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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Dupilumab for treating severe asthma [ID1213]

Appraisal Committee Meeting – 12 November 2020
2nd Committee meeting

The following documents are made available to the Committee:

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

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

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Asthma UK

4. **Comments on the Appraisal Consultation Document from experts:**
   - Dr Nicola Ridgway – patient expert, nominated by Asthma UK

5. **Comments on the Appraisal Consultation Document received through the NICE website**

6. **Evidence Review Group critique of company comments on the ACD –** to follow

7. **Company additional evidence response**
   - Company updated proposal
   - Additional clinical evidence input

8. **ERG critique of company additional evidence response**

9. **Appraisal Committee Meeting presentation slides**

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 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: March 2020

Note that this document is not NICE's final guidance on dupilumab. 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: 31 March 2020

Second appraisal committee meeting: 15 April 2020 Details of membership of the appraisal committee are given in section 4.

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 recommended starting dose of dupilumab is 400 mg, followed by 200 mg every other week, administered subcutaneously. For people with severe asthma on oral corticosteroids, or for people with severe asthma and co-morbid moderate-to-severe atopic dermatitis, a starting dose of 600 mg followed by 300 mg every other week can be administered. Dupilumab is intended for long-term treatment. Treatment should be reviewed by the specialist at least annually.

2.3 For full details of dosage schedules, see the summary of product characteristics.

Price

2.4 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 January 2020).

2.5 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 4) considered evidence from several sources. 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. 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:

- 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.
- The company's decision problem (base case) was in a subpopulation of people based on a posthoc analysis of the QUEST data (that is, a blood eosinophil count of 150 cells per microlitre or more, FeNO of 25 parts per billion or more, 3 or more exacerbations in the previous year and no maintenance oral corticosteroids). The company considered that this represented people with more severe asthma, who

it considers will get the most benefit from dupilumab.

The committee agreed that it was challenging to define the populations because they overlapped. It acknowledged that a mixed population on and off oral corticosteroids is not suitable for decision making. The clinical expert explained that maintenance treatment with oral corticosteroids is declining in clinical practice because it has been displaced by the increased use of biologicals. Therefore, there is uncertainty about the proportion of people having oral corticosteroids in clinical practice. This had an effect on the cost effectiveness of dupilumab in the mixed population. Also, the company's decision-problem population included both people who were and were not eligible for biologicals, for which the comparators would differ. The committee concluded that, if standard care is the comparator chosen, the population not eligible for biologicals would be the most suitable for decision making.

Comparators

Benralizumab, mepolizumab and reslizumab are appropriate comparators for dupilumab

3.6 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
  - a blood eosinophil count of between 150 and 399 cells per microlitre and 3 or more exacerbations
  - a blood eosinophil count of less than 150 cells per microlitre and FeNO of 25 parts per billion or more.

  The committee highlighted that omalizumab was not considered to be a relevant comparator. This was because dupilumab does not have a specific indication for IgE-mediated asthma and IgE has not been shown to be a predictor of response to dupilumab. It concluded that benralizumab, mepolizumab,reslizumab and standard of care were appropriate comparators for dupilumab.

Clinical evidence

The evidence on clinical effectiveness is relevant to NHS clinical practice

3.7 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 and is a relatively safe treatment

3.8 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.

Dupilumab is clinically effective as an addition to standard care in the post hoc subpopulation

3.9 The company's decision-problem subgroup analyses 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.

The clinical-effectiveness estimates for dupilumab are uncertain in the subgroup of people who are not currently eligible for biologicals

3.10 The results for the clinical effectiveness of dupilumab in people who would not currently be eligible for a biological were only available from QUEST for the annualised rate of severe exacerbations, and in a very small population (29 people randomised to 200 mg dupilumab). Dupilumab reduced the rate of severe exacerbation compared with placebo. The committee concluded that these results were uncertain.

The clinical effectiveness of dupilumab compared with reslizumab, benralizumab and mepolizumab is uncertain

3.11 There are no head-to-head data comparing dupilumab with current biologicals. The company provided 2 methods to compare them indirectly: the Bucher indirect treatment comparison for the company's base case and in a scenario analysis, and the matched adjusted indirect treatment comparison. Both these methods matched people in the dupilumab trials to those in the comparator trials. The committee noted the evidence review group's (ERG's) view that the results of these analyses needed to be interpreted with caution because they were exploratory analyses.

Nevertheless, the ERG considered them to be the best available options to compare dupilumab with other biologicals. The Bucher indirect treatment comparison suggested that treatment with dupilumab 200 mg leads to a lower rate of severe exacerbations than mepolizumab, benralizumab and reslizumab. It was also conducted for other outcomes, none of which showed meaningful results. The committee highlighted that there are no data on the efficacy of dupilumab in people in whom interleukin-5 inhibitor biologicals have failed to control their asthma. The committee therefore concluded that there was still uncertainty about the clinical effectiveness of dupilumab compared with mepolizumab, benralizumab and reslizumab because the results of the indirect comparisons were not robust.

The company's economic model

The model structure is appropriate for decision making

3.12 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

Estimates of severe asthma exacerbation rates in the placebo arm of QUEST do not reflect clinical practice in the NHS

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 estimated exacerbation rates from QUEST and VENTURE in the first year in its base case. However, it increased the number of severe exacerbations in subsequent years for both dupilumab and standard care by applying a multiplier, which the company considered confidential. The company considered that this was appropriate because it had excluded people with a recent severe exacerbation from the QUEST trial. The ERG's base case did not include an exacerbation multiplier and resulted in higher incremental cost effectiveness ratios (ICERs). The committee considered that the best measure of a difference was that seen between arms the trial. It concluded that the it was not appropriate to inflate the rates of exacerbation.

The use of an exacerbation multiplier is not the best method of adjusting severe asthma exacerbation rates

3.14 During consultation on the technical report, the ERG and clinical experts stated that an exacerbation multiplier would not necessarily give a more clinically plausible exacerbation rate for standard care. Another method of assessing the effectiveness of dupilumab could have been to use registry data for the baseline risk of exacerbations. Then, the efficacy of dupilumab could have been applied to this baseline risk. However, the registry data from the O'Neill et al. study (2015) is several years out of date. The committee would have preferred to have seen the effect of other means of adjusting for severe exacerbations, such as:

- the observed exacerbation rates from more up-to-date registry data for standard care
- the treatment effect of dupilumab from QUEST and VENTURE (or more up-to-date registry data) on the cost effectiveness of dupilumab compared with standard care.

The committee concluded that the exacerbation multiplier might not have been the best method of adjusting for the rate of severe exacerbations in standard care.

It is unclear what the best source of data is to inform the setting of treating exacerbations

3.15 The company assigned different mortality rates to severe exacerbations treated in hospital emergency care, inpatients and general practice. It based the resource use associated with severe exacerbations in its original base case on UK Difficult Asthma Registry registry data (O'Neill 2015). This assumed that 26.5% of severe exacerbations were treated in hospital (7.8% in emergency care, 18.7% in inpatients) and 74.0% in general practice. However, this was higher than the 6.7% of severe exacerbations treated in hospital in the QUEST trial (3.0% in emergency care, 3.7% in inpatients) and 93.3% in general practice. The ERG base-case model used the QUEST data for the setting of severe exacerbations. During consultation on the technical report, the ERG and clinical expert stated that the clinical trials were a more reliable source of these data. 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. This was because patients in trials are well monitored on optimised treatment, are more motivated and have better adherence to treatment. The committee concluded that it would have preferred to have seen exploration of different sources of data, for the setting of treating exacerbations, to inform the model.

Additional analyses should include 10-year mortality rates for dupilumab and standard care, and show the flow of patients though different health states

3.16 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 concluded that the model did not offer plausible estimates, and that any additional analyses presented by the company should include 10-year mortality rates for dupilumab and standard care. It also concluded that the analyses should show the flow of patients though different health states in the model for the purposes of model validation.

The population including people with an unmet need who are not eligible for biologicals is the most relevant for decision making

3.17 The population the company proposed for consideration by the committee was broad, including people who had:

- 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 and
- not been taking maintenance oral corticosteroids.

The company also provided exploratory analyses on the cost-effectiveness of dupilumab in the following 3 populations:

- A mixed population that contained 30% of people having maintenance oral corticosteroids (with a blood eosinophil count of 150 cells per microlitre or more or FeNO of 25 parts per billion or more, and 3 or more exacerbations)

- A population not eligible for biologicals in whom standard care was the only relevant comparator. This included 3 groups
  - people not eligible for mepolizumab or benralizumab (with a blood eosinophil count of 150 to 299 cells per microlitre and 3 exacerbations)
  - people not eligible for reslizumab or benralizumab (with a blood eosinophil count of 150 to 399 cells per microlitre and 4 exacerbations or more)
  - people who only had raised FeNO (with a blood eosinophil count of less than 150 cells per microlitre and FeNO 25 parts per billion or more).
- A population eligible for biologicals (either mepolizumab or benralizumab eligible: with a blood eosinophil count of 300 cells per microlitre or more and 4 or more exacerbations; or reslizumab or benralizumab eligible: with a blood eosinophil count of 400 cells per microlitre or more and 3 or more exacerbations).

The broad population proposed by the company (with a blood eosinophil count of 150 cells per microlitre or more or FeNO of 25 parts per billion, and 3 or more exacerbations in the previous year not on maintenance oral corticosteroids) was not considered by the committee to be relevant for decision making. This was because it combined both people eligible and not eligible for biologicals (mepolizumab, reslizumab or benralizumab; see section 3.5) The mixed population was also not considered to be relevant because of the declining use of maintenance oral corticosteroids in clinical practice with the rising use of NICE recommended biologicals (see section 3.5). The committee concluded that, if standard care is the comparator chosen, the population not eligible for biologicals would be the most suitable for decision making. The company provided evidence of dupilumab's clinical effectiveness in this population. The committee noted the unmet need in these patients, but highlighted that the evidence was based on

small patient numbers (see section 3.10). It also considered the evidence for the exploratory biological-eligible population, but noted that this subgroup was not part of the company's proposition.

The company's base-case economic analysis

The company's base-case ICER is £34,216 per QALY gained for dupilumab compared with standard care in the proposed population

3.18 The company's base-case deterministic ICER for dupilumab compared with standard care is £34,216 per quality-adjusted life year (QALY) gained in the broad population (that is, people with a blood eosinophil count of at least 150 cells per microlitre or FeNO of 25 parts per billion or more, 3 or more exacerbations in the previous year and not taking maintenance oral corticosteroids). This included the confidential discount for dupilumab. The ERG's base-case ICER (which did not include an exacerbation multiplier and used the QUEST trial data for the setting of treating exacerbations) was £55,348 per QALY gained. The committee concluded that this combined population, which included people who were and were not eligible for other biological treatments was not relevant for decision making. It also concluded that dupilumab is not cost effective in company's broad population.

Dupilumab cannot be recommended for treating severe asthma with type 2 inflammation

3.19 The committee considered the most relevant population for decision making to be people not eligible for other biologicals (because their eosinophil or exacerbation levels in the previous year were too low), and that this is where there is a significant unmet need. The company's combined ICER for people not eligible for reslizumab (that is, with a blood eosinophil count of 150 to 399 cells per microlitre, FeNO of 25 parts per billion and 3 or more exacerbations) and those not eligible for mepolizumab (that is, with a blood eosinophil count of 150 to 299 cells per microlitre, FeNO of 25 parts per billion or more, and 4 or more

exacerbations), which included the confidential discount for dupilumab, was £50,558 per QALY gained. The ERG's ICER for the same population was £81,676 per QALY gained). 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

The ICERs for dupilumab compared with each biological greatly exceeded what is normally considered to be a cost-effective use of NHS resources

3.20 The cost-effectiveness estimates for the exploratory analyses of dupilumab compared with biologicals in the biological-eligible populations included the confidential discount for dupilumab and comparator biologicals so are confidential and cannot be reported. However, the ICERs for dupilumab compared with each biological greatly exceeded what is normally considered to be a cost-effective use of resources in the NHS. Furthermore, the company had not proposed comparing dupilumab with biologicals in its decision problem. There was also considerable uncertainty in the ICERs for the population eligible for biologicals. This was because the efficacy data came from an indirect treatment comparison that was based on small patient numbers. The committee concluded that dupilumab does not represent a cost-effective use of resources when compared with other biologicals.

Alternative modelling methods may more accurately estimate the cost effectiveness of dupilumab

3.21 There may have been more appropriate ways to model the exacerbations rate in the placebo arm, so that it better reflected the exacerbation rate with standard care in clinical practice. The committee would have liked to have seen alternative modelling methods for adjusting the severe exacerbation rate in the placebo arm (see section 3.13). Also, it would like to have seen the effect of alternative modelling of exacerbations, and of using QUEST or updated registry data, on the ICER in people not eligible for biologicals at different exacerbation thresholds. For example:

- people with a blood eosinophil count of 150 cells per microlitre or more, or FeNO of 25 parts per billion or more and 3 exacerbations
- people with a blood eosinophil count of 150 cells per microlitre or more, or FeNO of 25 parts per billion or more, and 4 or more exacerbations.

The committee also thought that any further analysis should be accompanied by:

- data on the 10-year modelled mortality in the dupilumab and standard care arm
- an evaluation of whether the output is consistent with the current UK asthma mortality rate.

The committee was also interested in the results for people who had raised eosinophils or FeNO, and those in whom both were raised. It concluded that any further analysis should use alternative methods of modelling exacerbations in standard care and explore different exacerbation thresholds.

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

3.22 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

3.23 Dupilumab is licensed in people aged 12 years and over. The clinical trials included a small number of people aged under 18 years (n=52, QUEST; n=3, VENTURE), and the company did not provide a subgroup analysis

for this age group. There is an unmet need in this population with uncontrolled severe asthma with type 2 inflammation. Current NICE recommended biologicals are licensed for eosinophilic asthma only, so would not routinely be used for asthma with type 2 inflammation (if defined by blood eosinophil counts). 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

3.24 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 and people eligible for biologicals were high. The committee identified several uncertainties in the modelling assumptions, particularly about severe exacerbation rates and the source of data to inform the setting for treating exacerbations. 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
March 2020

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.

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.

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
Technical lead

Eleanor Donegan

Technical adviser

Joanne Ekeledo

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 Tuesday 31 March 2020 **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):	[**Sanofi**]
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:	[**Eleanor Saunders**]

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Unmet need Section 3.1 of the ACD states "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" that "dupilumab as add-on treatment is an option for managing uncontrolled severe asthma with type 2 inflammation" (section 3.4) and that "the most relevant population for decision making to be people not eligible for other biologicals (because their eosinophil or exacerbation levels in the previous year were too low), and that this is where there is a significant unmet need" (section 3.19). The committee also heard from the clinical expert that "raised blood eosinophils and FeNO are risk predictors for future exacerbations" and that raised FeNO "is more specific to type 2 inflammation" (sections 3.2 and 3.3, respectively). Sanofi advocates for treatments in patients with the greatest unmet need, including the adolescent population and has adopted the Committee's conclusions in the it's updated assumptions. The company presents an updated response for: **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**
2	Comparators Section 1 of the ACD states: "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" and that "if standard care is the comparator chosen, the population not eligible for biologicals would be the most suitable for decision making" (section 3.5). In the updated company base case, it is proposed dupilumab will be used for people with severe asthma for whom standard care, defined as high dose ICS plus at least one additional controller is the only treatment option or who have previously tried other biologics.
4	Efficacy and safety of dupilumab Section 3.9 of the ACD states: "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" The company supports the committee's conclusion and refer to comment 1 above. The company has updated the base case to patients with the highest unmet need, for patients with aged 12 and over who have both EOS and FeNO biomarkers.
5	Indirect Treatment Comparison (ITC) Section 3.11 of the ACD states "The committee noted the evidence review group's (ERG's) view that the results of these [ITC] analyses needed to be interpreted with caution because they were exploratory analyses" and "the results of the indirect treatment comparison were not robust." The indirect treatment comparisons were conducted to the highest standard, based on methodological advice received from an independent academic expert and limited only by the comparator evidence available. The cost-effectiveness analyses comparing dupilumab with existing biologicals in the company's original submission were considered "exploratory" because of the uncertainty inherent to analyses from ITC and confidential comparator prices. The company highlights the ERG conclusions that "ERG considered [the ITC and MAIC] to be the best available options to compare dupilumab with other biologicals."

