)	55 (8.7)
Infections and infestations	2 (1.3)	0	3 (1.9)	2 (1.4)	5 (3.2)	4 (1.3)	4 (0.6)	5 (1.6)	13 (2.1)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	1 (0.6)	1 (0.7)	4 (2.5)	0	0	4 (1.3)	7 (1.1)	2 (0.6)	5 (0.8)
Blood and lymphatic system disorders	0	0	0	0	1 (0.6)	0	0	1 (0.3)	1 (0.2)
Immune system disorders	0	0	1 (0.6)	0	1 (0.6)	0	2 (0.3)	0	1 (0.2)
Endocrine disorders	NR	NR	NR	NR	NR	1 (0.3)	0	0	0
Psychiatric disorders	0	0	1 (0.6)	0	0	1 (0.3)	2 (0.3)	1 (0.3)	2 (0.3)
Nervous system disorders	0	0	1 (0.6)	0	0	2 (0.6)	3 (0.5)	2 (0.6)	2 (0.3)
Eye disorders	NR	NR	NR	NR	NR	0	0	0	1 (0.2)
Cardiac disorders	0	1 (0.7)	2 (1.3)	0	0	0	4 (0.6)	0	10 (1.6)
Vascular disorders	0	0	0	1 (0.7)	0	1 (0.3)	1 (0.2)	1 (0.3)	1 (0.2)

	DRI12544					QUEST			
		Dupilumab				1.14mL/200 mg Q2W		2 mL/300 mg Q2W	
Primary System Organ Class group, n (%)	Placebo (N=158)	200 mg Q4W (N=150)	300 mg Q4W (N=157)	200 mg Q2W (N=148)	300 mg Q2W (N=156)	Placebo (N=313)	Dupilumab (N=631)	Placebo (N=321)	Dupilumab (N=632)
Respiratory, thoracic and mediastinal disorders	4 (2.5)	2 (1.3)	4 (2.5)	5 (3.4)	1 (0.6)	11 (3.5)	16 (2.5)	5 (1.6)	12 (1.9)
Gastrointestinal disorders	1 (0.6)	0	0	1 (0.7)	1 (0.6)	0	3 (0.5)	2 (0.6)	6 (0.9)
Hepatobiliary disorders	0	0	1 (0.6)	0	1 (0.6)	1 (0.3)	2 (0.3)	0	4 (0.6)
Skin and subcutaneous tissue disorders	0	1 (0.7)	0	0	1 (0.6)	NR	NR	NR	NR
Musculoskeletal and connective tissue disorders	NR	NR	NR	NR	NR	2 (0.6)	3 (0.5)	3 (0.9)	3 (0.5)
Renal and urinary disorders	NR	NR	NR	NR	NR	0	1 (0.2)	0	0
Pregnancy, puerperium and perinatal conditions	0	0	1 (0.6)	2 (1.4)	1 (0.6)	0	0	2 (0.6)	2 (0.3)
Reproductive system and breast disorders	0	0	0	0	1 (0.6)	0	1 (0.2)	0	1 (0.2)
Congenital, familial and genetic disorders	NR	NR	NR	NR	NR	0	1 (0.2)	0	0
General disorders and administration site conditions	NR	NR	NR	NR	NR	0	1 (0.2)	1 (0.3)	3 (0.5)

	DRI12544					QUEST			
		Dupilumab				1.14mL/200 mg Q2W		2 mL/300 mg Q2W	
Primary System Organ Class group, n (%)	**Placebo (N=158)**	**200 mg Q4W (N=150)**	**300 mg Q4W (N=157)**	**200 mg Q2W (N=148)**	**300 mg Q2W (N=156)**	**Placebo (N=313)**	**Dupilumab (N=631)**	**Placebo (N=321)**	**Dupilumab (N=632)**
Investigations	0	0	0	0	1 (0.6)	0	1 (0.2)	0	0
Injury, poisoning and procedural complications	1 (0.6)	1 (0.7)	2 (1.3)	1 (0.7)	1 (0.6)	4 (1.3)	3 (0.5)	4 (1.2)	5 (0.8)
Soft tissue injury	0	0	1 (0.6)	0	0	NR	NR	NR	NR
Social circumstances	NR	NR	NR	NR	NR	0	2 (0.3)	0	0
Product issues	NR	NR	NR	NR	NR	0	1 (0.2)	0	0

Source: CS Table 39 and Table 42
NR – event of this class not reported for this trial; PT, preferred term; Q2W, every 2 weeks; Q4W, every 4 weeks; SAE, serious adverse event.

Treatment-emergent SAEs that were considered to be related to the investigational medical product occurred in three patients (all receiving dupilumab) in the DRI12544 trial, five in QUEST (four receiving dupilumab 300mg and one receiving placebo) and four in VENTURE (three in the dupilumab group and one in the placebo group).

Table 68 Treatment emergent SAEs considered to be related to the investigational medical product in the DRI12544, QUEST and VENTURE RCTs

Trial arm	RCT		
	DRI12544	**QUEST**	**VENTURE**
Dupilumab	Severe colitis (one case, dupilumab dose not stated)	Eosinophilia (one case, dupilumab dose not stated)	Eosinophilia (two cases)
	Steroid-dependent hypereosinophilia (one case in dupilumab 300 mg Q2W arm)	Eosinophilic pneumonia chronic (one case, dupilumab dose not stated)	Pulmonary mass (one case)
	Unspecified eczema on scalp and feet of moderate intensity (one case in the dupilumab 300 mg Q2W arm)	Anaphylactic reaction (one case, dupilumab dose not stated)	
		Injection site erythema, injection site inflammation and injection site oedema (one case in the dupilumab 300 mg arm)	
Placebo		Neutropenia (one case)	Gastrointestinal stromal tumour (one case)

The proportion of TEAEs which led to treatment discontinuation ranged from 1-7% in the dupilumab arms of the three included RCTs and from 3.1% to 6.1% in the placebo arms. Injection site reactions (DRI12544) or injection site erythema (QUEST) were the most frequently reported TEAEs leading to permanent treatment discontinuation in these two trials (but this was not a reason for treatment discontinuation in the VENTURE RCT). Other events highlighted in the CS were that four patients (three in the dupilumab groups and one in the placebo group) had increased alanine aminotransferase that led to permanent treatment discontinuation in the DRI12544 RCT and one patient experienced each of the following in the VENTURE RCT: arthralgia (dupilumab group), gastrointestinal stromal tumour, eosinophilia, adrenal insufficiency, and asthmatic crisis (all in the placebo group).

Finally, the QUEST and VENTURE studies report on adverse events of special interest (AESIs). The CS states that these events were pre-defined in the study protocol but it does not list what types of events were treated as AESIs. The protocols that are available as supplementary material to the published papers for QUEST and VENTURE do provide this information. In brief, AESIs appear to have included (but not limited to) anaphylactic reactions, severe injection site reactions lasting longer than 24 hours, severe and serious infections (bacterial or viral), significant ALT elevation, pregnancy and symptomatic overdose with either dupilumab or placebo. Only severe injection site reactions are reported as AESIs for QUEST, it is not clear if this is because these were the only AESIs experienced or if they were the most common. Ten patients in QUEST dupilumab groups reported AESI injection site reactions but none were reported in the VENTURE RCT. In the VENTURE trial three patients had hypersensitivity (rash) two in the dupilumab group and one in the placebo group, none of these events were SAEs. No other AESI are reported in the CS for the VENTURE RCT.

3.4 Summary of the clinical effectiveness evidence

The dupilumab trials DRI12544, QUEST and VENTURE

The three included dupilumab RCTs provide evidence for a population of people with:
i) moderate-to-severe asthma who are not receiving treatment with oral corticosteroids (DRI12544 and QUEST)
ii) severe asthma who are receiving treatment with oral corticosteroids (VENTURE).

All three trials enrolled a wider population group than that specified by the NICE scope and the company's decision problem. In the DRI12544 and QUEST trials a minority of the ITT population match the decision problem population (14.9% and 10.7% respectively); in VENTURE more than two thirds (72%) of the ITT population match the decision problem population.

Results from the dupilumab trials

In the post-hoc subgroups of QUEST and VENTURE that reflected the decision problem population, dupilumab reduced rates of severe exacerbations. In dupilumab responder analyses in these post-hoc subgroups, the adjusted annualised rate of severe exacerbation events was lowered further in comparison to all placebo patients. No analysis for the decision problem population was presented for the DRI12544 RCT.

The ITT analyses of the three RCTs demonstrated that, for patients not receiving OCS (DRI12544 and QUEST) and for patients receiving OCS (VENTURE) dupilumab treatment:

- reduced the adjusted rate of severe asthma exacerbations in comparison to placebo,
- Delayed the time of the first severe exacerbation event
- Increased FEV1 at 12 weeks (DRI12544 and QUEST) and at 24 weeks (VENTURE).
- Improved asthma control as measured by the ACQ-5 (DRI12544) or ACQ-7 (QUEST)
- Reduced FeNO levels
- Did not lead to any significant differences in the change from baseline EQ-5D scores.

ITT analyses for patients not receiving OCS (DRI12544 and QUEST) also showed that dupilumab:

- Reduced the annualised risk of loss of asthma control in comparison to the placebo group.
- Improved both morning and evening PEF in the QUEST trial (outcome not reported for DRI12544).

ITT analysis for patients receiving OCS (VENTURE also showed that dupilumab:

- Led to a greater reduction in OCS dose at week 24 compared to the placebo group.
- Led to a higher probability at week 24 of patients achieving a ≥50% reduction in OCS dose, a reduction in OCS dose to <5mg/day or a 100% reduction in OCS dose in comparison to the placebo group.

Subgroup analyses of the primary outcomes for QUEST based on baseline EOS, baseline FeNO and baseline ICS provided some evidence that people with lower baseline blood eosinophil levels, and lower baseline FeNO levels obtained less benefit from dupilumab than people with higher levels of EOS and FeNO. Subgroup results for people receiving high dose ICS at baseline were consistent with those of the ITT population.

Subgroup analyses of the primary outcome for VENTURE based on baseline EOS and baseline FeNO provided some evidence that a reduction in OCS dose at week 24 (whilst maintaining asthma control) was achieved by all participants.

Participants in the dupilumab and placebo arms of each of the three trials experienced TEAEs and the ERG calculated that the proportions of participants experiencing serious events was similar in dupilumab and placebo treated patients (less than 8%). No deaths were attributed to dupilumab.

Bucher ITC results

Although the outcomes were numerically consistently in favour of dupilumab, the confidence intervals frequently crossed or reached the line of no effect. Therefore the majority of results would not be considered statistically significantly in favour of dupilumab. The exceptions were that in dupilumab subgroups matched to the comparator labels, dupilumab led to fewer severe exacerbations in the uncontrolled persistent asthma population than mepolizumab (rate ratio [redacted]) benralizumab (rate ratio [redacted]) or reslizumab (rate ratio [redacted]).

MAIC results

MAIC results were similar to the Bucher ITC results although for some comparisons and outcomes the numerical result was not in favour of dupilumab (and was not statistically significant).

There are limitations to both the Bucher ITC and MAIC methods (Section 3.1.7.5) and therefore caution is required in interpreting these results and the outcomes from the

exploratory cost-effectiveness analysis for dupilumab compared to the IL-5 biologics. However these ITC approaches, even though limited by the available data, are likely to be the best currently available option to enable comparisons between dupilumab and other IL-5 biologics in the NICE scope.

4 COST EFFECTIVENESS

4.1 Overview

The company submission includes:

- A systematic review of published economic evaluations of treatments for moderate-to-severe asthma (CS B.3.1.1)
- A description of the company's *de novo* model developed to assess the cost-effectiveness of dupilumab in its licensed indication as add-on therapy for adults and adolescents with severe asthma.
    - CS sections B.3.2 to B.3.11 and Appendix M describe the company's base case comparison with standard care alone for people with EOS≥150 or FeNO≥25 and at least 3 exacerbations in the previous 12 months; and a scenario for a mixed population also including people with EOS≥150 or FeNO≥25 on maintenance oral corticosteroids (mOCS).
    - Appendices P and Q present additional 'exploratory' analyses based on the Bucher indirect comparisons with other add-on biologic therapies: mepolizumab and benralizumab for people with EOS≥300 and at least 4 exacerbations in the previous 12 months or mOCS; and reslizumab and benralizumab for people with EOS≥400 and at least 3 exacerbations in the previous 12 months.

We summarise and critique these elements of the CS in sections 4.2 and 4.3 below. Additional ERG work, including model validation and alternative scenarios are presented in section 4.4.

All cost-effectiveness results presented in the CS and in this ERG report assume an NHS price discount for dupilumab (both 200 mg and 300 mg doses): the same as agreed in the existing Patient Access Scheme (PAS) arrangement for dupilumab in atopic dermatitis. For the comparisons with other biologics in CS Appendix Q, the company assumed a [redacted] discount on list prices for mepolizumab, reslizumab and benralizumab. Results including the actual agreed PAS discounts for comparators as well as the company's proposed PAS discount for dupilumab are presented in a confidential addendum to the ERG report.

4.2 Company's review of published economic evaluations

The company conducted a search to identify studies assessing the cost, healthcare use and cost-effectiveness of interventions for the treatment of moderate-to-severe asthma. The methods and results of the review of cost-effectiveness studies are described in CS section B.3.1 and Appendix G. The review of cost and healthcare use is described in section B.3.5 and Appendix I of the CS. As the searches were conducted in March 2019, we conducted a

focused literature search to identify any more recent relevant publications but did not identify any that were not previously identified by the company.

The company identified 29 economic evaluations of treatments for severe uncontrolled asthma. Of these, 15 studies included treatments identified in the NICE decision problem (described in CS Table 48). Five of these studies were UK based, of which three informed previous NICE TAs (TA479, TA431, and TA565). One of the included studies assessed the cost-effectiveness of dupilumab as an add-on therapy in adults and children aged ≥ 6 years with moderate-to-severe uncontrolled asthma with evidence of Type 2 inflammation. This US based study conducted for the Institute for Clinical and Economic Review (Tice et al.)[4] developed a Markov model for a lifetime horizon from the perspective of healthcare sector and reported the following ICERs:

- Dupilumab + standard care versus standard care: $351,000;
- Omalizumab + standard care versus standard care: $325,000;
- Mepolizumab + standard care versus standard care: $344,000;
- Reslizumab + standard care versus standard care: $391,000;
- Benralizumab + standard care versus standard care: $371,000;

ERG conclusion: The company's search strategy and eligibility criteria for their review of cost-effectiveness studies are appropriate. We view that the US based study by Tice et al. provides a relevant reference for comparison of the model outcomes of the current appraisal.

4.3 Critical appraisal of the company's submitted economic evaluation

4.3.1 NICE reference case

Table 69 NICE reference case

Criterion	Included?	Comment
Decision problem as in scope	Y	The modelled population is a restricted subgroup of the NICE decision problem and marketing authorisation
Comparators as listed in scope	N	Only standard care in base case (CS B.3). Indirect comparisons with add-on mepolizumab, reslizumab and benralizumab in CS Appendix Q. Omalizumab not included

Perspective on costs: NHS and PSS	Y	
Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Y	
Perspective on outcomes: All direct health effects, whether for patients or, when relevant, carers	Y	
Cost utility analysis with fully incremental analysis	Y	Incremental analysis for mepolizumab and reslizumab populations (CS Appendix Q)
Synthesis of evidence on outcomes based on a systematic review	Y	Results for Bucher pairwise ITC in CS Appendix Q (MAIC available in model)
Time horizon: Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Y	Effectively lifetime (to 100 years of age)
Health effect expressed in QALYs. EQ-5D is preferred measure of health-related quality of life	Y	
Health related quality of life reported directly by patients and/or carers.	Y	Base case uses EQ-5D-5L data from QUEST and VENTURE trials (B.3.4.2)
Preference data from representative sample the UK population	Y	Utilities mapped from EQ-5D-5L with van Hout cross walk algorithm (CS B.3.4.5)
An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	Y	
Discount rate: 3.5% pa for costs & health effects	Y	

4.3.2 Modelled decision problem

4.3.2.1 Population and subgroups

The economic model has in-built flexibility to include patients treated with or without mOCS (based on data from the VENTURE and QUEST clinical trials respectively), as well as a weighted combination of both groups. The model also allows selection of a range of subgroups defined by a combination of: EOS levels (≥150, ≥300 or ≥400); raised FeNo (≥25); and numbers of exacerbations in the previous 12 months (≥1, ≥2, ≥3 or ≥4). Small subgroups are implemented by adjustment of outcomes for a reference population using multipliers derived from a negative binomial regression model (see CS Appendix section P.1.1 and Clarification Response B5).

The CS reports cost-effectiveness results for four subgroups in total. These all fall within the NICE decision problem and the licensed indication (see 2.3 above), but with different definitions of severe asthma with type 2 inflammation and inadequate control under optimised standard therapy. In the main report, the company presents results for a base case population and a mixed mOCS/ non mOCS/ population scenario (CS B.3.2.1):

A. **Base case population**: EOS≥150 or FeNO≥25 and at least 3 exacerbations in the previous 12 months. This analysis is based on a subgroup from the QUEST trial, and hence excludes people on maintenance oral corticosteroids (non mOCS).

B. **Mixed mOCS/ non mOCS scenario**: EOS≥150 or FeNO≥25 and at least 3 exacerbations in the previous 12 month or on mOCS. This uses a combination of subgroup data from VENTURE for people on mOCS as well as subgroup data from QUEST for people not on mOCS. Overall results are calculated assuming that 41.7% of the relevant population are on mOCS, based on a UK registry of severe asthma (Heaney 2010).[22]

The CS presents standard care as the only comparator for the above populations, because NICE recommendations for other comparators are narrower (see Table 70 below). However, the company also presents 'exploratory' analyses with indirect comparisons for mepolizumab, reslizumab and benralizumab (CS Appendices P and Q). This requires two subgroups (CS Appendix P.1.2):

C. **Mepolizumab eligible subgroup**: EOS≥300 and at least 4 exacerbations in the previous 12 months or mOCS (TA431).

D. **Reslizumab eligible subgroup**: EOS≥400 and at least 3 exacerbations in the previous 12 months (TA479).

Benralizumab is recommended for both of the above populations in TA565.
The company does not model an omalizumab eligible population, because they consider omalizumab to be out of scope "*as allergic asthma, defined by IgE, is not considered to be part of the EMA licence for dupilumab*" (CS Appendix P introduction).

Table 70 NICE TA recommendations for comparators in the scope

NICE TA	Patient characteristics (approved by NICE)
TA278 (omalizumab)	People aged 6 and older with severe persistent confirmed allergic IgE-mediated asthma: • Who need continuous or frequent treatment with oral corticosteroids (defined as 4 or more courses in the previous year)
TA431 (mepolizumab)	Adult patients with: • blood eosinophil count of ≥300 cells/microliter or more in the previous 12 months; and • have had 4 or more asthma exacerbations needing systemic corticosteroids in the previous 12 months; or • have had continuous oral corticosteroids of at least the equivalent of prednisolone 5 mg per day over the previous 6 months
TA479 (reslizumab)	Adult patients with inadequately controlled severe eosinophilic asthma with: • blood eosinophil count of 400 cells/microliter or more; and • have had 3 or more severe asthma exacerbations needing systemic corticosteroids in the past 12 months
TA565 (benralizumab)	Adult patients with inadequately controlled severe eosinophilic asthma with: • blood eosinophil count of ≥300 cells/microliter • have had 4 or more exacerbations needing systemic corticosteroids in the previous 12 months, or has had continuous oral corticosteroids of at least the equivalent of prednisolone 5 mg per day over the previous 6 months (that is, the person is eligible for mepolizumab) • blood eosinophil count of ≥400 cells per microlitre with 3 or more exacerbations needing systemic corticosteroids in the past 12 months (that is, the person is eligible for reslizumab).

Table 71 below summarises baseline characteristics for patient subgroups that the company use in their cost-effectiveness analyses. These subgroups are described by the indicators of type 2 inflammation (i.e. blood eosinophil level or FeNO), the number of asthma exacerbations in the previous 12 months and use of mOCS.

Table 71 Patient characteristics for modelled subgroups

Subgroup	A. Base case & B. Mixed scenario		C. Mepolizumab eligible		D. Reslizumab eligible
Indicators of type 2 inflammation	EOS ≥150 or FeNO ≥25		EOS ≥300		EOS ≥400
Number of exacerbations in previous 12 months	≥3	Any	≥4	Any	≥3
Maintenance oral corticosteroids	No	mOCS	No	mOCS	No
NICE recommended add-on biologic therapy	None (standard care only)		Mepolizumab Benralizumab		Reslizumab Benralizumab
Baseline patient characteristics					
% female	59.4	61.2	62.1	68.4	59.3
Age, mean years	47.4	51.2	49.7	51.4	49.3
Weight, mean kg	79.0	79.0	79.0	79.0	79.2
Background therapy					
% on high-dose ICS/LABA	100.0	100.0	100.0	100.0	100.0
% on LTRA	40.6	26.5	37.9	27.6	34.7
% on LAMA	21.8	18.5	16.9	21.1	12.7
% on theophylline	5.9	9.9	4.0	9.2	4.7

ICS, inhaled corticosteroids; LABA, long-acting beta-agonists; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonists.
Source: QUEST data for non-mOCS subgroups, VENTURE for mOCS subgroups. Extracted from company model by ERG.

ERG conclusions: The four modelled populations in the CS are within the defined in the NICE scope and the marketing authorisation. The two subgroups used for the company's exploratory indirect comparisons with mepolizumab, reslizumab and benralizumab appropriately reflect NICE guidance.

The company base case restricts the population to people with at least 3 exacerbations in addition to indicators of type 2 inflammation (EOS ≥150 or FeNo ≥ 25). The company states that this is to align with UK clinical practice and the GINA guidelines. It also has the effect of improving the cost-effectiveness of dupilumab. However, the base case population still includes two groups for whom biologic treatments have not previously been recommended by NICE:

- people with EOS below 300 or FeNO ≥ 25; and

- those with EOS between 300 and 399 with 3 exacerbations in the previous year and not on mOCS.

It is uncertain whether dupilumab is cost-effective for these subgroups because the CS only presents ICERs for a pooled population including people with more severe disease who are currently eligible for benralizumab, mepolizumab and/or reslizumab add-on therapy.

In particular, we highlight that the committee in TA565 concluded that cost effectiveness evidence for this type of mixed population was not suitable for decision making because the range of asthma severity is not necessarily generalisable to the clinical practice population. We conduct ERG exploratory analysis to estimate the cost-effectiveness of excluding people with EOS≥300 from the company's base case population (see section 4.4.5.1 below).

A similar argument applies to the company's mixed population scenario which includes people treated with and without mOCS at baseline, as the cost-effectiveness may well differ between these groups. We also note that the TA565 committee expressed uncertainty over the proportion of patients on mOCS. Although the TA565 ERG used the same value of 41.7% (Heaney 2010) for the standard care comparison as in the current submission, the TA565 ERG used 60% for the mepolizumab comparison, and clinical experts advised the committee that in clinical practice between 66% and 80% of patients starting mepolizumab are on mOCS. We conduct additional scenario analysis around this parameter in section 4.4.5.2 below.

4.3.2.2 Intervention and comparators

The company outlines the modelled intervention and comparators in CS sections B.3.2.3 to B.3.2.5. As per the NICE scope, the economic model includes dupilumab as an add-on to standard therapy as the intervention. For their base case, the company compares the intervention with standard care alone. They argue that standard care is the relevant comparator for this appraisal as dupilumab is the only treatment indicated for severe asthma driven by Type 2 inflammation defined by raised EOS and/or raised FeNO.

The company notes that NICE has recommended three other biologics (mepolizumab, reslizumab and benralizumab) for patients with severe eosinophilic asthma and that although these treatments are not licensed for Type 2 inflammation, as defined in the company base

case, comparison of dupilumab against these treatments would be appreciated to support NICE decision making. They therefore conducted two sets of pairwise and incremental economic analyses, described in Appendix P:

- Dupilumab compared with mepolizumab, benralizumab and standard care alone for people with severe eosinophilic asthma defined as EOS ≥ 300 and either ≥ 4 exacerbations in the previous 12 months or mOCS (results in CS Q.1); and
- Dupilumab compared with reslizumab, benralizumab and standard care alone for people with severe eosinophilic asthma defined as EOS ≥ 400 and either ≥ 3 exacerbations in the previous 12 months (results in CS Q.2)

These analyses are described as exploratory and 'for information purposes only' due to limitations of the indirect comparisons: the Bucher pairwise approach (CS Appendix N) used for the results presented the CS; and the MAICs (CS Appendix O) also available in the model. See 3.1.7 above for discussion of the indirect comparison methods and 4.3.4.5 for the values used in the economic model.

Omalizumab, the fourth biologic named as a comparator in the NICE scope, is not included in the economic model. The company state that they do not consider omalizumab to be a relevant comparator for dupilumab for three reasons. First, because the licence indications differ: Type 2 inflammation for dupilumab and allergic IgE-mediated asthma for omalizumab. Second, the patient populations in the pivotal trials are not directly comparable because the dupilumab trials did not measure allergy with a skin-prick test. And thirdly, because dupilumab is 'significantly effective' irrespective of baseline serum IgE, so this would not be a relevant biomarker for dupilumab.

> ***ERG conclusions***: We agree that there are significant uncertainties over the indirect comparisons (Bucher and MAIC) because of differences in the trial populations and methodological and reporting limitations. Nevertheless, we understand that there are people who would be suitable for other biologics specified in the NICE scope as well as dupilumab. It is therefore important to consider the cost-effectiveness of dupilumab relative to these other comparators in the overlap populations as well as cost-effectiveness relative to standard practice for people for whom this is the only option. We therefore discuss the company's exploratory analyses alongside their base case analysis within this chapter.

4.3.3 Model structure

The company describes the structure and key features of their model in CS Section B.3.2.2. They summarise assumptions in CS Table 87 and the parameters in CS sections B.3.3 to 3.6.1. A Markov model is developed in Microsoft Excel® (see Figure 4) with a cycle length of 4 weeks and a half-cycle correction. The model uses a lifetime horizon (up to a maximum age of 100 years). Costs and QALYs are discounted at an annual rate of 3.5%.

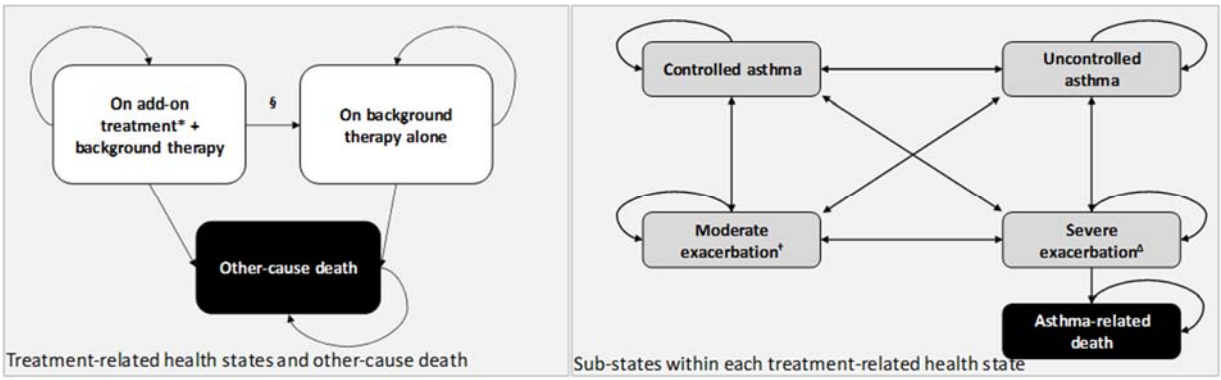


Figure 4 Markov model structure (Source: CS Figure 36)

The model estimates costs and health outcomes associated with a cohort of patients with severe asthma (driven by Type 2 inflammation) starting dupilumab or other add-on therapy (mepolizumab, reslizumab or benralizumab) compared with background therapy (standard care) alone. The model includes the flexibility to define the starting cohort according to the proportion of patients on mOCS and minimum levels of EOS, FeNo and number of exacerbations in the previous 12 months.

The model consists of four *live* health states: uncontrolled asthma; controlled asthma; moderate exacerbation; and severe exacerbation. In addition, the model includes states for asthma-related deaths and death from other causes. We present a summary of the health state definitions in Table 72. The cohort enters the model in the uncontrolled asthma health state. At each four-week cycle, people in the live health states may remain in the same health state, transition to one of the other three live health states or die from asthma-related or other causes. Rates of movement between the live states are determined by a transition probability matrix and mortality rates are applied for asthma and other deaths.

For patients who enter the model on mOCS, the proportion of patients taking a reduced dose (< 5mg per day) or withdrawing from OCS is estimated at each model cycle.

Table 72 Summary of the model health states

	Health states	Description
Live states	Uncontrolled asthma	Patients enter the model in this health state, defined by an ACQ score ≥1.5 and no exacerbation (consistent with inclusion criteria for the clinical trials).
	Controlled asthma	Patients in this health state have an ACQ score < 1.5 and no exacerbation.
	Moderate exacerbation	Defined by one or more of the following criteria: • ≥6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol in a 24-hour period on two consecutive days; • ≥20% decrease in pre-bronchodilator forced expiratory volume in 1 second (FEV1) compared with baseline; • Increase in inhaled corticosteroid (ICS) dose ≥4 times than the dose at Visit 2; • A decrease in AM or PM peak flow of 30% or more on 2 consecutive days of treatment, based on the defined stability limit. The treatment period stability limit is defined as the respective mean AM or PM peak expiratory flow (PEF) obtained over the last 7 days prior to randomisation (Day 1)
	Severe exacerbation	Patients experienced severe exacerbation if they met one of the following criteria: • Use of systemic corticosteroids for ≥3 days; or • Hospitalisation or A&E visit because of asthma, requiring systemic corticosteroids
Death	Asthma related mortality	Absorbing states; the model accounts for: • Death from asthma, which only occurs from severe exacerbation • Death from other causes (background mortality net of asthma mortality) occurs from all the health states
	Death from other causes	

Source: CS section B.3.2.2

For the add-on treatments, the model includes a response assessment at 52 weeks, at which time non-responders stop the add-on and continue on standard care alone. Responders may subsequently stop treatment as a constant long-term risk of discontinuation is applied after 52 weeks to reflect 'natural attrition'. No residual effect of treatment is assumed after discontinuation.

The model accumulates costs associated with drug acquisition, administration and monitoring as well, routine care and management by health state and treatment for OCS-related adverse events. QALYs are estimated by applying utilities to time spent in the

controlled and uncontrolled asthma health states and disutilities for moderate and severe exacerbations and OCS-related adverse events.
The model does not include any cost or disutility for adverse events associated with the biologic or other medications. The company notes that the most frequent adverse event in the dupilumab trials was injection site reactions (15.2% with dupilumab vs. 5.4% with placebo) but the number of serious site reactions that lasted longer than 24 hours were similar and very low (0.3% vs. 0%) (B.3.3.12). We discuss the overall safety evidence in section 3.3.12 above.

The model uses three sets of input parameters, which we describe and critique in the following sections:

- Clinical inputs to estimate transition probabilities, dose-reduction and withdrawal rates for mOCS, one-year response and subsequent discontinuation rates and rates of mortality from asthma-related and other causes (CS B.3.3 and Appendices M and P);
- Utilities for control health states and disutilities for exacerbations and mOCS-related adverse events (CS B.3.4); and
- Resource use and costs for drug acquisition and administration; monitoring, routine care and disease management costs; and exacerbation costs (CS B.3.5).

ERG conclusion: The overall model structure is appropriate, accurately implemented and similar to models developed to inform NICE technology appraisals for severe asthma.

Given the rates of adverse events reported in the dupilumab,, the decision not to model treatment-related adverse events for drugs other than oral corticosteroids is reasonable. This is very unlikely to make a substantive difference to overall cost and QALY estimates, and is consistent with the previous appraisal TA565.

4.3.4 Clinical parameters

4.3.4.1 Transition probabilities for asthma control and exacerbations

The probabilities of moving between the four live health states (uncontrolled asthma, controlled asthma, moderate exacerbation and severe exacerbation) in each four-week model cycle are estimated in a series of 4 by 4 transition matrices. Methods used to derive these matrices are described in CS B.3.3.2, with more detail in CS Appendix M.1.

Base case transition matrices (no mOCS)

The model uses three transition matrices for each intervention: for the time periods 0-12 weeks, 12-52 weeks and 52+ weeks. Base case transition matrices for standard care and dupilumab are estimated from QUEST data for people with EOS≥150 or FeNO≥25 and ≥3 exacerbations in the previous year.

The number of transitions between each pair of health states (N_{ij}) was calculated for every four-week period (excluding transitions after permanent discontinuation of the randomised treatment): N_{ij} is the number of transitions from health state i to health state j (i,j = 1,…,4, 1=controlled, 2= uncontrolled, 3=moderate exacerbation or 4= severe exacerbation). These data were used to calculate basic transition probabilities: $P_{ij} = N_{ij}/\sum_{k=1}^{4} N_{ik}$. Various adjustments were made to calculate the final transition matrices for the model, as described in the following six steps.

1) *Pooled exacerbation probabilities for 0-52 weeks*:
   The probabilities of moderate and severe exacerbations in the first year are calculated by pooling 0-12 week and 12-52 week transitions. The company states that this is appropriate given the small numbers of exacerbations observed and lack of evidence for a difference over time. They also present a scenario with separate exacerbation probabilities for 0-12 and 12-52 weeks.

2) *Separate control probabilities for 0-12 and 12-52 weeks*:
   Probabilities for the two periods are calculated excluding transitions to moderate or severe exacerbations in the same four-week cycle. Thus, the conditional probabilities for uncontrolled and controlled asthma in time period T (T= 1 for 0-12 weeks and T=2 for 12-52 weeks) are:

$$P_{i2}^{T} = [P_{i2}/(P_{i1} + P_{i2})] * (1 - P_{i3} - P_{i4}) \text{ and}$$

$$P_{i1}^{T} = (1 - P_{12}^{T} - P_{i3} - P_{i4})$$

The company argues that using separate asthma control rates for 0-12 and 12-52 weeks is appropriate because most of the improvement occurs in the first 12 weeks. To support this, they cite the higher rate of change of asthma control in QUEST (as indicated by mean ACQ-7 scores) in weeks 0-12 compared with weeks 12-52 (see CS Figure 19 for the ITT population). The company also compare probabilities of transition to the 'controlled asthma' health state before versus after 12 weeks (Clarification response Table 17). This shows a significant overall improvement in rates of control in all patients on dupilumab and in the subgroup with a response to dupilumab at 52 weeks, but no significant difference for the placebo group.

The net effect of using pooled control probabilities from the whole 0-52 week trial period for both placebo and dupilumab, as well as for dupilumab responders after 52 weeks is shown in a scenario analysis (Clarification response Table 19). This reduces the ICER for dupilumab compared with standard care alone, indicating that the base case assumption is conservative. The ERG agrees with this conclusion.

3) *Post-trial transition probabilities based on 12-52 week transition matrices:*
The company assumes that outcomes after the first 12 weeks are more reflective of long-term outcomes, so 12-52 week transition matrices are used as the basis for extrapolation. It is not clear whether this is appropriate, as the numbers of exacerbations are low and there are no significant differences in control rates between the two time periods in the QUEST placebo group. However, as noted above, the net effect of pooling all transition probabilities across 0-52 weeks is to reduce ICERs.

For dupilumab, transition probabilities after 52 weeks are based on analysis of QUEST data only for individuals who were classified as having a response at 52 weeks. For the base case population (non mOCS), response was defined as at least 50% reduction in severe exacerbations (CS Table 53). This included [redacted] patients ([redacted]) in the base case population.

4) *Adjustment of long-term severe exacerbation rates*:
It is apparent that the severe exacerbation rate among patients treated with placebo in QUEST was lower than in the preceding year: mean annualised rates 2.07 (SD 1.58) before the trial compared with [redacted] during the trial in the randomised population (CS Tables 13 and 19).

The company mention four possible reasons for this large difference in CS B.3.3.3 and in Appendix M.2:

- Regression to the mean: This is a statistical phenomenon whereby individuals with atypical values for some characteristic when first assessed will tend to have values closer to the population average when assessed again. Thus, people with a high number of exacerbations in the year before the trial may, on average, have fewer exacerbations in next year, even with no effective treatment.
- Better care in a clinical trial setting: Patients in a clinical trial may have better outcomes than in routine practice due to regular specialist follow up, optimised care and improved adherence. If so, the trial results may not be generalisable. However, we note that a similar improvement could occur in clinical practice when people with inadequately controlled severe asthma are first referred to specialist care to be assessed for initiation of biologic treatment. This would have different implications for the generalisability of the trial results.
- Exclusion criteria and impact on exacerbation rate: Patients in QUEST had a longer average time since their last severe exacerbation than would be expected at treatment initiation because those with a severe exacerbation from 1 month before screening up to and including the baseline visit were excluded. As time since last severe exacerbation (TSLSE) is a strong predictor for future exacerbations (TENOR cohort, Calhoun et al. 2014)[23], the number of severe exacerbations during QUEST follow up may be lower than an unselected cohort.
- Definition of exacerbation events: In QUEST, two exacerbations that started within a 28 day period were classified as a single event. On average, the duration of exacerbation symptoms was less than 28 days (median 10 days with dupilumab and 15-17 days with placebo). Thus the number of exacerbations for trial participants might have been underestimated.

A similar placebo effect was observed in the NICE reslizumab appraisal (TA479 paragraphs 4.12 and 4.13). The committee considered the possibilities of the first two explanations above (optimised treatment or regression to the mean) but concluded that these would be likely to affect both arms, so "*the most robust estimate of relative effectiveness was derived from the exacerbation rates shown in the clinical trials.*" However, the third and fourth issues were not raised in previous appraisals.

In their base case, the company applies a multiplier of [redacted] to severe exacerbation rates after the trial period (both arms) to estimate the increased risk without the QUEST exclusion criterion. The calculation is described in CS section M.2.1.1, with further explanation in Clarification Response B4. It uses an odds ratio for the increased risk of severe exacerbations for people with a recent severe exacerbation (TSLSE < 90 days) from TENOR[23] (2.99, 95% CI 2.57 to 3.47) and QUEST data on TSLSE at baseline (35.33% with TSLSE < 90 days) and at the end of the trial ([redacted] with TSLSE < 90 days).

$$\frac{2.99 * [redacted] + 1 * (1 - [redacted])}{2.99 * 0.3533 + 1 * (1 - 0.3533)} = [redacted]$$

This adjustment has the effect of proportionally increasing the absolute number of severe exacerbations in both arms and the absolute difference between the arms, hence improving cost-effectiveness.

The company also calculates a multiplier to adjust for the definition of a severe exacerbation event in QUEST (issue 4 above). This is estimated from the DRI study, as the ratio of severe exacerbation rates calculated without and with the 28-day interval definition: [redacted] (unadjusted rates across all study arms) (CS Appendix M Table 76).

The company presents four scenario analyses to explore different assumptions about long term severe exacerbation rates (after the trial period):

- No adjustment: observed rates from trial (multiplier 1.00)
- Rate from mepolizumab technology appraisal (multiplier 1.35)
- Combined adjustment for exclusion criteria and definition of severe exacerbation (multiplier [redacted] * [redacted] = [redacted])
- Rates increased to those observed before the trial (multiplier 1.813)

5) *Adjustment for null probabilities*:

In the base case, transition probabilities were adjusted when no events were observed for a specific transition. If any transition out of a given health state was 0, 1 was added to all transitions out of the state and the probabilities were re-calculated. This assumes that plausible transitions with no events were not observed either due to short follow-up or limited sample size and that there is a non-zero likelihood of the transition occurring. In practice, this has little impact on the base case transition probabilities.

6) *Scaling to ensure that the probabilities from each health state sum to 1*: Where necessary, a sequential approach is used working from the more severe health states and adjusting less severe states to fit within the residual probability. Thus $\sum_{k=1}^{4} P_{ik} = 1$ for each i.

The final set of transition matrices used in the base case model are reported in CS Appendix M Table 73 (reproduced in Table 73 below). The ERG has checked that these matrices match those in the model, and that the adjustments are correctly applied.

Transition matrices for scenario with mOCS

Similar methods were used to estimate transition matrices for patients on mOCS in the company mixed population scenario, with the following exceptions:

- Transition matrices are based on data from the VENTURE trial
- VENTURE did not collect information on moderate exacerbations, so this health state is omitted from the model for the mOCS group.
- The follow-up period for VENTURE is 24 weeks and trial transitions are collated for 0-12 week and 12-24 week periods. A similar approach is used as for the non mOCS population, with pooling of exacerbation rates across the whole trial duration, but use of separate control rates for 0-12 weeks and 12-24 weeks.
- Post 24-week transitions are based on the 12-24 week transition matrix, with adjustment for long-term severe exacerbation rate ([redacted] multiplier to adjust for trial exclusion criteria). This adjustment will have a greater impact in the mOCS population, since it is applied after only 24 weeks rather than 52 as for the non mOCS population.

The CS reports a set of transition matrices for the mOCS population in CS Appendix M Table 74, but this does not match the values in the submitted model (see Table 74 below). In response to clarification question B2, the company reported the numbers and probabilities of transitions to the Controlled Asthma health state (Clarification Response Table 18), which are consistent with the probabilities in the model, but data for transitions to the other health states were not reported. The model includes absolute numbers of transitions and the probabilities are correctly calculated from these numbers. In the Factual Accuracy Check, the company states that the transition probabilities in the model are correct.

ERG conclusions: The company's approach to estimation of transition probabilities between the live health states makes good use of QUEST and VENTURE data. The model

calculations are correct, although we note that the transition probabilities from VENTURE reported in CS Appendix M differ from those in the model. We have concerns about the use of a multiplier to inflate the observed rates of severe exacerbations from the trials after trial follow up (step 4 above), see section 4.4.4.1.

