Slides for public– Part 1 (no ACIC data)

NICE National Institute for Health and Care Excellence

Dupilumab for severe asthma with type 2 inflammation

Lead team presentation

1st appraisal committee B meeting

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ERG: Southampton Health Technology Assessments Centre

NICE technical team: Shelly Patel, Eleanor Donegan, Nicole Elliott

Company: Sanofi Genzyme

Key issues

- Where is dupilumab likely to be used in the treatment pathway for severe asthma?
- Which population is most suitable for decision making (people who are eligible or ineligible for other biologics) and what are the relevant comparators?
- Should an adjustment (multiplier) be made to the observed rates of severe exacerbation in the model?
- What source should be used to estimate the proportions of patients with severe exacerbations treated in emergency care and inpatient settings?

[redacted]

Disease background: severe asthma

- **Asthma** is a chronic, heterogeneous, reversible airway disease, influenced by both genetic and environmental factors. It is estimated that around 8% of the UK population aged 12 and over have asthma. Approximately three people in the UK die from an asthma exacerbation every day, with 1,320 people reported as dying from asthma in 2017 (CS).

- **Severe asthma** is defined as:
  - ‘asthma that requires treatment with high dose inhaled corticosteroids plus a second controller medicine to prevent it from becoming ‘uncontrolled’ or that remains ‘uncontrolled’ despite this therapy’ (NICE guideline NG80: asthma: diagnosis, monitoring and chronic asthma management and guidelines from the Global Initiative for Asthma 2019 [GINA])’
  - 200,000 people in the UK have severe asthma (Asthma UK) with the majority of patients having Type 2 inflammation (company: 74-83%, British Thoracic Society: 60-80%)

Disease background: Subtypes of severe asthma

- Subtypes of asthma

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

- Severe asthma with Type 2 inflammation is defined by GINA as

  - Blood eosinophils (EOS) ≥150 µl and/or
  - Fractional exhaled nitric oxide (FeNO) ≥20 ppb and/or
  - Sputum EOS ≥2% and/or
  - Asthma that is clinically allergen-driven and/or
  - Need for maintenance oral corticosteroids (mOCS)

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

Severe asthma

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

As needed low dose ICS-formoterol

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

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

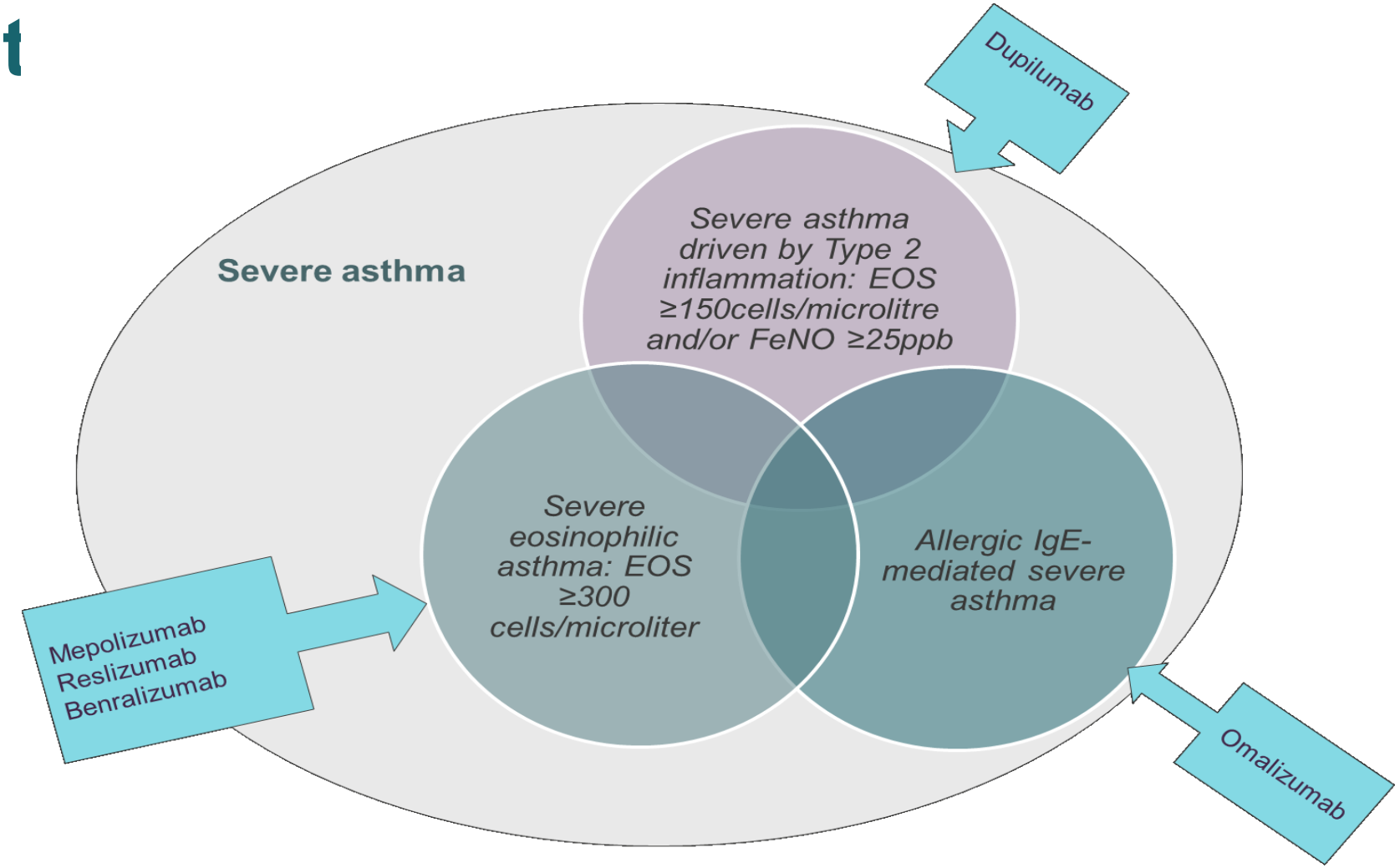
[redacted]

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

Dupilumab (Dupixent, Sanofi Genzyme)

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

Current biologics for severe asthma subt



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

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

NICE recommended biologics

Treatment options	NICE recommended population
Asthma sub-type: Severe eosinophilic asthma	
Reslizumab (TA479)	adults only if: • the blood eosinophil count (EOS) has been ≥400 cells/µl • ≥3 severe asthma exacerbations needing systemic corticosteroids past 12 months
Mepolizumab (TA431)	adults only if: • ≥ EOS 300 cells//µl in previous 12 months **AND** • Had ≥4 asthma exacerbations needing systemic corticosteroids past 12 months, or had continuous OCS of at least the equivalent of prednisolone 5 mg/day over the previous 6 months
Benralizumab (TA565)	adults only if: • EOS ≥ 300 cells/µl and the person has had ≥4 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** • EOS ≥400 cells/µl with ≥3 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 (TA278)	• as an add-on to optimised standard therapy in people aged 6 years and older who need continuous or frequent treatment with OCS (defined as ≥4 courses in the previous year)

Patient perspectives

- Living with severe asthma is very disruptive with regular hospital admissions and courses of oral steroids which can lead to [redacted]
- Uncontrolled asthma has a huge impact on work and school and can create a huge burden on family members.
- Existing treatments for severe asthma are extremely limited
- Use of mOCS causes toxic and debilitating side effects and contributes to increased sickness absence.
- Dupilumab could be an alternative for those who are 12 years and over and for those who are not eligible for current NICE recommended biologics.
- Patients prefer oral/inhaled administration methods and 2-weekly injections may be disruptive and costly when administering in hospital.
- Would patients welcome a treatment that could be home/self administered?

