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Dupilumab for treating severe asthma

Produced by Southampton Health Technology Assessments Centre

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Rider on responsibility for report

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

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Contributions of authors

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

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

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The company have made assumptions about the level of comparator PAS (cPAS) in their submission. All assumed cPAS information has been highlighted in the ERG report in green

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

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

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

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

SUMMARY

Scope of the company submission

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

The company's decision problem population is:

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

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

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

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

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

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

Summary of submitted clinical effectiveness evidence

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

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

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

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

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

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

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

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

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

Results from the three dupilumab RCTs

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

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

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

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

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

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

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

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

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

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

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

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

Indirect treatment comparisons

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

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

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

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

Bucher ITC methods

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

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

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

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

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

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

MAIC methods

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

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

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

Indirect treatment comparison results

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

<u>Bucher ITC results</u>

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

<u>MAIC results</u>

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

Summary of submitted cost effectiveness evidence

The CS includes:

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

Review of published economic analyses

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

Description of the company's economic model

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

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

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

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

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

The company's cost-effectiveness results

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

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

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

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

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

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

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

Source: CS Table 89

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

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

Source: CS Table 92

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

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

Source: CS Table 143

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

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

Source: CS Table 148

The company draw the following conclusions:

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

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

Commentary on the robustness of submitted evidence

Strengths

Clinical effectiveness

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

Cost effectiveness

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

Weaknesses and areas of uncertainty

Clinical effectiveness

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

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

Cost effectiveness

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

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

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

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

Summary of additional work undertaken by the ERG

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

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

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

ERG base case and scenarios

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

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

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

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

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

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

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

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

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

1 Introduction to ERG Report

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

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

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

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

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

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

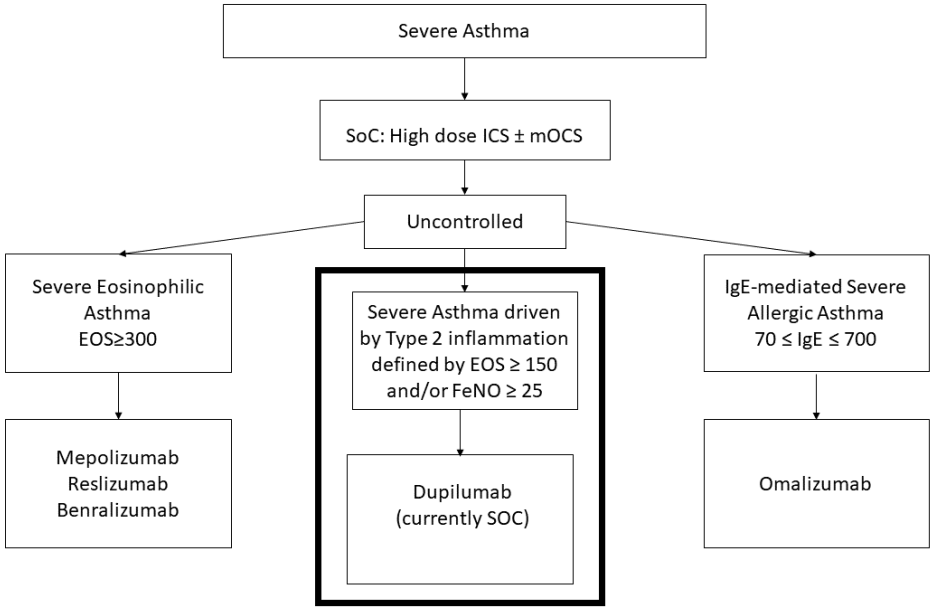
GINA[1]	Asthma that is uncontrolled despite adherence with maximal optimized therapy and treatment of contributory factors, or that worsens when high dose treatment is decreased
ATS/ERS[6]	Patients are defined as having severe asthma if they experience any of the following criteria: Poor symptom control: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

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

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

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

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



Source: reproduction of CS Figure 5

Figure 1 Position of dupilumab in the treatment pathway

2.2 Critique of company's overview of current service provision

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

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

Table 8 NICE recommended therapies for severe asthma subtypes

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

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

2.3 Critique of company's definition of decision problem

Population

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

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

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

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

Intervention

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

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

Comparators

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

Outcomes

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

Other relevant factors

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

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

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

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

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

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

3 CLINICAL EFFECTIVENESS

3.1 Critique of company's approach to systematic review

3.1.1 Description of company's search strategy

The CS details the following literature searches:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3.1.3 Identified studies

A total of five trials for dupilumab were included:

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

3.1.3.1 Key features of the DRI12544, QUEST and VENTURE RCTs

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

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

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

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

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

[a] Placebos in all trials were matched volume placebos

DRI12544 (CS Tables 8 to 10)

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

QUEST (CS Tables 8 to 10)

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

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

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

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

3.1.3.2 The decision problem population

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

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

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

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

[b] From clarification question response A2

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

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

DRI12544

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

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

VENTURE

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

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

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

Table 11 Baseline demographic characteristics of the clinical trials

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

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

Table 12 Baseline clinical characteristics of the clinical trials

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

Source: CS Tables 12 and 13

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

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

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

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

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

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

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

Source: CS Table 13

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

3.1.3.4 Ongoing studies

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

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

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

3.1.4 Description and critique of the approach to validity assessment

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

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

and

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

The CS and ERG assessments are compared in Table 14.

Table 14 Company and ERG assessment of trial quality

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

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

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

3.1.5 Description and critique of company’s outcome selection

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

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

Lung function

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

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

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

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

Asthma control

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

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

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

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

Exacerbations

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

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

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

HRQoL

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

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

Use of oral corticosteroids

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

Mortality and adverse effects of treatment

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

FeNO

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

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

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

Analysis populations in the clinical trials

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

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

Statistical analysis approaches in the clinical trials

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

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

Table 16 Overview of statistical approaches in the trials of dupilumab

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

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

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

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

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

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

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

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

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

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

ERG Conclusion: Overall the statistical approaches appear generally reasonable.

Proportion of missing data

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

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

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

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

Reporting of analyses

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

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

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

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

3.1.7.1 Rationale for ITCs and MAICs

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

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

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

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

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

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

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

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

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

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

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

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

Table 21 RCT evidence included in the indirect comparisons

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

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

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

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

3.1.7.3 Adjusted pair-wise Bucher ITCs

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

3.1.7.3.1 Generation of dupilumab subgroups

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

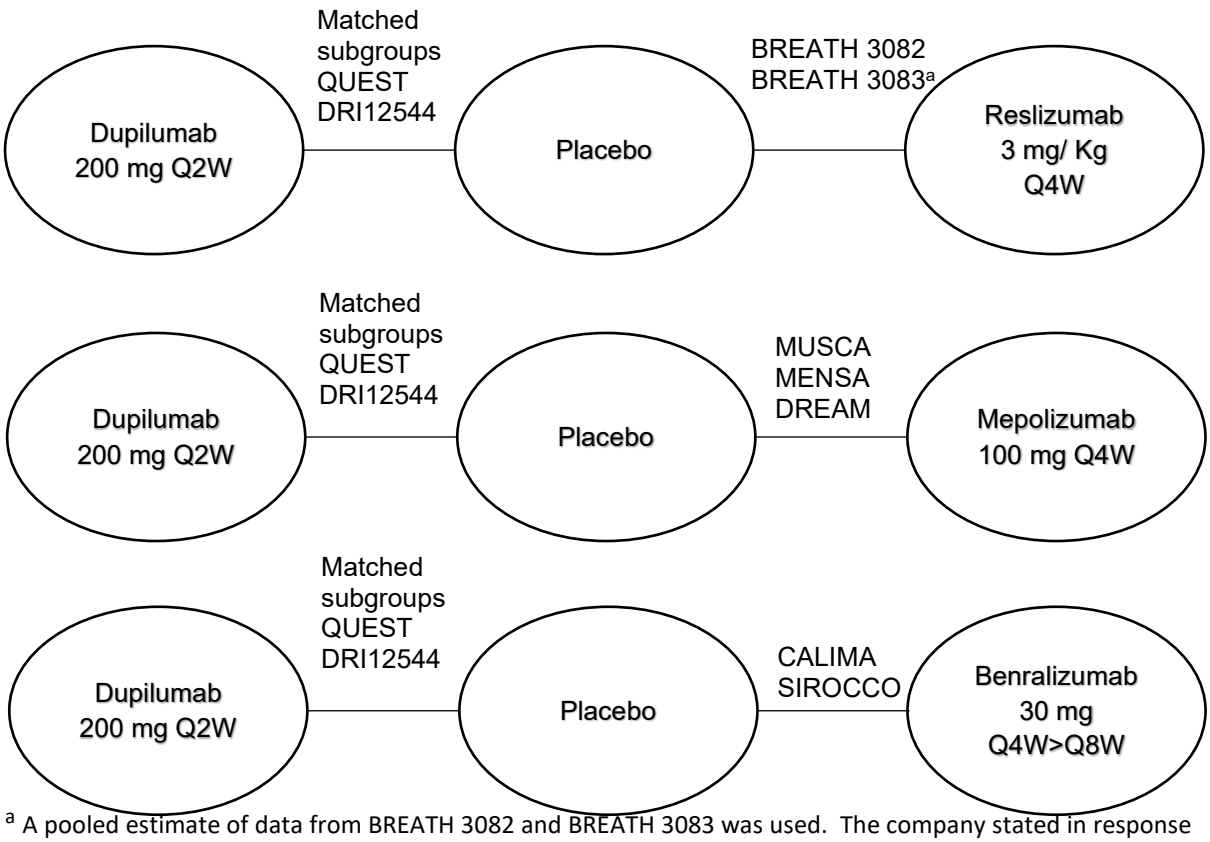
Table 22 Descriptors for the dupilumab trial subgroups formed for the Bucher ITCs

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

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

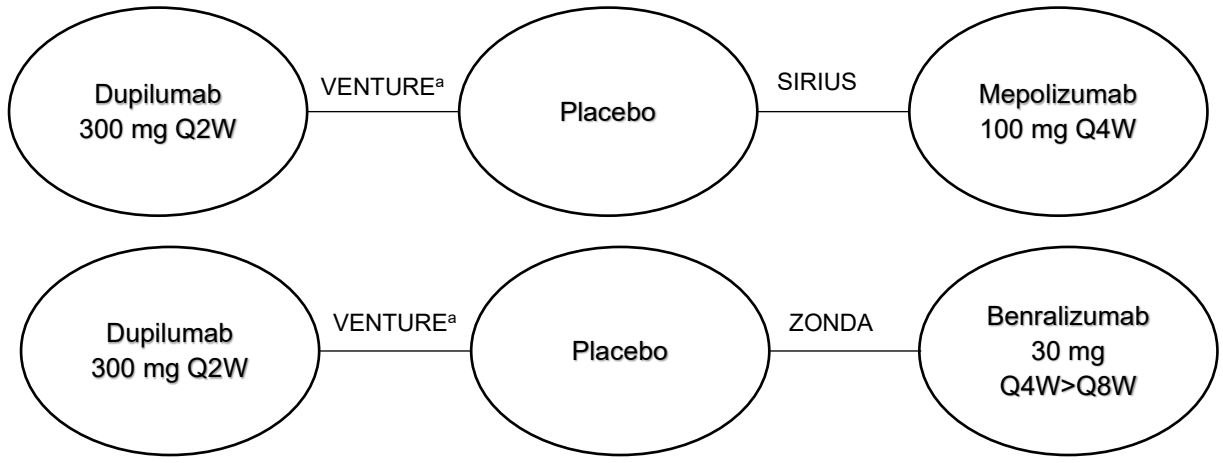
A series of pairwise indirect comparisons via the common placebo comparator were undertaken for subgroups of dupilumab patients matched against each of the comparator US/global labels in the uncontrolled persistent asthma population as shown in Figure 2.

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



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

Figure 2 ITC comparisons for uncontrolled persistent asthma population



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

Figure 3 ITC comparisons for the oral corticosteroid dependent asthma population

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3.1.7.3.1 Statistical methods for the Bucher ITC

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3.1.7.3.2 Bucher ITC quality assessment

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

ITC method

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

Similarity of treatment effects

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

3.1.7.4 Statistical methods for the MAIC

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

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

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

The limitations to the MAIC approach are:

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

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

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

The company states that the MAICs were:

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

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

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

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

Identification of treatment effect modifiers

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

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

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

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

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

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

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

MAIC models

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

Where there were multiple RCTs for each comparator, the matching was conducted for each comparator RCT separately then results were pooled (e.g CS Tables 47, 55).

The analyses were conducted using STATA v14.2, R v3.4.2 and SAS v9.4. The code used was not provided so this was requested by the ERG and NICE (clarification question A24). Stata and R code were provided, SAS code was not. The key constituent parts of the code to perform the MAIC are consistent with the NICE DSU guidance on methods for population-adjusted indirect comparisons.[2] As the ERG does not have access to the dupilumab IPD it was not possible to validate the analyses.

After matching the filtered dupilumab population with the comparator trial populations sample sizes were further reduced. The effective sample sizes (ESS) after matching are available in Appendix O Tables 116 – 122. In most cases the ESS seems reasonable but there are some low ESS where the ESS for the post-match arms has decreased by more than 50% (for the exploratory population). The company did not provide the post-match patient characteristics for the MAIC analyses so these were requested (Clarification A23). The Company reported that matching was successful and that “identical post-matching characteristics between dupilumab and comparator trials were observed”. A histogram of

weights was also requested for each MAIC (Clarification A28). Small proportions of patients attracted disproportionately high weights in certain mepolizumab analyses and thus the results would be driven by these relatively few patients.

3.1.7.5 Summary of the company's ITCs

- The anti-IL5 biologics are a relevant comparator to dupilumab for an overlap population of patients with the features of type 2 inflammation and eosinophilic asthma.
- The company conducted a feasibility assessment before proceeding with the ITCs but the results of the feasibility assessment were not reported in detail. In particular the company did not provide tables of baseline characteristics for the comparator studies. The ERG is therefore unable to confirm whether the company's conclusions about the similarity of treatment effects are correct.
- Results for severe asthma exacerbations and the results on steroid sparing for the OCS dependent asthma population (results for 100% reduction from OCS and reduction to a daily dose <5mg) from the exploratory Bucher ITCs inform the company's exploratory cost-effectiveness analyses. The results of some MAIC analyses are used in a scenario analysis in the economic model.
- The company indicated that Bucher ITC results were preferred for the exploratory cost-effectiveness analyses because of the limitations of the MAIC. The limitations of the MAIC predominantly seem to stem from limitations in the matching process (summarised in CS Appendix O.8).

Bucher ITCs

- Subgroup dupilumab data were generated by using the US/global labels for each comparator of interest to identify the patient phenotypes that were important to match. Individual patient data for dupilumab were then matched to the inclusion criteria and baseline values of the patients in the registrational trials. These dupilumab population subgroups therefore differ from the company's decision problem population and the populations described by the NICE guidance recommendation for each of the comparators.
- For two of the three comparators, mepolizumab and reslizumab, the company was able to match to and compare dupilumab data against a comparator subgroup that better matched (but was not identical to) the NICE recommended populations.

- In creating subgroups randomisation was effectively broken and a different subgroups of dupilumab patients was used to compare against each comparator in each pairwise ITC.
- The ERG have not been able to test or validate the R programming code for the Bucher ITCs because it was not executable (without a data file).

MAICs

- The choice of treatment effect modifiers seems appropriate. However some trials were matched on fewer than the four treatment effect modifiers because the necessary information for some treatment effect modifiers was not reported.
- Pre-match "filtering" appears not to have removed any patients with potential for inclusion in matching
- The methods of the MAIC appear to have been properly applied and the matching (where it was possible) appears to have been successful.
- It is difficult to ascertain from the CS how similar the comparator study populations were to patients that would be treated in the NHS. Therefore how well the results of the MAICs represent severe asthma patients treated in the NHS is uncertain.

A summary of the Bucher ITC and MAIC approaches is provided in Table 29.

Table 29 Comparison of aspects of the Bucher ITC and MAIC approaches

	Bucher ITC approach	**MAIC approach**
Strengths (in relation to this appraisal)	Simple transparent methodology. Methodology followed appropriately. Use of annualised relapse rate adjusts for differences in follow-up between trials.	Robust methodology to adjust for differences between trials. Matching successful in terms of balancing patient populations according to choice of treatment effect modifiers albeit there remain imbalances of other non-treatment-effect modifiers.
Limitations (in relation to this appraisal)	Method itself cannot adjust for heterogeneity between trials. An investigation of heterogeneity between studies is not fully described nor tabulated. Instead the	Assumption underlying MAIC is that comparator population is the target real-world population. The choice of treatment effect modifiers to

	Company has selected subgroups of their trial data to "match" the licenses/registrational trials of comparators. Use of subgroups breaks the randomisation within the dupilumab trials. Random effects meta-analysis used by default for comparator trials regardless of reported I^2 thereby increasing uncertainty.	match on is limited to four but some trials matched on fewer than four factors. Where there were multiple trials for comparators, each trial was matched to in turn, then results were pooled. No adjustment for different lengths of follow-up between trials.
What would be the changes that would be necessary in the data to make this approach as robust as possible (and are these feasible)?	Unclear	Comparator populations' approximation to real world population. No pooling of matched studies across comparators.
Any other key issues?	Results used in economic model. Instead of conducting a "global" NMA comprising all comparators, the Company have conducted a series of ITCs each using different subgroups of the dupilumab IPD set. This precludes comparison across more than one treatment at a time. An NMA would have included the ITT population for dupilumab and comparator trials. Bayesian analyses reportedly conducted but not reported.	Included as a scenario in the economic model but cost-effectiveness results not reported in the CS. The MAIC scenario does not change conclusions from the company's exploratory comparisons with other biologics.

3.2 Summary statement of company's approach

The ERG's quality assessment of the CS review is summarised in Table 30.

Table 30 Quality assessment (CRD criteria) of CS review

CRD Quality Item: score Yes/ No/ Uncertain with comments	
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes. The CS reports inclusion and exclusion criteria for their clinical effectiveness review (CS Table 7). These criteria are wider than the NICE scope and the company's decision problem. The review also informed the NMAs and MAICs using the same eligibility criteria. The ERG agrees that the eligibility are generally appropriate.
2. Is there evidence of a substantial effort to search for all relevant research? Ie all studies identified	Yes. The company made a sufficient effort to search for all relevant research. Appropriate bibliographic databases were searched and the results were supplemented with the results of a trey literature search and hand searching recent conference proceedings. The ERG updated the searches and did not find anything additional to include. The ERG does not believe that any key trials or publications have been missed.
3. Is the validity of included studies adequately assessed?	Yes. The company assessed the validity of the included studies using NICE's criteria for RCTs. This included assessing studies included in the NMAs and MAICs. For the majority of decisions on the company's three dupilumab trials the ERG agrees with the company judgements (slight disagreements are noted in Section 3.1.4). For the comparator studies we referred to previous ERG assessments conducted for NICE appraisals and found that overall the ERGs' and company judgements were in agreement apart from determining whether a true ITT or a modified ITT analysis had been conducted for some trials.
4. Is sufficient detail of the individual studies presented?	Yes. Sufficient details were reported.
5. Are the primary studies summarised appropriately?	Yes. The included studies have been well summarised. The results reported appear accurate.

The ERG considers the systematic review processes followed good practice although it was not reported whether a second reviewer checked the validity assessments. The evidence presented for dupilumab however comes from trials with wider inclusion criteria than the decision problem. Only one outcome, annualised rate of severe exacerbations, was reported for the post-hoc subgroups of two of the three dupilumab RCTs that matched the decision problem population definition.

3.3 Summary of submitted evidence

In this section we present whole trial (i.e. ITT) population results for each outcome, firstly for people not receiving treatment with oral corticosteroids (the DRI12544 and QUEST RCTs), and then for people with steroid-dependent severe asthma (the VENTURE RCT). For all the trials the ITT population is broader than the decision problem population. For one outcome, the annualised rate of severe exacerbations, the CS reports results for post-hoc subgroup analyses on those participants in the QUEST and VENTURE trials who reflected the decision problem population:

- QUEST: EOS ≥150 or FeNO≥25 and ≥ 3 exacerbations
- VENTURE: EOS ≥150 or FeNO≥25, in patients receiving oral corticosteroids.

The results from these post-hoc subgroups are presented below alongside the ITT results for comparison. The company do not state why the post-hoc subgroup analyses for the decision problem population were only conducted for one outcome.

The CS does not report post-hoc analysis of a decision problem population subgroup for the DRI12544 trial (n= 46, approximately 15% of the ITT population). In response to clarification question A2, the company stated that this trial was not included in the economic model as there would be methodological difficulties in pooling data between QUEST and DRI12544 to derive transition probabilities.

3.3.1 Annualised rate of severe exacerbations

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

DRI12544 and QUEST trials

In people with severe asthma who were not receiving treatment with oral corticosteroids the adjusted annualised rate of severe asthma exacerbations was lower among patients in the dupilumab 200mg Q2W arms than in the placebo arms of both DRI12544 and QUEST (Table 31). In the DRI12544 trial there was a 70% (95% CI 43.5% to 84.1%) lower rate of severe exacerbations than in the placebo group (p= 0.0002) whereas in the QUEST trial there was a 47.7% (95% CI 33.8% to 58.7%) lower rate of severe exacerbations in dupilumab group (p<0.0001). The unadjusted and adjusted annualised rates of severe

exacerbation events were similar in the QUEST trial (the unadjusted rate was not reported for DRI12544). In DRI12544 the mean annualised exacerbation rate for individual patients was just over 1 (SD 2.26) in the placebo group but this was only 0.3 (SD 1.19) in the dupilumab 200 mg Q2W group. In QUEST a smaller proportion of participants in the duplilumab group experienced at least 1 exacerbation event than in the placebo group (29.2% versus 42.3% respectively) (not reported for DRI12544).

In the QUEST trial decision problem population subgroup there was a [redacted] (95% CI [redacted]) lower rate of severe exacerbations in the dupilumab group in comparison to the placebo group (p<0.0001) (Table 31). The company also present the results of a dupilumab responder analysis, which included those patients in the dupilumab decision problem subgroup who experienced a reduction in annualised rate of severe asthma exacerbations of greater than 50% on the 52-week treatment period compared to the year prior to randomisation (the number of such patients is not reported). In this analysis, reported in CS Table 34, there was an [redacted] (95% CI [redacted]) lower rate of severe exacerbations in the dupilumab responders in comparison to all placebo group patients (p<0.0001).

Table 31 Severe exacerbations, ITT population

Outcome measure	DRI12544 On-treatment analysis		QUEST ITT population		QUEST decision problem population [a]	
	Dupilumab 200 mg Q2W	Placebo	Dupilumab 200 mg Q2W	Placebo	Dupilumab 200 mg Q2W	Placebo
	N=150	N=158	N=631	N=317	N=64	N=37
Adjusted annualised severe exacerbation event rate						
Estimate (95% CI)	0.269; (0.157, 0.461)	0.897 (0.619, 1.300)	0.456 (0.389, 0.534)	0.871 (0.724, 1.048)	[redacted]	[redacted]
Relative risk versus placebo (95% CI)	0.300 (0.159, 0.565); p=0.0002		0.523 (0.413, 0.662); p<0.0001		[redacted]; p<0.0001	
Risk difference vs placebo (95% CI)	-0.628[b] (NR)		–0.416 (–0.588, –0.243)		[redacted]	
Unadjusted annualised rate of severe exacerbation events[c]						
Estimate	NR	NR	0.481	0.980	[redacted]	[redacted]
Individual patient annualised severe exacerbation events rated						
n	148	158	NR	NR	NR	NR
Mean (SD)	0.30 (1.19)	1.07 (2.26)	NR	NR	NR	NR
Patients with ≥1 severe exacerbation event						
Mean (SD)	NR	NR	184 (29.2)	134 (42.3)	NR	NR
Number of severe exacerbation events, n (%)						
0	NR	NR	447 (70.8)	183 (57.7)	NR	NR
1	NR	NR	111 (17.6)	62 (19.6)	NR	NR
2	NR	NR	44 (7.0)	31 (9.8)	NR	NR
3	NR	NR	23 (3.6)	19 (6.0)	NR	NR
≥4	NR	NR	6 (1.0)	22 (6.9)	NR	NR

Source: CS Tables 17, 19, 34
NR not reported
[a] EOS ≥150 OR FeNO ≥25 AND ≥3 exacerbations.
[b] Calculated by ERG.
[c] The total number of events that occurred during the 52-week treatment period divided by the total number of patient-years followed in the 52-week treatment period.
[d] The number of severe exacerbation events for each patient divided by the number of years followed in the treatment period for that patient.

For the QUEST trial only the CS reports that dupilumab treatment did not have an effect on severe exacerbations resulting in hospitalisation of A&E visits (CS Table 24). Although the company note that the overall rate of events in the placebo groups was low no indication is given as to what a typical rate of events might be.

3.3.1.1 VENTURE trial

In the VENTURE trial population (people with asthma who were receiving treatment with oral corticosteroids) the adjusted annualised rate of severe asthma exacerbations was 59.3% (95% CI 37.0% to 73.7%) lower among patients in the dupilumab 300mg Q2W arm than in the placebo arm (Table 32).

In the VENTURE trial decision problem population subgroup there was a [redacted] (95% CI [redacted]) lower rate of severe exacerbations in the dupilumab group in comparison to the placebo group (p<0.0010) (Table 32). A responder analysis was conducted which included those dupilumab patients in the decision problem subgroup who reduced their OCS dose by 50% or more at week 12 or who had a reduction in the annualised rate of severe asthma exacerbation events over 50% on the 24-week treatment period compared to the year prior to randomisation (the number of such patients is not reported). In this analysis, reported in CS Table 35, there was a [redacted] (95% CI [redacted]) lower rate of severe exacerbations in the dupilumab responders in comparison to all patients in the placebo group (p=0.0002).

Table 32 Annualised rate of severe exacerbations

Outcome measure	ITT population		Decision problem population [a]	
	Dupilumab 300 mg Q2W	Placebo	Dupilumab 300 mg Q2W	Placebo
	N=103	N=107	N=78	N=74
Adjusted annualised rate of severe exacerbation events[b]				
Estimate (95% CI)	0.649 (0.442, 0.955)	1.597 (1.248, 2.043)	[redacted]	[redacted]
Risk ratio versus placebo (95% CI); p-value	0.407 (0.263, 0.630); p-value not reported		[redacted]; p=0.0010	
Risk difference versus placebo (95% CI)	–0.947 (–1.393, –0.501)		[redacted]	
Unadjusted annualised rate of severe exacerbation events at Week 52[c]				
Estimate	Not reported	Not reported	[redacted]	[redacted]

Source: CS Tables 31 and 35
[a] EOS ≥150 OR FeNO ≥25 AND mOCS
[b] Derived using negative binomial model with the total number of events onset from randomisation up to week 24 or last contact date (whichever comes earlier) as the response variable.
[c] The total number of events that occurred during the 24-week treatment period divided by the total number of patient-years followed in the 24-week treatment period.

The CS appendix (CS Appendix L. Table 70) shows that dupilumab treatment did not have a statistically significant effect on severe exacerbations resulting in hospitalisation of A&E visits.

3.3.2 Time to first severe exacerbation event

3.3.2.1 DRI12544 and QUEST trials

Time to the first severe exacerbation event is not reported in the CS for the DRI12544 trial but the published paper[16] states that dupilumab significantly delayed the time to first severe exacerbation. In the QUEST trial, the time to first severe exacerbation was also significantly delayed for the dupilumab 200mg Q2W group (HR = 0.611, p<0.001). The CS presents a Kaplan-Meier plot of time to asthma exacerbation in CS Figure 18.

3.3.2.2 VENTURE trial

The CS states that there was a significant delay in time to first severe exacerbation for the dupilumab group in the VENTURE trial in comparison to the placebo group. A hazard ratio is not report but the Kaplan-Meier plot is presented in CS Figure 26.