Table 73. Transition probabilities: EOS≥150 or FeNo≥25 and ≥3 exacerbations

	Controlled Asthma	Uncontrolled Asthma	Moderate Exacerbation	Severe Exacerbation
Standard care only				
0-12 weeks				
Controlled Asthma	69.9%	19.1%	1.8%	9.2%
Uncontrolled Asthma	14.3%	51.7%	11.8%	22.2%
Moderate Exacerbation	11.0%	33.1%	39.5%	16.3%
Severe Exacerbation	8.8%	61.4%	6.5%	23.4%
12-52 weeks				
Controlled Asthma	70.8%	18.2%	1.8%	9.2%
Uncontrolled Asthma	12.0%	54.0%	11.8%	22.2%
Moderate Exacerbation	2.9%	41.2%	39.5%	16.3%
Severe Exacerbation	18.3%	51.8%	6.5%	23.4%
52+ weeks				
Controlled Asthma	66.8%	18.2%	1.8%	13.1%
Uncontrolled Asthma	2.4%	54.0%	11.8%	31.7%
Moderate Exacerbation	2.8%	35.8%	37.9%	23.5%
Severe Exacerbation	8.2%	51.8%	6.5%	33.5%
Dupilumab + standard care				
0-12 weeks				
Controlled Asthma	75.0%	13.9%	7.7%	3.4%
Uncontrolled Asthma	21.6%	56.5%	13.1%	8.8%
Moderate Exacerbation	26.8%	35.7%	36.5%	1.0%
Severe Exacerbation	22.5%	67.5%	7.5%	2.5%
12-52 weeks				
Controlled Asthma	77.0%	11.8%	7.7%	3.4%
Uncontrolled Asthma	16.2%	62.0%	13.1%	8.8%
Moderate Exacerbation	25.6%	36.9%	36.5%	1.0%
Severe Exacerbation	41.8%	48.2%	7.5%	2.5%
52+ weeks (responders only)				
Controlled Asthma	79.6%	10.7%	6.9%	2.7%
Uncontrolled Asthma	17.1%	68.1%	9.4%	5.4%
Moderate Exacerbation	23.3%	28.2%	46.5%	2.0%
Severe Exacerbation	41.2%	35.3%	17.6%	5.9%

Source: Copied from the company model by ERG

Table 74. Transition probabilities: EOS≥150 or FeNo≥25 and mOCS

	Controlled Asthma	Uncontrolled Asthma	Moderate Exacerbation	Severe Exacerbation
Standard care only				
0-12 weeks				
Controlled Asthma	61.2%	20.4%	-	18.4%
Uncontrolled Asthma	6.4%	83.2%	-	10.4%
Moderate Exacerbation	-	-	-	-
Severe Exacerbation	47.7%	47.7%	-	4.7%
12-24 weeks				
Controlled Asthma	31.4%	50.2%	-	18.4%
Uncontrolled Asthma	10.5%	79.1%	-	10.4%
Moderate Exacerbation	-	-	-	-
Severe Exacerbation	32.9%	62.5%	-	4.7%
24+ weeks				
Controlled Asthma	23.4%	50.2%	-	26.3%
Uncontrolled Asthma	5.9%	79.1%	-	14.9%
Moderate Exacerbation	-	-	-	-
Severe Exacerbation	30.9%	62.5%	-	6.7%
Dupilumab + standard care				
0-12 weeks				
Controlled Asthma	88.0%	8.4%	-	3.7%
Uncontrolled Asthma	19.9%	74.2%	-	5.9%
Moderate Exacerbation	-	-	-	-
Severe Exacerbation	16.7%	75.0%	-	8.3%
12-24 weeks				
Controlled Asthma	84.4%	11.9%	-	3.7%
Uncontrolled Asthma	9.3%	84.7%	-	5.9%
Moderate Exacerbation	-	-	-	-
Severe Exacerbation	46.2%	46.2%	-	7.7%
24+ weeks (responders only)				
Controlled Asthma	84.4%	11.1%	-	4.5%
Uncontrolled Asthma	9.5%	86.8%	-	3.6%
Moderate Exacerbation	-	-	-	-
Severe Exacerbation	62.5%	25.0%	-	12.5%

Source: Copied from model by ERG

4.3.4.2 Maintenance oral corticosteroid use

Parameters used to model OCS dose reduction and withdrawal in the company's mixed population scenario (EOS≥150 or FeNO≥25 and mOCS) are described in CS B.3.3.7 and Table 55. The probabilities of dose reduction are estimated from VENTURE data on the proportions of the subgroup on less than 5mg per day at baseline, 12 and 24 weeks, assuming a constant rate of change between these time points, and no further change after 24 weeks. Only a small proportion of patients (0.66%) were on less than 5mg daily at baseline. This increased to 47% at 12 weeks and 41% at 24 weeks in the standard care group; and 58% and 73% respectively in the dupilumab group. The difference between dupilumab responders at week 24 (81%) and patients on standard care (41%) is assumed to persist while patients remain on add-on treatment. The same approach is used to estimate OCS withdrawal probabilities. For standard care, 15% withdrew by week 12 and 30% by week 24. This compared with 40% and 53% respectively in the dupilumab group, and 58% at week 24 for dupilumab responders.

4.3.4.3 Response and discontinuation

The base case model assumes that patients on dupilumab are assessed at 12 months and that non-responders stop treatment. Response is defined as at least 50% reduction in severe exacerbations or maintenance oral corticosteroid dose at 12 months. This is similar to the definition of adequate response in NICE mepolizumab guidance (TA431) (see CS Table 50). [redacted] ([redacted] patients) in the QUEST base case subgroup (EOS≥150 or FeNo≥25 and ≥3 exacerbations) and [redacted] ([redacted] patients) of the VENTURE mOCS scenario subgroup (EOS≥150 or FeNo≥25 and mOCS) met this definition of response (CS B..3.3.4).

The model also applies a constant annual rate of dupilumab discontinuation after 12 months (CS B.3.3.5). Discontinuation rates were estimated from the ITT populations of QUEST (12-52 weeks) and VENTURE (12-24 weeks): 0.107 per person year for the base case (dupilumab 200mg) and 0.042 per person year for the mOCS scenario (dupilumab 300mg) (CS Table 54). These discontinuation rates from the first year of treatment in a clinical trial context might not be generalisable to longer term treatment in practice.

As an alternative, the model includes a 'discontinuation rule' as a scenario. This assumes that patients discontinue treatment if they spend 12 consecutive cycles without controlled disease (i.e. in the uncontrolled asthma, moderate or severe exacerbation health states).

The company quotes the EMA licence for dupilumab:

> "*Dupilumab is intended for long-term treatment. The need for continued therapy should be considered at least on an annual basis as determined by physician assessment of the patient's level of asthma control.*" (SmPC page 3)

This suggests that a single response assessment is not sufficient, but that the need for continued treatment should be re-assessed annually. The NICE TA565 committee noted a similar recommendation in the summary of product characteristics for benralizumab and agreed that reviewing treatment every 12 months as for other biologics is appropriate.

> **ERG conclusions**: The company's model includes an appropriate assessment of response at 12 months and a constant subsequent rate of discontinuation estimated from the clinical trials. The latter might not be generalisable to ongoing treatment cessation rates in practice, but the company tests this in the 'alternative continuation rule' scenario, which the ERG consider to be reasonable. However, we note that the company's base case does not include any discontinuation prior to the 12 month response assessment. This seems unrealistic because some patients are likely to stop treatment for reasons other than lack of response (e.g. adverse effects, intolerance or inconvenience). We therefore include an additional ERG scenario applying the observed rates of discontinuation from the clinical trials before as well as after the 12 month response assessment (see section 4.4.3).

4.3.4.4 Multipliers for small populations

The exploratory analyses described in CS Appendix P compare dupilumab with other biologics in two subgroups based on NICE criteria for access to mepolizumab and reslizumab. These groups represent small proportions of the QUEST population:

- 35.6% (36/101) of patients in the placebo and 200mg dupilumab arms had EOS≥300 and ≥4 exacerbations in the previous year (NICE criteria for mepolizumab); and
- 46.5% (47/101) had EOS≥400 and ≥3 exacerbations in the previous year (NICE criteria for reslizumab) (CS P.1.1.1).

It was not feasible to calculate transition probabilities directly from data for these small subgroups. Instead, the model uses probability estimates from larger reference subgroups, with fewer prior exacerbations, which are then adjusted. For the mepolizumab and reslizumab eligible target groups, the reference groups are EOS≥300 with ≥2 prior exacerbations (n=202 across both arms) and EOS≥400 with ≥1 prior exacerbation (n=349),

respectively. In addition to severe and moderate exacerbations, this approach was used to estimate the proportion of patients with a response to dupilumab at 52 weeks.

Multipliers to inflate the reference exacerbation and response estimates for the target groups were calculated from negative binomial regression models. To provide sufficient power, the binomial regressions were conducted with QUEST data for people on high dose ICS with EOS≥150 (n=349). A similar approach was used to estimate multipliers for dupilumab responders (n=165). The company provided further information about the regression datasets in response to a clarification question (B5), Tables 23 and 24. The models included age, region, EOS level, number of severe exacerbations in the previous year and treatment group as covariates. The resulting multiplier estimates for the mepolizumab and reslizumab eligible subgroups are reported in CS Appendix P Table 123 (reproduced below for convenience). In response to Clarification Question B5, the company reported goodness-of-fit statistics and co-variate significance for the final models, but did not compare alternative specifications or assess the appropriateness of the negative binomial models (dispersion). It is therefore difficult to assess the robustness of the results. The economic model uses a simulation approach to estimate confidence ranges for the multiplier estimates.

Table 75: Multipliers for subgroups by treatment for patients not on mOCS

Severe Subgroup (pn/tn)	Corresponding reference subgroup (pn/tn)	Outcome	Background therapy alone	Dupilumab + background therapy: All patients	Dupilumab + background therapy: Responders
EOS≥300 AND ≥4 exacerbations (14/22)	EOS≥300 AND ≥2 exacerbations (48/79)	Severe exacerbation	1.46	1.27	1.99
		Moderate Exacerbation	1.18	1.48	1.56
		% response with dupilumab	N/A	1.02	
EOS≥400 AND ≥3 exacerbations (21/ 26)	EOS≥400 AND ≥2 exacerbation (57/93)	Severe exacerbation	1.67	1.22	2.85
		Moderate Exacerbation	0.63	1.21	1.29
		% response with dupilumab	N/A	1.12	

EOS, eosinophil; FeNO, fractional exhaled nitric oxide; Pn, n in placebo subgroup; PSER, placebo severe exacerbation rate; Tn, n in treatment subgroup.
Source: Reproduced from CS Appendix P Table 123

ERG conclusions: The ERG agree that it would not have been feasible to calculate transition probabilities directly from data for the small subgroups who meet NICE criteria for access to other add-on biologic comparators. The company therefore estimated the small group probabilities based on results for similar groups with fewer severe exacerbations in the previous year, adjusted with multipliers for the increased risks associated with a greater number of prior exacerbations. The ERG considers this to be a reasonable approach which is consistent with methods in TA479. We also think that the company's method of calculating the prior exacerbation multipliers using negative binomial regressions is appropriate, although we cannot assess the robustness of the fitted models due to limited diagnostic statistics.

4.3.4.5 Relative effects for other biologics

Transition probabilities for other biologic comparators are calculated by applying relative effects estimated from the company's indirect treatment comparisons: the Bucher ITC in the base case, and a scenario using the MAIC analyses (CS Appendix P.1). We discuss the relative strengths and weaknesses of the Bucher and MAIC methods in section 3.1.7.5 above.

Estimates of relative effects were only available for severe exacerbations and OCS-related outcomes (dose reduction and withdrawal). The company assumes that rates of moderate exacerbations and loss of control for other biologic comparators are the same as for dupilumab (relative risks = 1). This assumption is reasonable given the lack of comparative data, but it is a limitation of the exploratory comparison with other biologics.

The model uses relative risks to adjust rates of severe exacerbations and odds ratios to adjust the proportions of patients with reduced dose or withdrawal from OCS (reproduced in Table 76 and Table 77 respectively). Note that these ratios are reported for the comparator relative to dupilumab, so they are the inverse of the values reported in CS Appendix N (Table 88) and Appendix O (Table 114). We note one error in reporting: CS P.1 Table 127 gives the incorrect relative risk of severe exacerbations for the MAIC mepolizumab 'NICE-like' population. The values in the model appear to be correct, as they match the (inverted) values in Appendix O Table 114.

The model includes separate estimates (where available) for the relative effects of 'responders' based on subgroup data for trial participants with a treatment response at 12 months. However, the model applies relative effects for all patients to responders in the base

case, as the company considers this to be more robust. A scenario for the ITC uses estimates of relative effects reported in other NICE appraisals.

Table 76 Relative rates of severe exacerbations

Treatment	Relative risks versus dupilumab, mean (95% CI)	
	Non mOCS (all patients)	mOCS (all patients)
Bucher indirect treatment comparison		
Reslizumab	[redacted]	
Mepolizumab	[redacted]	[redacted]
Benralizumab	[redacted]	[redacted]
Matched adjusted indirect treatment comparison		
Reslizumab	[redacted]	
Mepolizumab label Population	[redacted]	[redacted]
Mepolizumab 'NICE-like'	[redacted]	[redacted]
Benralizumab	[redacted]	[redacted]

Source: Reproduced from CS Appendix P.1.10 Table 126 and 127
a As reported in model. Value differs from CS P.1.10 Table 127)

Table 77 Relative effects on OCS reduction

Treatment	Odds ratios versus dupilumab, mean (95% CI)	
	Withdrawal from OCS	Reduction to a daily dose <5mg
Indirect treatment comparison[a]		
Mepolizumab	0.862 (0.225 to 3.226)	0.667 (0.242 to 1.852)
Benralizumab	1.020 (0.218 to 4.762)	0.513 (0.136 to 1.961)
Matched adjusted indirect comparison[a]		
Mepolizumab	N/A	N/A
Mepolizumab: NICE-like population	1.967 (0.299 to 12.927)	
Benralizumab	1.075 (0.249 to 4.650)	0.513 (0.136 to 1.961)

Source: Reproduced from CS Appendix P.1.13 Table 131

ERG conclusions:
Relative effects of the biologics in the economic model are based on the Bucher ITC analyses, with results from the MAIC as a scenario. The company note that the decision to use the Bucher ITC in the base case was due to 'limitations of the MAIC'. They do not expand but we agree that the MAIC does have inherent limitations. There are also limitations with the Bucher ITC approach (see section 3.1.7.5 above).

Estimates of relative effects are only available for risks of severe exacerbations and OCS-related outcomes (dose reduction and withdrawal). The company assumes that incidence of moderate exacerbations and loss of control for other biologics are the same as for dupilumab. This assumption is reasonable given the lack of comparative data, but it is an important limitation of the comparison with other biologics.

The company report the comparative cost-effectiveness between biologics as 'exploratory' and emphasise that it is presented "for information purposes only and should be interpreted with appropriate caution" (CS Appendix Q). The ERG shares this caution due to limitations of both Bucher ITC and MAIC methods and the lack of data to assess comparative effects on moderate exacerbations and loss of control. However, we understand that there is overlap between the company's target subgroup for dupilumab and current criteria for access to other biologics in the English NHS. It is therefore necessary to make comparisons between dupilumab and other biologics in the NICE scope. The ITC, though flawed, presents the best currently-available data to make this comparison.

4.3.4.6 Mortality

In addition to general population mortality, the economic model includes mortality from severe asthma.

Asthma-related mortality

The company uses published literature to inform mortality data related to asthma. They state that previous NICE TAs have implemented a similar approach wherein patients could experience death from severe eosinophilic asthma. A detailed discussion of the approach adopted in the previous appraisals is presented in CS Appendix M.3.2.

Asthma related mortality is incorporated in the economic model as a fatality associated with severe exacerbations. The proportion of severe exacerbations that are fatal differ by age and

by location of treatment: hospital admission; A&E attendance; or other (which may include primary care or potentially self-management with emergency prescribed 'OCS burst').

For the base case, the company uses the estimates from the preferred committee assumption in NICE TA565. The mortality rate associated with exacerbations leading to hospitalisation is based on data from Watson et al.[24] and age-adjusted based on Roberts et al.[25], with further adjustment based on the most recent BTS audit. The fatality estimates by age and by setting of treatment of severe exacerbations are presented in CS Table 56, reproduced below in Table 78. The CS acknowledges that there remains considerable uncertainty over the mortality estimates and conducted two scenario analyses to assess the impact on cost effectiveness: use of asthma-related mortality from the mepolizumab submission; and asthma-related mortality set to 0.

Table 78 Probability of death after a severe exacerbation as used in model

Age band	Other		A&E visit		Hospitalisation	
	%	N	%	N	%	N
18–24 years	0.020	91	0.13	45	0.06	2,420
25–34 years	0.020	91	0.13	45	0.06	2,420
35–44 years	0.020	91	0.13	45	0.08	2,420
45–54 years	0.324	91	2.05	45	0.30	628
55–64 years	0.324	91	2.05	45	1.81	521
65–74 years	0.324	91	2.05	45	4.54	689
75–100 years	0.324	91	2.05	45	4.54	689

Source: CS Table 56

Table 79 Setting of severe exacerbations in model

Source (population)	Other		A&E visit		Hospitalisation	
	%	n	%	n	%	n
O'Neill et al. 2015 (BTS Difficult Asthma Registry) [a]	73.6%	2587	7.8%	274	18.7%	656
QUEST ITT [b]	93.3%	1122	3.0%	36	3.7%	44
VENTURE						
TA431 (EOS≥150, ≥2 Prior exacerbations) [c]	83.1%	373	8.7%	39	8.2%	37
TA565 (EOS≥400, ≥1 Prior exacerbations) [d]	87.3%	571	4.5%	30	8.2%	53

Castro et al. 2015 (EOS≥150 or FeNO≥25, ≥2 Prior exacerbations) [e]	91.4%	281	3.9%	12	4.7%	15

Source: Adapted by ERG from company model

a. O'Neill et al. 2015; 9.6% of unscheduled A&E or GP visits assumed to be A&E
b. QUEST post hoc analysis, Exacerbations, 29 Jun 2018, ITT population; Combined across all arms (all doses of dupilumab and placebo)
c. VENTURE post hoc analysis, Exacerbations, 25 Jun 2018, ITT population; Combined across all arms (dupilumab and placebo)
d. NICE TA431, Mepolizumab - company evidence submission, Table 105, page 198
e. Bleecker et al. 2016, Appendix 14, Table 3; Segregation of A&E visit and hospitalisation assumed based on distribution reported in NICE TA565
f. Castro et al. 2015; Pooled Study 1 and 2; Segregation of A&E visit and hospitalisation assumed based on distribution in QUEST

Another parameter that drives model estimates of asthma-related mortality is the distribution of locations for treatment of severe exacerbations (CS section B 3.5.7.1, Table 80). For the base case, the company use estimates reported by O'Neill et al (2015)[26], which analysed data from the British Thoracic Society Difficult Asthma Registry. The strength of this source is that it uses UK 'real-world' data. However, it is not clear whether the denominator includes all cases of severe exacerbation in the relevant population, because cases were only ascertained from hospital and primary care records. Patients who self-managed for 3 or more days with an emergency supply of oral corticosteroids ('OCS burst') would not have been included. The model includes two scenarios based on alternative sources: one with estimates from the QUEST and VENTURE trials; and another using estimates from other biologic trials (see Table 79). All of these other sources report smaller proportions of patients treated in A&E or with hospitalisation.

Other cause mortality

The model uses general population all-cause mortality rates by age and gender from Life tables for England and Wales. The CS appropriately adjusted these rates by removing the proportion of asthma-related deaths to avoid double-counting. The proportions of asthma-related deaths reported in CS Table 57 are calculated from the International Classification of Diseases, Tenth Revision codes J45-J46 for 2014-16, provided by the ONS.

> **ERG conclusions:** The company's general approach to modelling asthma-related mortality, in which excess mortality is only associated with severe exacerbations, is consistent with NICE previous appraisals for severe asthma. The fatality rates by age and location of treatment that are used in the base case model are the same as in NICE TA565, and were accepted as appropriate by the TA565 committee (paragraph

3.12). However, the assumed proportions of severe exacerbations treated in hospital or A&E are higher than in TA565. This has the effect of increasing the number of asthma-related deaths in the model, and hence QALY gain from avoiding severe exacerbations. We consider the impact and plausibility of the resulting mortality estimates in section 4.3.7.

The company's assumptions about other cause mortality are reasonable.

4.3.5 Utilities

The company model uses the following parameters to estimate the impact of the comparators on health-related quality of life:

- A baseline utility, adjusted for age and gender, for patients with controlled and uncontrolled asthma;
- Utility decrements to reflect the negative impact of moderate and severe exacerbations compared to uncontrolled asthma; and
- A utility decrement for mOCS-related adverse effects.

Values for these parameters were obtained from an analysis of EQ-5D data from the QUEST and VENTURE trials, supplemented with estimates from the literature.

Utilities from published sources

The company conducted a systematic literature review for studies that reported health-related quality of life of patients with severe asthma. The search strategy and inclusion criteria is shown in Appendix G. They included generic preference-based (eg. EQ-5D), generic (eg.SF-36) and disease-specific measures (eg. AQL-5D). We consider that the search strategy was satisfactory. After full-text screening, 18 studies met the inclusion criteria, three of which reported EQ-5D utilities (CS Table 64).

The company noted that the study by Lloyd et al.[28] could be used to inform the exacerbation disutility and has been used in a previous submission. However the numbers in this study are smaller than in QUEST. The company uses the disutilities from Lloyd et al. in a scenario analysis.

Utility data from the QUEST and VENTURE trials

EQ-5D-5L and AQLQ utility data were collected through questionnaires given to the patients during the QUEST and VENTURE trials. In QUEST, these were collected at weeks: 0 12, 24,

36, 52 (End of trial) and 64 (End of study). In VENTURE, these data were collected at weeks: -8 to -3, 0, 12, 24 (End of trial) and 36 (End of study). The company assumed the same utility for each health state, regardless of background therapy or add-on biologic, due to the small number of observations. Utility values were calculated for controlled asthma, uncontrolled asthma, moderate exacerbation and severe exacerbation.

EQ-5D-5L utility values were obtained by mapping to the EQ-5D-3L, using the van Hout crosswalk algorithm.[29] The ERG agrees that this is consistent with the NICE reference case and position statement on EQ-5D-5L data.[30]

The company noted that in previous appraisals for asthma, it had been suggested that the EQ-5D does not accurately capture benefits from treatment of severe asthma and that some of the limitations of the EQ-5D could be removed by mapping AQLQ to EQ-5D. The company used utility values from the asthma-specific preference-based index AQL-5D in sensitivity analyses. However, the ICER does not change significantly when the utilities were derived from AQLQ, rather than EQ-5D (CS Table 91).

The EQ-5D utility values from QUEST and VENTURE for patients with controlled and uncontrolled asthma are shown in Table 80 (CS Table 60). In response to a clarification question (B6), the company provided the total number of observations used to calculate the controlled and uncontrolled asthma utility values (Clarification response Table 25). These numbers are shown in Table 80. We note that values for controlled asthma are higher than general UK population norms for age 45-54 [31], which lacks face validity.

Table 80 Trial-based EQ-5D utilities: base case and mOCS populations

Health State	N	Mean	SE
ICS population (QUEST) EOS ≥150 OR FeNO ≥25 and ≥3 severe exacerbations			
Controlled asthma	329	0.906	0.0068
Uncontrolled asthma	327	0.735	0.0110
mOCS population (VENTURE) EOS ≥150 OR FeNO ≥25 and mOCS			
Controlled asthma	95	0.890	0.016
Uncontrolled asthma	173	0.713	0.014

CS Table 60
EOS, eosinophils; EQ-5D, EuroQol-5 dimensions; FeNO, fractional exhaled nitric oxide; mOCS, maintenance oral corticosteroids; SE, standard error.
Source: Data on file. Post-hoc analyses from QUEST; Post-hoc analyses from VENTURE

The company notes the small numbers of EQ-5D measurements for severe exacerbation. For this reason, they use data for the ITT population, rather than the particular subgroups of

interest. Utility decrements for severe exacerbation are shown in Table 81 (CS Table 63). These decrements are applied to the uncontrolled asthma health state. The company assumes that there is no decrement for moderate exacerbation.

Table 81 Disutility of severe exacerbations from QUEST ITT

	Type of exacerbation	No. exacerbations	Mean	SE
Severe exacerbation	Office visit	176	–0.075	0.016
	A&E visit	7	–0.086	0.128
	Hospitalisation	7	–0.145	0.128

CS Table 63
A&E, Accident and Emergency; ITT, intent to treat; SE, standard error.

The company includes scenario analyses based on published data for the controlled and uncontrolled asthma health states (Willson et al. 2014)[27] and for the exacerbation disutilities (Lloyd et al. 2007)[28], together with a scenario analysis using AQL-5D data (CS Table 91).

Exacerbation disutilities are applied in the model for the duration observed in QUEST ITT. The duration of exacerbation is shown in CS Table 67. The company notes that (as argued in the NICE submission for TA431), decrements may last beyond the time at which the exacerbation is considered to be resolved. The company includes a scenario where applying a disutility for the duration of a cycle (4 weeks).

Age-related utilities

Utilities in the economic model are adjusted for age and gender, based on the algorithm developed by Ara and Brazier[31] (CS Table 62). The company notes that this is in line with the NICE DSU Technical Document 12.[32] The model does not include disutility associated with any adverse events associated with biologic add-on treatment.

Disutilities for adverse events related to mOCS use

Long-term chronic use of steroids can have serious long-lasting side-effects and one of the benefits of biologic use is the opportunity to reduce maintenance OCS. The company includes the effect of these side-effects on quality of life. The model includes three categories for mOCS use: complete withdrawal of OCS, dose reduction to >1≤5mg/day or high dose of >5 mg/day.

The baseline incidence risk of AEs is for those patients not receiving mOCS (shown in CS Table 58). Odds ratios are used for the medium or high daily dose of OCS vs. no OCS use (CS Table 59). These data are from a large Clinical Practice Research Datalink (CPRD) study by Bloechliger et al[33] with between 165,900 and 269,368 asthma patients.

Utility decrements are applied in the model for adverse events related to mOCS use by multiplying the incidence of the AEs by the disutilities of the AEs. The disutilities for the AEs are shown in CS Table 68 and are from Sullivan et al,[34] a EQ-5D utility catalogue which provides disutilities for chronic diseases. The majority of AEs are for long-term illnesses and so the disutility is applied over the patient lifetime. Severe infection, herpes zoster and peptic ulcer are assumed to last for 4 weeks. In response to a clarification question (B7), the company provided more information on ICD codes used to identify the disutilities associated with each adverse event and these are shown in the Clarification response Table 26.

> ***ERG conclusion:*** The company's approach to estimating utility values is based upon EQ-5D-5L data collected from the company's QUEST and VENTURE trials. The company has used the cross-walk method to map these data to EQ-5D-3L data for use in the company model, which is consistent with NICE's current position statement on the EQ-5D-5L. The utility values collected are consistent with NICE's reference case and suitable for inclusion in the economic model. The ERG noticed that the utility values for controlled asthma appear to be higher than would be expected in the UK general population. This lacks face validity, and we conduct an additional scenario analysis to test the impact of constraining the utility for controlled asthma to the age-related mean for the general population (see section 4.4.3).

4.3.6 Resource use and costs

The model includes estimates of costs for drug acquisition and administration, monitoring and follow-up care and the treatment of serious infections (CS section 3.5).

The CS reports a systematic literature review conducted to identify resource use and costs. The search strategy and the inclusion criteria are reported in Appendix G. The inclusion criteria included studies from the UK and US with more than 20 patients with moderate to severe asthma. Forty-two studies were identified that presented costs and healthcare resource use (HCRU) measures, including total direct and indirect costs, hospitalisations, medical visits, and/or length of stay. Of these, three cost studies and nine resource studies were conducted in the UK and are reported in CS Table 69 and 70.

4.3.6.1 Drug acquisition costs

Dupilumab is administered by subcutaneous injection, with an initial dose of 400mg (two 200mg injections), followed by 200mg injections every two weeks. For patients with severe asthma who are on oral corticosteroids, patients receive an initial dose of 600mg (two 300mg injections), followed by 300mg injections every two weeks. The cost of dupilumab at list price is £1264.89 per pack of two injections. Dupilumab is provided to the NHS with a confidential PAS discount for atopic dermatitis and the company states that this will be applied to both 200mg and 300mg doses for severe asthma (CS Table 2). Results are shown in the CS with the discount applied.

Background therapy use was estimated based on the clinical trial distributions and the distribution of the ICS/LABA data was derived from previously published UK-specific market research.[11] The background therapy use are shown in CS Table 72 and 73. The unit costs of background therapies are shown in CS Table 76 and 77.

4.3.6.2 Drug administration costs

Dupilumab is assumed to be administered in hospital for the first three administrations at a cost of £18.75 per administration, after which patients would self-administer. There is a one-off training cost for patients of £22.50. Unit costs were from PSSRU[35] and the assumptions used to calculate these are shown in CS Table 78. The same assumptions were made in the exploratory analysis for the administration costs of other biologics administered by subcutaneous injections (mepolizumab and benralizumab).

The summary of product characteristics states that patients or caregivers may self-inject dupilumab "*if their healthcare professional determines that this is appropriate*", and if so, that proper training should be provided.(SmPC page 4)[36]. Clinical advice to the ERG is that self-administration, which is not currently considered for other biologic treatments, would be an advantage. However, this may not be immediately available and may have an effect on the efficacy of dupilumab as patients who self-administer no longer have regular contact with medical professionals. There were no administration costs for background therapy as these treatments are inhaled or taken orally.

4.3.6.3 Health care resources

Health care resources for the controlled and uncontrolled health states and moderate and severe exacerbations were taken from an economic evaluation of tiotropium in patients with

poorly controlled asthma by Wilson et al.[27] This study conducted a survey of 15 UK health care providers to obtain health state-specific estimates of resource use. Those resource data have been converted to the cycle length used in the economic model (4 weeks) using the assumptions reported in CS Section 3.5.7. The resource use for the controlled and uncontrolled health states are shown in Table 82 (CS Table 79) and the resource use for exacerbations are shown in Table 83 (CS Table 81).

Table 82 Routine care resource use per cycle (4 weeks)

	Resource use per cycle in the 'Controlled asthma' health state		Resource use per cycle in the 'Uncontrolled asthma' health state	
Resource	**Mean**	**SE**	**Mean**	**SE**
GP	0.162	0.033	0.552	0.144
Primary care nurse	0.236	0.033	0.632	0.213
Specialist (outpatient visit)	0.098	0.024	0.376	0.096
Airflow Studies	0.108	0.024	0.196	0.044

CS Table 79
DSA, deterministic sensitivity analysis; GP, General Practitioner; PSA, probabilistic sensitivity analysis; SD, standard deviation; SE, standard error.
Source: Calculated from Willson et al, 2014, Technical appendix, Tables 7 to 9

Table 83 Resource use per cycle (4 weeks) associated with exacerbations

Resource use per cycle (4 weeks)	Office visit or self-managed		A&E visit		Hospitalisation	
	Mean	**SE**	**Mean**	**SE**	**Mean**	**SE**
GP	1.643	0.219	1.416	0.171	0.866	0.146
Primary care nurse	1.219	0.217	1.462	0.267	1.696	0.464
Specialist (outpatient visit)	0.527	0.138	1.238	0.364	1.948	0.673
OCS per mg	350	35	491	49	759	76
Emergency room attendance			1.000	0.000	0.623	0.060
Ambulance use			0.065	0.013	0.065	0.013
Severe exacerbation-related hospitalisation (long stay)					1.000	0.000
Post-acute hospitalisation*					1.000	0.000

CS Table 81
A&E, Accident and Emergency; GP, General Practitioner; OCS, oral corticosteroid; SE, standard error.
Source: † Calculated from Willson et al, 2014, Technical appendix, Tables 7 to 9 [27]; ‡ Dose in mg: NICE TA431, Mepolizumab - MS, Table 123 (page 216) § For 'Emergency roomvisit': assumption; For

'Hospitalisation': NICE TA431, Mepolizumab - MS, Table 123 (page 216) (Calculated from Willson et al, 2014, Technical appendix, Table 11 †† Assumption. [27] *Used in scenario analysis only

The setting of the treatment for exacerbations was also informed by the study by O'Neill et al. 2015.[26] The assumptions used to estimate the proportions in each group are shown in CS section B 3.5.7.1. 74% of severe exacerbations were treated by GP, 7.8% were treated at A&E and 18.7% were hospitalised (CS Table 80). As noted above (section 4.3.4.6), we do have some concerns about the appropriateness of this source.

Unit costs were taken from the PSSRU [35] or NHS National tariff [37] and are shown in Table 84 (CS Table 74). For emergency room attendance and severe exacerbation related hospitalisation, the company has combined the NHS National Tariff costs with a weighted average of the HRG codes. The ERG prefer the NHS reference costs: emergency department attendance £176.26 and severe exacerbation related hospitalisation £1579.45. For completeness, we use Reference Costs in ERG analysis (section 4.4.4).

Table 84 Unit costs of health care resources

Resource	Unit Cost	Source
Outpatient visits: GP (incl. home visit)**	£37.00 per visit	PSSRU 2018; Outpatient GP consultation (lasting 9.22 minutes)
Outpatient visits: Nurse (incl. home visit)**	£42 per hour	PSSRU 2018; Nurse (GP practice)
Outpatient visits: Specialist	£124 per visit	NHS National Tariff 2019-2020 [37]; Respiratory Outpatient Attendance, TFC code 340 Multiprofessional.
Outpatient visit: Hospital-based nurse	£ 45.00 per hour	PSSRU 2018; Specialist nurse - Band 6
Airflow studies	£53.00	NHS National Tariff 2019–2020. Airflow studies
OCS	£0.0047 per mg	2.5mg gastro-resistant tablets £0.93 per 28
Emergency room attendance	£ 143.57	NHS National Tariff Workbook 2019-2020 Weighted average of currency codes VB01Z to VB09Z of resource use cited in 2017-2018 National Schedule of Reference Costs
Ambulance use	£ 219.00	NHS Cost Recovery Scheme 2019–2020
Severe exacerbation-related hospitalisation	£ 1,646.26	NHS National Tariff Workbook 2019–2020 [38]; Weighted HRG codes DZ15M-DZ15R of resource use cited in 2017–2018 National Schedule of Reference Costs

CS Table 74

GP, General Practitioner; HRG, Healthcare Resource Group; OCS, oral corticosteroids.
** It assumed that home visits have the same cost as a GP or nurse office visit.

To calculate the health state costs per cycle, the estimates of resource use were multiplied by their corresponding costs per cycle. The health state costs per cycle are shown in Table 85 (CS Table 82).

Table 85 Health state costs: costs per cycle

Health State/ Exacerbation setting	Routine care cost	Cost per cycle for moderate exacerbations	Cost per cycle for severe exacerbations
Controlled Asthma	£ 26.43		
Uncontrolled asthma	£ 84.29		
Exacerbation – office visit		£95.49	£141.02
Severe exacerbation – A&E visit			£381.84
Severe exacerbation – hospitalisation			£2,045.56

CS Table 82
A&E, accident and emergency.

Adverse events associated with maintenance OCS use

The costs associated with treating the AEs related to mOCS were shown in CS Table 83 and related to either acute or long-term costs. In response to clarification question B11, the company confirmed that the values reported in this table are incorrect and should be as used in the model. The correct values are reported in the clarification response Table 27.

> ***ERG conclusion:*** The approach taken by the company to estimate health care resources and costs is reasonable and in line with previous NICE technology appraisals for severe asthma. For consistency, the ERG suggested that the unit costs should be taken from NHS reference costs for emergency room attendance and severe exacerbation related hospitalisation, rather than from the NHS National Tariff Workbook.

4.3.7 Model validation

The company describes their approach to model validation in CS section B.3.10. They state that they conducted two advisory board meetings, consisting of clinicians and health economists, to validate the key cost-effectiveness assumptions including those relating to the model structure, response assessment, and OCS AE data. Further, technical experts unrelated to the project validated the model. As part of this exercise, external independent

health economists assessed the model via the preliminary independent model advice (PRIMA). Further details of the validation checks are presented in CS section B.3.10.2.

The key conclusions that the company drew from the validation exercise were:

- Any error identified in the model validation exercises were discussed and addressed;
- A range of extreme value tests reiterated the consistency in model behaviour.

4.3.8 Company cost effectiveness results

4.3.8.1 Base case population

Deterministic results

The company present their base case results in CS section B.3.7, comparing dupilumab with standard care alone for people with severe uncontrolled asthma with EOS ≥ 150 or FeNO ≥ 25, and at least 3 exacerbations in the previous year (and no mOCS at baseline). We reproduce the company's results in Table 86 below. These results incorporate a simple price discount for dupilumab.

Table 86 Deterministic results: base case EOS≥150 or FeNO≥25 and ≥3 exacerbations in previous year (non-mOCS), with discounted price for dupilumab

Technology	Cost	QALYs	ICER (£/QALY)
Standard care	[redacted]	[redacted]	Reference
Dupilumab	[redacted]	[redacted]	£28,087

Source: CS Table 89

This analysis includes standard care as the only comparator, although some people in the defined base case population would meet NICE criteria for access to other biologics. We discuss this in section 4.4.5.1 below and estimate results for subgroups of the company's base case not eligible for mepolizumab or for resulizumab.

Deterministic sensitivity analysis

The company briefly summarises their approach to Deterministic Sensitivity Analysis (DSA) in CS section B.3.6.2.1. The tornado plot for the base-case model results (CS Figure 37, reproduced in Figure 5 below) shows that the proportions of severe exacerbations that are fatal are key drivers of the model results. Other influential parameters are the unit cost of dupilumab, parameters that influence the long-term incidence of severe exacerbations under standard treatment and the constant in the age-related utility equation.

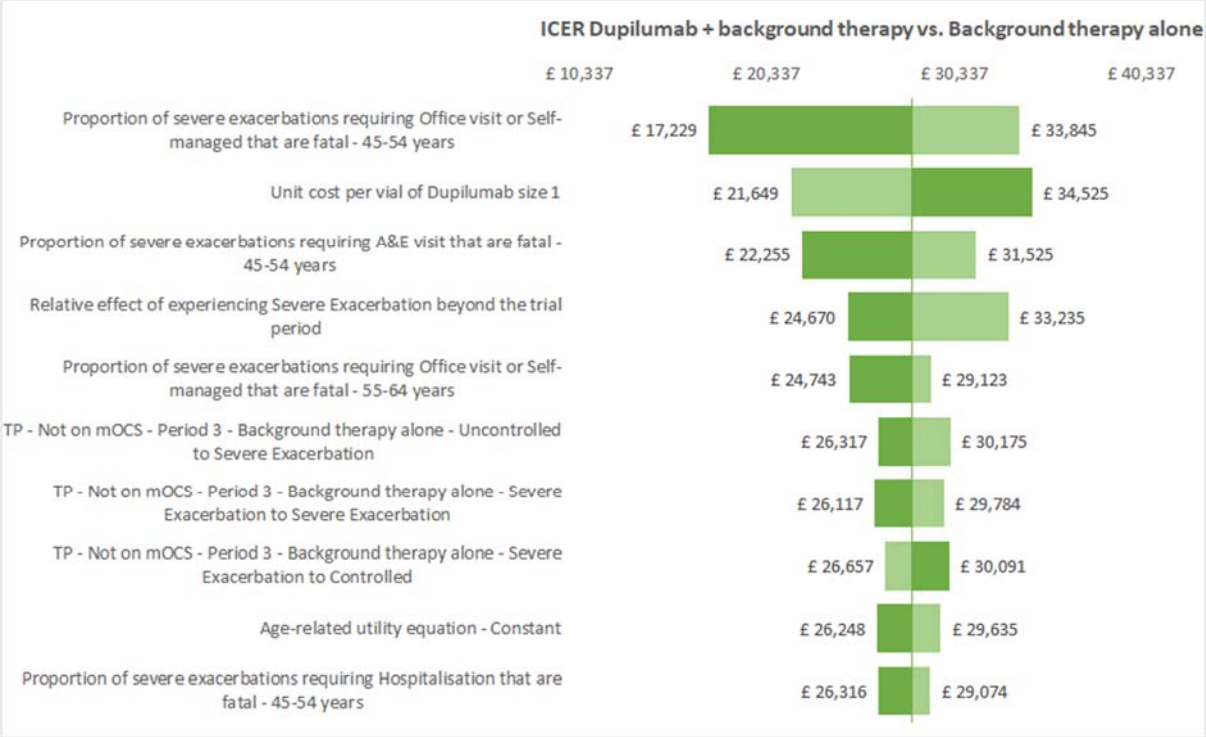


Figure 5 Tornado plot for base case analysis: EOS≥150 or FeNo≥25 and ≥3 exacerbations in previous year

Probabilistic sensitivity analysis

The company conducted a probabilistic sensitivity analysis (PSA) on their base-case model to assess parameter uncertainty. Assumptions used to characterise uncertainty are described in CS Section B.3.6.2.2 Table 86. Briefly, normal distributions are used for age and disutilities for exacerbations and AEs; gamma distributions for costs and resource quantities; log-normal distributions for relative effects on exacerbations, loss of control and mOCS-related AEs; beta distributions for utilities; and Dirichlet distributions for transition probabilities and setting of exacerbation.

Probabilistic results for the base case (CS Table 90) are similar to the deterministic results. The company provided a revised Cost-Effectiveness Acceptability Curve (CEAC) in response to clarification question B12. At a willingness-to-pay threshold of £30,000 per QALY gained, dupilumab had an estimated 51.2% probability of being cost-effective compared to standard care alone.

Scenario analysis

The company conducted scenario analysis to assess the impact of key variables on base case cost-effectiveness (CS Table 91 and Table 87 below). They concluded that cost effectiveness was pre-dominantly influenced by:

- Asthma-related mortality (proportion of severe exacerbations that are fatal)
- Assumptions about the rate of exacerbations after the clinical trial period
- Additional costs to the NHS after patients' discharge from hospital
- The discount rate for health effects
- Reduction in the model time horizon

The estimated ICERs for dupilumab compared with standard care alone in the base case population were below £30,000 per QALY in most of the modelled scenarios. We note two particular exceptions:

- Lower background rates of severe exacerbation after the trial (rate as observed in trial or with multiplier less than 1.35)
- Lower proportions of people with severe exacerbations treated in A&E or with hospitalisation (as in TA431 submission or as observed in QUEST ITT analysis)

The model is sensitive to these uncertain parameters. ICERs were also above £30,000 per QALY in the following scenarios:

- No response assessment at one year
- No excess mortality for asthma
- Short time horizon

These scenarios are useful for illustrative purposes but are not realistic or appropriate for the NICE reference case.

Table 87 Company scenario: base case, EOS≥150 or FeNO≥25 and ≥3 exacerbations in previous year (non-mOCS), discounted price for dupilumab

Scenario	Treatment	Cost	QALYs	ICER (£/QALY)
Base-case	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£ 28,087
Transition probabilities (Base case: QUEST data, CS Appendix M.1 Table 73)				
Separate exacerbation rates for weeks 0-12 and 12-52	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£ 26,869
No adjustment for null events	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£ 27,626
Post-trial severe exacerbation rate (Base case: multiplier [redacted], CS Appendix M.2.1)				
Pre-trial rates (1.813)	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£ 23,538
Adjusted for exclusion criterion & exacerbation definition ([redacted])	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£ 25,434
Mepolizumab appraisal (1.35)	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£ 30,009**
Observed in trial (1.00)	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£ 41,272**
Response and discontinuation (Base case: [redacted] response then 10.73% stop per year, CS B.3.3.4 and B.3.3.5)				
Annual discontinuation 0%	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£ 26,115
Annual discontinuation 10%	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£ 27,927
Alternative continuation rule (stop if not controlled for 12 months)	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£ 28,988
No response assessment	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£ 32,939**
Severe exacerbation fatality rate by setting (Base case: CS Table 56, from TA565)				
Mepolizumab submission	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£ 25,921

Scenario	Treatment	Cost	QALYs	ICER (£/QALY)
No excess mortality for asthma	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£ 71,950
Setting of severe exacerbations (Base case: CS Table 80, from O'Neill et al. 2015 73.56% office or self-managed, 7.79% A&E, 18.65% hospital)				
MENSA ITT, TA431 submission (83.07%, 8.69%, 8.24%)	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£ 30,425**
QUEST ITT (in model) (93.34%, 3.00%, 3.66%)	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£ 35,448**
Control utilities (QUEST EQ-5D: controlled 0.906, uncontrolled 0.735, CS Table 60)				
Willson et al. 2014[27] (0.922, 0.728)	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£ 27,201
QUEST AQL-5D mapping (0.943, 0.801)	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£ 28,133
Severe exacerbation utility loss (Base case: QUEST CS Tables 63 and 67)				
Utilities from Lloyd et al. 2007[28] (CS Table 65) for 28 days	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£ 25,601
Disutilities from Lloyd et al. (CS Table 64 & 65) for 28 days	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£ 27,274
Duration assumption from Lloyd et al. : 28 days	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£ 27,692
Post-acute hospitalisation costs (Base case £0, CS Table 81)				
Resource use after hospitalisation (£2,204)	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£ 23,742
General settings				
Discount health effects 1.5%	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£ 21,446
Time horizon 10 years	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£ 46,645**
Time horizon 5 years	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£ 62,536**

Source: Adapted from CS Table 91 by ERG with additional information from CS and model

4.3.8.2 Mixed mOCS/ non mOCS scenario

Deterministic results

CS Table 92 reports deterministic results for the mix of people taking mOCS with EOS150 or FeNO≥25 and (41.7%) and people not on mOCS with EOS≥150 or FeNO≥25 and at least 3 exacerbations in previous year (58.3%). The assumed proportion of patients on mOCS comes from a UK severe asthma registry[22], as used in the ERG analysis in TA565 (see section 4.3.2.1 above for discussion). We test the sensitivity of results to this parameter in section 4.4.5.2.

