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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Dupilumab for treating severe asthma [ID1213]

Appraisal Committee Meeting – 9 September 2021
3rd Committee meeting

The following documents are made available to the Company:

1. **Appraisal Consultation Document (ACD2)** as issued to consultees and commentators

2. **Comments on the Appraisal Consultation Document from Sanofi**

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a) Asthma UK & British Lung Foundation
   b) Association of Respiratory Nurse Specialists
   c) British Thoracic Society
   d) GlaxoSmithKline UK Ltd
   e) Novartis
   f) University of Oxford (not registered stakeholders)
4. **Comments on the Appraisal Consultation Document received through the NICE website**

5. **Evidence Review Group critique of company comments on the ACD**

6. **Appraisal Committee Meeting presentation slides** – to follow

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Dupilumab for treating severe asthma with type 2 inflammation

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using dupilumab in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: May 2021

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using dupilumab in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 28 May 2021

Third appraisal committee meeting: 9 September 2021

Details of membership of the appraisal committee are given in section 5

1 Recommendations

1.1 Dupilumab as add-on maintenance therapy is not recommended, within its marketing authorisation, for treating severe asthma with type 2 inflammation that is inadequately controlled in people aged 12 years and over, despite maintenance therapy with high-dose inhaled corticosteroids and another maintenance treatment.

1.2 This recommendation is not intended to affect treatment with dupilumab that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Severe asthma is usually treated with inhaled corticosteroids plus another drug, such as a long-acting beta-agonist. Oral corticosteroids may also be needed to prevent exacerbations (asthma attacks), but they cause long-term side effects. These treatments may not work well enough for severe asthma with type 2 inflammation, which can be difficult to control. Some people who have another type of severe asthma called eosinophilic asthma can have mepolizumab, reslizumab or benralizumab. These drugs, like dupilumab, are biological agents but work in a different way.

Clinical trial results show that having dupilumab plus standard asthma treatment reduces exacerbations and the use of oral corticosteroids more than placebo in people with severe asthma with type 2 inflammation. There are no trials directly comparing dupilumab with mepolizumab, reslizumab or benralizumab. Comparing these drugs indirectly suggests a reduction in asthma exacerbations with dupilumab but no difference in other asthma symptoms.

The company's population of people with type 2 inflammation is not suitable for considering the cost effectiveness of dupilumab compared with standard care. This

is because it combines people eligible for biologicals (mepolizumab, reslizumab or benralizumab) with people not eligible for biologicals who can only be offered standard care. The cost-effectiveness estimates for dupilumab vary depending on whether people are eligible for mepolizumab, reslizumab or benralizumab, and what their individual treatment options are. Regardless, the cost-effectiveness estimates for dupilumab are higher than what NICE usually considers a cost-effective use of NHS resources. Dupilumab cannot be recommended for treating inadequately controlled severe asthma with type 2 inflammation.

2 Information about dupilumab

Marketing authorisation indication

2.1 Dupilumab (Dupixent, Sanofi) has a marketing authorisation 'in adults and adolescents 12 years and older as an add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO [fractional exhaled nitric oxide]…who are inadequately controlled with high dose ICS [inhaled corticosteroid] plus another medicinal product for maintenance treatment'. The definition of type 2 inflammation is as in the Global Initiative for Asthma guideline.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics.

Price

2.3 The list price of dupilumab is £1,264.89 for 2 prefilled syringes of either the 200 mg per 1.44 ml or 300 mg per 2 ml dose (excluding VAT; British National Formulary online accessed November 2020).

2.4 The company has a commercial arrangement. This makes dupilumab available to the NHS for all indications with a discount and it would have also applied to this indication if the technology had been recommended. The size of the discount is commercial in confidence. It is the company's

responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Sanofi Genzyme, a review of this submission by the evidence review group (ERG), NICE's technical report, and responses from stakeholders. See the committee papers for full details of the evidence.

New treatment option

An additional treatment option that lowers the risk of exacerbations and may reduce the need for oral corticosteroids would be welcome

3.1 Severe asthma is a distressing and socially isolating condition. The patient expert explained that exacerbations can happen without warning, be life threatening, cause fear and result in hospitalisation. People are often unable to work or start a family, and may need help with day-to-day activities because of their symptoms. The clinical expert explained that, in addition to optimised inhaled treatment, standard treatment for severe asthma is oral systemic corticosteroids or, if the patient has eosinophilic asthma and depending on the blood eosinophil count, NICE recommended interleukin-5 inhibitors biologicals benralizumab, mepolizumab and reslizumab. Dupilumab is the only licensed treatment for severe asthma with type 2 inflammation. Although asthma can respond to systemic corticosteroids, the treatment can be associated with long-term complications (such as diabetes mellitus, weight gain, bone loss, immunosuppression and a negative effect on mental health). The patient expert explained that patients would welcome treatment options that replace the need for corticosteroids. The clinical expert explained that a blood eosinophil count and fractional exhaled nitric oxide (FeNO) are used to help define subtypes of severe asthma and help predict the people with severe asthma who are at highest risk of a future exacerbation. In people with severe asthma with type 2 inflammation, their condition does not

respond to interleukin-5 inhibitors but can respond to interleukin-13 inhibitors such as dupilumab. The committee concluded that there is a need for new treatments with a different mode of action for people with severe asthma with type 2 inflammation whose asthma does not respond with current standard care, and for people not eligible for current NICE recommended biologicals.

Clinical management

Severe asthma with type 2 inflammation is a subtype of asthma

3.2 Severe asthma with type 2 inflammation is associated with allergy, higher risk of exacerbations, hospitalisation, dependency on oral corticosteroids and increased risk of dying. The Global Initiative for Asthma (GINA) guideline on difficult to treat severe asthma (2019) lists 5 criteria in its definition of severe asthma with type 2 inflammation that are prognostics markers:

- a blood eosinophil count of 150 cells per microlitre or more
- FeNO of 20 parts per billion or more
- sputum eosinophils of 2% or more
- asthma that is clinically allergen driven
- the need for maintenance oral corticosteroids.

GINA suggests that 1 or more criterion can be used to make a diagnosis. The clinical expert explained that raised blood eosinophils and FeNO are risk predictors for future exacerbations. That is, the higher these biomarkers, the more likely you are to have an exacerbation. The committee concluded that this subtype of severe asthma exists.

Blood eosinophil count and FeNO are common biomarkers for diagnosis

3.3 The clinical expert explained that blood eosinophil counts and FeNO levels are routinely measured in clinical practice. They also explained that, while blood eosinophils counts are raised in both eosinophilic asthma and

asthma with type 2 inflammation, raised FeNO is more specific to type 2 inflammation. The committee noted the response of stakeholders during technical engagement that a blood eosinophil count of 150 cells per microlitre or more, FeNO of 20 parts per billion or more, or both, could be used for identifying people with type 2 inflammation. The committee acknowledged the complexity of diagnosing asthma subtypes, and the potential for overlap or misclassification between them, despite the use of blood eosinophil counts and FeNO levels.

Dupilumab as add-on treatment is an option for managing uncontrolled severe asthma with type 2 inflammation

3.4 The clinical expert explained that treatment for asthma in clinical practice follows the NICE guideline on diagnosis, monitoring and chronic asthma management and the GINA 2019 guideline (which includes the use of biologicals). If the asthma is still uncontrolled despite optimised inhaled therapy that includes corticosteroids, then low-dose oral corticosteroids or biologicals are added. The clinical and patient experts explained that biologicals are preferred over oral corticosteroids because they have fewer debilitating side effects. The choice of biological depends on the subtype of asthma. For severe eosinophilic asthma, according to NICE technology appraisal guidance for benralizumab, mepolizumab and reslizumab, the treatment of choice depends on the blood eosinophil count (300 cells per microlitre or more, or 400 cells per microlitre or more) and the number of exacerbations (3 or 4, or more) or the use of systemic corticosteroids. Omalizumab is another biological used for treating severe persistent allergic asthma. However, it is not used for eosinophilic asthma (see section 3.6). There are currently no NICE recommended biologicals for treating severe asthma with type 2 inflammation. The committee concluded that dupilumab as add-on treatment is an option for managing uncontrolled severe asthma with type 2 inflammation.

Populations

It is challenging to define which populations should be used for decision making

3.5 There are several subgroups to consider when deciding which population to use for decision making. At the first appraisal committee meeting, the committee considered whether the population would need to have a raised eosinophil count, raised FeNO or both based on the 'and/or' wording in the marketing authorisation and GINA recommendations for these biomarkers. The committee also acknowledged that there are subgroups on or off maintenance oral corticosteroids, or both (mixed proportions on and off oral corticosteroids), and populations eligible or not eligible for biologicals. In addition, it acknowledged the overlap between the populations in the marketing authorisation, trials and company decision problem at the first appraisal committee meeting:

- The marketing authorisation population is broad, consisting of people with uncontrolled severe asthma with type 2 inflammation on high-dose inhaled corticosteroids plus 1 maintenance treatment and with a blood eosinophil count and FeNO as described by GINA.
- The clinical trials (DRI12544, QUEST and VENTURE) recruited people with 1 or more exacerbation in the previous year and no restrictions on blood eosinophils and FeNO.

3.6 The company's updated decision problem (base case) was in a subpopulation of people who are not eligible for biologicals or who did not respond to biological therapy,based on a posthoc analysis of the QUEST data. They were people aged 12 and older, with blood eosinophils counts of 150 cells per microlitre or more and a fractional exhaled nitric oxide of 25 or more, who have had at least 4 exacerbations in the previous 12 months and who are not eligible for biologicals or did not respond to biological therapy and will be referred to as the updated population hereafter. The company considered that this narrower population represented people with highest unmet need

and can be split into 3 subgroups: adolescents who are aged 12 to 17, adults who are not eligible for biologicals (blood eosinophil count 150 to 299) and adults who previously received biologicals but did not respond (blood eosinophil count of 300 and more). The committee noted that the comparator for the updated population is standard care and other biologicals were only recommended in adults in NICE guidance. The committee concluded that the updated population was suitable for decision making.

Comparators

Standard care is the appropriate comparator in the updated population

3.7 The clinical trial populations included people with differing severity of asthma (defined by eosinophil level and the number of exacerbations in the previous year). These populations therefore included people who would be offered different treatment options in the NHS:

- People with a blood eosinophil count of 300 cells per microlitre or more, who have had at least 4 exacerbations in the previous 12 months or who are taking oral corticosteroids, can have mepolizumab or benralizumab.
- People with a blood eosinophil count of 400 cells per microlitre or more, who have had at least 3 exacerbations in the previous 12 months, can have reslizumab or benralizumab.
- People not eligible for biologicals (defined below) are offered standard care:
  - a blood eosinophil count of between 150 and 299 cells per microlitre and 4 or more exacerbations (not eligible for mepolizumab or benralizumab)
  - a blood eosinophil count of between 150 and 399 cells per microlitre and 3 or more exacerbations (not eligible for reslizumab or benralizumab)

  - a blood eosinophil count of less than 150 cells per microlitre and FeNO of 25 parts per billion or more (not eligible for any other biological)
- People who did not respond to biological therapy are offered standard care

  The committee concluded that standard care was an appropriate comparator in the company's updated population, that is people not eligible for biologicals or those who did not respond to biological therapy.

Clinical evidence

The evidence on clinical effectiveness is relevant to NHS clinical practice

3.8 The company's clinical evidence came from 3 randomised-controlled trials, DRI12544, QUEST and VENTURE. These compared dupilumab with placebo in people aged 12 years and over (except DRI12544, which only included people aged 18 years or over) with persistent asthma who had 1 or more exacerbations in the previous year. None of the trials had restrictions on blood eosinophils or FeNO. DRI12544 and QUEST included people with moderate-to-severe asthma not on maintenance oral corticosteroids. VENTURE included people with severe corticosteroid-dependent asthma (on maintenance corticosteroids). The 3 trials were conducted globally, and QUEST was the only trial that included people from the UK. The trial populations were based on use of moderate-to-high doses of inhaled corticosteroids. This was because they included people from countries like the US and Japan, where the clinical expert stated that there is reluctance to use high-dose inhaled corticosteroids. The committee concluded that there were some caveats, but that all 3 trials included were relevant to NHS clinical practice.

Dupilumab is more clinically effective than standard care in the clinical trial populations

3.9 All primary outcomes were reported for the intention-to-treat population in all 3 trials. In QUEST, the first coprimary outcome was annualised rate of severe exacerbations. There was a 47.7% (95% confidence interval [CI] 33.8% to 58.7%, p<0.0001) lower rate of severe exacerbations in the dupilumab group compared with placebo. Change from baseline in the forced expiratory volume in 1 second (FEV1) at 12 weeks was the second coprimary outcomes in QUEST and the primary outcome in DRI12544. There was an increase in FEV1 at 12 weeks when dupilumab was compared with placebo in DRI12544 (least squares [LS] mean difference 0.14 litre, 95% CI 0.08 to 0.19, p<0.0001) and QUEST (LS mean difference 0.20 litre, 95% CI 0.11 to 0.28, p<0.0001). In VENTURE, the primary outcome was the percentage reduction in oral corticosteroid dose from baseline. There was a greater reduction in oral corticosteroid use with dupilumab compared with placebo (LS mean difference 28 mg, 95% CI 16 to 41, p<0.0001) at 24 weeks. The proportion of people with treatment-related adverse events was similar within each trial between those having dupilumab and placebo. In DRI12544 and QUEST, the proportion of people with any treatment-related adverse events ranged from 74.7% to 84.1%. In VENTURE, a smaller proportion experienced any treatment-related adverse events (64.5% and 62.1% in the placebo and dupilumab arms respectively). The committee concluded that dupilumab was more clinically effective than standard care in the clinical trial populations and is a relatively safe treatment.

The clinical effectiveness estimates for dupilumab are uncertain in the company's updated population

3.10 The company's decision-problem subgroup analyses at the first appraisal committee meeting focused on the annualised rate of severe exacerbations for the posthoc population (that is, people with a blood eosinophil count of 150 cells per microlitre or more, FeNO of 25 parts per

billion or more and 3 or more exacerbations in the previous year) from QUEST and VENTURE. Dupilumab reduced the rate of severe exacerbations when compared with placebo within this subpopulation in QUEST and VENTURE, although in small posthoc subgroups with 101 and 152 people respectively. There were improvements in the placebo groups for the primary outcomes of these trials. This was possibly because of regression to the mean and the placebo effect. The committee concluded that dupilumab is clinically effective and safe as an addition to standard care in people with a blood eosinophil count of at least 150 cells per microlitre or FeNO of 25 parts per billion or more and 3 or more exacerbations in the previous year who may or may not be taking maintenance oral corticosteroids. However, there were very limited evidence clinical efficacy data provided for the company's updated population because of small number of patients in the QUEST trial corresponding to each subgroup. The committee concluded that the clinical effectiveness of dupilumab in the company's updated base case was highly uncertain.

The company's economic model

The model structure is appropriate for decision making

3.11 The company submitted a 4-state Markov model comparing dupilumab with standard care in people with severe asthma and type 2 inflammation. The model consisted of 4 live health states: uncontrolled asthma; controlled asthma; moderate exacerbation; and severe exacerbation. In addition, the model included states for asthma-related deaths and death from other causes. Response to treatment was defined as a 50% or greater reduction in the annual exacerbation rate, which was assessed at 52 weeks. People whose asthma responded continued on dupilumab and those whose did not transferred to standard care. The company derived the efficacy and clinical parameters in the model from the QUEST clinical trial. The committee concluded that the model structure was appropriate for decision making.