3.3.3 Change from baseline in FEV_1 at 12 weeks

Change from baseline in FEV_1 was reported in all three trials, but was reported as "FEV_1" in DRI12544 and as "pre-bronchodilator FEV_1" in QUEST and VENTURE. The ERG notes that the DRI12544 CSR states "Spirometry was to be performed between 6 and 10:30 AM after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for 6 hours and withholding the last dose of ICS/LABA for 12 hours and prior to administration of investigational product, if applicable" we therefore believe that the DRI12544 trial FEV_1 was also a "pre-bronchodilator FEV_1".

3.3.3.1 DRI12544 and QUEST trials

Change from baseline (CFB) in FEV1 at 12 weeks was the primary outcome in the DRI12544 trial and one of the two co-primary outcomes in the QUEST trial. Missing data (in DRI12544 9.3% in the dupilumab arm and 18.4% in the placebo arm; in QUEST approximately 3.2% in both the dupilumab and placebo arms) were not imputed in the primary analysis so therefore these results are not from ITT analyses. There was an

increase in FEV1 at 12 weeks in comparison to baseline in the placebo and dupilumab arms of both trials (Table 33). In asthma, an improvement in FEV1 of over 10% from baseline measurements is considered the minimal clinically important difference (MCID). This was achieved in the dupilumab arms but not the placebo arms (based on ERG calculations). The increase was greater in the dupilumab arms than in the placebo arms leading to least-squares mean differences of 0.20L and 0.14L in favour of dupilumab in the DRI12544 and QUEST trials respectively (p-value for the comparison against placebo 0.0001 in both trials).

Table 33 Change from baseline in FEV_1 at week 12 in DRI12544 and QUEST

	DRI12544: Change in FEV1		**QUEST: Change in pre-bronchodilator FEV1**	
FEV1 (L)	**Dupilumab 200 mg Q2W (N=150)**	**Placebo (N=158)**	**Dupilumab 200 mg Q2W (N=631)**	**Placebo (N=317)**
Baseline, n Mean (SD)	150 1.79 (0.52)	158 1.82 (0.55)	631 1.78 (0.62)	317 1.76 (0.61)
Week 12, n Mean (SD)	136 2.12 (0.68)	129 2.01 (0.69)	611 2.07 (0.76)	307 1.92 (0.70)
CFB primary analysis, n Mean (SD) LS mean (SE)	136 - 0.31 (0.03)	129 - 0.12 (0.03)	611 0.28 (0.45) 0.32 (0.02)	307 0.15 (0.36) 0.18 (0.02)
LS mean difference (95% CI)	0.20 (0.11, 0.28)		0.14 (0.08, 0.19)	
p value vs placebo	<0.0001		<0.0001	

Source: CS Tables 16 and 22
CFB: change from baseline; LS: least squares

The CS reports a number of sensitivity analyses conducted on the FEV_1 data from the DRI12544 trial (CS Table 16) which showed consistent results. The sensitivity analyses were conducted to test different methods of handling FEV_1 measurements confounded by the use of systemic corticosteroids during an asthma exacerbation episode, and different approaches to handling missing data.

The trial papers for the DRI12544[16] and QUEST[21] trials report the change in FEV_1 and the change in pre-bronchodilator FEV_1, respectively, to the end of the trial periods (24 weeks for DRI12544 and 52 weeks for QUEST) but the CS does not present or discuss these results. In both trials the improvement in FEV_1 in the dupilumab arm compared to placebo was sustained throughout the trial period.

3.3.3.2 VENTURE trial

Pre-bronchodilator FEV_1 in the VENTURE trial increased from baseline in the dupilumab arm but not in the placebo arm (Table 34). The mean difference between arms in the change from baseline at 24 weeks was statistically significant, being 0.22L in the dupilumab arm and close to zero in the placebo arm.

Table 34 Change from baseline in pre-bronchodilator FEV1 at week 24 in VENTURE

Outcome measure	**Dupilumab 300 mg Q2W (N=103)**	**Placebo (N=107)**
n	97	104
Mean (SD)	0.29 (0.46)	0.00 (0.51)
LS mean (SE)	0.22 (0.05)	0.01 (0.05)
LS mean difference from placebo (95% CI)	0.22 (0.09, 0.34)	
Source: CS Appendix Table 70 LS: least squares		

3.3.4 Reduction in OCS dose: VENTURE trial

Reduction in OCS dose at week 24 was the primary outcome in the VENTURE trial (participants in DRI12544 and QUEST were not on OCS at baseline and so OCS dose reduction outcomes are not relevant in these trials).

A reduction in OCS dose at week 24 was observed in the dupilumab and placebo arms of the VENTURE trial with a greater reduction in the dupilumab arm (mean reduction 73.85 mg/day vs 45.28 mg/day in the placebo arm). The LS mean difference versus placebo was 28.24 mg (95% CI 15.81 to 40.67, p<0.0001) (Table 35).

Table 35 Percentage reduction of OCS dose at Week 24 in VENTURE

OCS (mg/day)	Dupilumab 300 mg Q2W (N=103)	Placebo (N=107)
Baseline		
n	103	107
Mean (SD)	10.75 (5.90)	11.75 (6.31)
Week 24		
n	101	106
Mean (SD)	3.13 (5.44)	6.32 (6.75)
Percentage reduction from baseline		
n	101	106
Mean (SD)[a]	73.85 (39.78)	45.28 (50.73)
Median[†]	100.00	50.00
LS mean (SE)	70.09 (4.90)	41.85 (4.57)
LS mean difference vs placebo (95% CI)	28.24 (15.81, 40.67)	-
p value vs placebo	<0.0001	-

Source: CS Table 27
ANCOVA, analysis of covariance; CI, confidence interval; EOS, eosinophil; ITT, intent to treat; LS, least squares; OCS, oral corticosteroid; Q2W, every 2 weeks; SD, standard deviation; SE, standard error.
[a] Calculated from observed data only

The CS reports three further secondary outcomes regarding reductions in OCS use in the VENTURE trial (Table 36):

- Probability of patients achieving ≥50% reduction in OCS dose
- Probability of patients achieving reduction in OCS dose to <5mg/day
- Proportion of patients no longer requiring OCS

Results for these three outcomes related to reductions in OCS use at week 24 all show a statistically significant effect in favour of dupilumab (Table 36).

Table 36 Reduction in OCS use – other outcomes at week 24 in VENTURE

Outcome measure		Dupilumab 300 mg Q2W (N=103)	Placebo (N=107)
Patients achieving a reduction of ≥50% in OCS dose at Week 24			
Yes[a], %		81.0	53.3
Adjusted probability of achieving the reduction[b]	Estimate (95% CI)	0.80 (0.70, 0.87)	0.50 (0.40, 0.61)
	OR vs placebo (95% CI)	3.98 (2.06, 7.67)	
	p value vs placebo	<0.0001	
Patients achieving a reduction of OCS dose to <5 mg/day at Week 24			
Yes[a], %		72.9	37.4
Adjusted probability of achieving the reduction	Estimate (95% CI)	0.69 (0.58, 0.79)	0.33 (0.24, 0.44)
	OR vs placebo (95% CI)	4.48 (2.39, 8.39)	
	p value vs placebo	<0.0001	
Patients no longer requiring OCS at Week 24[b]			
Yes,[a] %		52.8	29.2
Adjusted probability of achieving the reduction	Estimate (95% CI)	0.48 (0.36, 0.59)	0.25 (0.17, 0.35)
	OR vs placebo (95% CI)	2.74 (1.47, 5.10)	
	p value vs placebo	0.0015	

Source: CS Tables 28 - 30
CI, confidence interval; EOS, eosinophil; OCS, oral corticosteroid; OR, odds ratio; Q2W, every 2 weeks.
[a] Calculated based on imputed data where the missing data are imputed from the primary missing data handling approach for the primary efficacy endpoint;. [b] Only the patients in the ITT population with a baseline optimised OCS dose ≤30mg/day were included in the analysis;

3.3.5 Asthma control

All three trials used an asthma control questionnaire (either the ACQ-5 or the ACQ-7) to measure the adequacy of asthma control. This is a patient-reported measure with a score ranging from 0 to 6 for both the ACQ-5 and the ACQ-7 (see section 0). The QUEST trial also reported on loss of asthma control (LOAC) events. The CS does not discuss the changes in ACQ scores in relation to the ACQ score cut-points for uncontrolled asthma (score ≥1.5) and well controlled asthma (score ≤0.75).

3.3.5.1 DRI12544 and QUEST trials

A reduction in ACQ score indicates improvement in asthma control, and the threshold for a minimal clinically important difference in the ACQ-5 and ACQ-7 is 0.5. The reduction in ACQ-5 score in the dupilumab and placebo arms of the DRI12544 trial exceeded this threshold and was greater in the dupilumab arm, with the difference between arms at 12

weeks being statistically significant (Table 37). In the QUEST trial the LS mean difference in the reduction in ACQ-7 score versus placebo was reported at week 24 and at week 52. At both time points the difference between the dupilumab and placebo arms was in favour of dupilumab and statistically significant.

The CS (CS p. 74) indicates that the ACQ-7 score was analysed separately for the adolescent patient population but these results are not reported in the CS. The ERG also notes that the QUEST publication[21] reports ACQ-5 data for 24 and 52 weeks but this is not mentioned in the CS.

Table 37 Change in asthma control questionnaire scores in DRI12544 and QUEST trials

Outcome measure	DRI12544: ACQ-5 score[a]		QUEST: ACQ-7 score	
	Dupilumab 200 mg Q2W (N=150)	Placebo (N=158)	Dupilumab 200 mg Q2W (N=631)	Placebo (N=317)
Baseline, n	150	158	631	317
Mean (SD)	2.73 (0.82)	2.69 (0.80)	2.86 (0.71)	2.84 (0.65)
Week 12, n	134	129	NR	NR
LS mean change from baseline (SE)	-1.35 (0.08)	-1.13 (0.08)	NR	NR
LS mean difference vs placebo (95% CI)[b]	–0.22 (–0.44, –0.01)		NR	
p value vs placebo	0.0398		NR	
Week 24, n	134	127	590	296
LS mean difference vs placebo (95% CI)	–0.35 (–0.57, –0.14)		–0.36 (–0.48, –0.24)	
p value vs placebo	0.0015		<0.0001	
Week 52, n	NA	NA	470	236
Mean	NA	NA	1.53	1.95
LS mean difference vs placebo (95% CI)	NA		–0.39 (–0.52, –0.27)	
p value vs placebo	NA		p<0.0001	

Source: CS Tables 13, 18 and 26 and CS section B.2.6.2.6 with additional data from the appendix to the published DRI12544 paper.[16]
ACQ, Asthma Control Questionnaire; NA, not applicable; NR, not reported; Q2W, every 2 weeks; SD, standard deviation; SE, standard error.
[a] ACQ-5 score collected from systemic corticosteroid start date to systemic corticosteroid end date +30 days for each exacerbation episode are excluded in order to reduce the confounding effect of systemic corticosteroids.

Loss of asthma control

Loss of asthma control (LOAC) (as defined above in section 3.1.5) was reported as a secondary outcome in DRI12544 (CS Appendix L.2.1.2.4) and QUEST (CS section

B.2.6.2.4) (Table 38). The CS states that LOAC event rates from QUEST were used in calculating the moderate exacerbation health state in the economic model (CS section B.3.2.2).

In both trials the adjusted LOAC event rate was lower in the dupilumab arm than the placebo arm. The annualised risk of loss of asthma control in the dupilumab group was 68.6% (95% CI 45.7% to 81.9%) lower in DRI12544 and 37.6% (95% CI 25.4% to 47.9%) lower in QUEST compared to the respective placebo group.

For DRI12544 the individual patient annualised LOAC events rate is also reported (CS Appendix Table 56). This rate was lower in the dupilumab 200mg Q2W arm (mean 0.38, SD 1.31, n=148) than in the placebo arm (mean 1.33, SD 2.51, n=158).

Table 38Annualised loss of asthma control event rates in DRI12544 and QUEST

Annualised rate of LOAC events	DRI12544		QUEST	
	Dupilumab 200 mg Q2W (N=150)	Placebo (N=158)	Dupilumab 200 mg Q2W (N=631)	Placebo (N=317)
Adjusted estimate (95% CI)	0.347 (0.217, 0.555)	1.107 (0.801, 1.530)	1.853 (1.654, 2.076)	2.972 (2.573, 3.432)
Relative risk vs placebo (95% CI)	0.314 (0.181, 0.543); <0.0001		0.624 (0.521, 0.746); p<0.0001	
Risk difference vs placebo (95% CI)	–0.76[a] (NR)		–1.119 (–1.586, –0.651)	

Source: CS Table 25 and CS Appendix Table 56
LOAC: loss of asthma control; NR: not reported
[a] calculated by ERG

3.3.5.2 VENTURE trial

At week 24 of the VENTURE trial there was a LS mean change in the ACQ-7 from baseline of -0.93 in the dupilumab group and -0.40 in the placebo group indicating a greater improvement in asthma control in the dupilumab group, with a mean difference relative to placebo of -0.53 (95% CI -0.80 to -0.25, no p-value reported).

Table 39 Change in ACQ-7 scores in the VENTURE trial

ACQ-7 global score	Dupilumab 300 mg Q2W (N=103)	Placebo (N=107)
Baseline, n	103	107
Mean (SD)	2.70 (0.98)	2.81 (1.00)
Week 24, n	87	87
CFB LS mean (SE)	–0.93 (0.10)	–0.40 (0.10)
CFB LS mean difference vs placebo (95% CI)	–0.53 (–0.80, –0.25)	

Source: CS Tables 13 and 31
CFB, change from baseline; LS, least squares; n, number; Q2W, every 2 weeks; SD, standard deviation; SE, standard error

Loss of asthma control

This outcome was not measured in the VENTURE trial.

3.3.6 Peak expiratory flow

Morning and evening PEF are reported in the CS for the QUEST trial only (Table 40). The CS reports baseline values and the difference in the change from baseline between the dupilumab and placebo arms but does not report the change from baseline per trial arm. The LS mean difference in the change from baseline favoured dupilumab over placebo, both for morning and evening PEF measurements. The CS reports the differences as being nominally statistically significant, although no confidence intervals are provided and there are some missing data that were not accounted for in the analyses.

Table 40 Mean difference between dupilumab and placebo in the change from baseline in morning and evening PEF at week 12 in QUEST

Outcome measure	Morning PEF		Evening PEF	
	Dupilumab 200 mg Q2W (N=631)	Placebo (N=317)	Dupilumab 200 mg Q2W (N=631)	Placebo (N=317)
Baseline, n	631	317	631	317
PEF, L/min, mean (SD)	281.37 (112.13)	286.84 (111.72)	293.55 (115.34)	298.31 (110.59)
CFB at week 12, n	608	305	606	306
LS mean difference vs placebo, L/min	18.24 (nominal p<0.0001)		15.92 (nominal p<0.0001)	

Sources: CS section B.2.6.2.8, CS Figures 21 and 22, and CS Appendix Table 44
CFB: Change from baseline; LS: least squares

Graphs presented in the CS show that the difference between dupilumab and placebo group PEF measurements observed at 12 weeks persisted through to the end of the trial at 52 weeks, both for morning PEF (CS Figure 21) and evening PEF (CS Figure 22).

3.3.7 Change from baseline in FeNO

FeNO is a biomarker of type-2 inflammation and the change from baseline in FeNO is reported in the CS for all three trials.

3.3.7.1 DRI12544 and QUEST trials

The CS presents figures showing the mean percent change in FeNO over time for the DRI12544 trial (CS Figure 12) and the mean FeNO as ppb over time for the QUEST trial (CS Figure 23). The published papers for these two trials provide additional numerical data, and these have been drawn together in Table 41 below.

A fall in FeNO levels in the dupilumab arms, but not in the placebo arms, of both trials had occurred by week 2 (CS Figure 12 and Figure 23). At week 12 the LS mean difference versus placebo was -35.60 (95% CI -54.63 to 16.57) in DRI12544. The LS mean difference versus placebo is not reported for the QUEST trial but the LS mean % change from baseline at 12 weeks in the dupilumab and placebo groups was -14.9 (SD 31.3) and -2.5 (SD 21.0) respectively (Table 41). The falls in FeNO were sustained to week 24 in DRI12544 and to week 24 and week 52 in QUEST. CS Figure 12 shows that after treatment stopped at 24 weeks in DRI12544 FeNO levels returned to baseline levels in the dupilumab arm at the post-treatment follow-ups (F1 to F4 in CS Figure 12).

Table 41 Change from baseline in FeNO (ppb) in DRI12544 and QUEST trials

Outcome measure	DRI12544		QUEST	
	DUP 200 mg Q2W (N=150)	Placebo (N=158)	DUP 200 mg Q2W (N=631)	Placebo (N=317)
Baseline, n	136	144	631	313
Mean (SD)	39.25 (36.67)	38.95 (34.78)	34.4 (34.9)	34.5 (28.7)
Week 12, n	117	131	579	284
LS mean % change from baseline	-24.02 (7.06[a])	11.58 (6.73[a])	-14.9 (SD 31.3)	-2.5 (SD 21.0)
LS mean difference vs placebo (95% CI)	-35.60 (-54.63 to -16.57)		NR	
p value vs placebo	0.0003		NR	
Week 24, n	114	120	542	271

Outcome measure	DRI12544		QUEST	
	DUP 200 mg Q2W (N=150)	Placebo (N=158)	DUP 200 mg Q2W (N=631)	Placebo (N=317)
LS mean % change from baseline	-21.86 (5.59[a])	10.91 (5.39[a])	-16.2 (SD 32.6)	-2.8 (SD 21.2)
LS mean difference vs placebo (95% CI)	-32.77 (-47.89 to -17.65)		NR	
p value vs placebo	<0.0001		NR	
Week 52, n	NA	NA	422	201
Mean	NA	NA	-16.0 (SD 27.1)	-2.1 (SD 20.2)
LS mean difference vs placebo (95% CI)	NA		NR	
p value vs placebo	NA		NR	

Sources: Appendices to the published DRI12544[16] and QUEST[21] published papers, CS Tables 12 and 13, CS Figure 23
[a] Published paper does not state if this is an SD or an SE
DUP: dupilumab; NA: not applicable; NR: not reported

3.3.7.2 VENTURE trial

For the VENTURE trial the CS presents a figure (CS Figure 27) showing the mean percent change in FeNO over time. The published paper for the VENTURE trial provides a numerical value for the mean change from baseline at week 24 (Table 42).

A similar pattern to that observed in DRI12544 and QUEST is reported for VENTURE. FeNO levels fell by week 2 in the dupilumab arm, but not the placebo arm (CS Figure 27). At week 24 the mean change from baseline was -17.3 (SE 27.9) in the dupilumab arm and 0.3 (SE 27.9) (Table 42).

Table 42 Change from baseline in FeNO in the VENTURE trial

	Dupilumab 300 mg Q2W (N=103)	Placebo (N=107)
Baseline, n	101	103
Mean (SD)	35.55 (28.34)	39.62 (34.12)
Week 24, n	88	87
Mean change from baseline (SE)	-17.3 (27.9)	0.3 (27.9)

Source: Appendix to the VENTURE trial published paper[12], CS Table 13 and CS Figure 27

3.3.8 Summary of Health related quality of life

The CS reports change from baseline in the EQ-5D-3L at weeks 12 and 24 for DRI12544 (CS Figure 11), change from baseline in the EQ-5D-5L at weeks 12, 24, 36 and 52 for QUEST (CS Figure 20) and the change from baseline in the EQ-5D-5L at week 24 for VENTURE (CS Table 31).

In response to Clarification question A8 the company provided all available EQ-5D results for these trials. The ERG has summarised these data for DRI12544 and QUEST in Table 43 and for VENTURE in Table 44.

Across the 24 week DRI12544 trial, no significant differences in the change from baseline EQ-5D scores were observed. In the 52 week QUEST trial no significant differences in the change from baseline EQ-5D scores were observed at weeks 12 or 36 whereas a statistically significant difference was observed at week 24 (p = 0.0412) and at week 52 (p=0.0133). In the QUEST trial the CS states that on the EQ-5D visual analogue scale (VAS) a difference was observed at weeks 12, 24 and 52. The ERG infers that no difference was observed at week 36.

Table 43 Change from baseline in EQ-5D single index utility scores in DRI12544 and QUEST trials

	DRI12544 trial: EQ-5D-3L		**QUEST trial: EQ-5D-5L**	
	Dupilumab 200 mg Q2W (N=150)	**Placebo (N=158)**	**Dupilumab 200 mg Q2W (N=631)**	**Placebo (N=317)**
Baseline, n	147	158	584	293
Mean (SD)	0.80 (0.19)	0.78 (0.20)	0.74 (0.19)	0.74 (0.18)
Week 12, n	132	132	567	280
LS mean change from baseline (SE)	0.09 (0.01)	0.05 (0.01)	0.09 (0.01)	0.08 (0.01)
LS mean diff vs placebo (95% CI)	0.03 (-0.01, 0.08)	-	0.01 (-0.01, 0.03)	-
p value vs placebo	0.0902	-	0.2673	-
Week 24, n	131	127	552	275
LS mean change from baseline (SE)	0.06 (0.01)	0.06 (0.01)	0.10 (0.01)	0.07 (0.01)
LS mean diff vs placebo (95% CI)	0.00 (-0.04, 0.04)	-	0.02 (0.00, 0.05)	

	DRI12544 trial: EQ-5D-3L		QUEST trial: EQ-5D-5L	
	Dupilumab 200 mg Q2W (N=150)	**Placebo (N=158)**	**Dupilumab 200 mg Q2W (N=631)**	**Placebo (N=317)**
p value vs placebo	0.9299	-	0.0412	
Week 36, n			548	264
LS mean change from baseline (SE)	N/A	N/A	0.10 (0.01)	0.08 (0.01)
LS mean diff vs matching placebo (95% CI)	N/A	-	0.02 (-0.01, 0.04)	
p value vs matching placebo	N/A	-	0.2131	
Week 52, n			457	220
LS mean change from baseline (SE)	N/A	N/A	0.10 (0.01)	0.07 (0.01)
LS mean diff vs matching placebo (95% CI)	N/A	-	0.03 (0.01, 0.06)	
p value vs matching placebo	N/A	-	0.0133	

Source: Clarification question A8

In the VENTURE RCT no differences were observed in the change in EQ-5D scores at week 12 or at week 14 (Table 44). The CS states that at Week 24 there was "*nominal significant improvement*" in the EQ VAS (p=0.0061).

Table 44 Change from baseline in EQ-5D single index utility scores in VENTURE

	VENTURE	
EQ-5D-5L single index score	**Dupilumab 300mg q2w (N=103)**	**Placebo (N= 107)**
Baseline, n	103	107
Mean (SD)	0.74 (0.18)	0.72 (0.19)
Week 12, n	98	105
LS Mean (SE)	0.04 (0.02)	0.04 (0.02)
LS Mean Diff vs. placebo (95% CI)[a]	0.01 (-0.04, 0.05)	
P-value vs. placebo[a]	0.7951	
Week 24, n	98	100
LS Mean (SE)	0.06 (0.02)	0.04 (0.02)
LS Mean Diff vs. placebo (95% CI)	0.01 (-0.03, 0.06)	
P-value vs. placebo	0.5518	

Source: Clarification question A8

3.3.9 Sub-group analyses results

This section reports on the pre-planned subgroup analyses conducted for DRI12544, QUEST and VENTURE, as reported in the CS (note that not all pre-planned subgroup analyses are presented in the CS). In addition to these pre-specified subgroup analyses, the company conducted post-hoc subgroup analyses based on a subset of patients in the QUEST and VENTURE trials who reflect the company's decision problem population. These post-hoc subgroups were used in the analyses of one outcome, the annualised rate of severe exacerbations, and are reported in section 3.3.1 above.

The company lists the pre-planned subgroups for each of the three included RCTs in CS Table 10. The relevant row of this table is reproduced below (Table 45).

Table 45 Pre-planned subgroups in the DRI12544, QUEST and VENTURE RCTs

<table>
<tr><th>DRI12544</th><th>QUEST</th><th>VENTURE</th></tr>
<tr><td rowspan="2">• Region
• Background ICS/LABA dose levels
• Baseline FEV1
• ACQ-5
• Number of asthma events prior to the study</td><td colspan="2">• Region
• Baseline EOS level Group 1 (<0.15 Giga/L or ≥0.15 Giga/L)
• Baseline EOS level Group 2 (<0.3 Giga/L or ≥0.3 Giga/L)
• ACQ-5 (≤2, >2)
• Baseline pre-BD FEV_1 (≤1.75, >1.75 L)
• Baseline predicted FEV_1% (<60%, 60–90%)
• Baseline weight
• Baseline BMI (<25, 25–<30, ≥30 kg/m^2)
• Smoking history (former, never)
• Age at onset of asthma (<18, 18–40, >40 years)
• Baseline FeNO (<25, ≥25–<50, ≥50 ppb)
• Atopic medical conditions (yes, no)
• Number of severe asthma exacerbations prior to the study</td></tr>
<tr><td>• Territory (North America, EU, rest of world)
• Background ICS dose level at randomisation (medium, high)
• Background controller at randomisation (ICS and LABA only, ICS and LABA and anti-leukotrienes only, Other; ICS, LABA and any third controller, Other)
• Baseline periostin (ng/mL) (<median, ≥median)</td><td>• Baseline optimised OCS dose strata (≤10 mg/day, >10 mg/day)</td></tr>
</table>

Subgroup analysis results are presented in CS section B.2.7. A narrative summary of the subgroup analysis for the primary outcome of DRI12544 (change from baseline at week 12 in FEV_1) is provided and numerical data are presented for the two co-primary outcomes of QUEST and the primary outcome of VENTURE for subgroups based on EOS and FeNO levels at baseline. Some secondary outcome results for subgroups of patients for baseline blood EOS and receipt of high dose ICS at baseline are reported within CS section B.2.6. The CS states that subgroup analyses for other outcomes and subgroups in all three included studies are presented in Appendix E. However, Appendix E directs the reader to the study CSRs, which were not included in the submission. Whilst the CSRs were subsequently provided by the company (Clarification question A30), only the CSR for DRI12544 was accessible, the CSRs for QUEST and VENTURE were password protected and accessible versions were not supplied in time for the ERG to take this information into consideration. Consequently the ERG has focused on the subgroup analyses for the primary outcome(s) of each study based on baseline EOS, baseline FeNO, baseline ICS. All subgroup analyses have smaller sample sizes than the ITT populations and this should be borne in mind when interpreting results.

3.3.9.1 DRI12544

A narrative summary of the subgroup analysis for the primary outcome of DRI12544 (change from baseline at week 12 in FEV_1) is provided. This states that "*generally consistent increases in FEV_1 from baseline at Week 12 with dupilumab vs placebo across a range of demographic and baseline characteristics*" but the CS does not present any numerical data.

3.3.9.2 QUEST

Subgroup analyses for the annualised rate of severe exacerbations (co-primary outcome) suggest there was less benefit from dupilumab compared to placebo, in participants with lower baseline blood eosinophil levels (EOS <0.3 G/L in group 1 and EOS <0.15 G/L in group 2) (relative risks 0.759 and 0.925 respectively) than for participants with higher EOS levels (EOS ≥0.3 in group 1 and EOS ≥ 0.15 in group 2) (relative risks of 0.342 and 0.442 respectively). For both the lower EOS subgroups, the 95% CI for the relative risk crosses 1, indicating no statistically significant effect (Table 46). A similar pattern is evident in the subgroup analyses of FeNO, with greater benefit of dupilumab being shown for participants with baseline FeNO levels above 25 ppb (which is indicative of type-2 inflammation).

For the other co-primary outcome, change from baseline in pre-bronchodilator FEV_1 at week 12, all subgroups experienced improvements but the observed improvements were greater in the subgroups of patients with higher baseline EOS levels or higher FeNO levels.