As in the base case, the company includes standard care as the only comparator. Although biologic add-on treatments are not available for everyone in this group, the EOS and prior exacerbation criteria do not have upper limits so there will be overlap with subgroups eligible for benralizumab, mepolizumab and/or reslizumab. See 4.4.5.1 for discussion and further analysis.

The analysis includes simple price discount for dupilumab. It can be seen that dupilumab is estimated to be less cost-effective in this mixed population (mOCS/ non-mOCS) than in the base case (no mOCS); with an ICER above £30,000 per QALY gained.

Table 88 Deterministic results: EOS≥150 or FeNO≥25 and ≥3 exacerbations in previous year or mOCS (41.7%), discounted price for dupilumab

Technology	Cost	QALYs	ICER (£/QALY)
Standard care	[redacted]	[redacted]	Reference
Dupilumab	[redacted]	[redacted]	**£ 35,486**

Source: CS Table 92

Deterministic sensitivity analysis

The DSA results for the mixed population are summarised in a tornado plot (CS Table 93, reproduced in Figure 6). This shows that the parameters with the greatest impact on the ICER in this population are: the proportions of severe exacerbations that are fatal; the unit cost of dupilumab, the multipliers for long-term severe exacerbation rates, the constant in the age-related utility equation and some of the transition probabilities beyond the trial period.

Probabilistic sensitivity analysis

The probabilistic results for the base case (CS Table 96) are similar to the deterministic results. At a willingness-to-pay threshold of £30,000 per QALY gained, dupilumab had an estimated 16.7% probability of being cost-effective compared to standard care alone.

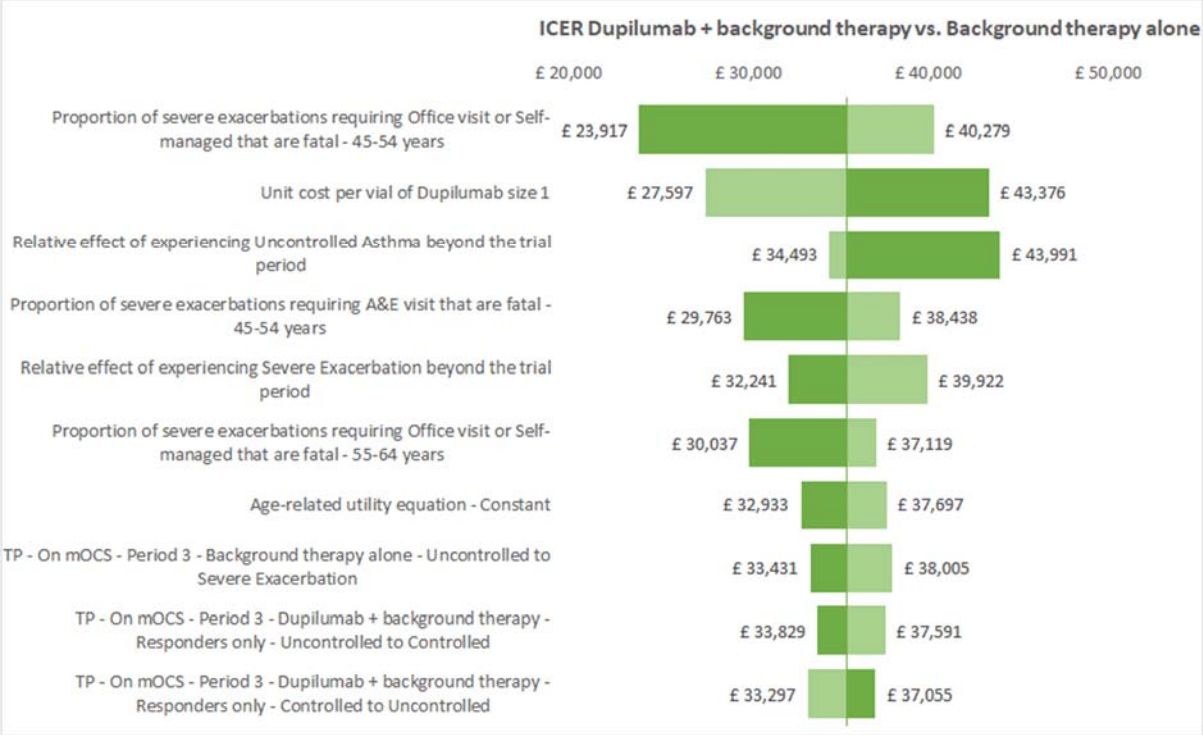


Figure 6 Tornado diagram: Dupilumab vs. standard care alone for EOS≥150 or FeNO≥25 and ≥3 exacerbations in previous year or mOCS

Scenario analysis

The company did not report scenario analyses for the mixed population, although the model includes the capacity to run the same range of scenarios as for the base case. This resulted in ICERs for dupilumab compared with standard care above £30,000 per QALY gained for all company scenarios except a discount rate of 1.5% for health effects (which does not meet current NICE Reference Case criteria).

4.3.8.3 Mepolizumab eligible subgroup

The results of the exploratory analysis for the subgroup that meet the NICE criteria for mepolizumab are shown in CS Appendix Q.1 Table 143 (reproduced in Table 89 below). This analysis includes a mix of people on mOCS with EOS≥300 (41.7%) and people not on mOCS with EOS≥300 and at least 4 exacerbations in the previous year (58.3%). The relevant comparators for this population are mepolizumab, benralizumab and standard care.

The company assumed the same proportion of people on mOCS as in their mixed population scenario (41.7%). There is uncertainty over this figure and the TA565 guidance noted that the ERG for that appraisal preferred an assumption of 60% of patients on mOCS for the mepolizumab comparison. We test the impact of different mOCS proportions in 4.4.5.2.

Relative effects of the biologics are based on the Bucher ITC analyses, with results from the MAIC in scenario analysis. There is a high degree of uncertainty over the estimates of relative effectiveness from both ITC and MAIC analysis (4.3.4.5).

The analysis includes a simple price discount for dupilumab and an assumed [redacted] price reduction for mepolizumab and benralizumab: we emphasise that this does not necessarily reflect actual prices paid in the NHS. The comparative cost-effectiveness results between biologics reported in this section are therefore only illustrative. We report results with all agreed PAS discounts in an Addendum to this report.

Table 89 Deterministic results: EOS ≥300 and ≥4 exacerbations or mOCS (41.7%), simple price discount for dupilumab and assumed [redacted] price discount for mepolizumab and benralizumab

Technology	Cost	QALY	ICER (£/QALY) incremental analysis	ICER (£/QALY) dupilumab vs. comparator
Standard care	[redacted]	[redacted]	-	£29,215
Mepolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Dupilumab	[redacted]	[redacted]	£ 29,215	Reference
Benralizumab	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS Table 143

The CS does not include scenario analyses for the mepolizumab eligible subgroup. The ERG ran the company's scenarios, which indicated:

- ICERs for dupilumab versus with standard care below £30,000 per QALY except under the following scenarios: time horizon 5 or 10 years; no response assessment; severe exacerbations after trial based on observed trial data; setting of severe exacerbations as in dupilumab or mepolizumab trials.

- ICERs for dupilumab compared with mepolizumab below £30,000 per QALY, except under the extreme scenarios of no asthma-related mortality or a very short time horizon of 5 years.
- Dupilumab was estimated to dominate benralizumab in all scenarios.

The company assumed the same proportion of people on mOCS as in their mixed population scenario (41.7%). However, there is uncertainty over this figure and the TA565 guidance noted that the ERG for that appraisal preferred an assumption of 60% of patients on mOCS for the mepolizumab comparison. We test the impact of different mOCS proportions in 4.4.5.2.

Relative effects of the biologics are based on the Bucher ITC analyses, with results from the MAIC used for scenario analysis. There is a high degree of uncertainty over the estimates of relative effectiveness from the ITC and MAIC analysis

4.3.8.4 Reslizumab eligible subgroup

Results for the comparison of dupilumab with reslizumab, benralizumab and standard care in the population who meet NICE criteria for reslizumab (EOS ≥400 and ≥3 exacerbations in the previous year) are reported in CS Appendix Q.2. We show the deterministic results, including pairwise and incremental ICERs in Table 90 below. As above, these results include a confidential PAS discount for dupilumab and an assumed discount of [redacted] for the other biologics. Based on these and other assumptions, dupilumab is dominates benralizumab and reslizumab (it costs less and has better effectiveness results). The ICER for dupilumab compared with standard care is below £30,000 per QALY.

Table 90 Deterministic results: EOS ≥400 and ≥3 exacerbations in previous year, confidential price discount for dupilumab and assumed price discount of [redacted] for benralizumab and reslizumab

Technology	Cost	QALY	ICER (£/QALY) incremental analysis	ICER (£/QALY) dupilumab vs. comparator
Standard care	[redacted]	[redacted]	Reference	£23,923
Dupilumab	[redacted]	[redacted]	£ 23,923	Reference
Benralizumab	[redacted]	[redacted]	[redacted]	[redacted]
Reslizumab	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS Table 148

The CS does not include scenario analysis around these results. The ERG ran the company's scenarios, which indicate that:

- The ICER for dupilumab compared with standard care is below £30,000 per QALY except for the extreme scenarios: very short time horizon (5 or 10 years); and no asthma-relate mortality.
- Dupilumab dominated benralizumab except for the scenario with the alternative long-term continuation rule (ICER [redacted] per QALY)
- Dupilumab dominated reslizumab or had a very low ICER across all scenarios.

4.3.8.5 Summary of company cost-effectiveness results

Base case analysis

The company base case compares dupilumab with standard treatment alone for people with severe asthma driven by Type 2 inflammation, defined by EOS≥150 or FeNO≥25 and at least 3 exacerbations in the previous year and not taking mOCS. The company's base case ICER is £28,087 per QALY gained. Probabilistic analysis indicates that the chance that the treatment would be cost-effective at a threshold of £30,000 per QALY is 51%. Other sensitivity and scenario analysis show that long-term rates of severe exacerbations and mortality are important drivers for the economic model.

In particular, we note that the ICER is sensitive to three key inputs to the economic model:

- The proportions of severe exacerbations that are fatal (by patient age and location of treatment: A&E attendance, hospital admission or other);
- The proportions of people with severe exacerbations who are treated in A&E or in hospital; and
- The relative rate of severe exacerbations after the clinical trial period, compared with the observed rates during the trial.

Mixed mOCS/ non mOCS scenario

The company also compared dupilumab with standard care alone in a mixed population with EOS≥150 or FeNO≥25 and at least 3 exacerbations in the previous year (58.7%) or mOCS (41.3%). Dupilumab appeared less cost-effective in this context than in the base case. The ICER for the mixed mOCS/ non mOCS population was £35,486 per QALY gained, with an

estimated probability of 16.7% of the ICER being above £30,000 per QALY. This result was robust to scenarios that are clinically appropriate and meet the NICE reference case.

Comparative analyses for people who are eligible for other biologics

Exploratory analyses comparing dupilumab against other biologic treatments are presented in appendices to the CS. Two sets of analysis are reported, one for people who meet NICE criteria for access to mepolizumab (EOS≥300 and at least 4 exacerbations in the previous year or taking mOCS) and the other for people meeting NICE criteria for reslizumab (EOS≥300 and at least 4 exacerbations in the previous year). Benralizumab was included as a comparator in both analyses, as it is also recommended for both subgroups. The results suggest that dupilumab is cost-effective in both contexts, either dominating or with ICERs below £30,000 per QALY gained versus all comparators.

However, the company urges caution in drawing conclusions from these results, due to limitations in the indirect comparisons. We also emphasise that these analyses are based on a confidential PAS price discount for dupilumab and an *assumed* price discount for the other biologics ([redacted] of list price), which does not reflect true prices paid in the NHS. We present results with agreed PAS price discounts for comparators as well as dupilumab in a confidential addendum to this report.

4.4 Additional work undertaken by the ERG

4.4.1 ERG model validation

4.4.1.1 Process of model checking

The ERG conducted a range of model checks:

- Comparison of input parameter values reported in the CS with values in the model, and where relevant with external sources. This identified two discrepancies:
    - Differences in the transition probability matrices estimated from VENTURE for the mOCS groups as reported in CS Appendix M Table 74 and in the model. The model reports numbers of transitions between each pair of states and calculations for the adjustments described in section 4.3.4.1 above. We confirm that the probabilities used the model are correct according to these reported numbers of transitions.

  - The costs for mOCS-related adverse events in CS Table 83 differed from the values used in the model. The company confirmed in Clarification Response B11 that the values in the model are correct.

- We checked all model results reported in the CS against live model outputs. All results were successfully replicated with the exception of two sensitivity analysis graphs: the CEAC in CS Figure 39 and the tornado diagram in CS Table 93. The differences were explained in the Clarification Responses.

- Manual checks on links and calculations from input data, to model parameters, the Markov engine sheets and results calculations. This included checks on calculations and adjustments used to estimate the transition probabilities, long-term exacerbation and small group multipliers and the relative risks for other biologics.

No important errors were identified and we have not made any corrections to the submitted model.

4.4.2 Face validity of model projections

The following tables summarise the company's predicted outcomes for the four patient groups considered in the company submission. The tables show the proportions of patients in the five main health states included in the model: controlled asthma; uncontrolled asthma (but no exacerbations), moderate or severe exacerbation (at least one month) and death.

We asked our clinical advisors whether the projected levels of asthma control, exacerbations and mortality with standard care seemed realistic and whether the estimated improvements with dupilumab were plausible. In response, one expert said the results for standard care alone seemed 'overly dramatic', and that 20% mortality after 10 years would be very surprising. This led us to question whether the model assumptions regarding exacerbation-related deaths and extrapolation of severe exacerbation rates might be over-estimated. We address these issues in the ERG base case analysis (4.4.4).

Table 91 Model predictions for company base case population: EOS≥150 or FeNO≥25 and at least 3 exacerbations in last year (no maintenance OCS)

Year (mean age)	Controlled asthma	Uncontrolled asthma	Moderate exacerbation	Severe exacerbation	Death
Dupilumab with standard care					
Baseline (47)	0%	100%	0%	0%	0%
1 year (48)	47%	34%	13%	5%	1%
5 years (52)	32%	37%	12%	14%	4%
10 years (57)	22%	37%	11%	18%	12%
Standard care alone					
Baseline (47)	0%	100%	0%	0%	0%
1 year (48)	29%	41%	11%	18%	1%
5 years (52)	11%	43%	11%	27%	9%
10 years (57)	9%	38%	10%	23%	20%

Table 92 Model predictions for company scenario: EOS≥150 or FeNO≥25 and maintenance OCS

Year (mean age)	Controlled asthma	Uncontrolled asthma	Moderate exacerbation [a]	Severe exacerbation	Death
Dupilumab with standard care					
Baseline (51)	0%	100%	-	0%	0%
1 year (52)	40%	52%	-	7%	1%
5 years (56)	37%	52%	-	7%	4%
10 years (61)	31%	52%	-	8%	10%
Standard care alone					
Baseline (51)	0%	100%	-	0%	0%
1 year (52)	12%	73%	-	15%	1%
5 years (56)	11%	69%	-	14%	6%
10 years (61)	10%	62%	-	13%	15%

a Estimates of moderate exacerbations not available from VENTURE trial

Table 93 Model predictions for mepolizumab eligible subgroup: EOS≥300 and ≥4 exacerbations in last year or mOCS (41.7%)

Year (mean age)	Controlled asthma	Uncontrolled asthma	Moderate exacerbation	Severe exacerbation	Death
Dupilumab with standard care					
Baseline (49)	0%	100%	0%	0%	0%
1 year (50)	50%	33%	11%	5%	1%
5 years (54)	35%	35%	12%	13%	4%
10 years (59)	26%	35%	10%	15%	13%
Standard care alone					
Baseline (49)	0%	100%	0%	0%	0%
1 year (50)	21%	49%	9%	20%	1%
5 years (54)	10%	46%	9%	25%	9%
10 years (59)	9%	40%	8%	22%	22%

Table 94 Model predictions for reslizumab eligible population: EOS≥400 and and ≥3 exacerbations in last year (no mOCS)

Year (mean age)	Controlled asthma	Uncontrolled asthma	Moderate exacerbation	Severe exacerbation	Death
Dupilumab with standard care					
Baseline (49)	0%	100%	0%	0%	0%
1 year (50)	53%	31%	11%	4%	0%
5 years (54)	37%	32%	11%	15%	4%
10 years (59)	24%	32%	10%	19%	14%
Standard care alone					
Baseline (49)	0%	100%	0%	0%	0%
1 year (50)	26%	42%	9%	21%	1%
5 years (54)	11%	40%	9%	30%	10%
10 years (59)	9%	33%	8%	25%	24%

4.4.3 ERG additional scenarios on company base case

We added four scenarios to the company's analysis:

1) **Utility limited to the general population mean**
   It lacks face validity to assume that people with severe asthma have a better quality of life than the average for people of the same age and gender, even when the asthma is controlled. We therefore added an option to the model to restrict the utility for the controlled health state to the general population mean. This is estimated in the model with adjustment for age and gender by the Ara and Brazier equation (CS Table 61).[31] The utility for the uncontrolled health state is then estimated with a decrement relative to the controlled asthma utility.

2) **Discontinuation during first year**
   The base case model assumes no discontinuation of add-on therapies before the response assessment at 52 weeks. In practice, some patients will inevitably stop treatment before this time, due to adverse events, other clinical factors or patient choice. We therefore included an option to allow treatment discontinuation before the response assessment, with the same constant monthly discontinuation rate estimated from the clinical trials that is used to model ongoing discontinuation after the response assessment.

3) NHS Reference Costs for health care unit costs
   As noted in section 4.3.6.3 above, we prefer consistent use of NHS Reference Costs, rather than NHS Tariff values, for the unit costs of healthcare resources. The submitted model included Tariff costs for A&E (£143.57) and severe exacerbation related hospitalisations (£1,646.26). For completeness, we add a scenario replacing these costs with Reference Cost estimates of £176.26 and £1,579.45.

4) Subcutaneous injections by healthcare professional
   The company assumed that the first three doses of drugs administered by subcutaneous injection (dupilumab, mepolizumab and benralizumab) would be administered by a healthcare professional, with self-administration (at no cost) after then. Self administration is new in this indication so may take time to implement. An ERG expert questioned how patients would collect and store the drug at home, how training would be provided and noted that high placebo effects for biologics may (in part) be due to regular healthcare professional contact. We test the impact of assuming ongoing professional administration of all subcutaneous injections.

Results for the four patient groups presented in the company submission are shown in Table 95 to Table 98. The scenarios lead to small to modest changes in the ICERS,

Table 95 ERG additional scenarios: company base case

Company base case and additional ERG scenarios	Treatment	Cost	QALYs	ICER (£/QALY)r
EOS>=150 or FeNO>=25 & >=3 exacerbations				
Company base case	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£28,087
Utility limited to general population mean	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£29,721
Include discontinuation in first year	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£27,974
Reference costs for A&E and hospitalisation	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£28,152
Subcutaneous injections by healthcare professional	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£28,973

Table 96 ERG additional scenarios; company mixed mOCS/ non-mOCS

Company base case and additional ERG scenarios	Treatment	Cost	QALYs	ICER (£/QALY)r
EOS>=150 or FeNO>=25 & >=3 exacerbations or mOCS (41.7%)				
Company base case	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£35,486**
Utility limited to general population mean	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£37,277**
Include discontinuation in first year	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£35,430**
Reference costs for A&E and hospitalisation	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£35,544**
Subcutaneous injections by healthcare professional	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£36,579**

Table 97 ERG additional scenarios; mepolizumab eligible patients

Company base case and additional ERG scenarios	Treatment	Cost	QALYs	ICER (£/QALY) dupilumab vs. comparator
EOS>=300 & >=4 exacerbations or mOCS (41.7%)				
Company base case	Standard care	[redacted]	[redacted]	£29,215
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
Utility limited to general population mean	Standard care	[redacted]	[redacted]	**£31,817**
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
Include discontinuation in first year	Standard care	[redacted]	[redacted]	£29,169
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
Reference costs for A&E and hospitalisation	Standard care	[redacted]	[redacted]	£29,271
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
Subcutaneous injections by healthcare professional	Standard care	[redacted]	[redacted]	**£30,122**
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]

Table 98 ERG additional scenarios; reslizumab eligible patients

Company base case and additional ERG scenarios	Treatment	Cost	QALYs	ICER (£/QALY)
EOS>=400 & >=3 exacerbations (no mOCS)				
Company base case	Standard care	[redacted]	[redacted]	£23,923
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
	Reslizumab	[redacted]	[redacted]	[redacted]
Utility limited to general population mean	Standard care	[redacted]	[redacted]	£25,696
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
	Reslizumab	[redacted]	[redacted]	[redacted]
Include discontinuation in first year	Standard care	[redacted]	[redacted]	£23,844
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
	Reslizumab	[redacted]	[redacted]	[redacted]
Reference costs for A&E and hospitalisation	Standard care	[redacted]	[redacted]	£23,988
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
	Reslizumab	[redacted]	[redacted]	[redacted]
Subcutaneous injections by healthcare professional	Standard care	[redacted]	[redacted]	£24,696
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
	Reslizumab	[redacted]	[redacted]	[redacted]

4.4.4 ERG base case analysis

4.4.4.1 Justification for ERG assumptions

We made the following five changes to the company's base case.

1) No adjustment to the long-term rate of severe exacerbations

The company apply a multiplier of [redacted] to increase severe exacerbation rates after the trial period. This is intended to adjust for the exclusion of patients with a recent severe exacerbation from the clinical trials, as the company argue this will have reduced the incidence of severe exacerbations during the trial period below the background rate for the patient population. We acknowledge that this may be a consideration. However, the has a large impact on the modelled rates of exacerbations and is subject to high uncertainty. We note that in other appraisals, no or lower adjustments were made to long term exacerbation rates. The NICE Committee for the appraisal of reslizumab (TA479) concluded that despite reductions in observed exacerbation rates for patients randomised to placebo and active treatment "*adjusted rates were no more likely than the unadjusted rates to reflect the true treatment benefit*". Therefore no adjustment was made to long-term exacerbation rates in TA479 or the subsequent TA565. The earlier appraisal of mepolizumab used a lower multiplier for background exacerbation (1.35).

2) Treatment settings for severe exacerbations from clinical trial data

We consider the trial data to be a better source for estimation of the proportions of patients with severe exacerbations treated in emergency care and inpatient settings. This is because the definitions of severe exacerbation events will be consistent with the clinical data used in the model, and the method of ascertainment is likely to be more complete than for a registry based on routine clinical data.

3) Utility limited to general population mean (by age)

The assumption of better quality of life with controlled asthma than for age/gender matched general population lacks face validity. We therefore constrain the utility for the controlled asthma health state to a maximum of the general population mean, and use a decrement to estimate the utility for uncontrolled asthma.

4) Include discontinuation during first year of treatment

We consider it unrealistic to assume no discontinuation before 12 month assessment, so include a constant rate of discontinuation as observed in the trials before as well as after the 12 month response assessment.

5) **Reference Costs for healthcare unit costs**

For consistency, we apply reference costs for emergency visits and inpatient stays, although this will have negligible impact on cost-effectiveness results.

4.4.4.2 ERG results for company base case population

The cumulative impact of the above five changes for patients with EOS>=150 or FeNO>=25 & >=3 exacerbations is shown in Table 99. This shows that the largest change is due to removing the multiplier to inflate post-trial severe exacerbation rates. The assumption about the distribution of treatment location for people with severe exacerbations. The next table (Table 100) shows the effects of applying selected scenario analyses that we consider plausible alternatives to the ERG base case (one at a time). The ICERs remain above £30,000 per QALY in all of these scenarios.

Table 99 Cumulative change from company to ERG base case

Additional ERG scenarios	Treatment	Cost	QALYs	ICER (£/QALY)
EOS>=150 or FeNO>=25 & >=3 exacerbations				
Company base case	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£28,087
+ Long term severe exacerbation rate: trial data (multiplier=1)	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£41,272**
+ Distribution of treatment for severe exacerbation: clinical trials	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£52,327**
+ Limit utility to general population mean	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£55,400**
+ Include discontinuation in first year	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£55,338**
ERG base case	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£55,348**

Table 100 ERG base case and scenarios: base case population

ERG base case & scenarios	Treatment	Cost	QALYs	ICER (£/QALY)
EOS>=150 or FeNO>=25 & >=3 exacerbations				
ERG base case	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£55,348**
Post-trial severe exacerbation rate				
Trial inclusion multiplier ([redacted])	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£37,533**
Combined trial inclusion and exacerbation definition multiplier ([redacted])	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£34,040**
Mepolizumab appraisal multiplier (1.35)	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£40,119**
Setting of severe exacerbations				
Distribution from O'Neill et al. 2015	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£43,549**
Distribution from MENSA ITT, TA431 submission	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£46,619**
Response and discontinuation				
No discontinuation in first year	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£55,410**
Alternative continuation rule	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£55,625**
Control utilities				
Absolute utility estimates from QUEST EQ-5D	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£52,278**

4.4.4.3 ERG results for mepolizumab eligible subgroup

The ERG base case and scenarios are applied to people who are eligible for mepolizumab

Table 101 ERG base case and scenarios: mepolizumab eligible subgroup

ERG base case & scenarios	Treatment	Cost	QALYs	ICER (£/QALY) dupilumab vs. comparator
EOS>=300 & >=4 exacerbations or mOCS (41.7%)				
ERG base case	Standard care	[redacted]	[redacted]	**£48,866**
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
Post-trial severe exacerbation rate				
Trial inclusion multiplier ([redacted])	Standard care	[redacted]	[redacted]	**£38,363**
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
Combined trial inclusion and exacerbation definition multiplier ([redacted])	Standard care	[redacted]	[redacted]	**£35,805**
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
Mepolizumab appraisal multiplier (1.35)	Standard care	[redacted]	[redacted]	**£39,937**
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
Setting of severe exacerbations				
Distribution from O'Neill et al. 2015	Standard care	[redacted]	[redacted]	**£40,592**
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
Distribution from MENSA ITT, TA431 submission	Standard care	[redacted]	[redacted]	**£46,851**
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]

ERG base case & scenarios	Treatment	Cost	QALYs	ICER (£/QALY) dupilumab vs. comparator
Response and discontinuation				
No discontinuation during first year	Standard care	[redacted]	[redacted]	**£48,876**
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Benralizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	*Reference*
Alternative continuation rule	Standard care	[redacted]	[redacted]	**£48,773**
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Benralizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	*Reference*
Control utilities				
Absolute utility estimates from QUEST EQ-5D	Standard care	[redacted]	[redacted]	**£45,133**
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
Relative effects				
MAIC (where available)	Standard care	[redacted]	[redacted]	**£48,866**
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
MAIC label population for mepolizumab	Standard care	[redacted]	[redacted]	**£48,866**
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
Reimbursement submissions for responders	Standard care	[redacted]	[redacted]	£48,866
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]

4.4.4.4 ERG results for reslizumab eligible subgroup

Table 102 ERG base case and scenarios: reslizumab eligible subgroup

ERG base case & scenarios	Treatment	Cost	QALYs	ICER (£/QALY) dupilumab vs. comparator
EOS>=400 & >=3 exacerbations				
ERG base case	Standard care	[redacted]	[redacted]	**£45,706**
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
	Reslizumab	[redacted]	[redacted]	[redacted]
Post-trial severe exacerbation rate				
Trial inclusion multiplier ([redacted])	Standard care	[redacted]	[redacted]	**£33,679**
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
	Reslizumab	[redacted]	[redacted]	[redacted]
Combined trial inclusion and exacerbation definition multiplier ([redacted])	Standard care	[redacted]	[redacted]	**£30,717**
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
	Reslizumab	[redacted]	[redacted]	[redacted]
Mepolizumab appraisal multiplier (1.35)	Standard care	[redacted]	[redacted]	**£35,429**
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
	Reslizumab	[redacted]	[redacted]	[redacted]
Setting of severe exacerbations				
Distribution from O'Neill et al. 2015	Standard care	[redacted]	[redacted]	**£34,848**
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
	Reslizumab	[redacted]	[redacted]	[redacted]
Distribution from MENSA ITT, TA431 submission	Standard care	[redacted]	[redacted]	**£44,099**
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
	Reslizumab	[redacted]	[redacted]	[redacted]

ERG base case & scenarios	Treatment	Cost	QALYs	ICER (£/QALY) dupilumab vs. comparator
Response and discontinuation				
No discontinuation during first year	Standard care	[redacted]	[redacted]	**£45,735**
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
	Reslizumab	[redacted]	[redacted]	[redacted]
Alternative continuation rule	Standard care	[redacted]	[redacted]	**£46,393**
	Benralizumab	[redacted]	[redacted]	[redacted]
	Reslizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	*Reference*
Control utilities				
Absolute utility estimates from QUEST EQ-5D	Standard care	[redacted]	[redacted]	**£42,577**
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
	Reslizumab	[redacted]	[redacted]	[redacted]
Relative effects				
MAIC (where available)	Standard care	[redacted]	[redacted]	**£45,706**
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
	Reslizumab	[redacted]	[redacted]	[redacted]
Reimbursement submissions for responders	Standard care	[redacted]	[redacted]	**£45,706**
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
	Reslizumab	[redacted]	[redacted]	[redacted]

4.4.5 ERG additional subgroups

4.4.5.1 Estimates for patients not eligible for other biologics

Given the information available in the CS and model it is not possible to calculate results for people in the company's target population for dupilumab for whom standard care would be the only current treatment option. But this can be approximated, by taking a weighted difference between the results for the base case population and subgroups who are eligible either for mepolizumab or reslizumab.

For example, the company reports that 36 out of 101 patients in the target population for dupilumab (in the combined placebo and 200mg arms of QUEST with EOS>=150 & >=3 exacerbations) were eligible for mepolizumab (EOS>=300 & >=4 exacerbations) (CS P.1.1.1). From the model we estimate costs and QALYs for the whole target population and also for the mepolizumab-eligible subgroup. Assuming that the latter group are 35.6% (36/101) of the target population we can estimate costs and QALYs for the residual non-mepolizumab-eligible subset of the target group.

We report ERG analysis results for the company's base case population excluding patients who meet NICE access criteria for mepolizumab and reslizumab in Table 103 and Table 104 respectively. This shows that dupilumab is likely to be less cost-effective (with higher ICERs) if people who are already suitable for treatment with other biologics are excluded from the company's target population. This doesn't change the substantive conclusions in the ERG analysis, as all ICERs are above the £30,000 per QALY threshold. However, it does illustrate the TA565 Committee's conclusion that cost-effectiveness results from a mixed population with a range of asthma severity is not suitable for decision making. However, we emphasise that the analyses below are only approximations, because they do not account for the overlap of people who meet access criteria for both reslizumab and mepolizmuab. Additional data would be required for a more accurate assessment of the cost-effectiveness of dupilumab in patients for whom standard care is the only treatment option.

Table 103 ERG base case and scenarios: not mepolizumab eligible

ERG base case & scenarios	Treatment	Cost	QALYs	ICER (£/QALY)
Base case population excluding patients eligible for mepolizumab (35.6%, 36/101)				
ERG base case	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£58,387**
Post-trial severe exacerbation rate				
Trial inclusion multiplier ([redacted])	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£38,404**
Combined trial inclusion and exacerbation definition multiplier ([redacted])	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£34,730**
Mepolizumab appraisal multiplier (1.35)	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£41,291**
Setting of severe exacerbations				
Distribution from O'Neill et al. 2015	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£46,940**
Distribution from MENSA ITT, TA431 submission	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£47,200**
Response and discontinuation				
No discontinuation during first year	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£58,465**
Alternative continuation rule	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£59,541**
Control utilities				
Absolute utility estimates from QUEST EQ-5D	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£55,219**

Table 104 ERG base case and scenarios: not reslizumab eligible

ERG base case & scenarios	Treatment	Cost	QALYs	ICER (£/QALY)
Base case population excluding patients eligible for reslizumab (46.5%, 47/101)				
ERG base case	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£68,542**
Post-trial severe exacerbation rate				
Trial inclusion multiplier ([redacted])	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£41,933**
Combined trial inclusion and exacerbation definition multiplier ([redacted])	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£37,789**
Mepolizumab appraisal multiplier (1.35)	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£45,653**
Setting of severe exacerbations				
Distribution from O'Neill et al. 2015	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£55,999**
Distribution from MENSA ITT, TA431 submission	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£49,254**
Response and discontinuation				
No discontinuation during first year	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£68,659**
Alternative continuation rule	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£88,708**
Control utilities				
Absolute utility estimates from QUEST EQ-5D	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£66,001**

4.4.5.2 Sensitivity to the proportion of patients on mOCS

Finally, we assess the sensitivity of results for mixed populations to the proportion of people taking mOCS. The company assumes 41.7% in their mixed analyses: in both the standard care only comparison (EOS>=150 or FeNO>=25) and the mepolizumab eligible comparison (EOS>=300). However, the TA565 NICE committee noted that it is difficult to determine the proportion of patients taking mOCS in practice. We test the sensitivity of the company's base case results and mepolizumab-based comparison in Table 105 and Table 106, respectively. These analyses do demonstrate sensitivity to this parameter, particularly in the group with less severe asthma (EOS>=150 or FeNO>=25), for whom treatment of patients on mOCS but without the additional risk factor of at least 3 exacerbations in the previous year is not cost-effective (ICER for dupilumab compared with standard care only was over £45,000 per QALY). However, the results in the mepolizumab eligible group are quite stable over a wide range of estimates for the proportion on mOCS.

Table 105 Sensitivity to the proportion of mOCS: company base case

Additional ERG scenarios	Treatment	Cost	QALYs	ICER (£/QALY)
EOS>=150 or FeNO>=25 & >=3 exacerbations or mOCS				
Base case (0% mOCS)	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£28,087
Proportion mOCS = 20%	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£31,682
Proportion mOCS = 41.7%	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£35,486
Proportion mOCS = 60%	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£38,620
Proportion mOCS = 100%	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£45,240

Table 106 Sensitivity to the proportion of mOCS: mepolizumab comparison

Additional ERG scenarios	Treatment	Cost	QALYs	ICER (£/QALY) dupilumab vs. comparator
EOS>=300 & >=4 exacerbations or mOCS				
Base case (0% mOCS)	Standard care	[redacted]	[redacted]	£25,661
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
Proportion mOCS = 20%	Standard care	[redacted]	[redacted]	£27,543
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	Reference
	Benralizumab	[redacted]	[redacted]	[redacted]
Proportion mOCS = 41.7%	Standard care	[redacted]	[redacted]	£29,215
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	Reference
	Benralizumab	[redacted]	[redacted]	[redacted]
Proportion mOCS = 60%	Standard care	[redacted]	[redacted]	£30,397
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	Reference
	Benralizumab	[redacted]	[redacted]	[redacted]
Proportion mOCS = 100%	Standard care	[redacted]	[redacted]	£32,459
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	Reference
	Benralizumab	[redacted]	[redacted]	[redacted]

4.4.6 Summary of ERG analysis results

Additional scenarios on the company's base case

The ERG conducted four additional scenario analyses to assess the robustness of the company's base case analysis.

- Utility for controlled asthma limited to the age-related general population mean
- Discontinuation of add-on biologic treatments at the same rate as observed in the clinical trial before the 12 month response assessment as well as after
- NHS Reference costs as source for unit cost estimates for A&E attendances and hospitalisation for severe exacerbation
- No self-administration of subcutaneous injections

The company's results were generally robust to these assumptions, across all four patient patient subgroups (base case, mixed mOCS/ non mOCS, mepolizumab eligible and reslizumab eligible). Capping utility at the general population mean led to a modest increase in the ICERs of around £1,000 to £2,000 per QALY. The other scenarios led to only small changes in the ICERs.

ERG base case and scenarios

We included five changes to the company base case in our preferred analysis:

6) No adjustment to severe exacerbation rates after the trial period
7) Distribution of treatment settings for severe exacerbations based on trial data
8) Utility for controlled asthma limited to the age-related general population mean
9) Discontinuation of add-on biologic treatments at the same rate as observed in the clinical trial before the 12 month response assessment as well as after
10) NHS Reference costs as source for unit cost estimates for A&E attendances and hospitalisation for severe exacerbation

The first two changes led to a sizeable increase in the estimated ICERs. The cap on utility led to a modest increase and the impact of the discontinuation and cost changes were negligible. The resulting ERG base case ICER for dupilumab compared with standard care alone in the company's target population (EOS≥150 or FeNO≥25 and ≥3 prior exacerbations) was £55,348 per QALY gained. This estimate remained above £30,000 per QALY gained across a range of scenarios, including use of the company's base case

multiplier for the long-term rate of severe exacerbations ([redacted]) which reduced the ICER to £37,533.

ERG subgroup analysis

The company's results for the mixed population are sensitive to the proportion of patients taking mOCS at baseline. The company's base case ICER increases from £28,087 with no mOCS patients; to £31,682 with 20% mOCS; £35,486 with 41.7% mOCS; and £45,240 with 100% mOCS.

We also considered cost-effectiveness in subgroup for whom standard care is the only treatment option. We approximated this by taking a weighted difference between results for the company's target population (EOS≥150 or FeNO≥25 and ≥3 prior exacerbations) and a subgroup who meet NICE criteria for access to either mepolizumab or reslizumab. In both cases, the ICERs increase when patients who would be eligible for other biologics are excluded. This is not surprising, given that biologic treatment is estimated to be more cost-effective for people with more 'severe' asthma (as indicated by higher EOS levels or more prior exacerbations).

Results of the ERG base case and scenarios for the subgroups of patients who are eligible for treatment with other biologics, which include confidential PAS discounts for other comparators as well as dupilumab, are presented in a confidential addendum to this report.

5 End of life

Dupilumab is not considered an end-of-life treatment.

6 Innovation

The company point out in CS B.2.12 that the current biologic treatments for severe asthma target either IL-5 (e.g. reslizumab, mepolizumab, benralizumab) or IgE (e,g, omalizumab). Dupilumab however, inhibits two distinctly different pathways via inhibition of the IL-4Rα subunit that is shared by both IL-4 and IL-13 receptor complexes. This means that dupilumab targets a patient population that is different from the populations targeted by the other current biological therapies (although, as noted there is some overlap between the different patient populations).

The mode of action of dupilumab means that it reduces FeNO levels, whereas levels of EOS are not affected. In contrast, the company points out that a literature review (no citation provided) has demonstrated that the anti-IL5 biologics reduce EOS levels but do not reduce FeNO levels.

In the pivotal trials of dupilumab which underpin the CS (DRI12544, QUEST and VENTURE) asthma exacerbations were reduced, and lung function improved and, for patients in receipt of OCS at baseline, OCS use was reduced. The company highlight that the reduction of OCS use is a high priority because chronic OCS treatment is associated with a number of side effects.

Finally, the CS notes there are other diseases that are mediated by type 2 inflammation (atopic dermatitis, allergic nasal polyps and eosinophilic oesophatitis). Dupilumab is already indicated for the treatment of moderate to severe atopic dermatitis[39] and for patients with severe asthma who have comorbidities that are also mediated by type 2 inflammation, dupilumab treatment might have additional effects. The CS does not indicate what proportion of the severe asthma population might have such comorbidities. One of the clinicians we consulted stated in their severe asthma cohort 13.5% had coexistent eczema and atopic dermatitis.

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8 APPENDICES

Appendix 8.1: Supplementary information on the ITCs and MAICs

Table 107 Company's critical appraisal judgements for the trials contributing data to the ITCs

First author and year (Primary Reference Only)	Trial name (JP draft – yellow if data in ITC)	Randomisation[a]	Allocation concealment[b]	Baseline comparability[c]	Blinding[d]	Unexpected imbalances in drop outs between groups[e]	More outcomes than reported[f]	ITT analysis appropriate with appropriate methods for missing data[g]
Dupilumab trials								
Wenzel S 2016a	DRI	Yes	Yes	Yes	Yes	No	No	Yes
Castro M 2018b	QUEST	Yes	Yes	Yes	Yes	No	No	Yes
Rabe KF 2018	VENTURE	Yes	Unclear	Yes	Yes	No	No	Yes
Reslizumab trials								
Castro M 2015-1	BREATH 3082	Yes	Yes	Yes	Yes	No	No	Yes
Castro M 2015-2	BREATH 3083	Yes	Yes	Yes	Yes	No	No	Yes
Mepolizumab trials								
Ortega HG 2014	MENSA	Yes	Yes	Yes	Unclear	No	No	Yes
Chupp GL 2017	MUSCA	Yes	Yes	Yes	Yes	No	No	Yes
Pavord ID 2012	DREAM	Yes	Yes	Yes	Unclear	No	No	Yes
Bel EH 2014	SIRIUS	Yes	Yes	Unclear	Unclear	No	No	Yes
Benralizumab trials								
Bleecker ER 2016	SIROCCO	Yes	Yes	Yes	Unclear	No	No	Yes

FitzGerald JM 2016	CALIMA	Yes	Yes	Yes	Yes	No	No	Yes
Nair P 2017	ZONDA	Yes	Yes	Unclear	Unclear	No	No	Yes

Source: Appendix D.1.3
For all questions responses could be: yes; no; not clear; N/A
[a] Was randomisation carried out appropriately? [b] Was the concealment of treatment allocation adequate? [c] Were the groups similar at the outset of the study in terms of prognostic factors? [d] Were the care providers, participants and outcome assessors blind to treatment allocation? [e] Were there any unexpected imbalances in drop-outs between groups? [f] Is there any evidence to suggest that the authors measured more outcomes than they reported? [g] Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

Table 108 RCTs contributing data to each ITC outcome

ITC Outcome	ITC Dupilumab vs placebo vs reslizumab	ITC Dupilumab vs placebo vs mepolizumab	ITC Dupilumab vs placebo vs benralizumab
Uncontrolled persistent asthma population			
Severe exacerbations	QUEST subgroup matched to reslizumab label DRI12544 subgroup matched to reslizumab label BREATH RCTs (pooled 3082/3083)	QUEST subgroup matched to mepolizumab label DRI12544 subgroup matched to mepolizumab label MENSA RCT MUSCA RCT DREAM RCT	QUEST subgroup matched to benralizumab label DRI12544 subgroup matched to benralizumab label SIROCCO RCT CALIMA RCT
Severe exacerbations, NICE-like subgroup	QUEST matched to NICE-like reslizumab BREATH subgroup DRI12544 matched to NICE-like reslizumab BREATH subgroup BREATH NICE-like subgroup (poster 3082/3082)	QUEST matched to NICE-like mepolizumab MENSA subgroup DRI12544 matched to NICE-like mepolizumab MENSA subgroup NICE-like MENSA subgroup	N/A
Oral corticosteroid dependent asthma population			

Reduction in OCS dose <5 mg/day	N/A	VENTURE[a] SIRIUS	VENTURE[a] ZONDA
≥50% reduction in OCS dose	N/A	VENTURE[a] SIRIUS	VENTURE[a] ZONDA
100% reduction in OCS dose	N/A	VENTURE[a] SIRIUS	VENTURE[a] ZONDA
Severe exacerbations	N/A	VENTURE[a] SIRIUS	VENTURE[a] ZONDA

[a] ITCs were conducted using subgroup data for VENTURE matched to the comparator population and using ITT VENTURE data

Data sources for each ITC

The data used for each ITC was reported in CS Appendix N.6 Tables 91, 92, 94, 95, and 97-105. It is not clear to the ERG why for the severe exacerbations outcome there were some slight differences between the data in the tables and the data shown in the corresponding figures. In response to clarification question A15 the company explained that they had used trial arm-level (i.e. odds) as opposed to contrast-level (i.e. odds ratio) data in the analysis which explains the slight differences. Similarly, the ERG observed that in several of the tables in Appendix N (e.g. Appendix N Tables 94, 97, 101) a footnote stated "person years were calculated for all trials, except the dupilumab trials". The company were asked to clarify this statement and provide calculations (clarification question A16). The company responded that person years were estimated as number of years of follow up multiplied by number of patients analysed (Clarification response Tables 4 to 9).