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6	Post-trial exacerbation rates The ACD highlights two key issues regarding exacerbation rates of concern for the committee: • *Estimates of severe asthma exacerbation rates in the placebo arm of QUEST do not reflect clinical practice in the NHS* • *The use of an exacerbation multiplier is not the best method of adjusting severe asthma exacerbation rates* The company considers the original methods an appropriate methodology as it utilises data from the QUEST clinical trial and an adjustment previously accepted by the committee (appraisal TA431). However, the company understands the committee's preference for data from the NHS to inform the economic model. Sanofi contacted severe asthma clinicians at the Wessex Asthma Cohort of Difficult Asthma (WATCH) (1) and the Unbiased BIOmarkers in PREDiction of respiratory disease outcomes (U-BIOPRED) (2) who were able to provide data on severe exacerbation rates. Additionally, Sanofi is currently conducting a case notes review at severe asthma centres in England and Scotland, and was able to utilise data already collected. Additional methods and date are presented in the Technical Appendix. The company updated base case uses the weighted average of severe exacerbation rates collected over 24 months' as part of the severe asthma case notes review (4.50).
7	Sources of treatment of exacerbation setting The committee concluded *it is unclear what the best source of data is to inform the setting of treating exacerbations* and *that it would have preferred to have seen exploration of different sources of data* (ACD (3) p. 15). During subsequent communications, the NICE technical team suggested use of real world UK data, if available. The company has explored two additional sources of exacerbation settings which were available: Sanofi real-world study in the UK and data from VENTURE clinical trial. As shown in the table below, VENTURE, TA431 and the UK real-world study show broadly similar data on the setting of severe exacerbations which provide reliability of the data. Sanofi considers utilising data from UK sources to be more reflective of UK clinical practice and therefore more appropriate for decision-making. Therefore, the Sanofi RWE study data was used in the updated company base case. Additional scenarios are run using the alternative sources.

Severe Exacerbation Setting	QUEST (4)	VENTURE (5)	UK Sanofi RWE	TA 431 (6)	O'Neill 2015 (7)
OCS burst, Physician Visit	93.34%	85.32%	83.33%	83.07%	73.57%
A&E admission	3.00%	6.42%	5.21%	8.69%	7.79%
Hospitalization	3.66%	8.26%	11.46%	8.24%	18.64%

8	Mortality The ACD states that *Additional analyses should include 10-year mortality rates for dupilumab and standard care and show the flow of patients though different health states (ACD p. 16).* 10-year mortality are presented alongside additional analyses in the technical appendix. The company wants to highlight that asthma-related mortality has been the subject of a lot of discussion

Dupilumab for treating Severe asthma [ID1213]

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	for 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 three technology appraisals in biologic therapy in severe asthma in recent years, the company is using evidence from these as a precedent for asthma-related mortality data from the benralizumab appraisal (TA565) (8) which was determined by the ERG and accepted by the same committee B.

Insert extra rows as needed

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References

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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**
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 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	As raised in the committee meeting, it is not just long-term *continuous* oral steroid use (equivalent of 5mg per day for six months) that leads to other debilitating conditions such as diabetes and osteoporosis. It has been shown that *four or more* courses in a year is associated with significantly greater odds of a person developing osteoporosis, hypertension, obesity, type 2 diabetes, gastrointestinal ulcers/bleeds, fractures, and cataracts. In fact, one study has shown that cumulative exposures, equivalent to just four courses of oral steroids over a lifetime, are associated with adverse outcomes. Therefore, the side effects of courses of steroids over someone's lifetime need to be adequately represented within the model.
3	The committee has recommended that the most relevant population for decision making is people not eligible for other biologics. We agree that this is where there is a significant unmet need as highlighted earlier. However, we know that not everyone will respond to current biologics, but they may well respond to Dupilumab as it targets a different mechanistic pathway. Dupilumab should therefore be available to the currently eligible population too. Other factors that make Dupilumab more suitable than other biologics need to be addressed and considered (for example, atopic dermatitis or nasal polyps).
4	Using exacerbation estimates from the trial data is likely to underestimate the hospitalisation rates that would occur in a real-world setting. We therefore agree that registry data or other real-world evidence should be used to inform the model.
5	
6	

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Example 1	We are concerned that this recommendation may imply that ……..
1	My main area of concern is that you appear to understand there is a severe unmet need for further treatments but focus on patients not currently eligible for biologics. As explained at the meeting, I have qualified for numerous biologics and tried Omalizumab (for 12months) and Mepolizumab (for 18 months) but neither helped to stabilise my asthma. My entire life was on hold as I was unwell and lived with daily attacks. Fortunately, I have been able to access Dupilumab through the compassionate use scheme and as explained at the TAC meeting, this has changed my life. Therefore, despite being eligible for other biologics, Dupilumab is the only one that has proven effective for me. Dupilumab successfully reduced my FENO measurements and gave me my life back. I feel if the committee only focus on considering Dupilumab for those that are not suitable for biologics then many people like myself would continue to face an uncertain future with the reality of long-term steroid use and potentially fatal asthma attacks. I understand I am very fortunate to have received the benefits of accessing Dupilumab but I am incredibly upset (knowing how awful my life was with uncontrolled severe asthma) that others may not get this benefit. No other asthma treatment has given me the improvement in asthma control that Dupilumab has and I've been an asthmatic for over 32 years and trialled many many different medications. Living my life with severe asthma (pre-Dupilumab) meant I relied on nebulisers and steroids (as well as other biologics) to try and get through each day. Unfortunately, I still had no stability with my asthma and I was scared I would have to give up work in the near future, never be healthy enough to have and care for a family and that the long-term impact of taking steroids (diabetes, continued weight gain and osteoporosis) would make my life even harder. I agree with the committee that there is an unmet need for treatments for asthmatics not eligible for biologics. However, in the committee meeting on 11th February 2020, I outlined my experiences with Dupilumab from a patient perspective following repeated unsuccessful biologic treatments (Omalizumab and Mepolizumab). I therefore do not feel the committee have assigned any weight to the evidence I presented in the meeting and the draft guidance does not reflect the need for patients who have High FENO and eosinophil readings who are not currently controlled by other biologics. There are substantial benefits for patients like me where other biologics have failed.
2	
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than 1 set of comments from each organisation.

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

Name	[redacted]
Role	
Other role	
Organisation	No
Location	
Conflict	
Notes	

Comments on the ACD:

The NICE appraisal on Dupilumab for treating severe asthma was welcomed by all who treat difficult/severe asthma in the NHS since it offered another potential treatment for a very diverse and heterogeneous disease state. As usual very rigorous cost-effectiveness models and scientific scrutiny have been applied in issuing the ultimate advice not to recommend this therapy for NHS usage. From a practicing clinician's perspective though the resulting draft recommendation is disappointing and removes a potentially valuable treatment option for our patients who may have limited alternatives to improve control of their difficult/ severe asthma. This point is emphasised by the NICE recommendations themselves which acknowledge that "dupilumab is effective for preventing exacerbations in people with severe asthma with type 2 inflammation compared with standard care". It is good to see that the NICE appraisal committee acknowledge the existence, nature and burden of severe asthma with type 2 inflammation. A key difficulty with their approach, though, comes in the context of assuming that the best indication for Dupilumab lies with those patients not suitable for the body of anti-IL5 biologics given the lack of comparative data between the different biologics. That isolated group of patients is potentially small. A key assumption being made in adopting that view is that being suitable for an anti-IL5 biologic implies that the patient will then both tolerate and respond well to that type of drug. This is clearly not the case as demonstrated in the published literature where some clinic series have reported 25% to 40% suboptimal responses to biologics like Mepolizumab. Our own clinic population at Southampton has a 30% non-responder rate to Mepolizumab for example. Furthermore, there are no clearly defined predictors of which biologic drug will give the best outcome for any individual patient where their disease characteristics meet criteria for more than 1 drug. In the absence of guiding biomarkers it is becoming increasingly apparent that some patients may end up cycling through sequential biologic drugs in the search for one that delivers optimal asthma control and better healthcare outcomes. The resulting delays to achieving good asthma control are neither good for the patient nor in health-economic terms due to ongoing added demand on healthcare resources from sustained poor control. Closing the door on another treatment option in that scenario seems clinically unwise and mistaken. For instance what next for the patient who has sequentially not responded to Mepolizumab or to Benralizumab but who has chronic eczema and chronic rhinosinusitis with recurrent nasal polyps? The present NICE recommendation would consign such a patient to long-term oral corticosteroids. It is worth recognising that Reslizumab is little used in UK clinical practice due to the need for intravenous administration and inability to administer via "Homecare" and therefore unlikely to be used in such a patient. However, in clinical terms it is not hard to suspect that Dupilumab would be a realistic option to improve their disease control/ outcomes where other drugs have failed. At Southampton in our tertiary severe/ difficult asthma service we already have several patients in that category who continue to take high amounts of oral steroids

and/or be admitted to hospital despite an anti-IL5 biologic. Should such situations not be recognised in determining the approval or not of this drug? An additional point is that we have 8 patients on Dupilumab in our difficult/ severe asthma clinic as they have comorbid severe eczema. In all 8 cases the patients have shown very significant improvements in asthma control. Therefore we can see that this is a clinically effective drug when used in the correct patients.
Ultimately difficult/ severe asthma is a very heterogeneous state and patient responsiveness to biologic drugs is likely to show individual variability as a reflection of the individuality of their disease states. Therefore carefully managed access to a diverse range of biologic agents that provide coverage for that diversity of disease states should be what NICE strives for in difficult/ severe asthma. Withholding NHS access to Dupilumab would be a retrograde step by NICE that is highly likely to add to the adverse health economic impact of severe asthma in the UK. It would be a bad mistake. It is not unreasonable that the company provide additional modelling data as recommended by NICE to demonstrate it's utility alongside existing treatment options. That may facilitate a re-evaluation of the best way in which to position Dupilumab for NHS usage. One point to consider, is that the proportion of patients who would suit Dupilumab in isolation and not also qualify for either anti-IL5 and/ or anti-IgE therapy is likely to be relatively low. However "overlap" patients who suit a range of biologic agents may not respond to anti-IL5 or anti-IgE therapy. If cost-effectiveness continues to be questioned on further data modelling, that observation naturally leads to the point whether positioning of Dupilumab as a potential 2nd line biologic agent for patients with evidence of type 2 inflammation who have failed to respond to an anti-IL5 agent and/ or anti-IgE should be an available treatment option. I would urge NICE to consider such options and not deny access to a very effective and safe therapeutic option for patients with difficult/severe asthma. Rather we should be seeking ways in which to carefully position it's use most effectively within NHS practice.

Dupilumab for treating severe asthma

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

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(Includes confidential commercial information)

Produced by	**Southampton Health Technology Assessments Centre**
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Date completed	19/05/2020

1 Introduction

This document is the Evidence Review Group's (ERG's) critique of the response made by the company (Sanofi) to the Appraisal Consultation Document (ACD) issued by NICE to consultees and commentators on 2nd March 2020. The company's response comprised seven comments on the content of the ACD (these are numbered 1, 2 and 5-8, there is no comment 3), a technical appendix (this describes the company's updated base case and scenario analyses) and an updated version of their economic model.

In this critique, we take the key issues raised by the NICE appraisal committee at their meeting on 11th February 2020, as described in the ACD, and we comment on the company's response to these. The key issues raised in the ACD are briefly summarised in Table 1.

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

Topic	Summary of issues raised	ACD section(s)
Population	A mixed population of those eligible for biologicals (mepolizumab, reslizumab or benralizumab) and those not eligible for biologicals who can only be offered standard care is not suitable for considering the cost effectiveness of dupilumab compared with standard care.	1, 3.5,
	A mixed population on and off oral corticosteroids is not suitable for decision making.	3.5
	If standard care is the comparator chosen, the population not eligible for biologicals would be the most suitable for decision making.	3.5, 3.17, 3.19
	Clinical effectiveness estimates for dupilumab are uncertain in the subgroup of people who are not currently eligible for biologicals. Results in this subgroup for the annualised rate of severe exacerbations are only available from QUEST[1] in a very small population (29 people randomised to 200mg dupilumab).	3.10
	There are no data on the efficacy of dupilumab in people in whom interleukin-5 inhibitor biologicals have failed to control their asthma.	3.11

	There are limited data available on dupilumab for young people.	3.23
Severe exacerbation rates	The committee would have liked to have seen: • alternative modelling methods for adjusting the severe exacerbation rate in the placebo arm • the effect of alternative modelling of exacerbations, and of using QUEST[1] or updated registry data, on the ICER in people not eligible for biologicals at different exacerbation thresholds.	3.13, 3.14, 3.21
Treatment setting for severe exacerbations	An exploration of different sources of data for the setting of treating exacerbations	3.15
Mortality rates	The committee thought any further analysis should be accompanied by: • data on the 10-year modelled mortality in the dupilumab and standard care arm • an evaluation of whether the output is consistent with the current UK asthma mortality rate.	3.16, 3.21

The company has conducted cost-effectiveness analyses to address key points raised in the ACD. The additional cost effectiveness analyses are presented in the company's technical appendix. We successfully replicated all of the company's analyses, with the exception of the analysis for adolescent population, see section 6.1 below.

2 Population

In Comment 1 of Sanofi's response to the NICE ACD they define an updated population group for their cost-effectiveness analysis:

> **"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".**

The comparator for the updated population group (Sanofi response document, comment 2) is standard care, defined as high dose ICS plus at least one additional controller.

The company interprets the groups covered by their new population in section 3.1.1 of their technical appendix. These three subgroups are:

Those ineligible for the biologics mepolizumab, reslizumab and benralizumab

A. Adults with blood eosinophil count (EOS) 150-299 cells/μl, fraction of exhaled nitric oxide (FeNO) ≥ 25 and ≥4 asthma exacerbations in the previous 12 months. This group are not eligible under NICE guidance to receive the biologics.
B. Those aged 12-17 years, with EOS ≥150, FeNO ≥ 25 and ≥4 asthma exacerbations. NICE guidance for the biologics is for adults only.

Those who have previously had biologic therapy

C. Adults with EOS ≥ 300, FeNO ≥ 25 and ≥ 4 asthma exacerbations who have previously had treatment with the existing biologics but did not respond to this treatment.

In practice, the only model parameters that differ for these three subgroups are case fatality rates for severe asthma exacerbations and general population utility and mortality, which are adjusted for age and so differ for the adolescent subgroup. The background risks and treatment effects that drive the model are the same for all three subgroups, estimated from QUEST trial data for people with EOS ≥ 150 and FeNO ≥ 25 and 4 or more severe asthma exacerbations in the previous year.

Effectiveness data from the VENTURE trial[2] are not used, so the updated base case and scenarios are only based on patients not prescribed maintenance oral corticosteroids at baseline. The revised model does still include the option to select a mOCS population driven by VENTURE data, although this option is hidden and it is not possible to apply the updated target population criteria (EOS≥150 and FeNo≥25 and 4 or more prior exacerbations) to the mOCS population.

The company provide limited information about how many participants in the QUEST trial match the characteristics of the updated population group (Table 2). The company do not state how many adults in QUEST had EOS 150-299 cells/µl, FeNO ≥ 25 and ≥4 exacerbations (subgroup A). However, we know that for the company's previous decision problem population (EOS ≥150 OR FeNO ≥25 AND ≥3 exacerbations) there were 64 matching QUEST participants in the dupilumab arm and 37 in the placebo arm. The numbers of adults with EOS 150-299 cells/µl, FeNO ≥ 25 and ≥4 exacerbations in the dupilumab and placebo arms of QUEST is likely to be fewer than this because it is a more restricted group. There were only two adolescents with EOS ≥150 cells/µl, FeNO ≥ 25 and ≥4 exacerbations and both were in the placebo arm (subgroup B). There were no participants who had previously received mepolizumab, reslizumab or benralizumab (subgroup C) included in QUEST because trials of these anti-IL5 biologics were ongoing at the time of the QUEST trial and because the QUEST protocol excluded patients who had been on a biologic within 6 months of Visit 1.

Table 2 QUEST trial participants matching the characteristics of the updated population group

Subgroups of the company's updated population group	QUEST RCT	
	DUP n=631	PBO=317
A) Adults, EOS 150-299 cells/µl, FeNO ≥ 25 and ≥4 exacerbations	Not stated	Not stated
B) Adolescents 12-17 yrs, EOS ≥150 cells/µl, FeNO ≥ 25 and ≥4 exacerbations	0/[redacted]	2/[redacted]
C) Adults EOS ≥ 300 cells/µl, FeNO ≥ 25 and ≥ 4 exacerbations who have not responded to biological therapy	0/0	0/0

Source: Company technical appendix to ACD response and QUEST CSR.
DUP – dupilumab; PBO - placebo

The company's technical appendix does not present efficacy results for subgroup A, the adult participants in the QUEST trial with EOS 150-299 cells/µl, FeNO ≥ 25 and ≥4 exacerbations. The technical appendix does report the relative risk of annualised severe exacerbations for the adolescent subgroup of the QUEST RCT in comparison to that for adults (Table 3). We have also included in Table 3 the relative risk of annualised severe exacerbations for the ITT population of the QUEST trial. The relative risks are similar, albeit the confidence intervals are wider and cross one for the subgroup of adolescents (which has a small sample size). As noted above, QUEST did not include participants for whom prior

IL-5 biologic therapy had failed (subgroup C), and hence no data are available for this subgroup.