For the subgroup of patients receiving high dose ICS at baseline the CS states that the reduction in the annualised rate of severe exacerbations and the increase in pre-bronchodilator FEV1 from baseline to week 12 were consistent with the results observed for the ITT population (CS B.2.6.2.1).

Table 46 Summary of relative risks in the annualised rate of severe exacerbations and in change from baseline in pre-BD FEV1 at week 12 in subgroups of the QUEST RCT population

Outcome	**Subgroup**		**n**	**relative risk (95% CI)**
Co-primary outcome 1: annualised event rate of severe exacerbations	Baseline blood eosinophil group 1 (Giga/L)	<0.3	535	0.759 (0.548, 1.052)
		≥0.3	412	0.342 (0.244, 0.480) p<0.0001[a]
	Baseline blood eosinophil group 2 (Giga/L)	<0.15	278	0.925 (0.580, 1.474
		≥0.15	669	0.442 (0.337, 0.581) p<0.0001[a]
	CS Figure 29 header suggests data for alternative baseline EOS cut-off criteria subgroups are available. However, there appears to be an error because CS Figure 29 is a duplicate of CS Figure 28.			
	Baseline FeNO (ppb)	<25	474	0.752 (0.541, 1.046)
		≥25 to <50	271	0.386 (0.243, 0.616)
		≥50	190	0.308 (0.183, 0.519)
	ICS dose at baseline[b]	High	489	0.539 (0.400, 0.725) p<0.0001

Co-primary outcome 2: CFB in pre-BD FEV_1 (L) at week 12	Baseline blood eosinophil group 1 (Giga/L)	<0.3	517	0.08 (0.01, 0.15)
		≥0.3	400	0.21 (0.13, 0.29) p<0.0001[c]
	Baseline blood eosinophil group 2 (Giga/L)	<0.15	268	0.06 (-0.04, 0.15)
		≥0.15	649	0.17 (0.11, 0.23) p<0.0001[c]
	Baseline blood eosinophil, alternative cut offs	<0.15	268	0.06 (-0.04, 0.15)
		≥0.15 to <0.3	249	0.11 (0.01, 0.21)
		≥0.3 to <0.5	182	0.15 (0.03, 0.26)
		≥0.5	218	0.28 (0.17, 0.39)
	Baseline FeNO (ppb)	<25	460	0.05 (-0.02, 0.12)
		≥25 to <50	262	0.19 (0.09, 0.28)
		≥50	183	0.30 (0.17, 0.44)
	ICS dose at baseline[c]	High	477	0.13 (0.06, 0.21) p = 0.0003

Source: CS Figure 28 to Figure 33, CS Table 20, CS Table 21, CS Table 23
[a] From CS Table 20
[b] From CS Table 21
[c] From CS Table 23

3.3.9.3 VENTURE

In the VENTURE trial population, a reduction in OCS dose at week 24 in comparison to baseline (whilst maintaining asthma control) was achieved in all baseline blood EOS count subgroups and all baseline FeNO level subgroups (Table 47).

Table 47 Summary of treatment difference on percentage reduction of OCS dose (mg/day) at week 24 in subgroups of the VENTURE RCT population

Primary outcome	Subgroup		n	LS Mean difference (95% CI)
Treatment difference on percentage reduction of OCS dose (mg/day) at week 24	Baseline blood eosinophil group 1 (Giga/L)	<0.15	58	26.89 (-0.73, 54.52)
		≥0.15	149	29.39 (15.67, 43.12)
	Baseline blood eosinophil group 2 (Giga/L)	<0.3	119	21.33 (3.90, 38.75)
		≥0.3	88	39.83 (18.94,54.71)
	Baseline FeNO (ppb)	<25	89	17.27 (-3.62, 38.16)
		≥25 to <50	60	38.31 (14.84, 61.78)
		≥50	52	33.64 (13.67, 53.61)

Source: CS Figures 34 and 35

3.3.10 Bucher ITC results

3.3.10.1 Uncontrolled persistent asthma population severe exacerbations

Dupilumab versus mepolizumab

As described in section 3.1.7.3.1 of this report the first step of the Bucher ITCs, when there were multiple trials or trial subgroups, was to pool the data using a random effects meta-analysis. The meta-analysis results for the DRI12544 and QUEST trial subgroups matched to the mepolizumab label indicate a lower rate of severe exacerbations among patients in receipt of dupilumab 200mg versus placebo. Similarly the meta-analysis of the three mepolizumab versus placebo trials contributing data to the Bucher ITC demonstrates a lower rate of severe exacerbations among patients in receipt of mepolizumab in comparison to those receiving placebo. When dupilumab and mepolizumab were compared with each other in a Bucher indirect treatment comparison the result suggests that treatment with dupilumab 200mg leads to a lower rate of severe exacerbations than

with mepolizumab in people with uncontrolled persistent asthma (ITC rate ratio [redacted])

Table 48 Severe exacerbations: Bucher ITC results (Dupilumab subgroup matched to mepolizumab label)

Comparison	Trial or subgroup	Rate ratio (95% CI)	Meta-analysis rate ratio (95% CI)
Dupilumab 200mg vs placebo	DRI12544 subgroup (matched to mepolizumab label)	[redacted]	[redacted]
	QUEST subgroup (matched to mepolizumab label)	[redacted]	
Mepolizumab vs placebo	DREAM	[redacted]	[redacted]
	MENSA	[redacted]	
	MUSCA	[redacted]	
		Bucher ITC rate ratio (95% CI)	
Dupilumab vs mepolizumab		[redacted]	

Source: Figure 1 Sanofi factual accuracy check form. This replaces CS Appendix Figure 35, which was submitted by the company in error.

The company were also able to form subgroups of dupilumab patients from the DRI12544 and QUEST trials who were similar to a subgroup of the MENSA mepolizumab trial reported within a NICE committee report (report not referenced in the CS). The patients in these RCT subgroups are more similar to, but not an exact match with, patients described in NICE guidance for mepolizumab. The size of the subgroups was small (individual subgroup arms ranging from 9 to 54 patients as reported in CS Table 92). The Bucher ITC rate ratio for dupilumab vs mepolizumab was 0.68 (95% CI 0.28 to 1.62) (Table 49). The company state that this result suggests dupilumab "offered a similar or a slight statistically non-significant advantage over mepolizumab". However, due to the small numbers in the subgroups (Table 28) these results have low precision (as evidenced by the wide confidence intervals).

Table 49 Severe exacerbations: Bucher ITC results (dupilumab subgroup matched to mepolizumab NICE-like subgroup)

Comparison	Trial subgroup	Rate ratio (95% CI)	Meta-analysis rate ratio (95% CI)
Dupilumab 200mg vs placebo	DRI12544 subgroup (matched to MENSA NICE-like subgroup)	[redacted]	[redacted]
	QUEST subgroup (matched to MENSA NICE-like subgroup)	[redacted]	
Mepolizumab vs placebo	MENSA NICE-like subgroup	[redacted]	Not applicable
		Bucher ITC rate ratio (95% CI)	
Dupilumab vs mepolizumab		[redacted]	

Source: Appendix N Figure 36

Dupilumab versus benralizumab

Dupilumab and benralizumab treatment both resulted in fewer severe exacerbations than placebo and when dupilumab and benralizumab were compared in a Bucher ITC the result suggests that treatment with dupilumab 200mg led to a lower rate of severe exacerbations than benralizumab in people with uncontrolled persistent asthma (ITC rate ratio [redacted]) (Table 50).

Table 50 Severe exacerbations: Bucher ITC results (Dupilumab subgroup matched to benralizumab label)

Comparison	Trial or subgroup	Rate ratio (95% CI)	Meta-analysis rate ratio (95% CI)
Dupilumab 200mg vs placebo	DRI12544 subgroup (matched to benralizumab label)	[redacted]	[redacted]
	QUEST subgroup (matched to benralizumab label)	[redacted]	

Benralizumab vs placebo	CALIMA, High ICS	[redacted]	[redacted]
	CALIMA, medium ICS	[redacted]	
	SIROCCO, High ICS	[redacted]	
		Bucher ITC rate ratio (95% CI)	
Dupilumab vs benralizumab		[redacted]	

Source: Figure 4 in the response to clarification question A19

Dupilumab versus reslizumab

Pooled results from the two BREATH RCTs were used for the ITC comparison between dupilumab and reslizumab because separate data from the individual BREATH RCTs were not available (response to clarification question A17). The Bucher ITC suggests that treatment with dupilumab 200mg led to a lower rate of severe exacerbations than treatment with reslizumab in people with uncontrolled persistent asthma (ITC rate ratio [redacted]) (Table 51).

Table 51 Severe exacerbations: Bucher ITC results (Dupilumab subgroup matched to reslizumab label)

Comparison	Trial	Rate ratio (95% CI)	Meta-analysis rate ratio (95% CI)
Dupilumab 200mg vs placebo	DRI12544 subgroup (matched to reslizumab label)	[redacted]	[redacted]
	QUEST subgroup (matched to reslizumab label)	[redacted]	
Reslizumab vs placebo	BREATH (3082 &3083)	[redacted]	Not applicable
		Bucher ITC rate ratio (95% CI)	
Dupilumab vs reslizumab		[redacted]	

Source: CS Appendix N Figure 37

The company were able to form a subgroup of dupilumab patients who were similar to a subgroup of the pooled BREATH 3082 and 3083 RCTs that better matched patients

described by the NICE reslizumab guidance (patients experiencing at least 3 severe exacerbations a year). The size of the subgroups was small (Table 28). The Bucher ITC rate ratio for dupilumab vs reslizumab was 0.77 (95% CI 0.25 to 2.39) (Table 52). The company state that this result suggests dupilumab "offered a similar or slight statistically non-significant advantage over reslizumab". However, due to the uncertainty caused by the small numbers in the subgroups (as evidenced by the wide confidence intervals), the ERG would be very cautious in generalising from this result.

Table 52 Severe exacerbations: Bucher ITC results (dupilumab subgroup matched to reslizumab NICE-like subgroup)

Comparison	Study	Study rate ratio (95% CI)	Meta-analysis rate ratio (95% CI)
Dupilumab 200mg vs placebo	DRI12544 subgroup (matched to BREATH NICE-like subgroup)	[redacted]	[redacted]
	QUEST subgroup (matched to BREATH NICE-like subgroup)	[redacted]	
Reslizumab vs placebo	BREATH (3082, 3083) NICE-like subgroup	[redacted]	N/A
		Bucher ITC rate ratio (95% CI)	
Dupilumab vs reslizumab		[redacted]	

Source: Appendix N Figure 38

3.3.10.2 OCS-dependent asthma population

For the OCS-dependent asthma population there was only a single dupilumab trial (VENTURE) and only single mepolizumab and benralizumab trials (SIRIUS and ZONDA respectively to include in the Bucher ITCs. For each ITC a dupilumab subgroup was formed by matching the patients in the dupilumab VENTURE trial to the mepolizumab (SIRIUS) or to the benralizumab (ZONDA) trial population characteristics.

3.3.10.2.1 Reduction in OCS dose <5mg/Day

Dupilumab versus mepolizumab

The Bucher ITC results favoured dupilumab 300mg suggesting that more people would achieve a reduction on OCS dose <5mg/day in comparison to mepolizumab, but this was not a statistically significant result (ITC odds ratio 1.50, 95% CI 0.54, 4.14) (Table 53).

Table 53 Reduction in OCS dose <5mg/Day: Bucher ITC results (Dupilumab subgroup matched to mepolizumab label)

Comparison	Trial or subgroup	Fixed-effect OR (95% CI)
Dupilumab 300mg vs placebo	VENTURE subgroup (matched to mepolizumab label)	3.71 (1.78, 7.74)
Mepolizumab vs placebo	SIRIUS	2.48 (1.23, 5.00)
		Bucher ITC OR (95% CI)
Dupilumab vs mepolizumab		1.50 (0.54, 4.14)

Source: CS Appendix N Figure 39

Dupilumab versus benralizumab

In a subgroup of the dupilumab VENTURE trial population formed by matching to the benralizumab US/global label there was a numerical, but not a statistically significant advantage over benralizumab (ITC OR 1.95 95% CI 0.51, 7.38) for the outcome of reduction in OCS dose to less than 5mg/day (Table 54).

Table 54 Reduction in OCS dose <5mg/Day: Bucher ITC results (Dupilumab subgroup matched to benralizumab label)

Comparison	Trial or subgroup	Fixed-effect odds ratio (95% CI)
Dupilumab 300mg vs placebo	VENTURE subgroup (matched to benralizumab label)	5.59 (1.77, 17.67)
Benralizumab vs placebo	ZONDA	2.87 (1.47, 5.60)

		Bucher ITC odds ratio (95% CI)
Dupilumab vs benralizumab		1.95 (0.51, 7.38)

Source: CS Appendix N Figure 43

3.3.10.2.2 Reduction in OCS dose ≥ 50%

Dupilumab versus mepolizumab

The Bucher ITC odds ratio (1.80, 95% CI 0.62, 5.21) favoured dupilumab 300mg in comparison to mepolizumab for the outcome of a reduction in OCS dose of 50% or more, but this was not a statistically significant result (Table 55).

Table 55 Reduction in OCS dose ≥50%: Bucher ITC results (Dupilumab subgroup matched to mepolizumab label)

Comparison	**Trial or subgroup**	**Fixed-effect odds ratio (95% CI)**
Dupilumab 300mg vs placebo	VENTURE subgroup (matched to mepolizumab label)	4.17 (1.88, 9.28)
Mepolizumab vs placebo	SIRIUS	2.31 (1.15, 4.64)
		Bucher ITC odds ratio (95% CI)
Dupilumab vs mepolizumab		1.80 (0.62, 5.21)

Source: CS Appendix N Figure 40

Dupilumab versus benralizumab

The Bucher ITC results for reduction on OCS dose of 50% or more favoured dupilumab 300mg in comparison to benralizumab, but this was not a statistically significant result (ITC odds ratio 1.15, 95% CI 0.30, 4.45) (Table 56).

Table 56 Reduction in OCS dose ≥50%: Bucher ITC results (Dupilumab subgroup matched to benralizumab label)

Comparison	Trial or subgroup	Fixed-effect odds ratio (95% CI)
Dupilumab 300mg vs placebo	VENTURE subgroup (matched to benralizumab label)	3.71 (1.15, 11.97)
Benralizumab vs placebo	ZONDA	3.22 (1.64, 6.32)
		Bucher ITC odds ratio (95% CI)
Dupilumab vs benralizumab		1.15 (0.30, 4.45)

Source: CS Appendix N Figure 44

3.3.10.2.3 Reduction in OCS dose 100%

Dupilumab versus mepolizumab

The result of the ITC for reduction in OCS dose of 100% offered a small numerical advantage to dupilumab over mepolizumab but the result is not statistically significant (ITC OR 1.16, 95% CI 0.31, 4.44) (Table 57).

Table 57 Reduction in OCS dose 100%: Bucher ITC results (Dupilumab subgroup matched to mepolizumab label)

Comparison	Trial or subgroup	Fixed-effect odds ratio (95% CI)
Dupilumab 300mg vs placebo	VENTURE subgroup (matched to mepolizumab label)	2.41 (1.18, 4.91)
Mepolizumab vs placebo	SIRIUS	2.07 (0.67, 6.41)
		Bucher ITC odds ratio (95% CI)
Dupilumab vs mepolizumab		1.16 (0.31, 4.44)

Source: CS Appendix N Figure 41

Dupilumab versus benralizumab

For the outcome of a 100% reduction in OCS dose the results of the Bucher ITC suggested that dupilumab 300mg and benralizumab demonstrate very similar efficacy (ITC OR 0.98 95% CI 0.21, 4.59) (Table 58).

Table 58 Reduction in OCS dose 100%: Bucher ITC results (Dupilumab subgroup matched to benralizumab label

Comparison	**Trial or subgroup**	**Fixed-effect odds ratio (95% CI)**
Dupilumab 300mg vs placebo	VENTURE subgroup (matched to benralizumab label)	4.57 (1.38, 15.11)
Benralizumab vs placebo	ZONDA	4.67 (1.76, 12.45)
		Bucher ITC odds ratio (95% CI)
Dupilumab vs benralizumab		0.98 (0.21, 4.59)

Source: CS Appendix N Figure 45

3.3.10.2.4 Severe exacerbations

Dupilumab versus mepolizumab

The Bucher ITC suggests there is no statistically significant difference between dupilumab and mepolizumab in terms of annualised severe exacerbation rates (ITC rate ratio 0.67, 95% CI 0.36, 1.28) (Table 59).

Table 59 Severe exacerbations on the treatment period: Bucher ITC results (Dupilumab subgroup matched to mepolizumab label)

Comparison	Trial or subgroup	Rate ratio (95% CI)
Dupilumab 300mg vs placebo	VENTURE subgroup (matched to mepolizumab label)	0.46 (0.27, 0.77)
Mepolizumab vs placebo	SIRIUS	0.68 (0.47, 0.99)

		Bucher ITC rate ratio (95% CI)
Dupilumab vs mepolizumab		0.67 (0.36, 1.28)

Source: CS Appendix N Figure 42

Dupilumab versus benralizumab

For the outcome of severe exacerbations, results from the ITC suggest that dupilumab 300mg does not have a statistically significant advantage over benralizumab (Bucher ITC rate ratio 0.86 95% CI 0.35, 2.13) (Table 60).

Table 60 Severe exacerbations on the treatment period: Bucher ITC results (Dupilumab subgroup matched to benralizumab label)

Comparison	Trial or subgroup	Rate ratio (95% CI)
Dupilumab 300mg vs placebo	VENTURE subgroup (matched to benralizumab label)	0.25 (0.12, 0.55)
Benralizumab vs placebo	ZONDA	0.30 (0.18, 0.48)
		Bucher ITC rate ratio (95% CI)
Dupilumab vs benralizumab		0.86 (0.35, 2.13)

Source: CS Appendix N Figure 46

3.3.11 MAIC results

As stated in section 3.1.7.1 the purpose of the MAICs was to compliment the findings from the Bucher ITCs. The results of the MAIC are not used in the basecase economic model but there is an option in the model settings to use data from the MAICs and the MAIC results were used in a scenario analysis. Consequently, we report summary results only. More detailed results (including details of the effective sample sizes after matching can be found in Appendix 8.2). For some analyses there was a low effective sample size and in others some effect modifiers had to be omitted from the model. These caveats need to be kept in mind and the results should be interpreted cautiously.

3.3.11.1 Uncontrolled persistent asthma population

In the uncontrolled persistent asthma population (DRI12544 and QUEST RCTs) the MAIC results for severe exacerbations were statistically in favour of dupilumab for the comparison against mepolizumab (ITT trial populations) and against benralizumab (rate ratios of 0.74, 95% CI 0.56 to 0.99 and 0.59, 95% CI 0.38 to 0.89 respectively). In the comparison against the mepolizumab MENSA trial subgroup and the comparison against reslizumab the rate ratios were numerically in favour of dupilumab but did not reach statistical significance.

Table 61 Uncontrolled persistent asthma population MAIC results: Severe exacerbations

MAIC comparison	Comparator trial(s)	Dupilumab vs comparator MAIC rate ratio (95%CI)
Dupilumab vs mepolizumab	MENSA (ITT)	0.74 (0.56, 0.99)
	DREAM (ITT)	
	MUSCA (ITT)	
Dupilumab vs mepolizumab subgroup	MENSA (Subgroup) EOS ≥300 in past year and ≥4 exacerbations or mOCS	0.56 (0.31, 1.01)
Dupilumab vs benralizumab	CALIMA (EOS ≥300)	0.59 (0.38, 0.89)
	SIROCCO (EOS ≥300)	
Dupilumab vs reslizumab	BREATH 82-83	0.66 (0.42, 1.04)

Source: CS Appendix O Figures 47, 48, 55, 59

3.3.11.2 OCS-dependent asthma population

In the OCS-dependent asthma population results for three outcomes, severe exacerbations, ≥50% reduction in OCS dose and 100% reduction in OCS dose are presented (Table 62 to Table 64). For all three of these outcomes when dupilumab was compared with the mepolizumab ITT population the result was numerically in favour of dupilumab but was not statistically significant. The comparison of dupilumab with the mepolizumab subgroup (EOS ≥300 in past year and ≥4 exacerbations or mOCS) was not statistically significant for any of the three outcomes and was numerically in favour of dupilumab for the outcomes of severe exacerbations and ≥50% reduction in OCS dose but was numerically in favour of the mepolizumab subgroup for the 100% reduction in OCS dose outcome.

In the MAICs comparing dupilumab against benralizumab none of the results were statistically significant. For the outcome of ≥50% reduction in OCS dose the results was numerically in favour of dupilumab but for the severe exacerbations and 100% reduction in OCS dose outcomes the result favoured benralizumab numerically.

Table 62 OCS-dependent asthma population MAIC results: Severe exacerbations

MAIC comparison	Comparator trial	Dupilumab vs comparator MAIC rate ratio (95%CI)
Dupilumab vs mepolizumab	SIRIUS ITT	0.48 (0.21, 1.1)
Dupilumab vs mepolizumab subgroup	SIRIUS subgroup EOS ≥300 in past year and ≥4 exacerbations or mOCS	0.56 (0.31, 1.01)
Dupilumab vs benralizumab	ZONDA ITT	1.52 (0.69, 3.36)

Source: CS Appendix O Figures 49, 52, 56

Table 63 OCS-dependent asthma population MAIC results: ≥50% reduction in OCS dose

MAIC comparison	Comparator trial	Dupilumab vs comparator MAIC odds ratio (95%CI)
Dupilumab vs mepolizumab	SIRIUS ITT	1.7 (0.53, 5.47)
Dupilumab vs mepolizumab subgroup	SIRIUS subgroup EOS ≥300 in past year and ≥4 exacerbations or mOCS	1.47 (0.43, 5.06)
Dupilumab vs benralizumab	ZONDA ITT	1.13 (0.33, 3.78)

Source: CS Appendix O Figures 50, 53, 57

Table 64 OCS-dependent asthma population MAIC results: 100% reduction in OCS dose

MAIC comparison	Comparator trial	Dupilumab vs comparator MAIC odds ratio (95%CI)
Dupilumab vs mepolizumab	SIRIUS ITT	1.36 (95% CI 0.3, 6.21)

Dupilumab vs mepolizumab subgroup	SIRIUS subgroup EOS ≥300 in past year and ≥4 exacerbations or mOCS	0.51 (95% CI 0.08, 3.34)
Dupilumab vs benralizumab	ZONDA ITT	0.93 (0.22, 4.02)

Source: CS Appendix O Figures 51, 54, 58

3.3.12 Summary of adverse events

Information on adverse events presented in the CS comes from the three included RCTs DRI12544, QUEST and VENTURE, including data from study arms that were not relevant to the current STA. The company do not indicate what the overall exposure to dupilumab was in the trials.

Treatment-emergent adverse events (TEAEs)

The proportion of participants with TEAEs was similar within each trial between participants receiving dupilumab (at any of the four doses used) and placebo (Table 65). In the DRI12544 and QUEST trials the proportion of participants with any TEAE ranged from 74.7% to 84.1% whereas in the VENTURE trial a smaller proportion experienced any TEAE (64.5% and 62.1% in the placebo and dupilumab arms respectively). The proportion of treatment-emergent serious adverse events ranged from 4.0% to 10.2% and overall, across all the study arms of the three RCTs the ERG estimates that 68/899 (7.56%) of placebo participants and 158/1977 (7.99%) of dupilumab participants experienced a treatment-emergent SAE. There were 10 deaths as a result of a TEAE, seven among dupilumab treated participants and three among placebo treated participants. None of the deaths were attributed to the investigational medicinal product. The proportion of participants who had to permanently discontinue treatment due to a TEAE ranged between 1% and 7% (the ERG calculates 4.23% across all the placebo treated participants and 4.60% across all the dupilumab treated participants).

Table 65 Summary of TEAEs in the DRI12544, QUEST and VENTURE RCTs

Trial	Trial arms	n (%)			
		Patients with any TEAE	Patients with any treatment-emergent SAE	Patients with any TEAE leading to death	Patients with any TEAE leading to permanent treatment discontinuation
DRI12544	Placebo (N=158)	118 (74.7)	9 (5.7)	0	5 (3.2)

	Dupilumab	200 mg Q4W (N=150)	113 (75.3)	6 (4.0)	0	7 (4.7)
		300 mg Q4W (N=157)	130 (82.8)	16 (10.2)	2 (1.3)	10 (6.4)
		200 mg Q2W (N=148)	119 (80.4)	10 (6.8)	0	6 (4.1)
		300 mg Q2W (N=156)	121 (77.6)	13 (8.3)	0	4 (2.6)
QUEST	1.14mL/200 mg Q2W	Placebo (N=313)	257 (82.1)	26 (8.3)	3 (1.0)	19 (6.1)
		Dupilumab (N=631)	508 (80.5)	49 (7.8)	1 (0.2)	19 (3.0)
	2 mL/300 mg Q2W	Placebo (N=321)	270 (84.1)	27 (8.4)	0	10 (3.1)
		Dupilumab (N=632)	515 (81.5)	55 (8.7)	4 (0.6)	44 (7.0)
VENTURE	Placebo (N=107)		69 (64.5)	6 (5.6)	0	4 (3.7)
	Dupilumab 300 mg Q2W (N=103)		64 (62.1)	9 (8.7)	0	1 (1.0)

Source: CS Table 37, Table 40 and Table 43
AE, adverse event; Q2W, every 2 weeks; Q4W, every 4 weeks; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

The TEAEs that occurred with a frequency of 5% of more in the DRI12544 and QUEST trials and a frequency of 2% or more in the VENTURE trial were reported. An overview of these events is reported in Table 66, with detail on the number of events and the types of event contributing to each class of event reported in the CS. Across all three trials the most common types of events were infections (42.1% to 67.6% across the four placebo arms, 40.8% to 59.7% across the seven dupilumab arms). Injection site reactions were another event that occurred in all trials. The CS highlights that in the DRI12544 trial, the two lower dupilumab dose groups (200mg and 300mg Q4weeks) had a similar frequency of injection site reactions to the placebo group, whereas the higher dose groups (200mg and 300mg Q2W, which are the doses relevant to this STA) had higher frequencies of injection site reactions than the placebo group.

Table 66 Number (%) of patients with TEAE(s) that occurred with a frequency ≥5% (DRI12544 and QUEST) or ≥2% (VENTURE) in any treatment arm by System Organ Class grouping (Safety Population)

	DRI12544					QUEST				VENTURE	
		Dupilumab				1.14mL/200 mg Q2W		2 mL/300 mg Q2W			
Primary System Organ Class Grouping, %	Placebo (N=158)	200 mg Q4W (N=150)	300 mg Q4W (N=157)	200 mg Q2W (N=148)	300 mg Q2W (N=156)	Placebo (N=313)	Dupilumab (N=631)	Placebo (N=321)	Dupilumab (N=632)	Placebo (N=107)	Dupilumab 300 mg Q2W (N=103)
Any class	74.7	75.3	82.8	80.4	77.6	82.1	80.5	84.1	81.5	64.5	62.1
Infections & infestations	53.2	56.0	59.2	52.0	54.5	63.9	57.7	67.6	59.7	42.1	40.8
Nervous system disorders	17.1	10.7	17.8	17.6	17.3	14.4	11.4	14.3	11.1	NR	NR
Blood & lymphatic system disorders	NR	NR	NR	NR	NR	NR	NR	NR	NR	0.9	9.7
Vascular disorders	NR	NR	NR	NR	NR	NR	NR	NR	NR	4.7	2.9
Respiratory, thoracic & mediastinal disorders	15.2	15.3	26.8	16.9	19.2	16.6	15.8	16.5	14.7	13.1	12.6
Gastrointestinal disorders	NR	NR	NR	NR	NR	NR	NR	NR	NR	8.4	8.7
Skin & subcutaneous tissue disorders	NR	NR	NR	NR	NR	NR	NR	NR	NR	3.7	9.7
Musculoskeletal & connective tissue disorders	13.9	15.3	14.6	14.2	20.5	16.3	14.7	15.9	15.7	12.1	13.6

	DRI12544					QUEST				VENTURE	
		Dupilumab				1.14mL/200 mg Q2W		2 mL/300 mg Q2W			
Primary System Organ Class Grouping, %	Placebo (N=158)	200 mg Q4W (N=150)	300 mg Q4W (N=157)	200 mg Q2W (N=148)	300 mg Q2W (N=156)	Placebo (N=313)	Dupilumab (N=631)	Placebo (N=321)	Dupilumab (N=632)	Placebo (N=107)	Dupilumab 300 mg Q2W (N=103)
General disorders & administration site conditions	19.0	16.7	16.6	22.3	30.1	11.2	19.3	15.3	23.9	10.3	10.7
Investigations	NR	NR	NR	NR	NR	NR	NR	NR	NR	3.7	10.7
Injury, poisoning & procedural complications	NR	NR	NR	NR	NR	14.7	13.9	13.1	17.1	13.1	9.7

Source: CS Table 38, Table 41, Table 44

Treatment-emergent serious adverse event (SAEs)

The company also report on treatment-emergent serious adverse event (SAEs) that occurred in the three included RCTs. A summary of the numbers and proportions of patients with treatment-emergent SAEs by System Organ Class groupings is presented below for DRI12544 and QUEST (data were not presented in this way for VENTURE) Table 67. Preferred Term information is reported in the CS.