Appendix 8.2: Detailed MAIC results

Table 109 MAIC results: Severe exacerbations. Dupilumab versus mepolizumab

Comparator trials	Data filters applied to dupilumab pooled data	DRI12544 and QUEST pooled data before filtering		Pooled data remaining after filtering, n	Effective sample size after matching	% Effective sample size reduction (from relevant sample size)	MAIC results: Severe exacerbations Rate ratio (95% CI)	Overall Dupilumab vs mepolizumab Rate ratio (95% CI)
		Trial arms	Total size, n					
MENSA (ITT)	- Medium or High ICS/LABA below 18 years and High/LABA over 18 years - Number of exacerbations in the past year ≥2	Dupilumab 200mg	781	223	197	11.6%	Dupilumab vs MENSA 0.75 (0.48, 1.18)	**0.74 (0.56, 0.99)**
		Placebo	796	150	144	4%		
DREAM	- High ICS/LABA - Number of exacerbations in the past year ≥2	Dupilumab 200mg	781	213	162	23.9%	Dupilumab vs DREAM 0.58 (0.32, 1.05)	
		Placebo	796	142	64	54.9%		
MUSCA (ITT)	- Medium or High ICS/LABA below 18 years and High ICS/LABA over 18 years - Number of exacerbations in the past year ≥2	Dupilumab 200mg	781	223	192	13.9%	Dupilumab vs MUSCA 0.86 (0.54, 1.37)	
		Placebo	796	150	120	20%		

Source: CS Appendix O Tables 106, 116 and Appendix O Figure 47

Table 110 MAIC results: Severe exacerbations. Dupilumab versus mepolizumab MENSA subgroup

Comparator trials	Data filters applied to dupilumab pooled data	DRI12544 and QUEST pooled data before filtering		Pooled data remaining after filtering, n	Effective sample size after matching	% Effective sample size reduction (from relevant sample size)		Overall Dupilumab vs mepolizumab Rate ratio (95% CI)
		Trial arms	Total size, n					
MENSA (Subgroup) EOS ≥300 in past year and ≥4 exacerbations or mOCS	- Medium or High ICS/LABA below 18 years and High/LABA over 18 years - Number of exacerbations in the past year ≥2	Dupilumab 200mg	781	223	95	57.4%		
		Placebo	796	150	73	51.3%		**0.56 (0.31, 1.01)**

Source: CS Appendix O Tables 114, 117 and Appendix O Figure 48

Table 111 MAIC results: Severe exacerbations. Dupilumab versus benralizumab

Comparator trials	Data filters applied to dupilumab pooled data	DRI12544 and QUEST data before filtering		Dupilumab data remaining after filtering, n	Dupilumab effective sample size after matching	% Effective sample size reduction (from relevant sample size)	MAIC results: Severe exacerbations Rate ratio (95% CI)	Overall Dupilumab vs benralizumab Rate ratio (95% CI)
		Trial arms	Total size, n					
CALIMA (EOS ≥300)	- High ICS/LABA - Baseline blood EOS level ≥300 cells/µl - Number of exacerbations in the past year ≥2	Dupilumab 200mg	781	101	86	14.9%	0.49 (0.27, 0.9)	**0.59 (0.38, 0.89)**
		Placebo	796	68	50	26.5%		
SIROCCO (EOS ≥300)	- High ICS/LABA - Baseline blood EOS level ≥300 cells/µl - Number of exacerbations in the past year ≥2	Dupilumab 200mg	781	101	78	22.8%	0.69 (0.38, 1.24)	
		Placebo	796	68	61	10.3%		

Source: CS Appendix O Tables 106, 120 and Appendix O Figure 55

Table 112 MAIC results: Severe exacerbations. Dupilumab versus reslizumab

Comparator trials	Data filters applied to dupilumab pooled data	DRI12544 and QUEST pooled data before filtering		Dupilumab data remaining after filtering, n	Dupilumab effective sample size after matching	% Effective sample size reduction (from relevant sample size)		Overall Dupilumab vs reslizumab Rate ratio (95% CI)
		Trial arms	Total size, n					
BREATH 82-83	- Medium or High ICS/LABA - Baseline blood EOS level ≥400 cells/µl - Number of exacerbations in the past year ≥1	Dupilumab 200mg	781	238	219	7.6%		0.66 (0.42, 1.04)
		Placebo	796	156	122	21.8%		

Source: CS Appendix O Tables 106, 122 and Appendix O Figure 59

OCS dependent population

Table 113 MAIC results: Severe exacerbations, ≥50% reduction and 100% reduction in OCS dose . Dupilumab versus mepolizumab

Comparator trials	Data filters applied to dupilumab pooled data	VENTURE data before filtering		VENTURE data remaining after filtering, n	Effective sample size after matching	% Effective sample size reduction (from relevant sample size)	Outcomes	Overall Dupilumab vs mepolizumab MAIC result
		Trial arms	Total size, n					
SIRIUS ITT	High ICS/LABA	Dupilumab 200mg	103	103	50	51.5%	Severe exacerbations	RR 0.48 (95% CI 0.21, 1.1)
		Placebo	107	107	71	33.6%	≥50% reduction in OCS dose	OR 1.7 (95% CI 0.53, 5.47)
							100% reduction in OCS dose	OR 1.36 (95% CI 0.3, 6.21)

Source: CS Appendix O Tables 107, 118 and Appendix O Figures 49-51

Table 114 Severe exacerbations, ≥50% reduction and 100% reduction in OCS dose . Dupilumab versus mepolizumab SIRIUS subgroup

Comparator trials	Data filters applied to VENTURE data	VENTURE data before filtering		VENTURE data remaining after filtering, n	Effective sample size after matching	% Effective sample size reduction (from relevant sample size)	Outcomes	Overall Dupilumab vs mepolizumab MAIC result
		Trial arms	Total size, n					
SIRIUS subgroup EOS ≥300 in past year and ≥4 exacerbations or mOCS	High ICS/LABA	Dupilumab 200mg	103	103	50	51.5%	Severe exacerbations	RR 0.56 (95% CI 0.31, 1.01)
							≥50% reduction in OCS dose	OR 1.47 (95% CI 0.43, 5.06)
		Placebo	107	107	61	43.6%	100% reduction in OCS dose	OR 1.51 (95% CI 0.08, 3.34)

Source: CS Appendix O Table 119 and Appendix O Figures 52-54

Table 115 Severe exacerbations, ≥50% reduction and 100% reduction in OCS dose . Dupilumab versus benralizumab

Comparator trials	Data filters applied to VENTURE data	VENTURE data before filtering		VENTURE data remaining after filtering, n	Effective sample size after matching	% Effective sample size reduction (from relevant sample size)	Outcomes	Overall Dupilumab vs benralizumab MAIC result
		Trial arms	Total size, n					
ZONDA ITT	-High ICS/LABA - Baseline blood EOS ≥150 cells/µl - Number of exacerbations in the past year ≥1 - Age ≥18	Dupilumab 200mg	103	64	53	17.2	Severe exacerbations	RR 1.52 (0.69, 3.36)
		Placebo	107	56	37	33.9	≥50% reduction in OCS dose	OR 1.13 (0.33, 3.78)
							100% reduction in OCS dose	OR 0.93 (0.22, 4.02)

Source: CS Appendix O Tables 107, 121 and Appendix O Figures 56-58

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report – factual accuracy check

Dupilumab for treating severe asthma [ID1213]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by the end of **12 November** using the below comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Incorrect copyright

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 2: “Copyright is retained by Janssen”	Copyright is retained by Sanofi or the companies who submitted evidence to NICE and that was used and reproduced in the Company and/or ERG reports.	Data presented in the report is copyright of Sanofi or the companies whose data is presented and used. Janssen is not a stakeholder.	The ERG apologises for inadvertently using the wrong company name in one part of the copyright statement. This has been corrected.

Issue 2 LOACs in VENTURE RCT

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 16: The ERG states that Loss of Asthma Control events (LOAC events) are not reported.	The statement could be misleading and requests it be clarified that LOAC events were not measured in VENTURE and therefore could not be reported	For clarity of facts.	Text has been altered to read “This outcome was not measured” both on p. 16 and in section 3.3.5.2.

Issue 3 FeNO

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 40: FeNO measurements as	The company decision problem focuses	For clarity of facts.	The ERG cannot find

markers of Type 2 inflammation	on EOS and/or FeNO as markers of Type 2 inflammation. Therefore, focusing on just one marker is not the complete picture.		anything on page 40 (or nearby pages) where FeNo is mentioned without EOS also being mentioned as a marker of Type 2 inflammation.

Issue 4 Incorrect data submitted

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG Response**
Table 48 Page 100: Figure 35 in appendix N.6.1. was submitted in error by the company.	The correct figure that matches the data reported in Table 88 in the CS Appendix (N4.2), and the matching methods and criteria described in the Company submission appendix, is shown in **Error! Reference source not found.**. The company requests these data and the resulting ERG conclusions from this forest plot be removed and replaced with the correct plot and data.	The company requests the figure be replaced with the correct figure to avoid confusion and diffusion of incorrect data.	This is not the ERG's factual error but an error made by the company in their original submission and unfortunately this was not identified earlier (e.g. Figure 35 is referred to in clarification question A15). The ERG cannot correct the company submission, but we

			have revised Table 48 in the ERG report to reflect the correct data the company supplied in Figure 1 of this factual error check document.

Issue 5 CSRs

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 57: CSRs for two of the included studies were not accessible to the ERG until five working days before submission of the ERG report	Unprotected CSRs were provided within 12 hours of being made aware of the issue. The statement in the report is misleading and the company kindly requests this phrasing be changed to the effect of "CSRs for two of the included studies were not originally not accessible but were received when requested"	For clarity of facts.	This is not a factual inaccuracy. The ERG received the clarification response on 24th September. Nevertheless the ERG has reworded this text.

Issue 6 MAIC matching

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 63: MAIC matching: "the company concede that "it was not	Every effort was made to match the dupilumab trial patients with those of the	For clarity of facts.	Not a factual error, no amendment

possible to create dupilumab subgroups that fully aligned with the populations assessed in the mepolizumab trials””	comparator trials based on inclusion criteria. One of the inherent limitations of indirect treatment comparisons is availability of comparator data.		necessary.

Issue 7 US label

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 63: “eosinophilic phenotype was used to match patients albeit it was not included in the US label” is not clear	ERG to clarify what is intended as this statement could be misleading. The biologics included in this appraisal are all indicated for eosinophilic asthma in the US.	For clarity of facts.	For clarity the ERG has altered the text to read “eosinophilic phenotype was used to match patients albeit it was not defined in the US labels” (as stated by the company in their response to clarification question A13).

Issue 8 MAIC methods

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 74: The ERG report states “where there were multiple RCTs	Clarify that the methods used are acceptable. According to NICE DSU	For clarity of facts.	The ERG has removed the

for each comparator, the matching was conducted for each comparator RCT separately then results were pooled (e.g CS Tables 47, 55). This approach is flawed; pooling is only justified if the data are independent"	Document 18, Section 3.1.2, performing identical MAICs into each comparator population and then pool the relative estimates is recommended.		statement and altered summary sections of the report in line with this.

Issue 9 Use of correct ITC data

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 122: "dupilumab led to fewer severe exacerbations in the uncontrolled persistent asthma population than either benralizumab (rate ratio [redacted]) or reslizumab (rate ratio [redacted]	Table 88 of the CS appendix shows that the ITC also found statistical significance versus mepolizumab. This data is used in the base case versus mepolizumab. Therefore, this statement should read "dupilumab led to fewer severe exacerbations in the uncontrolled persistent asthma population than [redacted], benralizumab (rate ratio [redacted]) or reslizumab (rate ratio [redacted])	The company requests the text be changed to reflect the correct data from the Table 88 in the CS and Figure 1 below (replacing Figure 35 in CS Appendix). This relates to Issue 4 above.	As noted above in the response to issue 4, this is not the ERG's factual error but an error made by the company in their original submission. The ERG has updated the ERG report to reflect the correct data the company supplied in Figure 1 of this factual error check document.

Issue 10 Population weight

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 129, Table 71. The model provides estimates of the weight in the population to enable estimation of weight-based drug costs for reslizumab. As reslizumab is only evaluated in a non-mOCS population average weight is only given for a non-mOCS population. Table 71 includes weight for patients on mOCS which is not provided in the model, nor is used in this analysis.	Revision of estimates of weight for mOCS population to "NA= Not applicable" or deletion of weight from table	For clarity of facts.	This is not a factual inaccuracy. Column D in ERG Table 71 for the reslizumab-eligible population is clearly labelled as non-mOCS, and the source is cited as QUEST as used in the economic model.

Issue 11 "Mixed" population from TA565

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 130: In relation to the base case population of people with at least 3 exacerbations in addition to indicators of type 2 inflammation (EOS ≥150 or FeNo ≥ 25) the ERG notes the following:	Either deletion of the statement or insertion of statement following subsequent paragraph that provides context on the mixed population scenario.	For clarity of facts.	This is not a factual inaccuracy. TA565 paragraph 3.7 (page 13) clearly refers to a "mixed population" including patients who are and are not

"In particular, we highlight that the committee in TA565 concluded that cost effectiveness evidence for this type of mixed population was not suitable for decision making because the range of asthma severity is not necessarily generalisable to the clinical practice population." This statement is made in reference to the incremental population, i.e. the base case population excluding patients who are currently eligible for biologics. In TA565 the mixed population refers to the "mix" of patients on mOCS and patients not on mOCS, not the "mix" of patients with varying levels of eosinophils.			currently eligible for biologics.

Issue 12 Exacerbation rates

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG Response**
Page 136: Following the description of the base case population and derivation of transition probabilities the ERG report states the following	Inclusion of "in the randomized population" at the end of the statement or revision of figures to reflect base case population:	For clarity of facts.	Thank you, for clarity we have added "in the randomised population" to the end

“It is apparent that the severe exacerbation rate among patients treated with placebo in QUEST was lower than in the preceding year: mean annualised rates 2.07 (SD 1.58) before the trial compared with 0.871 (95% CI: 0.724 to 1.048) during the trial (CS Tables 13 and 19). “ These figures relate to the randomized population, as opposed to the base-case population. Since the statement appears after a description of data relating to the base-case population, without further clarification it is possible that these may be misinterpreted to reflect the baseline characteristics and outcomes in the target population.	“rates 4.46 (SD 1.76) before the trial compared with 2.146 (95% CI: 1.415 - 3.255) during the trial”		of the statement.

Issue 13 VENTURE Transition Probabilities

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG Response**
Page 139: The CS reports a set of	Additional clarification on the VENTURE	For clarity of facts.	This is not a factual

transition matrices for the mOCS population in CS Appendix M Table 74, but this does not match the values in the submitted model	transition probabilities were requested at the clarification stage (Question B2), which was provided. The company highlights the ERG conclusions that the data in the model are correct.		inaccuracy. The response to clarification question B2 only reported transition probabilities to the "controlled asthma" health state, not the whole matrices. However, for clarity we have acknowledged the data provided in clarification question B2 and the statement in this FAC response that the data in the model are correct.

Issue 14 Binomial regression Fit statistics

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 144: The ERG report states that: "The clarification response did not include diagnostic statistics for goodness-of-fit or the appropriateness of the negative binomial models (dispersion). It is therefore difficult to assess the	Removal of statement.	Correction of fact.	We acknowledge that some information was provided in response to clarification question B5. However, this only relates to the final fitted models and there is no

robustness of the results." Fit statistics, and diagnostic plots were provided in the clarification response appendix for question B5.			comparison of alternative model specifications or diagnostic plots. We have added the following text to the ERG report: "In response to Clarification Question B5, the company reported goodness-of-fit statistics and co-variate significance for the final models, but did not compare alternative specifications or assess the appropriateness of the negative binomial models (dispersion)."

Issue 15 Mortality data

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 148: The ERG report notes the following with regards to mortality following a severe exacerbation leading to A&E visit or	Revision of statement to " For the fatality associated with exacerbations leading to A&E or 'office visit', the company uses the estimates derived	For clarity of facts.	This is not a factual inaccuracy, but we acknowledge that this paragraph is

office visit: “Similarly, for the fatality rate associated with exacerbations leading to A&E or ‘office visit’, the company uses the estimates from Watson et al.[24] and Roberts et al.[25], which are applied to patients experiencing severe exacerbations leading to hospitalisations. However, as per the statistics reported by the National Review of Asthma Deaths in the UK, this cohort constitutes of only 10% of people with asthma-related death that had been treated in a hospital setting within 28 days of experiencing the attacks that caused their deaths. “ Fatality rates following a severe exacerbation leading to A&E visit or office visit were based on TA565, derived based on Watson and Roberts among other sources. The statement may be misinterpreted, to	algebraically in TA565, based on estimates from Watson et al.[24] and Roberts et al.[25], the National Review of Asthma Deaths in the UK and the setting of exacerbation treatment”		repetitious and confusing and so have deleted the third and fourth sentences quoted here.

indicate that the same fatality rates with patients experiencing a severe exacerbation leading to hospital were used.			

Issue 16 Setting of exacerbations

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 149: The ERG report states that the source used to inform distribution of location for treatment of severe exacerbation were estimated from a study by Wilson et al. However, estimates were based on unscheduled visits to GP, A&E and hospital as analysed from the British Thoracic Society National Registry for dedicated UK Difficult Asthma Services. “Another parameter that drives model estimates of asthma-related mortality is the distribution of locations for treatment of severe exacerbations (CS section B	Deletion of “, which were estimated from a study by Wilson et al.” and insertion of “which analyzed data from the British Thoracic Society National Registry for dedicated UK Difficult Asthma Services”	For clarity of facts.	Thank you, correction made as suggested.

3.5.7.1, Table 80). For the base case, the company use estimates reported by O'Neill et al (2015)[26], which were estimated from a study by Wilson et al[27]."			

Issue 17 LOACs in VENTURE RCT

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 149: In relation to the sensitivity analyses conducted on the setting of severe exacerbation treatment the report states: "The model includes two scenarios based on alternative sources: one with estimates from the QUEST and VENTURE trials; and another using other published estimates for model subgroups (see **Error! Reference source not found.**)." The last part of the sentence may be misinterpreted without further context as the estimates do not relate to model subgroups rather the label populations of biologics.	Revision of underlined section to "using estimates from the randomized populations of other biologic trials"	For clarity of facts.	Thank you, correction made.

Issue 18 Dupilumab

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Pages 154-155: Dupilumab is misspelt as “dupilimab”	Correct drug name to “dupilumab”.	Correctly refers to drug name.	Typographical errors in the spelling of dupilumab have been corrected.

Issue 19 Source of data of setting of exacerbations

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 156: The ERG report states that the “The setting of the treatment for exacerbations was also informed by the study by Wilson et al[27]. “, however this was informed from O’Neill et al.	Revision of source to O’Neill et al.	For clarity of facts.	Correction made.

Issue 20 Reslizumab

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Table 104 Page 186: Table reads “Base case population excluding patients eligible for mepolizumab (46.5%, 47/101)”	As this table relates to patients not eligible for reslizumab, the company believes this is a type and should read “Base case population excluding	For clarity of facts.	Yes, thank you, we have corrected this.

	patients eligible for reslizumab”		

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft technical report

Dupilumab for treating severe asthma

This document is the draft technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- topic background based on the company's submission
- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

1. Topic background

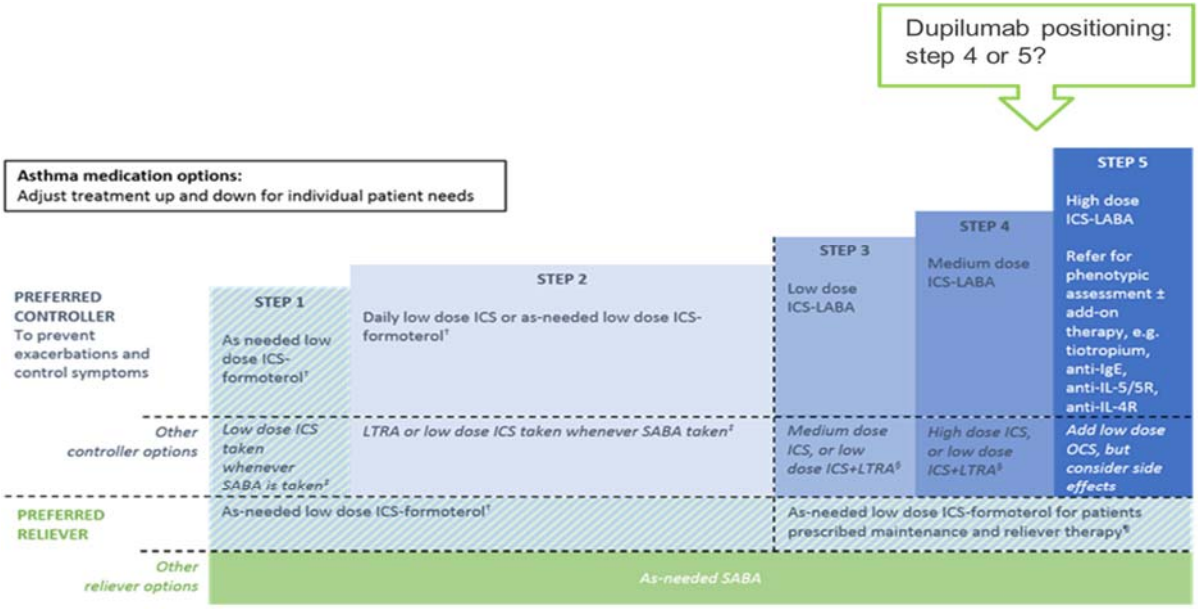
1.1 Disease background

- Asthma is a disease of the airways
- Symptoms include breathlessness, chest tightness, wheezing and cough
- Approximately 8 million people in the UK have asthma (CKS: asthma)
- In 2017 there were 1,484 deaths from an asthma attack in the UK (Asthma UK)
- 200,000 people in the UK have severe asthma (Asthma UK) defined as:
  - 'asthma that requires treatment with high dose inhaled corticosteroids plus a second controller medicine to prevent it from becoming 'uncontrolled' or that remains 'uncontrolled' despite this therapy' (NICE guideline NG80: asthma: diagnosis, monitoring and chronic asthma management and guidelines from the Global Initiative for Asthma 2019 [GINA])
- Severe asthma with type 2 inflammation is an important subtype of asthma when any of the following criteria are met (GINA 2019):
- Blood eosinophils (EOS) ≥150 µl and/or
- Fractional exhaled nitric oxide (FeNO) ≥20 ppb and/or
- Sputum EOS ≥2% and/or
- Asthma is clinically allergen-driven and/or
- Need for maintenance oral corticosteroids (mOCS)

1.2 The technology

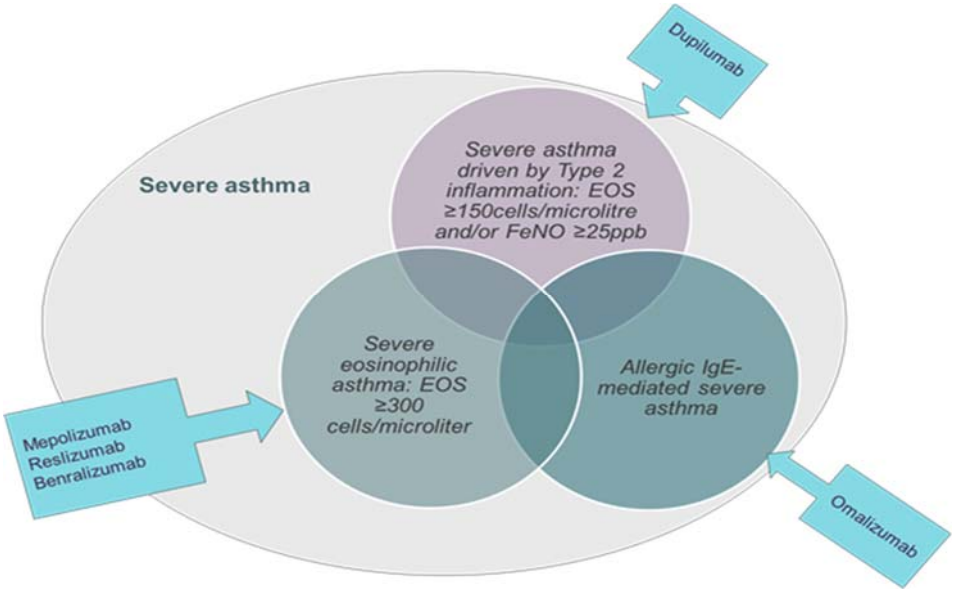
Technology	Dupilumab (Dupixent, Sanofi Genzyme) is a recombinant human immunoglobulin (Ig) monoclonal antibody that inhibits interleukin (IL)-4 and IL-13 signalling. IL-4 and IL-13 act as major drivers of Type 2 inflammation (T2i) by activating multiple cell types.
Marketing authorisation May 2019	Indicated in adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood EOS and/or raised FeNO, who are inadequately controlled with high dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment
Administration	• An initial dose of 400 mg, followed by 200 mg given every other week administered as subcutaneous injection. • For patients with severe asthma and who are on oral corticosteroids or for patients with severe asthma and co-morbid moderate-to-severe atopic dermatitis, an initial dose of 600 mg followed by 300 mg every other week administered as subcutaneous injection

1.3 Treatment pathway for severe asthma uncontrolled asthma (GINA 2019 guidelines) reproduced from the company submission B.1.3.1.2.



Abbreviations: HDM, house dust mite; ICS, inhaled corticosteroids; Ig, immunoglobulin; IL, interleukin; OCS, oral corticosteroids; R, receptor; LABA, long-acting β2-agonist; LTRA, leukotriene receptor antagonist; SABA, short-acting β2-agonist; SLIT, sublingual allergy immunotherapy. † Off-label, data only with budesonide-formoterol (bud-form); ‡ Off-label, separate or combination ICS and SABA inhalers; § Consider adding HDM SLIT for sensitised patients with allergic rhinitis and FEV_1 >70% predicted; ¶ Low dose ICS-form is the reliever for patients prescribed bud-form maintenance and reliever therapy.

1.4 Biologic treatments for severe uncontrolled asthma on standard care (high dose inhaled corticosteroids [ICS] [plus 1 or more controller therapy] with or without maintenance oral corticosteroids [mOCS])



1.5 Decision problem

	Final scope issued by NICE	Company submission
Population	People 12 years and older with severe asthma inadequately controlled with optimised standard therapy	Eosinophil (EOS)≥150/µl and/or fractional exhaled nitric oxide (FeNO) ≥25 ppb. - Restricted to 3+ exacerbations past 12 months
Intervention	Dupilumab as an add-on to optimised standard therapy	Dupilumab 200mg Q2W if **not on** maintenance oral corticosteroids Dupilumab 300 mg Q2W if **on** maintenance oral corticosteroids
Comparator	• The following biologics indicated and suitable for severe asthma (in accordance with NICE recommendations): - Reslizumab - Mepolizumab - Benralizumab - Omalizumab • Optimised standard therapy (with or without oral corticosteroids) when the biologics llsted above are not suitable or indicated	The company did not include omalizumab as a comparator because duplilumab is not indicated for lgE mediated asthma (ERG agree).
Outcomes	• Objective measures of lung function (e.g. FEV1, PEF) • Asthma control • Incidence of clinically significant exacerbations, including those which require unscheduled contact with healthcare professionals or hospitalisation • Use of oral corticosteroids • Mortality • Adverse effects of treatment • Health-related quality of life.	Matched the NICE scope

1.6 Clinical evidence used in the model – studies in red box used in the model, interventions in green box used in the model

Study	Population (ITT)	Intervention	Comparator	Primary outcomes
QUEST (n=1902) Dup 200mg, 300mg 6/389 UK centres (n=13 participants)	• 12 years and over • Moderate-severe uncontrolled asthma (as per GINA definition) • Moderate-high dose ICS + plus 1–2 of ; LABA, LAMA, LTRA, methylxanthines • 1+ exacerbations prior year	• 200mg SC injection Q2W for 52 wks after initial 400mg loading dose • 300mg SC injection Q2W for 24 wks after initial 600mg loading dose	Placebo Q2W	1) Annualised rate of severe exacerbation events during the 52-week placebo-controlled treatment period 2) Absolute change from baseline in pre-bronchodilator FEV1 at Week 12.
VENTURE (n=210) Dup 300mg No UK centres	• 12 years and over • Severe steroid-dependent asthma (5-35mg/day or equiv) • high dose ICS plus second controller (LABA or LTRA). • Blood EOS count of <150μl is limited to approximately 25% of the total sample size • 1+ exacerbations prior year	• 300mg SC injection Q2W for 24 wks after initial 600mg loading dose		Percentage reduction of OCS at wk 24 compared with the baseline dose, while maintaining asthma control.
DRI12544 Dup 200mg (n=308) No UK centres	• 18 years and over • Moderate-severe uncontrolled asthma (as per GINA definition) • Moderate-high dose ICS + LABA, • 1+ exacerbations prior year,	• 200mg SC injection Q2W for 24 wks • 300mg SC injection Q2W for 24 wks • 200mg SC injection Q4W for 24 wks • 300mg SC injection Q4W for 24 wks	Placebo Q2W or Q4W	Percentage reduction of OCS at wk 24 compared with the baseline dose, while maintaining asthma control.

1.7 Key clinical trial results

Key clinical trial results Intention to treat results for the trial population (1)

	DRI12544		QUEST		VENTURE	
	Dupilumab 200 mg Q2W (n=150)	Placebo (n=158)	Dupilumab 200 mg Q2W (n=631)	Placebo (n=317)	Dupilumab 300 mg Q2W (n=103)	Placebo (n=107)
Adjusted annualised rate of severe exacerbation events (ITT analysis)	0.269; (95%CI:0.157, 0.461)	0.897 (95%CI:0.619,1.300)	0.456 (95% CI: 0.389, 0.534)	0.871 (95% CI: 0.724, 1.048)	0.649 (95% CI :0.442, 0.955)	1.597 (95% CI: 1.248, 2.043)
Relative risk versus placebo (95% CI), p-value	0.300 (0.159, 0.565); p=0.0002		0.523 (0.413, 0.662); p<0.0001		0.407 (0.263, 0.630); p-value NR	
Change from baseline in FEV1 at 12 weeks, least squares (LS) mean (standard error, SE)	n= 136 0.31L (0.03)	n=129 0.12L (0.03)	n=611 0.32L (0.02)	n=307 0.18L (0.02)	n=97 0.22L (0.05)	n=104 0.01L (0.05)
LS mean difference (95% CI), p value vs placebo	0.20L (0.11, 0.28), p<0.0001		0.14L (0.08, 0.19), p<0.0001		0.22L (0.09, 0.34) p-value NR	
Percentage reduction of OCS dose at Week 24 from baseline, LS mean (SE)	-	-	-	-	n=101 70.09 (4.90)	N=106 41.85 (4.57)
LS mean difference vs placebo (95% CI), p value vs placebo	-	-	-	-	28.24 (15.81, 40.67), p<0.0001	

Intention to treat results for the trial population (2)

	DRI12544		QUEST		VENTURE	
	Dupilumab 200 mg Q2W (n=150)	Placebo (n=158)	Dupilumab 200 mg Q2W (n=631)	Placebo (n=317)	Dupilumab 300 mg Q2W (n=103)	Placebo (n=107)
Asthma control LS mean diff vs placebo (95% CI) at **week 24**	ACQ-5 –0.35 (–0.57, –0.14) p=0.0015		ACQ-7 –0.36 (–0.48, –0.24), p<0.0001		ACQ-7 –0.53 (–0.80, –0.25) p-value NR	
Annualised rate of LOAC events Relative risk vs placebo (95% CI)	0.314 (0.181, 0.543); p<0.0001		0.624 (0.521, 0.746); p<0.0001		-	-
Health-related QoL LS mean change from baseline (SE)	EQ-5D-3L 0.06 (0.01)	EQ-5D-3L 0.06 (0.01)	EQ-5D-5L 0.10 (0.01)	EQ-5D-5L 0.07 (0.01)	EQ-5D-5L 0.06 (0.02)	EQ-5D-5L 0.04 (0.02)
LS mean diff vs placebo (95% CI)	0.00 (-0.04, 0.04), p=0.9299		0.02 (0.00, 0.05), p=0.0412		0.01 (-0.03, 0.06), p=0.5518	
Adverse events						
Treatment-emergent SAE	6.8%	5.7%	7.8%	8.3%	8.7%	5.6%
TEAE leading to death	0	0	0.2%	1%	0	0
TEAE leading to permanent treatment discontinuation	4.1%	3.2%	3%	6.1%	1%	3.7%

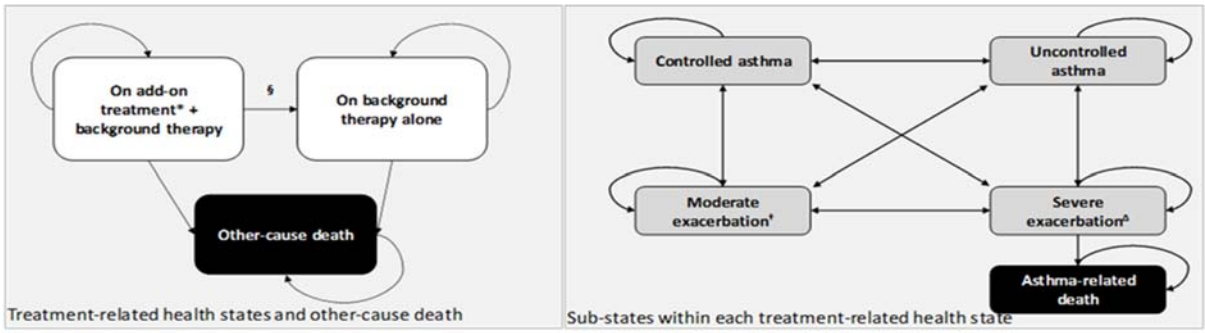
Results for company's post-hoc base case population (analysis) (EOS ≥150 OR FeNO ≥25 AND ≥3 exacerbations) (3)

	QUEST		VENTURE	
	Dupilumab 200 mg Q2W (n=64)	Placebo (n=37)	Dupilumab 300 mg Q2W (n=78)	Placebo (n=74)
Adjusted annualised rate of severe exacerbation events (post-hoc subgroup analysis)	[redacted]	[redacted]	[redacted]	[redacted]
Relative risk versus placebo (95% CI), p-value	[redacted] p<0.0001		[redacted]; p=0.0010	

Subgroup analysis by EOS, FeNO and ICS for primary outcomes for trial population reproduced from the ERG report tables 46 and 47 (4)

	QUEST				VENTURE	
	Co-primary outcome 1: annualised event rate of severe exacerbations		Co-primary outcome 2: Change from baseline in pre-BD FEV1 (L) at week 12		Treatment difference on percentage reduction of OCS dose (mg/day) at week 24	
	Subgroup	Relative risk (95% CI)	Subgroup	Relative risk (95% CI)	Subgroup	Relative risk (95% CI)
Baseline blood eosinophil group 1 (Giga/L)	<0.3 (n=535)	0.759 (0.548, 1.052)	<0.3 (n=517)	0.08 (0.01, 0.15)	<0.3 (n=119)	21.33 (3.90, 38.75)
	≥0.3 (n=412)	0.342 (0.244, 0.480) p<0.0001	≥0.3 (n=400)	0.21 (0.13, 0.29) p<0.0001	≥0.3 (n=88)	39.83 (18.94,54.71)
Baseline blood eosinophil group 2 (Giga/L)	<0.15 (n=278)	0.925 (0.580, 1.474	<0.15 (n=268)	0.06 (-0.04, 0.15)	<0.15 (n=58)	26.89 (-0.73, 54.52)
	≥0.15 (n=669)	0.442 (0.337, 0.581) p<0.0001	≥0.15 (n=649)	0.17 (0.11, 0.23) p<0.0001	≥0.15 (n=149)	29.39 (15.67, 43.12)
Baseline FeNO (ppb)	<25 (n=474)	0.752 0.541, 1.046)	<25 (n=460)	0.05 (-0.02, 0.12)	<25 (n=89)	17.27 (-3.62, 38.16)
	≥25 to <50 (n=271)	0.386 (0.243, 0.616)	≥25 to <50 (n=262)	0.19 (0.09, 0.28)	≥25 to <50 (n=60)	38.31 (14.84, 61.78)
	≥50 (n=190)	0.308 (0.183, 0.519)	≥50 (n=183)	0.30 (0.17, 0.44)	≥50 (n=52)	33.64 (13.67, 53.61)
ICS dose at baseline	High (n=489)	0.539 (0.400, 0.725) p<0.0001	High (n=477)	0.13 (0.06, 0.21) p=0.0003	-	-

1.8 Model structure and assumptions



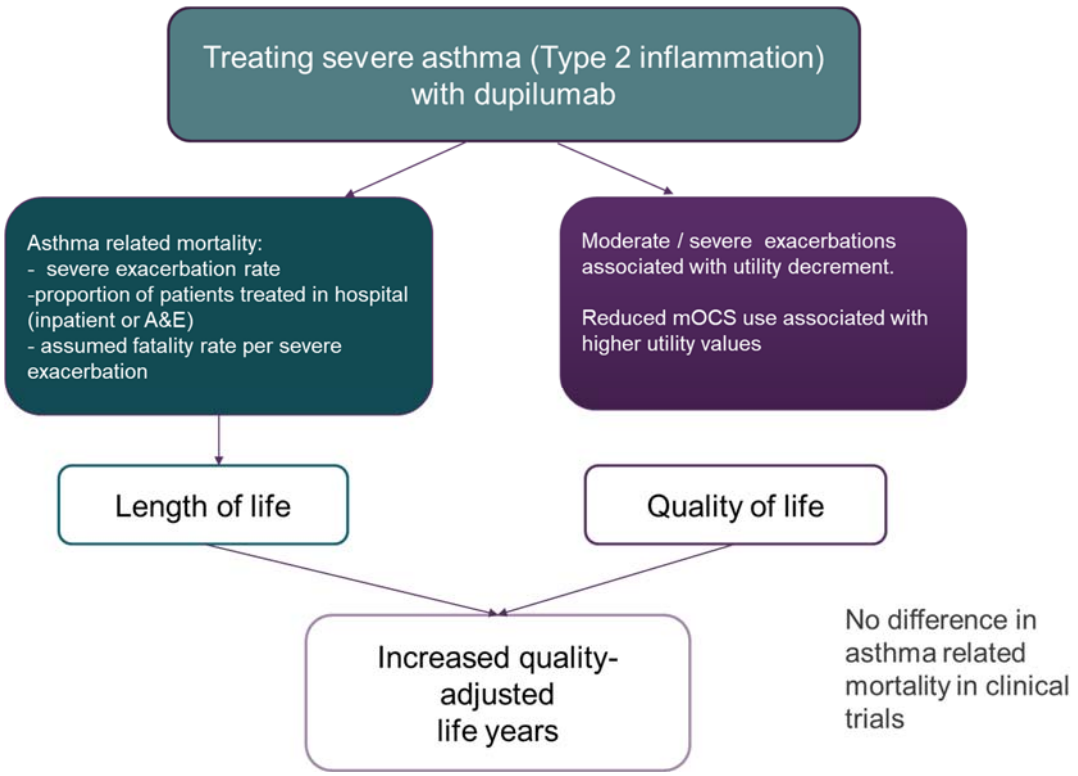
Markov model structure (Source: CS Figure 36)

Model parameters

- 4 live health states: uncontrolled asthma; controlled asthma; moderate exacerbation; and severe exacerbation. In addition, the model includes states for asthma-related deaths and death from other causes
- Uses a lifetime horizon (up to a maximum age of 100 years)
- Cycle length of 4 weeks and a half-cycle correction
- The model includes the flexibility to define the starting cohort according to the proportion of patients on mOCS and minimum levels of EOS, FeNo and number of exacerbations in the previous 12 months
- The cohort enters the model in the uncontrolled asthma health state
- Rates of movement between the live states are determined by a transition probability matrix and mortality rates are applied for asthma and other deaths.

Assumption	Justification (summary from company submission, table 87)
Severe asthma exacerbations increase after the clinical trial period.	It has been shown that recent severe exacerbations is the strongest predictor of future asthma exacerbations. This is in line with a previously accepted assumption for the mepolizumab HTA, where post-trial exacerbation rates for all patients were assumed to increase by 1.35.
Annual discontinuation rates are assumed constant	Similar to assumptions adopted in previous technology assumptions.
Mortality calculations are based on Watson et al, and adjusted based on Roberts et al.	The committee's preferred assumption from the most recent severe eosinophilic asthma appraisal is considered a conservative approach
Response is determined by ≥50% reduction in severe exacerbations; or ≥50% reduction in severe exacerbations or mOCS dose for steroid-dependent patients	This continuation rule is validated in an advisory board of severe asthma consultants and health economists, and is already used for a biologic in severe eosinophilic asthma
Duration of exacerbations and disutilities are derived from QUEST	The duration of exacerbations is derived from the modelled patient population
Disutilities are age-adjusted	Per NICE reference case
Setting of treatment severe exacerbations is informed by UK-specific published data	Using UK-specific data from a published observational study is considered to be more representative of UK clinical practice and therefore more appropriate for the base case
UK market research is used to inform the distribution of ICS/LABA combination therapy	UK specific combination inhalers were assumed to be more representative of UK clinical practice
Benefits of mOCS reduction may not be fully captured in the economic model.	The model tries to capture the burden and costs of adverse events caused by mOCS use based on prevalence from a UK observational study
Treatment setting of asthma exacerbations are taken from a UK observational study.	A UK observational study is considered more appropriate to estimate resource use of asthma exacerbations than the clinical trial data. The clinical trial data is used as a scenario analysis.

1.9 **Overview of how quality-adjusted life years accrue in the model – where do gains come from in the company's model?**



2. Summary of the draft technical report

2.1 In summary, the technical team considered the following:

Issue 1 How many people have severe asthma with Type 2 inflammation in the UK and how is it defined, diagnosed and treated in UK practice?

Issue 2 Generalisability of the population used in the model to people with Type 2 inflammation to UK clinical practice

Issue 3 Treatment of severe asthma caused by Type 2 inflammation (which informs the relevant comparators)

Issue 4 Which population is most relevant for decision making?

Issue 5 In the mixed population scenario (non-mOCS and mOCS populations) what proportion of patients should be on mOCS?

Issue 6 Should a mixed population of different severities of asthma be used in the base case (non-mOCS) model?

Issue 7 Should the rates of severe exacerbations be adjusted (increased) in the model?

Issue 8 Should discontinuation in the first 12 months be included in the model?

Issue 9 Should clinical trial or registry data inform the treatment settings for severe exacerbations in the model?

Issue 10 What are the most appropriate utility values for controlled and uncontrolled asthma?

Issue 11 Should a consistent source of unit costs be used in the model?

Issue 12 Should self-administration of dupilumab be assumed in the model?

2.2 The technical team recognised that the following uncertainties would remain in the analyses and could not be resolved:

- There are many limitations with the indirect treatment comparison (ITC) analyses
- The model used to assess trial data from VENTURE does not include the moderate exacerbation health state (no data was available for this health state).

2.3 The cost-effectiveness results include a commercial arrangement (patient access scheme/commercial access agreement) for dupilumab.

2.4 Dupilumab is not considered an end-of-life treatment.

2.5 Is dupilumab innovative because it targets a different patient population to the other current biological therapies (although, as noted there is some overlap between the different patient populations)? Is dupilumab innovative in its potential to make a significant and substantial effect on health-related benefits?