Table 3 Comparison of relative risk in annualised rate of severe exacerbations in the QUEST ITT population and in subgroups defined by age

Outcome: annualised rate of severe exacerbations	**QUEST relevant arms ITT population**	
Trial arms	Dupilumab 200 mg Q2W	Placebo
n	N=631	N=317
Relative risk versus placebo (95% CI); p-value	0.523 (0.413, 0.662); p<0.0001	
	QUEST Subgroup analysis by age	
Subgroup by age	<18 years	≥18 years
n	[redacted]	[redacted]
Relative risk versus placebo (95% CI)	0.536 (CI 0.238; 1.208)	0.517 (CI 0.405; 0.659)
p-value	p=0.7141	

Source: ERG report Table 31, Company technical appendix to ACD response (section 3.1.2) and QUEST CSR

ERG conclusion

The company's updated base case analysis targets a more restricted population than their original base case: the updated base case requires both EOS ≥150 and FeNo≥25, as well as at least 4 severe exacerbations in the previous year. The risk of asthma exacerbations is higher in the updated population, which reduces estimated ICERs for dupilumab compared with standard care.

It is not clear whether the population in the updated base case meets the committee's definition of the 'most relevant' population for decision making: 'people not eligible for other biologicals (because their eosinophil or exacerbation levels in the previous year were too low)' (ACD 3.19). The company does not present separate cost-effectiveness results for this subgroup (with EOS 150-299) in their target population and the model does not allow us to generate these results either.

The company argues that their base case covers two other subgroups in addition to those ineligible for other biologicals due to eosinophil levels (Sanofi Technical

Appendix 3.1.1). Firstly, adolescents (age 12-17), who are not currently eligible for biological treatments. QUEST data for this subgroup is sparse but does suggest a similar treatment effect for adolescents and people aged 18 and over. Separate cost-effectiveness estimates are presented for this population, but these are driven by mortality estimates in the adolescent population (Sanofi Technical appendix, sections 3.1.2 and 4.1.2).

Secondly, the company argues that their analysis includes people who have not responded to treatment with another biologic. However, we note that the QUEST data on which the updated analysis is based does not include any patients previously treated with another biologic. The company therefore implicitly assumes that outcomes for biologic non-responders are the same as for the biologic-eligible subgroup in the dataset. It is uncertain whether this assumption is correct.

The company does not present updated results for patients treated with maintenance oral corticosteroids (mOCS). Although the model does still include a mOCS population driven by VENTURE data, it is not possible to apply the updated target population criteria (EOS≥150 and FeNo≥25 and 4 or more prior exacerbations) to this population. Cost-effectiveness for the updated population who are also treated with mOCS is therefore uncertain.

3 Post-trial exacerbation rates

Issue 6 in the Sanofi ACD response relates to concerns raised by the committee that the severe exacerbation rates observed in the QUEST trial do not reflect clinical practice in the NHS and that the method of adjustment used in the model to adjust for this after the trial period (the exacerbation multiplier) is not the best approach.

3.1 Real world exacerbation rates

The Committee concluded that they would have preferred to see observed exacerbation rates from more up-to-date registry data for standard care (ACD 3.14). They also noted that the mean number of severe exacerbations in the placebo arm of the QUEST trial in the year after randomisation (2.39) was lower than in the year before (4.46), and that this was "possibly because of regression to the mean and the placebo effect" (ACD 3.9). Which of these possible explanations is correct – or the degree to which they each apply – matters, because it affects whether the improvement would be observed outside of the trial

environment. ‘Regression to the mean’ occurs when there is natural variation in a phenomenon over time, so that when an unusually high rate is observed in one time period it is likely that a lower rate will be observed in the next time period. Thus, when patients with 4 or more severe asthma exacerbations in a year are selected, one would expect to observe fewer exacerbations in the following year. This would apply in real world clinical practice if there is random variation in the incidence of severe exacerbations. However, if the improvement in the placebo arm was due to a ‘placebo effect’, this would not be observed in routine practice. Another possible reason for the improvement might be better monitoring and treatment in the trial context, which might not occur in routine practice, although it is also possible that in real world practice, clinicians do step up monitoring and treatment after patients have a period of poor asthma control.

The updated model includes data from three severe asthma cohorts, designed to reflect real world absolute exacerbation rates and to assess whether the improvement in the average exacerbation rate seen in the QUEST placebo arm would occur in routine practice:

- Sanofi Real Word Evidence (RWE) case note review
- Wessex Asthma Cohort of Difficult Asthma (WATCH); and
- Unbiased BIOmarkers in the PREDiction of respiratory outcomes (U-BIOPRED).

These studies are discussed in section 3.2 of the Sanofi Technical Appendix. We summarise the main features of these cohorts in Table 4.

Table 4 Key features of the UK Sanofi RWE, WATCH and U-BIOPRED cohorts

	UK Sanofi RWE[3]	WATCH[4]	U-BIOPRED[5]
Patients location	Severe asthma centres in England and Scotland	UHSFT Difficult Asthma service	11 European countries[a]
Study type	Case note review	Ongoing prospective cohort study	Cross sectional with longitudinal element[b]
Key inclusion criteria	Patients with severe asthma ≥ 14 years and a minimum of 24 months' data. Sites identify patients starting with the last eligible patient and then work backwards consecutively until the site's specific patient target is met	Attend the Adult or Transitional Regional Asthma Clinic at UHSFT or satellite clinics on the Isle of Wight. Managed with "high dose therapies" and/or "continuous or frequent use of oral steroids", according to the BTS Adult Asthma Management Guidelines 2016	Patients with severe asthma[c]
Number enrolled	Interim sample size 81 (from a planned estimated total of 150)	375 patients at the end of 2017	Severe non-smoking asthma n=311 Smokers and ex-smokers severe asthma n=110
Definition of a severe asthma exacerbation	The same as in the QUEST protocol	Not stated	Require high dose OCS or doubling of maintenance dose for ≥3 days or hospitalisation
Meet criteria for new Sanofi population?	n=20 with EOS ≥150 cells/µl and ≥4 exacerbations, FeNO not stated.	n=17 with EOS≥150 and ≥4 exacerbations. FeNO≥50 is higher than target population (FeNo≥25)	n=28 with EOS≥150 and FeNO≥25 and ≥4 exacerbations

FEV1 - forced expiratory volume in 1 s, UHSFT - University Hospital Southampton Foundation Trust
[a] Countries and centres (n=16) not reported.
[b] The full study includes adults with severe asthma, mild/moderate asthma & healthy controls (n=610)
[c] Severe asthma defined as either: airflow reversibility (increase in FEV1 >12% predicted or 200 mL following inhalation of 400 µg salbutamol), airway hyperresponsiveness (methacholine provocative concentration causing a 20% fall in FEV1 <8 mg·mL−1 , or diurnal peak expiratory flow amplitude >8% of mean), or a decrease in FEV1 of 12% predicted or 200 mL within 4 weeks after tapering maintenance treatment

The results of the three cohorts are shown in Table 11 of the Sanofi Technical Appendix, reproduced in Table 5 below for convenience. We note the small sample sizes for the population of interest in all three studies. Variations in the number of exacerbation rates within these samples are not reported, so we cannot assess the robustness of these estimates. There are also large differences between the studies in the reported exacerbation rates. It is therefore difficult to draw any conclusions about the absolute severe exacerbation rate for the population of interest based on these studies.

Table 5 Severe exacerbation rates in the NHS

	UK Sanofi RWE	WATCH[4]	U-BIOPRED[5]
Population	EOS≥150 + ≥4 exac	EOS≥150 + FeNO≥50 + ≥4 exac	EOS≥150 + FeNO≥25 + ≥4 exac
Sample size (n)	20	17	28
Exac. in 12 months prior to baseline	[redacted]	[redacted]	[redacted]
Exac. in following 12 months	[redacted]		
Used in model	[redacted]	[redacted]	[redacted]
Setting	UK	England	Europe

Source: Sanofi ACD Response, Technical Appendix Table 11

Furthermore, it is not clear that WATCH and U-BIOPRED provide information on the change in exacerbation rates over time: the mean numbers of exacerbations are only reported for one year (labelled “exacerbations in 12 months prior to baseline”). Consequently, these sources cannot inform an assessment of whether the reduction in exacerbation rates in the year before and during the QUEST study applies in clinical practice. Two years of exacerbation rates are reported for the Sanofi RWE study, indicating a reduction from [redacted] severe exacerbations in the year before baseline to [redacted] in the following year.

For their updated base case, the company uses a post-trial exacerbation multiplier (for both arms) calibrated so that the rate in the standard care arm equals the mean of the RWE pre and post-baseline values ([redacted]). They also report scenarios with a calibrated multiplier to adjust the standard care arm to the WATCH and U-BIOPRED rates, [redacted] and [redacted] respectively (Sanofi Technical appendix Table 12).

3.2 Method of adjustment

The company explain how they adapted the model to change the method of adjustment for long-term severe exacerbation rates in section 3.4 of their Technical Appendix.

3.2.1 The multiplier approach

The original model includes two sets of transition matrices, one set for each treatment arm. These govern the rate at which the model cohort moves between the four included health states (controlled asthma, uncontrolled asthma, moderate exacerbation and severe exacerbations). The two sets of matrices are estimated separately, from observed transitions in the dupilumab and placebo arms of the QUEST trial. For the updated base case, the transition probabilities are first estimated for a 'reference population' (the subgroup with EOS≥150 and FeNo≥25 and 2 or more prior exacerbations), and then adjusted for the higher risk subgroup with 4 rather than 2 prior exacerbations. In addition, the model includes a multiplier to adjust the rate of severe exacerbations after the first year. This multiplier is applied to the probabilities in both arms, and so inflates both arms by the same rate, retaining the between-arm relative risks.

In the original version of the model, the multiplier is treated as a user input. The company adopted a base case multiplier of [redacted], calculated to adjust for the exclusion of patients with a recent exacerbation from the QUEST trial (Company Submission appendix M.2). After technical engagement, the company changed their base case to include the post-trial severe exacerbation multiplier of 1.35 accepted in the NICE appraisal of mepolizumab (TA431[6]). This was derived from the ratio of the severe exacerbation rate for mepolizumab responders in the MENSA trial (CS M.2.1.3). The ERG base case assumed a multiplier of 1.00. This was based on the lack of direct evidence for an increase in the severe exacerbation rate after the trial period and is consistent with committee conclusions in the reslizumab appraisal (TA479[7]).

The updated model includes an alternative method of estimating the long-term multiplier. This uses the Excel Goal seek algorithm to calibrate the multiplier to achieve a target long-term severe exacerbation rate for standard care. To achieve their base case target of [redacted] severe exacerbations, the company estimates that a multiplier of [redacted] is required (Sanofi Technical Appendix Table 12).

3.2.2 Real-world risks for standard care with trial-based relative treatment effect

The company has also adapted the model to implement the approach suggested by the committee (ACD 3.14). This entails first estimating a transition matrix for standard care based on real-world data and then applying the relative treatment effect from the QUEST trial to estimate the transition matrix for dupilumab. In this case, the same transition matrix is

used for the first and subsequent years (in contrast to the multiplier approach in which the severe exacerbation rate increases after the first year).

This method requires a simplification of the model, so that a single relative treatment effect can be used (that for the severe exacerbation outcome). The company therefore merged the 'controlled asthma', 'uncontrolled asthma' and 'moderate exacerbation' health states to create two-state version of the model. This 2-state version of the model can also be used with the multiplier approach.

The company compare results for their base case using the three alternative methods for estimating transition probabilities in Table 15 of the Technical Appendix. The 4-state and 2-state versions of the model with a calibrated severe exacerbation multiplier produce very similar ICER estimates (£28,683 for the 4-state model versus £28,994 for the 2-state model). This is not surprising, given that the three health states merged in the 'no severe exacerbation' state are associated with modest costs and utility decrements and do not affect mortality. It is also not surprising that the 2-state models with alternative methods of adjusting for the 'real world' evidence yield almost identical results (£28,994 for the 'calibrated multiplier' approach versus £28,985 for the 'RWE direct input' method). These methods are different ways of making the same adjustments.

ERG conclusion

The alternative methods of adjusting for real-world evidence effectively apply the same assumptions and produce very similar results. We agree with the company's use of the 'calibrated multiplier' approach for their base-case analysis, as this allows retention of the 4-state version of the model and a more intuitive understanding of the impact of using real-world evidence: as a way to inflate the severe exacerbation rate after the trial period.

In practice, the real-world data provided in the company response is sparse and highly uncertain. We do not consider that the three reported studies can give a reliable estimate of the absolute rate of severe exacerbations for the population of interest in UK clinical practice.

Furthermore, these data do not resolve the question of why severe exacerbation rates fell during the QUEST trial for patients with a high rate of prior exacerbations who were randomised to placebo. This same phenomenon was observed in other severe asthma trials and discussed in previous NICE appraisals. Exacerbation rates

are only reported for one year for WATCH and U-BIOPRED, so these sources cannot indicate whether the reduction in exacerbation rates in the QUEST placebo arm reflects clinical practice. The Sanofi RWE does provide two-year data for the population of interest but indicates a similar proportional reduction in exacerbations as in the QUEST trial ([redacted] versus 46% respectively). This lends support to the hypothesis that the placebo improvement relates to a 'natural' regression to the mean and/or better real-world treatment after a period of poor asthma control, rather than a 'placebo effect' that should be adjusted away. However, we do not have any evidence about what happens after the trial period. Does the exacerbation rate stay at the rate observed during the trial or does it then tend to increase over time, back towards the pre-trial average?

The scenarios presented by the company (Technical appendix Table 13) all assume a post-trial increase, with multipliers ranging from [redacted] based on the two-year mean from the Sanofi RWE ([redacted]) to [redacted] based on the one-year rate in the WATCH cohort ([redacted]). We conduct additional scenarios to explore uncertainty over the post-trial exacerbation rate:

- Calibration to the Sanofi RWE year 2 exacerbation rate ([redacted]).
- A long-term exacerbation multiplier of 1.00: the ERG base case.

4 Data sources for setting of treating exacerbations

The company address the Committee's comments regarding the setting of treatment for severe exacerbations in Comment 7 of their ACD response document and section 3.3 of the Technical appendix. These parameters are influential because case fatality rates are estimated to be higher for people admitted to hospital or treated in Accident and Emergency than for those treated in primary care or at home with oral corticosteroids (OCS burst). The company report five sources of data for the proportions of severe exacerbation treated in these three settings (Sanofi Technical Appendix Table 3). They suggest that two of these sources (VENTURE and the Sanofi RWE study) are new, although we note the VENTURE estimates were used in previous analyses to estimate treatment settings for patients treated with maintenance oral corticosteroids.

The company use the Sanofi RWE study in their base case analysis. This is a case note review being conducted in NHS severe asthma centres, with data for 204 severe exacerbations in 77 patients. These exacerbations occurred in a wider patient group than the

new population for the model. The study used the same definition of a severe exacerbation as in the QUEST trial and yielded similar estimates of the proportion of severe exacerbations treated in hospital (admitted or A&E) as in the VENTURE trial and the MENSA trial that informed the NICE appraisal of mepolizumab (TA431).

Scenario analysis results for the five sources of exacerbation treatment setting are reported in Table 14 of the Sanofi technical appendix. The ICER ranged from £25,421 based on O'Neill 2015[8] to £32,923 with the QUEST clinical trial data.

ERG conclusion

We agree that estimates of the treatment setting for severe exacerbations should be based on data from UK clinical practice if possible. The Sanofi RWE data does seem to be of reasonable quality and it produces results that are consistent with other sources (VENTURE and MENSA trials). The reported proportion of severe exacerbations treated in hospital was much higher in the O'Neill 2015 study and we question whether this might relate to under-ascertainment of cases treated in primary care and home settings (by OCS burst). It is not clear why the proportion of exacerbations treated in hospital in the QUEST trial were so different to the estimates from other sources.

5 Modelling mortality

The final comment in Sanofi's ACD response relates to the Committee's request that additional analyses should be accompanied by model estimates of 10-year mortality rates for standard care and dupilumab and the flow of patients through the different health states. This request was motivated by the observation that the prediction of 20% mortality over 10 years under standard care in the original company base case "seemed high" compared with current UK asthma mortality of 1,300 deaths per year (ACD 3.16). The company observe that this is in large part due to the lack of granular data for the selected patient population and argue that they have followed precedent by using asthma-related mortality estimates which were accepted in the NICE benralizumab appraisal (TA565[9]).