The proportion of participants experiencing a treatment-emergent SAE was balanced between those receiving dupilumab and those receiving placebo (the ERG calculates 7.99% in dupilumab groups combined versus 7.56% in placebo groups combined). In all three trials the most frequent treatment-emergent SAE was asthma. In all cases the event was a severe asthma exacerbation that required hospitalisation (DRI12544: 1.6% in dupilumab groups vs 2.5% in the placebo group; QUEST: 1.7% in dupilumab 200 mg group and 0.9% in the dupilumab 300 mg group versus 3.2% and 1.2% in the corresponding placebo groups; VENTURE: 2.9% in the dupilumab group versus 2.8% in the placebo group).

In the QUEST RCT it was observed that there was an imbalance in the Cardiac Disorders System Organ Class group (dupilumab 200mg Q2W n=4, 300 mg Q2W n=10 versus zero in both the matching placebo groups). The CS notes that no imbalance in cardiac SAEs has been observed in any other dupilumab studies in either the asthma programme or the atopic dermatitis programmes. After a broad database search for cardiovascular events and a blinded adjudication analysis of potential cardiovascular events by three independent cardiologists it was concluded that the higher incidence rates in the 300mg Q2W group compared with the 200mg Q2W group were likely to be by chance. No cardiovascular SAEs were reported in the VENTURE RCT.

Table 67 Number (%) of patients with treatment-emergent SAEs by primary System Organ Class grouping in the DRI12544 and QUEST RCTs (Safety Population)

	DRI12544					QUEST			
		Dupilumab				1.14mL/200 mg Q2W		2 mL/300 mg Q2W	
Primary System Organ Class group, n (%)	Placebo (N=158)	200 mg Q4W (N=150)	300 mg Q4W (N=157)	200 mg Q2W (N=148)	300 mg Q2W (N=156)	Placebo (N=313)	Dupilumab (N=631)	Placebo (N=321)	Dupilumab (N=632)
Any class	9 (5.7)	6 (4.0)	16 (10.2)	10 (6.8)	13 (8.3)	26 (8.3)	49 (7.8)	27 (8.4)	55 (8.7)
Infections and infestations	2 (1.3)	0	3 (1.9)	2 (1.4)	5 (3.2)	4 (1.3)	4 (0.6)	5 (1.6)	13 (2.1)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	1 (0.6)	1 (0.7)	4 (2.5)	0	0	4 (1.3)	7 (1.1)	2 (0.6)	5 (0.8)
Blood and lymphatic system disorders	0	0	0	0	1 (0.6)	0	0	1 (0.3)	1 (0.2)
Immune system disorders	0	0	1 (0.6)	0	1 (0.6)	0	2 (0.3)	0	1 (0.2)
Endocrine disorders	NR	NR	NR	NR	NR	1 (0.3)	0	0	0
Psychiatric disorders	0	0	1 (0.6)	0	0	1 (0.3)	2 (0.3)	1 (0.3)	2 (0.3)
Nervous system disorders	0	0	1 (0.6)	0	0	2 (0.6)	3 (0.5)	2 (0.6)	2 (0.3)
Eye disorders	NR	NR	NR	NR	NR	0	0	0	1 (0.2)
Cardiac disorders	0	1 (0.7)	2 (1.3)	0	0	0	4 (0.6)	0	10 (1.6)
Vascular disorders	0	0	0	1 (0.7)	0	1 (0.3)	1 (0.2)	1 (0.3)	1 (0.2)

	DRI12544					QUEST			
		Dupilumab				1.14mL/200 mg Q2W		2 mL/300 mg Q2W	
Primary System Organ Class group, n (%)	**Placebo (N=158)**	**200 mg Q4W (N=150)**	**300 mg Q4W (N=157)**	**200 mg Q2W (N=148)**	**300 mg Q2W (N=156)**	**Placebo (N=313)**	**Dupilumab (N=631)**	**Placebo (N=321)**	**Dupilumab (N=632)**
Respiratory, thoracic and mediastinal disorders	4 (2.5)	2 (1.3)	4 (2.5)	5 (3.4)	1 (0.6)	11 (3.5)	16 (2.5)	5 (1.6)	12 (1.9)
Gastrointestinal disorders	1 (0.6)	0	0	1 (0.7)	1 (0.6)	0	3 (0.5)	2 (0.6)	6 (0.9)
Hepatobiliary disorders	0	0	1 (0.6)	0	1 (0.6)	1 (0.3)	2 (0.3)	0	4 (0.6)
Skin and subcutaneous tissue disorders	0	1 (0.7)	0	0	1 (0.6)	NR	NR	NR	NR
Musculoskeletal and connective tissue disorders	NR	NR	NR	NR	NR	2 (0.6)	3 (0.5)	3 (0.9)	3 (0.5)
Renal and urinary disorders	NR	NR	NR	NR	NR	0	1 (0.2)	0	0
Pregnancy, puerperium and perinatal conditions	0	0	1 (0.6)	2 (1.4)	1 (0.6)	0	0	2 (0.6)	2 (0.3)
Reproductive system and breast disorders	0	0	0	0	1 (0.6)	0	1 (0.2)	0	1 (0.2)
Congenital, familial and genetic disorders	NR	NR	NR	NR	NR	0	1 (0.2)	0	0
General disorders and administration site conditions	NR	NR	NR	NR	NR	0	1 (0.2)	1 (0.3)	3 (0.5)

	DRI12544					QUEST			
		Dupilumab				1.14mL/200 mg Q2W		2 mL/300 mg Q2W	
Primary System Organ Class group, n (%)	**Placebo (N=158)**	**200 mg Q4W (N=150)**	**300 mg Q4W (N=157)**	**200 mg Q2W (N=148)**	**300 mg Q2W (N=156)**	**Placebo (N=313)**	**Dupilumab (N=631)**	**Placebo (N=321)**	**Dupilumab (N=632)**
Investigations	0	0	0	0	1 (0.6)	0	1 (0.2)	0	0
Injury, poisoning and procedural complications	1 (0.6)	1 (0.7)	2 (1.3)	1 (0.7)	1 (0.6)	4 (1.3)	3 (0.5)	4 (1.2)	5 (0.8)
Soft tissue injury	0	0	1 (0.6)	0	0	NR	NR	NR	NR
Social circumstances	NR	NR	NR	NR	NR	0	2 (0.3)	0	0
Product issues	NR	NR	NR	NR	NR	0	1 (0.2)	0	0

Source: CS Table 39 and Table 42
NR – event of this class not reported for this trial; PT, preferred term; Q2W, every 2 weeks; Q4W, every 4 weeks; SAE, serious adverse event.

Treatment-emergent SAEs that were considered to be related to the investigational medical product occurred in three patients (all receiving dupilumab) in the DRI12544 trial, five in QUEST (four receiving dupilumab 300mg and one receiving placebo) and four in VENTURE (three in the dupilumab group and one in the placebo group).

Table 68 Treatment emergent SAEs considered to be related to the investigational medical product in the DRI12544, QUEST and VENTURE RCTs

Trial arm	RCT		
	DRI12544	**QUEST**	**VENTURE**
Dupilumab	Severe colitis (one case, dupilumab dose not stated)	Eosinophilia (one case, dupilumab dose not stated)	Eosinophilia (two cases)
	Steroid-dependent hypereosinophilia (one case in dupilumab 300 mg Q2W arm)	Eosinophilic pneumonia chronic (one case, dupilumab dose not stated)	Pulmonary mass (one case)
	Unspecified eczema on scalp and feet of moderate intensity (one case in the dupilumab 300 mg Q2W arm)	Anaphylactic reaction (one case, dupilumab dose not stated)	
		Injection site erythema, injection site inflammation and injection site oedema (one case in the dupilumab 300 mg arm)	
Placebo		Neutropenia (one case)	Gastrointestinal stromal tumour (one case)

The proportion of TEAEs which led to treatment discontinuation ranged from 1-7% in the dupilumab arms of the three included RCTs and from 3.1% to 6.1% in the placebo arms. Injection site reactions (DRI12544) or injection site erythema (QUEST) were the most frequently reported TEAEs leading to permanent treatment discontinuation in these two trials (but this was not a reason for treatment discontinuation in the VENTURE RCT). Other events highlighted in the CS were that four patients (three in the dupilumab groups and one in the placebo group) had increased alanine aminotransferase that led to permanent treatment discontinuation in the DRI12544 RCT and one patient experienced each of the following in the VENTURE RCT: arthralgia (dupilumab group), gastrointestinal stromal tumour, eosinophilia, adrenal insufficiency, and asthmatic crisis (all in the placebo group).

Finally, the QUEST and VENTURE studies report on adverse events of special interest (AESIs). The CS states that these events were pre-defined in the study protocol but it does not list what types of events were treated as AESIs. The protocols that are available as supplementary material to the published papers for QUEST and VENTURE do provide this information. In brief, AESIs appear to have included (but not limited to) anaphylactic reactions, severe injection site reactions lasting longer than 24 hours, severe and serious infections (bacterial or viral), significant ALT elevation, pregnancy and symptomatic overdose with either dupilumab or placebo. Only severe injection site reactions are reported as AESIs for QUEST, it is not clear if this is because these were the only AESIs experienced or if they were the most common. Ten patients in QUEST dupilumab groups reported AESI injection site reactions but none were reported in the VENTURE RCT. In the VENTURE trial three patients had hypersensitivity (rash) two in the dupilumab group and one in the placebo group, none of these events were SAEs. No other AESI are reported in the CS for the VENTURE RCT.

3.4 Summary of the clinical effectiveness evidence

The dupilumab trials DRI12544, QUEST and VENTURE

The three included dupilumab RCTs provide evidence for a population of people with:
i) moderate-to-severe asthma who are not receiving treatment with oral corticosteroids (DRI12544 and QUEST)
ii) severe asthma who are receiving treatment with oral corticosteroids (VENTURE).

All three trials enrolled a wider population group than that specified by the NICE scope and the company's decision problem. In the DRI12544 and QUEST trials a minority of the ITT population match the decision problem population (14.9% and 10.7% respectively); in VENTURE more than two thirds (72%) of the ITT population match the decision problem population.

Results from the dupilumab trials

In the post-hoc subgroups of QUEST and VENTURE that reflected the decision problem population, dupilumab reduced rates of severe exacerbations. In dupilumab responder analyses in these post-hoc subgroups, the adjusted annualised rate of severe exacerbation events was lowered further in comparison to all placebo patients. No analysis for the decision problem population was presented for the DRI12544 RCT.

The ITT analyses of the three RCTs demonstrated that, for patients not receiving OCS (DRI12544 and QUEST) and for patients receiving OCS (VENTURE) dupilumab treatment:

- reduced the adjusted rate of severe asthma exacerbations in comparison to placebo,
- Delayed the time of the first severe exacerbation event
- Increased FEV1 at 12 weeks (DRI12544 and QUEST) and at 24 weeks (VENTURE).
- Improved asthma control as measured by the ACQ-5 (DRI12544) or ACQ-7 (QUEST)
- Reduced FeNO levels
- Did not lead to any significant differences in the change from baseline EQ-5D scores.

ITT analyses for patients not receiving OCS (DRI12544 and QUEST) also showed that dupilumab:

- Reduced the annualised risk of loss of asthma control in comparison to the placebo group.
- Improved both morning and evening PEF in the QUEST trial (outcome not reported for DRI12544).

ITT analysis for patients receiving OCS (VENTURE also showed that dupilumab:

- Led to a greater reduction in OCS dose at week 24 compared to the placebo group.
- Led to a higher probability at week 24 of patients achieving a ≥50% reduction in OCS dose, a reduction in OCS dose to <5mg/day or a 100% reduction in OCS dose in comparison to the placebo group.

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

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

Participants in the dupilumab and placebo arms of each of the three trials experienced TEAEs and the ERG calculated that the proportions of participants experiencing serious events was similar in dupilumab and placebo treated patients (less than 8%). No deaths were attributed to dupilumab.

Bucher ITC results

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

MAIC results

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

There are limitations to both the Bucher ITC and MAIC methods (Section 3.1.7.5) and therefore caution is required in interpreting these results and the outcomes from the

exploratory cost-effectiveness analysis for dupilumab compared to the IL-5 biologics. However these ITC approaches, even though limited by the available data, are likely to be the best currently available option to enable comparisons between dupilumab and other IL-5 biologics in the NICE scope.

4 COST EFFECTIVENESS

4.1 Overview

The company submission includes:

- A systematic review of published economic evaluations of treatments for moderate-to-severe asthma (CS B.3.1.1)
- A description of the company's *de novo* model developed to assess the cost-effectiveness of dupilumab in its licensed indication as add-on therapy for adults and adolescents with severe asthma.
    - CS sections B.3.2 to B.3.11 and Appendix M describe the company's base case comparison with standard care alone for people with EOS≥150 or FeNO≥25 and at least 3 exacerbations in the previous 12 months; and a scenario for a mixed population also including people with EOS≥150 or FeNO≥25 on maintenance oral corticosteroids (mOCS).
    - Appendices P and Q present additional 'exploratory' analyses based on the Bucher indirect comparisons with other add-on biologic therapies: mepolizumab and benralizumab for people with EOS≥300 and at least 4 exacerbations in the previous 12 months or mOCS; and reslizumab and benralizumab for people with EOS≥400 and at least 3 exacerbations in the previous 12 months.

We summarise and critique these elements of the CS in sections 4.2 and 4.3 below. Additional ERG work, including model validation and alternative scenarios are presented in section 4.4.

All cost-effectiveness results presented in the CS and in this ERG report assume an NHS price discount for dupilumab (both 200 mg and 300 mg doses): the same as agreed in the existing Patient Access Scheme (PAS) arrangement for dupilumab in atopic dermatitis. For the comparisons with other biologics in CS Appendix Q, the company assumed a [redacted] discount on list prices for mepolizumab, reslizumab and benralizumab. Results including the actual agreed PAS discounts for comparators as well as the company's proposed PAS discount for dupilumab are presented in a confidential addendum to the ERG report.

4.2 Company's review of published economic evaluations

The company conducted a search to identify studies assessing the cost, healthcare use and cost-effectiveness of interventions for the treatment of moderate-to-severe asthma. The methods and results of the review of cost-effectiveness studies are described in CS section B.3.1 and Appendix G. The review of cost and healthcare use is described in section B.3.5 and Appendix I of the CS. As the searches were conducted in March 2019, we conducted a

focused literature search to identify any more recent relevant publications but did not identify any that were not previously identified by the company.

The company identified 29 economic evaluations of treatments for severe uncontrolled asthma. Of these, 15 studies included treatments identified in the NICE decision problem (described in CS Table 48). Five of these studies were UK based, of which three informed previous NICE TAs (TA479, TA431, and TA565). One of the included studies assessed the cost-effectiveness of dupilumab as an add-on therapy in adults and children aged ≥ 6 years with moderate-to-severe uncontrolled asthma with evidence of Type 2 inflammation. This US based study conducted for the Institute for Clinical and Economic Review (Tice et al.)[4] developed a Markov model for a lifetime horizon from the perspective of healthcare sector and reported the following ICERs:

- Dupilumab + standard care versus standard care: $351,000;
- Omalizumab + standard care versus standard care: $325,000;
- Mepolizumab + standard care versus standard care: $344,000;
- Reslizumab + standard care versus standard care: $391,000;
- Benralizumab + standard care versus standard care: $371,000;

ERG conclusion: The company's search strategy and eligibility criteria for their review of cost-effectiveness studies are appropriate. We view that the US based study by Tice et al. provides a relevant reference for comparison of the model outcomes of the current appraisal.

4.3 Critical appraisal of the company's submitted economic evaluation

4.3.1 NICE reference case

Table 69 NICE reference case

Criterion	Included?	Comment
Decision problem as in scope	Y	The modelled population is a restricted subgroup of the NICE decision problem and marketing authorisation
Comparators as listed in scope	N	Only standard care in base case (CS B.3). Indirect comparisons with add-on mepolizumab, reslizumab and benralizumab in CS Appendix Q. Omalizumab not included

Perspective on costs: NHS and PSS	Y	
Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Y	
Perspective on outcomes: All direct health effects, whether for patients or, when relevant, carers	Y	
Cost utility analysis with fully incremental analysis	Y	Incremental analysis for mepolizumab and reslizumab populations (CS Appendix Q)
Synthesis of evidence on outcomes based on a systematic review	Y	Results for Bucher pairwise ITC in CS Appendix Q (MAIC available in model)
Time horizon: Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Y	Effectively lifetime (to 100 years of age)
Health effect expressed in QALYs. EQ-5D is preferred measure of health-related quality of life	Y	
Health related quality of life reported directly by patients and/or carers.	Y	Base case uses EQ-5D-5L data from QUEST and VENTURE trials (B.3.4.2)
Preference data from representative sample the UK population	Y	Utilities mapped from EQ-5D-5L with van Hout cross walk algorithm (CS B.3.4.5)
An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	Y	
Discount rate: 3.5% pa for costs & health effects	Y	

4.3.2 Modelled decision problem

4.3.2.1 Population and subgroups

The economic model has in-built flexibility to include patients treated with or without mOCS (based on data from the VENTURE and QUEST clinical trials respectively), as well as a weighted combination of both groups. The model also allows selection of a range of subgroups defined by a combination of: EOS levels (≥150, ≥300 or ≥400); raised FeNo (≥25); and numbers of exacerbations in the previous 12 months (≥1, ≥2, ≥3 or ≥4). Small subgroups are implemented by adjustment of outcomes for a reference population using multipliers derived from a negative binomial regression model (see CS Appendix section P.1.1 and Clarification Response B5).

The CS reports cost-effectiveness results for four subgroups in total. These all fall within the NICE decision problem and the licensed indication (see 2.3 above), but with different definitions of severe asthma with type 2 inflammation and inadequate control under optimised standard therapy. In the main report, the company presents results for a base case population and a mixed mOCS/ non mOCS/ population scenario (CS B.3.2.1):

A. **Base case population**: EOS≥150 or FeNO≥25 and at least 3 exacerbations in the previous 12 months. This analysis is based on a subgroup from the QUEST trial, and hence excludes people on maintenance oral corticosteroids (non mOCS).

B. **Mixed mOCS/ non mOCS scenario**: EOS≥150 or FeNO≥25 and at least 3 exacerbations in the previous 12 month or on mOCS. This uses a combination of subgroup data from VENTURE for people on mOCS as well as subgroup data from QUEST for people not on mOCS. Overall results are calculated assuming that 41.7% of the relevant population are on mOCS, based on a UK registry of severe asthma (Heaney 2010).[22]

The CS presents standard care as the only comparator for the above populations, because NICE recommendations for other comparators are narrower (see Table 70 below). However, the company also presents 'exploratory' analyses with indirect comparisons for mepolizumab, reslizumab and benralizumab (CS Appendices P and Q). This requires two subgroups (CS Appendix P.1.2):

C. **Mepolizumab eligible subgroup**: EOS≥300 and at least 4 exacerbations in the previous 12 months or mOCS (TA431).

D. **Reslizumab eligible subgroup**: EOS≥400 and at least 3 exacerbations in the previous 12 months (TA479).

Benralizumab is recommended for both of the above populations in TA565.
The company does not model an omalizumab eligible population, because they consider omalizumab to be out of scope "*as allergic asthma, defined by IgE, is not considered to be part of the EMA licence for dupilumab*" (CS Appendix P introduction).

Table 70 NICE TA recommendations for comparators in the scope

NICE TA	Patient characteristics (approved by NICE)
TA278 (omalizumab)	People aged 6 and older with severe persistent confirmed allergic IgE-mediated asthma: • Who need continuous or frequent treatment with oral corticosteroids (defined as 4 or more courses in the previous year)
TA431 (mepolizumab)	Adult patients with: • blood eosinophil count of ≥300 cells/microliter or more in the previous 12 months; and • have had 4 or more asthma exacerbations needing systemic corticosteroids in the previous 12 months; or • have had continuous oral corticosteroids of at least the equivalent of prednisolone 5 mg per day over the previous 6 months
TA479 (reslizumab)	Adult patients with inadequately controlled severe eosinophilic asthma with: • blood eosinophil count of 400 cells/microliter or more; and • have had 3 or more severe asthma exacerbations needing systemic corticosteroids in the past 12 months
TA565 (benralizumab)	Adult patients with inadequately controlled severe eosinophilic asthma with: • blood eosinophil count of ≥300 cells/microliter • have had 4 or more exacerbations needing systemic corticosteroids in the previous 12 months, or has had continuous oral corticosteroids of at least the equivalent of prednisolone 5 mg per day over the previous 6 months (that is, the person is eligible for mepolizumab) • blood eosinophil count of ≥400 cells per microlitre with 3 or more exacerbations needing systemic corticosteroids in the past 12 months (that is, the person is eligible for reslizumab).

Table 71 below summarises baseline characteristics for patient subgroups that the company use in their cost-effectiveness analyses. These subgroups are described by the indicators of type 2 inflammation (i.e. blood eosinophil level or FeNO), the number of asthma exacerbations in the previous 12 months and use of mOCS.

Table 71 Patient characteristics for modelled subgroups

Subgroup	A. Base case & B. Mixed scenario		C. Mepolizumab eligible		D. Reslizumab eligible
Indicators of type 2 inflammation	EOS ≥150 or FeNO ≥25		EOS ≥300		EOS ≥400
Number of exacerbations in previous 12 months	≥3	Any	≥4	Any	≥3
Maintenance oral corticosteroids	No	mOCS	No	mOCS	No
NICE recommended add-on biologic therapy	None (standard care only)		Mepolizumab Benralizumab		Reslizumab Benralizumab
Baseline patient characteristics					
% female	59.4	61.2	62.1	68.4	59.3
Age, mean years	47.4	51.2	49.7	51.4	49.3
Weight, mean kg	79.0	79.0	79.0	79.0	79.2
Background therapy					
% on high-dose ICS/LABA	100.0	100.0	100.0	100.0	100.0
% on LTRA	40.6	26.5	37.9	27.6	34.7
% on LAMA	21.8	18.5	16.9	21.1	12.7
% on theophylline	5.9	9.9	4.0	9.2	4.7

ICS, inhaled corticosteroids; LABA, long-acting beta-agonists; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonists.
Source: QUEST data for non-mOCS subgroups, VENTURE for mOCS subgroups. Extracted from company model by ERG.

ERG conclusions: The four modelled populations in the CS are within the defined in the NICE scope and the marketing authorisation. The two subgroups used for the company's exploratory indirect comparisons with mepolizumab, reslizumab and benralizumab appropriately reflect NICE guidance.

The company base case restricts the population to people with at least 3 exacerbations in addition to indicators of type 2 inflammation (EOS ≥150 or FeNo ≥ 25). The company states that this is to align with UK clinical practice and the GINA guidelines. It also has the effect of improving the cost-effectiveness of dupilumab. However, the base case population still includes two groups for whom biologic treatments have not previously been recommended by NICE:

- people with EOS below 300 or FeNO ≥ 25; and

- those with EOS between 300 and 399 with 3 exacerbations in the previous year and not on mOCS.

It is uncertain whether dupilumab is cost-effective for these subgroups because the CS only presents ICERs for a pooled population including people with more severe disease who are currently eligible for benralizumab, mepolizumab and/or reslizumab add-on therapy.

In particular, we highlight that the committee in TA565 concluded that cost effectiveness evidence for this type of mixed population was not suitable for decision making because the range of asthma severity is not necessarily generalisable to the clinical practice population. We conduct ERG exploratory analysis to estimate the cost-effectiveness of excluding people with EOS≥300 from the company's base case population (see section 4.4.5.1 below).

A similar argument applies to the company's mixed population scenario which includes people treated with and without mOCS at baseline, as the cost-effectiveness may well differ between these groups. We also note that the TA565 committee expressed uncertainty over the proportion of patients on mOCS. Although the TA565 ERG used the same value of 41.7% (Heaney 2010) for the standard care comparison as in the current submission, the TA565 ERG used 60% for the mepolizumab comparison, and clinical experts advised the committee that in clinical practice between 66% and 80% of patients starting mepolizumab are on mOCS. We conduct additional scenario analysis around this parameter in section 4.4.5.2 below.

4.3.2.2 Intervention and comparators

The company outlines the modelled intervention and comparators in CS sections B.3.2.3 to B.3.2.5. As per the NICE scope, the economic model includes dupilumab as an add-on to standard therapy as the intervention. For their base case, the company compares the intervention with standard care alone. They argue that standard care is the relevant comparator for this appraisal as dupilumab is the only treatment indicated for severe asthma driven by Type 2 inflammation defined by raised EOS and/or raised FeNO.

The company notes that NICE has recommended three other biologics (mepolizumab, reslizumab and benralizumab) for patients with severe eosinophilic asthma and that although these treatments are not licensed for Type 2 inflammation, as defined in the company base

case, comparison of dupilumab against these treatments would be appreciated to support NICE decision making. They therefore conducted two sets of pairwise and incremental economic analyses, described in Appendix P:

- Dupilumab compared with mepolizumab, benralizumab and standard care alone for people with severe eosinophilic asthma defined as EOS ≥ 300 and either ≥ 4 exacerbations in the previous 12 months or mOCS (results in CS Q.1); and
- Dupilumab compared with reslizumab, benralizumab and standard care alone for people with severe eosinophilic asthma defined as EOS ≥ 400 and either ≥ 3 exacerbations in the previous 12 months (results in CS Q.2)

These analyses are described as exploratory and 'for information purposes only' due to limitations of the indirect comparisons: the Bucher pairwise approach (CS Appendix N) used for the results presented the CS; and the MAICs (CS Appendix O) also available in the model. See 3.1.7 above for discussion of the indirect comparison methods and 4.3.4.5 for the values used in the economic model.

Omalizumab, the fourth biologic named as a comparator in the NICE scope, is not included in the economic model. The company state that they do not consider omalizumab to be a relevant comparator for dupilumab for three reasons. First, because the licence indications differ: Type 2 inflammation for dupilumab and allergic IgE-mediated asthma for omalizumab. Second, the patient populations in the pivotal trials are not directly comparable because the dupilumab trials did not measure allergy with a skin-prick test. And thirdly, because dupilumab is 'significantly effective' irrespective of baseline serum IgE, so this would not be a relevant biomarker for dupilumab.

> ***ERG conclusions***: We agree that there are significant uncertainties over the indirect comparisons (Bucher and MAIC) because of differences in the trial populations and methodological and reporting limitations. Nevertheless, we understand that there are people who would be suitable for other biologics specified in the NICE scope as well as dupilumab. It is therefore important to consider the cost-effectiveness of dupilumab relative to these other comparators in the overlap populations as well as cost-effectiveness relative to standard practice for people for whom this is the only option. We therefore discuss the company's exploratory analyses alongside their base case analysis within this chapter.