2.6 No equalities issues were identified.

3. Key issues for consideration

Issue 1 – What proportion of patients in the UK have severe asthma with Type 2 inflammation and how is severe asthma with Type 2 inflammation defined, diagnosed and treated in UK practice

Questions for engagement	1. How many people in the UK have severe asthma with Type 2 inflammation? 2. How is severe asthma with Type 2 inflammation defined and diagnosed in clinical practice? 3. Are blood EOS level of ≥150 cells/microlitre and FeNO of ≥25 ppb (compared with ≥20 ppb in the GINA guideline) sufficient to identify people with Type 2 inflammation?
Background/description of issue	The company submission focuses on severe asthma driven by Type 2 inflammation in line with its marketing authorisation. **The company's** submission notes that people with severe uncontrolled asthma are those that are referred to severe asthma centres (as per previous NICE technology appraisals). The licensed indication is based on a subgroup of this population which consists of people with severe asthma driven by Type 2 inflammation (blood EOS ≥ 150 cells/microlitre and/or FeNO ≥25 ppb), on or not on mOCS. In addition, the company limits treatment eligibility to those who have had 3 or more exacerbations in the previous year if not on mOCS (this is narrower than the wording of the licenced

	indication) or that people should be receiving maintenance treatment with oral corticosteroids (mOCS) to align it with the exacerbation rate in NICE guidance for current biologics. **The ERG** notes that the company has a more restricted definition than the GINA guidelines which specify that severe asthma driven by Type 2 inflammation is indicated when any of the following GINA criteria are met: • Blood EOS ≥150 µl and/or • FeNO **≥20** ppb and/or • Sputum EOS ≥2% and/or • Asthma is clinically allergen-driven and/or • Need for mOCS The company's definition of asthma driven by Type 2 inflammation therefore rests solely on the first two items in the GINA list (with the threshold for FeNO being slightly higher at 25 ppb versus 20 ppb in the GINA list above). The proposed population also includes people who have had 3 or more exacerbations in the past 12 months because it is this group of patients who are referred to severe asthma centres in the UK where treatment with the other biologics is also initiated.
Why this issue is important	Estimating the proportion of the population with severe asthma with Type 2 inflammation in the UK is useful to identify the how many people actually have this condition and the extent of the decision problem. Determining the subtype of severe asthma that a patient has is important in guiding treatment decisions. The subtype of severe asthma also has an important influence on the comparisons made and analyses presented in the company submission.
Technical team preliminary judgement and rationale	Clinical experts to advise on: proportion of people with Type 2 inflammation; how people with the condition are identified and currently treated; and whether or not the licensed population is an appropriate definition for severe Type 2 inflammation in clinical practice.

Issue 2 – Generalisability of the population used in the model

Questions for engagement	4. Do the people in the post-hoc trial population proposed by the company represent patients in clinical practice who have severe asthma driven by Type 2 inflammation? What proportion of the post-hoc population were from the UK and how might this affect the generalisability of standard of care in the trial compared to clinical practice in the UK?

Background/description of issue	The post-hoc population was defined by the company as: QUEST: EOS ≥150 or FeNO≥25 and ≥ 3 exacerbations VENTURE: EOS ≥150 or FeNO≥25, in patients receiving oral corticosteroids. In DRI12544 and QUEST (participants not taking maintenance oral corticosteroids [non-mOCS], the ITT population consisted of people with moderate to severe asthma on moderate to high dose inhaled corticosteroids plus another controller with **at least 1 exacerbation in the previous year**. In these 2 trials, a minority of the ITT population matched the post-hoc population proposed by the company (14.7% and 15.2% in the dupilumab and placebo arms of DRI12544 and 10.1% and 11.7% in the dupilumab and placebo arms of QUEST). In VENTURE, the ITT population included people with severe steroid-dependent asthma (taking mOCS of 5-35 mg/day or equivalent [mOCS]) on high dose inhaled corticosteroids with at least 1 exacerbation in the previous year. Over half of the ITT population match matched decision problem population criteria (75.7% in the dupilumab and 69.2% in the placebo arms) in VENTURE. Post-hoc subgroup analyses for the decision problem population were only conducted and available for one outcome, annualised rate of severe exacerbation events. **The company** used post-hoc data from QUEST to inform the base case model and used both QUEST and VENTURE in the scenario for mixed population (non-mOCS and mOCS). For QUEST, this is a small percentage of the ITT population (note only 13 from the UK were enrolled in QUEST) **The technical team** note that the post-hoc population is in line with the population for whom dupilumab is licensed in for which the recommendation is sought, however there is no minimum exacerbation stated in the SmPC.
Why this issue is important	This is important because the subgroup of the ITT population in QUEST, which fits the company's proposed population includes a small number, and this may not be adequately powered to detect significant difference or may overestimate the efficacy results therefore reducing the incremental cost effectiveness ratio (ICER).
Technical team preliminary judgement and rationale	Input from clinical experts on the robustness of efficacy data based on the post-hoc population.

Issue 3 – Treatment of severe asthma caused by Type 2 inflammation

Questions for engagement	5. Is standard care (high dose ICS [plus 1 or more controller therapy], with or without oral corticosteroids) the most relevant comparator? Would adding oral corticosteroids be a relevant comparator for people with uncontrolled asthma without oral corticosteroids? 6. What proportion of patients with severe asthma driven by Type 2 inflammation (blood EOS ≥ 150 cells/microlitre and/or FeNO ≥25 ppb) would also be eligible for treatment with currently recommended biologics (mepolizumab, reslizumab, benralizumab, omalizumab)? 7. Will dupilumab be used in a population who have asthma that is of a similar severity to the population with severe asthma for whom biologics are currently recommended or will it be used in people with less severe asthma?
Background/description of issue	The company notes the difference between the blood eosinophil concentrations and number of exacerbations in the previous 12 months for dupilumab and current biologics mepolizumab (300 cells/microlitre or more/ 4 exacerbations or more), reslizumab (400 cells/microlitre or more/ 3 exacerbations or more), benralizumab (300 cells/microlitre or more/ 4 exacerbations or more), and omalizumab (allergic asthma with at least 4 courses or continuous oral corticosteroids). **The company** note that people who are eligible for dupilumab would not meet the criteria for other biologic treatments and therefore standard care is the only relevant comparator. It does not consider omalizumab to be a relevant comparator as only 2.5% of the QUEST population would meet the criteria for omalizumab. **The ERG** notes that the subtypes of severe asthma (eosinophilic, Type 2 inflammation and allergic mediated asthma) are not mutually exclusive and there is potential for overlap between these subgroups of patients. The ERG sought expert clinical advice regarding any potential overlap between these subgroups of patients. The clinicians were in agreement that in reality there would be overlap between the different subtypes of asthma and the groups are not as distinct as the company implies.

Why this issue is important	The subtype of severe asthma has an important influence on the comparisons made and analyses presented in the company submission.
Technical team preliminary judgement and rationale	This will be informed by clinical advice on the most relevant comparators

Issue 4 –Which population is most relevant for decision making?

Questions for engagement	8. Is the base case population with only non-mOCS patients (or a mixed population) most appropriate? 9. If the mixed population is appropriate, is standard care the only relevant comparator or should other biologics also be considered in the subset of people for whom they are eligible? 10. What is the cost-effectiveness of dupilumab compared with standard care in the mOCS only population?
Background/description of issue	The company's base case model is based on patients not taking mOCS (data used from QUEST study). However, a scenario is provided for a mixed population of non-mOCS (58.3%) and mOCS (41.7%) (QUEST and VENTURE respectively) and this includes clinical efficacy data from a mixed group of people with EOS≥150 or FeNO≥25 and at least 3 exacerbations in the previous 12 months. The economic model has in-built flexibility to include patients treated with or without mOCS (based on data from the VENTURE and QUEST clinical trials respectively), as well as a weighted combination of both groups. The ERG note that the mixed population scenario can also account for the different dose of dupilumab depending on non-mOCS or mOCS populations (see decision problem section. **The technical team** question whether the base case should be based on the mixed population (non-mOCS and mOCS populations) or if it would be more clinically appropriate to consider people with and without background mOCS use as separate groups.
Why this issue is important	Dupilumab is estimated to be less cost-effective compared with standard care in this mixed population (non-mOCS/mOCS) than in the base case (non-mOCS); with an ICER above £30,000 per QALY gained (assuming 41.7% are on mOCS, see issue 5). Of the people on mOCS some would also eligible for other biologics (mepolizumab or benralizumab) and standard of care would not be a relevant comparator. It may be more relevant to consider the

	clinical and cost effectiveness of dupilumab vs standard care by background treatment (on or off mOCS) than in a mixed population. Therefore, there is a gap in the provided analyses which does not cover cost-effectiveness analyses in the mOCS-only population which is requested from the company.
Technical team preliminary judgement and rationale	This will be informed by clinical advice on whether it is more appropriate to consider the clinical and cost effectiveness of dupilumab in a mixed population, by background therapy or any other relevant analyses. There is a current gap in analyses because we don't have all ICERs for all population scenarios.

Issue 5 –Assumptions relating to proportion of population on mOCS for mixed population scenario

Questions for engagement	11. In clinical practice, what proportion of patients are expected be on mOCS?
Background/description of issue	There is uncertainty regarding whether the proportion of patients with severe asthma on mOCS is reflective of clinical practice and what proportion of patients on mOCS should be used in the model. **The company** assumes 41.7% on mOCS in their mixed analyses: in both the standard care only comparison (EOS>=150 or FeNO>=25) and the mepolizumab eligible comparison (EOS>=300). This percentage of 41.7% is based on a UK registry of severe asthma. **The ERG** highlighted that the committee involved in the appraisal of benralizumab (TA565) noted that it is difficult to determine the proportion of patients taking mOCS in practice. They noted that the committee expressed uncertainty over the proportion of patients on mOCS. Although the TA565 ERG used the same value of 41.7% (Heaney 2010) for the standard care comparison as in the current submission, the TA565 ERG used 60% for the mepolizumab comparison, and clinical experts advised the committee that in clinical practice between 66% and 80% of patients starting mepolizumab are on mOCS.
Why this issue is important	ERG analyses demonstrated sensitivity to this parameter. Taking into account extreme scenarios of proportion of patients on mOCS being 20% up to 100%, the ICERs are £31,682 and £45,240 respectively. Note, the ERG have provided analyses for a range of other mOCS percentage scenarios.
Technical team preliminary judgement and rationale	A mixed analysis of dupilumab compared with standard care which includes people on and off mOCS and different severities of asthma (see issue 6) are likely to mask the cost effectiveness of dupilumab in people with different severities of asthma for whom different biological treatments are relevant comparators. If a mixed analysis of people on and off mOCS is appropriate, the percentage of people on mOCS should be informed by evidence and clinical opinion submitted during technical engagement.

Issue 6 – Mixed population of different severities of asthma in the base case (non-mOCS) model

Questions for engagement	12. Should a mixed population of different severities of asthma be used in the base case? 13. Can the company provide additional data for a more accurate assessment of the cost-effectiveness of dupilumab in patients for whom standard care is the only treatment option?
Background/description of issue	The company base case includes people with at least 3 exacerbations in addition to indicators of Type 2 inflammation (EOS ≥150 or FeNO ≥ 25). This population includes people with different severities of asthma (based on EOS counts) and some with higher eosinophil counts would also be eligible for other biologics that have been used as comparators in the scenarios (although biologic add-on treatments are not available for everyone in this group, the EOS and prior exacerbation criteria do not have upper limits so there will be overlap with subgroups eligible for benralizumab, mepolizumab and/or reslizumab). The base case population still includes 2 groups for whom biologic treatments have not previously been recommended by NICE: • people with EOS below 300 or FeNO ≥ 25; and • those with EOS between 300 and 399 with 3 exacerbations in the previous year and not on mOCS. **The company** do not provide a scenario analyses for the subgroups for whom standard care would be the only current treatment option. **The ERG** highlighted that the committee involved in the appraisal of benralizumab (TA565) concluded that cost effectiveness evidence for this type of mixed population was not suitable for decision making because the range of asthma severity is not necessarily generalisable to the clinical practice population. Additional data would be required for a more accurate assessment of the cost-effectiveness of dupilumab in patients for whom standard care is the only treatment option.
Why this issue is important	Using a mixed population of different severities of asthma gives an unrealistic estimate of the overall cost-effectiveness of dupilumab. The ERG conducted an analysis which excluded patients who meet NICE access criteria for mepolizumab and reslizumab. This shows that dupilumab is likely to be less cost-effective (with higher ICERs) if people who are already suitable for treatment with other biologics are excluded from the company's target population (i.e those with higher EOS count of 300 cells/microlitre or more). All ICERs are above the £30,000 per QALY threshold (excluding patients eligible for mepolizumab or reslizumab, £58,387 and £68,542 respectively). The base case population (EOS ≥150 cells/microlitre

	or FeNO ≥ 25 ppb) includes a range of severity of asthma by EOS level but there are is no analyses of the impact of different eosinophils levels on the ICER. The technical team would like the company to provide an analysis of the cost-effectiveness of dupilumab for different EOS and FeNO levels.
Technical team preliminary judgement and rationale	Comparisons of dupilumab with standard care should be restricted to patients who are not eligible for other biological treatment (such as those with EOS of 300cells/microlitre or less). The technical team request an updated base case model (non-mOCS population) which excludes people eligible for biological treatment defined by the relevant NICE recommendations

Issue 7 –Multiplier assumption for the observed rates of severe exacerbations

Questions for engagement	14. Should an adjustment be made to the observed rates of severe exacerbation in the model?
Background/description of issue	The company apply a multiplier of [redacted] to increase severe exacerbation rates after the trial period. It is apparent that the severe exacerbation rate among patients treated with placebo in QUEST was lower than in the preceding year: mean annualised rates 2.07 (SD 1.58) before the trial compared with 0.871 (95% CI: 0.724 to 1.048) during the trial (see company submission tables 13 and 19). **The company** uses an adjusted multiplier to take into account the exclusion of patients with a recent severe exacerbation from the clinical trials, as this will have reduced the incidence of severe exacerbations during the trial period below the background rate for the patient population. **The ERG notes** that in other appraisals, no or lower adjustments were made to long term exacerbation rates. The NICE Committee for the appraisal of reslizumab (TA479) concluded that despite reductions in observed exacerbation rates for patients randomised to placebo and active treatment, "adjusted rates were no more likely than the unadjusted rates to reflect the true treatment benefit". Therefore, no adjustment was made to long-term exacerbation rates in appraisals for reslizumab (TA479) or the subsequent benralizumab (TA565). The earlier appraisal of mepolizumab (TA431) used a lower multiplier for background exacerbation (1.35). The ERG makes no adjustments to the multiplier in their scenario analysis see ERG report p177
Why this issue is important	This has a large impact on the modelled rates of exacerbations and is subject to high uncertainty. A higher multiplier has the effect of improving the cost-effectiveness of dupilumab. Using the trial multiplier of 1 results in a higher ICER than using a multiplier of [redacted] (combined trial inclusion and exacerbation definition multiplier).

Technical team preliminary judgement and rationale	No adjustment should be made to the long-term exacerbation rate in the base case analysis because there is no evidence that the adjusted rates better reflect the true rate of severe exacerbation in this population.

Issue 8 – Assumption relating to discontinuation rates

Questions for engagement	15. Is no discontinuation within the first year of the model appropriate?
Background/description of issue	The base case model assumes no discontinuation of dupilumab before the response assessment at 52 weeks. The model applies a constant annual rate of dupilumab discontinuation after 12 months. Discontinuation rates used in the model were estimated from the ITT populations of QUEST (non-mOCS population, the base case) for 12-52 weeks at 0.107 per person year and VENTURE (mOCS population) for 12-24 weeks at 0.042 per person year, see company submission B table 54. **The company** quotes the EMA licence for dupilumab: "*Dupilumab is intended for long-term treatment. The need for continued therapy should be considered at least on an annual basis as determined by physician assessment of the patient's level of asthma control*." (see summary of product characteristics [SmPC] page 3). As an alternative, the model includes a 'discontinuation rule' as a scenario. This assumes that patients discontinue treatment if they spend 12 consecutive cycles without controlled disease (i.e. in the uncontrolled asthma, moderate or severe exacerbation health states). **The ERG notes** that these discontinuation rates from the first year of treatment in a clinical trial context might not be generalisable to longer term treatment in practice.
Why this issue is important	In practice, some patients will inevitably stop treatment before 12 months, due to adverse events, other clinical factors or patient choice. In the ERG preferred analysis, discontinuation was allowed in the first year based on the trial data but the impact of the discontinuation on the ICER was negligible.
Technical team preliminary judgement and rationale	The technical team considers it unrealistic to assume no discontinuation before 12-month assessment and prefers using the constant rate of discontinuation as observed in the trials before as well as after the 12-month response assessment.

Issue 9 – Treatment settings for severe exacerbations

Questions for engagement	16. Should trial data be used to estimate the proportions of patients with severe exacerbations treated in emergency care and inpatient settings in the model?
Background/description of issue	The locations for treatment of severe exacerbations drives model estimates of asthma-related mortality (company submission B 3.5.7.1, table 80). Depending on the source used, the proportion of patients treated in emergency care and inpatient settings varies which in turn impacts the model. **The company** uses estimates from the Difficult Asthma Registry reported by O'Neill et al (2015), which were estimated from a study by Wilson et al (18.7% hospitalised and 7.8% A&E) in the base case model. The model includes 2 scenarios based on alternative sources: one with estimates from the QUEST (3.4% hospitalised and 3.0% A&E) and VENTURE (% not reported by ERG) trials; and another using other published estimates for model subgroups. **The ERG** highlights that the assumed proportions of severe exacerbations treated in hospital or A&E are higher than the 8.2% in the appraisal for benralizumab (TA565) and query its validity when it is used to inform the projected number of deaths. The ERG also notes that in the O'Neill study, severe exacerbations cases were only ascertained from hospital and primary care records and so patients who self-managed with an emergency supply of oral corticosteroids ('OCS burst') would not have been included in their overall denominator. It is unclear what the impact of self-management of severe exacerbations would be in practice and how many people this would apply to. The ERG used the proportion of patients with severe exacerbations who were hospitalised or treated in A&E based on the trial data described above in their analyses.
Why this issue is important	Using the proportion of exacerbations treated as emergency or as inpatients based on the O'Neil data has the effect of increasing the number of asthma-related deaths in the model, and hence QALY gain from avoiding severe exacerbations. In the ERG base case analysis using data based on trial population results in a higher ICER.
Technical team preliminary judgement and rationale	The technical team considers the trial data to be a better source for estimation of the proportions of patients with severe exacerbations treated in emergency care and inpatient settings. This is because the definitions of severe exacerbation events will be consistent with the clinical data used in the model, and

	the method of ascertainment is likely to be more complete than for a registry based on routine clinical data.

Issue 10 –Utility values

Questions for engagement	17. Should the utility used for the controlled asthma (and uncontrolled asthma) health state be limited to general population mean? 18. Which utility best reflects people in the uncontrolled asthma health state: a) 0.735 and 0.713 in the non-mOCS and the mOCS population respectively based on RCT data in the company submission b) 0.701 and 0.697 for standard care in the non-mOCS and mOCS population respectively from clinical trials in TA565, or c) 0.702 and 0.682 in the non-mOCS and the mOCS population respectively based on ERG calculations?
Background/description of issue	The company's approach to estimating utility values is based upon EQ-5D-5L data (because the 5L version of the EQ-5D captures the health benefits more accurately) collected from the company's QUEST (non-mOCS) and VENTURE (mOCS) trials. The company assumed the same utility for each health state, regardless of background therapy or add-on biologic, due to the small number of observations. Utility values were calculated for controlled asthma, uncontrolled asthma, moderate exacerbation and severe exacerbation. **The ERG** noted that the utility values for controlled asthma were higher than would be expected in the UK general population possibly because they incorporated the disutility from a small number of severe exacerbations in this licensed population. The table below is reproduced from the company submission and shows trial-based mapped EQ-5D utilities base case for patients with severe asthma with Type 2 inflammation EOS ≥150 cells/microlitre OR FeNO ≥25 ppb, and either ≥3 severe exacerbations or mOCS

Health State for the licensed population	Mean	SE
ICS population (QUEST) EOS ≥150 OR FeNO ≥25 and ≥3 severe exacerbations		
Controlled asthma	0.906	0.0068

	<table><tr><td>Uncontrolled asthma</td><td>0.735</td><td>0.0110</td></tr><tr><td colspan="3">mOCS population (VENTURE) EOS ≥150 OR FeNO ≥25 and mOCS</td></tr><tr><td>Controlled asthma</td><td>0.890</td><td>0.016</td></tr><tr><td>Uncontrolled asthma</td><td>0.713</td><td>0.014</td></tr></table> **The ERG** highlights that it lacks face validity to assume that people with severe asthma have a better quality of life than the average for people of the same age and gender, even when the asthma is controlled. Limiting the utility for controlled asthma to the general population means for the QUEST and VENTURE populations (0.873 and 0.859 respectively) and subtracting the differences in QUEST and VENTURE EQ-5D utilities for controlled and uncontrolled asthma (0.171 and 0.177 respectively) gives estimates of 0.702 for QUESR and 0.682 for VENTURE for uncontrolled asthma.
Why this issue is important	The assumption of better quality of life with controlled asthma than for age/gender matched general population lacks face validity.
Technical team preliminary judgement and rationale	The technical team considers it appropriate to limit the utility for the controlled asthma health state to a maximum of the general population mean and use a decrement to estimate the utility for uncontrolled asthma.as calculated by the ERG: 0.702 and 0.682 in the non-mOCS and the mOCS population respectively.

Issue 11 –Unit costs

Questions for engagement	19. Is it appropriate to use weighted NHS National Tariff costs in the model?
Background/description of issue	Unit costs used in the economic model (such as outpatient visits, emergency attendence and ambulance use) were taken from published NHS sources, in line with the NICE reference case. Costs associated

with service use were taken from the Personal Social Services Research Unit (PSSRU, 2018), or the NHS National Tariff 2019-2020.

The company combined the NHS National Tariff costs with a weighted average of the Healthcare Resource Group codes for emergency room attendance and severe exacerbation related hospitalisation in the model. See table below for unit costs of healthcare resources reproduced from the CS table 74

Resource	Unit Cost	Source
Outpatient visits: GP (incl. home visit)**	£37.00 per visit	PSSRU 2018; Outpatient GP consultation (lasting 9.22 minutes)
Outpatient visits: Nurse (incl. home visit)**	£42 per hour	PSSRU 2018; Nurse (GP practice)
Outpatient visits: Specialist	£124 per visit	NHS National Tariff 2019-2020 [37]; Respiratory Outpatient Attendance, TFC code 340 Multiprofessional.
Outpatient visit: Hospital-based nurse	£ 45.00 per hour	PSSRU 2018; Specialist nurse - Band 6
Airflow studies	£53.00	NHS National Tariff 2019–2020. Airflow studies
OCS	£0.0047 per mg	*2.5mg gastro-resistant tablets £0.93 per 28*
Emergency room attendance	**£ 143.57**	**NHS National Tariff Workbook 2019-2020 Weighted average of currency codes VB01Z to VB09Z of resource use cited in 2017-2018 National Schedule of Reference Costs**
Ambulance use	£ 219.00	NHS Cost Recovery Scheme 2019–2020
Severe exacerbation-related hospitalisation	**£ 1,646.26**	**NHS National Tariff Workbook 2019–2020 [38]; Weighted HRG codes DZ15M-DZ15R of resource**

			use cited in 2017–2018 National Schedule of Reference Costs
	The ERG highlight that the unit costs should be taken from NHS reference costs for emergency room attendance and severe exacerbation related hospitalisation, rather than from the NHS National Tariff Workbook to be consistent.		
Why this issue is important	Although this will have negligible impact on cost-effectiveness results, this is important for consistency.		
Technical team preliminary judgement and rationale	The technical team suggest using the NHS reference costs: emergency department attendance £176.26 and severe exacerbation related hospitalisation £1579.45 for consistency.		

Issue 12 –Administration

Questions for engagement	20. How likely are patients to self-administer in practice? 21. Is the company's assumption of self-administration for 100% of patients for dose 4 onwards reasonable for the base case?
Background/description of issue	Dupilumab is administered via a subcutaneous injection every other week after the initial bolus dose. The medicine is available as a pre-filled syringe. There are no administration costs for background therapy as these treatments are inhaled or taken orally. **The company** assumed that the first 3 doses of drugs administered by subcutaneous injection would be administered by a healthcare professional, with self-administration (at no cost) after then. The summary of product characteristics states that patients or caregivers may self-inject dupilumab "if their healthcare

	professional determines that this is appropriate", and if so, that proper training should be provided (see SmPC page 4). **The ERG** report includes clinical advice it received in that self-administration, which is not currently considered for other biologic treatments, would be an advantage. However, an ERG expert questioned how patients would collect and store the drug at home, how training would be provided and noted that placebo effects for biologics may (in part) be due to regular healthcare professional contact.they highlighted that there may be issues with training and storage.
Why this issue is important	Self-administration is new in this indication so may take time to implement. Subcutaneous injections by self-administration compared with a healthcare professional increased the ICER slightly.
Technical team preliminary judgement and rationale	The proportion of people who are able to self-administer dupilumab should be informed by clinical opinion.

4. Issues for information

Tables 1 to 3 are provided to stakeholders for information only and we do not expect comments

Table 1: ERG preferred assumptions and impact on the cost-effectiveness estimate (based on the confidential discounted price of dupilumab) when compared with standard care

Alteration	ICER	Change from base case
Company base case EOS>=150 or FeNO>=25 & >=3 exacerbations not on mOCS	£28,087	
1. Long term severe exacerbation rate: trial data (multiplier=1)	£41,272	**+£13,185**
2. Utility limited to general population mean	£29,721	+£1,634
3. Include discontinuation in first year	£27,974	-£113

Alteration	ICER	Change from base case
4. Reference costs for A&E and hospitalisation	£28,152	+£65
5. Subcutaneous injections by healthcare professional	£28,973	+£886
Cumulative impact of the ERG's preferred assumptions on the cost-effectiveness estimate	£55,348	+£27,261
Company mixed population scenario EOS>=150 or FeNO>=25 & >=3 exacerbations with and without mOCS	£35,486	
1.Long term severe exacerbation rate: trial data (multiplier=1)	£46,437	+£10,951
2.Utility limited to general population mean	£37,277	+£1,791
3.Include discontinuation in first year	£35,430	-£56
4.Reference costs for A&E and hospitalisation	£35,544	+£58
5.Subcutaneous injections by healthcare professional	£36,579	+£1,093
Cumulative impact of the ERG's preferred assumptions on the cost-effectiveness estimate	£57,341	+£21,855

The ICERs for dupilumab compared with other biologics using their commercial price has been analysed and reported by the ERG in a separate confidential appendix. This is not presented in this technical report but will be considered by the committee.

An explanation and rationale of the changes made by the ERG which constitutes the ERG base case ICER is given in section 4.4.3 and 4.4.4 of the ERG report.

If the company or other stakeholders do not agree with the ERG assumptions underpinning the ERG base case a clear rationale and plausible alternative assumption should be given in the responses to consultation.

Table 2: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
There are many limitations in the ITC approaches.	For results comparing dupilumab with IL-5 biologics, NICE will need to interpret with caution.	Unknown
The model used to assess trial data from VENTURE does not include the moderate exacerbation health state (no data was available for this health state).	This is not consistent with the company's base case 4 health state model.	Unknown
The outcomes loss of asthma control (LOAC) event and severe exacerbation events seem to be overlapping, based on the definition provided for each	This may introduce double counting. The ERG asked about this in clarification question A7 because the footnotes to table 10 of the company submission gave the following definitions which overlap (and see Table 15 and p48/49 of ERG report): • LOAC event defined as any of the following: ≥6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol in a 24 hour period (compared with baseline) on 2 consecutive days, increase in ICS ≥4 times the dose at Visit 2, use or systemic corticosteroids for ≥3 days, hospitalisation or A&E visit because of asthma requiring corticosteroids; • A severe exacerbation event is defined as a use of systemic corticosteroids for ≥3 days (for VENTURE, at least double the	Unknown

	dose currently used), or hospitalisation or A&E visit because of asthma requiring systemic corticosteroids; The company have stated in clarification responses that severe exacerbations are excluded from moderate exacerbations in the model to avoid double counting.	
No long-term efficacy and safety data beyond trial period (52 weeks).	Long-term severe exacerbation rate would be useful if the data was available rather than being based on assumptions	Unknown

Table 3: Other issues for information

Issue	Comments
Adverse events	Treatment related adverse events were not considered in the economic model. The most frequent adverse event in the dupilumab trials was injection site reactions (15.2% with dupilumab vs. 5.4% with placebo) but the number of serious site reactions that lasted longer than 24 hours were similar and very low (0.3% vs. 0%) (see company submission B.3.3.12). The ERG notes that given the rates of adverse events reported in the dupilumab, the decision not to model treatment-related adverse events for drugs other than oral corticosteroids is reasonable. This is very unlikely to make a substantive difference to overall cost and QALY estimates and is consistent with the previous appraisal TA565.
Stopping rule	The marketing authorisation states that the need for continued therapy should be considered at least on an annual basis as determined by physician assessment of the patient's level of asthma control.

Issue	Comments
Continuation criteria	Response to treatment in the study was defined as at least 50% reduction in severe exacerbations or maintenance oral corticosteroid dose at 12 months. In practice, follow-up would be at least at 6 months.
Population	All 3 trials enrolled a wider population group than that specified by the NICE scope and the company's decision problem. The licensed indication is in a subgroup of the ITT population in the studies. In addition, the company further narrows this licensed indication population by limiting treatment to people who have had 3 or more exacerbations in the previous year in their proposed population to treat.
Exclusion of omalizumab as a comparator	The NICE scope includes omalizumab as a comparator. The company does not model an omalizumab eligible population, because they consider omalizumab to be out of scope "as allergic asthma, defined by IgE, is not considered to be part of the EMA licence for dupilumab". The ERG are of the same opinion.
Base case comparator	The company submission presents standard care as the only comparator for the base case, because NICE recommendations for other TA comparators are narrower (higher eosinophil counts). However, the company also presents 'exploratory' analyses with indirect comparisons for mepolizumab, reslizumab and benralizumab.
Outcomes	Data for the decision problem population is only available for 1 efficacy outcome that is based on post-hoc subgroup analysis.
Estimates of relative effects	Estimates of relative effects are only available for risks of severe exacerbations and OCS-related outcomes (dose reduction and withdrawal). The company assumes that incidence of moderate exacerbations and loss of control for other biologics are the same as for dupilumab. The ERG notes that this assumption is reasonable given the lack of comparative data, but it is an important limitation of the comparison with other biologics.
Equality considerations	No equalities issues were identified by the company, consultees and their nominated clinical experts and patient experts.

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Technical engagement response form

Dupilumab for treating severe asthma [ID1213]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **end of 10 January 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the) (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	**Eleanor Saunders**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Sanofi**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: What proportion of patients in the UK have severe asthma with Type 2 inflammation and how is severe asthma with Type 2 inflammation defined, diagnosed and treated in UK practice	
1. How many people in the UK have severe asthma with Type 2 inflammation?	The UK Severe Asthma Registry (UKSAR) contains data on over 2000 severe asthma patients and in their registry defined T2 inflammation ("T2 high") as blood eosinophil count (EOS) ≥150 cells/ µL EOS and Fractional Exhaled Nitric Oxide (FeNO) ≥25. This data published in December 2019, reports a prevalence of T2 inflammation as high as 83% (1) which supports the ranges presented in the company submission. The Wessex Severe Asthma Registry (WSAR) contains data on 273 patients and reported [redacted] as being T2 high.
2. How is severe asthma with Type 2 inflammation defined and diagnosed in clinical practice?	The Global Initiative for Asthma (GINA) guidelines define T2 inflammation as >150 EOS and/or >20 FeNO, sputum EOS >2%, and/or asthma that is clinically allergy-driven and/or need for maintenance OCS. There is currently no UK consensus on the definition of T2 inflammation driven severe asthma. In practice, a combination of clinical presentation (severity), raised biomarkers (EOS and/or FeNO) and +/- co-morbidities are all associated with severe asthma driven by type 2 inflammation. Both serum eosinophils and FeNO are collected routinely in secondary care when monitoring severe asthma patients and their measurement does not represent a change in clinical practice.
3. Are blood EOS level of ≥150 cells/microlitre and FeNO of ≥25 ppb (compared with ≥20 ppb in the GINA guideline) sufficient to identify people with Type 2 inflammation?	Yes according to the GINA guidelines and UK severe asthma registry, although as mentioned above; GINA has a lower FeNO limit of 20ppb. Other factors are the presence of co-morbid atopic conditions such as Atopic Dermatitis and nasal polyps.

Issue 2: **Generalisability of the population used in the model**	
4. Do the people in the post-hoc trial population proposed by the company represent patients in clinical practice who have severe asthma driven by Type 2 inflammation? What proportion of the post-hoc population were from the UK and how might this affect the generalisability of standard of care in the trial compared to clinical practice in the UK?	The number of patients from the UK that were included in the pivotal trials for dupilumab was 13, therefore the sub-total of UK patients from our trials is numerically too low to make generalisations about the national treatment landscape of these patients in the UK. Patients in the UK who are likely to benefit from dupilumab are similar to those in the pivotal trials. It is the company's position that observed effects would not differ and that treatment in the presented population from the clinical trials is consistent with UK current practice which was confirmed during the technical engagement call with the clinical expert. Therefore when comparing the SOC in these data sets with those in our trials, and through validation via UK key-opinion leaders, it is the company's position that the standard care in the clinical trials is generalisable to clinical practice in the UK.
Issue 3: Treatment of severe asthma caused by Type 2 inflammation	
5. Is standard care (high dose ICS [plus 1 or more controller therapy], with or without oral corticosteroids) the most relevant comparator? Would adding oral corticosteroids be a relevant comparator for people with uncontrolled asthma without oral corticosteroids?	Currently, standard care defined as high dose ICS [plus 1 or more controller therapy], with or without oral corticosteroids is the only treatment available for patients with EOS≥ 150 and/or FeNO ≥ 25 and ≥ 3 exacerbations. Standard care will include OCS for some patients. OCS is therefore already represented within current comparisons.
6. What proportion of patients with severe asthma driven by Type 2 inflammation (blood EOS ≥ 150 cells/microlitre and/or FeNO ≥25 ppb) would also be eligible for treatment with currently recommended	In the 150-299 EOS subgroup no patients would be eligible for the currently available anti-IL-5 monoclonal antibodies licensed in severe eosinophilic asthma due to NICE eligibility requirements of EOS ≥300 cells/microlitre. The proportion of patients in QUEST ITT with≥150 EOS – 299 EOS was 28% (507 patients). Clearly some of these patients will have concomitantly raised IgE and be eligible for Omalizumab. In our trials 2.5% of our total trial population would have been eligible for omalizumab within it's

biologics (mepolizumab, reslizumab, benralizumab, omalizumab)?	NICE recommendation. As per the clarification questions, omalizumab is not considered a comparator by NICE. This is because (i) dupilumab does not have a specific indication statement for IgE-mediated asthma; (ii) IgE has not been shown to be a predictor or response to dupilumab and (iii) the company believe that patients with convincing IgE-mediated severe asthma would be treated with omalizumab.
7. Will dupilumab be used in a population who have asthma that is of a similar severity to the population with severe asthma for whom biologics are currently recommended or will it be used in people with less severe asthma?	Dupilumab is licenced for patients with severe asthma driven by Type 2 inflammation with raised EOS and/or FeNO. Due to the referral pathway in the UK, patients seen in severe asthma hubs will be by default severe, with a minimum of 3 exacerbations in the last year. With severity denoted by exacerbations plus other clinical and diagnostic parameters, not biomarkers. The current biologics, specifically the anti-Il5 monoclonal antibodies target patients with severe asthma who have amongst other characteristics, raised eosinophils. Severe eosinophilic asthma is not more 'severe' than severe asthma with type 2 inflammation, but mediated by IL5 and not IL4 and IL13. An available analysis of the WSAR data has compared disease characteristics between patients that would be considered T2 high but with low and high eosinophilic signal groups. The groups were defined as follows: • *Low* eosinophilic signal (FeNO ≥25 to <50 or Blood Eosin ≥0.15 to <0.3 BUT with no criteria for high eosinophilic signal i.e. neither FeNO ≥50 or Blood Eosin ≥0.3) • *High* eosinophilic signal (FeNO ≥50 or Blood Eosin ≥0.3) Comparing between patients with 150-300 EOS & FeNO >25, vs >300 EOS & FeNO >50 groups showed burden of disease, treatments required, co-morbidity and lung function impairment, remained high across both groups. This data demonstrates that those patients with in the 150-300 eosinophil group still have significant disease burden, co-morbidity, poor control, reduced lung function, small airways disease and evidence of airway and peripheral inflammation despite

	treatment with high dose inhaled and oral corticosteroids, and have an unmet need that falls outside the current recommendations for anti-IL5 biologic treatment. Along with the high eosinophilic group, they also show airway reduction and reversibility, and may respond to a new treatment with a differentiated MOA, proven to reduce exacerbations and improve lung function. Cost-effectiveness results of patients with severe asthma and raised EOS (≥150) and raised FeNO (≥25 ppb) as well as in the severe eosinophilic asthma populations are also presented.
Issue 4: Which population is most relevant for decision making?	
8. Is the base case population with only non-mOCS patients (or a mixed population) most appropriate?	Clinical and cost-effectiveness varies between patients on high ICS only or on mOCS. Clinical practice indicates that mOCS use is declining, therefore analyses using a range of proportion of patients on OCS from 0% to 100% are presented. The 2010 study by Heaney demonstrated that 41.7% of patients in the UK with severe asthma are on maintenance OCS (2). A more recent study confirmed this number to be around 44% (1). However, these data may be over-estimating the proportion of patients on maintenance OCS, as the trend in OCS use has shifted with the introduction of biologic therapies. Most recently, the ERG and NICE technical team heard from a KOL during the technical engagement call, that no patients were initiated on maintenance OCS. Getting patients off maintenance OCS is a clinical priority, along with reducing severe exacerbations, due to the severe side effects of these treatments. Moving forwards, it is therefore estimated that the proportion of patients initiating biologic treatment from OCS will be even lower. In the updated company mixed population, the proportion of patients on maintenance OCS initiating dupilumab is an estimated 30%.
9. If the mixed population is appropriate, is standard care the only relevant comparator or should other biologics also be considered in the subset of people for whom they are eligible?	Both the mixed (ICS and mOCS) and ICS-only populations will include patients who are not eligible for anti-IL5 biologic therapies, therefore broadening access to treatment, and also will include patients who <u>are</u> currently eligible for anti IL5 biologics. Where anti-IL5 biologic treatment

	is the standard of care for that population, this should be the comparator. These data have been presented as scenarios with the revised assumptions.
10. What is the cost-effectiveness of dupilumab compared with standard care in the mOCS only population?	Scenarios with varying proportions of patients on maintenance OCS is provided in the confidential appendix.
Issue 5: Assumptions relating to proportion of population on mOCS for mixed population scenario	
11. In clinical practice, what proportion of patients are expected be on mOCS?	The original company base case of the mixed (ICS and mOCS) population used 41.7% (2), taken from a UK observational study of 5 severe asthma centres around the UK . A more recent publication estimated this proportion around 44%(1). However, both these studies may be overestimating the proportion of patients on maintenance OCS who would be initiating treatment. The availability of biologics for severe asthma patients (IGE mediated and severe eosinophilic asthma) has changed immensely over the past three years. Combined with clinical practice to prioritise patients on maintenance OCS to receive new treatments and stop or reduce OCS, it is understood that fewer patients are on maintenance OCS. This was confirmed by clinical opinion during the technical engagement call, who stated OCS use is decreasing all the time and was as low as 30% in some UK centres (Oxford).
Issue 6: Mixed population of different severities of asthma in the base case (non-mOCS) model	
12. Should a mixed population of different severities of asthma be used in the base case?	Asthma severity is defined by severe asthma exacerbations, lung function and other clinical parameters as well as impact on quality of life, not biomarkers (in isolation). Dupilumab is for severe asthma patients with Type 2 inflammation (EOS ≥150 and/or FeNO ≥25), which may include patients with severe eosinophilic asthma (recommended by NICE in EOS ≥300). Patients with severe eosinophilic asthma are not more severe than other patients with severe asthma as defined by other parameters.

	Analyses comparing dupilumab with existing biologics in severe eosinophilic asthma are presented.
13. Can the company provide additional data for a more accurate assessment of the cost-effectiveness of dupilumab in patients for whom standard care is the only treatment option?	The company has provided additional analyses for patients with severe asthma driven by Type 2 inflammation population who are not eligible for current anti-IL5 biologic therapies. The QUEST phase 3 clinical trial was conducted in 1902 patients and included more moderate patients on medium dose ICS or on the 300mg dose for dupilumab. Excluding these patients, and restricting to patients with the most severe asthma patients with Type 2 inflammation leads to a sample size of n= 101. This population is most representative of patients treated in severe asthma centres in the UK. Given the very small sample size, the company would request that these results are interpreted with the appropriate caution due to the width of confidence intervals which cause high uncertainty in the resulting ICER. The cost-effectiveness in the incremental population is presented in the Technical Appendix.
Issue 7: Multiplier assumption for the observed rates of severe exacerbations	
14. Should an adjustment be made to the observed rates of severe exacerbation in the model?	As noted in the submission the exacerbation rate among patients in the original company base case population treated with placebo in QUEST was considerably lower compared to the exacerbation rate in preceding year (2.391 versus 4.46). This can be attributed to three reasons, as confirmed with published evidence and clinical opinion: 1. Exclusion of patients with a recent severe exacerbation 2. Considering two exacerbation events occurring within 28 days to be one event 3. Improved adherence and monitoring in a clinical trial setting The lower rate of severe exacerbations during the trial is likely to underestimate the real world exacerbation rate in the target population treated with SOC. Therefore, a reasonable approach is making an informed adjustment to the post-trial exacerbation rates to enable a realistic estimate, and this is similar to the analysis adjustment recommended and undertaken in the mepolizumab NICE submission.

	It is estimated within the company submission and supported that inclusion of patients with a recent severe exacerbation would raise the risk of experiencing an exacerbation by a factor of [redacted] Relaxing the duration between exacerbation events to consider these separate would in fact raise the risk of experiencing exacerbations by a factor of [redacted]. Therefore, the likely combined effect of these aspects is [redacted] [redacted] was considered a conservative estimate. This aligns with estimates on the influence of adherence in the published literature and clinical expert opinion. For example, a systematic review and meta-analysis indicated that 25% increase in adherence was associated with an approximately a 10% (10%-25% reported across studies) reduction in severe exacerbations.(3) Mindful of the discussions during the technical engagement, a lower adjustment factor of 1.35 was applied to both the biologic and standard of care arm to match the adjustment previously accepted by the committee for the mepolizumab technology appraisal. This is an even more conservative approach, as calculations above have shown that the adjustment could be as high as [redacted]
Issue 8: Assumption relating to discontinuation rates	
15. Is no discontinuation within the first year of the model appropriate?	In the clinical trial, QUEST, some patients discontinued treatment before 12 months. Therefore, the company adopts the ERG preferred assumption of patients discontinuing treatment for any reason in the first year of treatment.
Issue 9: Treatment settings for severe exacerbations	
16. Should trial data be used to estimate the proportions of patients with severe exacerbations treated in emergency care and inpatient settings in the model?	Trial data is problematic as A&E and hospitalisation is a rare event in all severe asthma clinical trials, and exacerbations are treated differently by country according to local protocol (there are 22 countries in QUEST). Additionally, the ITT population in QUEST is much less severe than the presented population: 48.5% patients are on medium dose ICS and the mean rate of severe exacerbations is lower than the more severe population modelled in the company submission.