[redacted] Source: Patient group submissions

Clinicians perspectives

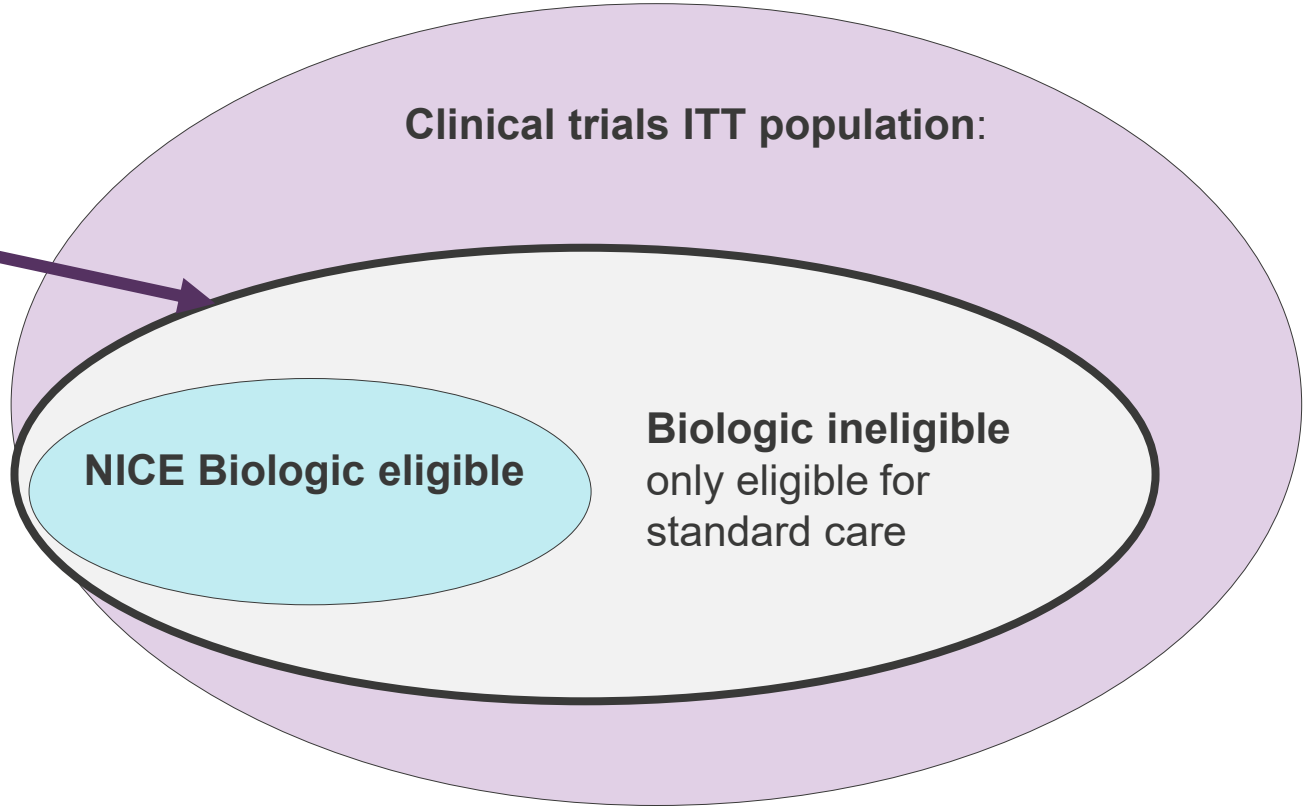
- Beneficial effects of Dupilumab are related to the patient's exhaled nitric oxide (FeNO) and blood eosinophil count.
- Dupilumab has the potential to meet unmet need:
  - first choice in patients with severe type-2 asthma with comorbid nasal disease or atopic dermatitis
  - in patients with inadequate response to anti-IL-5 and have a raised FeNO
- Likely to be used in a similar manner to other biologics
- Adverse events are thought to be similar to other biologics
- Current biologics treat approx. 50-60% of people with severe asthma & up to 30% fail a trial of anti-eosinophilic therapy

[redacted] Source: Clinical expert submissions

Populations

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

Company's decision problem population
EOS ≥150cells/µ/ or
FeNO≥25ppb &
≥3 exacerbations



Note: there are also populations who are on or not on maintenance oral corticosteroids (mOCS)