Clinical inputs to the model

The evidence for the company's updated population is limited and effectiveness estimates are based on assumptions

3.12 The committee noted that the company split the updated population into 3 subgroups: the adolescents who are aged 12 to 17, the adults who are not eligible for biologicals (blood eosinophil count 150 to 299) and adults who previously received biologicals but did not respond (blood eosinophil count of 300 and more). The committee noted that the clinical effectiveness evidence available for each of the subpopulations was limited because the number of patients included in the QUEST trial corresponding to each subgroup was small. The trial included 2 patients corresponding to the adolescent subgroup and 14 patients corresponding to the subgroup of adults who are not eligible to biologicals. The QUEST protocol excluded patients who had been on biologicals but 1 patient in the trial was included who had previously received a biological. The ERG noted that the estimates of transition probabilities for the company's updated population were highly uncertain, due to small sample sizes. The company assumed that clinical effectiveness was the same for each subgroup based on trial estimates for the overall company's updated population. The committee particularly considered the assumption of equal efficacy of dupilumab regardless of whether people had received prior biological therapy. The company provided clinical expert opinion that switching from other biologicals (interleukin-5 inhibitors: mepolizumab, reslizumab, benralizumab) to dupilumab (interleukin-4/13 inhibitor) was acceptable because the mechanisms of action were different enough. The committee was concerned about this assumption and considered that although it is plausible that people who did not respond to other biologicals could respond to dupilumab, assuming that the response rate would be as good as in people not eligible for other biologicals was optimistic. The committee considered this to be a key area of uncertainty and noted that it would have liked to see exploration of scenarios with a

range of alternative response rates for the group of adults who did not respond to biological therapy. The committee concluded that the effectiveness estimates in the company's updated population were highly uncertain.

The company's updated base case does not include a multiplier for long-term severe exacerbation rates

3.13 The committee noted that asthma-related mortality often drives cost effectiveness in asthma models. The annual severe exacerbation rate (2.39 exacerbations per year) in the placebo arm of the QUEST trial was lower than observed in clinical practice in the year before trial enrolment (4.46 exacerbations per year).The company's model after technical engagement used the exacerbation rates from QUEST and VENTURE in the first year of the model and increased the number of severe exacerbations in subsequent years for both dupilumab and standard care by applying a multiplier. The ERG considered the trial to be the best source of exacerbation data and did not include an exacerbation multiplier in its base case model which resulted in higher incremental cost effectiveness ratios (ICERs). The company provided evidence on severe exacerbation rates from 3 severe asthma cohorts: WATCH (Wessex Asthma Cohort of Difficult Asthma), U-BIOPRED (Unbiased BIOmarkers in PREDiction of respiratory disease outcomes) and the Sanofi Real World Evidence (RWE) study. It also accepted the committee and ERG's concerns about the uncertainty of using a multiplier. The exacerbation rates in the company's updated base case model were taken from the QUEST trial for the duration of the model without an exacerbation multiplier. The committee concluded that the updated base case without the exacerbation multiplier was appropriate.

Real world evidence is best source of data to inform the setting of treating severe exacerbations

3.14 The company assigned different mortality rates to severe exacerbations treated in hospital emergency care, inpatients and general practice. In the

QUEST trial 6.7% of severe exacerbations were treated in hospital (3.0% in emergency care, 3.7% in inpatients and 93.3% in general practice). The company originally based resource use associated with severe exacerbations on the UK Difficult Asthma Registry registry data (O'Neill 2015) with 26.5% (7.8% in emergency care, 18.7% in inpatients) and 74.0% in general practice) as a better estimate or resource use in the NHS. The ERG base-case model used the QUEST data for the setting of severe exacerbations. The clinical expert explained that the number of patients treated in hospital in clinical practice is likely to be higher than that seen in the trial because patients in trials are well monitored on optimised treatment, more motivated and have better adherence to treatment. The committee requested further exploration of different sources of data for the setting of treating exacerbations, to inform the model. The company submitted data on the setting of treating severe exacerbation rates from 3 different sources (WATCH, U-BIOPRED and the Sanofi RWE study). The Sanofi RWE study was based on case notes from severe asthma centres in the NHS, in which the definition of severe exacerbation was established to match the QUEST trial definition and was used in the company's updated model. The ERG considered the Sanofi RWE study to be of reasonable quality which produced consistent results with other sources. The committee concluded that the Sanofi RWE study on the setting of severe exacerbations was appropriate for use in the company's updated base case.

Mortality estimates are uncertain and probably overestimated in the company economic model

3.15 The ERG explained that the original company model (using the confidential exacerbation multiplier) predicted 20% mortality over 10 years in the standard care arm. The committee questioned the clinical plausibility of this estimate because it seemed high compared with the approximate 1,300 asthma-related deaths a year in the UK. The higher death rate was a result of interaction between the exacerbation multiplier (see section 3.13) and using registry data to inform the setting of treating

exacerbations (see section 3.15). The committee noted that the model did not offer plausible estimates, and requested that any additional analyses presented by the company include 10-year mortality rates for dupilumab and standard care and show the flow of patients though different health states in the model for the purposes of model validation. Following the first committee meeting, the company conducted a literature search for UK asthma-related mortality data, but no further publications were retrieved. The committee noted that when the exacerbation multiplier was removed (in the updated company model, see section 3.14), 10-year mortality with standard care was reduced to 18%. The ERG considered that the mortality was probably still overestimated, but the plausibility of model survival projections was difficult to judge without UK data available. The ERG explained that the model predicted a mean age of deaths of 70 years with standard care (73 years with dupilumab), compared to an estimated life expectancy of 80 years with standard care in the benralizumab appraisal TA565. The committee was concerned that mortality could be overestimated because asthma-related mortality was one of the drivers of the model. The committee also noted that alternative methods had been used in the benralizumab appraisal, to adjust for high mortality. The committee concluded that the mortality rates were uncertain, and that alternative scenarios could be tested to explore the impact of the mortality on the ICER.

The company's base-case economic analysis

The company's updated base-case ICER is £35,968 per QALY gained for dupilumab compared with standard care in the proposed population

3.16 The company's base-case deterministic ICER for dupilumab compared with standard care is £35,968 per quality-adjusted life year (QALY) gained in the company's updated population. This included the confidential discount for dupilumab. The committee concluded that dupilumab does not represent a cost-effective use of resources, so could not be recommended for treating severe asthma with type 2 inflammation.

Other factors

Additional benefits in people with severe asthma and type 2 inflammation, and nasal polyps or atopic dermatitis, may not have been adequately captured

3.17 The committee recognised that there is an unmet need for people with severe asthma caused by type 2 inflammation. The committee also heard that dupilumab is effective in people with comorbidities (such as nasal polyps and atopic dermatitis). It concluded that these additional benefits of dupilumab had not been captured in the QALY calculation.

There are limited data available on dupilumab for young people

3.18 Dupilumab is licensed in people aged 12 years and over. The company provided a subgroup analyses for the subgroup of people aged 12-17 years. The committee noted that the QUEST trial only included 2 patients aged under 18 years meeting the criteria of the updated base case population. There is an unmet need in this population with uncontrolled severe asthma with type 2 inflammation. Current NICE recommended biologicals are licensed in adults for eosinophilic asthma only. Mepolizumab is currently the only other biological that is licensed for treating children aged 6 years or over for severe refractory eosinophilic asthma. However NICE's technology appraisal guidance on mepolizumab recommends it for use in adults. The committee concluded that there are limited data available for dupilumab in young people, and acknowledged this during decision making.

Conclusion

Dupilumab is not recommended for treating severe asthma with type 2 inflammation

3.19 The committee acknowledged that dupilumab is effective for preventing exacerbations in people with severe asthma with type 2 inflammation compared with standard care. However, the cost-effectiveness estimates

for dupilumab compared with standard care were higher than what NICE considers a cost-effective use of NHS resources. The committee identified several uncertainties in the modelling assumptions, particularly about mortality estimates and response rates in adults who did not respond to biological therapy. These uncertainties resulted in uncertainty about the true ICER. Therefore, the committee was unable to recommend dupilumab as a cost-effective treatment for use in the NHS for treating severe asthma with type 2 inflammation.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Sanjeev Patel
Chair, appraisal committee
April 2021

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Shelly Patel, Caroline Bregman
Technical leads

Eleanor Donegan
Technical adviser

Joanne Ekeledo, Jeremy Powell, Shonagh D'Sylva
Project manager

ISBN: [to be added at publication]

NICE National Institute for Health and Care Excellence

Dupilumab for treating severe asthma [ID1213]

Consultation on the appraisal consultation document – deadline for comments 5pm on 28 May 2021 **email:** NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities.

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	Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
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.	**No past or current links to, or funding from, the tobacco industry**
Name of commentator person completing form:	[redacted]

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NICE National Institute for Health and Care Excellence

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Consultation on the appraisal consultation document – deadline for comments 5pm on 28 May 2021 **email:** NICE DOCS

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Sanofi agree with many of the conclusions of the committee but would like to address the outstanding areas of uncertainty highlighted by the ACD.** We are pleased that the appraisal committee has recognised the potential benefits of dupilumab in treating uncontrolled severe asthma with type 2 inflammation. We are reassured by many of the comments offered in the ACD. Of note, we welcome conclusions from the committee that: • there is a need for new treatments with a different mode of action for people with severe asthma with type 2 inflammation whose asthma does not respond with current standard care, and for people not eligible for current NICE recommended biologicals (3.1) • the updated population was suitable for decision making (EOS≥150, FeNO≥25 and ≥4 exacerbations) (3.6) • the comparator for the updated population is standard care (3.7) • Dupilumab is more clinically effective than standard care in the clinical trial populations (3.9)

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	• the model structure was appropriate for decision making (3.11) • the Sanofi RWE study on the setting of severe exacerbations was appropriate for use in the company's updated base case (3.14) • there are additional benefits of dupilumab that had not been captured in the QALY calculation (3.17) The ACD highlights three key areas of uncertainty within this appraisal: 1. Response rates in patients who previously received a biologic 2. Mortality estimates 3. Effectiveness of dupilumab in the proposed population Some uncertainties, such as post-trial exacerbation rates, can be mitigated by adopting the most conservative estimate in the base case, as has been done following the first ACD. For some other issues, such as efficacy estimates in the updated proposed population, projected mortality, and treatment effect in a post-anti-IL5 cohort, it is not possible to fully eliminate the uncertainty due to the paucity of data currently available. Nevertheless, additional scenarios are provided within this response to further explore these uncertainties. **Sanofi believe that the additional scenarios and justifications presented within this response alongside the revised simple PAS (outlined below) should allow NICE to consider dupilumab a cost-effective treatment for this patient population who have a particularly high unmet need.**

NICE National Institute for Health and Care Excellence

Dupilumab for treating severe asthma [ID1213]

Consultation on the appraisal consultation document – deadline for comments 5pm on 28 May 2021 **email:** NICE DOCS

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A revised simple PAS has been accepted by PASLU, increasing the cost-effectiveness of dupilumab in the proposed population

The base-case ICER reported in the ACD is £35,968 per QALY for dupilumab compared with standard care. The revised simple PAS of [redacted]. This revised PAS results in an updated base-case ICER in the proposed population of £28,156 per QALY gained using base-case modelling approached favoured by the committee and ERG.

Table 1 Base-case cost-effectiveness estimates for dupilumab verses standard care (Soc) including the revised PAS

Treatment	Total cost	Incremental cost	Total QALY	Incremental QALY	ICER
SoC	[redacted]		[redacted]		
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£28,156

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Dupilumab is clinically effective in the proposed population. This is supported by evidence from the QUEST trial.

<u>Dupilumab is efficacious in the proposed population</u>

Data from the QUEST trial for patients matching the proposed population who were treated with dupilumab 200 mg every two weeks (Q2W) or matching placebo were used to assess the clinical- and cost-effectiveness of dupilumab. The committee concluded that

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	dupilumab is more clinically effective than standard care in the clinical trial populations but the clinical effectiveness estimates for dupilumab are uncertain in the company's proposed population, and commented that only limited efficacy data had been provided with respect to this population. The proposed population constitute a very small number of the total patients included in the QUEST trial. Nevertheless, post-hoc analysis of the QUEST trial data demonstrates a strong treatment effect in patients with EOS≥150 AND FeNO≥25 AND ≥4 exacerbations. This patient group had an [redacted] reduction in the risk of a severe exacerbation compared to the placebo group ([redacted].). To address the uncertainty in efficacy estimates for this population, we provide evidence below alongside the proposed population for an analogous dual biomarker population with less restrictive exacerbation history. Raised type 2 biomarkers and high historical exacerbation rate together identify a population most likely to gain benefit from dupilumab treatment.

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	Table 2 Summary of efficacy outcomes for the proposed population and a comparable reference population with fewer exacerbation in the 12 months prior to baseline

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Efficacy outcomes	Dupilumab 200 mg Q2W			
	≥12 years old, high dose ICS, EOS≥150 cells/uL, ≥25 FeNO			
	Target population		Reference population	
	(≥4 severe exacerbations; N=[redacted]		(≥2 severe exacerbations; N=112)	
	Placebo	Dupilumab	Placebo	Dupilumab
	[redacted]	[redacted]	[redacted]	[redacted]
Annualised event rate of severe exacerbation during the 52 weeks				
Total number of severe exacerbation events	[redacted]	[redacted]	[redacted]	[redacted]
Total patient-years followed	[redacted]	[redacted]	[redacted]	[redacted]
Unadjusted annualised rate of severe exacerbation events at Week 52[†]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted annualised rate of severe exacerbation events at Week 52				
Estimate[‡] (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
RR[‡] vs matching placebo (95% CI)		[redacted]		[redacted]
		[redacted]		[redacted]
p value[‡] vs matching placebo		[redacted]		[redacted]
Risk difference[§] vs matching placebo (95% CI)		[redacted]		[redacted]
		[redacted]		[redacted]

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Dupilumab responder patients (reduction in annualised rate of severe asthma exacerbation events of greater than 50% on 52-week treatment period compared to the year prior to randomisation)

Dupilumab responders		[redacted]		[redacted]
Total number of severe exacerbation events		[redacted]		[redacted]
Total patient-years followed		[redacted]		[redacted]
Unadjusted annualised rate of severe exacerbation events†		[redacted]		[redacted]

CI, confidence interval; EOS, eosinophil; exac, exacerbations; FeNO, fractional exhaled nitric oxide; reported; Q2W, every 2 weeks; RR, relative risk.

For QUEST: All severe exacerbation events occurred during the 52-week treatment period are included, regardless if the patient is on-treatment or not.

† 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; ‡ Derived using negative binomial model with the total number of events onset from randomisation 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 EOS strata, baseline ICS dose level and number of severe exacerbation events within 1 year prior to the study as covariates and log-transformed standardised observation duration as an offset variable; § Derived using delta methodThe statistical analyses and adjusted results reported in Table 2 account for pre-defined covariates of interest such as treatment group, age, region, baseline EOS, baseline ICS dose, and baseline exacerbation rate. Nevertheless, and despite the small sample size, the results remain clinically and statistically significant for the proposed population.

Dupilumab treatment effect in the proposed population is supported by analysis across sub-groups of pre-trial exacerbation rates and type 2 biomarker combinations

i) Treatment effect by exacerbation count in the 12 months prior to QUEST

Data published at the European Academy of Allergy and Clinical Immunology (EAACI) conference in 2018 show that dupilumab demonstrates a strong and statistically significant treatment effect maintained even as the baseline historical exacerbation rate

	increases above 4, all else being equal. (Figure 1 overleaf). (1). These data demonstrate an increasing number of exacerbations during the treatment period occur in patients with higher historical exacerbation rates at baseline. In patients with ≥4 exacerbation in the year prior to the study the reduction versus placebo in the adjusted annualized exacerbation rate was both clinically and statistically significant (200 mg dose: -78%, p<0.0001). Therefore, in a larger cohort, unselected on baseline type 2 biomarkers, a higher historical exacerbation rate at baseline identifies patients more likely to experience future exacerbations and more likely to experience a significant rate reduction with dupilumab versus placebo.