	As an exacerbation is the strongest predictor of a future asthma exacerbation, including less severe patients with fewer exacerbations reduces numbers of patients requiring treatment at A&E or hospitalisation. The presented population is patients with ≥3 exacerbations. However, the mean number of exacerbations in the ITT, in the previous year was 2.09. 77.3% patients had at least 1 but less than 3 severe asthma exacerbations in the previous year, which will underestimate the occurrence of severe asthma exacerbations requiring hospitalisation or A&E attendance. Given this, QUEST trial data is not an accurate or representative source of data on exacerbation setting for UK patients. A better approximation of exacerbation setting is UK real-world data. Two observational studies have collected UK data: O'Neill 2015, which was used in the company's original base case ((4)), and Bloom, 2015 ((5)) which showed even higher rates of A&E and hospitalisation for patients. Whilst the UK specific data is likely more appropriate, it is understood that the ERG and NICE had concerns with the use of this data. To accommodate this, the updated company assumptions also include the resource use data accepted in the mepolizumab technology appraisal (6) which is conservative compared with UK specific data.
Issue 10: Utility values	
17. Should the utility used for the controlled asthma (and uncontrolled asthma) health state be limited to general population mean?	The company submission used the utility data from the dupilumab clinical trials, as outlined in the NICE reference case. However, the company agrees with the ERG and NICE technical team that these data should not be higher than the utility for the general population mean and the updated company assumptions limit the uncontrolled asthma utility to the general population mean.
18. Which utility best reflects people in the uncontrolled asthma health state: a) 0.735 and 0.713 in the non-mOCS and the mOCS population	The company updated base case limits the utility of the uncontrolled asthma population to 0.702 and 0.682 in the non-mOCS and the mOCS population respectively.

respectively based on RCT data in the company submission b) 0.701 and 0.697 for standard care in the non-mOCS and mOCS population respectively from clinical trials in TA565, or c) c) 0.702 and 0.682 in the non-mOCS and the mOCS population respectively based on ERG calculations?	
Issue 11: Unit costs	
19. Is it appropriate to use weighted NHS National Tariff costs in the model?	The original company submission considered the weighted NHS National Tariff Costs to be more reflective of service usage in the UK for severe asthma. However, noting preference from the ERG for the source of cost of A&E and hospitalisation to be consistent with previous submissions, the company has updated the costs to include the ERG preferred cost assumption.
Issue 12: Administration	
20. How likely are patients to self-administer in practice?	Self-administration will be determined by clinical opinion based on patient and physician factors. Most HCPs will want their patients with severe asthma to be treated in hospital for the first 3-6 months before transitioning to homecare to ensure compliance and response. However, the process of self-administration is simple and supported by a patient support programme (PSP). There are to date 3,249 patients on homecare (active on treatments) receiving dupilumab for atopic dermatitis (AD). Of these, 3,633 (90.5%) are considered persistent patients. In AD, patients have been very receptive and persistent with self-administration of dupilumab,

21. Is the company's assumption of self-administration for 100% of patients for dose 4 onwards reasonable for the base case?	Based on the company's experience with AD, and published evidence reporting preference for self-administration in severe asthma, it is expected that the majority of patients with severe asthma will self-administer biologic treatments at home after initiation and self-administration training. (7)

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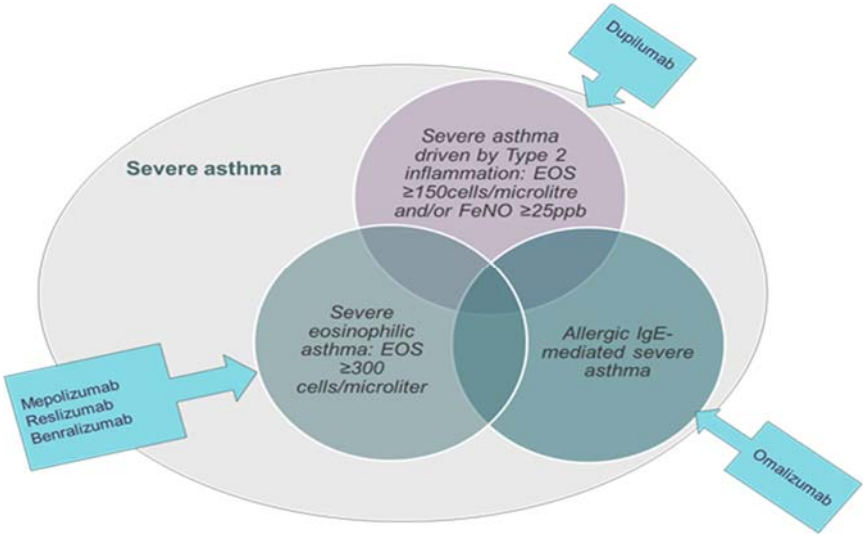
The company submission is for patients with severe asthma with Type 2 inflammation driven by EOS ≥ 150 and/or FeNO≥ 25 and ≥ 3 exacerbations. This population may include an overlapping population with existing biologics, as shown in

Figure 1.

Figure 1: **Biologic treatments for severe uncontrolled asthma on standard care (high dose inhaled corticosteroids [ICS]** [**plus 1 or more controller therapy] with or without maintenance oral corticosteroids [mOCS])**



Source: Draft Technical Report, Dupilumab, 2019

As discussed with the NICE technical team and the ERG, a request was made to include anti-IL-5 therapies in the economic comparison.

Using the company preferred assumptions following the technical engagement call, the ICERs were recalculated versus standard of care and anti-IL-5s. An additional restriction of EOS the base case was included for consideration, by restricting the base criteria to EOS≥150 and FeNO≥25 & ≥3 exacerbations.

Table 1: ICERs using company preferred assumptions vs SoC and anti-IL-5 biologics: ICS only

Population	Dupilumab		ICER
EOS≥150 and/or FeNO≥25 & ≥3 exacerbations without mOCS	**Incremental Cost**	**Incremental QALY**	
Vs. SoC	[redacted]	[redacted]	£ 34,216
EOS≥150 and FeNO≥25 & ≥3 exacerbations without mOCS	**Incremental Cost**	**Incremental QALY**	
Vs. SoC	[redacted]	[redacted]	£ 29,417
EOS≥ 300 and ≥4 exacerbations without OCS	[redacted]	[redacted]	
Vs. Mepolizumab	[redacted]	[redacted]	£ 18,606
Vs. Benralizumab	[redacted]	[redacted]	Dominant
EOS≥ 400 and ≥3 exacerbations	[redacted]	[redacted]	
Vs. Reslizumab	[redacted]	[redacted]	Dominant
Vs. Benralizumab	[redacted]	[redacted]	Dominant

The technical team and the ERG also requested these analyses with the inclusion of a proportion of patients on maintenance OCS. Following the technical engagement meeting and clinician direction, this proportion of patients was adjusted to 30%. See Sanofi response form.

Table 2: ICERs using company preferred assumptions vs SoC and anti-IL-5 biologics: mixed population (30% patients on mOCS)

Population	Dupilumab		ICER*
Company base case EOS≥150 or FeNO≥25 & (≥3 exacerbations or on mOCS)	**Incremental Cost**	**Incremental QALY**	
30% on mOCS (company base case for mixed population)	[redacted]	[redacted]	£ 40,172
Company base case EOS≥150 <u>and</u> FeNO≥25 & (≥3 exacerbations or on mOCS)	**Incremental Cost**	**Incremental QALY**	
30% on mOCS (company base case for mixed population)	[redacted]	[redacted]	£ 35,337
EOS≥ 300 and ≥4 exacerbations or on mOCS			
Vs. Mepolizumab	[redacted]	[redacted]	£ 25,034
Vs. Benralizumab	[redacted]	[redacted]	Dominant

Dupilumab has a novel mechanism of action via inhibition of the IL-4 and IL-13 pathways. Current biologics for severe asthma target either IL-5 or IgE and are only suitable for patients with severe eosinophilic asthma. Due to the distinct IL-4 and IL-13 pathways dupilumab targets a wider patient population compared with current biologic therapies.

APPENDIX: ADDITIONAL ANALYSES

As part of the NICE Technical Engagement for this technology appraisal, NICE have requested additional analyses of the dupilumab clinical trial data and using alternative assumptions to support the NICE Committee discussion and recommendation.

The cost-effectiveness model of dupilumab in patients with severe asthma driven by Type 2 inflammation defined by EOS ≥ 150 and/or FeNO ≥ 25 and ≥ 3 exacerbations, with or without maintenance oral corticosteroids (mOCS) is underpinned by assumptions. In response to the company submission (CS), the ERG base case had six alternative assumptions in the economic base case:

1. Long term severe exacerbation rate
2. Setting of severe asthma exacerbations
3. Utility limited to general population mean
4. Include discontinuation in first year
5. Reference costs for A&E and hospitalisation
6. Subcutaneous injections by healthcare professional

Additionally, it was also requested that analyses of different proportions of patients on maintenance OCS (varying between 0 and 100%) be presented and comparison with the anti-IL-5 biologics.

The company maintains that the assumptions in the original submission are a fair reflection of UK clinical practice. Specifically, based on clinical opinion and published data, it is reasonable to assume an exacerbation rate increase after the clinical trial period and to use accepted severe exacerbation settings from a previous technology appraisal. Subsequent to initial response, evidence suggests that retaining the self administration assumption is also appropriate and this is included in this appendix. Mindful of the discussions at the technical engagement step, adjustments have been made to the assumptions and are presented below.

a. Post-trial exacerbation adjustment

As noted in the submission the exacerbation rate among patients in the original company base case population treated with placebo in QUEST was considerably lower compared to the exacerbation rate in preceding year (2.391 versus 4.46). This can be attributed to three reasons, as confirmed with published evidence and clinical opinion:

1. Exclusion of patients with a recent severe exacerbation
2. Considering two exacerbation events occurring within 28 days to be one event
3. Improved adherence and monitoring in a clinical trial setting

The lower rate of severe exacerbations during the trial is likely to overestimate the benefit of placebo treatment. Therefore, an adjustment to the post-trial exacerbation rates is reasonable and has been performed and accepted in a previous technology appraisal for mepolizumab. These assumptions have been applied here.

b. Setting of exacerbations

Setting of severe exacerbations taken from trial data is problematic as A&E and hospitalisation is a rare event in all severe asthma clinical trials and exacerbations are

treated differently according to local protocol (there are 22 countries in QUEST). Additionally, the ITT population in QUEST is much less severe than the company base case: 48.5% patients are on medium dose ICS and the mean rate of severe exacerbations is lower than the inclusion criteria for the company base case.

As an exacerbation is the strongest predictor of a future asthma exacerbation, including less severe patients with fewer exacerbations reduces numbers of patients requiring treatment at A&E or hospitalisation.

The base case population is patients with ≥3 exacerbations. However, the mean number of exacerbations in the ITT, in the previous year was 2.09. 77.3% patients had at least 1 but less than 3 severe asthma exacerbations in the previous year, which will underestimate the occurrence of severe asthma exacerbations requiring hospitalisation or A&E attendance.

Given this, QUEST trial data is not an accurate or representative source for data on exacerbation setting for UK patients. A better approximation of exacerbation setting is UK real-world data. Two observational studies have collected UK data: O'Neill 2015, which was used in the company's original base case ((1)), and Bloom, 2015 ((2)) which showed even higher rates of A&E and hospitalisation for patients.

Whilst the UK specific data is likely more appropriate, it is understood that the ERG and NICE had concerns with the use of this data. To accommodate this, the updated company base case also includes the resource use data accepted in the mepolizumab technology appraisal (3) which is conservative compared with UK specific data.

c. Other assumptions

Assumptions of treatment cost, treatment discontinuation prior to the 12 month continuation criterion and utility of the controlled asthma population were aligned in the updated base case to align with the ERG/NICE preferred assumptions.

Additional Scenarios

NICE and the ERG have requested additional analyses to support the recommendation of dupilumab in severe asthma, considering the uncertainty around key assumptions, different populations, and proportion of patients on maintenance OCS. The parameters to be varied are shown in Table 3.

Permutations of all the available evidence to the updated assumptions lead to nearly 450 ICERs. The economic model has been updated to allow the user to run all the scenarios and permutations. Therefore, a pragmatic approach was taken, and the following key analyses are presented:

1. ERG base case
2. Company preferred assumptions
3. Additional Scenarios requested based on updated company base case
   - 3.1. Comparisons versus other biologics
   - 3.2. Assumptions of proportion of patients on maintenance OCS
   - 3.3. Assumptions for setting of exacerbations
   - 3.4. Assumptions for post-trial exacerbation rate
   - 3.5. Exploratory analysis of cost-effectiveness in incremental population

All scenarios are conducted using the company preferred assumptions.

Table 3: Parameters for additional analyses

Populations	Comparator	EOS	FeNO	% OCS	Post-trial exacerbation adjustment	Setting of Exacerbations
EOS ≥150 OR FeNO>= 25, ≥3 exacerbations +mOCS	Background therapy alone	≥150	OR	0%	1.000	Post-hoc analyses of QUEST & VENTURE
EOS ≥150 and <400 OR FeNO>= 25, =3 exacerbations +mOCS	Background therapy alone	≥150 and <400	OR	30%	[redacted]	Clinical trial data of similar population (TA431)
EOS ≥150 and <300 OR FeNO>= 25, ≥4 exacerbations +mOCS	Background therapy alone	≥150 and <300	OR	42%	[redacted]	Country-specific data (O'Neill 2015)
EOS ≥300, ≥4 exacerbations +mOCS	Benralizumab + background therapy	≥300	ANY	100%	1.350	
EOS ≥300, ≥4 exacerbations +mOCS	Mepolizumab + background therapy	≥300	ANY		[redacted]	
EOS ≥400, ≥3 exacerbations +mOCS	Benralizumab + background therapy	≥400	ANY			
EOS ≥400, ≥3 exacerbations	Reslizumab + background therapy	≥400	OR			

Results

1. Overview

The updated company submission includes changes to the six assumptions which the ERG highlighted in their report and included in their base case. Although the original assumptions are considered valid, the company has aligned with the ERG and NICE preferred assumptions:

1. Limit utility of controlled asthma patients to the general population
2. Include discontinuation of add-on treatment for any reason before the 12-month continuation assessment
3. Use the NHS Reference Costs

Therefore, these four assumptions are not explored further in the additional analyses.

In contrast, the ERG assumptions to not adjust the post-trial exacerbation rates and using the clinical trial setting of severe exacerbations (from the QUEST ITT) are considered to underestimate the value of treatment (see company response form). Instead, the company preferred assumptions includes data accepted in a previously accepted technology appraisal for severe asthma (TA 431, (4)).

Table 4: ERG and Company Assumptions in EOS≥ 150 and/or FeNO ≥ 25 and ≥ 3 exacerbations

Assumption	Company submission		ERG base case		Company preferred assumptions	
Long term severe exacerbation rate: trial data	[redacted]	Based on assumptions from QUEST and DRI trials	1	Assumes no adjustment to post-trial exacerbations	1.35	Adjustment accepted in previous technology appraisal for similar population (4)
Setting of treatment of severe exacerbations	**Exacerbation treatment setting** / **%** Office visit or Self-managed / 73.56% A&E visit / 7.79% Hospitalisation / 18.65%	Data from UK observational study (1)	**Exacerbation treatment setting** / **%** Office visit or Self-managed / 93.34% A&E visit / 3.00% Hospitalisation / 3.66%	QUEST ITT (5)	**Exacerbation treatment setting** / **%** Office visit or Self-managed / 83.07% A&E visit / 8.69% Hospitalisation / 8.24%	Setting accepted in previous technology appraisal for similar population (4)
Utility limited to general	No	Utilities for controlled and uncontrolled	Yes	Controlled asthma utility is unlikely to be	Yes	Sanofi accepts the ERG assumption

population mean		states were derived from QUEST		higher than utility of general population		
Include discontinuation in first year	No	It was assumed that all patients would continue treatment for 12 months	Yes	Patients may discontinue for any reason before 12 months	Yes	Sanofi accepts the ERG assumption
Reference costs for A&E and hospitalisation	No	From NHS National Tariff Workbook 2019-2020	Yes	NHS reference costs to match source used in previous appraisals	Yes	Sanofi accepts the ERG assumption
Subcutaneous injections by healthcare professional	No	Injections are assumed to be self-administered by the patient after the first 3	Yes	Injections are assumed to be administered by a healthcare professional	No	Injections are assumed to be self-administered by the patient after the first 3

2. ERG Base Case

The ERG preferred assumptions resulted in an ICER of £55,348.

3. Company Preferred Assumptions

3.1. Assumptions

Table 5: Company preferred assumptions

Assumption	#	Data	Justification
Long term severe exacerbation rate: trial data	1	1.35	KOLs were contacted to validate assumptions used in the economic model. One clinician specifically noted that removing these patients (i.e. with a recent exacerbation) will skew the data towards a lower rate. Both clinicians indicated that non-adherence to ICS would constitute another reason

<table>
<tr><td></td><td></td><td></td><td>for the difference in the rate observed among placebo patients during the trial versus the preceding year. This was also confirmed with the KOL during the technical engagement call.</td></tr>
<tr><td>Setting of treatment of severe exacerbations</td><td>2</td><td><table><tr><th>Exacerbation treatment setting</th><th>%</th></tr><tr><td>Office visit or Self-managed</td><td>83.07%</td></tr><tr><td>A&E visit</td><td>8.69%</td></tr><tr><td>Hospitalisation</td><td>8.24%</td></tr></table></td><td>The setting of exacerbations was taken from the accepted settings from TA431 (mepolizumab).
The UK data is the most appropriate to use as it reflects most closely the clinical practice in the UK rather than a global international clinical trial setting.
The clinical trial data was derived from the ITT population, as observations were too few in the specific population to derive reliable data. However, the ITT was a much broader a less severe population, including patients with few (<3) exacerbations at baseline, and patients on moderate ICS.
A second observational study (Bloom 2018) showed even higher rates of exacerbations treating in the hospital.
Therefore, we believe the rates from TA431 are a conservative estimate.</td></tr>
<tr><td>Subcutaneous injections by healthcare professional</td><td>3</td><td>100% patients are trained and self-administer biologic treatment after the first three (excluding reslizumab).</td><td>Experience in Atopic Dermatitis with dupilumab shows a high rate of persistent self-administration among users.
Additionally, a recent study shows the preference of self-administration of biologic treatment for patients with severe asthma. (6)</td></tr>
</table>

Additional analyses for a restricted population of patients with severe asthma with Type 2 inflammation and EOS ≥150 and FeNO ≥25 and ≥ 3 exacerbations is presented.

3.2. Results

Working off the ERG base case, the company revised base case with revised assumptions 1 and 2 shown in Table 6 is shown here.

Table 6: Results with updated company preferred assumptions: ICS only

Alteration	Dupilumab		SC		ICER
Populations	**QALY**	**Cost**	**QALY**	**Cost**	
EOS>=150 and/or FeNO>=25 & >=3 exacerbations not on mOCS	[redacted]	[redacted]	[redacted]	[redacted]	£34,216
EOS>=150 and FeNO>=25 & >=3 exacerbations not on mOCS	[redacted]	[redacted]	[redacted]	[redacted]	£29,417

4. Comparison to anti-IL-5 biologics

4.1. Assumptions

The analyses comparing dupilumab with anti-IL-5 biologic treatments were re-run to include the updated assumptions outlined in Table 4. In the mixed population (ICS/mOCS), it is assumed that 30% of patients are on maintenance OCS, consistent with the updated company preferred assumptions. A 40% discount is assumed on comparator treatment list prices.

4.2. Results

Table 7: Results in biologic-eligible populations

Population	Dupilumab		ICER
EOS≥ 300 and >=4 exacerbations without OCS	**Incremental Cost**	**Incremental QALY**	
Vs. Mepolizumab	[redacted]	[redacted]	£ 18,606
Vs. Benralizumab	[redacted]	[redacted]	Dominant
EOS≥ 300 and >=4 exacerbations and 30% mOCS	**Incremental Cost**	**Incremental QALY**	
Vs. Mepolizumab	[redacted]	[redacted]	£ 25,034
Vs. Benralizumab	[redacted]	[redacted]	Dominant
EOS≥ 400 and >=3 exacerbations	**Incremental Cost**	**Incremental QALY**	
Vs. Reslizumab	[redacted]	[redacted]	Dominant
Vs. Benralizumab	[redacted]	[redacted]	Dominant

5. Patients on maintenance OCS

5.1. Assumptions

The base case of the mixed population was also updated, and scenarios are presented below showing a range of OCS. During the technical engagement, the clinician confirmed that no new patients are initiated on maintenance OCS, and therefore the proportion of patients on maintenance OCS initiation biologic treatment is decreasing. As requested, we

present a range of the proportion of patients on maintenance OCS to the updated company base case, and the impact on the ICERs.

5.2. Results: Proportion of patients on maintenance OCS

Table 8: ICER by proportion of patients on mOCS versus Standard Care

Population	Dupilumab		ICER
EOS>=150 or FeNO>=25 & >=3 exacerbations or on mOCS	**Incremental Cost**	**Incremental QALY**	
0% on mOCS (company preferred assumption)	[redacted]	[redacted]	£ 34,216
30% on mOCS (company preferred assumption for mixed population)	[redacted]	[redacted]	£ 40,172
41.7% patients on mOCS (Heaney 2010) (original company base case in mixed population)	[redacted]	[redacted]	£ 42,507
44% patients on mOCS per clinical opinion	[redacted]	[redacted]	£ 42,894
100% patients on mOCS (Analysis requested by NICE)	[redacted]	[redacted]	£ 53,441

6. Setting of exacerbations

6.1. Assumptions

In the updated company base case, setting of treatment of severe exacerbations resource use was taken from the mepolizumab technology appraisal. The data is more comparable to the dupilumab modelled population compared with the QUEST ITT resource use. The clinical trial data was derived from the ITT population, as observations were too few in the specific population to derive reliable data. However, the ITT was a much broader a less severe population, including patients with few (<3) exacerbations at baseline, and patients on moderate ICS. QUEST is a phase 3 clinical trial conducted in patients with medium-high dose ICS and ≥1 severe asthma exacerbation in the previous year. 48.5% patients were on medium dose ICS and the mean number of exacerbations in the previous year was 2.09 and 77.3% patients had at least 1 but less than 3 severe asthma exacerbations in the previous year. As an exacerbation is the strongest predictor of a future asthma exacerbation, including these patients is likely to underestimate the occurrence of severe asthma exacerbations requiring medical attention.

Two observational studies collected resource use and setting of severe asthma exacerbations in the UK. Both studies, Bloom 2018 (2) and O'Neill 2015 (1) reported higher rates of treatment in A&E and hospitalisation than the dupilumab clinical trials. KOL input confirmed that in a clinical trial context, patients are more likely to be followed and controlled reducing the frequency of exacerbations, and exacerbations are likely to be less severe.

The company base case includes the treatment setting from the mepolizumab technology appraisal and considers this conservative data, compared to what could be expected in UK clinical practice.

6.2. Results: Impact of setting of exacerbations

Table 9: Results by setting of exacerbations

Alteration to setting of severe exacerbations	**Dupilumab**		**ICER**
EOS>=150 or FeNO>=25 & >=3 exacerbations	**Incremental Cost**	**Incremental QALY**	
QUEST Clinical Trial settings	[redacted]	[redacted]	£ 40,119
UK Observational trials (1)	[redacted]	[redacted]	£ 31,692
Company updated assumption: Mepolizumab technology appraisal data (3)	[redacted]	[redacted]	£ 34,216

7. Post-trial exacerbation adjustment

7.1. Assumptions

The company submission assumed an adjustment of severe exacerbation rates after the clinical trial of [redacted] to account for clinical trial protocol which is likely to underestimate the actual rate of severe asthma exacerbations for three reasons:

1. Exclusion of patients with a recent severe exacerbation, excludes patient most likely to have another severe exacerbation
2. Considering two exacerbation events occurring within 28 days to be one event
3. Improved adherence and monitoring in a clinical trial setting

In the updated company base case, post-trial exacerbation rate adjustment is 1.35, which was accepted in the mepolizumab technology appraisal (TA431 (4)).

7.2. Results

Table 10: Results by post-trial exacerbation rate adjustment: ICS only

Alteration by post-trial exacerbation rate adjustment	**Adjustment factor**	**Dupilumab**		**ICER**
EOS>=150 or FeNO>=25 & >=3 exacerbations		**Incremental Cost**	**Incremental QALY**	
No adjustment (ERG base case)	[redacted]	[redacted]	[redacted]	£ 46,619
Adjustment	[redacted]	[redacted]	[redacted]	£ 42,168
Adjustment	[redacted]	[redacted]	[redacted]	£ 38,699
Adjustment from mepolizumab technology appraisal (updated company preferred assumptions)	[redacted]	[redacted]	[redacted]	£ 34,216
Adjustment in original company base case	[redacted]	[redacted]	[redacted]	£ 32,110
Adjustment	[redacted]	[redacted]	[redacted]	£ 30,529

Table 11: Results by post-trial exacerbation rate adjustment: mixed population (30% mOCS)

Alteration by post-trial exacerbation rate adjustment	Adjustment factor	Dupilumab		ICER
EOS>=150 or FeNO>=25 & >=3 exacerbations (70%) or mOCS (30%)		**Incremental Cost**	**Incremental QALY**	
No adjustment (ERG base case)	[redacted]	[redacted]	[redacted]	£ 51,059
Adjustment	[redacted]	[redacted]	[redacted]	£ 47,291
Adjustment	[redacted]	[redacted]	[redacted]	£ 44,228
Adjustment from mepolizumab technology appraisal (updated company base case)	[redacted]	[redacted]	[redacted]	£ 40,172
Adjustment in CS	[redacted]	[redacted]	[redacted]	£ 38,217
Adjustment	[redacted]	[redacted]	[redacted]	£ 36,726

8. Incremental Analysis

The incremental population is defined as the severe asthma driven by Type inflammation defined as raised EOS (≥150) and/or raised FeNO (≥25) and ≥ 3 severe asthma exacerbations that does not have access to mepolizumab, benralizumab or reslizumab. This population is therefore defined as:

- Patients with 4+ exacerbations not eligible to IL-5 (mepolizumab, benralizumab or reslizumab): ≥4 exacerbations and ((EOS between 150-299) or (EOS<150 and FeNo≥25))

- Patients with =3 exacerbations not eligible to IL-5 (mepolizumab, benralizumab or reslizumab): =3 exacerbations and ((EOS between 150-399) or (EOS<150 and FeNo≥25))

8.1. Clinical data

The trial sample size who are not eligible for biologic treatment was considered too small to derive a meaningful incremental cost-effectiveness ratio (ICER).

Table 12: Trial sample size of modelled population not eligible for another biologic

	1.14mL/200mg q2w		2mL/300mg q2w		
n(%) in the ITT population	**Placebo (N=317)**	**Dupilumab (N=631)**	**Placebo (N=321)**	**Dupilumab (N=633)**	**All (N=1902)**
Incremental population	12 (3.8%)	29 (4.6%)	16 (5.0%)	36 (5.7%)	93 (4.9%)

The efficacy data of these data are shown here:

Table 13: Annualized event rate of severe exacerbation during the 52 weeks in the incremental population

	1.14mL/200mg q2w	
Incremental Population	**Placebo (N=12)**	**Dupilumab (N=29)**
Total number of severe exacerbation events	[redacted]	[redacted]
Total patient-years followed	[redacted]	[redacted]
Unadjusted annualized rate of severe exacerbation events	[redacted]	[redacted]
Adjusted annualized rate of severe exacerbation events		
Estimate (95% CI)	[redacted]	[redacted]
Relative risk (95% CI)		[redacted]
p-value		[redacted]
Risk difference (95% CI)		[redacted]

As the data were considered unreliable due to sample size, an alternative method for deriving the ICER in the population for which SC is the only alternative was used.

8.2. Methods to derive the cost-effectiveness in the incremental population

Deriving the cost and effectiveness for the incremental population was conducted in three steps to capture both populations:

1. The subgroup with ≥4 exacerbations and ((EOS between 150-299) or (EOS<150 and FeNo≥25)) was estimated by taking the subgroup with ≥ 1 exacerbation and ((EOS between 150-299) or (EOS<150 and FeNO ≥25)) as a reference and apply multipliers to these data to reflect the risk of exacerbation in the ≥4 exacerbations subgroup.
2. The subgroup with =3 exacerbations and ((EOS between 150-399) or (EOS<150 and FeNo≥ 25)) was estimated by taking the subgroup with 1+ exacerbation and ((EOS between 150-399) or (EOS<150 and Feno>=25)) as a reference and apply multipliers to these data to reflect the risk of exacerbation in the =3 exacerbations subgroup.
3. The weighted average of the cost and of the effectiveness of these two populations was calculated to estimate the cost effectiveness of dupilumab in the incremental population. A 60%/40% split was assumed in the patients with EOS ≥150 and <400 OR FeNO>= 25, =3 exacerbations +mOCS and EOS ≥150 and <300 OR FeNO>= 25, ≥4 exacerbations +mOCS, respectively.

8.3. Results

Table 14: Cost-effectiveness of incremental population vs SoC

Population	Incremental Cost	Incremental QALY	ICER
EOS ≥150 and <400 OR FeNO>= 25, =3 exacerbations no OCS	[redacted]	[redacted]	£ 56,441
EOS ≥150 and <300 OR FeNO>= 25, ≥4 exacerbations no OCS	[redacted]	[redacted]	£ 43,980
Updated company preferred assumptions	[redacted]	[redacted]	
EOS ≥150 and <400 OR FeNO>= 25, =3 exacerbations and EOS ≥150 and <300 OR FeNO>= 25, ≥4 exacerbations: ICS only	[redacted]	[redacted]	£ 50,558
EOS ≥150 and <400 OR FeNO>= 25, =3 exacerbations and EOS ≥150 and <300 OR FeNO>= 25, ≥4 exacerbations: 30% mOCS	[redacted]	[redacted]	£ 51,683

Given the very small sample size, these ICERs should be interpreted with caution.

Conclusion

Dupilumab has an innovative mechanism of action and offers an effective treatment for patients by targeting the IL-4 and IL-13 pathways complementing the current treatments for severe asthma targeting the IL-5 pathway.

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NICE National Institute for Health and Care Excellence

Technical engagement response form

Dupilumab for treating severe asthma [ID1213]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **end of 10 January 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Asthma UK**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: What proportion of patients in the UK have severe asthma with Type 2 inflammation and how is severe asthma with Type 2 inflammation defined, diagnosed and treated in UK practice	
1. How many people in the UK have severe asthma with Type 2 inflammation?	We estimate there are 200,000 people in the UK with severe asthma. Of these, the large majority will have Type 2 inflammation. Non-Type 2 asthma is approximately 30-50% of the general asthma population, but this is suspected to be much less in the severe asthma population (~5%- unpublished estimate). Our report 'Living in Limbo' found that 3.4% of the UK asthma population had three or more courses of OCS in 2016, this equates to 110,000-145,000 people with asthma.
2. How is severe asthma with Type 2 inflammation defined and diagnosed in clinical practice?	Severe asthma with Type 2 inflammation is currently diagnosed using blood eosinophils, FeNO or IgE levels and number of asthma attacks in the last 12 months. In order to get a diagnosis of severe asthma you must be referred from your GP or local hospital to a specialist asthma centre.
3. Are blood EOS level of ≥150 cells/microlitre and FeNO of ≥25 ppb (compared with ≥20 ppb in the GINA guideline) sufficient to identify people with Type 2 inflammation?	N/A
Issue 2: Generalisability of the population used in the model	
4. Do the people in the post-hoc trial population proposed by the company represent patients in clinical practice who have severe asthma driven by Type 2 inflammation? What proportion of the post-hoc population were from the UK and how might this affect the	Yes, in the QUEST trial the eosinophil count indicates Type 2 inflammation and the number of exacerbations indicates severe asthma in line with the BTS definition (more than 2 asthma attacks

generalisability of standard of care in the trial compared to clinical practice in the UK?	in the previous 12 months). For VENTURE, the eosinophil count indicates Type 2 inflammation and the population is on maintenance oral steroids which also indicates severe asthma. We know there is an issue with the patients recruited to biologic RCTs being less severe than the UK clinical setting. However, in practice this often means that the biologics have even greater efficacy when used in a real-world UK setting.
Issue 3: Treatment of severe asthma caused by Type 2 inflammation	
5. Is standard care (high dose ICS [plus 1 or more controller therapy], with or without oral corticosteroids) the most relevant comparator? Would adding oral corticosteroids be a relevant comparator for people with uncontrolled asthma without oral corticosteroids?	Yes, this is the usual standard care for people with severe asthma. No, maintenance oral steroids have devastating side effects and can lead to diabetes and osteoporosis. No one should now be started on maintenance oral steroids and this line of treatment should be avoided if possible. We know that since biologics have been introduced, severe asthma specialists are no longer starting people on maintenance oral steroids.
6. What proportion of patients with severe asthma driven by Type 2 inflammation (blood EOS ≥ 150 cells/microlitre and/or FeNO ≥25 ppb) would also be eligible for treatment with currently recommended biologics (mepolizumab, reslizumab, benralizumab, omalizumab)?	It has been estimated that 41% of people eligible for an anti-IL5 biologic are also eligible for omalizumab (IgE mediated). It is therefore expected that there will be some overlap with dupilumab. However, it is important to note that dupilumab blocks a different mechanistic pathway to the already existing biologics. Therefore, if someone has not responded to one of the other biologics, they may respond well to dupilumab. There will also be a group of people who will only be eligible for dupilumab, as the existing criteria for the anti-IL5 biologics have much higher blood eosinophil counts, it therefore could treat many people who are having frequent and life-threatening asthma attacks and are currently not eligible for a biologic.
7. Will dupilumab be used in a population who have asthma that is of a similar severity to the population with severe asthma for whom biologics are currently	The proposal is that dupilumab will be used on a population who are on optimised standard therapy (high dose ICS and a controller) but experiencing more than two asthma attacks a year. This is the same number of asthma attacks to qualify for reslizumab and benralizumab, which indicates similar severity. EOS level can help identify people with more severe disease, however

recommended or will it be used in people with less severe asthma?	the number of asthma attacks should be the prime indicator of severity (when on optimised standard therapy).
Issue 4: Which population is most relevant for decision making?	
8. Is the base case population with only non-mOCS patients (or a mixed population) most appropriate?	It should be considered by NICE that maintenance oral steroids are no longer a justifiable line of treatment for people with asthma and we should see this treatment declining. Instead, people with asthma should be prescribed a biologic where possible.
9. If the mixed population is appropriate, is standard care the only relevant comparator or should other biologics also be considered in the subset of people for whom they are eligible?	N/A
10. What is the cost-effectiveness of dupilumab compared with standard care in the mOCS only population?	N/A
Issue 5: Assumptions relating to proportion of population on mOCS for mixed population scenario	
11. In clinical practice, what proportion of patients are expected be on mOCS?	Kerkhof et al. (2017) estimate 2.9% of the general population are on mOCS and 16.6% of those with severe uncontrolled eosinophilic asthma (defined as high dose ICS and LABA, two or more asthma attacks, a high blood eosinophil count (≥0.3×109/L) in the last year).
Issue 6: Mixed population of different severities of asthma in the base case (non-mOCS) model	
12. Should a mixed population of different severities of asthma be used in the base case?	N/A

13. Can the company provide additional data for a more accurate assessment of the cost-effectiveness of dupilumab in patients for whom standard care is the only treatment option?	The company should be considering the long-term devastating side effects of oral steroids. It has been shown that even one course of steroids can have lasting consequences on people with asthma's health and there are long-term financial costs to the NHS because of this. Therefore, the economic model should consider the benefits of stopping or reducing oral steroid use (maintenance or short courses) because of biologic treatment.
Issue 7: Multiplier assumption for the observed rates of severe exacerbations	
14. Should an adjustment be made to the observed rates of severe exacerbation in the model?	N/A
Issue 8: Assumption relating to discontinuation rates	
15. Is no discontinuation within the first year of the model appropriate?	N/A
Issue 9: Treatment settings for severe exacerbations	
16. Should trial data be used to estimate the proportions of patients with severe exacerbations treated in emergency care and inpatient settings in the model?	N/A
Issue 10: Utility values	
17. Should the utility used for the controlled asthma (and uncontrolled asthma) health state be limited to general population mean?	N/A
18. Which utility best reflects people in the uncontrolled asthma health state:	N/A

a) 0.735 and 0.713 in the non-mOCS and the mOCS population respectively based on RCT data in the company submission b) 0.701 and 0.697 for standard care in the non-mOCS and mOCS population respectively from clinical trials in TA565, or c) c) 0.702 and 0.682 in the non-mOCS and the mOCS population respectively based on ERG calculations?	
Issue 11: Unit costs	
19. Is it appropriate to use weighted NHS National Tariff costs in the model?	N/A
Issue 12: Administration	
20. How likely are patients to self-administer in practice?	From our qualitative research we know that people with severe asthma, who are on hospital administered biologics, are very keen to have the option to self-administer at home because of the amount of time it takes to go to an appointment at a specialist centre. However, they are keen to ensure they receive regular specialist check-ups and so this should be part of a shared decision-making process with the clinician.
21. Is the company's assumption of self-administration for 100% of patients for dose 4 onwards reasonable for the base case?	N/A

NICE National Institute for Health and Care Excellence

Technical engagement response form

Dupilumab for treating severe asthma [ID1213]

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Deadline for comments **end of 10 January 2020**

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- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Association of Respiratory Nurse Specialists**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: What proportion of patients in the UK have severe asthma with Type 2 inflammation and how is severe asthma with Type 2 inflammation defined, diagnosed and treated in UK practice	
1. How many people in the UK have severe asthma with Type 2 inflammation?	**Around 40-50,000**
2. How is severe asthma with Type 2 inflammation defined and diagnosed in clinical practice?	**Ongoing symptoms despite compliance with high dose, multi-drug regimens and with persistently raised eosinophil levels.**
3. Are blood EOS level of ≥150 cells/microlitre and FeNO of ≥25 ppb (compared with ≥20 ppb in the GINA guideline) sufficient to identify people with Type 2 inflammation?	**Yes**
Issue 2: Generalisability of the population used in the model	
4. Do the people in the post-hoc trial population proposed by the company represent patients in clinical practice who have severe asthma driven by Type 2 inflammation? What proportion of the post-hoc population were from the UK and how might this affect the generalisability of standard of care in the trial compared to clinical practice in the UK?	**This information, where available, is contained within the trial data. As the UK has one of the highest levels of asthma morbidity and mortality, this is likely to be representative of and applicable to UK populations.**

Issue 3: Treatment of severe asthma caused by Type 2 inflammation	
5. Is standard care (high dose ICS [plus 1 or more controller therapy], with or without oral corticosteroids) the most relevant comparator? Would adding oral corticosteroids be a relevant comparator for people with uncontrolled asthma without oral corticosteroids?	**Yes, but the risk benefit profile of doing so v this intervention is likely to be less favourable.**
6. What proportion of patients with severe asthma driven by Type 2 inflammation (blood EOS ≥ 150 cells/microlitre and/or FeNO ≥25 ppb) would also be eligible for treatment with currently recommended biologics (mepolizumab, reslizumab, benralizumab, omalizumab)?	**Not possible to state as this is assessed individually.**
7. Will dupilumab be used in a population who have asthma that is of a similar severity to the population with severe asthma for whom biologics are currently recommended or will it be used in people with less severe asthma?	**See q6**
Issue 4: Which population is most relevant for decision making?	
8. Is the base case population with only non-mOCS patients (or a mixed population) most appropriate?	