– company's base case is based on people not on mOCS

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

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

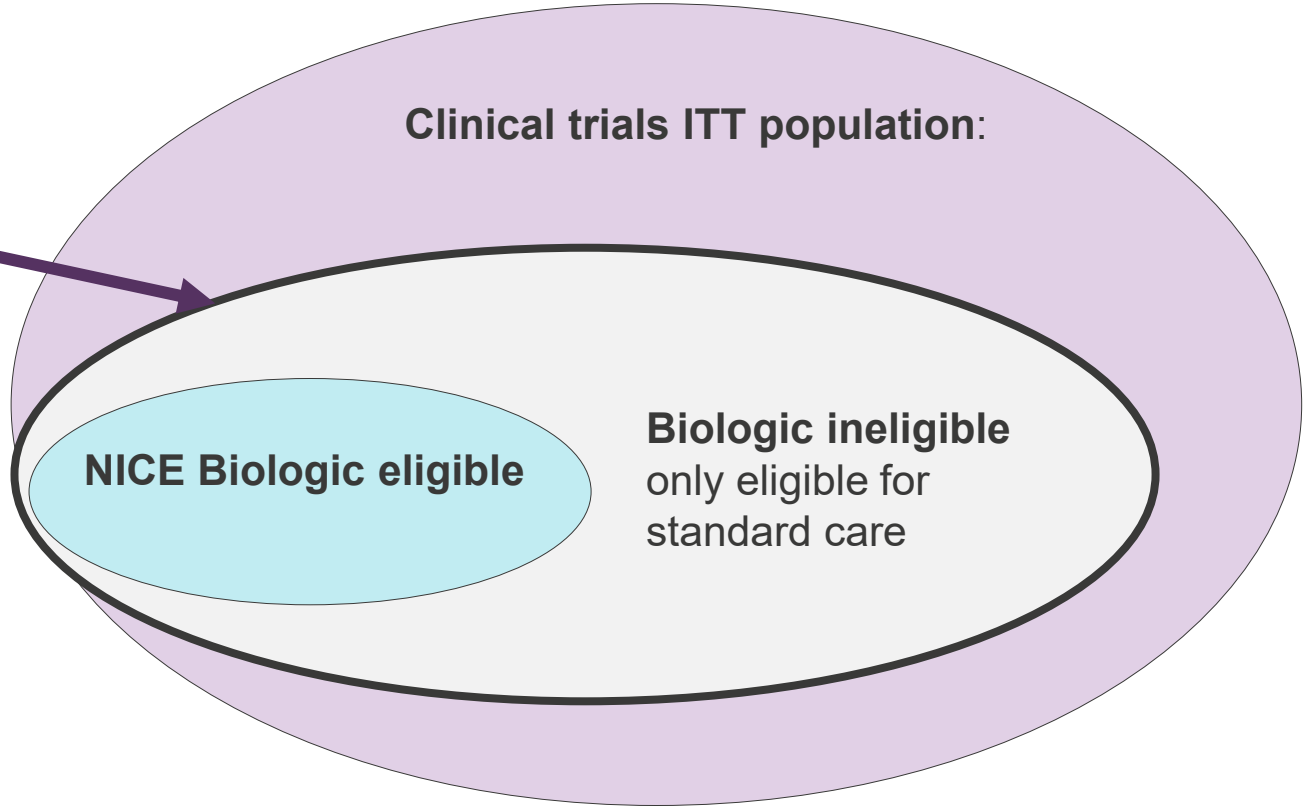
[redacted]

Clinical effectiveness

Populations

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

Company's decision problem population
EOS ≥150cells/µ/ or
FeNO≥25ppb &
≥3 exacerbations



NICE biologic eligible
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EOS≥400 cells/µl & 3 Ex

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

[redacted]

Clinical Trials (1) Dupilumab versus placebo

interventions in red boxes used in the model (source CS B.2.3):

Study	Patient characteristics	Intervention	Primary outcomes
QUEST (n=1902) **Dup 200 mg, 300mg** **(no mOCS)** **6/389 UK centres, (n=13 participants)** **52 weeks**	• **≥12 years old** • **Moderate to severe** uncontrolled asthma (per GINA definition) • **Moderate-high** dose ICS + 1-2 of: LABA, LAMA, LTRA, methylxanthines • **1+ exacerbations** prior year	• **200 mg SC** injection **Q2W** for **52 weeks** • **300 mg SC** injection **Q2W** for **24 weeks**	1) Annualised rate of severe exacerbations over 52 weeks 2) Absolute change from baseline in pre-bronchodilator FEV1 at 12 weeks
VENTURE (n=210) **Dup 300mg** **(mOCS)** **No UK centres** **24 weeks**	• **12 years and over** • **Severe steroid-dependent asthma** (5-35mg/day or equiv) • **high dose ICS plus second controller** (LABA or LTRA). • **Blood EOS count** of <150µl is limited to approximately 25% of the total sample size • **1+ exacerbations** prior year	• **300mg** SC injection Q2W for **24 wks**	1) Percentage reduction of OCS at wk 24 compared with the baseline dose, while maintaining asthma control.

Note: the EOS cut-off was <150 cells/µl, mean baseline FeNO range across the studies was 34.45 to 39.62 ppb

Abbreviations: EOS, eosinophils; FEV1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic receptor antagonists; LTRA, leukotriene receptor antagonists; mOCS, maintenance oral corticosteroids; Q2W, 2 weekly; Q4W, 4 weekly; SC, subcutaneous; ;

Clinical Trials (2) Dupilumab versus placebo

DRI12544 not used in the model because of technical difficulties in pooling QUEST and DRI12544 data

Study	Patient characteristics	Intervention	Primary outcomes
DRI12544 **Dup 200mg** **(n=308)** **(no mOCS)** **No UK centres** **24 weeks**	• **18 years and over** • **Moderate-severe uncontrolled asthma** (as per GINA definition) • **Moderate-high dose** ICS + LABA, • **1+ exacerbations** prior year,	• **200mg** SC injection Q2W for 24 wks • **300mg** SC injection Q2W for 24 wks • **200mg** SC injection Q4W for 24 wks • **300mg** SC injection Q4W for 24 wks	Change from baseline in FEV1 at week 12
Note: In DRI12544 the EOS cut-off was <200 cells/µl (<150 cells/µl in the other trials), mean baseline FeNO range across the studies was 34.45 to 39.62 ppb			

Abbreviations: EOS, eosinophils; FEV1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic receptor antagonists; LTRA, leukotriene receptor antagonists; mOCS, maintanence oral corticosteroids; Q2W, 2 weekly; Q4W, 4 weekly; SC, subcutaneous;

Results (1) Efficacy - QUEST & DRI12544 (no mOCS)

Note: this population had to have at least ≥1 exacerbation, moderate to severe asthma, on moderate-high dose ICS, **no mOCS** and there were no cut-offs for EOS or FeNO values

	DRI12544		QUEST	
	Dupilumab 200 mg Q2W (n=150)	**Placebo (n=158)**	**Dupilumab 200 mg Q2W (n=631)**	**Placebo (n=317)**
Adjusted annualised rate of severe exacerbation events*	0.26; (95%CI:0.15, 0.46)	0.89 (95%CI:0.61,1.30)	0.45 (95% CI: 0.38, 0.53)	0.87 (95% CI: 0.72, 1.04)
Relative risk versus placebo (95% CI), p-value	0.30 (0.15, 0.56); p=0.0002		0.52 (0.41, 0.66); p<0.0001	
Change from baseline in FEV1 at 12 weeks, LS mean (SE)	n= 136 0.31L (0.03)	n=129 0.12L (0.03)	n=611 0.32L (0.02)	n=307 0.18L (0.02)
LS mean difference (95% CI), p value vs placebo	0.20L (0.11, 0.28), p<0.0001		0.14L (0.08, 0.19), p<0.0001	
*This was a secondary outcome in DRI12544				
Abbreviations: CI, confidence interval; EOS, eosinophils; FeNO, fractional concentration of exhaled nitric oxide; ICS, inhaled corticosteroids; LS, least squares; mOCS, maintenance oral corticosteroids; Q2W, 2 weekly; SE, standard error,				

[redacted]