The company tabulate the proportions of the model cohort by health state and the overall death rate after 1, 5 and 10 years for standard care and dupilumab in Tables 6 and 7 for their base case, and Tables 9 and 10 for the adolescent subgroup (Sanofi Technical Appendix). For the updated base case population, the 10-year death rate is 21% under

standard care and 12.5% with dupilumab. We show these results, together with the breakdown of death rates by cause in Table 6. This suggests that a large majority of the modelled deaths in this high-risk population are asthma related: 86% and 75% respectively at 10 years for standard care and dupilumab.

Table 6 Modelled patient flow and mortality: updated company base case

Year	Controlled Asthma	Uncontrolled Asthma	Moderate Exac.	Severe Exac.	Asthma related deaths	Other deaths	Total deaths
Dupilumab							
1	54.5%	24.3%	14.8%	5.9%	0.3%	0.2%	0.5%
5	37.0%	27.4%	15.0%	16.4%	2.9%	1.3%	4.2%
10	24.9%	28.9%	12.8%	21.0%	9.4%	3.1%	12.5%
Standard care							
1	24.0%	38.4%	11.4%	24.7%	1.3%	0.2%	1.5%
5	10.8%	36.4%	11.7%	31.7%	8.3%	1.2%	9.5%
10	9.4%	31.7%	10.2%	27.6%	18.2%	2.9%	21.0%

Source: estimated by ERG from company revised model

We also note that for this updated company base case population with an initial age of 48 years, the model predicts the mean (median) age of death as: 70.1 (69.4) years with standard care; and 72.9 (72.6) years with dupilumab. For comparison, the ERG for the benralizumab appraisal TA565 estimated life expectancy for the severe asthma population with standard care at 80.4 years and noted that UK life expectancy for a 50-year old person was 83.1 years (Tikhonova et al, PenTAG 2018).

For illustration, we also show the Markov trace graphs for standard care and dupilumab over the lifetime horizon from the company's updated base case model (Figure 1).

ERG conclusion

We agree with company that mortality data is not available for the high-risk subgroup in their updated base case analysis (severe asthma with type 2 inflammation, EOS≥150, FeNo≥25 and at least 4 severe exacerbation in the previous year). It is therefore difficult to judge the plausibility of the survival projections from the model.

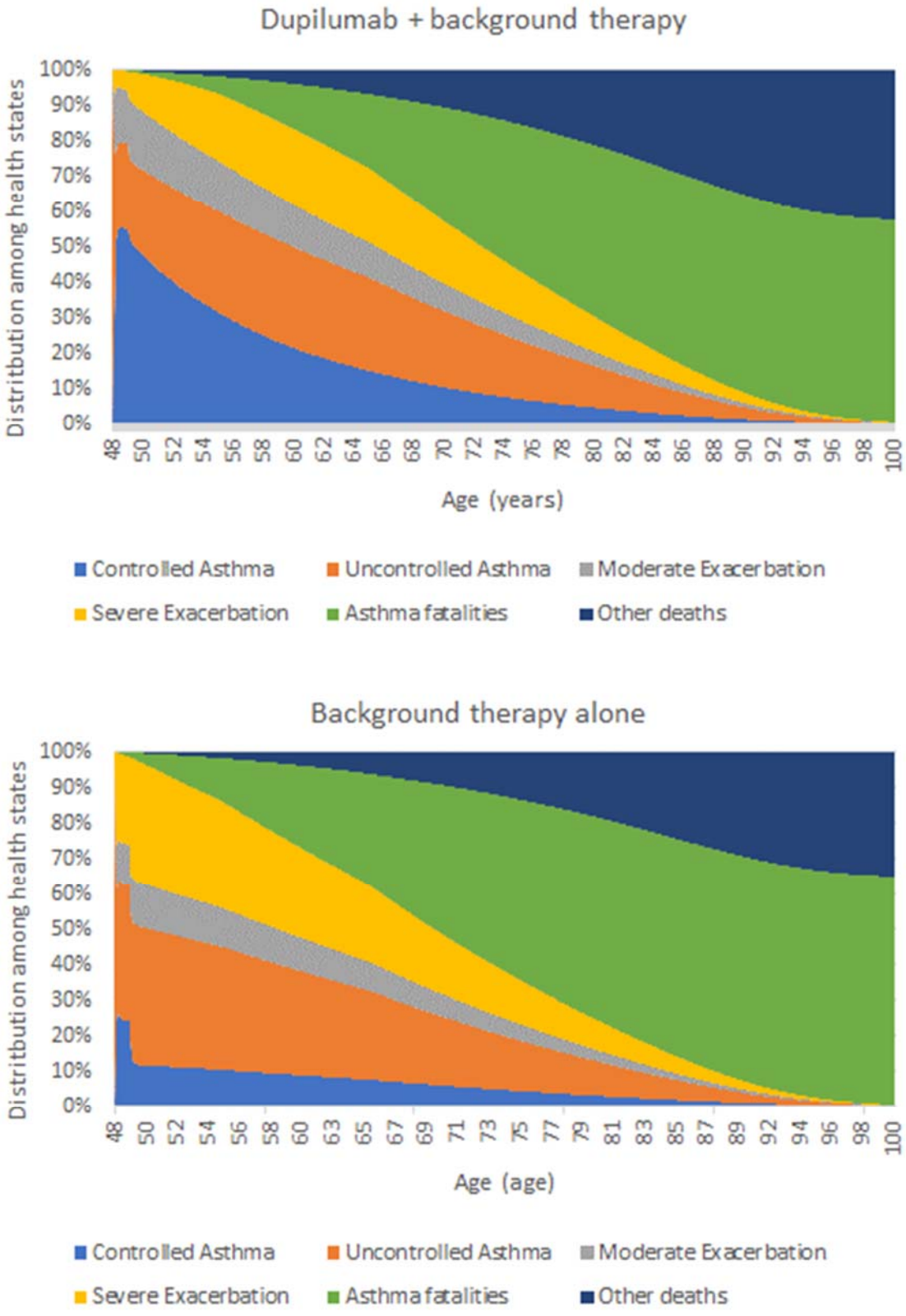

Figure 1 Markov traces for standard care and dupilumab: updated company base case

6 Company updated base case results

6.1 ERG replication of company results

We successfully replicated most of the results reported in section 4 of the company's Technical Appendix. The only real exception was the analysis for the adolescent population, reported in Table 8 of the Technical Appendix. The method for running this analysis was not explained in the Sanofi ACD response. Changing just the initial age of the modelled cohort by typing "12" in the override cell, K87 in the Parameters sheet, we obtained the results in Table 7 below. This is similar to the company's reported result (ICER £61,458 versus £61,042).

Table 7 ERG analysis: attempt to replicate company analysis for adolescents

Treatment	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY)
Standard care	[redacted]	[redacted]	[redacted]	[redacted]	
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£ 61,458

After re-calibrating the model, we did sometimes find trivial discrepancies with the company's reported results. For example, after running the subgroup analyses below, and then reverting to the company's updated base case population, we got an ICER of £28,687 rather than £28,683.

6.2 ERG additional subgroup analysis

For illustrative purposes, we show the effect of changing the population criteria in Table 8 below. This shows that the ICER increases when some people with a lower exacerbation risk are added to the population (e.g. people with only 3 prior exacerbations, or those with either raised eosinophils or raised FeNO but not both).

Table 8 ERG analysis: alternative subgroups

Treatment	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY)
EOS≥150 and FeNo≥25 and 4 or more exacerbations (updated company base case)					
Standard care	[redacted]	[redacted]	[redacted]	[redacted]	
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£ 28,683
EOS≥150 and FeNo≥25 and 3 or more exacerbations					
Standard care	[redacted]	[redacted]			

Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£ 30,719
EOS≥150 OR FeNo≥25 and 3 or more exacerbations (original company base case)					
Standard care	[redacted]	[redacted]			
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£ 35,398

6.3 ERG scenarios for long-term severe exacerbation rates

The company only report scenarios with a higher long-term standard care exacerbation rate than that observed for the QUEST placebo group (Sanofi Technical Appendix Table 13). We add two, more conservative scenarios, with lower long-term exacerbation rates (Table 9):

- An analysis assuming an ongoing annual rate of exacerbation as observed in the second year of the Sanofi case note review ([redacted]): ICER = £37,817; and
- The ERG base case, which assumes an ongoing annual rate of exacerbations as in the QUEST trial (multiplier = 1): ICER = £35,968.

It is interesting that the first of these scenarios produced a calibrated multiplier less than one. This suggests that patients with 4 or more prior exacerbations in one year in the case note review had fewer exacerbations in the following year than would have been expected based on placebo data from the QUEST trial.

Table 9 ERG analysis: scenarios

Treatment	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY)
Sanofi RWE mean rate [redacted], multiplier [redacted] (Updated company base case)					
Standard care	[redacted]	[redacted]			
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£ 28,683
Sanofi RWE year 2 rate [redacted], multiplier [redacted]					
Standard care	[redacted]	[redacted]			
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£ 37,817
User input multiplier 1.00 (ERG base case)					
Standard care	[redacted]	[redacted]			
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	£ 35,968

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Dupilumab for treating Severe Asthma [ID1213]

Company updated proposal

1. Introduction

The company has updated its base case based on the ERG report on the company response to the ACD and discussions with NICE. The company is mindful of NICE and committee resources, particularly during this exceptional time and the impact of COVID-19 on all aspects of the technology appraisal process. In particular, the company is hopeful to achieve a positive recommendation at the next committee for the patients with severe asthma who are a highly vulnerable group.

The company response (CR) to the ACD included an updated company base case, additional data to support modelling assumptions and additional analyses. The CR was then reviewed by NICE and the ERG and a report was produced. The purpose of this document is to address the issues raised in this report before the next committee meeting.

2. Objective

The company is committed to working with NICE to achieve a positive outcome at the next committee meeting. This document will address the issues raised by the ERG in the report, provide the additional analyses requested, and present the updated company base case. Specifically:

- Updated company base case
    - Population
    - Adolescent population
    - Post-trial exacerbations
    - [redacted]
- Efficacy of dupilumab in patients who have previous use of a biologic

3. Company Base Case

3.1. Population

> **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.**

This includes three sub-populations outlined in the ERG report as follows:

A. Adults with blood eosinophil count (EOS) 150-299 cells/µl, fraction of exhaled nitric oxide (FeNO) ≥ 25 and ≥4 asthma exacerbations in the previous 12 months. This group are not eligible under NICE guidance to receive any other biologics.
B. Those aged 12-17 years, with EOS ≥150, FeNO ≥ 25 and ≥4 asthma exacerbations. Current NICE guidance for the other biologics is for adults only.

Those who have previously had biologic therapy

c. Adults with EOS ≥ 300, FeNO ≥ 25 and ≥ 4 asthma exacerbations who have previously had treatment with the existing biologics but did not respond to this treatment.

The results of the updated base case are presented in the Results section below. Scenario analyses of the subgroups are also presented, although we urge caution in the interpretation of these results due to the very small patient numbers. 14 patients in QUEST, across all four trial arms, corresponded to sub-population A. Consistent with previous analyses for small sub-population, a reference subgroup was used as proxy to increase sample size, defined as EOS>=150 – 299, FeNO>=25 and >=1 exacerbation in the previous 12 months. Despite this, the sample size is still very low (N=14 and 36 in placebo and Dupilumab 200mg, respectively).

3.2. Adolescent population

The ERG queried the results of the adolescent population in the company's response to the ACD, as the group could not replicate the results based on a starting age of 12 years. The scenario analysis presented by Sanofi was based on a starting age of 14.2, based on the median age of the adolescent population in the QUEST clinical trial. (1) The sub-population analysis was re-run to incorporate [redacted].

3.3. Post-trial exacerbations

The company maintains that severe exacerbations were likely to be underestimated in the clinical trial because the patients most likely to exacerbate were excluded from the clinical trial protocol, and exacerbations needed to be separated by >28 days to count as separate events. These assumptions were validated by external clinicians.

However, the committee and ERG have noted that the impact of these issues is uncertain and therefore it is preferred to maintain the QUEST exacerbation rates for the duration of the model (multiplier = 1). This assumption is used in the updated company base case and is considered a conservative assumption

3.4. [redacted]

3.4.1. [redacted]

3.4.2. [redacted]

[redacted]

XXXXXXX XXXXXXX XXXXXXX

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

[redacted]

1. 1 [redacted]

[redacted]

2. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4. Clinical input on key assumptions

The population included in the company base case includes a population of patients who have previously received a biologic treatment for severe asthma. NICE and the ERG queried the assumption that patients who had previously been on a biologic were assumed to have the same efficacy as people in the trial who were not treated with a biologic.

The dupilumab phase 3 trial (QUEST) included 1 patient with previous biologic experience, therefore external clinical validation of this assumption was sought. The full response of the consultant in respiratory medicine, [redacted], is available in an appendix; below we highlight a few of his comments most central to this point.

There is some early evidence that a patient with severe asthma may still show a clinical response to a second biologic having failed on the first one, but there are no head-to-head trials of the order of biologics and clinical efficacy.

Switching biologic treatments remains an accepted practice despite this lack of evidence, because the mechanisms or efficacy of action are sufficiently different between the currently approved biologics, as long as the biomarkers are still present to indicate a patient may respond to a second biologic.(4) For brevity, biologic therapies in severe asthma are indicated for "T2-high" disease that is further characterised by the allergic and eosinophilic status of a patient. Currently licensed treatments include omalizumab (anti-IgE), mepolizumab, reslizumab and benralizumab (anti IL-5) and dupilumab (anti IL4/13). Assume these are groups A and B (all NICE approved), and C respectively.

Switching more often occurs from A to B, or B to A, and sometimes from B to another biologic in B. As the mechanisms of action from A to B and B to A is very different, there is no clinical reason as to why a patient may not respond as long as the asthma remains uncontrolled and there is a baseline biomarker present at the initiation of the second biologic to indicate treatment responsiveness. In support of switching from A to B, an open-label, single-arm, multicenter study was designed with a pragmatic approach of switching from one biologic (omalizumab) to another (mepolizumab). This switch resulted in significant improvement in asthma control at 32 weeks, and also a significant reduction of blood eosinophils and serum markers of eosinophil activation. (5)

Switching from B to another biologic in B (anti IL5) is less common, but there is some evidence of clinical benefit. Ten oral corticosteroid- dependent asthma patients who remained poorly controlled despite treatment with mepolizumab, showed significant improvements in lung function, asthma control and blood and sputum eosinophilia when switched to reslizumab. (6)

If Dupilumab is approved for NHS use, switching may occur between A to C and B to C. We are advised by our clinical experts that a sense of equipoise is recommended, in the absence of any evidence of a reduction in efficacy of such a switch. That is, we cannot assume there is either increased or decreased efficacy when making such a switch despite some evidence that such a switch may be beneficial. Clinically the mechanisms of action between A and C, and between B and C are significantly different that target different aspects of the asthmatic inflammatory cascade that makes such a switch clinically acceptable.

5. Results

The eligible population is a very restricted sub-population of the QUEST trial. In addition to the base case, cost-effectiveness results are presented for the biologic- ineligible population (A), adolescent population (B) and patients who have previously had a biologic (C). Population sizes are even more limited in these three, and we urge caution in their interpretation in isolation. Rather, the results of the base case as a whole are the most appropriate to determining the cost-effectiveness of this population.

5.1. Base case

The company base case is for dupilumab 200mg 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. Post-trial exacerbation rates are taken from QUEST (multiplier = 1) and [redacted]

Table 1: Base case cost-effectiveness results

Treatment	Total costs	Incremental costs	Total QALY	Incremental QALY	ICER
Standard of care	[redacted]		[redacted]		
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5.2. Sub-populations

A. Adults with blood eosinophil count (EOS) 150-299 cells/µl, fraction of exhaled nitric oxide (FeNO) ≥ 25 and ≥4 asthma exacerbations in the previous 12 months. This group are not currently eligible under NICE guidance to receive asthma biologics.

Treatment	Total costs	Incremental costs	Total QALY	Incremental QALY	ICER
Standard of care	[redacted]		[redacted]		
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B. Those aged 12-17 years, with EOS ≥150, FeNO ≥ 25 and ≥4 asthma exacerbations. The NICE guidance for current biologics is for adults only.

Treatment	Total costs	Incremental costs	Total QALY	Incremental QALY	ICER
Standard of care	[redacted]		[redacted]		
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Those who have previously had biologic therapy

C. Adults with EOS ≥ 300, FeNO ≥ 25 and ≥ 4 asthma exacerbations who have previously had treatment with the existing biologics but did not respond to this treatment.

Treatment	Total costs	Incremental costs	Total QALY	Incremental QALY	ICER
Standard of care	[redacted]		[redacted]		
Dupilumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6. Conclusion

Dupilumab 200mg can be considered cost-effective in the updated population base case, defined as 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.

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QUESTION:

<u>Subpopulation who have been treated with but not responded to a previous biologic</u>

"In your response to consultation you have provided analyses for this group but assumed the same efficacy as people in the trial who were not treated with a biologic (because QUEST did not include people who had received a biologic treatment).