4.3.3 Model structure

The company describes the structure and key features of their model in CS Section B.3.2.2. They summarise assumptions in CS Table 87 and the parameters in CS sections B.3.3 to 3.6.1. A Markov model is developed in Microsoft Excel® (see Figure 4) with a cycle length of 4 weeks and a half-cycle correction. The model uses a lifetime horizon (up to a maximum age of 100 years). Costs and QALYs are discounted at an annual rate of 3.5%.

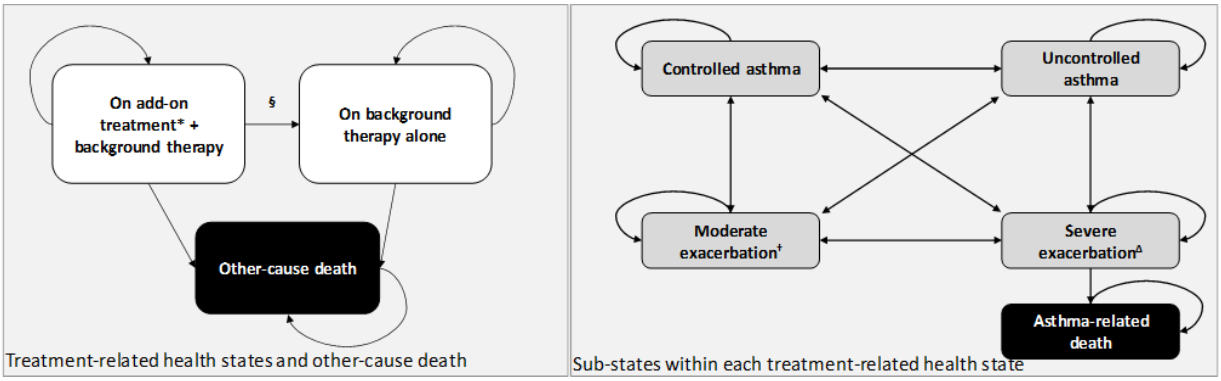


Figure 4 Markov model structure (Source: CS Figure 36)

The model estimates costs and health outcomes associated with a cohort of patients with severe asthma (driven by Type 2 inflammation) starting dupilumab or other add-on therapy (mepolizumab, reslizumab or benralizumab) compared with background therapy (standard care) alone. The model includes the flexibility to define the starting cohort according to the proportion of patients on mOCS and minimum levels of EOS, FeNo and number of exacerbations in the previous 12 months.

The model consists of four *live* health states: uncontrolled asthma; controlled asthma; moderate exacerbation; and severe exacerbation. In addition, the model includes states for asthma-related deaths and death from other causes. We present a summary of the health state definitions in Table 72. The cohort enters the model in the uncontrolled asthma health state. At each four-week cycle, people in the live health states may remain in the same health state, transition to one of the other three live health states or die from asthma-related or other causes. Rates of movement between the live states are determined by a transition probability matrix and mortality rates are applied for asthma and other deaths.

For patients who enter the model on mOCS, the proportion of patients taking a reduced dose (< 5mg per day) or withdrawing from OCS is estimated at each model cycle.

Table 72 Summary of the model health states

	Health states	Description
Live states	Uncontrolled asthma	Patients enter the model in this health state, defined by an ACQ score ≥1.5 and no exacerbation (consistent with inclusion criteria for the clinical trials).
	Controlled asthma	Patients in this health state have an ACQ score < 1.5 and no exacerbation.
	Moderate exacerbation	Defined by one or more of the following criteria: • ≥6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol in a 24-hour period on two consecutive days; • ≥20% decrease in pre-bronchodilator forced expiratory volume in 1 second (FEV1) compared with baseline; • Increase in inhaled corticosteroid (ICS) dose ≥4 times than the dose at Visit 2; • A decrease in AM or PM peak flow of 30% or more on 2 consecutive days of treatment, based on the defined stability limit. The treatment period stability limit is defined as the respective mean AM or PM peak expiratory flow (PEF) obtained over the last 7 days prior to randomisation (Day 1)
	Severe exacerbation	Patients experienced severe exacerbation if they met one of the following criteria: • Use of systemic corticosteroids for ≥3 days; or • Hospitalisation or A&E visit because of asthma, requiring systemic corticosteroids
Death	Asthma related mortality	Absorbing states; the model accounts for: • Death from asthma, which only occurs from severe exacerbation • Death from other causes (background mortality net of asthma mortality) occurs from all the health states
	Death from other causes	

Source: CS section B.3.2.2

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

The model accumulates costs associated with drug acquisition, administration and monitoring as well, routine care and management by health state and treatment for OCS-related adverse events. QALYs are estimated by applying utilities to time spent in the

controlled and uncontrolled asthma health states and disutilities for moderate and severe exacerbations and OCS-related adverse events.
The model does not include any cost or disutility for adverse events associated with the biologic or other medications. The company notes that the most frequent adverse event in the dupilumab trials was injection site reactions (15.2% with dupilumab vs. 5.4% with placebo) but the number of serious site reactions that lasted longer than 24 hours were similar and very low (0.3% vs. 0%) (B.3.3.12). We discuss the overall safety evidence in section 3.3.12 above.

The model uses three sets of input parameters, which we describe and critique in the following sections:

- Clinical inputs to estimate transition probabilities, dose-reduction and withdrawal rates for mOCS, one-year response and subsequent discontinuation rates and rates of mortality from asthma-related and other causes (CS B.3.3 and Appendices M and P);
- Utilities for control health states and disutilities for exacerbations and mOCS-related adverse events (CS B.3.4); and
- Resource use and costs for drug acquisition and administration; monitoring, routine care and disease management costs; and exacerbation costs (CS B.3.5).

ERG conclusion: The overall model structure is appropriate, accurately implemented and similar to models developed to inform NICE technology appraisals for severe asthma.

Given the rates of adverse events reported in the dupilumab,, the decision not to model treatment-related adverse events for drugs other than oral corticosteroids is reasonable. This is very unlikely to make a substantive difference to overall cost and QALY estimates, and is consistent with the previous appraisal TA565.

4.3.4 Clinical parameters

4.3.4.1 Transition probabilities for asthma control and exacerbations

The probabilities of moving between the four live health states (uncontrolled asthma, controlled asthma, moderate exacerbation and severe exacerbation) in each four-week model cycle are estimated in a series of 4 by 4 transition matrices. Methods used to derive these matrices are described in CS B.3.3.2, with more detail in CS Appendix M.1.

Base case transition matrices (no mOCS)

The model uses three transition matrices for each intervention: for the time periods 0-12 weeks, 12-52 weeks and 52+ weeks. Base case transition matrices for standard care and dupilumab are estimated from QUEST data for people with EOS≥150 or FeNO≥25 and ≥3 exacerbations in the previous year.

The number of transitions between each pair of health states (N_{ij}) was calculated for every four-week period (excluding transitions after permanent discontinuation of the randomised treatment): N_{ij} is the number of transitions from health state i to health state j (i,j = 1,…,4, 1=controlled, 2= uncontrolled, 3=moderate exacerbation or 4= severe exacerbation). These data were used to calculate basic transition probabilities: $P_{ij} = N_{ij}/\sum_{k=1}^{4} N_{ik}$. Various adjustments were made to calculate the final transition matrices for the model, as described in the following six steps.

1) *Pooled exacerbation probabilities for 0-52 weeks*:
   The probabilities of moderate and severe exacerbations in the first year are calculated by pooling 0-12 week and 12-52 week transitions. The company states that this is appropriate given the small numbers of exacerbations observed and lack of evidence for a difference over time. They also present a scenario with separate exacerbation probabilities for 0-12 and 12-52 weeks.

2) *Separate control probabilities for 0-12 and 12-52 weeks*:
   Probabilities for the two periods are calculated excluding transitions to moderate or severe exacerbations in the same four-week cycle. Thus, the conditional probabilities for uncontrolled and controlled asthma in time period T (T= 1 for 0-12 weeks and T=2 for 12-52 weeks) are:

$$P_{i2}^{T} = [P_{i2}/(P_{i1} + P_{i2})] * (1 - P_{i3} - P_{i4}) \text{ and}$$

$$P_{i1}^{T} = (1 - P_{12}^{T} - P_{i3} - P_{i4})$$

The company argues that using separate asthma control rates for 0-12 and 12-52 weeks is appropriate because most of the improvement occurs in the first 12 weeks. To support this, they cite the higher rate of change of asthma control in QUEST (as indicated by mean ACQ-7 scores) in weeks 0-12 compared with weeks 12-52 (see CS Figure 19 for the ITT population). The company also compare probabilities of transition to the 'controlled asthma' health state before versus after 12 weeks (Clarification response Table 17). This shows a significant overall improvement in rates of control in all patients on dupilumab and in the subgroup with a response to dupilumab at 52 weeks, but no significant difference for the placebo group.

The net effect of using pooled control probabilities from the whole 0-52 week trial period for both placebo and dupilumab, as well as for dupilumab responders after 52 weeks is shown in a scenario analysis (Clarification response Table 19). This reduces the ICER for dupilumab compared with standard care alone, indicating that the base case assumption is conservative. The ERG agrees with this conclusion.

3) *Post-trial transition probabilities based on 12-52 week transition matrices:*
The company assumes that outcomes after the first 12 weeks are more reflective of long-term outcomes, so 12-52 week transition matrices are used as the basis for extrapolation. It is not clear whether this is appropriate, as the numbers of exacerbations are low and there are no significant differences in control rates between the two time periods in the QUEST placebo group. However, as noted above, the net effect of pooling all transition probabilities across 0-52 weeks is to reduce ICERs.

For dupilumab, transition probabilities after 52 weeks are based on analysis of QUEST data only for individuals who were classified as having a response at 52 weeks. For the base case population (non mOCS), response was defined as at least 50% reduction in severe exacerbations (CS Table 53). This included [redacted] patients ([redacted]) in the base case population.

4) *Adjustment of long-term severe exacerbation rates*:
It is apparent that the severe exacerbation rate among patients treated with placebo in QUEST was lower than in the preceding year: mean annualised rates 2.07 (SD 1.58) before the trial compared with 0.871 (95% CI: 0.724 to 1.048) during the trial in the randomised population (CS Tables 13 and 19).

The company mention four possible reasons for this large difference in CS B.3.3.3 and in Appendix M.2:

- Regression to the mean: This is a statistical phenomenon whereby individuals with atypical values for some characteristic when first assessed will tend to have values closer to the population average when assessed again. Thus, people with a high number of exacerbations in the year before the trial may, on average, have fewer exacerbations in next year, even with no effective treatment.
- Better care in a clinical trial setting: Patients in a clinical trial may have better outcomes than in routine practice due to regular specialist follow up, optimised care and improved adherence. If so, the trial results may not be generalisable. However, we note that a similar improvement could occur in clinical practice when people with inadequately controlled severe asthma are first referred to specialist care to be assessed for initiation of biologic treatment. This would have different implications for the generalisability of the trial results.
- Exclusion criteria and impact on exacerbation rate: Patients in QUEST had a longer average time since their last severe exacerbation than would be expected at treatment initiation because those with a severe exacerbation from 1 month before screening up to and including the baseline visit were excluded. As time since last severe exacerbation (TSLSE) is a strong predictor for future exacerbations (TENOR cohort, Calhoun et al. 2014)[23], the number of severe exacerbations during QUEST follow up may be lower than an unselected cohort.
- Definition of exacerbation events: In QUEST, two exacerbations that started within a 28 day period were classified as a single event. On average, the duration of exacerbation symptoms was less than 28 days (median 10 days with dupilumab and 15-17 days with placebo). Thus the number of exacerbations for trial participants might have been underestimated.

A similar placebo effect was observed in the NICE reslizumab appraisal (TA479 paragraphs 4.12 and 4.13). The committee considered the possibilities of the first two explanations above (optimised treatment or regression to the mean) but concluded that these would be likely to affect both arms, so "*the most robust estimate of relative effectiveness was derived from the exacerbation rates shown in the clinical trials.*" However, the third and fourth issues were not raised in previous appraisals.

In their base case, the company applies a multiplier of [redacted] to severe exacerbation rates after the trial period (both arms) to estimate the increased risk without the QUEST exclusion criterion. The calculation is described in CS section M.2.1.1, with further explanation in Clarification Response B4. It uses an odds ratio for the increased risk of severe exacerbations for people with a recent severe exacerbation (TSLSE < 90 days) from TENOR[23] (2.99, 95% CI 2.57 to 3.47) and QUEST data on TSLSE at baseline (35.33% with TSLSE < 90 days) and at the end of the trial ([redacted] with TSLSE < 90 days).

$$\frac{2.99 * [redacted] + 1 * (1 - [redacted])}{2.99 * 0.3533 + 1 * (1 - 0.3533)} = [redacted]$$

This adjustment has the effect of proportionally increasing the absolute number of severe exacerbations in both arms and the absolute difference between the arms, hence improving cost-effectiveness.

The company also calculates a multiplier to adjust for the definition of a severe exacerbation event in QUEST (issue 4 above). This is estimated from the DRI study, as the ratio of severe exacerbation rates calculated without and with the 28-day interval definition: 0.575/0.516 = 1.114 (unadjusted rates across all study arms) (CS Appendix M Table 76).

The company presents four scenario analyses to explore different assumptions about long term severe exacerbation rates (after the trial period):

- No adjustment: observed rates from trial (multiplier 1.00)
- Rate from mepolizumab technology appraisal (multiplier 1.35)
- Combined adjustment for exclusion criteria and definition of severe exacerbation (multiplier 1.114 * [redacted] = [redacted])
- Rates increased to those observed before the trial (multiplier 1.813)

5) *Adjustment for null probabilities*:

In the base case, transition probabilities were adjusted when no events were observed for a specific transition. If any transition out of a given health state was 0, 1 was added to all transitions out of the state and the probabilities were re-calculated. This assumes that plausible transitions with no events were not observed either due to short follow-up or limited sample size and that there is a non-zero likelihood of the transition occurring. In practice, this has little impact on the base case transition probabilities.

6) *Scaling to ensure that the probabilities from each health state sum to 1*: Where necessary, a sequential approach is used working from the more severe health states and adjusting less severe states to fit within the residual probability. Thus $\sum_{k=1}^{4} P_{ik} = 1$ for each i.

The final set of transition matrices used in the base case model are reported in CS Appendix M Table 73 (reproduced in Table 73 below). The ERG has checked that these matrices match those in the model, and that the adjustments are correctly applied.

Transition matrices for scenario with mOCS

Similar methods were used to estimate transition matrices for patients on mOCS in the company mixed population scenario, with the following exceptions:

- Transition matrices are based on data from the VENTURE trial
- VENTURE did not collect information on moderate exacerbations, so this health state is omitted from the model for the mOCS group.
- The follow-up period for VENTURE is 24 weeks and trial transitions are collated for 0-12 week and 12-24 week periods. A similar approach is used as for the non mOCS population, with pooling of exacerbation rates across the whole trial duration, but use of separate control rates for 0-12 weeks and 12-24 weeks.
- Post 24-week transitions are based on the 12-24 week transition matrix, with adjustment for long-term severe exacerbation rate ([redacted] multiplier to adjust for trial exclusion criteria). This adjustment will have a greater impact in the mOCS population, since it is applied after only 24 weeks rather than 52 as for the non mOCS population.

The CS reports a set of transition matrices for the mOCS population in CS Appendix M Table 74, but this does not match the values in the submitted model (see Table 74 below). In response to clarification question B2, the company reported the numbers and probabilities of transitions to the Controlled Asthma health state (Clarification Response Table 18), which are consistent with the probabilities in the model, but data for transitions to the other health states were not reported. The model includes absolute numbers of transitions and the probabilities are correctly calculated from these numbers. In the Factual Accuracy Check, the company states that the transition probabilities in the model are correct.

ERG conclusions: The company's approach to estimation of transition probabilities between the live health states makes good use of QUEST and VENTURE data. The model

calculations are correct, although we note that the transition probabilities from VENTURE reported in CS Appendix M differ from those in the model. We have concerns about the use of a multiplier to inflate the observed rates of severe exacerbations from the trials after trial follow up (step 4 above), see section 4.4.4.1.

Table 73. Transition probabilities: EOS≥150 or FeNo≥25 and ≥3 exacerbations

	Controlled Asthma	Uncontrolled Asthma	Moderate Exacerbation	Severe Exacerbation
Standard care only				
0-12 weeks				
Controlled Asthma	69.9%	19.1%	1.8%	9.2%
Uncontrolled Asthma	14.3%	51.7%	11.8%	22.2%
Moderate Exacerbation	11.0%	33.1%	39.5%	16.3%
Severe Exacerbation	8.8%	61.4%	6.5%	23.4%
12-52 weeks				
Controlled Asthma	70.8%	18.2%	1.8%	9.2%
Uncontrolled Asthma	12.0%	54.0%	11.8%	22.2%
Moderate Exacerbation	2.9%	41.2%	39.5%	16.3%
Severe Exacerbation	18.3%	51.8%	6.5%	23.4%
52+ weeks				
Controlled Asthma	66.8%	18.2%	1.8%	13.1%
Uncontrolled Asthma	2.4%	54.0%	11.8%	31.7%
Moderate Exacerbation	2.8%	35.8%	37.9%	23.5%
Severe Exacerbation	8.2%	51.8%	6.5%	33.5%
Dupilumab + standard care				
0-12 weeks				
Controlled Asthma	75.0%	13.9%	7.7%	3.4%
Uncontrolled Asthma	21.6%	56.5%	13.1%	8.8%
Moderate Exacerbation	26.8%	35.7%	36.5%	1.0%
Severe Exacerbation	22.5%	67.5%	7.5%	2.5%
12-52 weeks				
Controlled Asthma	77.0%	11.8%	7.7%	3.4%
Uncontrolled Asthma	16.2%	62.0%	13.1%	8.8%
Moderate Exacerbation	25.6%	36.9%	36.5%	1.0%
Severe Exacerbation	41.8%	48.2%	7.5%	2.5%
52+ weeks (responders only)				
Controlled Asthma	79.6%	10.7%	6.9%	2.7%
Uncontrolled Asthma	17.1%	68.1%	9.4%	5.4%
Moderate Exacerbation	23.3%	28.2%	46.5%	2.0%
Severe Exacerbation	41.2%	35.3%	17.6%	5.9%

Source: Copied from the company model by ERG

Table 74. Transition probabilities: EOS≥150 or FeNo≥25 and mOCS

	Controlled Asthma	Uncontrolled Asthma	Moderate Exacerbation	Severe Exacerbation
Standard care only				
0-12 weeks				
Controlled Asthma	61.2%	20.4%	-	18.4%
Uncontrolled Asthma	6.4%	83.2%	-	10.4%
Moderate Exacerbation	-	-	-	-
Severe Exacerbation	47.7%	47.7%	-	4.7%
12-24 weeks				
Controlled Asthma	31.4%	50.2%	-	18.4%
Uncontrolled Asthma	10.5%	79.1%	-	10.4%
Moderate Exacerbation	-	-	-	-
Severe Exacerbation	32.9%	62.5%	-	4.7%
24+ weeks				
Controlled Asthma	23.4%	50.2%	-	26.3%
Uncontrolled Asthma	5.9%	79.1%	-	14.9%
Moderate Exacerbation	-	-	-	-
Severe Exacerbation	30.9%	62.5%	-	6.7%
Dupilumab + standard care				
0-12 weeks				
Controlled Asthma	88.0%	8.4%	-	3.7%
Uncontrolled Asthma	19.9%	74.2%	-	5.9%
Moderate Exacerbation	-	-	-	-
Severe Exacerbation	16.7%	75.0%	-	8.3%
12-24 weeks				
Controlled Asthma	84.4%	11.9%	-	3.7%
Uncontrolled Asthma	9.3%	84.7%	-	5.9%
Moderate Exacerbation	-	-	-	-
Severe Exacerbation	46.2%	46.2%	-	7.7%
24+ weeks (responders only)				
Controlled Asthma	84.4%	11.1%	-	4.5%
Uncontrolled Asthma	9.5%	86.8%	-	3.6%
Moderate Exacerbation	-	-	-	-
Severe Exacerbation	62.5%	25.0%	-	12.5%

Source: Copied from model by ERG

4.3.4.2 Maintenance oral corticosteroid use

Parameters used to model OCS dose reduction and withdrawal in the company's mixed population scenario (EOS≥150 or FeNO≥25 and mOCS) are described in CS B.3.3.7 and Table 55. The probabilities of dose reduction are estimated from VENTURE data on the proportions of the subgroup on less than 5mg per day at baseline, 12 and 24 weeks, assuming a constant rate of change between these time points, and no further change after 24 weeks. Only a small proportion of patients (0.66%) were on less than 5mg daily at baseline. This increased to 47% at 12 weeks and 41% at 24 weeks in the standard care group; and 58% and 73% respectively in the dupilumab group. The difference between dupilumab responders at week 24 (81%) and patients on standard care (41%) is assumed to persist while patients remain on add-on treatment. The same approach is used to estimate OCS withdrawal probabilities. For standard care, 15% withdrew by week 12 and 30% by week 24. This compared with 40% and 53% respectively in the dupilumab group, and 58% at week 24 for dupilumab responders.

4.3.4.3 Response and discontinuation

The base case model assumes that patients on dupilumab are assessed at 12 months and that non-responders stop treatment. Response is defined as at least 50% reduction in severe exacerbations or maintenance oral corticosteroid dose at 12 months. This is similar to the definition of adequate response in NICE mepolizumab guidance (TA431) (see CS Table 50). [redacted] ([redacted] patients) in the QUEST base case subgroup (EOS≥150 or FeNo≥25 and ≥3 exacerbations) and [redacted] ([redacted] patients) of the VENTURE mOCS scenario subgroup (EOS≥150 or FeNo≥25 and mOCS) met this definition of response (CS B..3.3.4).

The model also applies a constant annual rate of dupilumab discontinuation after 12 months (CS B.3.3.5). Discontinuation rates were estimated from the ITT populations of QUEST (12-52 weeks) and VENTURE (12-24 weeks): 0.107 per person year for the base case (dupilumab 200mg) and 0.042 per person year for the mOCS scenario (dupilumab 300mg) (CS Table 54). These discontinuation rates from the first year of treatment in a clinical trial context might not be generalisable to longer term treatment in practice.

As an alternative, the model includes a 'discontinuation rule' as a scenario. This assumes that patients discontinue treatment if they spend 12 consecutive cycles without controlled disease (i.e. in the uncontrolled asthma, moderate or severe exacerbation health states).

The company quotes the EMA licence for dupilumab:

> "*Dupilumab is intended for long-term treatment. The need for continued therapy should be considered at least on an annual basis as determined by physician assessment of the patient's level of asthma control.*" (SmPC page 3)

This suggests that a single response assessment is not sufficient, but that the need for continued treatment should be re-assessed annually. The NICE TA565 committee noted a similar recommendation in the summary of product characteristics for benralizumab and agreed that reviewing treatment every 12 months as for other biologics is appropriate.

> **ERG conclusions**: The company's model includes an appropriate assessment of response at 12 months and a constant subsequent rate of discontinuation estimated from the clinical trials. The latter might not be generalisable to ongoing treatment cessation rates in practice, but the company tests this in the 'alternative continuation rule' scenario, which the ERG consider to be reasonable. However, we note that the company's base case does not include any discontinuation prior to the 12 month response assessment. This seems unrealistic because some patients are likely to stop treatment for reasons other than lack of response (e.g. adverse effects, intolerance or inconvenience). We therefore include an additional ERG scenario applying the observed rates of discontinuation from the clinical trials before as well as after the 12 month response assessment (see section 4.4.3).

4.3.4.4 Multipliers for small populations

The exploratory analyses described in CS Appendix P compare dupilumab with other biologics in two subgroups based on NICE criteria for access to mepolizumab and reslizumab. These groups represent small proportions of the QUEST population:

- 35.6% (36/101) of patients in the placebo and 200mg dupilumab arms had EOS≥300 and ≥4 exacerbations in the previous year (NICE criteria for mepolizumab); and
- 46.5% (47/101) had EOS≥400 and ≥3 exacerbations in the previous year (NICE criteria for reslizumab) (CS P.1.1.1).

It was not feasible to calculate transition probabilities directly from data for these small subgroups. Instead, the model uses probability estimates from larger reference subgroups, with fewer prior exacerbations, which are then adjusted. For the mepolizumab and reslizumab eligible target groups, the reference groups are EOS≥300 with ≥2 prior exacerbations (n=202 across both arms) and EOS≥400 with ≥1 prior exacerbation (n=349),

respectively. In addition to severe and moderate exacerbations, this approach was used to estimate the proportion of patients with a response to dupilumab at 52 weeks.

Multipliers to inflate the reference exacerbation and response estimates for the target groups were calculated from negative binomial regression models. To provide sufficient power, the binomial regressions were conducted with QUEST data for people on high dose ICS with EOS≥150 (n=349). A similar approach was used to estimate multipliers for dupilumab responders (n=165). The company provided further information about the regression datasets in response to a clarification question (B5), Tables 23 and 24. The models included age, region, EOS level, number of severe exacerbations in the previous year and treatment group as covariates. The resulting multiplier estimates for the mepolizumab and reslizumab eligible subgroups are reported in CS Appendix P Table 123 (reproduced below for convenience). In response to Clarification Question B5, the company reported goodness-of-fit statistics and co-variate significance for the final models, but did not compare alternative specifications or assess the appropriateness of the negative binomial models (dispersion). It is therefore difficult to assess the robustness of the results. The economic model uses a simulation approach to estimate confidence ranges for the multiplier estimates.

Table 75: Multipliers for subgroups by treatment for patients not on mOCS

Severe Subgroup (pn/tn)	Corresponding reference subgroup (pn/tn)	Outcome	Background therapy alone	Dupilumab + background therapy: All patients	Dupilumab + background therapy: Responders
EOS≥300 AND ≥4 exacerbations (14/22)	EOS≥300 AND ≥2 exacerbations (48/79)	Severe exacerbation	1.46	1.27	1.99
		Moderate Exacerbation	1.18	1.48	1.56
		% response with dupilumab	N/A	1.02	
EOS≥400 AND ≥3 exacerbations (21/ 26)	EOS≥400 AND ≥2 exacerbation (57/93)	Severe exacerbation	1.67	1.22	2.85
		Moderate Exacerbation	0.63	1.21	1.29
		% response with dupilumab	N/A	1.12	

EOS, eosinophil; FeNO, fractional exhaled nitric oxide; Pn, n in placebo subgroup; PSER, placebo severe exacerbation rate; Tn, n in treatment subgroup.
Source: Reproduced from CS Appendix P Table 123

ERG conclusions: The ERG agree that it would not have been feasible to calculate transition probabilities directly from data for the small subgroups who meet NICE criteria for access to other add-on biologic comparators. The company therefore estimated the small group probabilities based on results for similar groups with fewer severe exacerbations in the previous year, adjusted with multipliers for the increased risks associated with a greater number of prior exacerbations. The ERG considers this to be a reasonable approach which is consistent with methods in TA479. We also think that the company's method of calculating the prior exacerbation multipliers using negative binomial regressions is appropriate, although we cannot assess the robustness of the fitted models due to limited diagnostic statistics.

4.3.4.5 Relative effects for other biologics

Transition probabilities for other biologic comparators are calculated by applying relative effects estimated from the company's indirect treatment comparisons: the Bucher ITC in the base case, and a scenario using the MAIC analyses (CS Appendix P.1). We discuss the relative strengths and weaknesses of the Bucher and MAIC methods in section 3.1.7.5 above.