Source CS B.2.6

Results (2) Efficacy - VENTURE (on mOCS)

Note: this population had to have at least ≥1 exacerbation, severe asthma, on high dose ICS **on mOCS** and there were no cut-offs for EOS and FeNO values

	VENTURE	
	Dupilumab 300 mg Q2W (n=103)	**Placebo (n=107)**
Percentage reduction of OCS dose at Week 24 from baseline, LS mean (SE) – primary outcome	n=101 70.09 (4.90)	n=106 41.85 (4.57)
LS mean difference vs placebo (95% CI), p value vs placebo	28.24 (15.81, 40.67), p<0.0001	
Patients achieving a reduction of ≥50% in OCS dose at Week 24	81%	53.3%
p value vs placebo	<0.0001	
Patients no longer requiring OCS at Week 24	52.8%	29.2%
p value vs placebo	0.0015	

Abbreviations: CI, confidence interval; EOS, eosinophils; FeNO, fractional concentration of exhaled nitric oxide; ICS, inhaled corticosteroids; LS, least squares; mOCS, maintenance oral corticosteroids; Q2W, 2 weekly; SE, standard error,

[redacted] Source CS B.2.6.3

Results (3) Safety - Intention to treat population

	DRI12544		QUEST		VENTURE	
	Dupilumab 200 mg Q2W (n=150)	Placebo (n=158)	Dupilumab 200 mg Q2W (n=631)	Placebo (n=317)	Dupilumab 300 mg Q2W (n=103)	Placebo (n=107)
Adverse events						
Treatment-emergent SAE	6.8%	5.7%	7.8%	8.3%	8.7%	5.6%
TEAE leading to death	0	0	0.2%	1%	0	0
TEAE leading to permanent treatment discontinuation	4.1%	3.2%	3%	6.1%	1%	3.7%

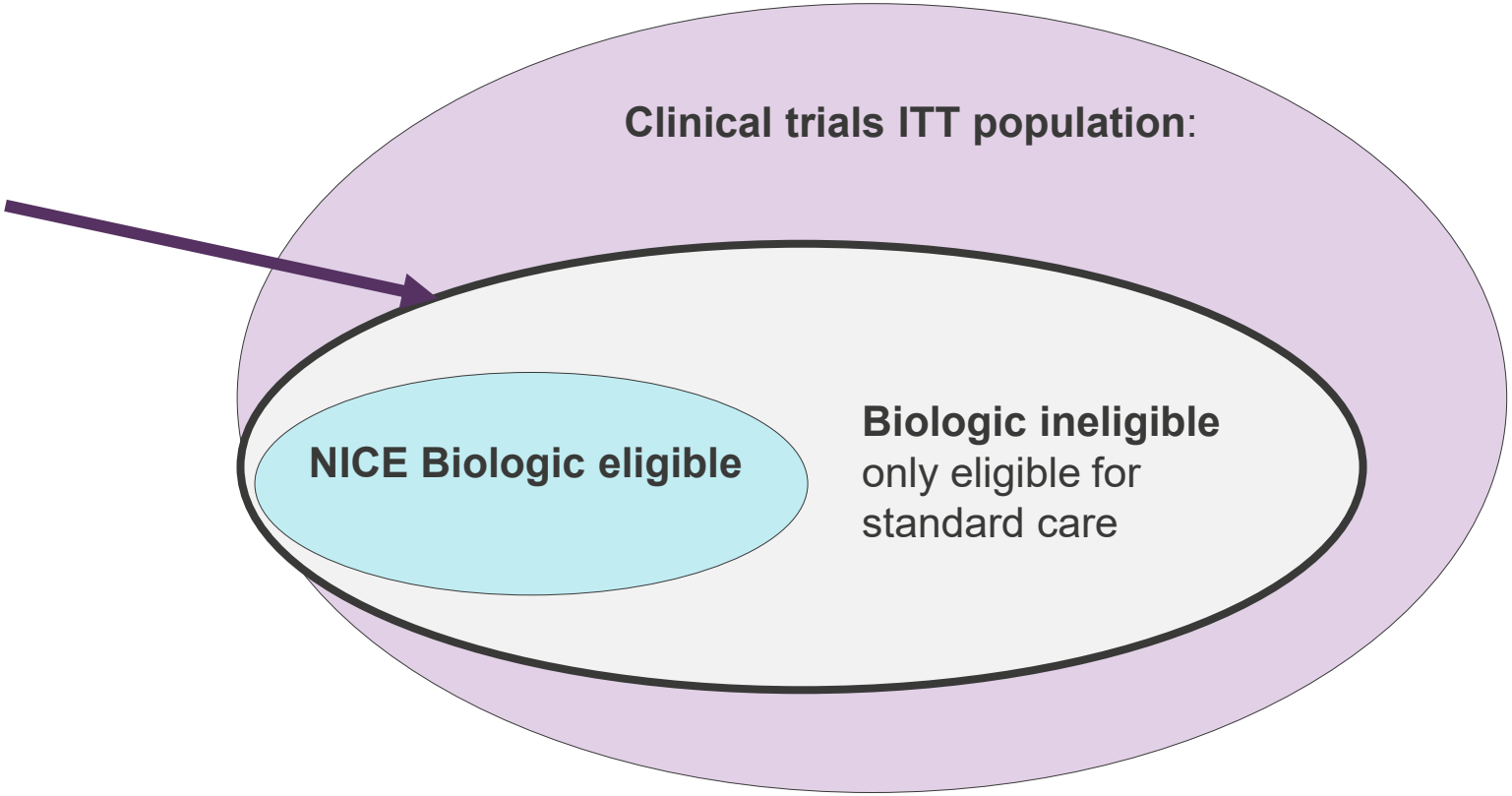
Abbreviations: Q2W, 2 weekly; SAE, serious adverse events; TEAE, treatment-emergent adverse events

[redacted] Source: CS B.2.10

Populations

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

Company's decision problem population
EOS ≥150cells/µ/ or
FeNO≥25ppb &
≥3 exacerbations



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

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

[redacted]

Results (1) Efficacy - company's decision problem population

High dose ICS with (**EOS ≥150 cells/µl OR FeNO ≥25 ppb**) and **≥3 exacerbations (no mOCS)**

	QUEST (no mOCS)	
	Dupilumab 200mg, Q2W (n=64)	Placebo (n=37)
Adjusted annualised rate of severe exacerbation events (post-hoc analyses)	[redacted]	[redacted]
Relative risk versus placebo (95% CI), p-value	[redacted]	

Scenario population: **same criteria as above AND mOCS**

	VENTURE (mOCS)	
	Dupilumab 300mg, Q2W (n=78)	Placebo (n=74)
Adjusted annualised rate of severe exacerbation events (post-hoc analyses)	[redacted]	[redacted]
Relative risk versus placebo (95% CI), p-value	[redacted]	