Please can you provide a rationale for this assumption and any supporting evidence if it is available?"

The availability of an increasing number of biologics in severe asthma has increased the potential for patients to be switched from one biologic to another if they fail to respond or experience a significant side-effect. The patient phenotype and endotype inform the choice of primary biologic treatment supported by an appropriate biomarker that indicates treatment responsiveness.

There is some early evidence that a patient with severe asthma may still show a clinical response to a second biologic having failed on the first one, but there are no head-to-head trials of the order of biologics and clinical efficacy.

Switching biologic treatments remains an accepted practice despite this lack of evidence, because the mechanisms or efficacy of action are sufficiently different between the currently approved biologics, as long as the biomarkers are still present to indicate a patient may respond to a second biologic.[1] For brevity, biologic therapies in severe asthma are indicated for "T2-high" disease that is further characterised by the allergic and eosinophilic status of a patient. Currently licensed treatments include omalizumab (anti-IgE), mepolizumab, reslizumab and benralizumab (anti IL-5) and dupilumab (anti IL4/13). Assume these are groups A and B (all NICE approved), and C respectively.

Switching more often occurs from A to B, or B to A, and sometimes from B to another biologic in B. As the mechanisms of action from A to B and B to A is very different, there is no clinical reason as to why a patient may not respond as long as the asthma remains uncontrolled and there is a baseline biomarker present at the initiation of the second biologic to indicate treatment responsiveness. In support of switching from A to B, an open-label, single-arm, multicenter study was designed with a pragmatic approach of switching from one biologic (omalizumab) to another (mepolizumab). This switch resulted in significant improvement in asthma control at 32 weeks, and also a significant reduction of blood eosinophils and serum markers of eosinophil activation.[2]

Switching from B to another biologic in B (anti IL5) is less common, but there is some evidence of clinical benefit. Ten oral corticosteroid- dependent asthma patients who remained poorly controlled despite treatment with mepolizumab, showed significant improvements in lung function, asthma control and blood and sputum eosinophilia when switched to reslizumab.[3]

If Dupilumab is approved for NHS use, switching may occur between A to C and B to C. We are advised by our clinical experts that a sense of equipoise is recommended, in the absence of any evidence of a reduction in efficacy of such a switch. That is, we cannot assume there is either increased or decreased efficacy when making such a switch despite some evidence that such a switch may be beneficial. Clinically the mechanisms of action between A and C, and between B and C are significantly different that target different aspects of the asthmatic inflammatory cascade that makes such a switch clinically acceptable.

We also draw on the wealth of experience in switching between NICE approved treatments in rheumatic and inflammatory bowel diseases, where switching also occurs between reference biologics and biosimilars.[4] This practice has continued because clinical research and experience

suggests that TNF antagonists in rheumatoid arthritis (RA), for example are not interchangeable, as meaningful differences have been observed in their efficacy and safety profiles after switching.

A meta-analysis performed 10 years ago of 20 observational switching studies including 2705 patients with RA, concluded that patients who discontinued use of one TNF antagonist owing to lack or loss of efficacy or intolerance were found to benefit from switching to another agent within the same class, and that the particular sequence of TNF antagonists used or the reason for switching did not appear to influence outcomes.[5] This has led to several professional associations, including the American College of Rheumatology (ACR), the European League Against Rheumatism (EULAR), and the Consensus Group on Advances in Targeted Therapy recommend switching between TNF antagonists when the first agent is associated with an inadequate response or poor tolerability. Switching trials are also difficult to design which in part explains the lack of evidence – the results of any switching study that shows a reduction in response rates is prone to significant selection bias because switchers represent treatment failures.

We therefore conclude that switching may occur in severe asthma, that the biologics are sufficiently different to warrant this practice, and there is some evidence that switching biologics even within the same class can lead to clinical benefit, and that lessons from other chronic inflammatory conditions with a longer experience of biologic therapy also show that switching from one biologic to another can lead to improvements. We have therefore made no assumptions on reduced efficacy as the early clinical evidence shows continued benefit in patients who remain poorly controlled and who still manifest the biomarkers of responsiveness despite failure of the first biologic.

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Dupilumab for treating severe asthma

Evidence Review Group comments on Sanofi additional evidence submission 210820

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1 Introduction

Sanofi have submitted a revised base case analysis for consideration by the committee. This is described in an 'additional evidence' document and revised cost-effectiveness model dated 21/08/20.

Over the course of this appraisal, the company has submitted four base case analyses:

1. Company Submission (CS) base case
2. Technical Engagement (TE) company response base case
3. Appraisal Consultation Document (ACD) company response base case
4. Additional evidence base case, dated 21/08/20

The latest proposal (base case 4) includes three additional changes to the base case that the company proposed in their initial ACD response (base case 3). These changes are described in section 3 of the additional evidence response. We comment on these changes below.

2 Changes to company base case

2.1 Target population and subgroups

As in their ACD response, the company's new base case applies to a restricted target population:

> **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.**

This revised population is narrower than that in earlier base cases (1 and 2), which also included people with 3 exacerbations in the previous year and people with raised levels of either EOS or FeNO but not both. The revised population has a greater baseline risk of future exacerbations, so one would expect a greater absolute risk reduction and lower ICER with dupilumab add-on therapy.

The company report a breakdown of cost-effectiveness estimates for three subgroups that comprise the revised target population.

A. Adults who are not eligible for other biologics
B. Adolescents (age 12-17 years)
C. Adults who have previously had biologic therapy

2.1.1 Group A: adults not eligible for other biologics

The analysis for group A is based on a newly estimated set of transition probabilities for people with EOS 150-299 and FeNO≥25 and 4 or more exacerbations in the previous year. The company notes that only 14 patients in the QUEST RCT met these criteria and rightly urges caution in the interpretation of results for this subpopulation.

As for other small subgroups in the model, transition probabilities were first estimated for a larger reference group (in this case, EOS 150-299 cells/μl and FeNO ≥ 25 and 1 or more exacerbations in the previous year) and then adjusted using multipliers to reflect the higher risks for people with more previous exacerbations. The multipliers were estimated from a binomial regression model. This approach is reasonable for larger subgroups, but it is unlikely to be reliable when data are so sparse as for the subgroups of the (already small) revised target population.

We also suggest that the results for the adult subgroups (A and C) lack face validity. The model estimates that with standard care, there are better health outcomes for group C ([redacted] QALYs) than for group A ([redacted] QALYs). This is counterintuitive, given that patients in group C have a higher baseline EOS than those in group A and are similar in other respects, so group C are at higher risk of future exacerbations. This reason for this discrepancy is not clear, although it may relate to the use of different reference populations to estimate transition probabilities for the two groups.

2.1.2 Group C: adults for whom prior biologic therapy has failed

As for group A, the transition probability estimates for group C are highly uncertain. The company does not state the number of patients in the QUEST trial who meet the EOS, FeNO and prior exacerbation criteria for this group.

The company has stated that only one patient in QUEST had previously received a biologic drug, and it is uncertain whether estimates of treatment effectiveness from this almost exclusively biologic-naïve trial population are applicable to patients for whom previous treatment with another biologic has failed. The company address this point in their additional evidence submission with clinical expert opinion.

The expert discusses differences in the mechanism of action of three groups of biologics:

- omalizumab (anti IgE);
- mepolizumab, reslizumab and benralizumab (anti IL-5); and
- dupilumab (anti IL4/13).

He cites some evidence of effectiveness for switching between omalizumab and the NICE approved anti IL-5 drugs, and also for switching between different anti IL-5 drugs.

We suggest that the arguments regarding omalizumab are less relevant to this current appraisal, given that both the company and the NICE committee have ruled out omalizumab as a comparator for dupilumab. There is a lack of evidence regarding switching between anti IL5 and anti IL4/13 treatments, but the expert argues that the mechanisms of action for these treatments are sufficiently different to justify adoption of 'a sense of equipoise'.

2.1.3 Group B: adolescents

The company explained that they ran the subgroup analysis for adolescents (age 12 to 17) by entering a starting age of 14.2 for the cohort (the median age of adolescents in QUEST). Based on this, we confirm that we have replicated the company's results for this subgroup.

As for the other subgroups, specific clinical and cost-effectiveness estimates for adolescents are very uncertain. The QUEST trial only included two adolescents within the company's revised target population, both in the placebo arm. The cost-effectiveness results presented for this subgroup therefore relied on the same estimates of clinical effectiveness as for the adult population (based on data for QUEST participants aged 12 and over). The higher estimated ICER for adolescents compared with that for adults was driven by lower case fatality rates associated with severe exacerbations for people aged under 18.

2.2 Post-trial exacerbation rate

The revised company base case maintains the observed exacerbation rates from the clinical trial through the modelled lifetime: exacerbation multiplier = 1. We agree that this assumption is conservative but consider it appropriate in the absence of longer post-trial follow-up or real-world evidence to rule out regression to the mean as the explanation for the reduction in the rate of exacerbations in the year after randomisation for the placebo arm.

2.3 [redacted]

3 Cost-effectiveness results

3.1 Base case results

The ERG successfully replicated all of the company's results and we checked that the revised model could reproduce previous base case results. Table 1 below shows how results have changed from the original base case through three revised base cases. The rows below each base case show subsequent changes that the company made to generate the next base case. For example, the change in the ICER from £28,685 in base case 3 to [redacted] in base case 4 results from two changes (exacerbation multiplier = 1 [redacted]). Individual changes between the base cases are shown in a cumulative fashion. Thus, each row incorporates all of the previous changes.

Table 1 Cumulative cost-effectiveness of changes to the company's base case

Analysis	Incremental (Dup vs. SC alone)		
	Cost	QALYs	ICER
1 Original company base case	[redacted]	[redacted]	£ 28,087
+ cap utility at general population means	[redacted]	[redacted]	£ 29,721
+ allow discontinuation in year 1	[redacted]	[redacted]	£ 29,601
+ reference costs for exacerbations	[redacted]	[redacted]	£ 29,669
+ exacerbation multiplier = 1.35 (TA431)	[redacted]	[redacted]	£ 31,692
+ exacerbation settings as in TA431	[redacted]	[redacted]	£ 34,216
2 TE company response base case	[redacted]	[redacted]	£ 34,216
+ narrower target population [a]	[redacted]	[redacted]	£ 27,544
+ calibrated multiplier from RWE [b]	[redacted]	[redacted]	£ 27,832
+ exacerbation settings from RWE	[redacted]	[redacted]	£ 28,685
3 ACD company response base case [b]	[redacted]	[redacted]	£ 28,685
+ exacerbation multiplier = 1	[redacted]	[redacted]	£ 35,968
[redacted]	[redacted]	[redacted]	[redacted]
4 ACD additional analysis base case	[redacted]	[redacted]	[redacted]

Abbreviations: ACD Appraisal consultation document; Dup dupilumab plus standard care; ICER incremental cost-effectiveness ratio (£ per QALY gained); RWE real world evidence (Sanofi UK case note review, n=20); SC standard care; TE technical engagement

a People with severe asthma, not treated with maintenance oral corticosteroids, age 12 and over with EOS≥150 and FeNO≥25 and 4 or more exacerbations in previous 12 months

b The calibration for the exacerbation multiplier is a volatile process, so there can be small changes in results when the model is re-run. Results reported here have been generated from the model by the ERG and hence there are small differences in the results for the ACD response (£28,683 per QALY reported in the company's ACD response, compared with £28,685 per QALY in the ERG replication.

4 ERG conclusion

The company's base case ICER considered at the Appraisal Committee Meeting was £34,216 per QALY gained for dupilumab compared with standard care alone. This was revised to [redacted] per QALY gained in company's most recent additional evidence submission. This change results from the adoption of more conservative assumptions about long-term exacerbation rates (multiplier = 1) and the location of treatment for severe exacerbations (fewer people treated in hospital, which reduces the estimated number of case fatalities) being offset by a narrower target population more likely to benefit from treatment [redacted].

The ERG is broadly supportive of these changes. We welcome the company's decision to maintain observed exacerbation rates from the clinical trial throughout the model time horizon and their data source for the proportion of people with severe exacerbations who are treated in hospital. We also consider it reasonable to focus on a group of patients who cannot receive recommended biological treatments despite indications that they are at high risk of harm from asthma exacerbations. There is, though, considerable uncertainty over the quantitative estimates of risk (and hence of cost-effectiveness) due to the limited data available for this focussed population. We agree with the company's caution over the ICER estimates for subgroups within this population and conclude that currently available data does not support more accurate estimation.

[redacted]

Slides for Public– Part 1 (Redacted)

NICE National Institute for Health and Care Excellence

Dupilumab for severe asthma with type 2 inflammation

Chair presentation

2nd appraisal committee B meeting

Chair: Sanjeev Patel

Lead team: Gareth Hooper, Veline L'Esperance, Tony Wootton

ERG: Southampton Health Technology Assessments Centre

NICE technical team: Caroline Bregman, Eleanor Donegan, Henry Edwards

Company: Sanofi Genzyme

History

- First committee meeting February 2020
  - Dupilumab ‘not recommended 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.’
- ACD (appraisal consultation document) sent out for consultation April 2020
  - Topic paused due to covid-19
- Company submitted revised base case
  - Narrower population focussing on unmet need
    - people not eligible for biologics or who have not responded to biologics
  - Removed asthma exacerbation multiplier
  - Explored literature for other sources for asthma exacerbations treatment settings
  - Explored different ways of mortality modelling
  - Updated PAS ([redacted])

Key issues

Is the proposed narrower population (and subgroups) appropriate?

Severe asthma – blood eosinophil count (EOS) ≥150 cells/µl **And** Fractional exhaled nitric oxide (FeNO) ≥25 ppb with ≥4 exacerbations in the previous year who are:

- Adolescents (aged 12-17)
- Adults and not eligible for biologics (EOS 150-299)
- Adults who previously received biologics but did not respond (EOS ≥ 300)

Is the company's approach to asthma exacerbation rates appropriate?

- The company now applies the observed severe exacerbation rates from the clinical trial through the modelled lifetime without adjustment (multiplier =1)

Is the source of where asthma exacerbations are treated appropriate?

- What source should be used to estimate the proportions of patients with severe exacerbations treated in emergency care and inpatient setting? – impacts mortality

Has the company adequately explored 10- year mortality modelling as requested?