Estimates of relative effects were only available for severe exacerbations and OCS-related outcomes (dose reduction and withdrawal). The company assumes that rates of moderate exacerbations and loss of control for other biologic comparators are the same as for dupilumab (relative risks = 1). This assumption is reasonable given the lack of comparative data, but it is a limitation of the exploratory comparison with other biologics.

The model uses relative risks to adjust rates of severe exacerbations and odds ratios to adjust the proportions of patients with reduced dose or withdrawal from OCS (reproduced in Table 76 and Table 77 respectively). Note that these ratios are reported for the comparator relative to dupilumab, so they are the inverse of the values reported in CS Appendix N (Table 88) and Appendix O (Table 114). We note one error in reporting: CS P.1 Table 127 gives the incorrect relative risk of severe exacerbations for the MAIC mepolizumab 'NICE-like' population. The values in the model appear to be correct, as they match the (inverted) values in Appendix O Table 114.

The model includes separate estimates (where available) for the relative effects of 'responders' based on subgroup data for trial participants with a treatment response at 12 months. However, the model applies relative effects for all patients to responders in the base

case, as the company considers this to be more robust. A scenario for the ITC uses estimates of relative effects reported in other NICE appraisals.

Table 76 Relative rates of severe exacerbations

Treatment	Relative risks versus dupilumab, mean (95% CI)	
	Non mOCS (all patients)	mOCS (all patients)
Bucher indirect treatment comparison		
Reslizumab	1.724 (1.25 to 2.326)	
Mepolizumab	1.471 (1.075 to 2.000)	1.493 (0.781 to 2.778)
Benralizumab	2.174 (1.515 to 3.125)	1.163 (0.469 to 2.857)
Matched adjusted indirect treatment comparison		
Reslizumab	1.521 (0.961 to 2.406)	
Mepolizumab label Population	1.343 (1.010 to 1.784)	2.090 (0.909 to 4.804)
Mepolizumab 'NICE-like'	1.795 (0.987 to 3.265)	1.274 (0.620 to 2.615) [a]
Benralizumab	1.709 (1.122 to 2.601)	0.657 (0.297 to 1.453)

Source: Reproduced from CS Appendix P.1.10 Table 126 and 127
a As reported in model. Value differs from CS P.1.10 Table 127)

Table 77 Relative effects on OCS reduction

Treatment	Odds ratios versus dupilumab, mean (95% CI)	
	Withdrawal from OCS	Reduction to a daily dose <5mg
Indirect treatment comparison[a]		
Mepolizumab	0.862 (0.225 to 3.226)	0.667 (0.242 to 1.852)
Benralizumab	1.020 (0.218 to 4.762)	0.513 (0.136 to 1.961)
Matched adjusted indirect comparison[a]		
Mepolizumab	N/A	N/A
Mepolizumab: NICE-like population	1.967 (0.299 to 12.927)	
Benralizumab	1.075 (0.249 to 4.650)	0.513 (0.136 to 1.961)

Source: Reproduced from CS Appendix P.1.13 Table 131

ERG conclusions:
Relative effects of the biologics in the economic model are based on the Bucher ITC analyses, with results from the MAIC as a scenario. The company note that the decision to use the Bucher ITC in the base case was due to 'limitations of the MAIC'. They do not expand but we agree that the MAIC does have inherent limitations. There are also limitations with the Bucher ITC approach (see section 3.1.7.5 above).

Estimates of relative effects are only available for risks of severe exacerbations and OCS-related outcomes (dose reduction and withdrawal). The company assumes that incidence of moderate exacerbations and loss of control for other biologics are the same as for dupilumab. This assumption is reasonable given the lack of comparative data, but it is an important limitation of the comparison with other biologics.

The company report the comparative cost-effectiveness between biologics as 'exploratory' and emphasise that it is presented "for information purposes only and should be interpreted with appropriate caution" (CS Appendix Q). The ERG shares this caution due to limitations of both Bucher ITC and MAIC methods and the lack of data to assess comparative effects on moderate exacerbations and loss of control. However, we understand that there is overlap between the company's target subgroup for dupilumab and current criteria for access to other biologics in the English NHS. It is therefore necessary to make comparisons between dupilumab and other biologics in the NICE scope. The ITC, though flawed, presents the best currently-available data to make this comparison.

4.3.4.6 Mortality

In addition to general population mortality, the economic model includes mortality from severe asthma.

Asthma-related mortality

The company uses published literature to inform mortality data related to asthma. They state that previous NICE TAs have implemented a similar approach wherein patients could experience death from severe eosinophilic asthma. A detailed discussion of the approach adopted in the previous appraisals is presented in CS Appendix M.3.2.

Asthma related mortality is incorporated in the economic model as a fatality associated with severe exacerbations. The proportion of severe exacerbations that are fatal differ by age and

by location of treatment: hospital admission; A&E attendance; or other (which may include primary care or potentially self-management with emergency prescribed 'OCS burst').

For the base case, the company uses the estimates from the preferred committee assumption in NICE TA565. The mortality rate associated with exacerbations leading to hospitalisation is based on data from Watson et al.[24] and age-adjusted based on Roberts et al.[25], with further adjustment based on the most recent BTS audit. The fatality estimates by age and by setting of treatment of severe exacerbations are presented in CS Table 56, reproduced below in Table 78. The CS acknowledges that there remains considerable uncertainty over the mortality estimates and conducted two scenario analyses to assess the impact on cost effectiveness: use of asthma-related mortality from the mepolizumab submission; and asthma-related mortality set to 0.

Table 78 Probability of death after a severe exacerbation as used in model

Age band	Other		A&E visit		Hospitalisation	
	%	N	%	N	%	N
18–24 years	0.020	91	0.13	45	0.06	2,420
25–34 years	0.020	91	0.13	45	0.06	2,420
35–44 years	0.020	91	0.13	45	0.08	2,420
45–54 years	0.324	91	2.05	45	0.30	628
55–64 years	0.324	91	2.05	45	1.81	521
65–74 years	0.324	91	2.05	45	4.54	689
75–100 years	0.324	91	2.05	45	4.54	689

Source: CS Table 56

Table 79 Setting of severe exacerbations in model

Source (population)	Other		A&E visit		Hospitalisation	
	%	n	%	n	%	n
O'Neill et al. 2015 (BTS Difficult Asthma Registry) [a]	73.6%	2587	7.8%	274	18.7%	656
QUEST ITT [b]	93.3%	1122	3.0%	36	3.7%	44
VENTURE						
TA431 (EOS≥150, ≥2 Prior exacerbations) [c]	83.1%	373	8.7%	39	8.2%	37
TA565 (EOS≥400, ≥1 Prior exacerbations) [d]	87.3%	571	4.5%	30	8.2%	53

Castro et al. 2015 (EOS≥150 or FeNO≥25, ≥2 Prior exacerbations) [e]	91.4%	281	3.9%	12	4.7%	15

Source: Adapted by ERG from company model

a. O'Neill et al. 2015; 9.6% of unscheduled A&E or GP visits assumed to be A&E
b. QUEST post hoc analysis, Exacerbations, 29 Jun 2018, ITT population; Combined across all arms (all doses of dupilumab and placebo)
c. VENTURE post hoc analysis, Exacerbations, 25 Jun 2018, ITT population; Combined across all arms (dupilumab and placebo)
d. NICE TA431, Mepolizumab - company evidence submission, Table 105, page 198
e. Bleecker et al. 2016, Appendix 14, Table 3; Segregation of A&E visit and hospitalisation assumed based on distribution reported in NICE TA565
f. Castro et al. 2015; Pooled Study 1 and 2; Segregation of A&E visit and hospitalisation assumed based on distribution in QUEST

Another parameter that drives model estimates of asthma-related mortality is the distribution of locations for treatment of severe exacerbations (CS section B 3.5.7.1, Table 80). For the base case, the company use estimates reported by O'Neill et al (2015)[26], which analysed data from the British Thoracic Society Difficult Asthma Registry. The strength of this source is that it uses UK 'real-world' data. However, it is not clear whether the denominator includes all cases of severe exacerbation in the relevant population, because cases were only ascertained from hospital and primary care records. Patients who self-managed for 3 or more days with an emergency supply of oral corticosteroids ('OCS burst') would not have been included. The model includes two scenarios based on alternative sources: one with estimates from the QUEST and VENTURE trials; and another using estimates from other biologic trials (see Table 79). All of these other sources report smaller proportions of patients treated in A&E or with hospitalisation.

Other cause mortality

The model uses general population all-cause mortality rates by age and gender from Life tables for England and Wales. The CS appropriately adjusted these rates by removing the proportion of asthma-related deaths to avoid double-counting. The proportions of asthma-related deaths reported in CS Table 57 are calculated from the International Classification of Diseases, Tenth Revision codes J45-J46 for 2014-16, provided by the ONS.

ERG conclusions: The company's general approach to modelling asthma-related mortality, in which excess mortality is only associated with severe exacerbations, is consistent with NICE previous appraisals for severe asthma. The fatality rates by age and location of treatment that are used in the base case model are the same as in NICE TA565, and were accepted as appropriate by the TA565 committee (paragraph

3.12). However, the assumed proportions of severe exacerbations treated in hospital or A&E are higher than in TA565. This has the effect of increasing the number of asthma-related deaths in the model, and hence QALY gain from avoiding severe exacerbations. We consider the impact and plausibility of the resulting mortality estimates in section 4.3.7.

The company's assumptions about other cause mortality are reasonable.

4.3.5 Utilities

The company model uses the following parameters to estimate the impact of the comparators on health-related quality of life:

- A baseline utility, adjusted for age and gender, for patients with controlled and uncontrolled asthma;
- Utility decrements to reflect the negative impact of moderate and severe exacerbations compared to uncontrolled asthma; and
- A utility decrement for mOCS-related adverse effects.

Values for these parameters were obtained from an analysis of EQ-5D data from the QUEST and VENTURE trials, supplemented with estimates from the literature.

Utilities from published sources

The company conducted a systematic literature review for studies that reported health-related quality of life of patients with severe asthma. The search strategy and inclusion criteria is shown in Appendix G. They included generic preference-based (eg. EQ-5D), generic (eg.SF-36) and disease-specific measures (eg. AQL-5D). We consider that the search strategy was satisfactory. After full-text screening, 18 studies met the inclusion criteria, three of which reported EQ-5D utilities (CS Table 64).

The company noted that the study by Lloyd et al.[28] could be used to inform the exacerbation disutility and has been used in a previous submission. However the numbers in this study are smaller than in QUEST. The company uses the disutilities from Lloyd et al. in a scenario analysis.

Utility data from the QUEST and VENTURE trials

EQ-5D-5L and AQLQ utility data were collected through questionnaires given to the patients during the QUEST and VENTURE trials. In QUEST, these were collected at weeks: 0 12, 24,

36, 52 (End of trial) and 64 (End of study). In VENTURE, these data were collected at weeks: -8 to -3, 0, 12, 24 (End of trial) and 36 (End of study). The company assumed the same utility for each health state, regardless of background therapy or add-on biologic, due to the small number of observations. Utility values were calculated for controlled asthma, uncontrolled asthma, moderate exacerbation and severe exacerbation.

EQ-5D-5L utility values were obtained by mapping to the EQ-5D-3L, using the van Hout crosswalk algorithm.[29] The ERG agrees that this is consistent with the NICE reference case and position statement on EQ-5D-5L data.[30]

The company noted that in previous appraisals for asthma, it had been suggested that the EQ-5D does not accurately capture benefits from treatment of severe asthma and that some of the limitations of the EQ-5D could be removed by mapping AQLQ to EQ-5D. The company used utility values from the asthma-specific preference-based index AQL-5D in sensitivity analyses. However, the ICER does not change significantly when the utilities were derived from AQLQ, rather than EQ-5D (CS Table 91).

The EQ-5D utility values from QUEST and VENTURE for patients with controlled and uncontrolled asthma are shown in Table 80 (CS Table 60). In response to a clarification question (B6), the company provided the total number of observations used to calculate the controlled and uncontrolled asthma utility values (Clarification response Table 25). These numbers are shown in Table 80. We note that values for controlled asthma are higher than general UK population norms for age 45-54 [31], which lacks face validity.

Table 80 Trial-based EQ-5D utilities: base case and mOCS populations

Health State	N	Mean	SE
ICS population (QUEST) EOS ≥150 OR FeNO ≥25 and ≥3 severe exacerbations			
Controlled asthma	329	0.906	0.0068
Uncontrolled asthma	327	0.735	0.0110
mOCS population (VENTURE) EOS ≥150 OR FeNO ≥25 and mOCS			
Controlled asthma	95	0.890	0.016
Uncontrolled asthma	173	0.713	0.014

CS Table 60
EOS, eosinophils; EQ-5D, EuroQol-5 dimensions; FeNO, fractional exhaled nitric oxide; mOCS, maintenance oral corticosteroids; SE, standard error.
Source: Data on file. Post-hoc analyses from QUEST; Post-hoc analyses from VENTURE

The company notes the small numbers of EQ-5D measurements for severe exacerbation. For this reason, they use data for the ITT population, rather than the particular subgroups of

interest. Utility decrements for severe exacerbation are shown in Table 81 (CS Table 63). These decrements are applied to the uncontrolled asthma health state. The company assumes that there is no decrement for moderate exacerbation.

Table 81 Disutility of severe exacerbations from QUEST ITT

	Type of exacerbation	No. exacerbations	Mean	SE
Severe exacerbation	Office visit	176	–0.075	0.016
	A&E visit	7	–0.086	0.128
	Hospitalisation	7	–0.145	0.128

CS Table 63
A&E, Accident and Emergency; ITT, intent to treat; SE, standard error.

The company includes scenario analyses based on published data for the controlled and uncontrolled asthma health states (Willson et al. 2014)[27] and for the exacerbation disutilities (Lloyd et al. 2007)[28], together with a scenario analysis using AQL-5D data (CS Table 91).

Exacerbation disutilities are applied in the model for the duration observed in QUEST ITT. The duration of exacerbation is shown in CS Table 67. The company notes that (as argued in the NICE submission for TA431), decrements may last beyond the time at which the exacerbation is considered to be resolved. The company includes a scenario where applying a disutility for the duration of a cycle (4 weeks).

Age-related utilities

Utilities in the economic model are adjusted for age and gender, based on the algorithm developed by Ara and Brazier[31] (CS Table 62). The company notes that this is in line with the NICE DSU Technical Document 12.[32] The model does not include disutility associated with any adverse events associated with biologic add-on treatment.

Disutilities for adverse events related to mOCS use

Long-term chronic use of steroids can have serious long-lasting side-effects and one of the benefits of biologic use is the opportunity to reduce maintenance OCS. The company includes the effect of these side-effects on quality of life. The model includes three categories for mOCS use: complete withdrawal of OCS, dose reduction to >1≤5mg/day or high dose of >5 mg/day.

The baseline incidence risk of AEs is for those patients not receiving mOCS (shown in CS Table 58). Odds ratios are used for the medium or high daily dose of OCS vs. no OCS use (CS Table 59). These data are from a large Clinical Practice Research Datalink (CPRD) study by Bloechliger et al[33] with between 165,900 and 269,368 asthma patients.

Utility decrements are applied in the model for adverse events related to mOCS use by multiplying the incidence of the AEs by the disutilities of the AEs. The disutilities for the AEs are shown in CS Table 68 and are from Sullivan et al,[34] a EQ-5D utility catalogue which provides disutilities for chronic diseases. The majority of AEs are for long-term illnesses and so the disutility is applied over the patient lifetime. Severe infection, herpes zoster and peptic ulcer are assumed to last for 4 weeks. In response to a clarification question (B7), the company provided more information on ICD codes used to identify the disutilities associated with each adverse event and these are shown in the Clarification response Table 26.

> ***ERG conclusion:*** The company's approach to estimating utility values is based upon EQ-5D-5L data collected from the company's QUEST and VENTURE trials. The company has used the cross-walk method to map these data to EQ-5D-3L data for use in the company model, which is consistent with NICE's current position statement on the EQ-5D-5L. The utility values collected are consistent with NICE's reference case and suitable for inclusion in the economic model. The ERG noticed that the utility values for controlled asthma appear to be higher than would be expected in the UK general population. This lacks face validity, and we conduct an additional scenario analysis to test the impact of constraining the utility for controlled asthma to the age-related mean for the general population (see section 4.4.3).

4.3.6 Resource use and costs

The model includes estimates of costs for drug acquisition and administration, monitoring and follow-up care and the treatment of serious infections (CS section 3.5).

The CS reports a systematic literature review conducted to identify resource use and costs. The search strategy and the inclusion criteria are reported in Appendix G. The inclusion criteria included studies from the UK and US with more than 20 patients with moderate to severe asthma. Forty-two studies were identified that presented costs and healthcare resource use (HCRU) measures, including total direct and indirect costs, hospitalisations, medical visits, and/or length of stay. Of these, three cost studies and nine resource studies were conducted in the UK and are reported in CS Table 69 and 70.

4.3.6.1 Drug acquisition costs

Dupilumab is administered by subcutaneous injection, with an initial dose of 400mg (two 200mg injections), followed by 200mg injections every two weeks. For patients with severe asthma who are on oral corticosteroids, patients receive an initial dose of 600mg (two 300mg injections), followed by 300mg injections every two weeks. The cost of dupilumab at list price is £1264.89 per pack of two injections. Dupilumab is provided to the NHS with a confidential PAS discount for atopic dermatitis and the company states that this will be applied to both 200mg and 300mg doses for severe asthma (CS Table 2). Results are shown in the CS with the discount applied.

Background therapy use was estimated based on the clinical trial distributions and the distribution of the ICS/LABA data was derived from previously published UK-specific market research.[11] The background therapy use are shown in CS Table 72 and 73. The unit costs of background therapies are shown in CS Table 76 and 77.

4.3.6.2 Drug administration costs

Dupilumab is assumed to be administered in hospital for the first three administrations at a cost of £18.75 per administration, after which patients would self-administer. There is a one-off training cost for patients of £22.50. Unit costs were from PSSRU[35] and the assumptions used to calculate these are shown in CS Table 78. The same assumptions were made in the exploratory analysis for the administration costs of other biologics administered by subcutaneous injections (mepolizumab and benralizumab).

The summary of product characteristics states that patients or caregivers may self-inject dupilumab "*if their healthcare professional determines that this is appropriate*", and if so, that proper training should be provided.(SmPC page 4)[36]. Clinical advice to the ERG is that self-administration, which is not currently considered for other biologic treatments, would be an advantage. However, this may not be immediately available and may have an effect on the efficacy of dupilumab as patients who self-administer no longer have regular contact with medical professionals. There were no administration costs for background therapy as these treatments are inhaled or taken orally.

4.3.6.3 Health care resources

Health care resources for the controlled and uncontrolled health states and moderate and severe exacerbations were taken from an economic evaluation of tiotropium in patients with

poorly controlled asthma by Wilson et al.[27] This study conducted a survey of 15 UK health care providers to obtain health state-specific estimates of resource use. Those resource data have been converted to the cycle length used in the economic model (4 weeks) using the assumptions reported in CS Section 3.5.7. The resource use for the controlled and uncontrolled health states are shown in Table 82 (CS Table 79) and the resource use for exacerbations are shown in Table 83 (CS Table 81).

Table 82 Routine care resource use per cycle (4 weeks)

	Resource use per cycle in the 'Controlled asthma' health state		Resource use per cycle in the 'Uncontrolled asthma' health state	
Resource	**Mean**	**SE**	**Mean**	**SE**
GP	0.162	0.033	0.552	0.144
Primary care nurse	0.236	0.033	0.632	0.213
Specialist (outpatient visit)	0.098	0.024	0.376	0.096
Airflow Studies	0.108	0.024	0.196	0.044

CS Table 79
DSA, deterministic sensitivity analysis; GP, General Practitioner; PSA, probabilistic sensitivity analysis; SD, standard deviation; SE, standard error.
Source: Calculated from Willson et al, 2014, Technical appendix, Tables 7 to 9

Table 83 Resource use per cycle (4 weeks) associated with exacerbations

Resource use per cycle (4 weeks)	Office visit or self-managed		A&E visit		Hospitalisation	
	Mean	**SE**	**Mean**	**SE**	**Mean**	**SE**
GP	1.643	0.219	1.416	0.171	0.866	0.146
Primary care nurse	1.219	0.217	1.462	0.267	1.696	0.464
Specialist (outpatient visit)	0.527	0.138	1.238	0.364	1.948	0.673
OCS per mg	350	35	491	49	759	76
Emergency room attendance			1.000	0.000	0.623	0.060
Ambulance use			0.065	0.013	0.065	0.013
Severe exacerbation-related hospitalisation (long stay)					1.000	0.000
Post-acute hospitalisation*					1.000	0.000

CS Table 81
A&E, Accident and Emergency; GP, General Practitioner; OCS, oral corticosteroid; SE, standard error.
Source: † Calculated from Willson et al, 2014, Technical appendix, Tables 7 to 9 [27]; ‡ Dose in mg: NICE TA431, Mepolizumab - MS, Table 123 (page 216) § For 'Emergency roomvisit': assumption; For

'Hospitalisation': NICE TA431, Mepolizumab - MS, Table 123 (page 216) (Calculated from Willson et al, 2014, Technical appendix, Table 11 †† Assumption. [27] *Used in scenario analysis only

The setting of the treatment for exacerbations was also informed by the study by O'Neill et al. 2015.[26] The assumptions used to estimate the proportions in each group are shown in CS section B 3.5.7.1. 74% of severe exacerbations were treated by GP, 7.8% were treated at A&E and 18.7% were hospitalised (CS Table 80). As noted above (section 4.3.4.6), we do have some concerns about the appropriateness of this source.

Unit costs were taken from the PSSRU [35] or NHS National tariff [37] and are shown in Table 84 (CS Table 74). For emergency room attendance and severe exacerbation related hospitalisation, the company has combined the NHS National Tariff costs with a weighted average of the HRG codes. The ERG prefer the NHS reference costs: emergency department attendance £176.26 and severe exacerbation related hospitalisation £1579.45. For completeness, we use Reference Costs in ERG analysis (section 4.4.4).

Table 84 Unit costs of health care resources

Resource	Unit Cost	Source
Outpatient visits: GP (incl. home visit)**	£37.00 per visit	PSSRU 2018; Outpatient GP consultation (lasting 9.22 minutes)
Outpatient visits: Nurse (incl. home visit)**	£42 per hour	PSSRU 2018; Nurse (GP practice)
Outpatient visits: Specialist	£124 per visit	NHS National Tariff 2019-2020 [37]; Respiratory Outpatient Attendance, TFC code 340 Multiprofessional.
Outpatient visit: Hospital-based nurse	£ 45.00 per hour	PSSRU 2018; Specialist nurse - Band 6
Airflow studies	£53.00	NHS National Tariff 2019–2020. Airflow studies
OCS	£0.0047 per mg	2.5mg gastro-resistant tablets £0.93 per 28
Emergency room attendance	£ 143.57	NHS National Tariff Workbook 2019-2020 Weighted average of currency codes VB01Z to VB09Z of resource use cited in 2017-2018 National Schedule of Reference Costs
Ambulance use	£ 219.00	NHS Cost Recovery Scheme 2019–2020
Severe exacerbation-related hospitalisation	£ 1,646.26	NHS National Tariff Workbook 2019–2020 [38]; Weighted HRG codes DZ15M-DZ15R of resource use cited in 2017–2018 National Schedule of Reference Costs

CS Table 74

GP, General Practitioner; HRG, Healthcare Resource Group; OCS, oral corticosteroids.
** It assumed that home visits have the same cost as a GP or nurse office visit.

To calculate the health state costs per cycle, the estimates of resource use were multiplied by their corresponding costs per cycle. The health state costs per cycle are shown in Table 85 (CS Table 82).

Table 85 Health state costs: costs per cycle

Health State/ Exacerbation setting	Routine care cost	Cost per cycle for moderate exacerbations	Cost per cycle for severe exacerbations
Controlled Asthma	£ 26.43		
Uncontrolled asthma	£ 84.29		
Exacerbation – office visit		£95.49	£141.02
Severe exacerbation – A&E visit			£381.84
Severe exacerbation – hospitalisation			£2,045.56

CS Table 82
A&E, accident and emergency.

Adverse events associated with maintenance OCS use

The costs associated with treating the AEs related to mOCS were shown in CS Table 83 and related to either acute or long-term costs. In response to clarification question B11, the company confirmed that the values reported in this table are incorrect and should be as used in the model. The correct values are reported in the clarification response Table 27.

> ***ERG conclusion:*** The approach taken by the company to estimate health care resources and costs is reasonable and in line with previous NICE technology appraisals for severe asthma. For consistency, the ERG suggested that the unit costs should be taken from NHS reference costs for emergency room attendance and severe exacerbation related hospitalisation, rather than from the NHS National Tariff Workbook.

4.3.7 Model validation

The company describes their approach to model validation in CS section B.3.10. They state that they conducted two advisory board meetings, consisting of clinicians and health economists, to validate the key cost-effectiveness assumptions including those relating to the model structure, response assessment, and OCS AE data. Further, technical experts unrelated to the project validated the model. As part of this exercise, external independent

health economists assessed the model via the preliminary independent model advice (PRIMA). Further details of the validation checks are presented in CS section B.3.10.2.

The key conclusions that the company drew from the validation exercise were:

- Any error identified in the model validation exercises were discussed and addressed;
- A range of extreme value tests reiterated the consistency in model behaviour.

4.3.8 Company cost effectiveness results

4.3.8.1 Base case population

Deterministic results

The company present their base case results in CS section B.3.7, comparing dupilumab with standard care alone for people with severe uncontrolled asthma with EOS ≥ 150 or FeNO ≥ 25, and at least 3 exacerbations in the previous year (and no mOCS at baseline). We reproduce the company's results in Table 86 below. These results incorporate a simple price discount for dupilumab.

Table 86 Deterministic results: base case EOS≥150 or FeNO≥25 and ≥3 exacerbations in previous year (non-mOCS), with discounted price for dupilumab

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

Source: CS Table 89

This analysis includes standard care as the only comparator, although some people in the defined base case population would meet NICE criteria for access to other biologics. We discuss this in section 4.4.5.1 below and estimate results for subgroups of the company's base case not eligible for mepolizumab or for resulizumab.

Deterministic sensitivity analysis

The company briefly summarises their approach to Deterministic Sensitivity Analysis (DSA) in CS section B.3.6.2.1. The tornado plot for the base-case model results (CS Figure 37, reproduced in Figure 5 below) shows that the proportions of severe exacerbations that are fatal are key drivers of the model results. Other influential parameters are the unit cost of dupilumab, parameters that influence the long-term incidence of severe exacerbations under standard treatment and the constant in the age-related utility equation.