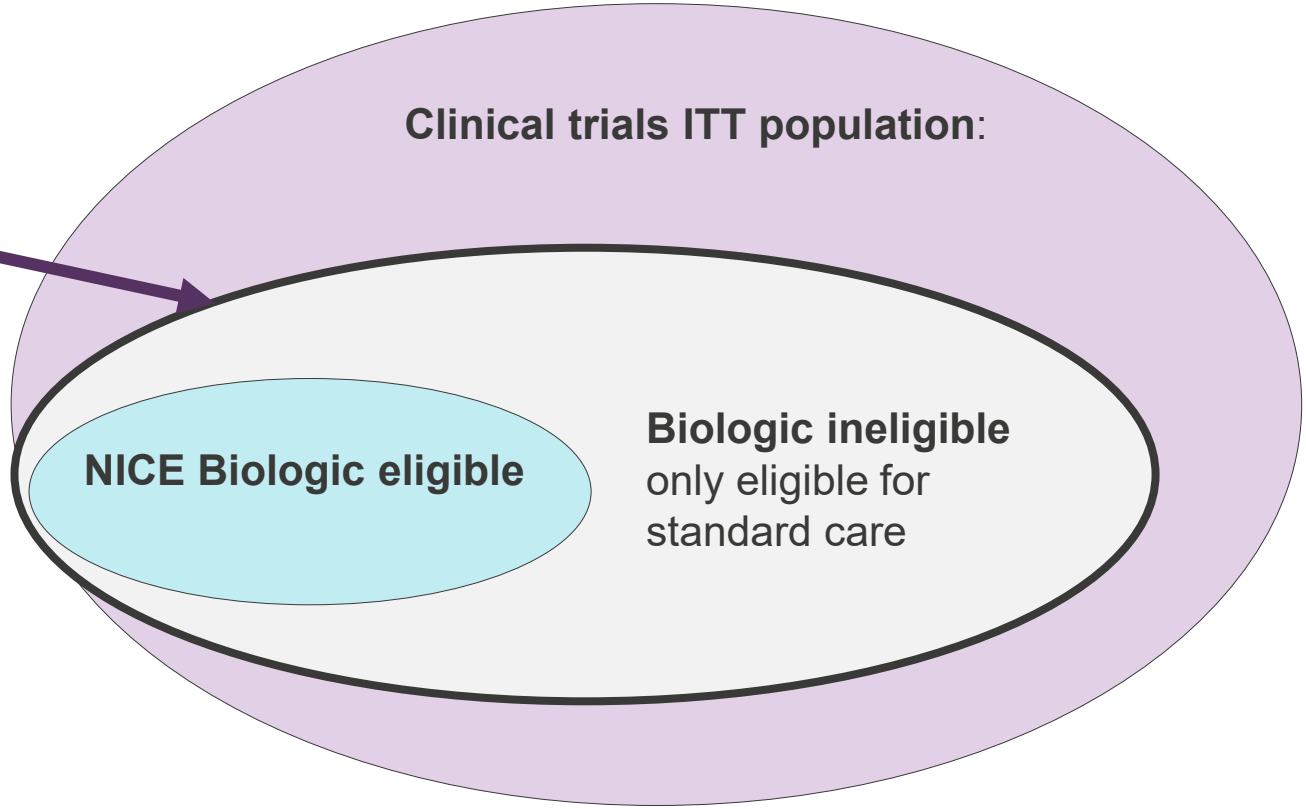
Abbreviations: CI, confidence interval; EOS, eosinophils; FeNO, fractional concentration of exhaled nitric oxide; ICS, inhaled corticosteroids; mOCS, maintenance oral corticosteroids; Q2W, 2 weekly

Source: Table 34 and 35 CS B.2.7.2

Populations

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

Company's decision problem population
EOS ≥150cells/μ/ or
FeNO≥25ppb &
≥3 exacerbations



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

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

[redacted]

Results (2) Efficacy - NICE biologic ineligible population

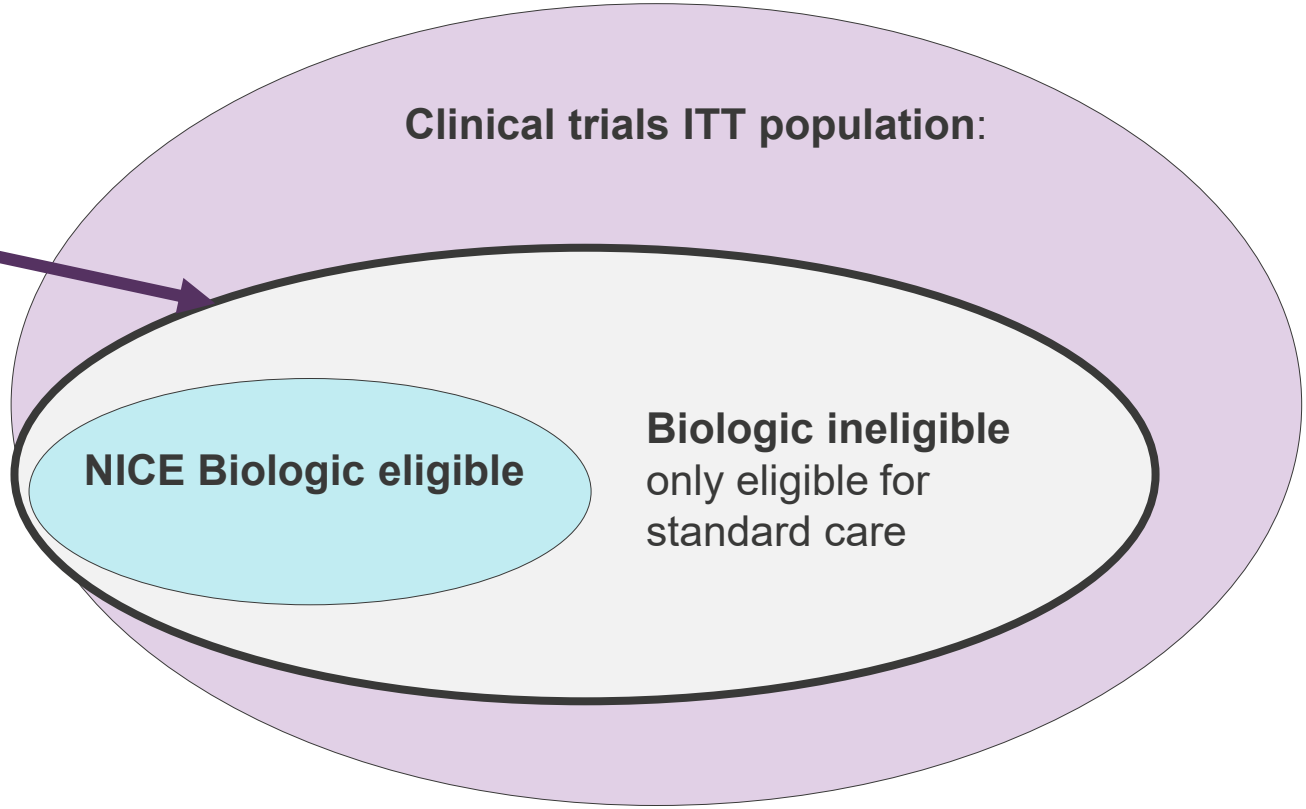
	QUEST (non mOCS)	
	Dupilumab 200 mg Q2W (n=29)	Placebo (n=12)
Total number of severe exacerbation events	[redacted]	[redacted]
Total patient-years followed	[redacted]	[redacted]
Adjusted annualised rate of severe exacerbation events		
Relative risk (95% CI)	[redacted]	
P-value	[redacted]	
Risk difference (95% CI)	[redacted]	
NOTE: No data for VENTURE provided by company.		
Abbreviations: CI, confidence interval; EOS, eosinophils; FeNO, fractional concentration of exhaled nitric oxide; ICS, inhaled corticosteroids; mOCS, maintenance oral corticosteroids; Q2W, 2 weekly		