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	Figure 1 Subgroup analysis of severe exacerbation rates by number of exacerbations in the 12 months prior to QUEST baseline; presented at EAACI 2018

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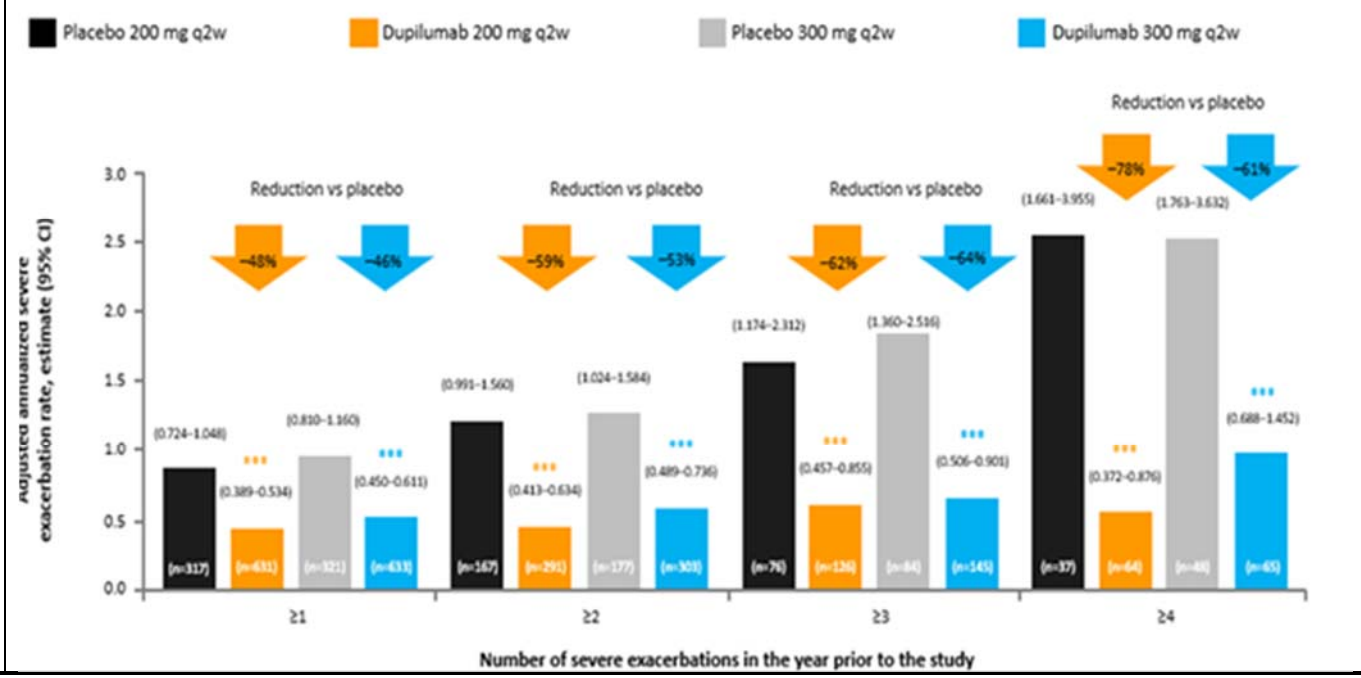

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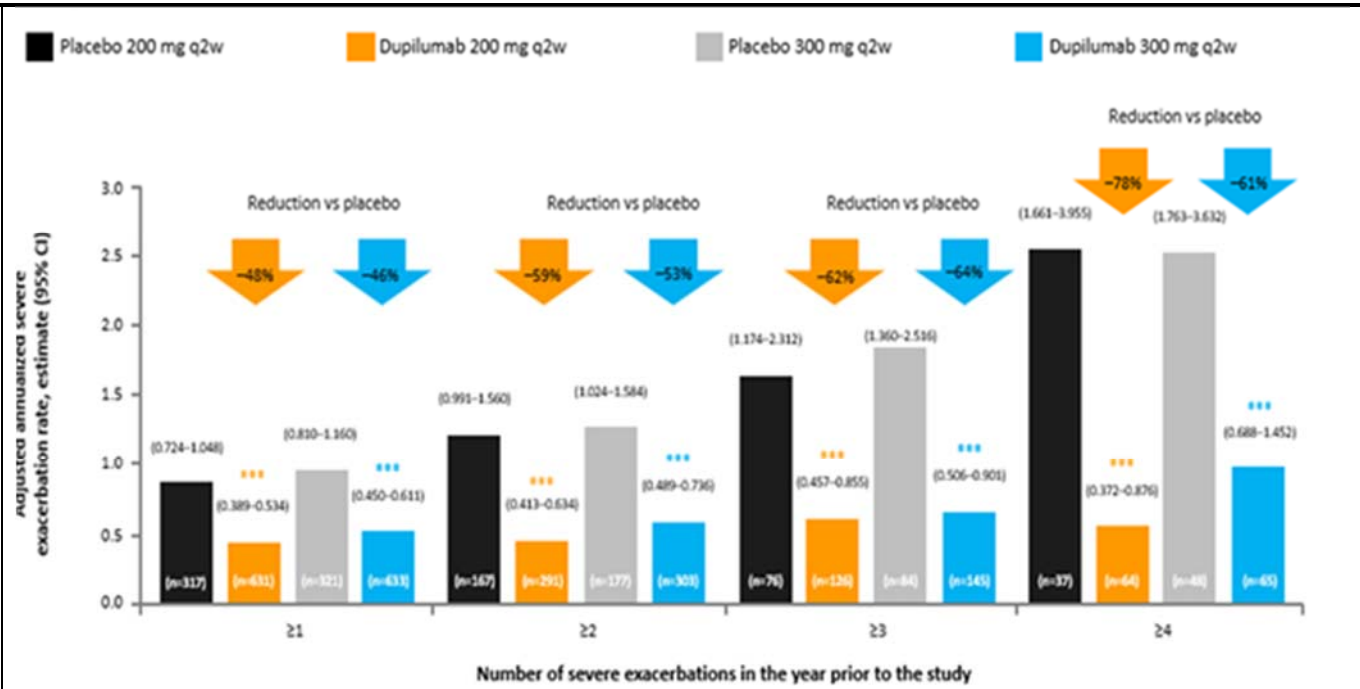

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	Table 3 Subgroup analysis of severe exacerbation rates by number of exacerbations in the 12 months prior to QUEST baseline; adapted from Pavord et al. 2018

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	Pts with ≥1 exacerbations				Pts with ≥2 exacerbations				Pts with ≥3 exacerbations				Pts with ≥4 exacerbations			
	PBO (N = 317)	DPL 200 mg (N = 631)	PBO (N = 321)	DPL 300 mg (N = 633)	PBO (N = 167)	DPL 200 mg (N = 291)	PBO (N = 177)	DPL 300 mg (N = 303)	PBO (N = 76)	DPL 200 mg (N = 128)	PBO (N = 84)	DPL 300 mg (N = 145)	PBO (N = 37)	DPL 200 mg (N = 64)	PBO (N = 48)	DPL 300 mg (N = 65)
Adjusted annualized severe exacerbation rate over 52 weeks, estimate (95% CI); N	0.871 (0.724, 1.048); 317	0.456 (0.389, 0.534); 631	0.970 (0.810, 1.160); 321	0.524 (0.450, 0.611); 633	1.234 (0.991, 1.560); 167	0.512 (0.413, 0.634); 291	1.274 (1.024, 1.584); 177	0.600 (0.489, 0.736); 303	1.648 (1.174, 2.312); 76	0.625 (0.457, 0.855); 126	1.850 (1.360, 2.516); 84	0.675 (0.506, 0.901); 145	2.563 (1.661, 3.955); 37	0.571 (0.372, 0.876); 64	2.530 (1.763, 3.632); 48	0.999 (0.688, 1.452); 65
Relative risk vs PBO (95% CI); P value vs PBO		0.523 (0.413, 0.662); <0.0001		0.540 (0.430, 0.680); <0.0001		0.412 (0.305, 0.557); <0.0001		0.471 (0.353, 0.629); <0.0001		0.379 (0.244, 0.589); <0.0001		0.365 (0.242, 0.551); <0.0001		0.233 (0.124, 0.399); <0.0001		0.395 (0.238, 0.654); 0.0004
Baseline pre-BD FEV_1 (L), mean (SD)	1.76 (0.61)	1.78 (0.62)	1.75 (0.57)	1.78 (0.60)	1.74 (0.55)	1.76 (0.64)	1.69 (0.53)	1.73 (0.59)	1.71 (0.52)	1.69 (0.64)	1.64 (0.48)	1.66 (0.57)	1.69 (0.53)	1.71 (0.58)	1.62 (0.47)	1.59 (0.56)
Change from baseline in pre-BD FEV_1 (L) at Week 12, LS mean (SE); N	0.18 (0.02);307	0.32 (0.02);611	0.21 (0.02); 313	0.34 (0.02); 610	0.17 (0.03); 160	0.34 (0.02); 285	0.22 (0.03); 174	0.39 (0.02); 292	0.17 (0.05); 73	0.33 (0.04); 125	0.18 (0.04); 82	0.40 (0.03);140	0.20 (0.07); 35	0.32 (0.05); 63	0.15 (0.06); 47	0.40 (0.05); 62
Difference vs PBO (95% CI); P value vs PBO		0.14 (0.08, 0.19); <0.0001		0.13 (0.08, 0.18); <0.0001		0.17 (0.09, 0.24); <0.0001		0.17 (0.10, 0.24); <0.0001		0.16 (0.05, 0.27); 0.0042		0.22 (0.12, 0.33) <0.0001		0.12 (−0.03, 0.28); 0.1240		0.25 (0.11, 0.39); 0.0008

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	Pts with ≥1 exacerbations				Pts with ≥2 exacerbations				Pts with ≥3 exacerbations				Pts with ≥4 exacerbations			
	PBO (N = 317)	DPL 200 mg (N = 631)	PBO (N = 321)	DPL 300 mg (N = 633)	PBO (N = 167)	DPL 200 mg (N = 291)	PBO (N = 177)	DPL 300 mg (N = 303)	PBO (N = 76)	DPL 200 mg (N = 128)	PBO (N = 84)	DPL 300 mg (N = 145)	PBO (N = 37)	DPL 200 mg (N = 64)	PBO (N = 48)	DPL 300 mg (N = 65)
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Relative risk vs PBO (95% CI); P value vs PBO		0.523 (0.413, 0.662); <0.0001		0.540 (0.430, 0.680); <0.0001		0.412 (0.305, 0.557); <0.0001		0.471 (0.353, 0.629); <0.0001		0.379 (0.244, 0.589); <0.0001		0.365 (0.242, 0.551); <0.0001		0.233 (0.124, 0.399); <0.0001		0.395 (0.238, 0.654); 0.0004
Baseline pre-BD FEV_1 (L), mean (SD)	1.76 (0.61)	1.78 (0.62)	1.75 (0.57)	1.78 (0.60)	1.74 (0.55)	1.76 (0.64)	1.69 (0.53)	1.73 (0.59)	1.71 (0.52)	1.69 (0.64)	1.64 (0.48)	1.66 (0.57)	1.69 (0.53)	1.71 (0.58)	1.62 (0.47)	1.59 (0.56)
Change from baseline in pre-BD FEV_1 (L) at Week 12, LS mean (SE); N	0.18 (0.02);307	0.32 (0.02);611	0.21 (0.02); 313	0.34 (0.02); 610	0.17 (0.03); 160	0.34 (0.02); 285	0.22 (0.03); 174	0.39 (0.02); 292	0.17 (0.05); 73	0.33 (0.04); 125	0.18 (0.04); 82	0.40 (0.03);140	0.20 (0.07); 35	0.32 (0.05); 63	0.15 (0.06); 47	0.40 (0.05); 62
Difference vs PBO (95% CI); P value vs PBO		0.14 (0.08, 0.19); <0.0001		0.13 (0.08, 0.18); <0.0001		0.17 (0.09, 0.24); <0.0001		0.17 (0.10, 0.24); <0.0001		0.16 (0.05, 0.27); 0.0042		0.22 (0.12, 0.33) <0.0001		0.12 (−0.03, 0.28); 0.1240		0.25 (0.11, 0.39); 0.0008

ii) Treatment effect by type 2 biomarker combinations

Data published at the European Respiratory Society (ERS) conference in 2019 show that dupilumab demonstrates a strong and statistically significant treatment effect, most pronounced in those with raised blood eosinophils AND raised FeNO together, compared to those subgroups with only one or no raised biomarkers(2). Adjusted annualised exacerbation rates in the placebo arms were highest for the subgroup defined by baseline EOS ≥150 cells/μL and FeNO ≥20 ppb (48% of the QUEST population) whilst the dupilumab treatment effect was greater in this subgroup compared to other sub-groups (200mg dose [n=292]: rate reduction versus placebo was

	66%, p<0.001 [n=158]). Therefore, in a larger cohort, unselected on baseline historical exacerbations, raised baseline levels of two type 2 biomarkers (EOS AND FeNO) at the same time identifies patients more likely to experience future exacerbations and more likely to experience a rate reduction with dupilumab versus placebo.

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	Figure 2 Subgroup analysis of severe exacerbation rates EOS and FeNO biomarkers

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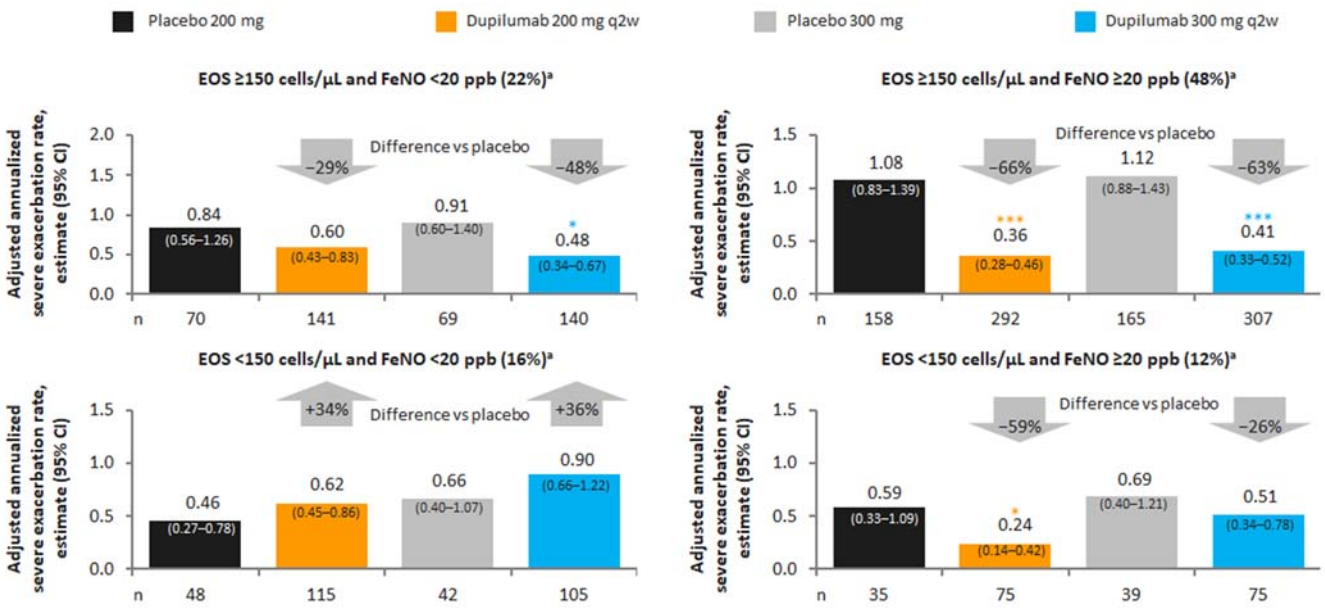

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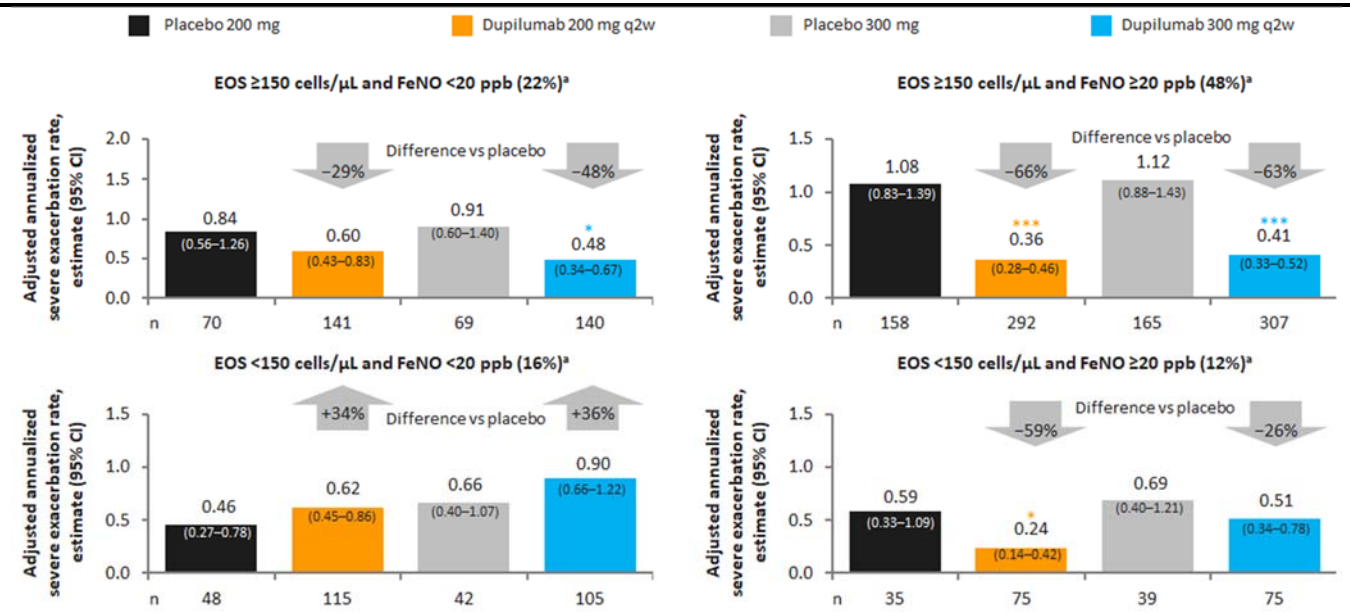

The committee should be reassured that when restricting the dupilumab population to those with type 2 biomarkers and higher exacerbation rates at baseline, dupilumab remains a clinically effective intervention.