9. If the mixed population is appropriate, is standard care the only relevant comparator or should other biologics also be considered in the subset of people for whom they are eligible? 9. If the mixed population is appropriate, is standard care the only relevant comparator or should other biologics also be considered in the subset of people for whom they are eligible?	
10. What is the cost-effectiveness of dupilumab compared with standard care in the mOCS only population?	
Issue 5: Assumptions relating to proportion of population on mOCS for mixed population scenario	
11. In clinical practice, what proportion of patients are expected be on mOCS?	
Issue 6: Mixed population of different severities of asthma in the base case (non-mOCS) model	
12. Should a mixed population of different severities of asthma be used in the base case?	Potentially, yes.
13. Can the company provide additional data for a more accurate assessment of the cost-effectiveness of dupilumab in patients for whom standard care is the only treatment option?	Not known – for the company to decide
Issue 7: Multiplier assumption for the observed rates of severe exacerbations	

14. Should an adjustment be made to the observed rates of severe exacerbation in the model?	
Issue 8: Assumption relating to discontinuation rates	
15. Is no discontinuation within the first year of the model appropriate?	
Issue 9: Treatment settings for severe exacerbations	
16. Should trial data be used to estimate the proportions of patients with severe exacerbations treated in emergency care and inpatient settings in the model?	
Issue 10: Utility values	
17. Should the utility used for the controlled asthma (and uncontrolled asthma) health state be limited to general population mean?	
18. Which utility best reflects people in the uncontrolled asthma health state: a) 0.735 and 0.713 in the non-mOCS and the mOCS population respectively based on RCT data in the company submission b) 0.701 and 0.697 for standard care in the non-mOCS and mOCS population respectively from clinical trials in TA565, or c) c) 0.702 and 0.682 in the non-mOCS and the mOCS population	

respectively based on ERG calculations?	
Issue 11: Unit costs	
19. Is it appropriate to use weighted NHS National Tariff costs in the model?	
Issue 12: Administration	
20. How likely are patients to self-administer in practice?	Self-administration is not suitable for every patient. Some patients are confident to do this and others are not. Some patients are not reliable so self-administration would not be recommended in such patients.
21. Is the company's assumption of self-administration for 100% of patients for dose 4 onwards reasonable for the base case?	No – I think it is feasible for patients to self-administer for dose 4 onwards but I do not this you can make the assumption that 100% of patients will be able to or willing to do this.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Dupilumab for treating severe asthma [ID1213]

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**British Thoracic Society**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: What proportion of patients in the UK have severe asthma with Type 2 inflammation and how is severe asthma with Type 2 inflammation defined, diagnosed and treated in UK practice	
1. How many people in the UK have severe asthma with Type 2 inflammation?	**Between 60-80% of people with severe asthma in the UK have Type 2 inflammation. Approximately 3.5-5% of people with asthma in the UK have severe asthma.** **UK data for children is not easy to find but it is estimated that approximately 5% of children with asthma have severe asthma and the majority of children have type 2 inflammation.**
2. How is severe asthma with Type 2 inflammation defined and diagnosed in clinical practice?	**Different guidance contains slightly different cut off levels but broadly speaking it is diagnosed on the presence of either raised peripheral blood eosinophils and/or FeNO in people taking at least GINA step IV background therapy and with uncontrolled symptoms (ACT<20, ACQ>1.5)**
3. Are blood EOS level of ≥150 cells/microlitre and FeNO of ≥25 ppb (compared with ≥20 ppb in the GINA guideline) sufficient to identify people with Type 2 inflammation?	**Yes, presuming that they are adherent with background therapy** **Pivotal clinical trials in drugs used to block T2 inflammation, generally start to show a signal once values are ≥150 and ≥25. However, higher cut offs, more clearly identify patients with T2 high asthma, and are also associated with more significant, clearer benefits with these drugs.** **Dupilumab is licensed from 12 years only and the current evidence would suggest that the cut-offs proposed (blood eosinophils ≥150 cells/microlitre and FeNO of ≥25 ppb) would be appropriate. There is much less robust data in adolescents however compared to adults. In addition corticosteroid treatment suppresses type 2 inflammation.**

Issue 2: Generalisability of the population used in the model	
4. Do the people in the post-hoc trial population proposed by the company represent patients in clinical practice who have severe asthma driven by Type 2 inflammation? What proportion of the post-hoc population were from the UK and how might this affect the generalisability of standard of care in the trial compared to clinical practice in the UK?	**We would suggest a combination of eos ≥ 150 and FeNO ≥ 25ppb, to ensure that patients with Type 2 inflammation are targeted. Only 13 subjects from the UK participated in the phase III pivotal trials, however, the standard of care in the trial was identical to UK practice.** **We would also suggest that the population includes people on continuous OCS as well as frequent exacerbators, i.e. a mixed population.** **We disagree with the statement to not to include omalizumab as a comparator as IgE mediated asthma is invariably driven by Type 2 inflammation.** **A combination of blood eosinophils ≥ 300 and FeNO ≥ 25ppb may be best for adolescents. Only 68 adolescents (12 to 17 years) internationally received dupilumab as part of the Phase III study compared to > 1000 adults. If only 13 participants were form the UK the number of adolescents was likely very low or non-existent but I do not have this data.** **The standard of care in the trial was identical to UK practice.** **I would also tend to disagree with the statement to not to include omalizumab as a comparator.**
Issue 3: Treatment of severe asthma caused by Type 2 inflammation	
5. Is standard care (high dose ICS [plus 1 or more controller therapy], with or without oral corticosteroids) the most relevant comparator? Would adding oral corticosteroids be a relevant comparator for	**Yes, this is the relevant comparator. Adding OCS is not a relevant comparator given the significant morbidity associated with OCS exposure, unless the patients are not eligible for any of the other available biologics.**

people with uncontrolled asthma without oral corticosteroids?	
6. What proportion of patients with severe asthma driven by Type 2 inflammation (blood EOS ≥ 150 cells/microlitre and/or FeNO ≥25 ppb) would also be eligible for treatment with currently recommended biologics (mepolizumab, reslizumab, benralizumab, omalizumab)?	**There is considerable overlap with blood eos ≥ 300 for mepolizumab and benralizumab and with eos ≥ 400 with reslizumab and benralizumab given the current HTA. There would also be overlap with omalizumab, although no biomarker is pre-specified in the HTA. Use of FeNO to guide patient selection for dupilumab is unique amongst asthma biologics and a logical step towards personalised therapy. The only way to get precise percentages would be to use data from the UK severe asthma registry, it is likely that at least 50% of patients will overlap between the different biologic choices.** **This is hard to say for adolescents as there is no national funding for severe asthma in children and no reliable database.**
7. Will dupilumab be used in a population who have asthma that is of a similar severity to the population with severe asthma for whom biologics are currently recommended or will it be used in people with less severe asthma?	**It will be used in the same population**
Issue 4: Which population is most relevant for decision making?	
8. Is the base case population with only non-mOCS patients (or a mixed population) most appropriate?	**It is inappropriate to exclude patients on mOCS as there is a very significant unmet need in this group and mOCS have a multitude of both short term and long term side effects. We strongly advise a mixed population.**
9. If the mixed population is appropriate, is standard care the only relevant comparator or should other biologics also be considered in the subset of people for whom they are eligible?	**Other biologics should also be considered.**

10. What is the cost-effectiveness of dupilumab compared with standard care in the mOCS only population?	**Patients on mOCS continue to exacerbate and dupilumab will decrease their exacerbation frequency. Multiple publications are available on both the short term and long term impact of OCS including the cumulative dose risk and the increased prescribing required to treat OCS induced co-morbidities. Dupilumab will impact on this by its OCS sparing effect.** **Cost effectiveness of dupilumab will be a combination of direct savings i.e. reduction in costs associated with severe exacerbations (hospital admissions, ambulance costs etc) and indirect costs (time not lost at work) with additional reductions in costs associated with the management of steroid side effects (fractures, diabetes etc)**
Issue 5: Assumptions relating to proportion of population on mOCS for mixed population scenario	
11. In clinical practice, what proportion of patients are expected be on mOCS?	**50% of adult patients are on OCS at the time of referral to a UK severe asthma centre. With the increasing use of biologics the overall proportion on mOCS would be expected to reduce significantly as this is the target population** **The proportion in children and adolescents is lower. There are no reliable data sources for children but I would estimate numbers in tertiary clinics to be no more than 5 to 10% although there is likely to be regional variation.**
Issue 6: Mixed population of different severities of asthma in the base case (non-mOCS) model	
12. Should a mixed population of different severities of asthma be used in the base case?	**No, the focus should be on severe asthma (ERS/ATS definition). Asthma severity is not predicated on eos count, it is simply a predictor of response to biologic. Dupilumab should**

	be positioned as a first line option for the correct patient, please refer to GINA 2019 pocketbook on severe asthma. **Dupilumab should be positioned for now in adolescents as an alternative to mepolizumab where this treatment was either not tolerated or failed to control the severe asthma.**
13. Can the company provide additional data for a more accurate assessment of the cost-effectiveness of dupilumab in patients for whom standard care is the only treatment option?	**NA**
Issue 7: Multiplier assumption for the observed rates of severe exacerbations	
14. Should an adjustment be made to the observed rates of severe exacerbation in the model?	**No. There is no published evidence to support an adjustment to the long-term exacerbation rate in the base case analysis.**
Issue 8: Assumption relating to discontinuation rates	
15. Is no discontinuation within the first year of the model appropriate?	**No, we would expect a minimum of 10-20% discontinuation starting at 6 months.**
Issue 9: Treatment settings for severe exacerbations	
16. Should trial data be used to estimate the proportions of patients with severe exacerbations treated in emergency care and inpatient settings in the model?	**Yes, but with caution as the numbers are low** **The numbers are likely to be too low in adolescents to be meaningful**
Issue 10: Utility values	

17. Should the utility used for the controlled asthma (and uncontrolled asthma) health state be limited to general population mean?	**Yes, there is no evidence to suggest that people with controlled asthma have a better quality of life than the general population.**
18. Which utility best reflects people in the uncontrolled asthma health state: a) 0.735 and 0.713 in the non-mOCS and the mOCS population respectively based on RCT data in the company submission b) 0.701 and 0.697 for standard care in the non-mOCS and mOCS population respectively from clinical trials in TA565, or c) c) 0.702 and 0.682 in the non-mOCS and the mOCS population respectively based on ERG calculations?	
Issue 11: Unit costs	
19. Is it appropriate to use weighted NHS National Tariff costs in the model?	**Yes**
Issue 12: Administration	
20. How likely are patients to self-administer in practice?	**After initiation in hospital and a decision to continue treatment it is likely that the majority will self administer, i.e. after a successful 6 month trial. This will vary initially by region as services are established. The majority of patients will not start to self administer until after the first 3 doses.**

	It is unlikely in the immediate future that children/families will self administer the medication after initiation in hospital and a decision to continue treatment.
21. Is the company's assumption of self-administration for 100% of patients for dose 4 onwards reasonable for the base case?	**No – but proportion should ultimately be over 80%**

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About you

Your name	**Jessica Gordon**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**AstraZeneca**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

Questions for engagement

Issue A: Appropriate comparators (Issue 3, Q5 and 6 in technical report)

In their submission, the manufacturer states that "dupilumab is the only biologic indicated for patients with severe uncontrolled asthma driven by T2i defined by EOS ≥150 and/or FeNO ≥25", and therefore considers that other biologic agents used to treat patients with severe asthma are not relevant comparators. We see issue with this, as the manufacturer positioning for dupilumab (patients with EOS ≥150 and/or FeNO ≥25 and ≥3 exacerbations) clearly overlaps with the NICE recommended populations for benralizumab, mepolizumab and reslizumab (patients with EOS ≥300 and ≥4 exacerbations OR EOS ≥400 and 3 exacerbations). As precedent dictates in the only previous NICE appraisal of a biologic in severe asthma where other biologic agents had already been recommended (benralizumab TA565), when there was an overlap in populations between those agents, comparisons between biologics were key for decision making. This is also clearly stated in the appraisal's final scope which was published on the NICE website on 17th June 2019. Please see below table for a visual representation of the dupilumab base case populations and available treatments.

Table 1: Sub populations and comparators within the dupilumab Base Case population

Population	**FeNO < 25**	**FeNO ≥ 25**
EOS <150	SoC	SoC Dupilumab (3+ Exacerbations)
EOS 150 – 299	SoC Dupilumab (3+ Exacerbations)	SoC Dupilumab (3+ Exacerbations)
EOS 300 – 399	Dupilumab (3+ Exacerbations) Mepolizumab and Benralizumab (4+ Exacerbations)	Dupilumab (3+ Exacerbations) Mepolizumab and Benralizumab (4+ Exacerbations)
EOS ≥ 400	Dupilumab (3+ Exacerbations) Benralizumab and Reslizumab (3 + Exacerbations) Mepolizumab (4+ Exacerbations)	Dupilumab (3+ Exacerbations) Benralizumab and Reslizumab (3 + Exacerbations) Mepolizumab (4+ Exacerbations)

Therefore, in line with precedent and the final scope, the base case analysis for dupilumab should include comparisons versus other biologics within their NICE recommended populations.

Issue B: Population (Issue 3, Q7 in technical report)

In their submission, the manufacturer's base case analysis focuses on the cost effectiveness of dupilumab versus standard of care (SOC) (defined as high dose ICS plus a second controller) in a population of patients with EOS ≥150 and/or FeNO ≥25 and ≥3 exacerbations. However, should the previous identified issue (Issue A) hold, then a significant proportion of this population is already covered by other biologics and therefore SOC is not the relevant comparator.

As in the NICE appraisal of benralizumab (TA565) where there was an overlap of populations between the biologics, the committee decided that the correct comparators for this appraisal were the already existing biologics within the overlap population and SOC in the population where patients were not currently eligible for treatment with biologics:

"The committee considered the mixed population proposed by the company of people with a blood eosinophil count of at least 300 cells per microlitre, who had had 3 or more exacerbations or were taking maintenance oral corticosteroids. The modelled population requires assumptions to be made about the proportion of patients who would be considered for benralizumab in clinical practice depending on use of maintenance oral corticosteroids, number of prior exacerbations, and blood eosinophil count. The committee noted that within this population some people would be eligible for treatment with other biologicals, and it was therefore only interested in the incremental cost effectiveness ratio (ICER) compared with standard care in people who were not eligible for biologicals"

Therefore, as shown in table 1 above, in this appraisal, the correct comparators and populations should be:

1. Benralizumab in patients with EOS ≥300 and ≥4 exacerbations OR EOS ≥400 and 3 exacerbations
2. Mepolizumab in patients with EOS ≥300 and ≥4 exacerbations
3. Reslizumab in patients with EOS ≥400 and ≥3 exacerbations
4. SOC in patients with EOS between 150 and 300 and ≥4 Exacerbations OR EOS between 150 and 400 and 3 exacerbations OR EOS <150 and FeNO ≥25

Issue C: Adjustment of long-term severe exacerbation rates (Issue 7, Q14 in technical report)

The company base case incorporates a multiplier that is applied to the rate of severe exacerbations for both arms of the model after 12 months. The ERG rightly notes that this assumption has a significant effect on the modelled rates of exacerbations and is subject to high levels of uncertainty.

Previous appraisals of biologics in severe asthma (TA479 and TA565) do not undertake this approach, and, when a multiplier was initially used in the company base case in TA479, it was rejected by the committee because "*the most robust estimate of relative effectiveness was derived from the exacerbation rates shown in the clinical trials".*

We therefore agree with the ERG and consider this approach to not only be out of keeping with the precedent set in previous appraisals but also subject to significant levels of uncertainty. It should therefore be removed from the analysis.

Issue D: Treatment settings for severe exacerbations (Issue 9, Q16 in technical report)

The company base case assumes that the treatment setting for severe exacerbations will be in accordance with data from the difficult asthma registry rather than from the clinical trial data.

This presents significant levels of uncertainty as the registry data will not accurately reflect the population of interest in the company submission and, as the ERG notes, this data may not accurately reflect those patients who self-administer an OCS burst and will therefore underestimate the true proportion of these types of exacerbations and therefore over estimate more severe types of exacerbations.

Furthermore, in terms of face validity, the proportions of A+E and hospitalised exacerbations used in the company base case are significantly higher than those seen in previous appraisals and therefore suggest that they are overestimated. This is shown comparatively in the table below.

Table 2: Treatment settings of severe exacerbations by NICE TA

NICE technology appraisal	% estimate for ER/hospitalised exacerbations
Dupilumab	26.5%
Benralizumab (TA 565)	8.2%

As a result, we agree with the ERG and believe that, in line with previous appraisals and therefore precedent, the treatment settings for severe exacerbations should be derived from the trials.

Issue E: Use of Reference costs (Issue 11, Q19 in technical report)

We agree with the ERG that the correct source for NHS costs should be from the National Schedule of Reference Costs and not from weighted tariff estimates.
Issue F: Discontinuation in year 1 (Issue 8, Q15 in technical report)
We agree with the ERG that discontinuation should be applied in all years including year 1.
Issue G: Mortality (additional issue identified)

The company reports the below table (Table 56 in their submission) as their assumption on mortality arising due to severe exacerbations and attributes it to the committee preferred assumption in the NICE appraisal of benralizumab.

Table 3: Asthma related Mortality rates from company submission

Age band	Other		A&E visit		Hospitalisation	
	%	N	%	N	%	N
18–24 years	0.02	91	0.13	45	0.06	2,420
25–34 years	0.02	91	0.13	45	0.06	2,420
35–44 years	0.02	91	0.13	45	0.08	2,420
45–54 years	0.32	91	2.05	45	0.30	628
55–64 years	0.32	91	2.05	45	[redacted]	521
65–74 years	0.32	91	2.05	45	4.54	689
75–100 years	0.32	91	2.05	45	4.54	689

However, the number in the highlighted cell (% hospitalisation 55-64 years) is incorrect and should be corrected from 1.81% to 0.86%, as stated in TA565.

Issue H: % of patients on mOCS in scenario analysis (additional issue identified)

The company scenario analysis incorporating patients who are taking mOCS assumes that the proportion of patients receiving mOCS in that population would be 41.7%, and attributes this to the NICE appraisal of benralizumab (TA565). However, this is not the most plausible figure from this appraisal.

Table 4: Numbers of patients by EOS count, OCS status and exacerbation history from Kerkhoff et al (note sample data, unprojected)

Number of exacerbations in prior year	*Number of OCS prescriptions*	*≥200 EOS*	*≥300 EOS*	*≥400 EOS*	*≥500 EOS*
0	*<6*	XXXX	XXXX	XXXX	XXXX
	≥6	XXXX	XXXX	XXXX	XXXX
1	*<6*	XXXX	XXXX	XXXX	XXXX
	≥6	XXXX	XXXX	XXXX	XXXX
≥1	*<6*	XXXX	XXXX	XXXX	XXXX
	≥6	XXXX	XXXX	XXXX	XXXX
<2	*<6*	XXXX	XXXX	XXXX	XXXX
	≥6	XXXX	XXXX	XXXX	XXXX
≥2	*<6*	XXXX	XXXX	XXXX	XXXX
	≥6	XXXX	XXXX	XXXX	XXXX

≥3	<6	XXXX	XXXX	XXXX	XXXX
	≥6	XXXX	XXXX	XXXX	XXXX
≥4	<6	XXXX	XXXX	XXXX	XXXX
	≥6	XXXX	XXXX	XXXX	XXXX
≥5	<6	XXXX	XXXX	XXXX	XXXX
	≥6	XXXX	XXXX	XXXX	XXXX

The above table, presented as part of the ACD consultation and accepted by the ERG for the NICE appraisal of benralizumab, is taken from the raw data source of a UK real world evidence study (Kerkhoff et al).

The table shows the number of patients within the study who are adults, on a high dose ICS/LABA and are then subdivided by their EOS count, OCS status (being on mOCS is defined as a minimum of 6 months continuous use of OCS), and number of exacerbations at baseline.

As shown in the table, the population for the company's scenario analysis in question is made up of those patients with an EOS count of ≥200 (proxy for ≥150), an exacerbation history of ≥3, and <6 mOCS prescriptions (the orange box), plus those patients with an EOS count of ≥200, an exacerbation history of <2 or ≥2, and ≥6 mOCS prescriptions (the green boxes).

The total analysis population therefore who would meet the criteria for the scenario analysis population would be [redacted], of which [redacted] would be receiving mOCS, (unprojected sample data) yielding a percentage of 55.8% of patients receiving mOCS at baseline.

Therefore when estimating the cost effectiveness of dupilumab in the company scenario analysis it would be more accurate to use a figure of 55.8% of patients being on mOCS.

Issue I: Inclusion of mOCS patients in company base case (additional issue identified)
The company's base case population is patients with EOS ≥150 and/or FeNO ≥25 and ≥3 exacerbations. However, it appears that the patients within this population who will also be receiving mOCS have not been accounted for here. As demonstrated in Table 4, above, the company base case consists of both the orange and the red boxes and therefore 22.3% of those patients will be receiving mOCS. This is an important factor to consider when assessing the cost effectiveness of dupilumab for two reasons: 1. The company has ascertained that dupilumab has different levels of effectiveness dependent on whether the patient is also receiving mOCS or not – the current company base case uses data from the QUEST study – this study excluded patients from participating should they have been receiving mOCS and therefore the data within this submission more accurately reflects the population - patients with EOS ≥150 and/or FeNO ≥25 and ≥3 exacerbations ***excluding those who require treatment with mOCS.*** Therefore, in order to accurately reflect the company base case population as it has been presented a proportion of patients within it should be deemed as requiring mOCS and should therefore be modelled according to the outcomes seen in the VENTURE trial. 2. Dupilumab has two different doses, one for patients who are receiving mOCS and one for patients who are not receiving mOCS, and therefore should there be a difference in the price of these doses this would significantly impact the cost effectiveness of dupilumab Therefore the company base case analysis should either be amended to reflect the effectiveness and cost of dupilumab in those patients within its base case population who would be receiving mOCS, or it should be clearly stated that patients who are receiving mOCS regardless of the number of exacerbations they have had in the past year would not be eligible for treatment with dupilumab.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Dupilumab for treating severe asthma [ID1213]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **end of 10 January 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**GlaxoSmithKline**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: What proportion of patients in the UK have severe asthma with Type 2 inflammation and how is severe asthma with Type 2 inflammation defined, diagnosed and treated in UK practice	
1. How many people in the UK have severe asthma with Type 2 inflammation?	Severe asthma is defined as asthma that requires treatment with high dose inhaled corticosteroids plus a second controller and/or systemic corticosteroids to prevent it from becoming "uncontrolled" or that remains "uncontrolled" despite this therapy [1]. We are not aware of any published studies that have aimed to quantify the proportion of patients based on the company's definition of severe asthma with type 2 inflammation. Dupilumab demonstrated efficacy in moderate-severe eosinophilic asthma. Dupilumab did not demonstrate efficacy on clinically significant exacerbations in the patient group with baseline blood eosinophil count of <150 cells/microlitre [3]. The blood eosinophil count is most predictive of an exacerbation prone phenotype and is the best available biomarker for predicting response to biologics targeting the IL5 and IL4/13 pathways [2][3]. FeNO is a biomarker of ICS responsiveness [4-6]. Directly observed ICS treatment over 7 days in subjects with a high FeNO (FeNO≥45 ppb) or remotely monitored FeNO suppression testing can identify subjects with difficult-to-control severe asthma who are responsive to ICS and nonadherent with maintenance ICS treatment [7][8]. FeNO suppression testing using directly observed ICS treatment or remotely monitored therapy has become part of routine assessment at the majority of severe asthma specialist centres in the UK. Therefore, to identify severe asthma with type 2 inflammation an elevated blood eosinophil count with or without a combination of a raised FeNO following FeNO suppression testing should be used. A raised FeNO without an elevated blood eosinophil count or a FeNO level that is suppressed following directly observed or remotely monitored ICS therapy is likely to indicate moderate disease that will respond to inhaled

	ICS if the patient is adherent to an optimised inhaled treatment plan. Therefore, FeNO as a biomarker cannot be used in isolation to identify severe asthma with type 2 inflammation particularly in the context of UK clinical practice where FeNO suppression testing is used. Published analyses are available that estimate the proportion of patients with an eosinophilic phenotype. These analyses should be used when considering the proportion of patients who may be eligible in the future for dupilumab.
2. How is severe asthma with Type 2 inflammation defined and diagnosed in clinical practice?	Severe asthma is defined as asthma that requires treatment with high dose inhaled corticosteroids plus a second controller and/or systemic corticosteroids to prevent it from becoming "uncontrolled" or that remains "uncontrolled" despite this therapy [1]. In clinical practice in the NHS, specialist centres confirm the diagnosis and optimise treatment plans including an assessment of adherence to inhaled high dose ICS and controller therapies. Optimisation of patients with inhaled ICS and controller medicines may bring the symptoms under control. This is completed prior to assessing eligibility for biological treatment. This in part explains why uptake of mepolizumab and reslizumab is seemingly low, because patients having optimised care at specialist centres may not need a biological treatment. The blood eosinophil count is most predictive of an exacerbation prone phenotype and is the best available biomarker for predicting response to biologics targeting the IL5 and IL4/13 pathways [2][3]. FeNO is a biomarker of ICS responsiveness [4-6]. Directly observed ICS treatment over 7 days in subjects with a high FeNO (FeNO≥45 ppb) or remotely monitored FeNO suppression testing can identify subjects with difficult-to-control severe asthma who are responsive to ICS and nonadherent with maintenance ICS treatment [7][8]. FeNO suppression testing using directly observed ICS treatment or remotely monitored therapy has become part of routine assessment at the majority of severe asthma specialist centres in the UK. Therefore, to identify severe asthma with type 2 inflammation an elevated blood eosinophil count with or without a combination of a raised FeNO following FeNO suppression testing should be used. A raised FeNO without an elevated blood eosinophil count or a FeNO level that is suppressed following directly observed or

	remotely monitored ICS therapy is likely to indicate moderate disease that will respond to inhaled ICS if the patient is adherent to an optimised inhaled treatment plan. Therefore, FeNO as a biomarker cannot be used in isolation to identify severe asthma with type 2 inflammation particularly in the context of UK clinical practice where FeNO suppression testing is used. During the NICE review of mepolizumab the company's populations proposed at the first committee meeting included a criterion of blood eosinophil count of 150 cells/microlitre or more when starting treatment. The committee heard from the clinical experts that a threshold of 150 cells/microlitre was considered within the normal range. The clinical experts confirmed that a blood eosinophil count of 300 cells/microlitre or more in the previous 12 months better reflects clinical practice. In its response to the first appraisal consultation document, the company presented evidence using a threshold of 300 cells/microlitre. The committee concluded that a population based on a blood eosinophil count of 300 cells/microlitre or more in the previous 12 months would be relevant to clinical practice [10]. Therefore, to be consistent with currently reimbursed anti-IL5 biologic populations (mepolizumab, reslizumab and benralizumab) and previous ERG recommendations a blood eosinophil count of 300 cells/microlitre or more should be selected as the threshold for dupilumab. In order to confirm type 2 inflammation in the context of severe asthma, an elevated blood eosinophil count (≥300cells/microlitre) with or without a positive FeNO test should be present. The company should present a combined analysis by baseline blood eosinophil count (EOS) and FeNO (i.e. EOS high-FeNO low; EOS high-FeNO high; EOS low-FeNO high; EOS low-FeNO low) excluding patients from QUEST without severe asthma (i.e. those on moderate dose ICS). In order to simplify prescribing in the specialist centres and to avoid confusion, the eligibility criteria threshold for blood eosinophils for dupilumab (subject to reimbursement decision) should be consistent with other reimbursed anti-IL5 biologics (reslizumab, mepolizumab, benralizumab) in England, i.e. at least 300 cells/microlitre, subject to the available supportive evidence for each IL-5 respectively.

3. Are blood EOS level of ≥150 cells/microlitre and FeNO of ≥25 ppb (compared with ≥20 ppb in the GINA guideline) sufficient to identify people with Type 2 inflammation?	The blood eosinophil count is most predictive of an exacerbation prone phenotype and is the best available biomarker for predicting response to biologics targeting the IL5 and IL4/13 pathways [2][3]. FeNO is a biomarker of ICS responsiveness [4-6]. Directly observed ICS treatment over 7 days in subjects with a high FeNO (FeNO≥45 ppb) or remotely monitored FeNO suppression testing can identify subjects with difficult-to-control severe asthma who are responsive to ICS and nonadherent with maintenance ICS treatment [7][8]. FeNO suppression testing using directly observed ICS treatment or remotely monitored therapy has become part of routine assessment at the majority of severe asthma specialist centres in the UK. Therefore, to identify severe asthma with type 2 inflammation an elevated blood eosinophil count with or without a combination of a raised FeNO following FeNO suppression testing should be used. A raised FeNO without an elevated blood eosinophil count or a FeNO level that is suppressed following directly observed or remotely monitored ICS therapy is likely to indicate moderate disease that will respond to inhaled ICS if the patient is adherent to an optimised inhaled treatment plan. Therefore, FeNO as a biomarker cannot be used in isolation to identify severe asthma with type 2 inflammation particularly in the context of UK clinical practice where FeNO suppression testing is used. During the NICE review of mepolizumab the company's populations proposed at the first committee meeting included a criterion of blood eosinophil count of 150 cells/microlitre or more when starting treatment. The committee heard from the clinical experts that a threshold of 150 cells/microlitre was considered within the normal range. The clinical experts confirmed that a blood eosinophil count of 300 cells/microlitre or more in the previous 12 months better reflects clinical practice. In its response to the first appraisal consultation document, the company presented evidence using a threshold of 300 cells/microlitre. The committee concluded that a population based on a blood eosinophil count of 300 cells/microlitre or more in the previous 12 months would be relevant to clinical practice [10]. Therefore, to be consistent with currently reimbursed anti-IL5 biologic populations (mepolizumab, reslizumab and benralizumab) and

	previous ERG recommendations a blood eosinophil count of 300 cells/microlitre or more should be selected as the threshold for dupilumab. In order to confirm type 2 inflammation in the context of severe asthma, an elevated blood eosinophil count (≥300cells/microlitre) with or without a positive FeNO test should be present. The company should present a combined analysis by baseline blood eosinophil count (EOS) and FeNO (i.e. EOS high-FeNO low; EOS high-FeNO high; EOS low-FeNO high; EOS low-FeNO low) excluding patients from QUEST without severe asthma (i.e. those on moderate dose ICS). In order to simplify prescribing in the specialist centres and to avoid confusion, the eligibility criteria threshold for blood eosinophils for dupilumab (subject to reimbursement decision) should be consistent with other reimbursed anti-IL5 biologics (reslizumab, mepolizumab, benralizumab) in England, i.e. at least 300 cells/microlitre, subject to the available supportive evidence for each IL-5 respectively.
Issue 2: Generalisability of the population used in the model	
4. Do the people in the post-hoc trial population proposed by the company represent patients in clinical practice who have severe asthma driven by Type 2 inflammation? What proportion of the post-hoc population were from the UK and how might this affect the generalisability of standard of care in the trial compared to clinical practice in the UK?	Severe asthma is defined as asthma that requires treatment with high dose inhaled corticosteroids plus a second controller and/or systemic corticosteroids to prevent it from becoming “uncontrolled” or that remains “uncontrolled” despite this therapy [1]. Dupilumab is indicated in adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with high dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment [12]. The post-hoc trial population in QUEST includes approximately 48.5% of patients on moderate dose ICS [3]. Therefore, the moderate dose ICS population do not meet the definition of severe asthma and the EMA license for dupilumab and should be excluded from the post-hoc analysis. Inclusion of the population on moderate dose ICS may exaggerate the treatment effect of dupilumab as these patients are not optimised on inhaled therapies prior to initiation of dupilumab. Current clinical practice in the NHS, means that patients in the specialist centres follow an

	optimised treatment plan prior to consideration for a biologic. This includes assessing and addressing adherence to high dose ICS and other controller therapies [4]. Dupilumab did not demonstrate efficacy on clinically significant exacerbations in the patient group with baseline blood eosinophil count of <150 cells/microlitre [3]. A post hoc analysis of mepolizumab and dupilumab data stratified by combined criteria of baseline blood eosinophil count (EOS) and FeNO demonstrated that the efficacy of mepolizumab and dupilumab was most marked in participants in the EOS high-FeNO high group with 61% and 68% reductions compared with placebo respectively, compared with 33% and 33% respectively, in the EOS high-FeNO low group. In the EOS low-FeNO low group, neither dupilumab nor mepolizumab had a significant effect on exacerbations. In the EOS low-FeNO high group a 39% reduction was seen with dupilumab compared with a 6% increase with mepolizumab (caution should be exercised in interpreting these results from this group due to low patient numbers). The fact that dupilumab did not demonstrate efficacy on clinically significant exacerbations in the EOS <150cells/microlitre group and a modest 39% reduction in those patients who were EOS-low-FeNO high in the combined analysis provides evidence that FeNO should not be used in isolation of an elevated blood eosinophil count i.e. the post hoc analysis population should be elevated EOS +/- elevated FeNO plus ≥3 exacerbations. During the NICE review of mepolizumab the company's populations proposed at the first committee meeting included a criterion of blood eosinophil count of 150 cells/microlitre or more when starting treatment. The committee heard from the clinical experts that a threshold of 150 cells/microlitre was considered within the normal range. The clinical experts confirmed that a blood eosinophil count of 300 cells/microlitre or more in the previous 12 months better reflects clinical practice. In its response to the first appraisal consultation document, the company presented evidence using a threshold of 300 cells/microlitre. The committee concluded that a population based on a blood eosinophil count of 300 cells/microlitre or more in the previous 12 months would be relevant to clinical practice [10]. Therefore, to be consistent with currently reimbursed anti-IL5 biologic criteria (mepolizumab, reslizumab and benralizumab) and previous

	ERG recommendations a blood eosinophil count of ≥300 cells/microlitre should be the selected threshold for the post-hoc analysis population. In summary, an appropriate post-hoc analysis population representative of severe asthma with type 2 inflammation would include patients on high dose ICS with criteria of EOS ≥300 cells/microlitre +/- FeNO ≥25ppb plus ≥3 exacerbations.
Issue 3: Treatment of severe asthma caused by Type 2 inflammation	
5. Is standard care (high dose ICS [plus 1 or more controller therapy], with or without oral corticosteroids) the most relevant comparator? Would adding oral corticosteroids be a relevant comparator for people with uncontrolled asthma without oral corticosteroids?	Due to the availability of biologic medicines, the GINA guidelines state that mOCS should only be considered in patients if they have failed biologic treatments. Therefore, standard of care should be those patients on high dose ICS plus 1 or more controller therapies. The post-hoc trial population in QUEST includes approximately 48.5% of patients on moderate dose ICS [3]. Therefore, the moderate dose ICS population do not meet the definition of severe asthma and the EMA license for dupilumab and should be excluded from the post-hoc analysis. Inclusion of the population on moderate dose ICS may exaggerate the treatment effect of dupilumab as these patients are not optimised on inhaled therapies prior to initiation of dupilumab. Current clinical practice in the NHS means that patients in the specialist centres follow an optimised treatment plan prior to consideration for a biologic. This includes assessing and addressing adherence to high dose ICS and other controller therapies [4].
6. What proportion of patients with severe asthma driven by Type 2 inflammation (blood EOS ≥ 150 cells/microlitre and/or FeNO ≥25 ppb) would also be eligible for treatment with currently recommended biologics (mepolizumab, reslizumab, benralizumab, omalizumab)?	The company have underestimated the overlap in clinical practice in the proportion of patients who would also be eligible for treatment with currently available biologics (mepolizumab, reslizumab, benralizumab and omalizumab). The NICE eligibility criteria for mepolizumab is ≥300 cells and ≥4 exacerbations [10]. These criteria have been demonstrated in the real-world as effective criteria for initiation of mepolizumab when considering real-world outcomes [15]. In order to simplify prescribing in the specialist centres and to avoid confusion, the eligibility criteria for blood eosinophil threshold for dupilumab should be consistent with other reimbursed anti-IL5 biologics (reslizumab, mepolizumab,

	benralizumab) in England, i.e. at least 300 cells/microlitre, subject to the available supportive evidence for each IL-5 respectively.
7. Will dupilumab be used in a population who have asthma that is of a similar severity to the population with severe asthma for whom biologics are currently recommended or will it be used in people with less severe asthma?	The company have proposed a population that would result in the treatment of patients with dupilumab with a lower burden of disease than those treated with the currently available biologics. This is because FeNO which is a marker of ICS responsiveness [4-6] and surrogate for adherence to inhaled ICS [7] [8] has been included as an "or" rather than an "and" criterion. Dupilumab did not demonstrate significant reduction in exacerbations in the population with blood eosinophils ≤150 cells /microlitre. FeNO as an "or" criterion could enable prescribing in a patient group where efficacy has not been demonstrated i.e. those with a blood eosinophil count ≤150 cells/microlitre [3]. Increasing blood eosinophil count is associated with increasing risk of exacerbations and is a biomarker of response to anti-IL5 and anti-IL4/13 biologics, the company have selected a blood eosinophil threshold of ≥150 cells/microlitre which is lower than the threshold for mepolizumab (≥300 cells/microlitre), benralizumab (≥300 or ≥400 cells/microlitre) and reslizumab (≥400 cells/microlitre) [10] [13] [14]. This would enable treatment in a population with lower blood eosinophilia and therefore lower risk of exacerbations. A more appropriate population would be those patients on high dose ICS with criteria of blood eosinophils ≥300 cells/microlitre +/- FeNO ≥25ppb plus ≥3 exacerbations. The NICE eligibility criteria for mepolizumab is ≥300 cells and ≥4 exacerbations [10]. These criteria have been demonstrated in the real-world as effective criteria for initiation of mepolizumab in severe asthma patients when considering real-world outcomes [15]. In order to simplify prescribing in the specialist centres and to avoid confusion, the eligibility criteria threshold for blood eosinophils for dupilumab (subject to reimbursement decision) should be consistent with other reimbursed anti-IL5 biologics (reslizumab, mepolizumab, benralizumab) in England, i.e. at least 300 cells/microlitre, subject to the available supportive evidence for each IL-5 respectively.
Issue 4: Which population is most relevant for decision making?	

8. Is the base case population with only non-mOCS patients (or a mixed population) most appropriate?	It would be more clinically and health economically appropriate to consider people with and without background mOCS use as separate groups.
9. If the mixed population is appropriate, is standard care the only relevant comparator or should other biologics also be considered in the subset of people for whom they are eligible? 9. If the mixed population is appropriate, is standard care the only relevant comparator or should other biologics also be considered in the subset of people for whom they are eligible?	The company have underestimated the overlap in clinical practice in the proportion of patients who would also be eligible for treatment with currently available biologics (mepolizumab, reslizumab, benralizumab and omalizumab). An appropriate post-hoc analysis population representative of severe asthma with type 2 inflammation would include patients on high dose ICS with criteria of EOS ≥300 cells/microlitre +/- FeNO ≥25ppb plus ≥3 exacerbations. In this population or the company's proposed less severe population, there would be significant overlap in eligibility with the currently available biologics. Therefore, mepolizumab, reslizumab and benralizumab are relevant comparators.
10. What is the cost-effectiveness of dupilumab compared with standard care in the mOCS only population?	This analysis in the mOCS only population should be provided to understand cost-effectiveness in this group.
Issue 5: Assumptions relating to proportion of population on mOCS for mixed population scenario	
11. In clinical practice, what proportion of patients are expected to be on mOCS?	TA431 and TA565 ERGs have addressed this question. It is anticipated that in the future fewer severe asthma patients will be initiated on maintenance OCS due to the use of biologics prior to initiation of mOCS as per the GINA guidelines [10] [13].
Issue 6: Mixed population of different severities of asthma in the base case (non-mOCS) model	
12. Should a mixed population of different severities of asthma be used in the base case?	In the non-mOCS model, only the population on high dose ICS should be included. The post-hoc trial population in QUEST includes approximately 48.5% of patients on moderate dose ICS [3]. Therefore, the moderate dose ICS population do not meet the definition of severe asthma and the EMA license for dupilumab and should be excluded from the post-hoc analysis. Inclusion of the population on moderate dose ICS may exaggerate the treatment effect of dupilumab as these

	patients are not optimised on inhaled therapies prior to initiation of dupilumab. Current clinical practice in the NHS means that patients in the specialist centres follow an optimised treatment plan prior to consideration for a biologic. This includes assessing and addressing adherence to high dose ICS and other controller therapies [4].
13. Can the company provide additional data for a more accurate assessment of the cost-effectiveness of dupilumab in patients for whom standard care is the only treatment option?	This population is limited to the population with a blood eosinophil count between 150 and 300 cells/microlitre. FeNO alone is not an appropriate biomarker for initiation of a biologic. FeNO is a biomarker of ICS responsiveness [4-6]. Directly observed ICS treatment over 7 days in subjects with a high FeNO (FeNO≥45 ppb) or remotely monitored FeNO suppression testing can identify subjects with difficult-to-control severe asthma who are responsive to ICS and nonadherent with maintenance ICS treatment [7][8]. FeNO suppression testing using directly observed ICS treatment or remotely monitored therapy has become part of routine assessment at the majority of severe asthma specialist centres in the UK. Therefore, to identify severe asthma with type 2 inflammation an elevated blood eosinophil count with or without a combination of a raised FeNO following FeNO suppression testing should be used. A raised FeNO without an elevated blood eosinophil count or a FeNO level that is suppressed following directly observed or remotely monitored ICS therapy is likely to indicate moderate disease that will respond to inhaled ICS if the patient is adherent to an optimised inhaled treatment plan. Therefore, FeNO as a biomarker cannot be used in isolation to identify severe asthma with type 2 inflammation particularly in the context of UK clinical practice where FeNO suppression testing is used.
Issue 7: Multiplier assumption for the observed rates of severe exacerbations	
14. Should an adjustment be made to the observed rates of severe exacerbation in the model?	An appropriate adjustment could be made to the observed rates of severe exacerbations, if there is an appropriate rationale for the uplift. There were four reasons given for adjusting the rate of severe exacerbations in the model. Data from clinical trials would be the gold standard to estimate effectiveness of a technology. The placebo effect in a clinical trial and any regression to the mean would apply to both arms of the trial. The issues with exclusion criteria and the definition of exacerbations can be attributed to the study design. A further analysis of the exacerbation events in the trial could be conducted to

	separate where two exacerbations were classed as one (owing to the 28-day rule applied in the trial). The base case applies a multiplier to both arms of the study. This multiplier will increase the number of severe exacerbations in both arms and could over-estimate the cost-effectiveness of dupilumab. The company presented four scenario analyses with the base case multiplier being confidential. One of the analysis incorporated the multiplier used for mepolizumab. The study design, patient population and clinical trial results might not be generalisable or appropriate to dupilumab. Applying a multiplier increases the level of uncertainty regarding the cost effectiveness of dupilumab. This has a major impact on the ICER and the cost effectiveness, as demonstrated by the analyses conducted by the ERG. The appraisal of mepolizumab used a lower exacerbation multiplier than in the company base case. A similar rate should be applied to dupilumab, only if this would be deemed appropriate. NICE guidance for the more recently appraised benralizumab and reslizumab (TA565 and TA479) was based on observed trial data only with no multipliers applied to severe exacerbation rates [13] [14].
Issue 8: Assumption relating to discontinuation rates	
15. Is no discontinuation within the first year of the model appropriate?	No discontinuation within the first year of the model is not appropriate. Some patients may stop treatment due to adverse events, personal preference or tolerability issues during the first 12 months of treatment. The model applies a constant annual rate of discontinuation after the first year. The discontinuation rate should be applied to the first year and subsequent cycles within the model. This data would be available from the clinical trials.

	However, the ICERs from the analyses all demonstrate minimal change when discontinuation is applied in the first year. The reason is that a lifetime horizon is applied to the base case, so making the change to the first year would have minimal effect overall.
Issue 9: Treatment settings for severe exacerbations	
16. Should trial data be used to estimate the proportions of patients with severe exacerbations treated in emergency care and inpatient settings in the model?	Trial data should be used to estimate the proportion of patients with severe exacerbations treated in the respective settings. The clinical trials will have the most robust data and will align with the pre-determined definition of a severe exacerbations.
Issue 10: Utility values	
17. Should the utility used for the controlled asthma (and uncontrolled asthma) health state be limited to general population mean?	Unless a problem has been identified with the collection of the utility data during the clinical trials, it would seem reasonable to use the EQ-5D-5L data from these trials. Once the appropriate severe asthma sub-population has been identified i.e. excluding patients with moderate asthma, who have not been optimised on standard care treatments, the trial derived utility values may be lower and more as expected.
18. Which utility best reflects people in the uncontrolled asthma health state: a) 0.735 and 0.713 in the non-mOCS and the mOCS population respectively based on RCT data in the company submission b) 0.701 and 0.697 for standard care in the non-mOCS and mOCS population respectively from clinical trials in TA565, or c) c) 0.702 and 0.682 in the non-mOCS and the mOCS population respectively based on ERG calculations?	Utilities from the clinical trial data would best reflect people in the uncontrolled asthma health state. The clinical trials used EQ-5D-5L data from the relevant trails and would provide the most robust estimate. An alternative source could be used if there is a relevant reason i.e. a more robust dataset applicable to the UK population.

Issue 11: Unit costs	
19. Is it appropriate to use weighted NHS National Tariff costs in the model?	A weighted average of NHS National Tariff would be appropriate to reflect costs in the model. This would apply a weighting based on the frequency and cost per event per severe asthma patient.
Issue 12: Administration	
20. How likely are patients to self-administer in practice?	To support a patient to self-administer in a home-setting which includes a minimum of drug delivery and waste collection a commissioned service (e.g. Homecare) will be required by the NHS. If the NHS is expected to cover the unit cost to support patients to self-administer this cost should be included in the modelling and may have an impact on the ICER, i.e. the current ICER may be under-estimated. If the manufacturer will be funding this service then it is appropriate not to include these costs. There are no available data to inform on the likelihood of severe asthma patients to self-administer in clinical practice. Insights gathered from severe asthma specialist centres indicate that the societal and health demographics of the population and opinions of healthcare professionals in the centre determine the proportion of patients who may transition to self-administration. Insights from healthcare professionals in severe asthma specialist centres range from 50 to 90% of patients to be suitable for homecare self-administration. Deciding factors include; appropriateness i.e. degree of asthma disease control, presence of comorbidities, social and psychosocial factors, side effects and degree of healthcare professional experience with the biologic; patient choice – patients want to receive their injection in a hospital setting; willingness - is the patient willing to try self-administration; and suitability - is the patient competent to self-administer measured by a competency assessment. GSK have 15 months experience supporting severe asthma specialist centres with a homecare service. The Homecare service was originally set up to provide nurse administration of mepolizumab in a home-setting with drug delivery and waste management inclusive. The

	consensus amongst severe asthma specialists is homecare is not suitable for all severe asthma patients due to the above non-exhaustive deciding factors. The uptake of a new homecare service is dependent on clinical demand and capacity within a trust to implement a new homecare service. Homecare is a new concept amongst severe asthma centres. Compared to other disease e.g. diabetes there is very little experience and therefore low confidence referring patients out to such service. Assuming all trusts prescribing a severe asthma biologic will be signed up to a new homecare service within 2 years is an optimistic estimate based on current experience within GSK. In August 2019 GSK funded a homecare service to support appropriate patients transition to self-administration. So far there are only approximately 15% of mepolizumab patients referred to a homecare service for self-administration in a home-setting. GSK forecast at the end of 2020 approximately 40% of mepolizumab patients will be referred to a homecare service for self-administration and 10% referred to a homecare service requiring nurse administration. The remainder will still receive administration in a hospital clinic. The model assumes patients will only require one device training visit i.e. dose 4 at the hospital. Based on insight gathered by GSK, the assumption that 100% of patients are signed off as competent to self-administer after one device training visit is unreasonable. The model assumes unit cost of a device training visit at £22.50 per hour. An outpatient visit is costed at £45 per hour which is the most likely setting and tariff to use for this activity.
21. Is the company's assumption of self-administration for 100% of patients for dose 4 onwards reasonable for the base case?	There are no available data to inform on the likelihood of severe asthma patients to self-administer in clinical practice. Insights gathered from severe asthma specialist centres indicate that the societal and health demographics of the population and opinions of healthcare professionals in the centre determine the proportion of patients who may transition to self-administration. Insights from healthcare professionals in severe asthma specialist centres range from 50 to 90% of patients to be suitable for self-administration. Deciding factors include; appropriateness i.e. degree of asthma disease control, presence of comorbidities, social and psychosocial factors, side effects and degree of healthcare professional experience with the biologic; patient choice – not all patients

	want to self-inject; willingness – is the patient willing to try self-administration; and suitability – is the patient competent to self-administer measured by a competency assessment. A more reasonable assumption for the base case would be 40% of patients transitioning to self-administration after 12 months of treatment based on observed decisions made in the current climate. Insight gathered by GSK show clinical opinion of referral to a homecare setting varies from patient being established on mepolizumab at 4 months up to 12 months. Based on this insight a patient referred to self-administration in a home-setting after dose 4 (established on drug for 2 months) is unreasonable to use for the base case.