[redacted] Source: Table 11 CS additional analyses appendix

Populations

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

Company's decision problem population
EOS ≥150cells/µ/ or
FeNO≥25ppb &
≥3 exacerbations



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

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

[redacted]

Indirect treatment comparison for biologic eligible dupilumab population

- The company provided 2 methods of comparing dupilumab with current biologics:
  - Bucher Indirect Treatment Comparison (ITC) results using subgroup data from the dupilumab trial (used in the model)
    - Data from multiple trials were pooled (random effect meta analysis)
    - Study data or pooled estimates for biologic vs placebo used to generate the results for dupilumab vs biologics
  - Matched Adjusted Indirect Comparison (MAIC) (scenario analysis) using pooled data from QUEST and DR12544.
    - matching was conducted for each comparator RCT separately then results were pooled
- Company exploratory analyses – interpret with caution?
- ERG considered there to be limitations to both the ITC and MAIC but considered these to be best currently available option to compare dupilumab with biologics.

[redacted]

ITC results biologic eligible dupilumab population: dupilumab subgroup matched to biologic for annualised rate of severe exacerbations

ITC included other outcomes none of which showed statistically significant results

Comparison	Bucher indirect treatment comparison rate ratio (95% CI)
Dupilumab vs mepolizumab (NICE recommended population)	[redacted]
Dupilumab vs benralizumab (marketing authorisation population)	[redacted]
Dupilumab vs reslizumab (NICE recommended population)	[redacted]

Note: ITC included other outcomes, none of which showed statistically significant results (ERG report p.18)
Mepolizumab eligible EOS≥ 300 cells/µl and ≥4 exacerbations no mOCS
Benralizumab eligible EOS≥ 300 cells/µl and ≥2 exacerbations no mOCS
Reslizumab eligible EOS≥ 400 cells/µl and ≥3 exacerbations no mOCS

[redacted]

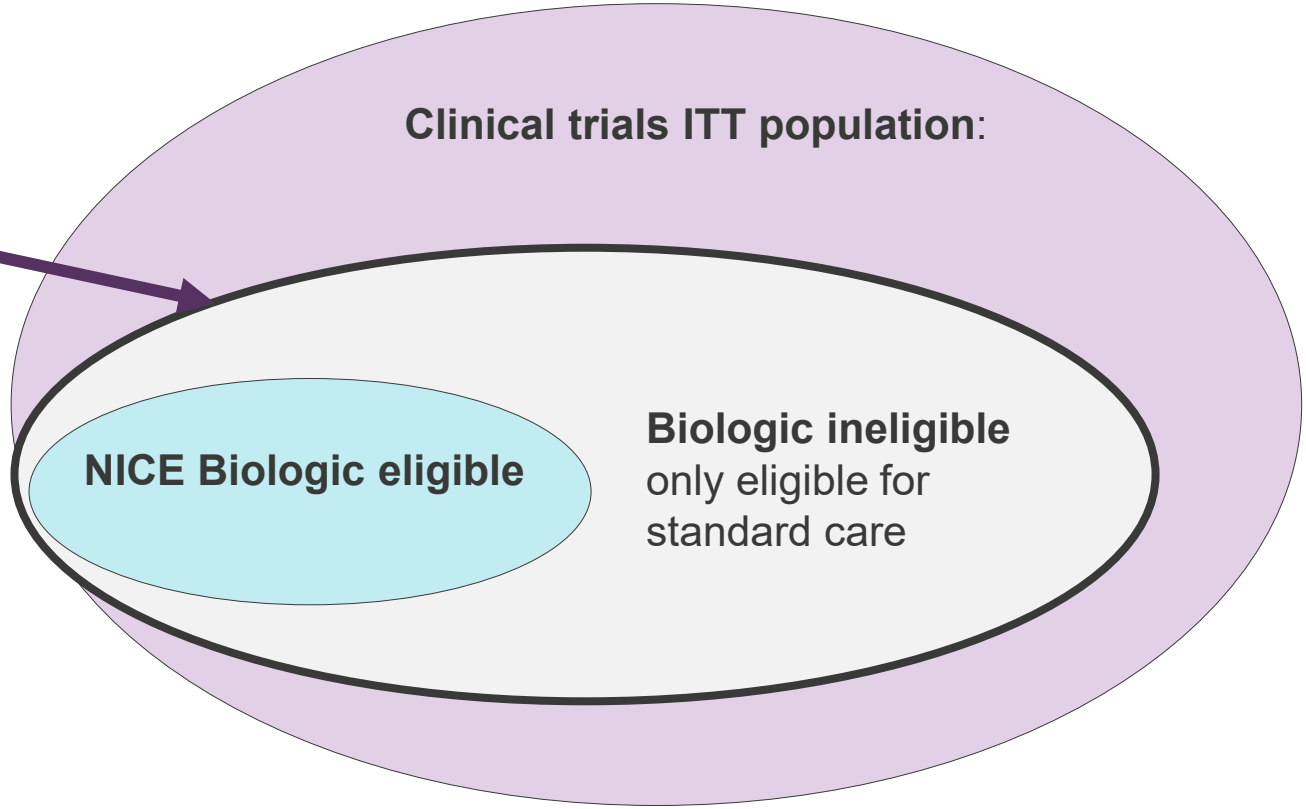
Source: CS appendices N.6 and ERG 3.3.10

Cost-effectiveness

Populations

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

Company's decision problem population
EOS ≥150cells/µ/ or
FeNO≥25ppb &
≥3 exacerbations