Disease background: Subtypes of severe asthma

- Subtypes of asthma
  - Severe eosinophilic asthma
  - IgE mediate allergic asthma
  - Severe asthma with type 2 inflammation

- Severe asthma with Type 2 inflammation is defined by the Global Initiative for Asthma (GINA) as
  - Blood eosinophils (EOS) ≥150 µl and/or
  - Fractional exhaled nitric oxide (FeNO) ≥20 ppb and/or
  - Sputum EOS ≥2% and/or
  - Asthma that is clinically allergen-driven and/or
  - Need for maintenance oral corticosteroids (mOCS)

GINA 2019 treatment pathway for asthma green box indicates controller, amber box is reliever

Severe asthma

Step 1	Step 2	Step 3	Step 4	Step 5
As needed low dose inhaled corticosteroid (ICS)-formoterol or short-acting β2-agonist (SABA)	Daily low dose ICS or Step 1 or leukotriene receptor antagonist (LTRA) or low dose ICS when SABA taken	Low dose ICS-long-acting β2-agonist; (LABA) or medium dose ICS or low dose ICS + LTRA	Medium dose ICS-LABA or high dose ICS or low dose ICS + LTRA	High dose ICS-LABA Refer for phenotypic assessment ± add on therapy for e.g. tiotropium, biologics or add low dose oral corticosteroids (OCS)

As needed low dose ICS-formoterol

As needed low dose ICS-formoterol for patients on maintenance and reliever therapy

Consultees at technical engagement highlighted that specialists are less frequently initiating mOCS at step 5

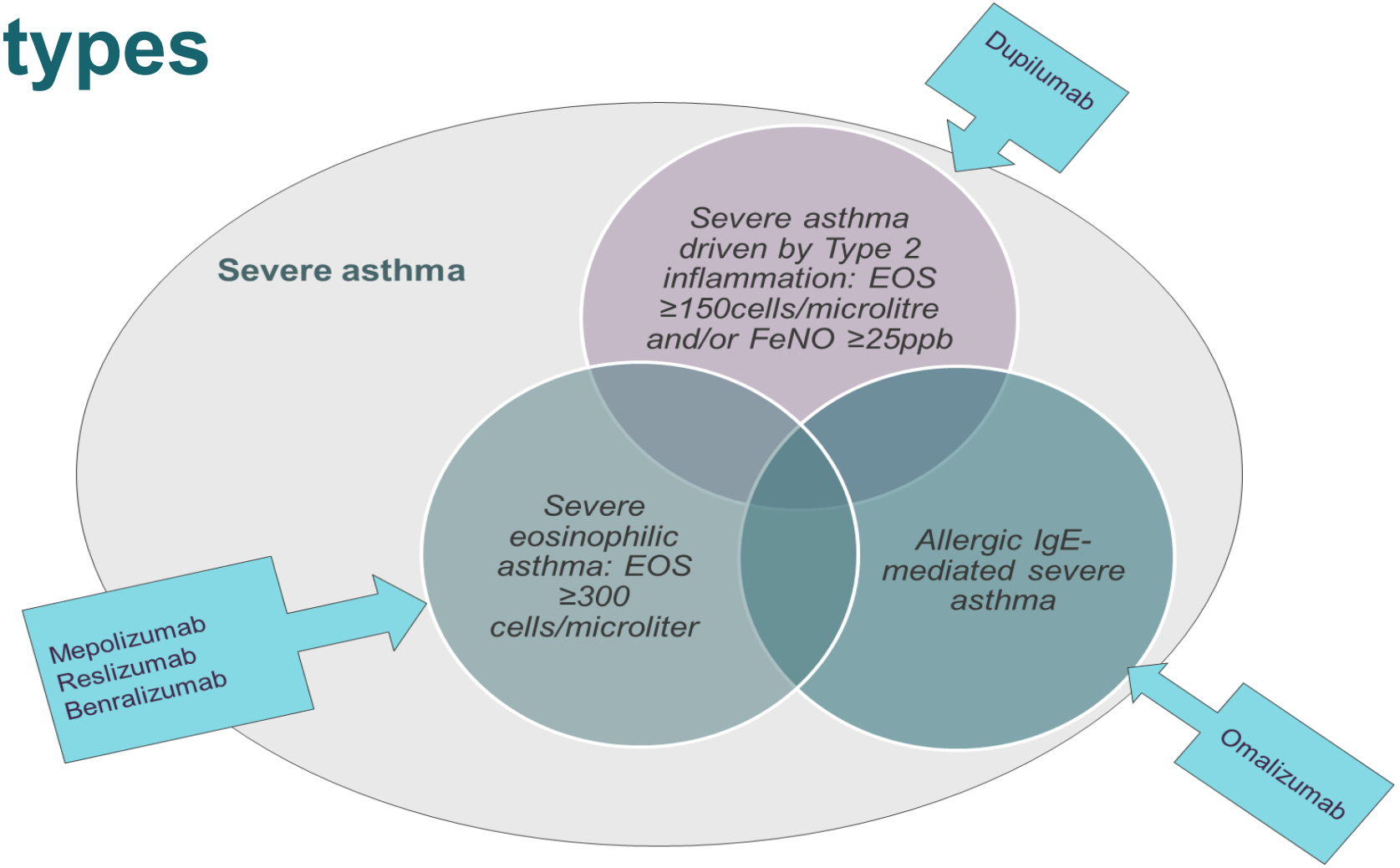
Dupilumab positioning step 4 or 5?
1st treatment specifically for treating T2i

NICE

Dupilumab (Dupixent, Sanofi Genzyme)

Technology	Dupilumab (Dupixent, Sanofi Genzyme) is a recombinant human immunoglobulin (Ig) monoclonal antibody that inhibits interleukin (IL)-4 and IL-13 signalling. IL-4 and IL-13 act as major drivers of Type 2 inflammation (T2i) by activating multiple cell types.
Marketing authorisation May 2019	Dupilumab (Dupixient, Sanofi Genzyme) is indicated in adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with T2i characterised by raised blood eosinophils (≥ 150 cells/µl) and/or raised fractional concentration of exhaled nitric oxide (FeNO **≥ 20 parts per billion** [ppb]) who are inadequately controlled with high dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment
Company's proposed updated population	People aged 12 +, with EOS≥150 **And** FeNo≥25 **and** ≥4 exacerbations who are ineligible for biologics or have not responded to biologic therapy
Administration	• Initial 400 mg dose followed by 200 mg given every other week by subcutaneous injection (patients **not** on oral corticosteroids). • Initial 600 mg dose followed by 300 mg every other week administered by subcutaneous injection (patients on oral corticosteroids or with severe asthma **and** co-morbid moderate-to-severe atopic dermatitis)

Current biologics for severe asthma subtypes



Source: **Company response** to technical engagement additional analysis – figure 1

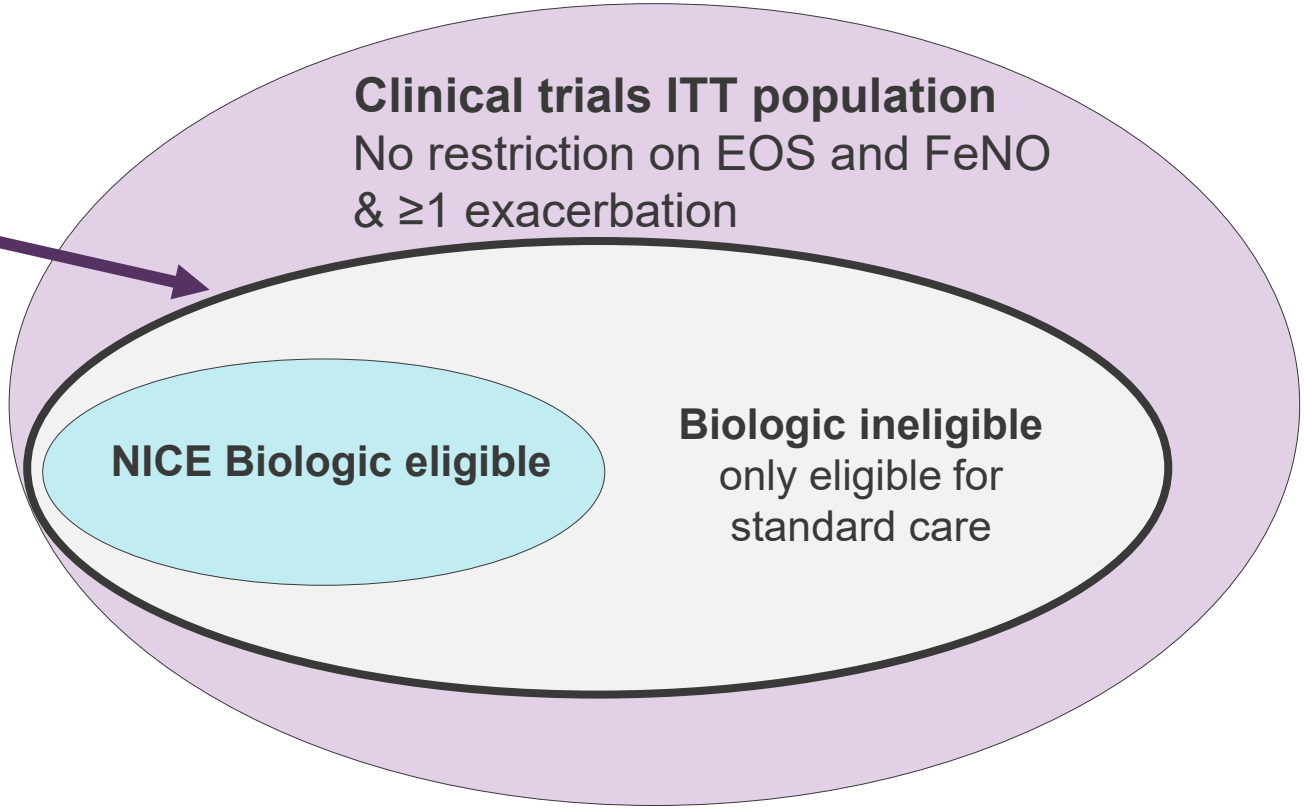
Treatments for severe asthma depend on biomarkers such as EOS and other clinical symptoms. **Omalizumab is not considered a relevant comparator**

Clinical effectiveness at first appraisal committee meeting (Feb 2020)

Populations at first committee meeting (1)

Company's decision problem population at first committee meeting

EOS ≥150 cells/µl or
FeNO≥25ppb &
≥3 exacerbations



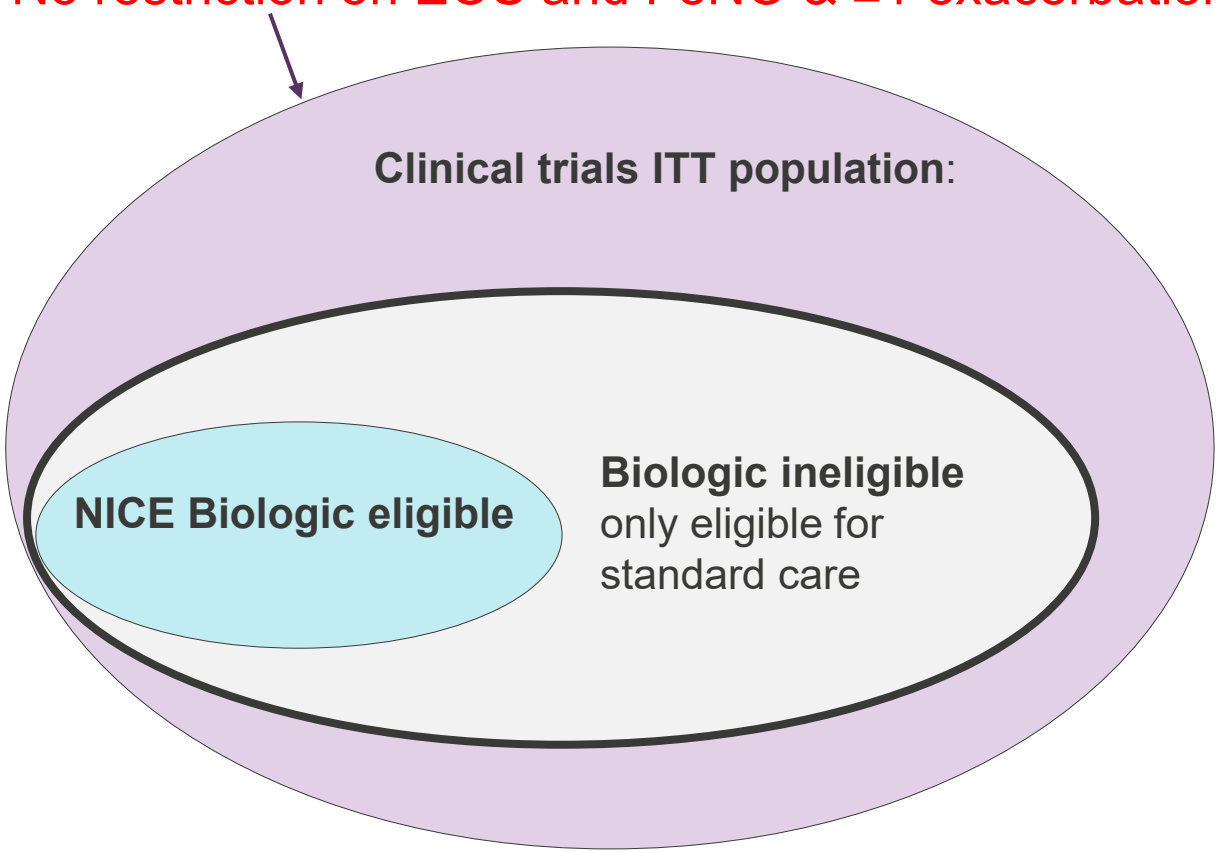
NICE biologic eligible
EOS≥300 cells/µl & ≥4 Ex, or
EOS≥400 cells/µl & 3 Ex

Biologic ineligible
EOS ≥150 to 299 cells/µl + 4 Ex, or
EOS ≥150 to 399 cells/µl + 3 Ex, or
EOS<150 cells/µl & FeNO≥25

Ex = exacerbations

Results at first committee meeting (1)

Clinical trials ITT population
No restriction on EOS and FeNO & ≥1 exacerbation



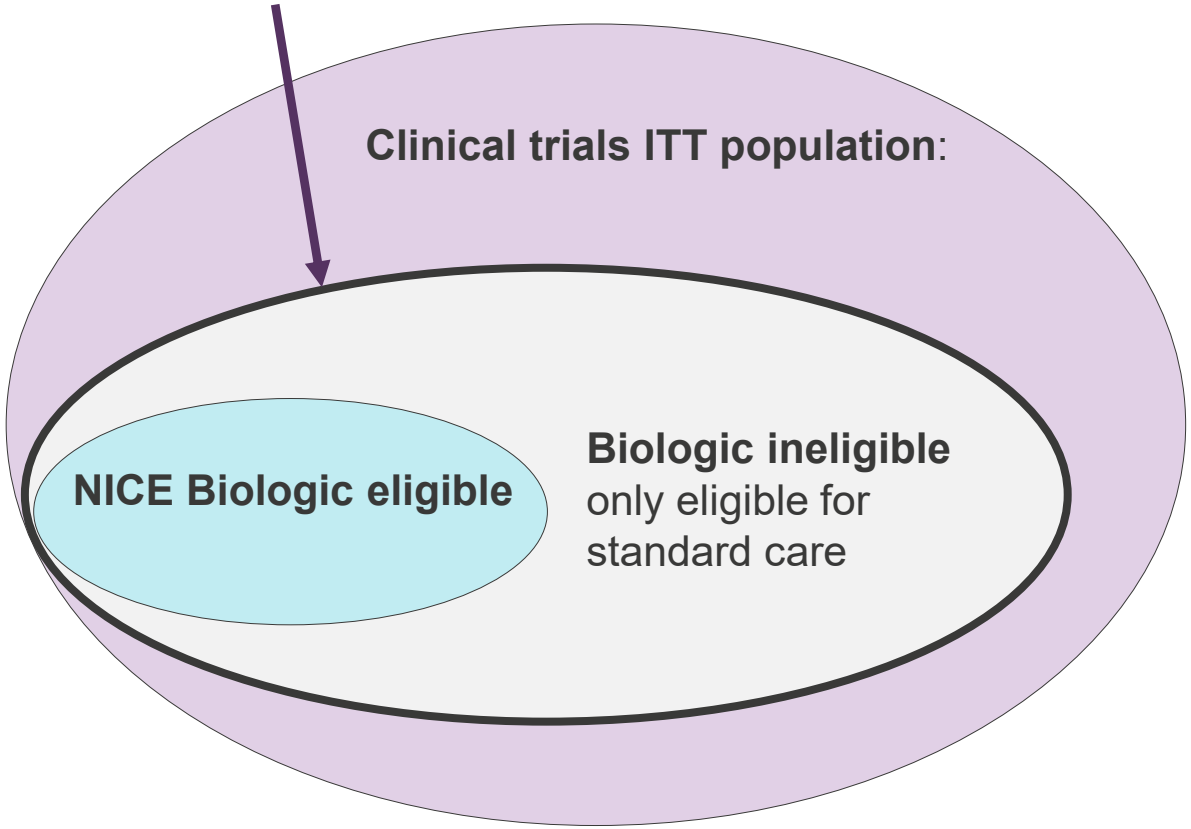
QUEST n=1902	
Adjusted annualised rate of severe exacerbation events Relative risk versus placebo (95% CI)	**0.52** (0.41, 0.66); p<0.0001
Change from baseline in FEV1 at 12 weeks, LS mean (SE) LS mean difference (95% CI), p value vs placebo	**0.14L** (0.08, 0.19), p<0.0001
VENTURE n=210 (with mOCS)	
Percentage reduction of OCS dose at Week 24 from baseline, LS mean (SE) – primary outcome LS mean difference vs placebo (95% CI), p value vs placebo	**28** (16, 41), p<0.0001

mOCS: maintenance oral corticosteroids, LS: least squares, SE: standard error

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

Results at first committee meeting (2)