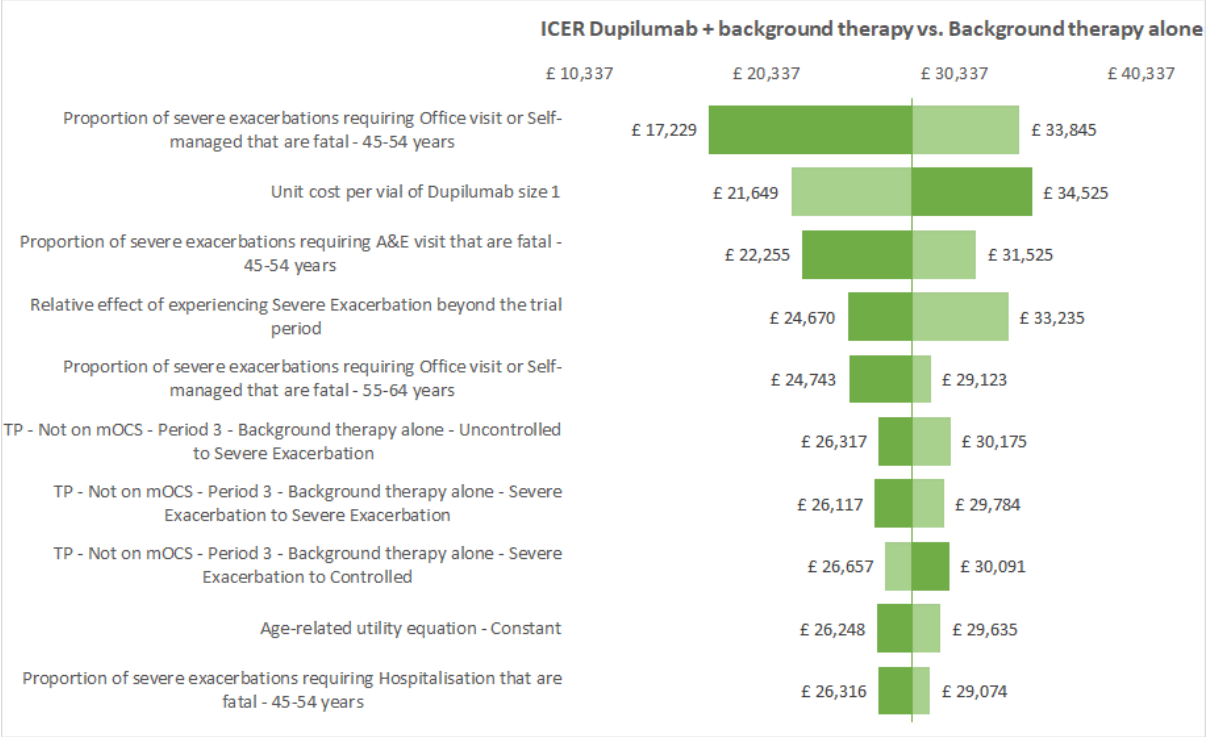


Figure 5 Tornado plot for base case analysis: EOS≥150 or FeNo≥25 and ≥3 exacerbations in previous year

Probabilistic sensitivity analysis

The company conducted a probabilistic sensitivity analysis (PSA) on their base-case model to assess parameter uncertainty. Assumptions used to characterise uncertainty are described in CS Section B.3.6.2.2 Table 86. Briefly, normal distributions are used for age and disutilities for exacerbations and AEs; gamma distributions for costs and resource quantities; log-normal distributions for relative effects on exacerbations, loss of control and mOCS-related AEs; beta distributions for utilities; and Dirichlet distributions for transition probabilities and setting of exacerbation.

Probabilistic results for the base case (CS Table 90) are similar to the deterministic results. The company provided a revised Cost-Effectiveness Acceptability Curve (CEAC) in response to clarification question B12. At a willingness-to-pay threshold of £30,000 per QALY gained, dupilumab had an estimated 51.2% probability of being cost-effective compared to standard care alone.

Scenario analysis

The company conducted scenario analysis to assess the impact of key variables on base case cost-effectiveness (CS Table 91 and Table 87 below). They concluded that cost effectiveness was pre-dominantly influenced by:

- Asthma-related mortality (proportion of severe exacerbations that are fatal)
- Assumptions about the rate of exacerbations after the clinical trial period
- Additional costs to the NHS after patients' discharge from hospital
- The discount rate for health effects
- Reduction in the model time horizon

The estimated ICERs for dupilumab compared with standard care alone in the base case population were below £30,000 per QALY in most of the modelled scenarios. We note two particular exceptions:

- Lower background rates of severe exacerbation after the trial (rate as observed in trial or with multiplier less than 1.35)
- Lower proportions of people with severe exacerbations treated in A&E or with hospitalisation (as in TA431 submission or as observed in QUEST ITT analysis)

The model is sensitive to these uncertain parameters. ICERs were also above £30,000 per QALY in the following scenarios:

- No response assessment at one year
- No excess mortality for asthma
- Short time horizon

These scenarios are useful for illustrative purposes but are not realistic or appropriate for the NICE reference case.

Table 87 Company scenario: base case, EOS≥150 or FeNO≥25 and ≥3 exacerbations in previous year (non-mOCS), discounted price for dupilumab

Scenario	Treatment	Cost	QALYs	ICER (£/QALY)
Base-case	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£ 28,087
Transition probabilities (Base case: QUEST data, CS Appendix M.1 Table 73)				
Separate exacerbation rates for weeks 0-12 and 12-52	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£ 26,869
No adjustment for null events	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£ 27,626
Post-trial severe exacerbation rate (Base case: multiplier [redacted], CS Appendix M.2.1)				
Pre-trial rates (1.813)	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£ 23,538
Adjusted for exclusion criterion & exacerbation definition ([redacted])	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£ 25,434
Mepolizumab appraisal (1.35)	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£ 30,009**
Observed in trial (1.00)	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£ 41,272**
Response and discontinuation (Base case: [redacted] response then 10.73% stop per year, CS B.3.3.4 and B.3.3.5)				
Annual discontinuation 0%	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£ 26,115
Annual discontinuation 10%	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£ 27,927
Alternative continuation rule (stop if not controlled for 12 months)	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£ 28,988
No response assessment	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£ 32,939**
Severe exacerbation fatality rate by setting (Base case: CS Table 56, from TA565)				
Mepolizumab submission	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£ 25,921

Scenario	Treatment	Cost	QALYs	ICER (£/QALY)
No excess mortality for asthma	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£ 71,950
Setting of severe exacerbations (Base case: CS Table 80, from O'Neill et al. 2015 73.56% office or self-managed, 7.79% A&E, 18.65% hospital)				
MENSA ITT, TA431 submission (83.07%, 8.69%, 8.24%)	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£ 30,425**
QUEST ITT (in model) (93.34%, 3.00%, 3.66%)	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£ 35,448**
Control utilities (QUEST EQ-5D: controlled 0.906, uncontrolled 0.735, CS Table 60)				
Willson et al. 2014[27] (0.922, 0.728)	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£ 27,201
QUEST AQL-5D mapping (0.943, 0.801)	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£ 28,133
Severe exacerbation utility loss (Base case: QUEST CS Tables 63 and 67)				
Utilities from Lloyd et al. 2007[28] (CS Table 65) for 28 days	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£ 25,601
Disutilities from Lloyd et al. (CS Table 64 & 65) for 28 days	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£ 27,274
Duration assumption from Lloyd et al. : 28 days	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£ 27,692
Post-acute hospitalisation costs (Base case £0, CS Table 81)				
Resource use after hospitalisation (£2,204)	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£ 23,742
General settings				
Discount health effects 1.5%	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£ 21,446
Time horizon 10 years	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£ 46,645**
Time horizon 5 years	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£ 62,536**

Source: Adapted from CS Table 91 by ERG with additional information from CS and model

4.3.8.2 Mixed mOCS/ non mOCS scenario

Deterministic results

CS Table 92 reports deterministic results for the mix of people taking mOCS with EOS150 or FeNO≥25 and (41.7%) and people not on mOCS with EOS≥150 or FeNO≥25 and at least 3 exacerbations in previous year (58.3%). The assumed proportion of patients on mOCS comes from a UK severe asthma registry[22], as used in the ERG analysis in TA565 (see section 4.3.2.1 above for discussion). We test the sensitivity of results to this parameter in section 4.4.5.2.

As in the base case, the company includes standard care as the only comparator. Although biologic add-on treatments are not available for everyone in this group, the EOS and prior exacerbation criteria do not have upper limits so there will be overlap with subgroups eligible for benralizumab, mepolizumab and/or reslizumab. See 4.4.5.1 for discussion and further analysis.

The analysis includes simple price discount for dupilumab. It can be seen that dupilumab is estimated to be less cost-effective in this mixed population (mOCS/ non-mOCS) than in the base case (no mOCS); with an ICER above £30,000 per QALY gained.

Table 88 Deterministic results: EOS≥150 or FeNO≥25 and ≥3 exacerbations in previous year or mOCS (41.7%), discounted price for dupilumab

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

Source: CS Table 92

Deterministic sensitivity analysis

The DSA results for the mixed population are summarised in a tornado plot (CS Table 93, reproduced in Figure 6). This shows that the parameters with the greatest impact on the ICER in this population are: the proportions of severe exacerbations that are fatal; the unit cost of dupilumab, the multipliers for long-term severe exacerbation rates, the constant in the age-related utility equation and some of the transition probabilities beyond the trial period.

Probabilistic sensitivity analysis

The probabilistic results for the base case (CS Table 96) are similar to the deterministic results. At a willingness-to-pay threshold of £30,000 per QALY gained, dupilumab had an estimated 16.7% probability of being cost-effective compared to standard care alone.

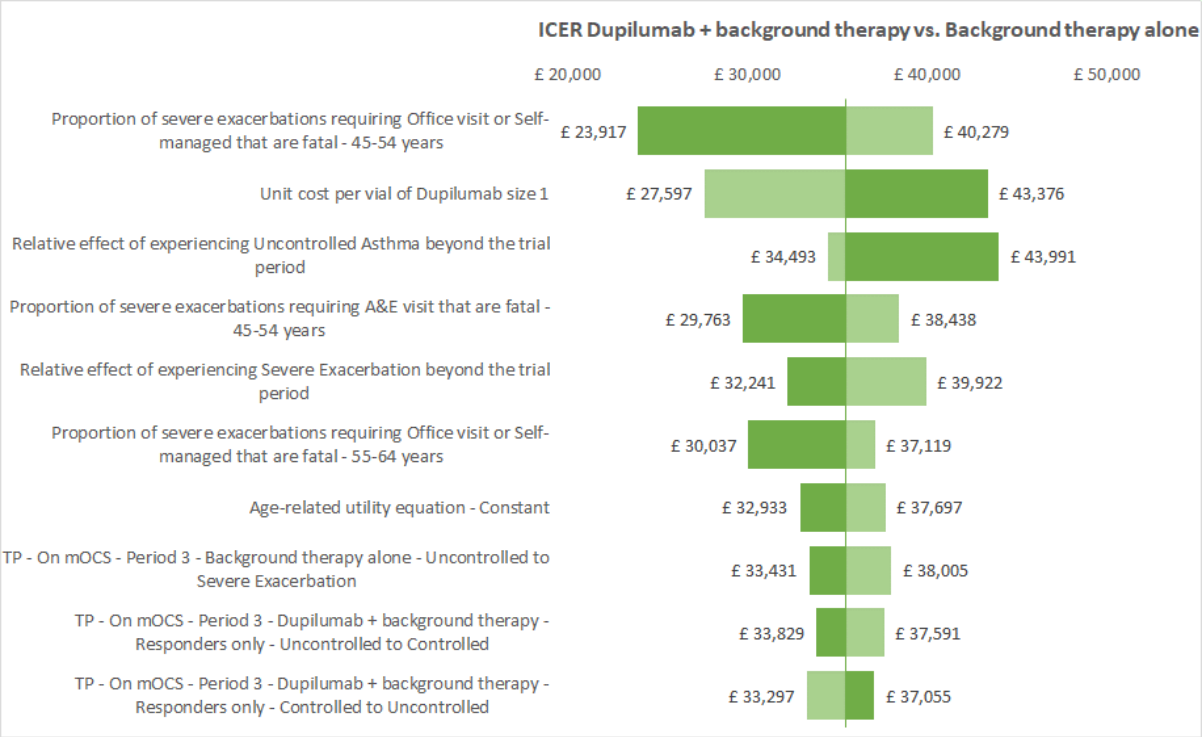


Figure 6 Tornado diagram: Dupilumab vs. standard care alone for EOS≥150 or FeNO≥25 and ≥3 exacerbations in previous year or mOCS

Scenario analysis

The company did not report scenario analyses for the mixed population, although the model includes the capacity to run the same range of scenarios as for the base case. This resulted in ICERs for dupilumab compared with standard care above £30,000 per QALY gained for all company scenarios except a discount rate of 1.5% for health effects (which does not meet current NICE Reference Case criteria).

4.3.8.3 Mepolizumab eligible subgroup

The results of the exploratory analysis for the subgroup that meet the NICE criteria for mepolizumab are shown in CS Appendix Q.1 Table 143 (reproduced in Table 89 below). This analysis includes a mix of people on mOCS with EOS≥300 (41.7%) and people not on mOCS with EOS≥300 and at least 4 exacerbations in the previous year (58.3%). The relevant comparators for this population are mepolizumab, benralizumab and standard care.

The company assumed the same proportion of people on mOCS as in their mixed population scenario (41.7%). There is uncertainty over this figure and the TA565 guidance noted that the ERG for that appraisal preferred an assumption of 60% of patients on mOCS for the mepolizumab comparison. We test the impact of different mOCS proportions in 4.4.5.2.

Relative effects of the biologics are based on the Bucher ITC analyses, with results from the MAIC in scenario analysis. There is a high degree of uncertainty over the estimates of relative effectiveness from both ITC and MAIC analysis (4.3.4.5).

The analysis includes a simple price discount for dupilumab and an assumed [redacted] price reduction for mepolizumab and benralizumab: we emphasise that this does not necessarily reflect actual prices paid in the NHS. The comparative cost-effectiveness results between biologics reported in this section are therefore only illustrative. We report results with all agreed PAS discounts in an Addendum to this report.

Table 89 Deterministic results: EOS ≥300 and ≥4 exacerbations or mOCS (41.7%), simple price discount for dupilumab and assumed [redacted] price discount for mepolizumab and benralizumab

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

Source: CS Table 143

The CS does not include scenario analyses for the mepolizumab eligible subgroup. The ERG ran the company's scenarios, which indicated:

- ICERs for dupilumab versus with standard care below £30,000 per QALY except under the following scenarios: time horizon 5 or 10 years; no response assessment; severe exacerbations after trial based on observed trial data; setting of severe exacerbations as in dupilumab or mepolizumab trials.

- ICERs for dupilumab compared with mepolizumab below £30,000 per QALY, except under the extreme scenarios of no asthma-related mortality or a very short time horizon of 5 years.
- Dupilumab was estimated to dominate benralizumab in all scenarios.

The company assumed the same proportion of people on mOCS as in their mixed population scenario (41.7%). However, there is uncertainty over this figure and the TA565 guidance noted that the ERG for that appraisal preferred an assumption of 60% of patients on mOCS for the mepolizumab comparison. We test the impact of different mOCS proportions in 4.4.5.2.

Relative effects of the biologics are based on the Bucher ITC analyses, with results from the MAIC used for scenario analysis. There is a high degree of uncertainty over the estimates of relative effectiveness from the ITC and MAIC analysis

4.3.8.4 Reslizumab eligible subgroup

Results for the comparison of dupilumab with reslizumab, benralizumab and standard care in the population who meet NICE criteria for reslizumab (EOS ≥400 and ≥3 exacerbations in the previous year) are reported in CS Appendix Q.2. We show the deterministic results, including pairwise and incremental ICERs in Table 90 below. As above, these results include a confidential PAS discount for dupilumab and an assumed discount of [redacted] for the other biologics. Based on these and other assumptions, dupilumab is dominates benralizumab and reslizumab (it costs less and has better effectiveness results). The ICER for dupilumab compared with standard care is below £30,000 per QALY.

Table 90 Deterministic results: EOS ≥400 and ≥3 exacerbations in previous year, confidential price discount for dupilumab and assumed price discount of [redacted] for benralizumab and reslizumab

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

Source: CS Table 148

The CS does not include scenario analysis around these results. The ERG ran the company's scenarios, which indicate that:

- The ICER for dupilumab compared with standard care is below £30,000 per QALY except for the extreme scenarios: very short time horizon (5 or 10 years); and no asthma-relate mortality.
- Dupilumab dominated benralizumab except for the scenario with the alternative long-term continuation rule (ICER [redacted] per QALY)
- Dupilumab dominated reslizumab or had a very low ICER across all scenarios.

4.3.8.5 Summary of company cost-effectiveness results

Base case analysis

The company base case compares dupilumab with standard treatment alone for people with severe asthma driven by Type 2 inflammation, defined by EOS≥150 or FeNO≥25 and at least 3 exacerbations in the previous year and not taking mOCS. The company's base case ICER is £28,087 per QALY gained. Probabilistic analysis indicates that the chance that the treatment would be cost-effective at a threshold of £30,000 per QALY is 51%. Other sensitivity and scenario analysis show that long-term rates of severe exacerbations and mortality are important drivers for the economic model.

In particular, we note that the ICER is sensitive to three key inputs to the economic model:

- The proportions of severe exacerbations that are fatal (by patient age and location of treatment: A&E attendance, hospital admission or other);
- The proportions of people with severe exacerbations who are treated in A&E or in hospital; and
- The relative rate of severe exacerbations after the clinical trial period, compared with the observed rates during the trial.

Mixed mOCS/ non mOCS scenario

The company also compared dupilumab with standard care alone in a mixed population with EOS≥150 or FeNO≥25 and at least 3 exacerbations in the previous year (58.7%) or mOCS (41.3%). Dupilumab appeared less cost-effective in this context than in the base case. The ICER for the mixed mOCS/ non mOCS population was £35,486 per QALY gained, with an

estimated probability of 16.7% of the ICER being above £30,000 per QALY. This result was robust to scenarios that are clinically appropriate and meet the NICE reference case.

Comparative analyses for people who are eligible for other biologics

Exploratory analyses comparing dupilumab against other biologic treatments are presented in appendices to the CS. Two sets of analysis are reported, one for people who meet NICE criteria for access to mepolizumab (EOS≥300 and at least 4 exacerbations in the previous year or taking mOCS) and the other for people meeting NICE criteria for reslizumab (EOS≥300 and at least 4 exacerbations in the previous year). Benralizumab was included as a comparator in both analyses, as it is also recommended for both subgroups. The results suggest that dupilumab is cost-effective in both contexts, either dominating or with ICERs below £30,000 per QALY gained versus all comparators.

However, the company urges caution in drawing conclusions from these results, due to limitations in the indirect comparisons. We also emphasise that these analyses are based on a confidential PAS price discount for dupilumab and an *assumed* price discount for the other biologics ([redacted] of list price), which does not reflect true prices paid in the NHS. We present results with agreed PAS price discounts for comparators as well as dupilumab in a confidential addendum to this report.

4.4 Additional work undertaken by the ERG

4.4.1 ERG model validation

4.4.1.1 Process of model checking

The ERG conducted a range of model checks:

- Comparison of input parameter values reported in the CS with values in the model, and where relevant with external sources. This identified two discrepancies:
    - Differences in the transition probability matrices estimated from VENTURE for the mOCS groups as reported in CS Appendix M Table 74 and in the model. The model reports numbers of transitions between each pair of states and calculations for the adjustments described in section 4.3.4.1 above. We confirm that the probabilities used the model are correct according to these reported numbers of transitions.

  - The costs for mOCS-related adverse events in CS Table 83 differed from the values used in the model. The company confirmed in Clarification Response B11 that the values in the model are correct.

- We checked all model results reported in the CS against live model outputs. All results were successfully replicated with the exception of two sensitivity analysis graphs: the CEAC in CS Figure 39 and the tornado diagram in CS Table 93. The differences were explained in the Clarification Responses.

- Manual checks on links and calculations from input data, to model parameters, the Markov engine sheets and results calculations. This included checks on calculations and adjustments used to estimate the transition probabilities, long-term exacerbation and small group multipliers and the relative risks for other biologics.

No important errors were identified and we have not made any corrections to the submitted model.

4.4.2 Face validity of model projections

The following tables summarise the company's predicted outcomes for the four patient groups considered in the company submission. The tables show the proportions of patients in the five main health states included in the model: controlled asthma; uncontrolled asthma (but no exacerbations), moderate or severe exacerbation (at least one month) and death.

We asked our clinical advisors whether the projected levels of asthma control, exacerbations and mortality with standard care seemed realistic and whether the estimated improvements with dupilumab were plausible. In response, one expert said the results for standard care alone seemed 'overly dramatic', and that 20% mortality after 10 years would be very surprising. This led us to question whether the model assumptions regarding exacerbation-related deaths and extrapolation of severe exacerbation rates might be over-estimated. We address these issues in the ERG base case analysis (4.4.4).

Table 91 Model predictions for company base case population: EOS≥150 or FeNO≥25 and at least 3 exacerbations in last year (no maintenance OCS)

Year (mean age)	Controlled asthma	Uncontrolled asthma	Moderate exacerbation	Severe exacerbation	Death
Dupilumab with standard care					
Baseline (47)	0%	100%	0%	0%	0%
1 year (48)	47%	34%	13%	5%	1%
5 years (52)	32%	37%	12%	14%	4%
10 years (57)	22%	37%	11%	18%	12%
Standard care alone					
Baseline (47)	0%	100%	0%	0%	0%
1 year (48)	29%	41%	11%	18%	1%
5 years (52)	11%	43%	11%	27%	9%
10 years (57)	9%	38%	10%	23%	20%

Table 92 Model predictions for company scenario: EOS≥150 or FeNO≥25 and maintenance OCS

Year (mean age)	Controlled asthma	Uncontrolled asthma	Moderate exacerbation [a]	Severe exacerbation	Death
Dupilumab with standard care					
Baseline (51)	0%	100%	-	0%	0%
1 year (52)	40%	52%	-	7%	1%
5 years (56)	37%	52%	-	7%	4%
10 years (61)	31%	52%	-	8%	10%
Standard care alone					
Baseline (51)	0%	100%	-	0%	0%
1 year (52)	12%	73%	-	15%	1%
5 years (56)	11%	69%	-	14%	6%
10 years (61)	10%	62%	-	13%	15%

a Estimates of moderate exacerbations not available from VENTURE trial

Table 93 Model predictions for mepolizumab eligible subgroup: EOS≥300 and ≥4 exacerbations in last year or mOCS (41.7%)

Year (mean age)	Controlled asthma	Uncontrolled asthma	Moderate exacerbation	Severe exacerbation	Death
Dupilumab with standard care					
Baseline (49)	0%	100%	0%	0%	0%
1 year (50)	50%	33%	11%	5%	1%
5 years (54)	35%	35%	12%	13%	4%
10 years (59)	26%	35%	10%	15%	13%
Standard care alone					
Baseline (49)	0%	100%	0%	0%	0%
1 year (50)	21%	49%	9%	20%	1%
5 years (54)	10%	46%	9%	25%	9%
10 years (59)	9%	40%	8%	22%	22%

Table 94 Model predictions for reslizumab eligible population: EOS≥400 and and ≥3 exacerbations in last year (no mOCS)

Year (mean age)	Controlled asthma	Uncontrolled asthma	Moderate exacerbation	Severe exacerbation	Death
Dupilumab with standard care					
Baseline (49)	0%	100%	0%	0%	0%
1 year (50)	53%	31%	11%	4%	0%
5 years (54)	37%	32%	11%	15%	4%
10 years (59)	24%	32%	10%	19%	14%
Standard care alone					
Baseline (49)	0%	100%	0%	0%	0%
1 year (50)	26%	42%	9%	21%	1%
5 years (54)	11%	40%	9%	30%	10%
10 years (59)	9%	33%	8%	25%	24%

4.4.3 ERG additional scenarios on company base case

We added four scenarios to the company's analysis:

1) **Utility limited to the general population mean**
   It lacks face validity to assume that people with severe asthma have a better quality of life than the average for people of the same age and gender, even when the asthma is controlled. We therefore added an option to the model to restrict the utility for the controlled health state to the general population mean. This is estimated in the model with adjustment for age and gender by the Ara and Brazier equation (CS Table 61).[31] The utility for the uncontrolled health state is then estimated with a decrement relative to the controlled asthma utility.

2) **Discontinuation during first year**
   The base case model assumes no discontinuation of add-on therapies before the response assessment at 52 weeks. In practice, some patients will inevitably stop treatment before this time, due to adverse events, other clinical factors or patient choice. We therefore included an option to allow treatment discontinuation before the response assessment, with the same constant monthly discontinuation rate estimated from the clinical trials that is used to model ongoing discontinuation after the response assessment.

3) **NHS Reference Costs for health care unit costs**
   As noted in section 4.3.6.3 above, we prefer consistent use of NHS Reference Costs, rather than NHS Tariff values, for the unit costs of healthcare resources. The submitted model included Tariff costs for A&E (£143.57) and severe exacerbation related hospitalisations (£1,646.26). For completeness, we add a scenario replacing these costs with Reference Cost estimates of £176.26 and £1,579.45.

4) **Subcutaneous injections by healthcare professional**
   The company assumed that the first three doses of drugs administered by subcutaneous injection (dupilumab, mepolizumab and benralizumab) would be administered by a healthcare professional, with self-administration (at no cost) after then. Self administration is new in this indication so may take time to implement. An ERG expert questioned how patients would collect and store the drug at home, how training would be provided and noted that high placebo effects for biologics may (in part) be due to regular healthcare professional contact. We test the impact of assuming ongoing professional administration of all subcutaneous injections.

Results for the four patient groups presented in the company submission are shown in Table 95 to Table 98. The scenarios lead to small to modest changes in the ICERS,

Table 95 ERG additional scenarios: company base case

Company base case and additional ERG scenarios	Treatment	Cost	QALYs	ICER (£/QALY)r
EOS>=150 or FeNO>=25 & >=3 exacerbations				
Company base case	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£28,087
Utility limited to general population mean	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£29,721
Include discontinuation in first year	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£27,974
Reference costs for A&E and hospitalisation	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£28,152
Subcutaneous injections by healthcare professional	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£28,973

Table 96 ERG additional scenarios; company mixed mOCS/ non-mOCS

Company base case and additional ERG scenarios	Treatment	Cost	QALYs	ICER (£/QALY)r
EOS>=150 or FeNO>=25 & >=3 exacerbations or mOCS (41.7%)				
Company base case	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£35,486**
Utility limited to general population mean	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£37,277**
Include discontinuation in first year	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£35,430**
Reference costs for A&E and hospitalisation	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£35,544**
Subcutaneous injections by healthcare professional	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£36,579**

Table 97 ERG additional scenarios; mepolizumab eligible patients

Company base case and additional ERG scenarios	Treatment	Cost	QALYs	ICER (£/QALY) dupilumab vs. comparator
EOS>=300 & >=4 exacerbations or mOCS (41.7%)				
Company base case	Standard care	[redacted]	[redacted]	£29,215
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
Utility limited to general population mean	Standard care	[redacted]	[redacted]	**£31,817**
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
Include discontinuation in first year	Standard care	[redacted]	[redacted]	£29,169
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
Reference costs for A&E and hospitalisation	Standard care	[redacted]	[redacted]	£29,271
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
Subcutaneous injections by healthcare professional	Standard care	[redacted]	[redacted]	**£30,122**
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]

Table 98 ERG additional scenarios; reslizumab eligible patients

Company base case and additional ERG scenarios	Treatment	Cost	QALYs	ICER (£/QALY)
EOS>=400 & >=3 exacerbations (no mOCS)				
Company base case	Standard care	[redacted]	[redacted]	£23,923
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
	Reslizumab	[redacted]	[redacted]	[redacted]
Utility limited to general population mean	Standard care	[redacted]	[redacted]	£25,696
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
	Reslizumab	[redacted]	[redacted]	[redacted]
Include discontinuation in first year	Standard care	[redacted]	[redacted]	£23,844
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
	Reslizumab	[redacted]	[redacted]	[redacted]
Reference costs for A&E and hospitalisation	Standard care	[redacted]	[redacted]	£23,988
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
	Reslizumab	[redacted]	[redacted]	[redacted]
Subcutaneous injections by healthcare professional	Standard care	[redacted]	[redacted]	£24,696
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
	Reslizumab	[redacted]	[redacted]	[redacted]

4.4.4 ERG base case analysis

4.4.4.1 Justification for ERG assumptions

We made the following five changes to the company's base case.

1) No adjustment to the long-term rate of severe exacerbations

The company apply a multiplier of [redacted] to increase severe exacerbation rates after the trial period. This is intended to adjust for the exclusion of patients with a recent severe exacerbation from the clinical trials, as the company argue this will have reduced the incidence of severe exacerbations during the trial period below the background rate for the patient population. We acknowledge that this may be a consideration. However, the has a large impact on the modelled rates of exacerbations and is subject to high uncertainty. We note that in other appraisals, no or lower adjustments were made to long term exacerbation rates. The NICE Committee for the appraisal of reslizumab (TA479) concluded that despite reductions in observed exacerbation rates for patients randomised to placebo and active treatment "*adjusted rates were no more likely than the unadjusted rates to reflect the true treatment benefit*". Therefore no adjustment was made to long-term exacerbation rates in TA479 or the subsequent TA565. The earlier appraisal of mepolizumab used a lower multiplier for background exacerbation (1.35).