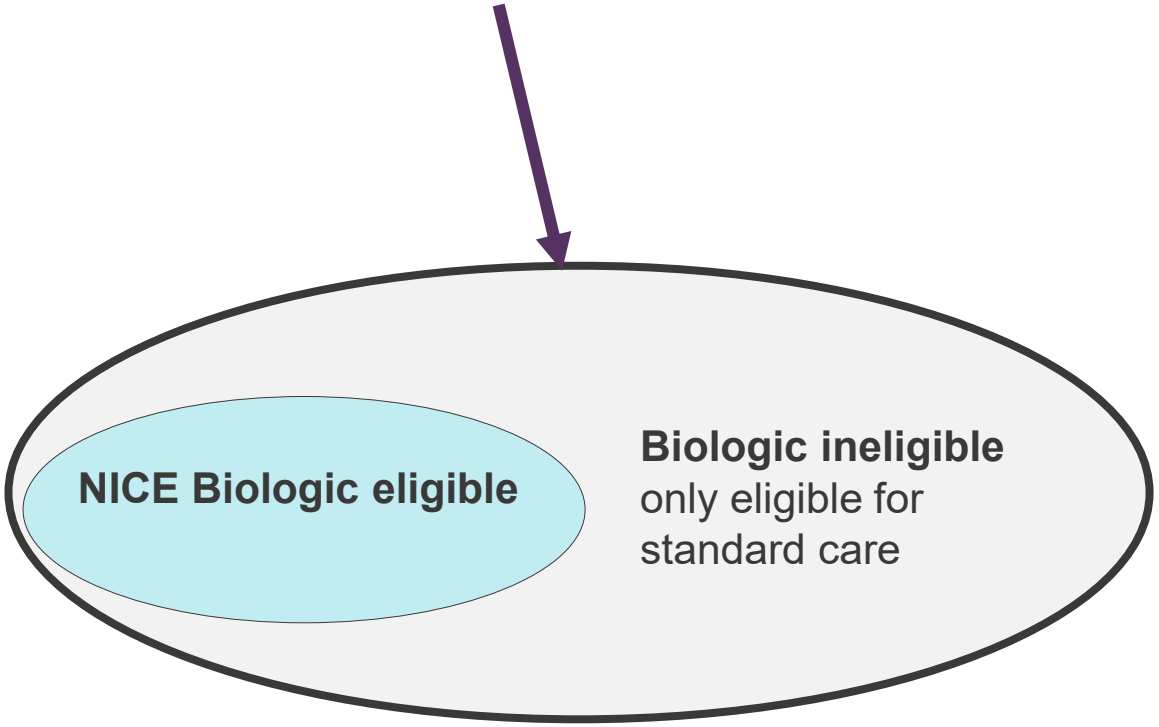
NICE biologic eligible
EOS≥300 cells/µl & ≥4 Ex, or
EOS≥400 cells/µl & 3 Ex

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

[redacted]

Company's decision problem population

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



Company also presented scenarios on varying proportions of use of mOCS

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

[redacted]