Company's decision problem population

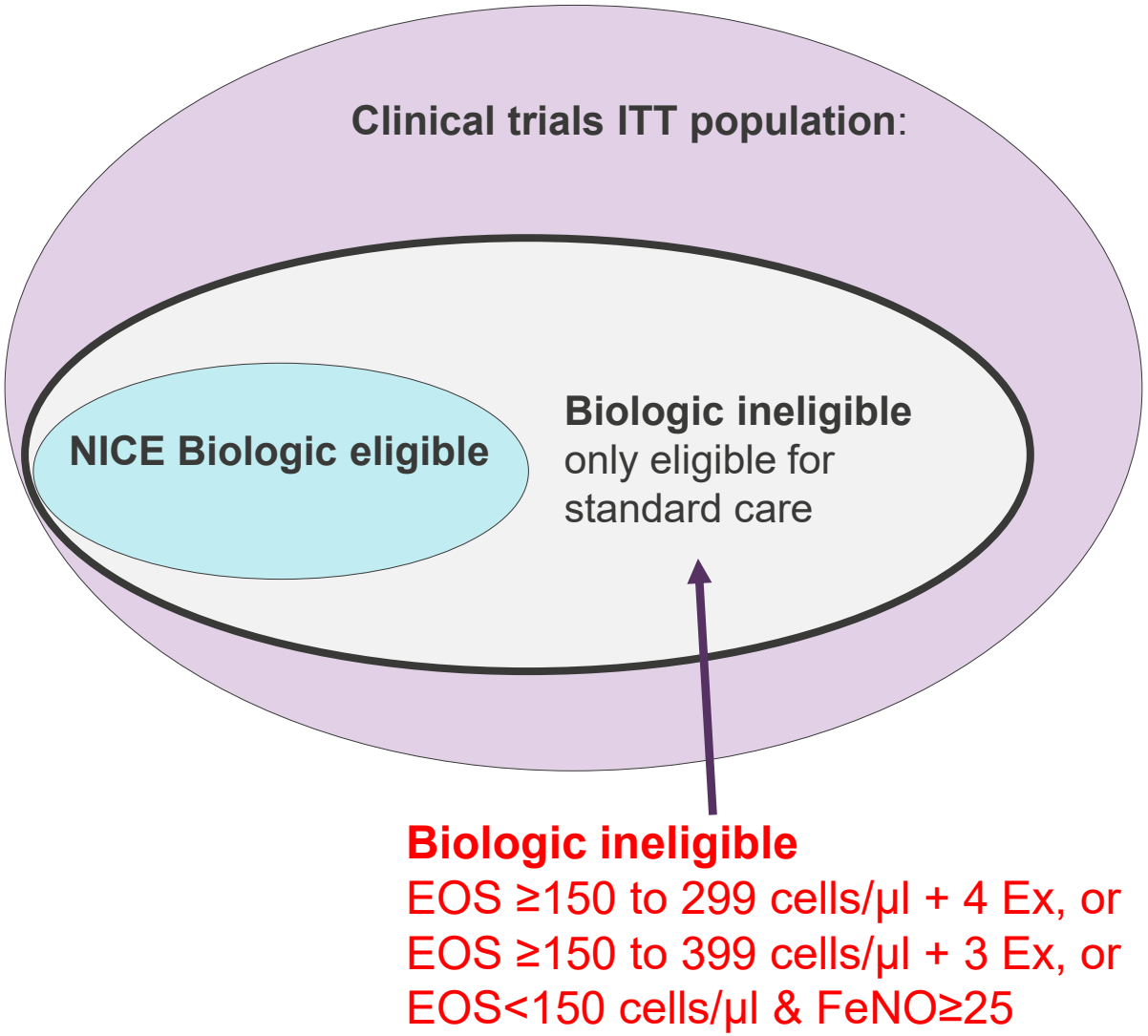


QUEST	
Adjusted annualised rate of severe exacerbation events Relative risk versus placebo (95% CI), p-value	[redacted]; p<0.0001
VENTURE (mOCS)	
Adjusted annualised rate of severe exacerbation events Relative risk versus placebo (95% CI), p-value	[redacted]; p=0.0010

Note: Small numbers
QUEST n=64 dupilumab and n=37 placebo
VENTURE n=78 dupilumab and n=74 placebo

Dupilumab more effective than standard care in company's proposed population

Results at first committee meeting (3)



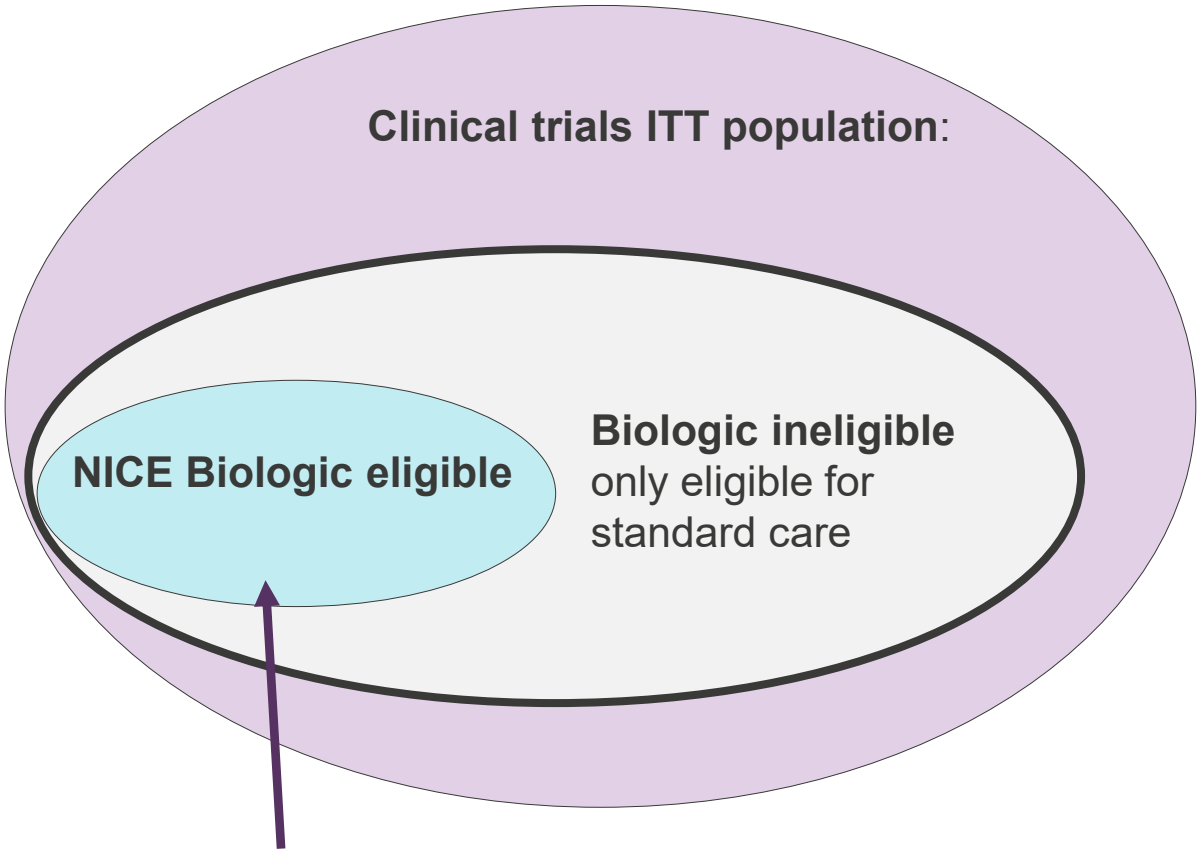
QUEST	
Adjusted annualised rate of severe exacerbation events	
Relative risk (95% CI)	[redacted]
P-value	[redacted]
Risk difference (95% CI)	[redacted]

No data for VENTURE provided by company.

Note: Small numbers (n=29 dupilumab and n=12 placebo)

Clinical effectiveness uncertain- estimates only available from QUEST

Results at first committee meeting (4)



NICE biologic eligible
EOS≥300 cells/µl & ≥4 Ex, or
EOS≥400 cells/µl & 3 Ex

Indirect treatment comparison for biologic eligible dupilumab population compared to other biologics

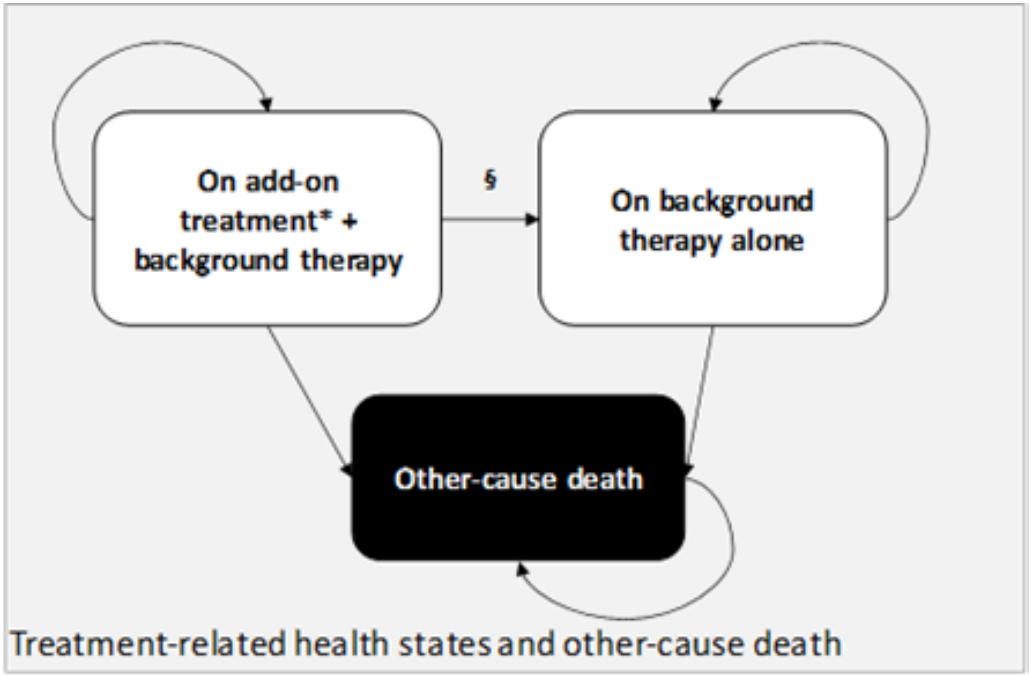
- Bucher Indirect Treatment Comparison
- Matched Adjusted Indirect Comparison

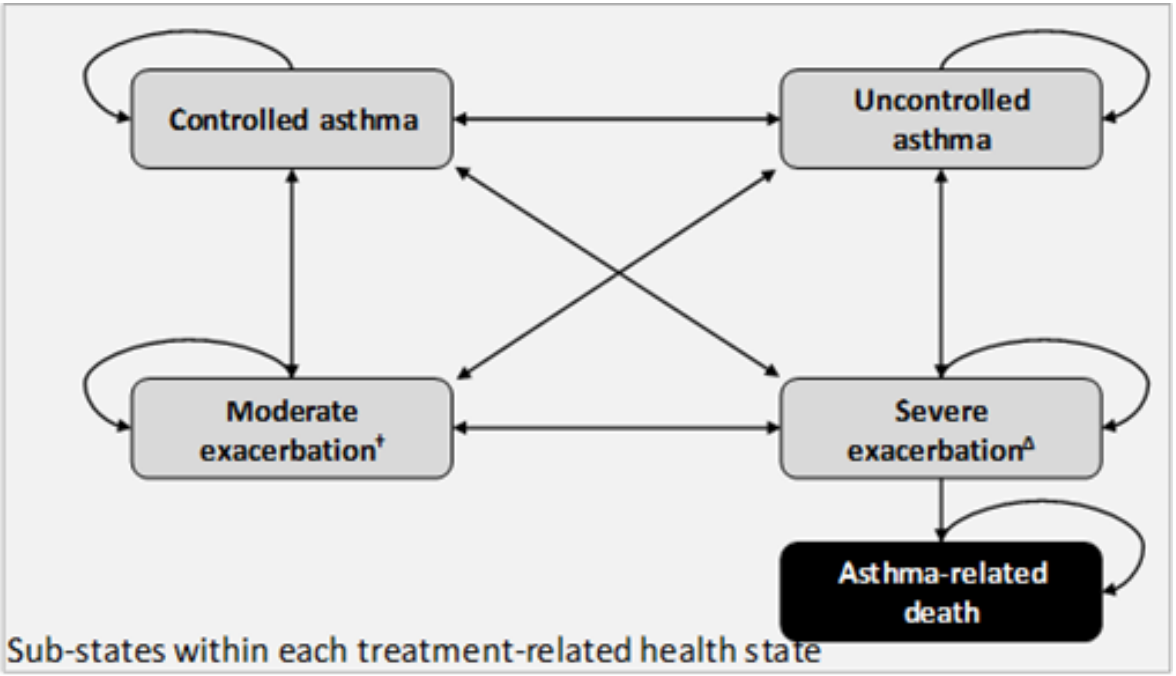
Clinical effectiveness uncertain - indirect comparisons not robust

Cost effectiveness at first appraisal committee meeting (Feb 2020)

Model structure

ACD: The committee concluded that the model was appropriate for decision making





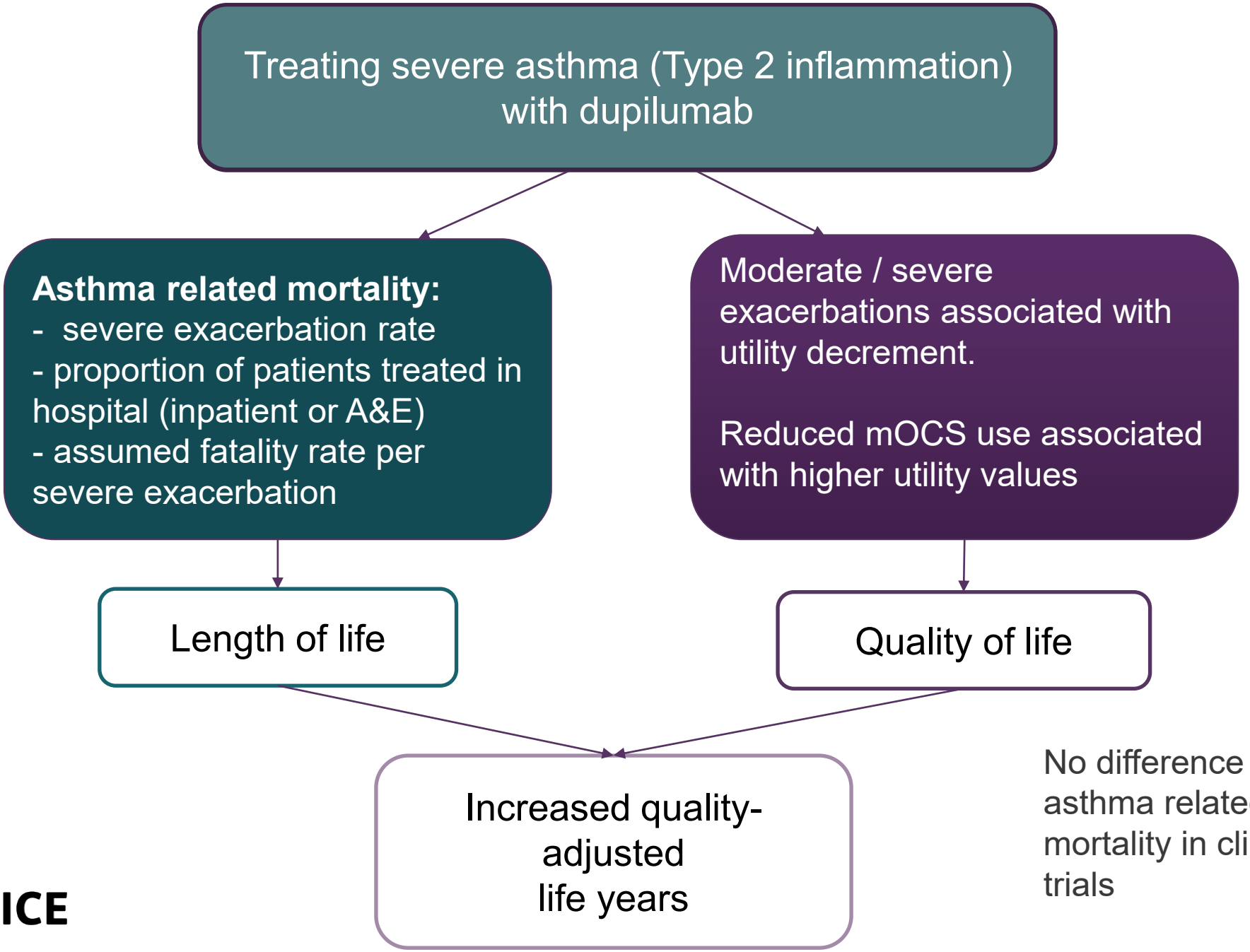
Markov model structure (Source: CS Figure 36)

Model parameters

- Lifetime horizon (maximum age of 100 years) with 4 week cycle length and half-cycle correction
- The starting cohort can be varied by the proportion of patients on mOCS, minimum levels of EOS, FeNO and the number of exacerbations in the previous 12 months
- Response (determined by ≥50% reduction in severe exacerbations; or ≥50% reduction in severe exacerbations or mOCS dose for steroid-dependent patients) assessed at 12 months, non responders stop treatment
- The cohort enters the model in the uncontrolled asthma health state
- Rates of movement between the live states are determined by a transition probability matrix and mortality rates are applied for asthma and other deaths.