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4	**Available evidence indicates dupilumab is as effective in patients who have not previously responded to biologic therapies.** The ACD queried the assumption that dupilumab would be as efficacious in patients who had previously received a biologic as in biologic naïve patients (Quest trial). We have previously provided an assessment of the validity of this assumption by a UK severe asthma physician and Director of Research at Portsmouth Hospitals NHS Trust (Appendix 1). The committee also heard from a patient with severe asthma who had not responded to multiple biologics prior to successful treatment with dupilumab. **Real world data to support treatment effect in patients who have previously not responded to a biologic therapy.** Published real-world studies from France, Germany and the US further support real world effectiveness in heavily pre-treated patients. In these studies, enrolled patients had not responded to anti-IL-5 or anti-IgE treatment and in some cases both anti-IL-5 and anti-IgE. The French study reported that 78.4% of patients treated with Dupilumab had a 50% or more reduction in exacerbation rate (3). The German study reported a 76% response to Dupilumab following failure on either anti-IgE or anti-IL5 therapy, as measured by a composite criteria relating to Asthma Control Test score, reduction in oral corticosteroid use, and FEV1 improvement (4). Most notably regarding this German study, although there were no exacerbation rate criteria for entry, 92% of patients (n=35/38) experienced a reduction in their exacerbation rate while receiving dupilumab compared to their previous biologic therapy. The US medical records review identified 72 patients being treated with dupilumab, 21 of whom had previously not responded to previous treatment with a biologic agent. 20 of the 21 patients (95%) experienced a subjective improvement whilst on dupilumab treatment measured by combinations of: increase in ACT score, FEV1 increase and decrease in FeNO and Eosinophil counts(5). These studies provide evidence that biologic experienced patients receiving dupilumab respond similarly to those in the pivotal trials for dupilumab.

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[redacted]

[redacted]

[redacted]

Table 4 [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]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Given dupilumab's different mechanism of action to existing biologic therapies and the available evidence we believe that the treatment effect of dupilumab in biologic experienced patients would be maintained. Nevertheless, exploratory analyses within the model have been conducted to explore the uncertainty. These are reported in Table 5 and Table 6 below.

Modelling uncertainty in the treatment effect.

Patients who have previously not responded to a biologic therapy and subsequently also not responded to dupilumab will discontinue treatment at 12-months in the model. Alternative response rates for these patients were explored in model by adjusting the proportion of patients who respond to dupilumab treatment at 12 months downwards. As the model does not allow for a different response rate to be entered specifically for those patients who did not respond to anti-IL-5 treatments (which represent a proportion of the proposed population), the response rate was varied downwards for the entire proposed population. This represents a conservative set of scenarios. The results are presented in Table 5 below. These analyses show that varying the response rate at 12 months has no substantive effect on the ICER.

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Table 5 Scenario analysis of adjusting dupilumab response rate

Varying dupilumab response	Treatment	Total Cost	Incremental Cost	Total QALY	Incremental QALY	ICER
Base Case (86.8%)	SoC	[redacted]		[redacted]		
	Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£ 28,156.04
Base Case*0.9 (78.1%)	SoC	[redacted]		[redacted]		
	Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£ 28,188.30
Base Case*0.8 (69.4%)	SoC	[redacted]		[redacted]		
	Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£ 28,228.06
Base Case*0.7 (60.7%)	SoC	[redacted]		[redacted]		
	Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£ 28,278.34

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Base Case*0.6 (52.11%)	SoC	[redacted]		[redacted]		
	Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£ 28,341.85

To further explore the uncertainty, we also explored an alternative approach in which the relative risk of experiencing a severe exacerbation for dupilumab versus SoC was varied. The results are presented in Table 6 below. Technical details regarding how this has been implemented in the model are provided in appendix 2. As above, the relative risk was varied in the model for the entire proposed population and not only for the proportion who did not respond to anti-IL-5 treatments. Again, this represents a conservative approach.

Table 6 Scenario analysis of varying the relative risk of experiencing a severe exacerbation with dupilumab versus standard of care

Varying relative risk*	***Treatment***	***Total Cost***	***Incremental Cost***	***Total QALY***	***Incremental QALY***	***ICER***
Base Case	*SoC*	[redacted]		[redacted]		
	Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£ 28,156.04
10%	SoC	[redacted]		[redacted]		
	Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£ 29,316.45

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20%	SoC	[redacted]		[redacted]		
	Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£ 29,849.02
25%	SoC	[redacted]		[redacted]		
	Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£ 30,121.21
30%	SoC	[redacted]		[redacted]		
	Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£ 30,397.44

* the same % reduction is applied simultaneously to dupilumab all patients and to dupilumab responders. Relative effects of 0.191 and 0.153 were used for some of the transitions instead of varying them by 10%, 20% etc (as they would be = 0 otherwise).

Available evidence strongly suggests dupilumab is equally effective in patient groups who have previously not responded to existing biologic therapies. Based on the emerging real world evidence and the additional scenarios presented above, the large majority of which do not offend the £30,000/QALY threshold, the committee should feel reassured that dupilumab is a cost-effective treatment option for patients who have previously been treated with a biologic and for whom this treatment has failed, currently leaving them with no effective options.

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5

The ACD has highlighted that mortality estimates used in the company model were uncertain and may overestimate mortality. We are confident mortality estimates are reliable and are consistent with published literature

Clarification of ACD statement

The ACD reports an 18% 10-year mortality in the standard care arm of the ERG's base-case model. We were unable to reproduce the ERG mortality and life expectancy estimates for standard care patients using the ERG's base-case assumptions and believe these estimates reported in the ACD are incorrect. The company model estimates a 10-year mortality of 16.7% for standard care patients and 10.1% for dupilumab patients (Table 7). These mortality projections result in a life expectancy of 72.7 years for standard care patients and 75.1 years for dupilumab patients.

Table 7 Dupilumab and standard care base-case markov traces for the proposed population

Patient age	Year	Controlled	Uncontrolled	Mod Exacerbation	Severe Exacerbation	Death
Dupilumab						
49.06	1	54.5%	24.3%	14.8%	5.9%	0.5%
50.06	2	51.4%	23.4%	16.2%	7.9%	1.1%
53.06	5	43.1%	26.8%	14.6%	12.1%	3.5%
58.06	**10**	**33.0%**	**28.9%**	**12.3%**	**15.7%**	**10.1%**

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63.06	15	26.0%	28.1%	10.5%	16.5%	18.9%
68.06	20	20.4%	25.2%	8.7%	15.3%	30.5%
Standard care						
49.06	1	24.0%	38.4%	11.4%	24.7%	1.5%
50.06	2	23.6%	37.8%	11.3%	24.4%	3.0%
53.06	5	22.5%	36.0%	10.7%	23.2%	7.6%
58.06	**10**	**20.3%**	**32.4%**	**9.7%**	**20.9%**	**16.7%**
63.06	15	17.9%	28.6%	8.5%	18.4%	26.6%
68.06	20	15.1%	24.0%	7.2%	15.5%	38.2%

Evidence for asthma mortality has been critiqued by previous ERGs and produces outputs consistent with published literature

Asthma-related mortality has been the subject of extensive discussion in every technology assessment for severe asthma. This is in large part due to the lack of granular data that can be used in an economic model for this specific patient population. However, because there have been several appraisals by NICE and the SMC of biologic therapies in severe asthma in recent years, precedent exists regarding preferred data sources and approaches to asthma-related mortality. In the absence of newly published data, we have used in particular, data and assumptions consistent with the most recent NICE severe asthma appraisal (benralizumab TA565 during which

asthma-related mortality was examined at length), including the parameter values identified by the ERG and accepted by the committee.

Available evidence suggests that mortality estimates from the company's model produces results which are consistent with mortality estimates reported in literature. A 2019 case-control study in France using medical claims data estimated a 3-year severe asthma mortality of 7.1% (6). For this study a total of 690 patients with severe asthma were identified in a claims database and followed for 3 years. The mean age at index was 61 years. Adjusting the company model to a mean starting age of 61 years produces an estimate of 7.6% mortality at 3 years in the standard care arm (Table 8). It should be noted that the French Bourdin et al. study included all severe asthma patients without any restriction on asthma control, biomarkers, or exacerbation rates. Given the high disease burden and characteristics of the proposed population, a higher 3-year mortality rate would be expected in the standard care arm of the proposed population compared to that estimated by Bourdin at al.

Table 8 Markov traces for standard care arm using base-case assumptions. Starting age modified to 61 years.

Patient age	Year	Controlled	Uncontrolled	Mod Exacerbation	Severe Exacerbation	Death
62.00	1	23.8%	38.0%	11.3%	24.5%	2.4%
63.00	2	23.1%	37.0%	11.0%	23.8%	5.0%
64.00	**3**	**22.5%**	**36.0%**	**10.7%**	**23.2%**	**7.6%**
66.00	5	21.1%	33.7%	10.1%	21.7%	13.4%

71.00	10	17.1%	27.3%	8.2%	17.6%	29.7%
76.00	15	13.3%	21.2%	6.3%	13.7%	45.5%
81.00	20	9.6%	15.3%	4.6%	9.8%	60.8%

Results of the dupilumab model are robust and should not be compared across different severe asthma populations

The committee compared life expectancy and mortality estimates projected by the Sanofi company model to those reported in the benralizumab NICE appraisal TA565. We believe this comparison is inappropriate as it does not take into account the differing severe asthma populations and their inherent risk factors.

Firstly, the baseline age (50.2 years) in the benralizumab appraisal was 2.04 years older than that modelled in the Sanofi company model ([redacted])(7). All things being equal, we would therefore expect life expectancy in TA565 to be greater than that estimated in our company model. But all things are not equal, and the submitted population in TA565 from which these estimates are derived are a less severe asthma population to Sanofi's proposed population. The population in TA565 represents those patients with only 3 exacerbations in the year prior to initiation. Referring back to placebo columns in Figure 1, higher exacerbation rates at baseline are a marker of severity and a predictor of higher exacerbations in the subsequent year. This is highly relevant when estimating life expectancy as asthma-related mortality is predominantly dependent on the severe exacerbation rate. This observation can be validated by the clinical trial data of the respective relevant subgroups. Of particular note, the pooled SIROCCO/CALIMA subgroup efficacy

analysis reported an annualised exacerbation rate (AER) of 1.83 in the standard care arm, compared to [redacted] in the QUEST post-hoc analysis of Sanofi's proposed population(7).

The ACD has highlighted a scenario presented during benralizumab appraisal (TA565) to further adjust mortality estimates.

The methodology for deriving mortality estimates was based on that previously presented in the benralizumab company submission. Following ERG critique during the appraisal the base-case estimates first proposed by the submitting company were adjusted downwards by a factor of 2.5. Those adjusted values were subsequently accepted by the committee and are the ones used in our base case. However, upon further investigation, it seems that the values reported in the ERG report (Table 60) for hospitalised exacerbations for the age band 55-64 years old may have been erroneous and should have been 2.142%/2.5 = 0.8568%, instead of 1.8144% (7). We have conducted an analysis using this revised estimate (Table 9). The impact on the base-case ICER is marginal (£28,929 vs £28,156).

Table 9 Scenario analysis using a lower mortality estimate for hospitalised patients aged 55-64 years

Varying mortality risks for hospitalised exacerbations in patients aged 55-64 years	**Treatment**	**Total Cost**	**Incremental Cost**	**Total QALY**	**Incremental QALY**	**ICER**
Base Case (1.814%)	SoC	[redacted]		[redacted]		

	Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£28,156
Revised hospitalised mortality risk in patients 55-64 years (0.8568%)	SoC	[redacted]		[redacted]		
	Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£28,929

Base-case methodology is more conservative than previous appraisals

In addition, the settings of treatment of severe exacerbations are each associated with a different probability of death. Therefore, the setting of exacerbations also impacts on overall life expectancy. Whilst inherent differences in the programming of the economic model prevented testing the benralizumab inputs for the setting of exacerbations (TA565 applied different distributions by treatment arm and Markov state), applying the setting of exacerbations from TA431 (the mepolizumab appraisal) results in a lower ICER. (See Table 10 overleaf).