2) Treatment settings for severe exacerbations from clinical trial data

We consider the trial data to be a better source for estimation of the proportions of patients with severe exacerbations treated in emergency care and inpatient settings. This is because the definitions of severe exacerbation events will be consistent with the clinical data used in the model, and the method of ascertainment is likely to be more complete than for a registry based on routine clinical data.

3) Utility limited to general population mean (by age)

The assumption of better quality of life with controlled asthma than for age/gender matched general population lacks face validity. We therefore constrain the utility for the controlled asthma health state to a maximum of the general population mean, and use a decrement to estimate the utility for uncontrolled asthma.

4) Include discontinuation during first year of treatment

We consider it unrealistic to assume no discontinuation before 12 month assessment, so include a constant rate of discontinuation as observed in the trials before as well as after the 12 month response assessment.

5) **Reference Costs for healthcare unit costs**

For consistency, we apply reference costs for emergency visits and inpatient stays, although this will have negligible impact on cost-effectiveness results.

4.4.4.2 ERG results for company base case population

The cumulative impact of the above five changes for patients with EOS>=150 or FeNO>=25 & >=3 exacerbations is shown in Table 99. This shows that the largest change is due to removing the multiplier to inflate post-trial severe exacerbation rates. The assumption about the distribution of treatment location for people with severe exacerbations. The next table (Table 100) shows the effects of applying selected scenario analyses that we consider plausible alternatives to the ERG base case (one at a time). The ICERs remain above £30,000 per QALY in all of these scenarios.

Table 99 Cumulative change from company to ERG base case

Additional ERG scenarios	Treatment	Cost	QALYs	ICER (£/QALY)
EOS>=150 or FeNO>=25 & >=3 exacerbations				
Company base case	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£28,087
+ Long term severe exacerbation rate: trial data (multiplier=1)	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£41,272**
+ Distribution of treatment for severe exacerbation: clinical trials	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£52,327**
+ Limit utility to general population mean	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£55,400**
+ Include discontinuation in first year	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£55,338**
ERG base case	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£55,348**

Table 100 ERG base case and scenarios: base case population

ERG base case & scenarios	Treatment	Cost	QALYs	ICER (£/QALY)
EOS>=150 or FeNO>=25 & >=3 exacerbations				
ERG base case	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£55,348**
Post-trial severe exacerbation rate				
Trial inclusion multiplier ([redacted])	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£37,533**
Combined trial inclusion and exacerbation definition multiplier ([redacted])	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£34,040**
Mepolizumab appraisal multiplier (1.35)	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£40,119**
Setting of severe exacerbations				
Distribution from O'Neill et al. 2015	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£43,549**
Distribution from MENSA ITT, TA431 submission	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£46,619**
Response and discontinuation				
No discontinuation in first year	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£55,410**
Alternative continuation rule	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£55,625**
Control utilities				
Absolute utility estimates from QUEST EQ-5D	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£52,278**

4.4.4.3 ERG results for mepolizumab eligible subgroup

The ERG base case and scenarios are applied to people who are eligible for mepolizumab

Table 101 ERG base case and scenarios: mepolizumab eligible subgroup

ERG base case & scenarios	Treatment	Cost	QALYs	ICER (£/QALY) dupilumab vs. comparator
EOS>=300 & >=4 exacerbations or mOCS (41.7%)				
ERG base case	Standard care	[redacted]	[redacted]	**£48,866**
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
Post-trial severe exacerbation rate				
Trial inclusion multiplier ([redacted])	Standard care	[redacted]	[redacted]	**£38,363**
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
Combined trial inclusion and exacerbation definition multiplier ([redacted])	Standard care	[redacted]	[redacted]	**£35,805**
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
Mepolizumab appraisal multiplier (1.35)	Standard care	[redacted]	[redacted]	**£39,937**
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
Setting of severe exacerbations				
Distribution from O'Neill et al. 2015	Standard care	[redacted]	[redacted]	**£40,592**
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
Distribution from MENSA ITT, TA431 submission	Standard care	[redacted]	[redacted]	**£46,851**
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]

ERG base case & scenarios	Treatment	Cost	QALYs	ICER (£/QALY) dupilumab vs. comparator
Response and discontinuation				
No discontinuation during first year	Standard care	[redacted]	[redacted]	**£48,876**
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Benralizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	*Reference*
Alternative continuation rule	Standard care	[redacted]	[redacted]	**£48,773**
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Benralizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	*Reference*
Control utilities				
Absolute utility estimates from QUEST EQ-5D	Standard care	[redacted]	[redacted]	**£45,133**
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
Relative effects				
MAIC (where available)	Standard care	[redacted]	[redacted]	**£48,866**
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
MAIC label population for mepolizumab	Standard care	[redacted]	[redacted]	**£48,866**
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
Reimbursement submissions for responders	Standard care	[redacted]	[redacted]	£48,866
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]

4.4.4.4 ERG results for reslizumab eligible subgroup

Table 102 ERG base case and scenarios: reslizumab eligible subgroup

ERG base case & scenarios	Treatment	Cost	QALYs	ICER (£/QALY) dupilumab vs. comparator
EOS>=400 & >=3 exacerbations				
ERG base case	Standard care	[redacted]	[redacted]	**£45,706**
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
	Reslizumab	[redacted]	[redacted]	[redacted]
Post-trial severe exacerbation rate				
Trial inclusion multiplier ([redacted])	Standard care	[redacted]	[redacted]	**£33,679**
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
	Reslizumab	[redacted]	[redacted]	[redacted]
Combined trial inclusion and exacerbation definition multiplier ([redacted])	Standard care	[redacted]	[redacted]	**£30,717**
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
	Reslizumab	[redacted]	[redacted]	[redacted]
Mepolizumab appraisal multiplier (1.35)	Standard care	[redacted]	[redacted]	**£35,429**
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
	Reslizumab	[redacted]	[redacted]	[redacted]
Setting of severe exacerbations				
Distribution from O'Neill et al. 2015	Standard care	[redacted]	[redacted]	**£34,848**
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
	Reslizumab	[redacted]	[redacted]	[redacted]
Distribution from MENSA ITT, TA431 submission	Standard care	[redacted]	[redacted]	**£44,099**
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
	Reslizumab	[redacted]	[redacted]	[redacted]

ERG base case & scenarios	Treatment	Cost	QALYs	ICER (£/QALY) dupilumab vs. comparator
Response and discontinuation				
No discontinuation during first year	Standard care	[redacted]	[redacted]	**£45,735**
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
	Reslizumab	[redacted]	[redacted]	[redacted]
Alternative continuation rule	Standard care	[redacted]	[redacted]	**£46,393**
	Benralizumab	[redacted]	[redacted]	[redacted]
	Reslizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	*Reference*
Control utilities				
Absolute utility estimates from QUEST EQ-5D	Standard care	[redacted]	[redacted]	**£42,577**
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
	Reslizumab	[redacted]	[redacted]	[redacted]
Relative effects				
MAIC (where available)	Standard care	[redacted]	[redacted]	**£45,706**
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
	Reslizumab	[redacted]	[redacted]	[redacted]
Reimbursement submissions for responders	Standard care	[redacted]	[redacted]	**£45,706**
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
	Reslizumab	[redacted]	[redacted]	[redacted]

4.4.5 ERG additional subgroups

4.4.5.1 Estimates for patients not eligible for other biologics

Given the information available in the CS and model it is not possible to calculate results for people in the company's target population for dupilumab for whom standard care would be the only current treatment option. But this can be approximated, by taking a weighted difference between the results for the base case population and subgroups who are eligible either for mepolizumab or reslizumab.

For example, the company reports that 36 out of 101 patients in the target population for dupilumab (in the combined placebo and 200mg arms of QUEST with EOS>=150 & >=3 exacerbations) were eligible for mepolizumab (EOS>=300 & >=4 exacerbations) (CS P.1.1.1). From the model we estimate costs and QALYs for the whole target population and also for the mepolizumab-eligible subgroup. Assuming that the latter group are 35.6% (36/101) of the target population we can estimate costs and QALYs for the residual non-mepolizumab-eligible subset of the target group.

We report ERG analysis results for the company's base case population excluding patients who meet NICE access criteria for mepolizumab and reslizumab in Table 103 and Table 104 respectively. This shows that dupilumab is likely to be less cost-effective (with higher ICERs) if people who are already suitable for treatment with other biologics are excluded from the company's target population. This doesn't change the substantive conclusions in the ERG analysis, as all ICERs are above the £30,000 per QALY threshold. However, it does illustrate the TA565 Committee's conclusion that cost-effectiveness results from a mixed population with a range of asthma severity is not suitable for decision making. However, we emphasise that the analyses below are only approximations, because they do not account for the overlap of people who meet access criteria for both reslizumab and mepolizmuab. Additional data would be required for a more accurate assessment of the cost-effectiveness of dupilumab in patients for whom standard care is the only treatment option.

Table 103 ERG base case and scenarios: not mepolizumab eligible

ERG base case & scenarios	Treatment	Cost	QALYs	ICER (£/QALY)
Base case population excluding patients eligible for mepolizumab (35.6%, 36/101)				
ERG base case	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£58,387**
Post-trial severe exacerbation rate				
Trial inclusion multiplier ([redacted])	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£38,404**
Combined trial inclusion and exacerbation definition multiplier ([redacted])	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£34,730**
Mepolizumab appraisal multiplier (1.35)	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£41,291**
Setting of severe exacerbations				
Distribution from O'Neill et al. 2015	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£46,940**
Distribution from MENSA ITT, TA431 submission	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£47,200**
Response and discontinuation				
No discontinuation during first year	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£58,465**
Alternative continuation rule	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£59,541**
Control utilities				
Absolute utility estimates from QUEST EQ-5D	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£55,219**

Table 104 ERG base case and scenarios: not reslizumab eligible

ERG base case & scenarios	Treatment	Cost	QALYs	ICER (£/QALY)
Base case population excluding patients eligible for reslizumab (46.5%, 47/101)				
ERG base case	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£68,542**
Post-trial severe exacerbation rate				
Trial inclusion multiplier ([redacted])	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£41,933**
Combined trial inclusion and exacerbation definition multiplier ([redacted])	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£37,789**
Mepolizumab appraisal multiplier (1.35)	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£45,653**
Setting of severe exacerbations				
Distribution from O'Neill et al. 2015	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£55,999**
Distribution from MENSA ITT, TA431 submission	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£49,254**
Response and discontinuation				
No discontinuation during first year	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£68,659**
Alternative continuation rule	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£88,708**
Control utilities				
Absolute utility estimates from QUEST EQ-5D	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	**£66,001**

4.4.5.2 Sensitivity to the proportion of patients on mOCS

Finally, we assess the sensitivity of results for mixed populations to the proportion of people taking mOCS. The company assumes 41.7% in their mixed analyses: in both the standard care only comparison (EOS>=150 or FeNO>=25) and the mepolizumab eligible comparison (EOS>=300). However, the TA565 NICE committee noted that it is difficult to determine the proportion of patients taking mOCS in practice. We test the sensitivity of the company's base case results and mepolizumab-based comparison in Table 105 and Table 106, respectively. These analyses do demonstrate sensitivity to this parameter, particularly in the group with less severe asthma (EOS>=150 or FeNO>=25), for whom treatment of patients on mOCS but without the additional risk factor of at least 3 exacerbations in the previous year is not cost-effective (ICER for dupilumab compared with standard care only was over £45,000 per QALY). However, the results in the mepolizumab eligible group are quite stable over a wide range of estimates for the proportion on mOCS.

Table 105 Sensitivity to the proportion of mOCS: company base case

Additional ERG scenarios	Treatment	Cost	QALYs	ICER (£/QALY)
EOS>=150 or FeNO>=25 & >=3 exacerbations or mOCS				
Base case (0% mOCS)	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£28,087
Proportion mOCS = 20%	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£31,682
Proportion mOCS = 41.7%	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£35,486
Proportion mOCS = 60%	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£38,620
Proportion mOCS = 100%	Standard care	[redacted]	[redacted]	
	Dupilumab	[redacted]	[redacted]	£45,240

Table 106 Sensitivity to the proportion of mOCS: mepolizumab comparison

Additional ERG scenarios	Treatment	Cost	QALYs	ICER (£/QALY) dupilumab vs. comparator
EOS>=300 & >=4 exacerbations or mOCS				
Base case (0% mOCS)	Standard care	[redacted]	[redacted]	£25,661
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	*Reference*
	Benralizumab	[redacted]	[redacted]	[redacted]
Proportion mOCS = 20%	Standard care	[redacted]	[redacted]	£27,543
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	Reference
	Benralizumab	[redacted]	[redacted]	[redacted]
Proportion mOCS = 41.7%	Standard care	[redacted]	[redacted]	£29,215
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	Reference
	Benralizumab	[redacted]	[redacted]	[redacted]
Proportion mOCS = 60%	Standard care	[redacted]	[redacted]	£30,397
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	Reference
	Benralizumab	[redacted]	[redacted]	[redacted]
Proportion mOCS = 100%	Standard care	[redacted]	[redacted]	£32,459
	Mepolizumab	[redacted]	[redacted]	[redacted]
	Dupilumab	[redacted]	[redacted]	Reference
	Benralizumab	[redacted]	[redacted]	[redacted]

4.4.6 Summary of ERG analysis results

Additional scenarios on the company's base case

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

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

The company's results were generally robust to these assumptions, across all four patient patient subgroups (base case, mixed mOCS/ non mOCS, mepolizumab eligible and reslizumab eligible). Capping utility at the general population mean led to a modest increase in the ICERs of around £1,000 to £2,000 per QALY. The other scenarios led to only small changes in the ICERs.

ERG base case and scenarios

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

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

The first two changes led to a sizeable increase in the estimated ICERs. The cap on utility led to a modest increase and the impact of the discontinuation and cost changes were negligible. The resulting ERG base case ICER for dupilumab compared with standard care alone in the company's target population (EOS≥150 or FeNO≥25 and ≥3 prior exacerbations) was £55,348 per QALY gained. This estimate remained above £30,000 per QALY gained across a range of scenarios, including use of the company's base case

multiplier for the long-term rate of severe exacerbations ([redacted]) which reduced the ICER to £37,533.

ERG subgroup analysis

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

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

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

5 End of life

Dupilumab is not considered an end-of-life treatment.

6 Innovation

The company point out in CS B.2.12 that the current biologic treatments for severe asthma target either IL-5 (e.g. reslizumab, mepolizumab, benralizumab) or IgE (e,g, omalizumab). Dupilumab however, inhibits two distinctly different pathways via inhibition of the IL-4Rα subunit that is shared by both IL-4 and IL-13 receptor complexes. This means that dupilumab targets a patient population that is different from the populations targeted by the other current biological therapies (although, as noted there is some overlap between the different patient populations).

The mode of action of dupilumab means that it reduces FeNO levels, whereas levels of EOS are not affected. In contrast, the company points out that a literature review (no citation provided) has demonstrated that the anti-IL5 biologics reduce EOS levels but do not reduce FeNO levels.

In the pivotal trials of dupilumab which underpin the CS (DRI12544, QUEST and VENTURE) asthma exacerbations were reduced, and lung function improved and, for patients in receipt of OCS at baseline, OCS use was reduced. The company highlight that the reduction of OCS use is a high priority because chronic OCS treatment is associated with a number of side effects.

Finally, the CS notes there are other diseases that are mediated by type 2 inflammation (atopic dermatitis, allergic nasal polyps and eosinophilic oesophatitis). Dupilumab is already indicated for the treatment of moderate to severe atopic dermatitis[39] and for patients with severe asthma who have comorbidities that are also mediated by type 2 inflammation, dupilumab treatment might have additional effects. The CS does not indicate what proportion of the severe asthma population might have such comorbidities. One of the clinicians we consulted stated in their severe asthma cohort 13.5% had coexistent eczema and atopic dermatitis.

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8 APPENDICES

Appendix 8.1: Supplementary information on the ITCs and MAICs

Table 107 Company's critical appraisal judgements for the trials contributing data to the ITCs

First author and year (Primary Reference Only)	Trial name (JP draft – yellow if data in ITC)	Randomisation[a]	Allocation concealment[b]	Baseline comparability[c]	Blinding[d]	Unexpected imbalances in drop outs between groups[e]	More outcomes than reported[f]	ITT analysis appropriate with appropriate methods for missing data[g]
Dupilumab trials								
Wenzel S 2016a	DRI	Yes	Yes	Yes	Yes	No	No	Yes
Castro M 2018b	QUEST	Yes	Yes	Yes	Yes	No	No	Yes
Rabe KF 2018	VENTURE	Yes	Unclear	Yes	Yes	No	No	Yes
Reslizumab trials								
Castro M 2015-1	BREATH 3082	Yes	Yes	Yes	Yes	No	No	Yes
Castro M 2015-2	BREATH 3083	Yes	Yes	Yes	Yes	No	No	Yes
Mepolizumab trials								
Ortega HG 2014	MENSA	Yes	Yes	Yes	Unclear	No	No	Yes
Chupp GL 2017	MUSCA	Yes	Yes	Yes	Yes	No	No	Yes
Pavord ID 2012	DREAM	Yes	Yes	Yes	Unclear	No	No	Yes
Bel EH 2014	SIRIUS	Yes	Yes	Unclear	Unclear	No	No	Yes
Benralizumab trials								
Bleecker ER 2016	SIROCCO	Yes	Yes	Yes	Unclear	No	No	Yes

FitzGerald JM 2016	CALIMA	Yes	Yes	Yes	Yes	No	No	Yes
Nair P 2017	ZONDA	Yes	Yes	Unclear	Unclear	No	No	Yes

Source: Appendix D.1.3
For all questions responses could be: yes; no; not clear; N/A
[a] Was randomisation carried out appropriately? [b] Was the concealment of treatment allocation adequate? [c] Were the groups similar at the outset of the study in terms of prognostic factors? [d] Were the care providers, participants and outcome assessors blind to treatment allocation? [e] Were there any unexpected imbalances in drop-outs between groups? [f] Is there any evidence to suggest that the authors measured more outcomes than they reported? [g] Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

Table 108 RCTs contributing data to each ITC outcome

ITC Outcome	ITC Dupilumab vs placebo vs reslizumab	ITC Dupilumab vs placebo vs mepolizumab	ITC Dupilumab vs placebo vs benralizumab
Uncontrolled persistent asthma population			
Severe exacerbations	QUEST subgroup matched to reslizumab label DRI12544 subgroup matched to reslizumab label BREATH RCTs (pooled 3082/3083)	QUEST subgroup matched to mepolizumab label DRI12544 subgroup matched to mepolizumab label MENSA RCT MUSCA RCT DREAM RCT	QUEST subgroup matched to benralizumab label DRI12544 subgroup matched to benralizumab label SIROCCO RCT CALIMA RCT
Severe exacerbations, NICE-like subgroup	QUEST matched to NICE-like reslizumab BREATH subgroup DRI12544 matched to NICE-like reslizumab BREATH subgroup BREATH NICE-like subgroup (poster 3082/3082)	QUEST matched to NICE-like mepolizumab MENSA subgroup DRI12544 matched to NICE-like mepolizumab MENSA subgroup NICE-like MENSA subgroup	N/A
Oral corticosteroid dependent asthma population			

Reduction in OCS dose <5 mg/day	N/A	VENTURE[a] SIRIUS	VENTURE[a] ZONDA
≥50% reduction in OCS dose	N/A	VENTURE[a] SIRIUS	VENTURE[a] ZONDA
100% reduction in OCS dose	N/A	VENTURE[a] SIRIUS	VENTURE[a] ZONDA
Severe exacerbations	N/A	VENTURE[a] SIRIUS	VENTURE[a] ZONDA

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

Data sources for each ITC

The data used for each ITC was reported in CS Appendix N.6 Tables 91, 92, 94, 95, and 97-105. It is not clear to the ERG why for the severe exacerbations outcome there were some slight differences between the data in the tables and the data shown in the corresponding figures. In response to clarification question A15 the company explained that they had used trial arm-level (i.e. odds) as opposed to contrast-level (i.e. odds ratio) data in the analysis which explains the slight differences. Similarly, the ERG observed that in several of the tables in Appendix N (e.g. Appendix N Tables 94, 97, 101) a footnote stated "person years were calculated for all trials, except the dupilumab trials". The company were asked to clarify this statement and provide calculations (clarification question A16). The company responded that person years were estimated as number of years of follow up multiplied by number of patients analysed (Clarification response Tables 4 to 9).

Appendix 8.2: Detailed MAIC results

Table 109 MAIC results: Severe exacerbations. Dupilumab versus mepolizumab

Comparator trials	Data filters applied to dupilumab pooled data	DRI12544 and QUEST pooled data before filtering		Pooled data remaining after filtering, n	Effective sample size after matching	% Effective sample size reduction (from relevant sample size)	MAIC results: Severe exacerbations Rate ratio (95% CI)	Overall Dupilumab vs mepolizumab Rate ratio (95% CI)
		Trial arms	Total size, n					
MENSA (ITT)	- Medium or High ICS/LABA below 18 years and High/LABA over 18 years - Number of exacerbations in the past year ≥2	Dupilumab 200mg	781	223	197	11.6%	Dupilumab vs MENSA 0.75 (0.48, 1.18)	**0.74 (0.56, 0.99)**
		Placebo	796	150	144	4%		
DREAM	- High ICS/LABA - Number of exacerbations in the past year ≥2	Dupilumab 200mg	781	213	162	23.9%	Dupilumab vs DREAM 0.58 (0.32, 1.05)	
		Placebo	796	142	64	54.9%		
MUSCA (ITT)	- Medium or High ICS/LABA below 18 years and High ICS/LABA over 18 years - Number of exacerbations in the past year ≥2	Dupilumab 200mg	781	223	192	13.9%	Dupilumab vs MUSCA 0.86 (0.54, 1.37)	
		Placebo	796	150	120	20%		

Source: CS Appendix O Tables 106, 116 and Appendix O Figure 47

Table 110 MAIC results: Severe exacerbations. Dupilumab versus mepolizumab MENSA subgroup

Comparator trials	Data filters applied to dupilumab pooled data	DRI12544 and QUEST pooled data before filtering		Pooled data remaining after filtering, n	Effective sample size after matching	% Effective sample size reduction (from relevant sample size)		Overall Dupilumab vs mepolizumab Rate ratio (95% CI)
		Trial arms	Total size, n					
MENSA (Subgroup) EOS ≥300 in past year and ≥4 exacerbations or mOCS	- Medium or High ICS/LABA below 18 years and High/LABA over 18 years - Number of exacerbations in the past year ≥2	Dupilumab 200mg	781	223	95	57.4%		
		Placebo	796	150	73	51.3%		**0.56 (0.31, 1.01)**

Source: CS Appendix O Tables 114, 117 and Appendix O Figure 48

Table 111 MAIC results: Severe exacerbations. Dupilumab versus benralizumab

Comparator trials	Data filters applied to dupilumab pooled data	DRI12544 and QUEST data before filtering		Dupilumab data remaining after filtering, n	Dupilumab effective sample size after matching	% Effective sample size reduction (from relevant sample size)	MAIC results: Severe exacerbations Rate ratio (95% CI)	Overall Dupilumab vs benralizumab Rate ratio (95% CI)
		Trial arms	Total size, n					
CALIMA (EOS ≥300)	- High ICS/LABA - Baseline blood EOS level ≥300 cells/µl - Number of exacerbations in the past year ≥2	Dupilumab 200mg	781	101	86	14.9%	0.49 (0.27, 0.9)	**0.59 (0.38, 0.89)**
		Placebo	796	68	50	26.5%		
SIROCCO (EOS ≥300)	- High ICS/LABA - Baseline blood EOS level ≥300 cells/µl - Number of exacerbations in the past year ≥2	Dupilumab 200mg	781	101	78	22.8%	0.69 (0.38, 1.24)	
		Placebo	796	68	61	10.3%		

Source: CS Appendix O Tables 106, 120 and Appendix O Figure 55

Table 112 MAIC results: Severe exacerbations. Dupilumab versus reslizumab

Comparator trials	Data filters applied to dupilumab pooled data	DRI12544 and QUEST pooled data before filtering		Dupilumab data remaining after filtering, n	Dupilumab effective sample size after matching	% Effective sample size reduction (from relevant sample size)		Overall Dupilumab vs reslizumab Rate ratio (95% CI)
		Trial arms	Total size, n					
BREATH 82-83	- Medium or High ICS/LABA - Baseline blood EOS level ≥400 cells/µl - Number of exacerbations in the past year ≥1	Dupilumab 200mg	781	238	219	7.6%		0.66 (0.42, 1.04)
		Placebo	796	156	122	21.8%		

Source: CS Appendix O Tables 106, 122 and Appendix O Figure 59

OCS dependent population

Table 113 MAIC results: Severe exacerbations, ≥50% reduction and 100% reduction in OCS dose . Dupilumab versus mepolizumab

Comparator trials	Data filters applied to dupilumab pooled data	VENTURE data before filtering		VENTURE data remaining after filtering, n	Effective sample size after matching	% Effective sample size reduction (from relevant sample size)	Outcomes	Overall Dupilumab vs mepolizumab MAIC result
		Trial arms	Total size, n					
SIRIUS ITT	High ICS/LABA	Dupilumab 200mg	103	103	50	51.5%	Severe exacerbations	RR 0.48 (95% CI 0.21, 1.1)
		Placebo	107	107	71	33.6%	≥50% reduction in OCS dose	OR 1.7 (95% CI 0.53, 5.47)
							100% reduction in OCS dose	OR 1.36 (95% CI 0.3, 6.21)

Source: CS Appendix O Tables 107, 118 and Appendix O Figures 49-51

Table 114 Severe exacerbations, ≥50% reduction and 100% reduction in OCS dose . Dupilumab versus mepolizumab SIRIUS subgroup

Comparator trials	Data filters applied to VENTURE data	VENTURE data before filtering		VENTURE data remaining after filtering, n	Effective sample size after matching	% Effective sample size reduction (from relevant sample size)	Outcomes	Overall Dupilumab vs mepolizumab MAIC result
		Trial arms	Total size, n					
SIRIUS subgroup EOS ≥300 in past year and ≥4 exacerbations or mOCS	High ICS/LABA	Dupilumab 200mg	103	103	50	51.5%	Severe exacerbations	RR 0.56 (95% CI 0.31, 1.01)
							≥50% reduction in OCS dose	OR 1.47 (95% CI 0.43, 5.06)
		Placebo	107	107	61	43.6%	100% reduction in OCS dose	OR 1.51 (95% CI 0.08, 3.34)

Source: CS Appendix O Table 119 and Appendix O Figures 52-54

Table 115 Severe exacerbations, ≥50% reduction and 100% reduction in OCS dose . Dupilumab versus benralizumab

Comparator trials	Data filters applied to VENTURE data	VENTURE data before filtering		VENTURE data remaining after filtering, n	Effective sample size after matching	% Effective sample size reduction (from relevant sample size)	Outcomes	Overall Dupilumab vs benralizumab MAIC result
		Trial arms	Total size, n					
ZONDA ITT	-High ICS/LABA - Baseline blood EOS ≥150 cells/µl - Number of exacerbations in the past year ≥1 - Age ≥18	Dupilumab 200mg	103	64	53	17.2	Severe exacerbations	RR 1.52 (0.69, 3.36)
		Placebo	107	56	37	33.9	≥50% reduction in OCS dose	OR 1.13 (0.33, 3.78)
							100% reduction in OCS dose	OR 0.93 (0.22, 4.02)

Source: CS Appendix O Tables 107, 121 and Appendix O Figures 56-58