NICE **Note: model assumptions can be found in table 87 of the company submission**

How QALYs accrue in the economic model



No difference in asthma related mortality in clinical trials

First committee meeting – model evidence

QUEST
Multinational, randomised, double-blind, placebo-controlled trial
(52 week duration)

VENTURE
Multinational, randomised, double-blind, placebo-controlled trial
(24 week duration)

Published literature/registries/ other sources

Parameters in model

- Transition probabilities for asthma control and exacerbations
- Probabilities of mOCS dose reduction and withdrawal
- Response (≥50% reduction in exacerbations) assessed at 12 months (as per SmPC)
- Discontinuation
- Utility values from EQ-5D-5L data supplemented with estimates from the literature
- Disutilities for adverse events related to mOCS use
- Adverse events associated with maintenance OCS use

Parameters in model

- Asthma related mortality
- **Long-term exacerbation rates**
- **Setting of severe exacerbations**
- **Resource use and costs**
- Drug acquisition, administration costs
- Health care resources

Exacerbation lower in trials than clinical practice (1st committee meeting: multiplier 1.35 TA431 mepolizumab)

At 1st meeting: Settings and resource use for exacerbations based on TA431

Exacerbation multiplier rationale (Feb 2020)

Severe exacerbations rate impacts model estimates of asthma-related mortality

ACD: Committee concluded that using a exacerbation multiplier was not the best method of adjusting severe asthma exacerbation rates

Background

- Severe annual exacerbation rate in QUEST placebo arm (2.39) **was lower than observed in clinical practice** in the preceding year (4.46).
- The company state that this reduced rate could be caused by:
  - **Better care in a clinical trial setting**
  - **Regression to the mean**
  - **Exclusion of patients with severe exacerbations**
  - **Definition of exacerbation**
- Similar placebo effects in other biologic RCTs
- Company used **multiplier for the rate of severe exacerbation after the trial period** in the base case (=1.35 from TA 431 mepolizumab) - previous TAs for similar biologics do not use a multiplier.

ERG's preferred assumption is to not apply any adjustment (multiplier = 1)

Resource use - setting of severe exacerbations (Feb 2020)

The clinical setting of severe exacerbations rates impact model estimates of asthma-related mortality

ACD: Committee would like to see exploration of different sources of data for the setting of severe exacerbations

Background

- Company's original model used **UK real world registry data** (O'Neil 2015, BTS Difficult Asthma Registry) with higher emergency care and hospitalisation proportions than QUEST.
- The company considers that QUEST trial data is **not an accurate or representative source** of data on exacerbation setting for UK patients
- ERG -this was taken from hospital and primary care records and may not include patients who self-manage with OCS.
- **ERG preferred trial data** because the definitions of severe exacerbations would be consistent with the clinical data in the model
- The company's model (following technical engagement) uses resource data from the **mepolizumab appraisal (TA431 based on the MENSA trial**).

10 year mortality rates (Feb 2020)

Asthma-related mortality drive the cost-effectiveness estimates in the model

ACD: Committee concluded that mortality estimates were not plausible – additional analyses should include 10-year mortality rates and patients flow through health states

Background

- Predicted **20% mortality** over 10 years under standard care **seemed high** compared with current UK asthma mortality (1,300 asthma-related deaths a year in UK)
- Higher death rate due to interaction between the exacerbation multiplier and the source used to inform setting of severe exacerbations

Appraisal consultation document (AC)

Recommendations

- Cost effectiveness estimates for dupilumab higher than what NICE considers a cost effective use of NHS resources

- 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.

ACD consultation responses

Patient organisation	• Asthma UK
Expert	• Patient expert
Company	• Sanofi
Public (web) comments	• NHS clinician

Comments themes

- **Disappointed and concerned that dupilumab is not recommended**
  - "I am incredibly upset that others may not get this benefit."
  - disappointing as removes a potentially valuable treatment for people with limited alternatives
- **Significant unmet need in people not eligible for biologics, but also in those eligible who did not respond to biologics**
  - "I have qualified for numerous biologics but they have not helped stabilise my asthma"
  - "Clinic series reported 25-40% suboptimal responses to biologics"
  - "Dupilumab would be a realistic option to improve their disease control/ outcomes where other drugs have failed"
- **Dupilumab is an effective and safe treatment option**
  - "Urge NICE to consider options and not deny access to a very effective and safe therapeutic option"
  - "dupilumab was the only effective treatment for me … provided substantial benefits"
- **People with other comorbidities such as chronic eczema or rhinosinusitis need to be considered – dupilumab more suitable for them**

Company response - Summary

To address key points raised in the ACD, the company **updated the population** and conducted additional cost-effectiveness analyses and explored:

- Long-term severe exacerbation rates from different sources
- Settings for severe exacerbation from different sources
- Mortality rates model estimates at 1, 5 and 10 years
- Alternative model structure for adjusting exacerbation rates (scenario analyses)

The company's base case was updated with:

- An updated target population – relevant comparator is standard of care only
- Long-term severe exacerbation rates from the QUEST trial, no adjustment (multiplier = 1)
- Setting for severe exacerbation from a real-world study (Sanofi RWE study)
- [redacted]

Summary of company ACD response

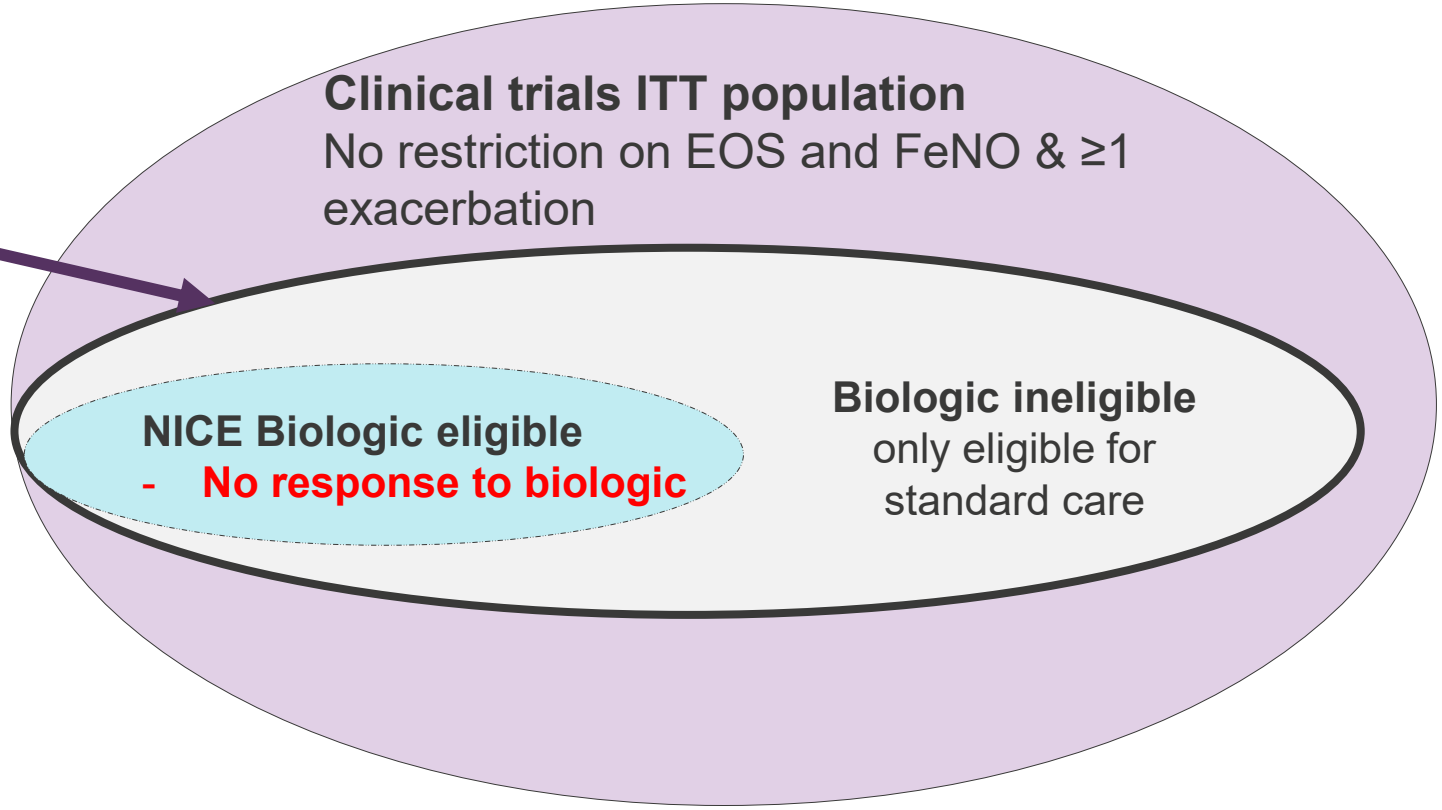
Issue	Committee preferences	Company response
Population	People with an unmet need who are not eligible for other biologicals is the most relevant for decision making	Updated population
Asthma exacerbation multiplier	Not appropriate to use an exacerbation multiplier	Updated base case uses QUEST exacerbation without adjustment (multiplier = 1)
Source of data for clinical setting for asthma exacerbations	Exploration of different sources of data (Company only used data from O'Neill 2015)	Explored and changed to Sanofi RWE study
Mortality modelling	Analyses should include 10 year mortality rates for dupilumab and standard of care and show the flow of patients through different health states	Searched for UK asthma-related mortality, no further data available

NICE

Updated Population – narrower with more severe asthma

In its response to ACD, the company updated its base-case population:

Company's decision problem population <u>at ACM2</u>
EOS ≥150cells/µ/ **AND**
FeNO≥25ppb &
≥4 exacerbations
Not eligible for biologics or have not responded to biologic therapy



NICE biologic eligible
EOS≥300 cells/µl & ≥4 Ex, or
EOS≥400 cells/µl & 3 Ex

Biologic ineligible
EOS ≥150 to 299 cells/µl + 4 Ex, or
EOS ≥150 to 399 cells/µl + 3 Ex, or
EOS<150 cells/µl & FeNO≥25

Note: QUEST included 1 patient with previous biologic treatment

Updated base case population

ACD: Defining population is challenging - people with an unmet need who are not eligible for other biologicals is the most relevant for decision making

- Company's updated population: "People with severe asthma on high dose inhaled corticosteroids (ICS), aged 12 and over and **EOS≥150 And FeNo≥25 with ≥4 exacerbations**". Can be split in **3 subgroups:**
  - Adolescents (aged 12-17)
  - Adults and not eligible for biologics (EOS 150-299)
  - Adults who previously received biologics but did not respond (EOS ≥ 300) (Note: QUEST excluded people who had biological treatment)

- The **comparator** for the updated population(s) is **standard care**

- Adolescents: NICE guidance for other biologicals only covers adults

ERG response – Limitations on subgroups (1)

- **Effectiveness**: **treatment effects are the same in all 3 subgroups**, estimated from trial data for people with EOS ≥ 150, FeNO ≥ 25 and ≥ 4 exacerbations.
- Paucity of data – Caution in interpretation of ICERs
  - **Adolescents -** 2 patients in trial (placebo arm); Company assumes clinical effectiveness in adolescents is the same as for adults
  - **Adults, biologic ineligible -** 14 patients in trial; Clinical effectiveness based on the broader trial group, transition probabilities uncertain due to sample size
  - **Adults, previous biologic but not responded -** 1 patient in trial; Company assumes clinical effectiveness in biologic non-responders is the same as for biologic-ineligible subgroup
  - Assumption based on clinical expert opinion: switch from biologics to dupilumab is acceptable due to different mechanisms of action – response can be expected

ERG response – Limitations on subgroups (2)

- Model parameters that **differ for subgroups** are **fatality rates for severe exacerbations, general population utility and mortality,** (age adjusted, differ for the adolescent subgroup).
- **Transition probabilities highly uncertain**
  - Estimated first for a larger reference group (EOS 150-299 cells/µl and FeNO ≥ 25 and 1 or more exacerbations in the previous year) and then adjusted using multipliers to reflect the higher risks for people with more previous exacerbations – This approach applies to all subgroups
  - This approach is **unlikely to be reliable for such small subgroups**
- Higher estimated ICER for adolescents - driven by lower case fatality rates in severe exacerbations for people <18, rather than difference in trial results.
- **Risk of asthma exacerbations higher** in this updated population, **reduces** the estimated ICERs for dupilumab compared with standard care

Company comments: Post trial exacerbation rates

ACD: Use of exacerbation multiplier is not the best method of adjusting severe asthma exacerbation rates – request exploration of other means of adjusting for severe exacerbations

- **In ACD response, company explored** different 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)
  - **Sanofi RWE study**
- Additional ACD response - **August 2020**:
  - company **updated base case** includes **QUEST exacerbation rates** for duration of the model (**no adjustment, multiplier = 1**) – considers it is a conservative
- **Note: long-term exacerbation rates impact asthma-related mortality in the model**

ERG response

- ERG agrees the observed exacerbation rate from trial (multiplier = 1) is conservative but the **most appropriate**
- **ERG welcomes the company's updated base case**

Company comments: Sources for exacerbation setting

ACD: Best source of data to inform the setting of treating exacerbations is unclear – request exploration of different sources of data to inform the model

- Company explored
  - **WATCH (**Wessex Asthma Cohort of Difficult Asthma)
  - **U-BIOPRED (**Unbiased BIOmarkers in PREDiction of respiratory disease outcomes)
  - **Sanofi RWE study**
- **Sanofi RWE study** considered **most appropriate** source for company's updated base case, as specifically UK data and definition aligned with trial – hospitalisation rates changed from 8.24% to 11.46%

Severe Exacerbation Setting (%)	**QUEST**	VENTURE	**UK Sanofi RWE**	TA 431 (MENSA)	O'Neill 2015
OCS burst, Physician Visit	93.34	85.32	**83.33**	83.07	73.57
A&E admission	3.00	6.42	**5.21**	8.69	7.79
Hospitalisation	3.66	8.26	**11.46**	8.24	18.64

Note: exacerbation settings impact asthma-related mortality in the model

ERG response

- **ERG agrees with company's choice**, Sanofi RWE study seems to be of **reasonable quality** and **results produced consistent with other sources (VENTURE and MENSA trials)**

Source: Company's ACD response, table 3

Company comments: Mortality modelling

ACD: Additional analyses should include 10-year mortality rates for dupilumab and standard care, show the flow of patients through different health states and whether output is consistent with UK asthma mortality rate

- Fist meeting: predicted **20% mortality** over 10 years under standard care
- When removing multiplier for exacerbation rates and sourcing exacerbation rates setting from Sanofi RWE study (company's updated base case), **10-year mortality reduced to 18%** with standard care
- Company conducted a literature search for UK asthma-related mortality – **no further publications found**

Note: Mortality drives cost-effectiveness in model – higher mortality leads to lower ICER

ERG response

- Mortality probably overestimated
- **difficult to judge plausibility of model survival projections** without data available
- **Model predictions** for updated base-case population**:** mean age of deaths **70.1 years with standard care; and 72.9 years with dupilumab**
- In comparison:
  - estimated life expectancy **with standard care: 80.4 years** in TA565 (benralizumab)
  - UK life expectancy: **83.1 years** for a 50-year old person

Company's updated base case

- Company's base case ICER at **first appraisal meeting** (Feb 2020): **£34,216/QALY** (deterministic, simple Patient Access Scheme [PAS])
- ICERs for company's updated base case with simple PAS:
  - An updated target population
  - Long-term severe exacerbation rates from the QUEST trial, no adjustment (multiplier = 1)
  - Setting for severe exacerbation from a real-world study (Sanofi RWE study)

[redacted]

Population	Deterministic ICER (£/QALY) Simple PAS
Updated base case	**£35,968**
Adolescents	£83,379
Adults not eligible to biologics	£33,537
Adults who did not respond to biologics	£38,379

Innovation

Company's position	Clinician's position	Committee's position
Due to the distinct interleukin (IL)-4 and IL-13 pathways, dupilumab targets a different patient population compared to current biologic therapies.	Innovative because it targets a different patient population to the other current biological therapies (although, as noted there is some overlap between the different patient populations)	ACD: Committee acknowledge there are additional benefits not captured in the QALY calculation (in people with comorbidities such as nasal polyps and atopic dermatitis)

Have all the health benefits been captured in the QALY?

Equalities

- No equalities issues were identified.

Key issues

Is the proposed narrower population (and subgroups) appropriate?

Severe asthma – serum eosinophil count (EOS) ≥150 cells/µl **And** Fractional exhaled nitric oxide (FeNO) ≥25 ppb with ≥4 exacerbations in the previous year who are:

- Adolescents (aged 12-17)
- Adults and not eligible for biologics (EOS 150-299)
- Adults who previously received biologics but did not respond (EOS ≥ 300)

Is the company's approach to asthma exacerbation rates appropriate?

- The company now applies the observed severe exacerbation rates from the clinical trial through the modelled lifetime without adjustment (multiplier =1)

Is the source of where asthma exacerbations are treated appropriate?

- What source should be used to estimate the proportions of patients with severe exacerbations treated in emergency care and inpatient setting? – impacts mortality

Has the company adequately explored 10- year mortality modelling as requested?