Table 10 Scenario analysis using setting of exacerbation from TA431

Setting of severe exacerbation	Treatment	Total Cost	Incremental Cost	Total QALY	Incremental QALY	ICER

	Base Case	SoC	[redacted]		[redacted]		
		Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£28,156
	Settings from TA431	SoC	[redacted]		[redacted]		
		Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£27,257
6	**Using nominal exacerbation rates from the QUEST trial to extrapolate longer term exacerbation rates in practice is an excessively conservative assumption** There has been much discussion throughout NICE appraisals in severe asthma concerning the most appropriate method of modelling post-trial exacerbation rates. For the mepolizumab appraisal, TA431, the company wished to apply pre-trial exacerbation rates to the standard care arm. In the base-case, the ERG decided the best approach was to apply an adjustment factor, or 'multiplier', derived from mepolizumab clinical trials (8). Similarly, in the reslizumab 3082 and 3083 clinical trials, a marked reduction in exacerbations was observed in the placebo arm compared to 12 months prior to baseline. During the NICE appraisal, TA479, to account for a placebo effect, the submitting company's submission model applied increasing exacerbation rates from trial-end until exacerbation rates returned to the rate observed immediately pre-trial. This was not accepted by the committee on the basis that "*there is no evidence that the adjusted rates better reflect the true rate of severe exacerbation in this population*"(9). The methodology utilised to account for post-trial exacerbation rates in benralizumab appraisal TA565 is less clear, but it was decided that the comparison versus standard care was not suitable for decision making. Nevertheless, it was stated "*the ERG could not verify*						

	assumptions on treatment effectiveness and health-related quality of life in the company's model (health state transition probabilities and utilities in particular)"(7). In the case of dupilumab it is noted in the ACD that the exacerbation rate in the placebo arm during the QUEST trial decreased significantly compared to the 12 months prior to baseline. Whilst this may be partly explained by phenomenon such as the 'placebo effect', 'hawthorn effect', or 'regression to the mean', it is also the case that there were inherent limitations in the QUEST trial protocol which prevented the reporting of some exacerbations in frequent exacerbators. In the base-case, it is conservatively assumed that the low exacerbation rates derived from trial data are applied indefinitely as preferred by the ERG. The base-case ICER of £28,156 per QALY gained therefore represents the most conservative cost-effectiveness estimate, and likely an overestimate of the true dupilumab ICER. Evidence and rationale for this are explored further below. The most relevant issues are a) The QUEST trial protocol prevented the reporting of all clinically relevant exacerbations b) In practice, patients in NHS commissioned Severe Asthma Centres are optimised on standard-of-care (SoC) prior to being considered for biologic therapy. c) A regression to the mean effect in QUEST data does not explain why exacerbation rates derived from trial data should be applied indefinitely d) Available evidence indicates that patients who would be candidates for dupilumab in practice have a high year-on-year AER **<u>a) QUEST trial protocol prevented the reporting of clinically relevant exacerbations</u>** i) exacerbation rates should be adjusted upwards by a minimum of 11.4%

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	In the QUEST trial protocol, with respect to severe exacerbations, it stated that "two events will be considered as different if the start dates are separated by at least 4 weeks", meaning that two exacerbations occurring within a 28 day period would only be recorded as single event. Clinical experts have confirmed that such a restriction would have prevented the reporting of clinically meaningful exacerbations. This restriction was not applied in the dupilumab phase 2B DRI12544 trial. Sensitivity analysis from this trial demonstrated that exacerbation rates were 11.4% higher when this restriction is lifted compared to when exacerbation start dates are required to be separated by at least 4 weeks. This 11.4% is calculated from all arms of the trial as it is not considered a treatment-dependent phenomenon. Nevertheless, the estimate for the placebo group (11.9%) remains consistent. This evidence is provided in more detail in Appendix 3. The cost-effectiveness results for dupilumab compared to standard care when this limitation is accounted for are presented in Table 11 below and should be considered a more robust estimate than when using nominally reported exacerbation rates for the proposed population. ii) Pre-trial exacerbation-free period suppresses exacerbation rate below what would be expected in practice. The QUEST trial excluded patients who experienced a severe asthma exacerbation within 7 to 9 weeks of trial start. Exclusion criteria in the protocol meant that any patient experiencing a severe exacerbation between 1 month before the screening visit and the beginning of the trial were prevented from entering the trial. Therefore, the minimum duration since last severe exacerbation for a patient had to be 7.35 weeks (observed average 169 days [range 52-412]; median 148 days). It is well documented that the time since last severe asthma exacerbation (TSLSE) is a strong predictor of future exacerbations(10-18). By excluding patients with a severe exacerbation within about 2 months prior to the trial, the trial protocol likely resulted in exacerbation rates observed in the trial being lower than what would be expected in clinical practice.

The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) is a 3-year, observational study of the natural history, treatment regimens, and outcomes of subjects with severe or difficult-to-treat asthma (19). A 1.5-year prospective analysis of 2780 patients ≥12 years of age from this study investigated this relationship between TSLSE and future exacerbations. It reported that patients with a recent exacerbation were more likely to report a future exacerbation, even after adjusting for severity classification, ATAQ control index and/or demographic and clinical characteristics. It reported an odds ratio of 2.99 (95% CI 2.57, 3.47) for a future severe exacerbation for patients with a recent exacerbation compared to those without.

In order to account for this limitation imposed by the QUEST protocol, exacerbation rates would need to be adjusted upwards by a factor of [redacted]. The detailed methodology adopted to estimate this factor is presented in Appendix 4. The results of the scenario applying this factor beyond the first 52 weeks in the model are presented in Table 11, alongside other scenarios which account for QUEST trial protocol limitations.

Table 11 Scenario analysis using multiplier to account for QUEST protocol restrictions

Scenario **(*Value of long-term multiplier*)**	**Multiplier**	**Treatment**	**Total Cost**	**Incremental Cost**	**Total QALY**	**Incremental QALY**	**ICER**
	1	SoC	[redacted]		[redacted]		

1. ERG Base case		Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£28,156
2. Lifting 28-day restriction between exacerbations	[redacted]	SoC	[redacted]		[redacted]		
		Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£ 25,784
3. Accounting for exacerbation-free run in period	[redacted]	SoC	[redacted]		[redacted]		
		Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£ 21,033
4. Adjustments for both QUEST protocol restriction (Scenarios 2 and 3)	[redacted]	SoC	[redacted]		[redacted]		
		Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£19,678

We must conclude that both baseline and in-trial exacerbation rates for dupilumab and placebo patients' arms are lower than what would be expected if measured in the real world. Similarly, modelling this patient group with these more real world-applicable exacerbation rates would result in dupilumab being more cost-effective than the existing base-case result.

b) Severe asthma patients in the UK are optimised on standard care prior to being considered for biologic therapy. This would not have occurred in all patients recruited into the QUEST clinical trial

In the UK, patients referred to NHS commissioned severe asthma tertiary care are subject to a standardised optimisation of standard care over a period of approximately 6 months. This involves maintenance inhaler dose optimisation, adherence monitoring, and evaluation of non-biologic maintenance therapies. This optimisation occurs obligatorily before any biologic treatment is considered. Clinician feedback is that for most patients there is no significant reduction in AER from the baseline/referral values over this SoC

	assessment period. In addition, they appropriately ration biologic therapies to only those patients who remain in need of advanced therapies despite this standard care optimisation. Therefore, it is not rational to assume the same reduction of exacerbation rates pre- and post-trial for standard care patients would occur in practice as in the QUEST trial. The clinical improvements observed in asthma clinical trials in placebo groups has been well documented, with benefits attributed to both placebo effects and also the effect of adhering to trial protocol (an optimised standard care) (20). According to clinical feedback received by Sanofi, including a principle investigator involved in asthma clinical trials, this is particularly relevant in multi-national trials where some patients do not receive optimised standard-of-care prior to trial. For some jurisdictions, this level of pre-trial care can contrast to during the clinical trial where there is increased monitoring, absence of affordability concerns, improved access to healthcare and improved adherence to standard therapies. Even within the UK, where clinicians apply a good standard-of-care for patients as part of an NHS commissioned severe asthma service, the standard would not meet trial levels of patient care in the long term. The improvement in exacerbation rates because of inclusion in a clinical trial should be considered when modelling beyond the trial horizon. **c) Regression to the mean does not justify the use of exacerbation rates derived from trial data beyond the trial horizon** The 'regression to the mean' effect assumes that an initial unnaturally small or large measurement, in this case the baseline AER, tends to be followed by measurements closer to the mean. In this case, the suggestion is that patients in the placebo arm of QUEST started with an inflated AER, and that the improved AER over the course of the trial was a result of regression to the (real) mean. This phenomenon may explain some of the decrease in exacerbation rates observed in the placebo arm of the trial, but it fails to support the ERG's assumption that the reported exacerbation rates in the trial are most appropriate for extrapolating beyond the trial horizon.

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	For reasons outlined above, baseline exacerbation rates in UK clinical practice are expected to closely approximate the patient's true longer term mean AER. Furthermore, available evidence suggests that severe exacerbation rates ≥4 or 5 per year is not unusual in the UK. Evidence from the UK Severe Asthma Registry (UKSAR) show that severe asthma patients uncontrolled at GINA step 4 or 5 in the UK have an average of 5 exacerbations per year (n=696)(21). A similar publication from UKSAR examining a broader group of severe asthma patients reports a mean severe exacerbation rate of 4 in the previous 12 months (n=2225)(22). The ERG to date has been critical of adjusting the observed trial exacerbation rates when modelling beyond the trial horizon, despite the evidence outlined above. The most conservative approach is to apply within-trial exacerbation rates indefinitely, which is adopted in the base case and results in an ICER of £28,156 per QALY gained. The primary rationale for this is because of a possible 'regression to the mean'. We would argue that there is less evidence for this phenomenon being applicable to the decision problem than the alternative justifications proposed above. The ERG has proposed that the baseline exacerbation rate is an outlier of the subgroup's true exacerbation rate, and the within-trial rates are the best representation of the population's true AER. Clinical experts have confirmed to us that they would expect the within trial exacerbation rates to be the most optimistic due to patient behaviours within trial (the "hawthorn effect"), a placebo effect, and other clinical benefits of being included in a clinical trial. Indeed, the ERG recognised that the low exacerbation rate observed in the trial is at least partly as a result of this placebo effect, which is similarly recognised by the clinical expert referenced in the ACD. Therefore, it is much more likely that the true long-term AER for the standard care arm lies between the baseline AER for the updated subgroup and exacerbation rates derived from trial data.

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d) Available evidence indicates that patients who would be candidates for dupilumab in practice have a high year-on-year AER

i) Real world evidence using registry data demonstrates a high exacerbation rate is maintained in a patient group representative of the proposed population

Clinicians involved in the UBioPred registry have provided us with baseline and follow-up data for a cohort of patients satisfying the dual biomarker and exacerbation criteria of the proposed dupilumab population (23). Of note, UBioPred registry specifies ≥6 months historical standard care prior to indexing at baseline. This patient group may be considered representative of prospective dupilumab of patients who would be optimised on standard care prior to being considered candidates for therapy in a severe asthma centre. [redacted] patients were identified in total, [redacted] of whom have 12 months of follow-up data. Of the [redacted] patients, the average (median) number of exacerbations in the 12 months prior to baseline was [redacted]. The median number of exacerbations over the subsequent 12 months was [redacted]. For the given sample, it can be observed that while the number of exacerbations may fluctuate year-on-year for individual patients, the average number of exacerbations is maintained for the group. A regression to a significantly lower mean was not observed.

Table 12 UBioPred data for patients meeting the proposed dupilumab population criteria

	All patients	Patients at baseline with 12 months follow-up	
	All patients at baseline ([redacted])	Patients at baseline ([redacted])	Patients at 12 months ([redacted])

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Asthma exacerbation; median (min-max)	[redacted]	[redacted]	[redacted]	
Blood EOS median (min-max)	[redacted]	[redacted]	[redacted]	
FeNO median (min-max)	[redacted]	[redacted]	[redacted]	
ACQ median (min-max)	[redacted]	[redacted]	[redacted]	

ii) Patients who have not responded to a previous biologic therapy have a documented history of high exacerbation rates.

In practice, patients in the proposed population who have not responded to an existing biologic therapy would need to have experienced a minimum of two successive years of high exacerbation rates in order to be considered for treatment with dupilumab. These patients would have experienced a high number of exacerbations in the year prior to initiating their first biologic, as per guidance in TA431, TA565 and TA479. Subsequently, relevant patients would need to maintain a high exacerbation rate over another 12 months to be considered a non-responder. This duration would be longer for patients who fail on existing biologic therapy and maintain that high exacerbation rate when moved on to on standard care alone. This patient group in practice would be characterised by consistently high AER over multiple years indicating a true mean in excess of 4 severe exacerbations per year.

Whilst regression to the mean can explain some of the reduction in QUEST placebo arm exacerbation rate compared to prior to baseline, it fails to provide evidence as to the true longer-term exacerbation rates for the population in UK practice. Table 13 presents cost-effectiveness results in scenarios varying longer-term exacerbation rates. We believe the base-case ICER of £28,156 is an overestimation of the true ICER, which lies somewhere between an upper limit of £28,156 and a lower limit £19,678 (scenario 4, Table 11 above).

Table 13 Scenario analysis of adjusting post-trial exacerbation rates

Scenario* (***Value of calibrated long-term multiplier***)	**Standard care AER**	**Treatment**	**Total Cost**	**Incremental Cost**	**Total QALY**	**Incremental QALY**	**ICER**
Base-case (1)	[redacted]	SoC	[redacted]		[redacted]		
		Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£ 28,156
Scenario with standard care AER 3.5 (*1.063*)	[redacted]	SoC	[redacted]		[redacted]		
		Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£ 26,793
Scenario with standard care AER 3.8 (1.145)	[redacted]	SoC	[redacted]		[redacted]		
		Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£ 25,226
Scenario with standard care AER 4 *(1.198)*	[redacted]	SoC	[redacted]		[redacted]		
		Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£ 24,303

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	Scenario with standard care AER 4.3 *(1.278)*	[redacted]	SoC	[redacted]		[redacted]		
			Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£ 23,060
	Scenario with standard care AER 4.5 *(1.331)*	[redacted]	SoC	[redacted]		[redacted]		
			Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£ 22,319

*Scenarios are modelled using the MS Excel goal-seek function to adjust the standard care AER outcome to a set value. The multiplier required to achieve this outcome is applied to both dupilumab and standard care arms

7	**A case for change is being made for discount rates in economic evaluation is the NICE methods review.** Consistent with the NICE Guide to the methods of technology appraisal, 2013, within the company model discounting is applied at a rate 3.5% per annum equally to both costs and benefits. The methods also recommend scenario analysis adjusting the discount rates to 1.5%. Alternative discount rates, such as a 1.5% rate, are currently being discussed as a case for change within the on-going CHTE methods review. It has been highlighted that the 3.5% discounting rates recommended by the HM Treasury Green Book is not applicable to health economic evaluations in its entirety. Specifically, it points out that the wealth effect of 2% is not applicable for these analyses

because the value of health does not decline as real incomes rise. Whether or not the methods review will ultimately revise the discount rate downwards from 3.5% is yet unclear, nevertheless the suggested scenario analysis at 1.5% is provided in Table 14.

Whilst this 1.5% discount rate has only been considered in the base case below it is important to keep in mind the equivalent reduction that would be expected in all of the scenarios discussed above. In no cases would there be an ICER above £30,000 / QALY. The majority would be under £25,000 / QALY and a significant number of the scenarios would fall below £20,000 / QALY.

Table 14 Scenario analysis with alternative discount rate

Costs and benefits discount rate	***Treatment***	***Total Cost***	***Incremental Cost***	***Total QALY***	***Incremental QALY***	***ICER***
Base Case (3.5%)	*SoC*	[redacted]		[redacted]		
	Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	*£28,156*
1.5%	SoC	[redacted]		[redacted]		
	Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	*£24,482*

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8

A revised PAS price for dupilumab results in a lower gross budget impact for the NHS

It is estimated that there are approximately 8,371 patients in England who would be eligible for treatment with dupilumab, increasing to 8,594 in 5 years' time (treated patient estimate provided in Appendix 5). Projected uptake of dupilumab is expected to be [redacted] patients in year 1, increasing annually to 1,[redacted] in year 5.

Table 15 Estimated eligible population size and projected uptake

Uptake	Year 1	Year 2	Year 3	Year 4	Year 5
Total patients eligible for dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated uptake	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
New patients on dupilumab (incident)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Existing patients on dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total dupilumab patients per year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The gross dupilumab drug spend is expected to be [redacted] at the end of Year 1, increasing to [redacted] in Year 5. The cumulative budget impact over the 5 years is expected to be [redacted] (Table 16). This gross budget impact does not consider cost savings accruing from reduced use of standard care interventions and reduced healthcare resource utilisation from exacerbation and disease control benefits.

Neither does it consider the wider implications of the PAS in the atopic dermatitis (AD) indication. This is explored below in the next section.

Table 16 Estimated 5-year gross budget impact

	Year 1	Year 2	Year 3	Year 4	Year 5	Cumulative
Drug cost Incident patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug cost prevalent patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

7

A simple revised PAS for a multi-indication dosage form generates immediate saving for all existing and future indications

Dupilumab solution for injection is also licensed for the treatment of atopic dermatitis (AD). The 200 mg dose is used in treating adolescent patients aged 12 to 17 years, and in child patients aged 6 to 11 years, as per a weight-based posology. For adolescents aged 12 to 17 years weighing <60 kg, 200 mg every two weeks (Q2W) is the recommended dose, whilst for children aged 6 to 11 years

a 200 mg Q2W posology is recommended for those not achieving an adequate response with 300 mg every four weeks (Q4W). Both the child and adolescent AD indications are reimbursed in the Scottish, English, and Welsh NHS systems. As of April 2021, there were [redacted] patients in the UK being treated with the dupilumab 200 mg dose for the treatment of atopic dermatitis (AD), approximately [redacted] of whom are in England. This is expected to increase to [redacted] patients in September of this year.