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NICE National Institute for Health and Care Excellence

Technical engagement response form

Dupilumab for treating severe asthma [ID1213]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **end of 10 January 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Novartis Pharmaceuticals UK Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Not applicable**

Questions for engagement

Issue 1: What proportion of patients in the UK have severe asthma with Type 2 inflammation and how is severe asthma with Type 2 inflammation defined, diagnosed and treated in UK practice	
1. How many people in the UK have severe asthma with Type 2 inflammation?	No comment.
2. How is severe asthma with Type 2 inflammation defined and diagnosed in clinical practice?	No comment.
3. Are blood EOS level of ≥150 cells/microlitre and FeNO of ≥25 ppb (compared with ≥20 ppb in the GINA guideline) sufficient to identify people with Type 2 inflammation?	No comment.
Issue 2: Generalisability of the population used in the model	
4. Do the people in the post-hoc trial population proposed by the company represent patients in clinical practice who have severe asthma driven by Type 2 inflammation? What proportion of the post-hoc population were from the UK and how might this affect the generalisability of standard of care in the trial compared to clinical practice in the UK?	No comment.
Issue 3: Treatment of severe asthma caused by Type 2 inflammation	
5. Is standard care (high dose ICS [plus 1 or more controller therapy], with or without oral	No comment

corticosteroids) the most relevant comparator? Would adding oral corticosteroids be a relevant comparator for people with uncontrolled asthma without oral corticosteroids?	
6. What proportion of patients with severe asthma driven by Type 2 inflammation (blood EOS ≥ 150 cells/microlitre and/or FeNO ≥25 ppb) would also be eligible for treatment with currently recommended biologics (mepolizumab, reslizumab, benralizumab, omalizumab)?	Omalizumab is for a patient population with a different phenotype, it is for a population with severe persistent allergic IgE-mediated asthma Therefore, the overlap is expected to be minimal. There are a number of additional criteria for omalizumab eligibility including medication history, concomitant medication, courses of OCS, asthma symptoms, lung function, exacerbation history, baseline IgE level and body weight which would limit any minimal overlap further.
7. Will dupilumab be used in a population who have asthma that is of a similar severity to the population with severe asthma for whom biologics are currently recommended or will it be used in people with less severe asthma?	See comment 6.
Issue 4: Which population is most relevant for decision making?	
8. Is the base case population with only non-mOCS patients (or a mixed population) most appropriate?	A mixed population approach was not accepted in appraisal TA565. Therefore, consistency in decision-making should apply if there is no difference in evidence to support a different approach.
9. If the mixed population is appropriate, is standard care the only relevant comparator or should other biologics also be considered in the subset of people for whom they are eligible? 9. If the mixed population is appropriate, is standard care	See comment 6.

the only relevant comparator or should other biologics also be considered in the subset of people for whom they are eligible?	
10. What is the cost-effectiveness of dupilumab compared with standard care in the mOCS only population?	No comment.
Issue 5: Assumptions relating to proportion of population on mOCS for mixed population scenario	
11. In clinical practice, what proportion of patients are expected be on mOCS?	No comment.
Issue 6: Mixed population of different severities of asthma in the base case (non-mOCS) model	
12. Should a mixed population of different severities of asthma be used in the base case?	See comment 8.
13. Can the company provide additional data for a more accurate assessment of the cost-effectiveness of dupilumab in patients for whom standard care is the only treatment option?	No comment.
Issue 7: Multiplier assumption for the observed rates of severe exacerbations	
14. Should an adjustment be made to the observed rates of severe exacerbation in the model?	No adjustment was made to long-term exacerbation rates in appraisals for other biologics. Therefore, consistency in decision-making should apply if there is no difference in evidence to support a different approach.
Issue 8: Assumption relating to discontinuation rates	

15. Is no discontinuation within the first year of the model appropriate?	No discontinuation within year 1 is in line with the NICE appraisals for mepolizumab, reslizumab and benralizumab.
Issue 9: Treatment settings for severe exacerbations	
16. Should trial data be used to estimate the proportions of patients with severe exacerbations treated in emergency care and inpatient settings in the model?	No comment.
Issue 10: Utility values	
17. Should the utility used for the controlled asthma (and uncontrolled asthma) health state be limited to general population mean?	No comment.
18. Which utility best reflects people in the uncontrolled asthma health state: a) 0.735 and 0.713 in the non-mOCS and the mOCS population respectively based on RCT data in the company submission b) 0.701 and 0.697 for standard care in the non-mOCS and mOCS population respectively from clinical trials in TA565, or c) c) 0.702 and 0.682 in the non-mOCS and the mOCS population respectively based on ERG calculations?	No comment.
Issue 11: Unit costs	

19. Is it appropriate to use weighted NHS National Tariff costs in the model?	No comment.
Issue 12: Administration	
20. How likely are patients to self-administer in practice?	No comment.
21. Is the company's assumption of self-administration for 100% of patients for dose 4 onwards reasonable for the base case?	It is unlikely that all patients will administer 100% of doses from dose 4 onwards. Some reasons that not all patients will be able to self- administer are: • People with needle phobia for whom self-administration may present difficulties • Older patients who may be less agile and less able to self-inject • Patients with other severe co-morbidities • Patients with a history of not being compliant with other asthma treatments • Very severe patients with high risk of exacerbations are likely to be kept under closer supervision by the clinicians • The syringe is made from glass, which means this will need to be handled with care and may not be suitable for self-administration for all patients. Costs for training for self-administration should be included.

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Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

Dupilumab for treating severe asthma

Evidence Review Group's comments on the company's response to the technical report

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Date completed	21 January 2020

1. Introduction

This document is the ERG's critique of the response by the company (Sanofi) to the draft technical report for technical engagement issued by NICE to stakeholders on 05/12/2019. The ERG received the company's response on 14/01/2020.

The ERG has focussed on commenting on the company's response to issues 4 to 12. The ERG has no comments to add for the first three issues in the draft technical report which concern questions primarily for the clinical community.

Question for engagement		ERG response
Issue 4: Which population is most relevant for decision making?		
8. Is the base case population with only non-mOCS patients (or a mixed population) most appropriate?	Clinical and cost-effectiveness varies between patients on high ICS only or on mOCS. Clinical practice indicates that mOCS use is declining, therefore analyses using a range of proportion of patients on OCS from 0% to 100% are presented. The 2010 study by Heaney demonstrated that 41.7% of patients in the UK with severe asthma are on maintenance OCS (2). A more recent study confirmed this number to be around 44% (1). However, these data may be over-estimating the proportion of patients on maintenance OCS, as the trend in OCS use has shifted with the introduction of biologic therapies. Most recently, the ERG and NICE technical team heard from a KOL during the technical engagement call, that no patients were initiated on maintenance OCS. Getting patients off maintenance OCS is a clinical priority, along with reducing severe exacerbations, due to the severe side effects of these treatments. Moving forwards, it is therefore estimated that the proportion of patients initiating biologic treatment from OCS will be even lower.	The ERG considers that cost-effectiveness should be estimated separately for mOCS and non-mOCS populations, rather than for a mixed population. As noted in the Sanofi response: clinical and cost-effectiveness differ for non-mOCS and mOCS populations; and the proportion of patients currently treated with mOCS is uncertain and likely to be still changing in response to availability of alternative treatments. Furthermore, we argue that there is no practical, clinical or economic advantage to pooling cost and QALY results for the mOCS and non-mOCS populations. Information about mOCS use is obviously available to clinicians at the time of decision making. The ICER for the mixed population is a weighted sum of separate cost and QALY estimates for the two sub-populations, based on different clinical evidence sources and model assumptions. And it is misleading to infer cost-effectiveness for the mOCS subgroup based on the ICER for the mixed population. We note that the dupilumab model does include estimates of treatment effects on mOCS dose reduction

	In the updated company mixed population, the proportion of patients on maintenance OCS initiating dupilumab is an estimated 30%.	and withdrawal and consequent utility gains and cost savings from avoiding mOCS-related adverse events.
9. If the mixed population is appropriate, is standard care the only relevant comparator or should other biologics also be considered in the subset of people for whom they are eligible?	Both the mixed (ICS and mOCS) and ICS-only populations will include patients who are not eligible for anti-IL5 biologic therapies, therefore broadening access to treatment, and also will include patients who are currently eligible for anti IL5 biologics. Where anti-IL5 biologic treatment is the standard of care for that population, this should be the comparator. These data have been presented as scenarios with the revised assumptions.	The mixed population includes subgroups for whom other biologics are currently available and subgroups for whom standard care is the only relevant comparator. To optimise cost-effectiveness all available comparators should be considered for relevant subgroups.
10. What is the cost-effectiveness of dupilumab compared with standard care in the mOCS only population?	Scenarios with varying proportions of patients on maintenance OCS is provided in the confidential appendix.	The company reports an ICER of £55,008 for dupilumab versus standard care for the mOCS-only population (EOS≥150 or FeNO≥25) and other company preferred assumptions (Sanofi TE Response Appendix Table 6). This compares with £45,240 for the same population with original company base case assumptions and £59,224 with ERG preferred assumptions. The ERG has checked the revised version of the economic model submitted with the company response to technical engagement. We successfully replicated previous company and ERG base cases and scenarios with the revised model. Note, that all cost-effectiveness results in the Sanofi TE response appendix include a confidential price discount for dupilumab (and assumed discount of 40% for other biologics).

Question for engagement		ERG response
Issue 5: Assumptions relating to proportion of population on mOCS for mixed population scenario		
11. In clinical practice, what proportion of patients are expected be on mOCS?	The original company base case of the mixed (ICS and mOCS) population used 41.7% (2), taken from a UK observational study of 5 severe asthma centres around the UK . A more recent publication estimated this proportion around 44%(1). However, both these studies may be overestimating the proportion of patients on maintenance OCS who would be initiating treatment. The availability of biologics for severe asthma patients (IGE mediated and severe eosinophilic asthma) has changed immensely over the past three years. Combined with clinical practice to prioritise patients on maintenance OCS to receive new treatments and stop or reduce OCS, it is understood that fewer patients are on maintenance OCS. This was confirmed by clinical opinion during the technical engagement call, who stated OCS use is decreasing all the time and was as low as 30% in some UK centres (Oxford).	We note that the cited clinical opinion that mOCS use "is decreasing all the time" and "was as low as 30% in some UK centres" does not mean that 30% reflects current average use across the UK. Nevertheless, we acknowledge that the proportion of patients taking mOCS is likely to be still changing in response to availability of alternative drugs. In our view, the resulting uncertainty over current and future mOCS use strengthens arguments to consider mOCS and non-mOCS populations separately, rather than to pool them in a mixed population.

Question for engagement		ERG response
Issue 6: Mixed population of different severities of asthma in the base case (non-mOCS) model		
12. Should a mixed population of different severities of asthma be used in the base case?	Asthma severity is defined by severe asthma exacerbations, lung function and other clinical parameters as well as impact on quality of life, not biomarkers (in isolation). Dupilumab is for severe asthma patients with Type 2 inflammation (EOS ≥150 and/or FeNO ≥25), which may include patients with severe eosinophilic asthma (recommended by NICE in EOS ≥300). Patients with severe eosinophilic asthma are not more severe than	The ERG considers that, where possible, separate cost-effectiveness estimates should be provided for subgroups with more/less severe asthma. This is consistent with Committee conclusions in TA565. We acknowledge that 'severity' is not a simple function of EOS alone. However, the company model does predict more exacerbations and reduced life-expectancy and QALYs for patients who meet existing biologic-eligibility criteria (including EOS thresholds of 300 or 400) than

	other patients with severe asthma as defined by other parameters. Analyses comparing dupilumab with existing biologics in severe eosinophilic asthma are presented.	for the 'incremental population' who do not (EOS less than 300). Following the company's revised base-case assumptions, dupilumab is more cost-effective in the biologic-eligible than in the 'less severe' incremental populations. The company presents ICERs for dupilumab compared with the other biologics in Appendix Table 5. They omit ICERs for dupilumab versus standard care, but the ERG has calculated these as: £36,587 for the mepolizumab-eligible population; and £30,717 for the reslizumab-eligible population. These compare with the company estimate of £53,163 for patients not currently eligible for any biologic (company TE response Appendix Table 12). The above ICER estimates would be higher with ERG preferred assumptions. We note that the ICERs for biologic comparisons in Appendix Table 5 are based on an assumed 40% price discount for comparators, rather than the actual agreed PAS discounts.
13. Can the company provide additional data for a more accurate assessment of the cost-effectiveness of dupilumab in patients for whom standard care is the only treatment option?	The company has provided additional analyses for patients with severe asthma driven by Type 2 inflammation population who are not eligible for current anti-IL5 biologic therapies. The QUEST phase 3 clinical trial was conducted in 1902 patients and included more moderate patients on medium dose ICS or on the 300mg dose for dupilumab. Excluding these patients, and restricting to patients with the most severe asthma patients with Type 2 inflammation leads to a sample size of n= 101. This population is most representative of patients treated in severe asthma centres in the UK. Given the very small sample size, the company would request that these results are interpreted with the appropriate	The company state that n=101 patients from the QUEST RCT are representative of the patients treated in severe asthma centres in the UK. However, in the company's 'Appendix: Additional Analyses' document, Table 10 the total incremental population is reported as n=93. The only clinical effectiveness results presented by the company for the 'incremental population' is the annualised event rate for the 41 patients randomised to placebo (n=12) or dupilumab 200mg (n=29) who were not eligible for other biologics (Appendix: Additional Analyses Table 11). The small sample size does increase the width of the confidence intervals as can be see in ERG Response Table 1 (appears below this table).

	caution due to the width of confidence intervals which cause high uncertainty in the resulting ICER. The cost-effectiveness in the incremental population is presented in the Technical Appendix.	The company reports an alternative method used to estimate cost-effectiveness for the incremental population in Appendix section 4.5.2 and Table 12. This involves taking a weighted sum of costs and QALYs for subgroups not currently eligible for biologics. Small subgroups with 3 or more exacerbations are estimated with multipliers to inflate risks for subgroups with defined EOS and FeNO levels and one or more exacerbation in the previous year. The multipliers were obtained from a negative binomial regression of QUEST data (see CS Appendix P and ERG report section 4.3.4.4). The ERG view is that this approach is reasonable, given data limitations, and is consistent with methods in TA479. However, there is uncertainty over the robustness of the fitted models. The ERG used the revised model submitted with the Sanofi TE response to replicate the ICER estimate of £51,982 for dupilumab versus standard care in the non-mOCS incremental population, which comprises: • Patients with 3 severe exacerbations in the previous year and EOS between 150 and 399; • Patients with 4 or more severe exacerbations in the previous year and EOS between 150 and 299; and • Patients with 3 or more exacerbations in the previous year, EOS<150 and FeNO≥25. However, we do not understand how the company derived the ICER of £53,163 for the mixed incremental population (30% mOCS). The model does not allow selection of mOCS patients not eligible for mepolizumab: EOS between 150 and 299; or EOS<105 and FeNo≥25.

ERG response: Table 1 - A comparison of annualised rates of severe exacerbations in the QUEST ITT population, the QUEST decision problem population and the QUEST population not eligible for another biologic.

Outcome measure	QUEST ITT population		QUEST decision problem population [a]		QUEST not eligible other biologic	
	Dupilumab 200 mg Q2W	Placebo	Dupilumab 200 mg Q2W	Placebo	Dupilumab 200 mg Q2W	Placebo
	N=631	N=317	N=64	N=37	N=29	N=12
Adjusted annualised severe exacerbation event rate						
Estimate (95% CI)	0.456 (0.389, 0.534)	0.871 (0.724, 1.048)	[redacted]	[redacted]	[redacted]	[redacted]
Relative risk versus placebo (95% CI)	0.523 (0.413, 0.662); p<0.0001		[redacted] p<0.0001		[redacted]	
Risk difference vs placebo (95% CI)	–0.416 (–0.588, –0.243)		[redacted]		[redacted]	
Unadjusted annualised rate of severe exacerbation events						
Estimate	0.481	0.980	[redacted]	[redacted]	[redacted]	[redacted]

Source: ERG report Table 31 and company technical engagement response "Appendix: Additional Analyses" Table 11
[a] EOS ≥150 OR FeNO ≥25 AND ≥3 exacerbations.

Question for engagement		ERG response
Issue 7: Multiplier assumption for the observed rates of severe exacerbations		
14. Should an adjustment be made to the observed rates of severe exacerbation in the model?	As noted in the submission the exacerbation rate among patients in the original company base case population treated with placebo in QUEST was considerably lower compared to the exacerbation rate in preceding year (2.391 versus 4.46). This can be attributed to three reasons, as confirmed with published evidence and clinical opinion: 1. Exclusion of patients with a recent severe exacerbation 2. Considering two exacerbation events occurring within 28 days to be one event 3. Improved adherence and monitoring in a clinical trial setting	This response repeats arguments made in the company submission (B.3.3.3 and Appendix M.2), which we addressed in ERG sections 4.3.4.1 and 4.4.4.1. Our views have not changed. In addition to the 3 possible reasons for reduced exacerbation rates during the trial cited in the company response, we note that the statistical phenomenon of 'regression to the mean' may also play a part (although one might expect this to be mitigated by the exclusion of patients with a recent severe exacerbation).

	The lower rate of severe exacerbations during the trial is likely to underestimate the real world exacerbation rate in the target population treated with SOC. Therefore, a reasonable approach is making an informed adjustment to the post-trial exacerbation rates to enable a realistic estimate, and this is similar to the analysis adjustment recommended and undertaken in the mepolizumab NICE submission. It is estimated within the company submission and supported that inclusion of patients with a recent severe exacerbation would raise the risk of experiencing an exacerbation by a factor of [redacted]. Relaxing the duration between exacerbation events to consider these separate would in fact raise the risk of experiencing exacerbations by a factor of [redacted] Therefore, the likely combined effect of these aspects is [redacted] [redacted] was considered a conservative estimate. This aligns with estimates on the influence of adherence in the published literature and clinical expert opinion. For example, a systematic review and meta-analysis indicated that 25% increase in adherence was associated with an approximately a 10% (10%-25% reported across studies) reduction in severe exacerbations.(6) Mindful of the discussions during the technical engagement, a lower adjustment factor of 1.35 was applied to both the biologic and standard of care arm to match the adjustment previously accepted by the committee for the mepolizumab technology appraisal. This is an even more conservative approach, as calculations above have shown that the adjustment could be as high as [redacted]	The company's revised base case assumption of 1.35 from the mepolizumab appraisal (TA431) was superceded by the decision not to apply an adjustment for post-trial exacerbation rates in the reslizumab (TA479) and benralizumab (TA565) appraisals. The company presents scenarios for a range of exacerbation rate multipliers in Appendix Tables 8 and 9 (for non-mOCS and mixed populations respectively). The ERG preferred assumption of no adjustment (multiplier = 1) increases the ICER from £35,199 in the company's revised no-mOCS base case to £47,936.

Question for engagement		ERG response
Issue 8: Assumption relating to discontinuation rates		
15. Is no discontinuation within the first year of the model appropriate?	In the clinical trial, QUEST, some patients discontinued treatment before 12 months. Therefore, the company adopts the ERG preferred assumption of patients discontinuing treatment for any reason in the first year of treatment.	We agree.

Question for engagement		ERG response
Issue 9: Treatment settings for severe exacerbations		
16. Should trial data be used to estimate the proportions of patients with severe exacerbations treated in emergency care and inpatient settings in the model?	Trial data is problematic as A&E and hospitalisation is a rare event in all severe asthma clinical trials, and exacerbations are treated differently by country according to local protocol (there are 22 countries in QUEST). Additionally, the ITT population in QUEST is much less severe than the presented population: 48.5% patients are on medium dose ICS and the mean rate of severe exacerbations is lower than the more severe population modelled in the company submission. As an exacerbation is the strongest predictor of a future asthma exacerbation, including less severe patients with fewer exacerbations reduces numbers of patients requiring treatment at A&E or hospitalisation. The presented population is patients with ≥3 exacerbations. However, the mean number of exacerbations in the ITT, in the previous year was 2.09. 77.3% patients had at least 1 but less than 3 severe asthma exacerbations in the previous year, which will underestimate the occurrence of severe asthma exacerbations requiring hospitalisation or A&E attendance. Given this, QUEST trial data is not an accurate or representative source	This is an important assumption because the only asthma-related deaths that occur in the model are for patients hospitalised with severe exacerbation. Thus the proportion of patients with severe exacerbations who are hospitalised impacts on survival, and hence QALYs, as well as healthcare costs. We discuss the strengths and weaknesses of alternative sources of estimates for the setting of severe exacerbation treatment in section 4.3.4.6 of the ERG report. We note that the real-world O'Neill et al. UK registry data has the advantage of being more generalisable than trial data. But we question the completeness of case ascertainment from the community in this study (patients who self-managed with 'OCS burst' may not have been included in the registry). We accept that hospitalisation is a rare event, but note that the number of observations in QUEST exceeded that in the company's preferred source from TA431, which is derived from the MENSA trial (TA431 ERG Table 79). We also acknowledge that the QUEST ITT population (from which hospitalisation rates were derived) was at lower risk of exacerbation

	of data on exacerbation setting for UK patients. A better approximation of exacerbation setting is UK real-world data. Two observational studies have collected UK data: O'Neill 2015, which was used in the company's original base case ((7)), and Bloom, 2015 ((8)) which showed even higher rates of A&E and hospitalisation for patients. Whilst the UK specific data is likely more appropriate, it is understood that the ERG and NICE had concerns with the use of this data. To accommodate this, the updated company assumptions also include the resource use data accepted in the mepolizumab technology appraisal (9) which is conservative compared with UK specific data.	than the subgroup of interest (with three or more exacerbations in the previous year). However, the parameter of interest in the model is a probability of hospitalisation for patients with a severe exacerbation. It is not obvious that patients with a lower prior risk of exacerbation, also have a lower risk of hospitalisation once they have had a severe exacerbation. On balance, we consider the trial data to be a better source for estimation of the proportions of patients with severe exacerbations treated in emergency care and inpatient settings. This is because the definitions of severe exacerbation events will be consistent with the clinical data used in the model, and the method of ascertainment is likely to be more complete than for a registry based on routine clinical data. The company present ICERs for scenarios with alternative sources for the setting of exacerbation treatment in Appendix Table 7. This shows that the revised base case ICER (£35,199) increases to £41,246 with QUEST trial hospitalisation rates. When also combined with the assumption of no adjustment of post-trial exacerbation rates, the ICER increases to £56,886 per QALY gained.

Question for engagement		**ERG response**
Issue 10: Utility values		
17. Should the utility used for the controlled asthma (and uncontrolled asthma) health state be limited to general population mean?	The company submission used the utility data from the dupilumab clinical trials, as outlined in the NICE reference case. However, the company agrees with the ERG and NICE technical team that these data should not be higher than the utility for the general population mean and the updated company assumptions	We agree.

	limit the uncontrolled asthma utility to the general population mean.	
18. Which utility best reflects people in the uncontrolled asthma health state: a) 0.735 and 0.713 in the non-mOCS and the mOCS population respectively based on RCT data in the company submission b) 0.701 and 0.697 for standard care in the non-mOCS and mOCS population respectively from clinical trials in TA565, or c) c) 0.702 and 0.682 in the non-mOCS and the mOCS population respectively based on ERG calculations?	The company updated base case limits the utility of the uncontrolled asthma population to 0.702 and 0.682 in the non-mOCS and the mOCS population respectively.	We agree.

Question for engagement		**ERG response**
Issue 11: Unit costs		
19. Is it appropriate to use weighted NHS National Tariff costs in the model?	The original company submission considered the weighted NHS National Tariff Costs to be more reflective of service usage in the UK for severe asthma. However, noting preference from the ERG for the source of cost of A&E and hospitalisation to be consistent with previous submissions, the company has updated the costs to include the ERG preferred cost assumption.	We agree.

Question for engagement		ERG response
Issue 12: Administration		
20. How likely are patients to self-administer in practice?	Self-administration will be determined by clinical opinion based on patient and physician factors. Most HCPs will want their patients with severe asthma to be treated in hospital for the first 3-6 months before transitioning to homecare to ensure compliance and response. However, the process of self-administration is simple and supported by a patient support programme (PSP). There are to date 3,249 patients on homecare (active on treatments) receiving dupilumab for atopic dermatitis (AD). Of these, 3,633 (90.5%) are considered persistent patients. In AD, patients have been very receptive and persistent with self-administration of dupilumab,	No comment.
21. Is the company's assumption of self-administration for 100% of patients for dose 4 onwards reasonable for the base case?	Based on the company's experience with AD, some patients will receive homecare from dose 4, however, for the purposes of the model for conservatism, it is assumed in the updated company preferred assumptions that all patients will be administered dupilumab in hospital.	We investigated a scenario with 100% HCP administration of subcutaneous injections, but did not include this in the ERG base case (ERG report sections 4.4.3 and 4.4.4). This made little difference to our ICER estimate: ERG base case £55,348; compared with £56,886 for the scenario with costs for 100% HCP administration.

CONFIDENTIAL

Single technology appraisal

ERG Addendum 2: Updated analysis after technical engagement for comparisons with standard care

Dupilumab for treating severe asthma

ID1213

Produced by Southampton Health Technology Assessments Centre (SHTAC)

Authors Joanne Lord, Joanna Picot

Addendum date 7 February 2020

Commercial in confidence information relating to the company's PAS discount for dupilumab is redacted [redacted]

1 Introduction

The company submitted their response to the NICE technical engagement (TE) with an updated model and additional analysis appendix, dated 10 January 2020. The ERG has commented on this in our response dated 21 January 2020. Subsequently, the company submitted a revised version of their TE response appendix (file 'ID1213 dupilumab additional analysis Appendix v02 240110'). In this addendum, we comment on the revised appendix and provide some additional analysis based on the updated base case and model. Results including PAS price discounts for other comparisons are reported in a separate addendum.

2 Patient populations and subgroups

The company reports cost-effectiveness results for various patient subgroups (see Table 1).

Table 1 Subgroups in company TE response appendix

Patient subgroup	Table	Comparators	Areas in Figure 1
Company population	6, 8, 9 & 10	Standard care	A to H
Raised EOS and FeNO	6	Standard care	Subset of B, C, D, F, G, H
Mixed population, 30% mOCS	8 & 11	Standard care	A to L
Mepolizumab eligible, no mOCS	7	Standard care Mepolizumab Benralizumab	G, H
Mepolizumab eligible, 30% mOCS	7	Standard care Mepolizumab Benralizumab	G, H, K, L
Reslizumab eligible	7	Standard care Reslizumab Benralizumab	D, H
Incremental, no mOCS	14	Standard care	A, B, C, E, F
Incremental, 30% mOCS	14	Standard care	A, B, C, E, F, I, J

Definitions of these groups are complex because they combine four sets of patient characteristics:

- Use of maintenance oral corticosteroids (mOCS);
- Numbers of severe exacerbations in the previous year;
- Blood eosinophil (EOS) levels; and
- Fractional exhaled nitric oxide (FeNO) measurements.

Figure 1 below divides the population of interest into 12 mutually exclusive subgroups (the squares labelled A to L), which we use to clarify definitions.

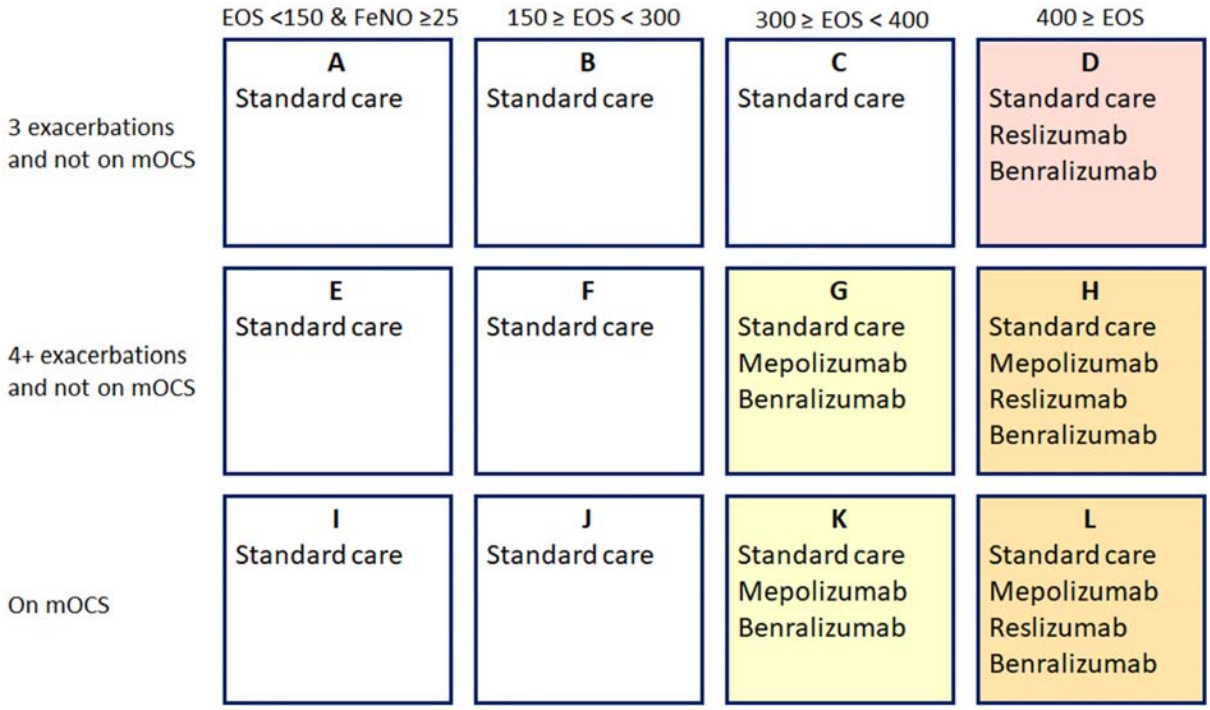

Figure 1 Illustration of patient subgroups by eligibility for comparators

The company's model estimates ICERs for some combinations of these subgroups, but not all due to data constraints. For example, the model cannot produce ICERs for mOCS patients with an EOS≥400 (L) or for the total biologic-eligible group (D, G, H, K, L). We note uncertainty over ICERs for the smaller subgroups and for the 'exploratory' comparisons with other biologic drugs.

However, the ERG considers that ICERs for the whole of the company's proposed population (A to H) and the wider 'mixed population' including patients on mOCS (A to L) are misleading, because they pool costs and QALYs for people who are eligible for different comparators and with different levels of exacerbation risk.

We therefore argue that there are four populations that are most relevant for decision making and for which ICERs can be produced:

- People only eligible for standard care not taking mOCS (areas A, B, C, E and F)
- People only eligible for standard care taking mOCS (areas I and J)
- People eligible for mepolizumab or benralizumab, with or without mOCS (G, H, K and L)
- People eligible for reslizumab or benralizumab (areas D and H)

We also show results for other subgroups for comparison with company results and consideration of the Committee, including the company's proposed population, mixed population and the raised EOS and FeNO subgroup.

3 ERG critique of company's revised TE response appendix

The revised TE response appendix contains one change to the company's updated base case: reverting to their original base case assumption that all patients would self-administer subcutaneous injections (after administration by a health care professional (HCP) for the first 3 weeks of therapy and with training).

We note that the revised appendix reports that the ERG base case includes an assumption that all injections would be administered by a HCP (page 3 and Table 4). This is not correct. We ran a scenario to test the impact of 100% HCP administration (ERG report section 4.4.3, Table 95), but the ICER was not sensitive to this assumption and we did not include it in our final base case (ERG report section 4.4.4, Table 99). We made this decision based on clinical advice that self-administration would be attractive to patients and efficient for the NHS. However, we note that the implementation of routine self-administration in routine NHS practice is a matter of uncertainty.

The ERG has checked the results in the company's revised appendix using the version of the model that the company submitted with their TE response. We identified two errors:

- **Revised appendix Table 8**: With 41.7% of patients assumed to be taking maintenance oral corticosteroids (mOCS) we obtained an incremental cost of [redacted] and ICER of £42,449 for dupilumab compared with standard care. These values are a little lower than

those reported in the revised appendix: [redacted] and £42,507 respectively, but do not materially affect the results.

- **Revised appendix Table 14**: We replicated the ICER for the mixed 'incremental population' with 30% mOCS (£51,683) but believe it to be incorrect, as it includes all mOCS patients with (EOS≥150 or FeNO≥25) rather than just those who are ineligible for other biologics (EOS<300). We estimate an ICER of £58,615 for the mixed incremental population with 30% mOCS. To make this calculation we assumed that [redacted] of patients on mOCS would be eligible for mepolizumab: [redacted] out of 152 patients in VENTURE (Clarification response Table 16 and ERG Table 10).

4 Company's updated base case

Table 2 Dupilumab vs standard care: company updated base case
(deterministic analysis with confidential discounted price for dupilumab)

Technology	Total cost	Total QALYs	ICER (£/QALY)
Company's proposed population (A to H)			
Standard care	[redacted]	[redacted]	-
Dupilumab	[redacted]	[redacted]	£ 34,216
Raised EOS and FeNO (subset of B, C, D, F, G and H)			
Standard care	[redacted]	[redacted]	-
Dupilumab	[redacted]	[redacted]	£ 29,417
Mixed population, 30% mOCS (A to L)			
Standard care	[redacted]	[redacted]	-
Dupilumab	[redacted]	[redacted]	£ 40,172
Incremental population not eligible for biologics, no mOCS (A, B, C, E, F)			
Standard care	[redacted]	[redacted]	-
Dupilumab	[redacted]	[redacted]	£ 50,558
Incremental population not eligible for biologics, mOCS only (I and J) [a]			
Standard care	[redacted]	[redacted]	-
Dupilumab	[redacted]	[redacted]	£ 77,972

[a] Estimated by ERG, assuming [redacted] ([redacted]/152) mOCS patients meet mepolizumab criteria

Table 3 Post trial severe exacerbation multiplier: company updated base case
(deterministic analysis with confidential discounted price for dupilumab)

Exacerbation multiplier	Technology	Total cost	Total QALYs	ICER (£/QALY)
Company's proposed population (A to H)				
No increased risk after trial (1.00)	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 46,619
Adjustment from TA431, MENSA ITT (1.35)	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 34,216
Adjustment for trial inclusion criteria ([redacted])	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 32,110
Raised EOS and FeNO (subset of B, C, D, F, G and H)				
No increased risk after trial (1.00)	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 37,906
Adjustment from TA431, MENSA ITT (1.35)	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 29,417
Adjustment for trial inclusion criteria ([redacted])	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 27,959
Mixed population, 30% mOCS (A to L)				
No increased risk after trial (1.00)	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 51,059
Adjustment from TA431, MENSA ITT (1.35)	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 40,172
Adjustment for trial inclusion criteria ([redacted])	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 38,217
Incremental population not eligible for biologics, no mOCS (A, B, C, E, F)				
No increased risk after trial (1.00)	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 66,976
Adjustment from TA431, MENSA ITT (1.35)	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 50,558
Adjustment for trial inclusion criteria [redacted])	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 47,797
Incremental population not eligible for biologics, mOCS only (I and J) [a]				
No increased risk after trial (1.00)	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 80,132
Adjustment from TA431, MENSA ITT (1.35)	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 77,972
Adjustment for trial inclusion criteria ([redacted])	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 77,521

[a] Estimated by ERG, assuming [redacted] ([redacted]/152) mOCS patients meet mepolizumab criteria

Table 4 Treatment setting for severe exacerbations: company updated base case
(deterministic analysis with confidential discounted price for dupilumab)

Treatment setting (% A&E, %hospital)	Technology	Total cost	Total QALYs	ICER (£/QALY)
Company's proposed population (A to H)				
QUEST (3.0%, 3.7%) no mOCS VENTURE (6.4%, 8.3%) mOCS	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 40,119
TA431, MENSA (8.7%, 8.2%) for non mOCS only	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 34,216
O'Neill 2015 registry for mOCS and non mOCS (7.8%, 18.7%)	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 31,692
Raised EOS and FeNO (subset of B, C, D, F, G and H)				
QUEST (3.0%, 3.7%) no mOCS VENTURE (6.4%, 8.3%) mOCS	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 34,744
TA431, MENSA (8.7%, 8.2%) for non mOCS only	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 29,417
O'Neill 2015 registry for mOCS and non mOCS (7.8%, 18.7%)	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 26,946
Mixed population, 30% mOCS (A to L)				
QUEST (3.0%, 3.7%) no mOCS VENTURE (6.4%, 8.3%) mOCS	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 44,638
TA431, MENSA (8.7%, 8.2%) for non mOCS only	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 40,172
O'Neill 2015 registry for mOCS and non mOCS (7.8%, 18.7%)	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 37,029
Incremental population not eligible for biologics, no mOCS (A, B, C, E, F)				
QUEST (3.0%, 3.7%) no mOCS VENTURE (6.4%, 8.3%) mOCS	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 61,192
TA431, MENSA (8.7%, 8.2%) for non mOCS only	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 50,558
O'Neill 2015 registry for mOCS and non mOCS (7.8%, 18.7%)	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 46,107
Incremental population not eligible for biologics, mOCS only (I and J) [a]				
QUEST (3.0%, 3.7%) no mOCS VENTURE (6.4%, 8.3%) mOCS	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 77,972
TA431, MENSA (8.7%, 8.2%) for non mOCS only	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 77,972
O'Neill 2015 registry for mOCS and non mOCS (7.8%, 18.7%)	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 71,468

[a] Estimated by ERG, assuming [redacted] ([redacted]/152) mOCS patients meet mepolizumab criteria

5 ERG base case

Table 5 ERG base case: dupilumab vs standard care by subgroup
(deterministic analysis with confidential discounted price for dupilumab)

Technology	Total cost	Total QALYs	ICER (£/QALY)
Company's proposed population (A to H)			
Standard care	[redacted]	[redacted]	-
Dupilumab	[redacted]	[redacted]	£ 55,348
Raised EOS and FeNO (subset of B, C, D, F, G and H)			
Standard care	[redacted]	[redacted]	-
Dupilumab	[redacted]	[redacted]	£ 45,185
Mixed population, 30% mOCS (A to L)			
Standard care	[redacted]	[redacted]	-
Dupilumab	[redacted]	[redacted]	£ 56,852
Incremental population not eligible for biologics, no mOCS (A, B, C, E, F)			
Standard care	[redacted]	[redacted]	-
Dupilumab	[redacted]	[redacted]	£ 81,676
Incremental population not eligible for biologics, mOCS only (I and J) [a]			
Standard care	[redacted]	[redacted]	-
Dupilumab	[redacted]	[redacted]	£ 80,132

[a] Estimated by ERG, assuming [redacted] ([redacted]/152) mOCS patients meet mepolizumab criteria

Table 6 Issue 7 severe exacerbation multiplier: ERG base case
(deterministic analysis with confidential discounted price for dupilumab)

Multiplier	Technology	Total cost	Total QALYs	ICER (£/QALY)
Company's proposed population (A to H)				
No increased risk after trial (1.00)	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 55,348
Adjustment from TA431, MENSA ITT (1.35)	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 40,119
Adjustment for trial inclusion criteria ([redacted])	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 37,533
Raised EOS and FeNO (subset of B, C, D, F, G and H)				
No increased risk after trial (1.00)	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 45,185
Adjustment from TA431, MENSA ITT (1.35)	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 34,744
Adjustment for trial inclusion criteria ([redacted])	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 32,944
Mixed population, 30% mOCS (A to L)				
No increased risk after trial (1.00)	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 56,852
Adjustment from TA431, MENSA ITT (1.35)	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 44,638
Adjustment for trial inclusion criteria ([redacted])	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 42,422
Incremental population not eligible for biologics, no mOCS (A, B, C, E, F)				
No increased risk after trial (1.00)	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 81,676
Adjustment from TA431, MENSA ITT (1.35)	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 61,192
Adjustment for trial inclusion criteria ([redacted])	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 57,743
Incremental population not eligible for biologics, mOCS only (I and J) [a]				
No increased risk after trial (1.00)	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 80,132
Adjustment from TA431, MENSA ITT (1.35)	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 77,972
Adjustment for trial inclusion criteria ([redacted])	Standard care	[redacted]	[redacted]	-
	Dupilumab	[redacted]	[redacted]	£ 77,521

[a] Estimated by ERG, assuming [redacted] ([redacted]/152) mOCS patients meet mepolizumab criteria

Table 7 Issue 9 Treatment setting for severe exacerbations: ERG base case
(deterministic analysis with confidential discounted price for dupilumab)

Source (% A&E, % hospital)	Technology	Total cost	Total QALYs	ICER (£/QALY)
Company's proposed population (A to H)				
QUEST (3.0%, 3.7%) no mOCS VENTURE (6.4%, 8.3%) mOCS	Standard care Dupilumab	[redacted] [redacted]	[redacted] [redacted]	- £ 55,348
TA431, MENSA (8.7%, 8.2%) for non mOCS only	Standard care Dupilumab	[redacted] [redacted]	[redacted] [redacted]	- £ 46,619
O'Neill 2015 registry for mOCS and non mOCS (7.8%, 18.7%)	Standard care Dupilumab	[redacted] [redacted]	[redacted] [redacted]	- £ 43,549
Raised EOS and FeNO (subset of B, C, D, F, G and H)				
QUEST (3.0%, 3.7%) no mOCS VENTURE (6.4%, 8.3%) mOCS	Standard care Dupilumab	[redacted] [redacted]	[redacted] [redacted]	- £ 45,185
TA431, MENSA (8.7%, 8.2%) for non mOCS only	Standard care Dupilumab	[redacted] [redacted]	[redacted] [redacted]	- £ 37,906
O'Neill 2015 registry for mOCS and non mOCS (7.8%, 18.7%)	Standard care Dupilumab	[redacted] [redacted]	[redacted] [redacted]	- £ 35,047
Mixed population, 30% mOCS (A to L)				
QUEST (3.0%, 3.7%) no mOCS VENTURE (6.4%, 8.3%) mOCS	Standard care Dupilumab	[redacted] [redacted]	[redacted] [redacted]	- £ 56,852
TA431, MENSA (8.7%, 8.2%) for non mOCS only	Standard care Dupilumab	[redacted] [redacted]	[redacted] [redacted]	- £ 51,059
O'Neill 2015 registry for mOCS and non mOCS (7.8%, 18.7%)	Standard care Dupilumab	[redacted] [redacted]	[redacted] [redacted]	- £ 47,258
Incremental population not eligible for biologics, no mOCS (A, B, C, E, F)				
QUEST (3.0%, 3.7%) no mOCS VENTURE (6.4%, 8.3%) mOCS	Standard care Dupilumab	[redacted] [redacted]	[redacted] [redacted]	- £ 81,676
TA431, MENSA (8.7%, 8.2%) for non mOCS only	Standard care Dupilumab	[redacted] [redacted]	[redacted] [redacted]	- £ 66,976
O'Neill 2015 registry for mOCS and non mOCS (7.8%, 18.7%)	Standard care Dupilumab	[redacted] [redacted]	[redacted] [redacted]	- £ 61,230
Incremental population not eligible for biologics, mOCS only (I and J) [a]				
QUEST (3.0%, 3.7%) no mOCS VENTURE (6.4%, 8.3%) mOCS	Standard care Dupilumab	[redacted] [redacted]	[redacted] [redacted]	- £ 80,132
TA431, MENSA (8.7%, 8.2%) for non mOCS only	Standard care Dupilumab	[redacted] [redacted]	[redacted] [redacted]	 £ 80,132
O'Neill 2015 registry for mOCS and non mOCS (7.8%, 18.7%)	Standard care Dupilumab	[redacted] [redacted]	[redacted] [redacted]	 £ 74,538

[a] Estimated by ERG, assuming [redacted] ([redacted]/152) mOCS patients meet mepolizumab criteria