A positive recommendation for this asthma indication would result in the revised PAS being applied to all current and future dupilumab indications utilizing the 200 mg strength. [redacted]. Applying this only to the currently treated AD patients will see their annual budget impact reduce from £[redacted] to £[redacted], a cost saving £[redacted]

However, patient uptake onto the 200 mg strength is expected to rise from the [redacted] currently on treatment to a peak of [redacted] patients in 2024.

Table 17 Child and adolescent AD patients treated with dupilumab 200 mg

Uptake		**2021**	**2022**	**2023**	**2024**	**2025**	**2026**
Patients on treatment (April 2021)	[redacted]						
Expected patients on treatment (September 2021)	[redacted]						
New Adolescent patients on dupilumab (incident)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
New Child patients on dupilumab (incident)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Existing patients on dupilumab		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Total dupilumab patients per year		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Dupilumab 200 mg annual drugs spend in the English NHS in expected to increase from £[redacted] at present to [redacted] at the end of 2026. Implementation of the revised PAS in September of this year would result in a significant reduction in drug spend on the 200 mg strength thereafter. We estimate the annual drug spend will decrease from [redacted] to £[redacted] at 1 year (2022), and £[redacted] to [redacted] at year 5 (2026). **Cumulative savings between September 2021 to 2026 within AD alone as a result of the revised PAS are expected to be** [redacted] Further breakdown of these costings is presented in Table 18.

Table 18 Savings in AD due to the revised PAS for dupilumab 200 mg

Cost with no additional discount	**2021**	**2022**	**2023**	**2024**	**2025**	**2026**	**Cumulative**
Drug cost Incident patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug cost prevalent patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost with 20% additional discount in September 2021	**2021**	**2022**	**2023**	**2024**	**2025**	**2026**	**Cumulative**
Drug cost Incident patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Drug cost prevalent patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost difference with 20% discount in September 2021	**2021**	**2022**	**2023**	**2024**	**2025**	**2026**	**Cumulative**
Annual savings	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£[redacted]
Cumulative savings	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

The following assumption were used in the cost savings analysis:

- English patients account for 85% of all UK patients (population estimates, ONS)
- The existing proportion of child (aged 6 to 11 years) patients receiving 200 mg Q2W ([redacted]) is maintained in projected patient numbers
- Adolescent patients receive a loading dose in their first year (incident adolescent patients accrue a higher cost)
- Prevalent patients in 2021 are those on treatment prior to September 2021
- Incident patient numbers in 2021 are those initiated between September and year-end
- Revised PAS savings do not apply to 2021 prevalent patients (costs accrued prior to NICE asthma recommendation)

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Dupilumab for treating severe asthma [ID1213]

Consultation on the appraisal consultation document – deadline for comments 5pm on 28 May 2021 **email:** NICE DOCS

10	**The committee should be reassured that a positive recommendation will provide a treatment option for a group of patients with a significant unmet need and burden of illness, whilst representing good value-for-money to the NHS** We recognise that previous technology appraisals in this therapy area have been challenging but we have learned from, and built on, the work done by NICE and its stakeholders in order to demonstrate the clinical and cost-effectiveness of dupilumab in patient groups where a significant unmet need still exists. The committee has highlighted areas of uncertainty which have also been examined in previous technology appraisals for asthma therapies. These uncertainties have so far precluded the committee from issuing a positive recommendation for dupilumab for the treatment of severe asthma. In this ACD response we have examined these uncertainties, both by presenting scenarios which have been explored in previous appraisals, and by including additional scenarios which we hope will be helpful to the committee in their decision making. As such, we have been able to adopt conservative assumptions favoured by the current ERG and ERGs from previous appraisals. This approach has resulted in a base-case ICER of £28,156 for dupilumab with all credible scenarios below £30,000 per QALY. Dupilumab is either in development or is approved for the treatment of several atopic diseases due to its mechanism of action which targets type 2 inflammation. We welcome that the committee has recognised that dupilumab has additional benefits not captured in the QALY. More tangibly, because it is currently used for the treatment of atopic dermatitis in England the revised PAS would offer cost savings to the NHS amounting to [redacted] over the next 5 years.

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	We have shown that Dupilumab is both clinically effective and cost-effective in the proposed population. Scenario and sensitivity analysis to explore key areas of uncertainty overwhelmingly demonstrate that at the revised PAS price dupilumab is a cost-effective option for the treatment patients with severe asthma and represents good value for money to the NHS.

Insert extra rows as needed

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also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.

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Dupilumab for treating severe asthma [ID1213]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[Asthma UK & British Lung Foundation]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**N/A**]
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that Dupilumab has not been recommended for treating severe asthma with type 2 inflammation. As acknowledged in the ACD, Dupilumab has the potential to serve an unmet need. We estimate there are about 200,000 people with severe asthma in the UK, but only 30% are currently eligible for biologic treatment. As highlighted extensively in our previous responses, severe asthma is a debilitating, life-threatening and isolating condition. The introduction of biologics for treating the condition has truly transformed the lives of many with severe asthma, but thousands may not be eligible for current treatments and even those that are eligible may not respond. Therefore, we urgently need more biologic treatments for those who have not responded to current biologics, but also those who have no other option than to take oral steroids, with their well-known terrible side effects such as weight gain, diabetes and osteoporosis.
2	The committee has recommended that the most relevant population for decision making is people not eligible for other biologics as well as those who have failed previously on existing biologics. We agree this is where there is significant unmet need and are pleased to see that the committee is now considering those who have not responded to existing biologics.
3	We do not believe all the relevant evidence has been taken into account. As we understand the UK severe asthma registry holds data on ~30-40 patients being treated with dupilumab. We think this data could help mitigate some of the uncertainty in the modelling and provide a better understanding of the response rate of those who have failed on previous biologics.
4	Dupilumab has recently been recommended in Scotland by the SMC for people who have failed on previous biologics. We are therefore also concerned there may be an equity of access issue across the UK.
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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.	Not applicable
Name of commentator person completing form:	[redacted]

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Having read the documents and collated responses from ARNS committee and sub-committee members we can confirm that we would support NICE's view that more information is needed for the review and appraisal of the appropriate place for dupilumab.
2	We agree there is a need for further studies and clarification re cost effectiveness
3	We agree that all of the relevant evidence appears to have been taken into account
4	The summaries of clinical and cost effectiveness appear to be reasonable interpretations of the evidence
5	The recommendation to seek further information appears to be a sound and suitable basis for guidance to the NHS
6	There are no aspects of the recommendations that suggest that there is any unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[None]
Name of commentator person completing form:	[redacted]

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned with the recommendation that Dupilumab is NOT recommended for treating severe asthma with type 2 inflammation because the cost-effectiveness estimates for dupilumab are higher than what NICE usually considers a cost-effective use of NHS resources. The consultation agrees that severe asthma is associated with significant morbidity and mortality. Currently available biologics are useful in severe eosinophilic asthma and severe atopic asthma. While the majority of patients with severe asthma will have an eosinophilic phenotype (the international severe asthma registry suggests this is >80%), there remains an unmet need because: • some patients do not respond to currently available biologics- this can be ~30%. Non-responders continue to be reliant on oral steroids, either in bursts or daily use. This is associated with significant side effects. Studies have shown that the side effects associated with steroids begin above a cumulative lifetime dose of 1g- this is equivalent to 4 courses of prednisolone. The benefits associated with reduced reliance on oral steroids will not be fully reflected in the ICER A recent review of UK primary care data has shown that over 70% of patients with potentially severe asthma have not yet been referred to secondary or tertiary care (Ryan et al 2021). The NHSE supported Accelerated Access Collaborative on asthma biologics is developing initiatives to facilitate earlier identification of patients with potential severe asthma with the ultimate aim of increasing appropriate use of biologics. With increased use of biologics, it is likely that there will be a larger number of patients who fail to respond to the first choice biologic, highlighting he need for 'second-line' treatment. Dupilumab would be extremely appropriate as a 'second line' biologic. Within the consultation, there is considerable emphasis on asthma mortality and the impact dupilumab may have on asthma mortality. However, the National Review of Asthma Deaths (2014) suggested that patients who died due to acute severe asthma were more likely to have mild/moderate asthma rather than severe asthma. Therefore I do not think it is necessary to place so much emphasis on mortality. The Scottish Medicines Consortium have recently approved the use of dupilumab in patients who have not responded to a biologic (and have raised biomarkers). I would suggest that the economic analysis should be repeated, but for this group only. Blueteq can be used to obtain the numbers of patients currently on a biologic nationally and if it is presumed 20-30% will be non-responders, the potential group suitable for Dupilumab can be obtained. While it has been decided not to use a multiplier for exacerbations, this has likely increased the ICER. This is relevant as there was a significant 'placebo' effect seen in the clinical trials- this is not dissimilar to the other biologics trials and likely underestimates the benefit of duplilumab. The Scottish Medicines Consortium did use the multiplier, and this lead to a much lower ICER. In QUEST the reduction in exacerbations in patients with eos≥300 was most significant, while the benefit was not statistically significant in patients with eos≥150 and on 200mg dosage. While combined biomarkers (eosinophils and FENO) are included to define the intended population, I wonder if the economic analysis needs to be done on the higher eosinpil cut off group, as it is likely the benefit seen will be greater and this would affect the ICER. In summary, Dupilumab provides the option of new treatment with a different mode of action. It is ideally positioned as a second line biologic agent. The consultation should review the position of dupilumab within the treatment options for patients with type2-inflammation high severe asthma.
2	

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	GlaxoSmithKline UK Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	**Page 9, Comparators, Section 3.7. The second bullet point is missing "mepolizumab", please include. See updated guidance for mepolizumab TA671** "People with a blood eosinophil count of 400 cells per microlitre or more, who have had at least 3 exacerbations in the previous 12 months, can have reslizumab, mepolizumab or benralizumab."
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Insert extra rows as needed

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Dupilumab for treating severe asthma [ID1213]

Consultation on the appraisal consultation document – deadline for comments 5pm on 28 May 2021 **email:** NICE DOCS

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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.	NA
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row.

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Dupilumab for treating severe asthma [ID1213]

Consultation on the appraisal consultation document – deadline for comments 5pm on 28 May 2021 **email:** NICE DOCS

	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Factual Inaccuracy:** Paragraph 3.2 references The Global Initiative for Asthma (GINA) guideline on difficult to treat severe asthma (2019). This guideline was updated in 2021. We suggest updating any wording in the document relating to this reference.
2	**Factual Inaccuracy:** Paragraph 3.18 states that "current NICE recommended biologicals are licensed in adults for eosinophilic asthma only." There is in fact a biological recommended for treating severe allergic asthma. TA278 recommends omalizumab for treating severe persistent allergic asthma.
3	
4	
5	
6	

Insert extra rows as needed

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- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
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Dupilumab for treating severe asthma [ID1213]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**University of Oxford**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**None**
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row.

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Dupilumab for treating severe asthma [ID1213]

Consultation on the appraisal consultation document – deadline for comments 5pm on 28 May 2021 **email:** NICE DOCS

	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	This is very disappointing for patients, doctors and for the pharma industry. It's hard to think what more a pharma company could do to establish their drug as a viable treatment option for severe asthma. They have shown that it has unprecedented efficacy against the three biggest problems our patients with severe type-2 high asthma have: asthma attacks (68% reduction vs placebo): a requirement for regular or frequent as needed oral corticosteroids (OCS), with attendant adverse effects (reduced by 74% on active treatment vs 40% with placebo); and morbidity due to the commonest type-2 inflammation associated comorbidity, chronic rhinosinusitis and nasal polyposis (CRSNP). CRSNP is present in 30% of patients with severe asthma and is the commonest reason for failure of OCS weaning in a patient treated with anti-IL-5. In addition, for a given type-2 biomarker level, dupilumab is associated with roughly double the benefits of the anti-IL-5 on lung function, asthma related symptom scores and rhinitis symptom scores. Finally, and most compellingly, the drug developers have identified three clinically accessible predictive variables (prior asthma attack rate, blood eosinophils and exhaled nitric oxide), providing the opportunity for organisations such as NICE to ration access on a rational basis.
2	Contrast this with the situation with Omalizumab, an approved treatment for severe allergic asthma available at a list price of up to twice that of Dupilumab and the anti-IL-5 biologics. The phase 3 studies were only significant after a post hoc statistical fudge and showed a modest 28% reduction in asthma attacks. There was no OCS sparing data, no improvement in symptoms, no effect on lung function and the drug is still prescribed using variables that are neither risk factors for poor outcomes or predictors of treatment efficacy (IgE, presence of allergy, patient weight). The company (Novartis) have completely ignored compelling evidence that the treatment works preferentially in patients with type-2 high asthma. It is hugely demotivating for drug developers and clinical researchers to see such striking inequity.
3	NICE is alone amongst Westernised countries regulatory authorities (including Scotland) in not approving Dupilumab for severe type-2 asthma. I have been involved in the approval process in other countries and there really has not been much debate. This is not a comfortable position to be in.
4	It looks to me like NICE have been lost in the details of a questionable pharmacoepidemiological modelling exercise and have failed to see the big picture. That is a game changing new class of treatment that is having a huge impact on patients with very severe disease and terrible associated morbidityb. There is a real opportunity to come up with a rational compromise position acceptable to all.
5	The analysis of dupilumab efficacy by baseline exhaled nitric oxide (FeNO) and blood eosinophils in the phase 3 QUEST study was pre-specified, not post-hoc. The relationship between treatment effect and these biomarkers had been identified very clearly in the phase 2b study.
6	In the document there is confusion around the terms type-2 high, eosinophilic and allergic asthma. We regard type-2 high and eosinophilic asthma as synonymous. Allergy is a very peripheral process in severe asthma and is not that closely associated with type-2 inflammation. Positive skin tests and serum IgE have not proved to be predictive of anything important. All of the biologics work well in patients with type-2 high/eosinophilic asthma identified by a raised FeNO and blood eosinophils

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Dupilumab for treating severe asthma [ID1213]

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	(including omalizumab). It may well be that FeNO is a better predictive biomarker for Dupilumab and blood eosinophils for the anti-IL-5 (see Shrimanker et al. Am J Resp Crit Care Med 2019) but this concept is not well enough developed for clinical practice. The clinical impact of the different biologics is related to how completely they block the components of type-2 immunity. This is large for Dupilumab, moderate for anti-IL-5 and marginal for omalizumab.
7	One key fact overlooked by NICE and the cost analysis modellers is that in placebo treated patients the risk of asthma attacks is 3-5 times higher in patients with type-2 high asthma (i.e. FeNO >25 ppb, blood eosinophils >150 cells/mcl) vs low. This was shown in QUEST and in the placebo group of every other placebo controlled biologic trial I am aware of. It is also seen consistently in real world populations. The risk associated with these biomarkers is independent of other measures of asthma severity. The cost analysis must take this into account, whether they use trial or real-world data.
8	A strong case could be made for restricting access of dupilumab to patients with FeNO >25ppb and blood eos >150 cells/mcl. This population comprised just under half the QUEST population and had the clearest benefit of treatment (see first point). Efficacy was more marginal in patients with discordant biomarkers and was not seen at all in those with low biomarkers. In addition, clinicians would like the opportunity to use Dupilumab as a first line therapy in patients who have severe type-2 high asthma and comorbid CRSNP. Dupilumab is known to have a big positive impact on both conditions. Finally, as in other areas such as rheumatology, there is an appetite to swap biologics in patients who have had an incomplete response. Dupilumab would be the most logical swap in patients who have evidence of persistent type-2 inflammation on their current biologic (i.e. raised FeNO, continued response to rescue prednisolone) and in those whose persistent problems are related to CRSNP.

Insert extra rows as needed

Checklist for submitting comments

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
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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.

Comments on the ACD received from the public through the NICE Website

Name	[redacted]
Role	
Other role	
Organisation	Royal College of Pathologists / Royal College of Physicians
Location	
Conflict	
Notes	

Comments on the ACD:

1 We are in agreement that Dupilumab is not cost-effective compared to other biologics for severe asthma

2 However Dupilumab has a different mode of action compared to all other available biologics targeting IL4/IL13 receptors and hence cannot be directly compared to other biologics. Dupilumab is likely to be most cost-effective in those with severe asthma in association with a comorbidity such as generalised eczema or recurrent nasal polyps. If it were possible to model cost-effectiveness using co-morbidity then the cost-effectiveness calculations may change.

3 Clearly the cost per treatment is higher than other available biologics however rather than refusing a recommendation, NICE should consider allowing a limited recommendation for the subset of patients with comorbidities such as recurrent nasal polyps, severe eczema, rhinosinusitis and allergic bronchopulmonary aspergillosis. These are conditions for which current biologics have only limited efficacy.

4 Dupilumab in clinical practice also appears effective in those with both an allergic and eosinophilic hybrid phenotype for which the other biologics may be least effective. Therefore treatment failures with other biologics should have the opportunity to be treated with Dupilumab.

5 The last 12 months has seen >90% patients on biologics transferring to home care and self-injecting. This greatly reduces the cost and inconvenience of the higher frequency of injections (every 2 wks) for Dupilumab compared to other biologics eg benralizumab which is injected every 8 wks.

[ID1213] Dupilumab for treating severe asthma

Name	[redacted]
Role	
Other role	
Organisation	Individual
Location	
Conflict	
Notes	
Comments on the ACD:	
I suffer from severe eosinophilic asthma which severely disrupts my life. My consultant has prescribed 2 of the available monoclonal antibody drugs, Omalizumab and Benralizumab. Unfortunately, I did not respond to either. With Benralizumab, which has an 87% response rate, I came in the 13% who did not. I am desperate to try Dupilumab which may be able to help me. Would it be possible to recommend the drug for patients such as myself who have failed to respond to Benralizumab and Omalizumab? Many thanks	

Name	[redacted]
Role	
Other role	
Organisation	Welsh Difficult Asthma Group
Location	
Conflict	
Notes	

Comments on the ACD:

I respond on behalf of the Welsh Difficult Asthma Group (WeDAG). We are disappointed with the current outcome of the NICE consultation given the unmet need in this patient group with severe asthma with type 2 inflammation, in particular those who have either not responded or are ineligible for current biologics. This is particularly true for those on maintenance prednisolone which is associated with considerable increased morbidity. NICE do appear to acknowledge this unmet need.

It is inequitable for patients to be offered this treatment in Scotland but not in other UK nations. It is also recommended as a treatment in international severe asthma guidelines including Global Initiative for Asthma (GINA) 2019 and joint American Thoracic Society/ European Respiratory Society 2019. This puts England and Wales as outliers in being able to offer this option in the management of severe asthma.

Clinical trials show that having Dupilumab plus standard asthma treatment reduces exacerbations and the use of oral corticosteroids more than placebo. In QUEST there was an almost 50% reduction in severe exacerbations in the Dupilumab group compared to placebo (95% confidence interval 33.8%-58.7% $p<0.0001$). Whilst unfortunately the numbers in the updated populations considered by NICE (those with severe asthma, raised eosinophils/feno and 4 exacerbations) were small Dupilumab continued to show efficacy and this is clinically very meaningful within this population. We would urge NICE to work with the company and severe asthma centres who have patients accessing Dupilumab through early access schemes to review real world evidence in this population.

A further subpopulation that has not been considered in the evidence are those with overlapping conditions in which there is clinical trial evidence of benefit for Dupilumab -those with severe eczema (who do not meet stand alone dermatological criteria for Dupilumab) or nasal polyposis. Clinical experience from the group reports a number of examples of eczema flaring on anti IL5 therapy.

Finally we would strongly advocate review by the guidance executive in a more timely manner than the 3 years currently planned after publication of the guidance. We would suggest discussion with the company as to when further evidence will be available to review in the UK severe asthma population so that appropriate review occurs as soon as possible.

Name	[redacted]
Role	
Other role	
Organisation	Individual / Addenbrookes
Location	
Conflict	
Question	Has all of the relevant evidence been taken into account?
There is emerging, real world evidence from an early access scheme in the UK. This was in a very limited population (failed on other biologics, fullfililng biomarkers.). Of note, these were usually patients with very high health care utilisation and at real risk of emerging steroid induced complications. In our hands, on most of these patients, dupilumab has been a highly successful agent. I note that restrictions to patient populations that are different to the trials are being proposed by NICE, limiting the amount of patients that are suitable for modelling in this exact population. In our hands, dupilumab has been a very succesful agent in these patient groups (failure of anti IL-5 with evidence of type 2 inflammation)	
Question	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
I find it surprising to note that in 3.10 the reduction in the exacerbations is thought to be secondary to a 'regression to the mean'. This is an odd concept to apply to eosinophilic asthma. Eosinophilic asthma is typically a progressive disease, and patients who have frequent exacerbation rates tend to have similar or increasing exacerbation rate over the years, until placed on an effective treatment.	
Question	Are the recommendations sound and a suitable basis for guidance to the NHS?
It is a disappointing recommendation, as it will leave individuals not eligible for or not responding to current therapies at a continued high treatment burden.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Question	Has all of the relevant evidence been taken into account?
Yes	
Question	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
The modelling does nit take account if young people, thise with nasal polyposis or severe eczema.	
Question	Are the recommendations sound and a suitable basis for guidance to the NHS?
No	
Question	Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
No	
Comments on the ACD:	
The decision not to give NICE approval to dupilumab leaves a clear unmet need for those patients with severe asthma. We run the East of England severe asthma service, and have seen marked benefit in some patients who, having failed treatment with either omalizumab, anti-IL5 treatments, or both, went on to receive dupilumab as part of the free of charge scheme. We have seen significant reductions in daily oral corticosteroid use in some of these patients, as well as exacerbation reduction. Clearly these patients are in a minority group, but have important, severe disease. It is notable that the committee mentions young people as being in a group with particular unmet need, and that patients with nasal polyposis may improve and not have the improvement in QALY recognised in the current modelling. I agree this this. Some of our most clinically challenging non responders to other biologics fit this description. I cannot comment the accuracy with which you have decided on how to use mortality data or the magnitude of clinical response in the base case, but I would urge the committee to find a way to permit the use of dupilumab for patients who have not responded to other biological therapies and who have clear evidence of T2 inflammation and severe disease. All medication use in England is well stewarded and closely monitored for clinical response.	

Dupilumab for treating severe asthma

Evidence Review Group comments on the company's response (and technical appendix) to the second Appraisal Consultation Document (ACD 1.0)

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Date completed	09/07/2021

1 Introduction

This document is the Evidence Review Group's (ERG's) critique of the response made by the company (Sanofi) to the second Appraisal Consultation Document (ACD 1.0) issued by NICE to consultees and commentators on 29 April 2021. The company's response comprised ten comments on the content of the ACD (these are numbered 1-8, 7 and 10, the second comment numbered 7 presumably should have been numbered 9), an appendix (this contains four appendices) and an updated version of their economic model.

In this critique, we take the key issues raised by the NICE appraisal committee at their second meeting for this STA on 12th November 2020, as described in ACD 1.0, and we comment on the company's response to these. The key issues raised in the ACD are briefly summarised in Table 1 and we provide further comment and critique in the following sections.

Table 1 Summary of key issues raised by NICE in the ACD

Topic	Summary of issues raised	ACD section(s)
Population	The company's population of people with type 2 inflammation is not suitable for considering the cost effectiveness of dupilumab compared with standard care. This is because it combines people eligible for biologicals (mepolizumab, reslizumab or benralizumab) with people not eligible for biologicals who can only be offered standard care.	1
	The company had proposed an updated decision problem in a subpopulation of people who are not eligible for biologicals or who did not respond to biological therapy, based on a post hoc analysis of the QUEST data. The committee concluded that this updated population was suitable for decision making.	3.6
	There were very limited clinical efficacy data provided for the company's updated population because of the small number of patients in the QUEST trial corresponding to each subgroup. The committee concluded that the clinical	3.10

	effectiveness of dupilumab in the company's updated base case was highly uncertain.	
Subgroup – prior biological therapy	For the subgroup of adults who previously received biologicals but did not respond (blood eosinophil count of 300 and more) the committee considered: • that although it is plausible that people who did not respond to other biologicals could respond to dupilumab, assuming that the response rate would be as good as in people not eligible for other biologicals was optimistic • this to be a key area of uncertainty and noted that it would have liked to see exploration of scenarios with a range of alternative response rates for the group of adults who did not respond to biological therapy The committee concluded that the effectiveness estimates in the company's updated population were highly uncertain.	3.12, 3.19
Mortality rates	The committee was concerned that mortality could be overestimated because asthma-related mortality was one of the drivers of the model. The committee also noted that alternative methods had been used in the benralizumab appraisal, to adjust for high mortality. The committee concluded that the mortality rates were uncertain, and that alternative scenarios could be tested to explore the impact of the mortality on the ICER.	3.15, 3.19
Cost-effectiveness	The cost-effectiveness estimates for dupilumab vary depending on whether people are eligible for mepolizumab, reslizumab or benralizumab, and what their individual treatment options are.	1
	The cost-effectiveness estimates for dupilumab are higher than what NICE usually considers a cost-effective use of NHS resources. The committee concluded that dupilumab does not represent a cost-effective use of resources, so could not be recommended for treating severe asthma with type 2 inflammation	1, 3.16, 3.19

2 Population

The company's updated decision problem (base case) population (which was defined in response to the first NICE ACD for this appraisal) is:

> **"People with severe asthma on high dose inhaled corticosteroids (ICS), aged 12 and over and EOS≥150 And FeNo≥25 with ≥4 Exacerbations who are ineligible for biologics or have previously had biologic therapy".**

In comment 3 of the company's response to ACD 1.0, the company present evidence from their QUEST trial (one patient in the trial had previously received a biological but the majority were biologic naïve patients) for the clinical efficacy of dupilumab in patients aged 12 years and over, in receipt of high dose inhaled corticosteroids [ICS] and with EOS≥150 AND FeNO≥25 AND ≥4 exacerbations in the previous 12 months. In comment 4, the company provides data from other sources to support their assumption that dupilumab is as effective in patients who have not previously responded to biological therapies and we discuss this below in section 3 of this ERG critique.

Within the QUEST trial, there were 32 patients with severe asthma who were naïve to biologic therapy, aged 12 and over, received high dose ICS and who had EOS≥150 AND FeNo≥25 with ≥4 severe exacerbations. The company acknowledge that a very small number of patients in the QUEST trial ([redacted] out of a total trial population of n=948; placebo group [redacted]; dupilumab group [redacted]) match the criteria of their updated decision problem (base case) population. The company's post-hoc analysis of the trial data for this small subgroup shows that these patients had an [redacted] reduction in the risk of a severe asthma exacerbation in comparison to the placebo group ([redacted]).

The company also present evidence from a 'reference population' (n=112; placebo group [redacted]; dupilumab group [redacted]) that also meets the criteria of being aged 12 and over, received high dose ICS and who had EOS≥150 AND FeNo≥25 but with only ≥2 severe exacerbations. The source of this 'reference population' is not stated but the ERG believes this is the reference population from the QUEST trial that the company uses in the model to estimate transition probabilities between health states. Therefore, the target population (n= [redacted]) will be included within the reference population (n=112). This evidence is provided by the company '*To address the uncertainty in efficacy estimates for this population*'. In this less restricted population, there was an [redacted] reduction in the risk of a severe asthma exacerbation in

comparison to the placebo group. Full details are presented in Table 2 of the company's response to ACD 1.0.

To further support the dupilumab treatment effect in the company's proposed population the company present:

i) Figure 1 and Table 3 within comment 3 of the company's response. These show a subgroup analysis of severe exacerbation rates by the number of exacerbations in the 12 months prior to QUEST baseline. Data are grouped for all patients in the QUEST trial with ≥1, ≥2, ≥3 or ≥4 exacerbations. In the 200 mg placebo group (black bars in the figure) the adjusted annualised severe exacerbation rate increases with increasing number of exacerbations in the 12 months prior to baseline from 0.871 (0.724 to 1.048) in those with ≥1 exacerbations (n=317) to more than 2.563 (1.661 to 3.955 in those (n=37) with ≥4 exacerbations. In contrast, in people receiving the 200 mg dose of dupilumab (yellow bars in the figure) a statistically significant reduction in the adjusted annualised severe exacerbation rate is seen in all groups ranging from a 48% reduction versus placebo in the ≥1 exacerbation group to a 77% reduction versus placebo in the ≥4 exacerbations group (Table 2).

ii) Figure 2 within comment 3 of the company's response. This shows data for four groups of patients based on whether baseline levels of EOS and FeNO are raised (EOS ≥150, FeNO ≥20) or not. The subgroup with EOS ≥150 and FeNO ≥20 (48% of the QUEST population) had the highest adjusted annualised exacerbation rate in the placebo arm and the most pronounced treatment effect (rate reduction versus placebo 66%, $p<0.001$) (Table 3).

Table 2 Subgroup analysis of severe exacerbation rates by number of exacerbations in the 12 months prior to QUEST baseline

	Number of exacerbations in the 12 months prior to QUEST baseline							
	≥1 exacerbations		≥2 exacerbations		≥3 exacerbations		≥4 exacerbations	
	PBO	DUP 200 mg	PBO	DUP 200 mg	PBO	DUP 200 mg	PBO	DUP 200 mg
Adjusted annualised severe exacerbation rate over 52 weeks, estimate (95% CI); N	0.871 (0.724, 1.048); N=317	0.456 (0.389, 0.534); N=631	1.234 (0.991, 1.560); N=167	0.512 (0.413, 0.634); N=291	1.648 (1.174, 2.312); N=76	0.625 (0.457, 0.855); N=126	2.563 (1.661, 3.955); N=37	0.571 (0.372, 0.876); N=64
Relative risk vs placebo (95% CI)		0.523 (0.413, 0.662)		0.412 (0.305, 0.557)		0.379 (0.244, 0.589)		0.233 (0.124, 0.399)
p-value vs placebo		<0.0001		<0.0001		<0.0001		<0.0001

Source: Company response to ACD 1.0, Table 3

Table 3 Subgroup analysis of severe exacerbation rates by EOS and FeNO biomarkers at baseline

	EOS <150 & FeNO <20		EOS ≥150 & FeNO <20		EOS <150 & FeNO ≥20		EOS ≥150 & FeNO ≥20	
	PBO	DUP 200 mg	PBO	DUP 200 mg	PBO	DUP 200 mg	PBO	DUP 200 mg
Adjusted annualised severe exacerbation rate over 52 weeks, estimate (95% CI)	0.46 (0.27, 0.78)	0.62 (0.45, 0.86)	0.84 (0.56, 1.26)	0.60 (0.43, 0.83)	0.59 (0.33, 1.09)	0.24 (0.14, 0.42)	1.08 (0.83, 1.39)	0.36 (0.28, 0.46)
N	N=48	N=115	N=70	N=141	N=35	N=75	N=158	N=292
Difference vs placebo		+34%		-29%		-59%		-66%
p-value vs placebo						*		<0.001

Source: Company response to ACD 1.0, Figure 2 and text within comment 3 of the company's response.

* - asterisk present in Company response to ACD 1.0, Figure 2 for this comparison but p-value not reported in footnote or text.

ERG conclusion

A post-hoc subgroup analysis of data from [redacted] patients in QUEST, aged 12 and over, who received high dose ICS and who had EOS≥150 AND FeNo≥25 with ≥4 severe exacerbations, shows that the patients in the dupilumab group (n=[redacted]) had an [redacted] reduction in the risk of a severe asthma exacerbation in comparison to the [redacted] patients in the placebo group. The company acknowledge this is a very small number of patients and therefore provide supporting information, also taken from the QUEST trial, '*To address the uncertainty in efficacy estimates for this population*' which shows that:

- During the trial the adjusted annualised severe exacerbation rate in the placebo group increases across subgroups defined by increasing number of exacerbations (≥1, ≥2, ≥3 or ≥4) in the 12 months prior to baseline. In contrast, for the same subgroups of people receiving dupilumab there is a statistically significant reduction in the severe exacerbation rate which is greatest in the ≥4 exacerbations group.
- Subgroup analyses of patient groups defined by baseline EOS and FeNO levels show that patients with EOS ≥150 and FeNO ≥20 (48% of the QUEST population) had the highest adjusted annualised exacerbation rate in the placebo arm and the most pronounced treatment effect.

3 Subgroup: Prior biological therapy

In comment 4 of the company's response to ACD 1.0 the company present additional evidence to support their assumption that dupilumab would be as efficacious in patients who had previously received a biologic as it is in biologic naïve patients. The evidence comes from three published real-world studies which we have summarised in Table 4. The three retrospective studies had sample sizes ranging from 38 to 72 patients. In comparison to the company's updated decision problem (base case) population (people with severe asthma on high dose ICS, aged 12 and over and EOS≥150 And FeNo≥25 with ≥4 exacerbations who are ineligible for biologics or have previously had biologic therapy) we note the following:

- In two studies[1 2] all the patients had severe asthma but a high proportion of patients were receiving oral corticosteroids (OCS) (i.e. more like the VENTURE trial population than the QUEST trial population). Most patients had received a prior biological therapy. In both these studies all patients received 300 mg dupilumab every two weeks (the dupilumab dose in QUEST was 200 mg)

- In one study[3] most patients had severe asthma (61%) with only 12.5% of patients receiving OCS. Less than a third of patients (29%) had received prior biological therapy. The median dupilumab dose was 300 mg every two weeks (range 200-300 mg).

The results from all three studies were consistent with each other and showed that measures of asthma control improved and the rate of asthma exacerbations decreased with respect to baseline values or values during previous antibody therapy in the majority of patients (proportions of patients ranging from 62.5% to 78% across different outcomes and measures, Table 4). The ERG is aware of one other similar study of 18 patients conducted in Italy[4] which reports results consistent with the three studies included by the company.

Finally, the company include one further source of information [redacted] (Table 4 within comment 4 of the company's response). [redacted]

The company present two sets of scenario analyses to explore the impact of uncertainty over treatment effects on the cost-effectiveness results. See section 5.2 below for ERG comments.

ERG conclusion

The real-world studies included by the company consistently demonstrate an improvement in asthma control and a reduction in asthma exacerbations in groups of patients that include those with severe asthma who have previously received biologic therapy. There are some differences between the patients included in the published studies and the company's proposed population, notably that the dose of dupilumab was typically 300 mg and a high proportion of patients were receiving OCS. The ERG agrees that that evidence indicates a proportion of people who have previously received a biologic will respond to dupilumab. However, from the small amount of data available, it is difficult to judge what the proportion of responders will be.

Table 4 Real world evidence on dupilumab effectiveness for people with previous biologic therapy

	Dupin et al. 2020[1]	**Mummler et al. 2021[2]**	**Nowsheen et al. 2021[3]**
Country/design	France/retrospective cohort	Germany/retrospective	USA/retrospective
Included patients	Uncontrolled severe asthma, no other treatment option, poor asthma control &/or severe steroid side-effects	Severe asthma (ERS/ATS definition), prior anti-IgE or anti-IL5/anti-IL-5Rα therapy with switch to dupilumab <6 months after discontinuation of this.	Diagnosis of uncontrolled asthma by a pulmonologist or allergist (61% severe) and treatment with dupilumab for at least 1 dose
N patients	64 (51 at 12 months)	38	72
Previous biologic therapy	Mepolizumab 17%, Omalizumab 84%	Mepolizumab 29%, Reslizumab 5%, benralizumab 50%; omalizumab 16%	29.2%
Baseline OCS	75.8%	64%	12.5%
Dupilumab dose	600 mg loading; 300 mg thereafter [a]	600 mg loading; 300 mg thereafter [a]	median 300 mg (range 200-300 mg)
Follow-up	12 months	3-6 months	median 13 months
Asthma control results	Median ACT score increased from 14 to 22 ($p<0.001$) and was >20 for 67% of patients. Score did not differ by prior omalizumab or mepolizumab.	ACT score increased by 2.9±4.6 ($p<0.001$) in comparison to values during previous antibody therapy. 76% of patients were classified as responders. Patients with FeNo ≥25 ppb were more likely than patients with low FeNo to be responders.	Mean ACT score increased from 16 to 22 ($p<0.05$). 62.5% of patients had a clinically meaningful response. 20/21 patients who had failed treatment with other biologics responded to dupilumab
Exacerbation rate results	Exacerbation rate reduced by 75% compared with baseline and 78% of patients had ≥ 50% reduction	Annualised exacerbations decreased by a median of 0.81/y ($p=0.001$) in comparison to values during previous antibody therapy. One patient in the non-responder group experienced an increase in exacerbations.	Mean annual exacerbation frequency fell from 2.7 at baseline to 0.1

[a] The 300 mg dupilumab dose every other week is for patients with severe asthma who are oral corticosteroids (VENTURE trial population). For the company's updated decision problem (base case) population the appropriate dose of dupilumab is 200 mg.

4 Mortality rates

The company questions the 18% 10-year mortality estimate for standard care cited in ACD 1.0 (paragraph 3.15) and slide 32 of the Chair's presentation for the second appraisal committee meeting. We cannot find the source for or replicate this estimate, so it does appear to be an error. The predicted mean ages of death cited in the ACD and committee slide 32 (70.1 years with standard care and 72.9 years with dupilumab) are consistent with the mortality estimates in Table 6 of the ERG critique dated 19/05/2020 of the company's initial ACD response dated 05/05/2020 (slide 51 in the Chair's presentation slides). This analysis relates to the company's base case in their initial response to the first ACD, which included a calibrated multiplier for long-term exacerbation rates based on real-world evidence. In this analysis, the 10-year mortality rate with standard care was 21%. Removing the long-term exacerbation multiplier produces mortality estimates that are consistent with those cited in section 5 of the company's response to ACD 1.0: 10-year mortality with standard care of 16.7% (and mean ages of death of 73 years with standard care and 75 years with dupilumab). The ERG confirms that the Markov trace results in Table 7 of the company's response match those from their most recently revised base case, and do not include a multiplier for long-term exacerbations.

The company argues that these estimates are consistent with reported mortality for a French severe asthma cohort (n=690) identified from medical claims data (Bourdin et al. 2019).[5] The cohort had at least one prescription for omalizumab and/or at least 10 prescriptions of medium or high-dose ICS and a LABA for asthma during 2012. 58.7% had received at least one prescription of oral corticosteroids (mean 3.3 boxes during 2012) and 6.7% had been prescribed omalizumab. All-cause mortality in the cohort was 7.1% over 3 years, which compares with 7.6% for a population of the same age (61 years) estimated from the revised base case model (company response Table 8). We replicated these results. The company argues that as the French cohort was not restricted by asthma control, biomarkers or exacerbation rates, one would expect a bigger difference in mortality.

The company also argues that the comparison of modelled life expectancy from the current appraisal with that from the NICE appraisal of benralizumab (80 years with standard care with a baseline age of 50.2 years) is inappropriate as it does not account for the lower-risk profile of the population in TA565. The company's revised base case model predicts a mean age of death of 73.5 years with standard care, 75.8 years with dupilumab.

ERG conclusion

The company has questioned the accuracy of the 18% figure cited in the ACD (paragraph 3.15) for 10-year mortality with standard care in the company's revised base case (without an exacerbation multiplier). The ERG agrees and considers that this is an error, and that the correct 10-year mortality in this analysis is 16.7% for standard care and 10.1% for dupilumab, and the predicted ages of death are 73 years with standard care and 75 years with dupilumab.

In response to the committee's comment that the mortality rates were uncertain, the company cites a retrospective case-control study based on French claims data.[5] This reported 7.1% mortality over three years for patients with severe asthma, compared with 7.6% for a population of the same age (61 years) from the revised base case model. The company suggests that as the modelled cohort is a high-risk subgroup, with raised EOS, FeNo and prior exacerbations, they would expect a larger difference in mortality. However, we consider that the French cohort study does not resolve uncertainty over whether the modelled mortality is over-estimated for current UK clinical practice, due to differences in the population, treatments and setting.

The company also argue that it is difficult to interpret the differences in predicted life expectancy from the current base case model and reported estimates from the benralizumab NICE appraisal TA565. We accept that there are differences in the population and assumptions of these appraisals. The company apply a correction to the case fatality rate for people aged 55-64 year admitted to hospital with a severe asthma exacerbation, however this has little impact on the ICER and does not resolve uncertainty over the mortality estimates (see 5.3 below).

5 Cost effectiveness results

5.1 Revised simple PAS

The base case ICER cited in the ACD is £35,968. This includes the existing Patient Access Scheme (PAS) price discount for dupilumab ([redacted], CS Table 2), [redacted].

In section 2 of their response, the company report that a revised simple PAS has been accepted by PASLU. The ERG confirms that this revised discount of [redacted] reduces the base case ICER to £28,156, as reported in Table 1 of the company's response.

5.2 Scenario analyses for prior biological therapy subgroup

In section 4 of their response, the company reports two sets of scenario analyses intended to address the committee's request to explore the impact of uncertainty over the effectiveness of dupilumab for people who did not respond to previous biologic therapy:

- Varying the one-year response rate for dupilumab (consultation response Table 5).
- Varying the relative risks of severe exacerbations for dupilumab compared with standard care alone (consultation response Table 6).

Both sets of scenarios were applied to the base case model, with the broad target population (age 12+ and EOS>=150 and FeNo>=25 and 4+ prior exacerbations). The company argue that this is conservative, as the treatment effects are "varied downwards for the entire proposed population" and conclude that the results show that dupilumab is a cost-effective treatment option for people for whom previous treatment with a biologic has failed. We replicated the results of these scenarios, but question whether they really are conservative, as they test a narrow range of uncertainty over the treatment effects in the subgroup who have not responded to previous biological therapy.

5.2.1 Varying the treatment response rate

In the first set of scenarios (consultation response Table 5), the company reduces the proportion of people in the dupilumab arm with a response at 12 months, which has little impact on the ICER. However, the ERG does not consider this to be a meaningful illustration of the impact of uncertainty over dupilumab effectiveness. This is because, although 'non-responders' are assumed to stop dupilumab add-on therapy at 12 months, the model predicts that they have the same QALY gain as 'responders' during this year. Hence incremental costs and incremental QALYs are reduced in similar proportions when the response rate is reduced. We note that at the extreme, with 0% response to dupilumab, the model estimates an ICER of £30,093 per QALY gained. This does not seem realistic.

5.2.2 Varying the relative risks of severe exacerbations

In the second approach, the company vary the relative risks of severe exacerbations with dupilumab compared with standard care alone (consultation response Table 6). This entailed recoding to estimate transition probabilities into the severe exacerbation health state for the dupilumab arm by adjusting standard care transition probabilities with a set of relative effect parameters (consultation response Appendix 2). Transitions into the other health states (controlled asthma, uncontrolled asthma and moderate exacerbations) are adjusted proportionately, so that the total transitions per 4-week model cycle sum to one.

The severe exacerbation relative effects are estimated from the base case transition matrices, derived from QUEST trial data. Although the company refer to ‘relative risks’, these parameters are appropriately estimated as hazard ratios (HRs) before multiplication with hazards, and back calculated to transition probabilities for the four-week model cycle.

Additional adjustments are made to avoid zero transition probabilities when no transitions were observed in the reference population. Without these adjustments, the ICER in this version of the model is the same as in the base case model (£28,156 per QALY gained); but with the null event adjustments, the ICER is a little higher (£28,799 per QALY gained).

The company varied the HR parameters up to 130% of the base case estimates. Above about 123% of base case, the ICER is greater than £30,000 per QALY gained. We show the magnitude of the HR values and transition probabilities (four-week incidence of severe exacerbations) associated with 100%, 123%, 130% and 250% of the base case estimates in Table 5.

[redacted]

Health outcomes and cost-effectiveness results associated with this set of scenarios are shown in Table 6 below. The wider range of variation gives an upper ICER estimate of £38,514 per QALY gained. The ERG considers that this is more reflective of the range of uncertainty over the effectiveness of dupilumab in patients who have not responded to previous biological therapy than the narrower range tested in the company’s scenarios.

Table 5 Parameter values used in scenario analysis on relative effects of dupilumab

Health state	All patients (year 1)			Dupilumab responders		
	HR	TP SC	TP Dup	HR	TP SC	TP Dup
100% of base case HRs						
Controlled Asthma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled Asthma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
123% of base case HRs						
Controlled Asthma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled Asthma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
130% of base case HRs						
Controlled Asthma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled Asthma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
250% of base case HRs						
Controlled Asthma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uncontrolled Asthma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe Exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: obtained from company model by ERG
Abbreviations: Dup dupilumab add on therapy; HR, hazard ratio; TP 4-week transition probability; SC standard care. * imputed values for null transitions.

Table 6 Cost effectiveness for scenario analysis on relative effects of dupilumab

	Costs	Severe exacerbations		Life years	QALYs	ICER
		Total	Per year			
Base case model						
Standard care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£ 28,156
100% of base case HRs						
Standard care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£ 28,799
123% of base case HRs						
Standard care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£ 30,012
130% of base case HRs						
Standard care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£ 30,397
250% of base case HRs						
Standard care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£ 38,514

Source: obtained from company model by ERG

5.3 Mortality estimates

In Table 9 of their consultation response, the company provides a correction to the case fatality rate for 55 to 64 year-old patients admitted to hospital due to a severe exacerbation: the company (CS Table 56) and ERG (Table 78) reported a rate of 1.81% rather than 0.85% as accepted in the TA565 appraisal (see section 5.3 below). This correction leads to a small increase in the company's base case ICER: from £28,156 to £28,929 per QALY gained. The ERG replicated this result.

5.4 Long-term exacerbation rates

The company provides further commentary on the plausibility of different explanations for the placebo effects observed in trials of biological treatments for severe asthma and the different approaches taken to estimating long-term exacerbation rates in previous NICE appraisals (consultation response section 6). This is an important source of uncertainty and a driver of cost-effectiveness, as discussed in previous documents for this and other NICE asthma appraisals.

The company presents two sets of scenario analyses in their ACD response. In both, a 'multiplier' is used to inflate the number of severe exacerbations (in both arms) after the end of QUEST trial follow up (52 weeks). This assumes that the reduced number of exacerbations seen in the trial placebo arm compared with the number reported for the previous year would not persist in the real world. It has the effect of increasing the difference in the predicted number of severe exacerbations in the standard care and dupilumab arms, hence reducing the ICER.

- Table 11 repeats scenario analysis from the original company submission based on arguments that the QUEST trial protocol would have underestimated severe exacerbations (CS B.3.3.3 and Appendix M.2; and ERG report section 4.3.4.1).
- Table 13 presents a range of scenarios with multipliers calibrated to achieve defined long-term average exacerbation rates: from [redacted] severe exacerbations per year in the base case up to 4.5 severe exacerbations per year.

For all of these scenarios, we found similar results to those reported in the company response. There were some small discrepancies in the ICERs, which are likely to be due to rounding as the multipliers were only reported to three decimal places.

5.5 Discount rates

The company conducts a scenario analysis with discount rate of 1.5% per year for costs and QALYs, rather than 3.5% as the base case. This gives a lower ICER of £24,482 per QALY gained (consultation response Table 14).

5.6 Budget impact

The company put forward estimates of the budget impact for the NHS due to the effect of the increased PAS discount for dupilumab for patients with asthma and other indications (consultation response sections 8 and 9). The ERG is not expected to comment on budget impact estimates.

6 References

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