Evidence used in the economic model

QUEST

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

VENTURE

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

Published literature/registries/ other sources

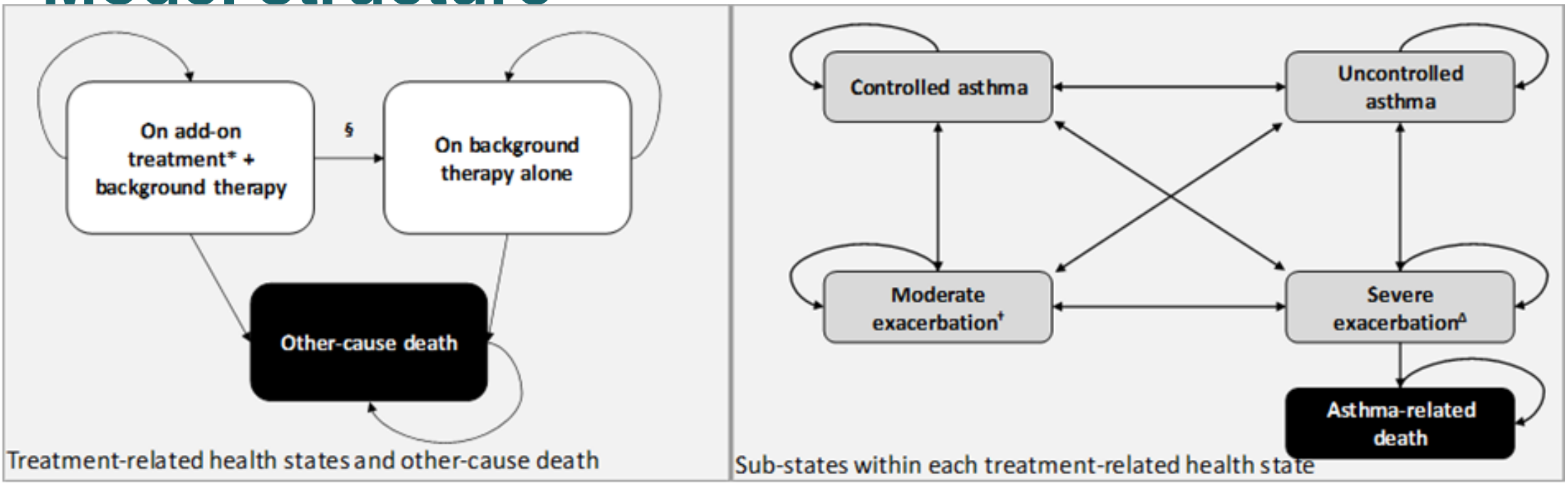
Parameters in model

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

Parameters in model

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

Model structure



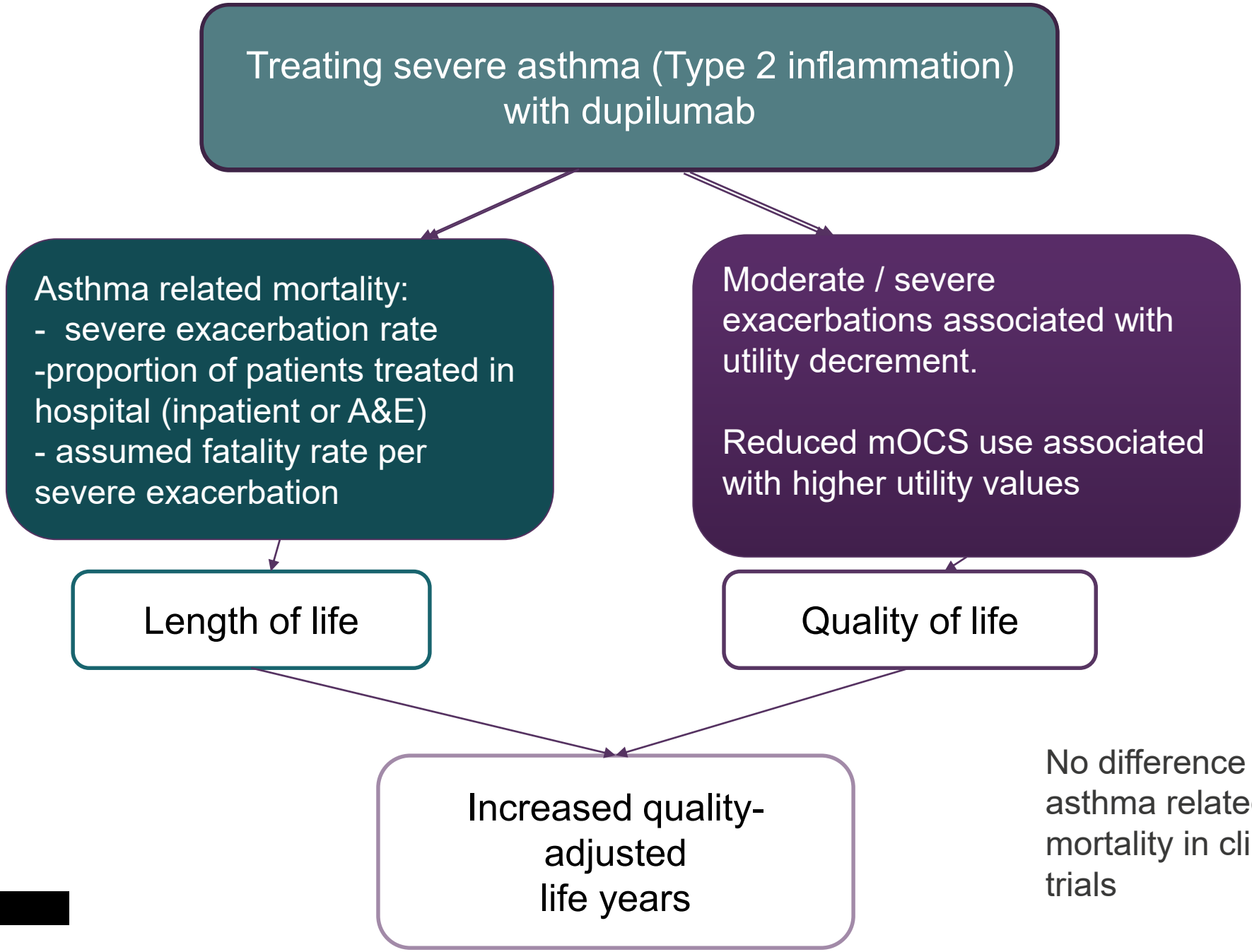
Markov model structure (Source: CS Figure 36)

Model parameters

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

[redacted] **Note: model assumptions can be found in table 87 of the company submission**

How QALYs accrue in the economic model



No difference in asthma related mortality in clinical trials

Base case assumptions (1)

Company's original base case	Company's amended base case after engagement	ERG base case preferred assumptions
1. **Long term severe exacerbation rate**		
Used multiplier of XXXX based on assumptions from QUEST and DRI trials	Used multiplier of 1.35 based on TA431 - mepolizumab	Multiplier of 1 - assumes no adjustment to post-trial exacerbations
2. **Setting for treatment of severe asthma exacerbations**		
Uses estimates from the Difficult Asthma Registry reported by O'Neill et al (2015)	Used settings used in TA431, mepolizumab	Uses trial data from QUEST
3. Utility limited to general population mean		
No, utilities for controlled and uncontrolled states were derived from QUEST.	Accepted ERG's assumption	Yes, controlled asthma utility is unlikely to be higher than utility of general population

[redacted]

Base case assumptions (2)

Company's original base case	Company's amended base case after engagement	ERG base case preferred assumptions
4. Include discontinuation in first year		
No, assumed that all patients would continue treatment for 12 months	Accepted ERGs assumption	Yes, patients may discontinue for any reason before 12 months
5. Reference costs for A&E and hospitalisation		
From NHS National Tariff Workbook 2019-2020	Accepted ERGs assumption	NHS reference costs to match source used in previous appraisals
6 Administration settings		
Injections are assumed to be self-administered by the patient after the first 3 doses	No amendment to assumption	Self-administration is new in this indication so may take time to implement. Agreed with company as has little impact on ICER

[redacted]

Exacerbation multiplier rationale

Severe annual exacerbation rate in QUEST placebo arm (2.391) was lower than observed in clinical practice the preceding year (4.46).

The company state this could be caused by:

- **Better care in a clinical trial setting**
  Better outcomes because of optimised care, adherence to treatment and regular follow up.
- **Regression to the mean**

  People with extreme values when first assessed (a high number of exacerbations in the year before the trial) may when subsequently assessed (during the trial) have fewer exacerbations in next year, even if there is no treatment effect.

However;

- Similar placebo effects were seen in other biologic trials.

Is it plausible that these effects would only be observed in the placebo arm or both arms of the trials?

Source: CS B.3.3.3 and in Appendix M.2

[redacted]

Exacerbation multiplier rationale

Additionally; the company state the low exacerbation rate in QUEST could be caused by:

- **Exclusion of patients with a recent severe exacerbation**
  QUEST excluded people with severe exacerbation within a month of screening/trial starting - longer average time since their last severe exacerbation.

- **Definition of exacerbation events**
  2 exacerbations in a month classified as 1 exacerbation.

Are these unique to the QUEST trial?

If so, do they justify the use of an exacerbation rate multiplier of 1.35?

Source: CS B.3.3.3 and in Appendix M.2

[redacted]

Multiplier assumptions for long term severe exacerbation rate

Source	Multiplier	Notes
Company submission, base case	XXXX	Based on assumptions from QUEST and DRI12544 trials. Adjusted multiplier used to account for excluding people with recent severe exacerbation from the trials
Company submission, updated base case	1.35	A lower adjustment factor of 1.35 was applied to the biologic and standard of care arm to match the adjustment previously accepted by the committee B for the mepolizumab, TA431
ERG	1	The ERG notes that in other appraisals, no or lower adjustments were made to long term exacerbation rates. No adjustments to the multiplier in ERG scenario analysis
Reslizumab (TA479) (comm A)	1	Committee concluded, “adjusted rates were no more likely than the unadjusted rates to reflect the true treatment benefit”.
Benralizumab (TA565) Comm A	1	No multiplier was proposed
Mepolizumab (TA431) Comm B	1.35	Used a lower multiplier for background exacerbation

Source of data - setting of severe exacerbations

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

Source: ERG report 4.3.4.6, company technical engagement appendix and ERG critique

[redacted]

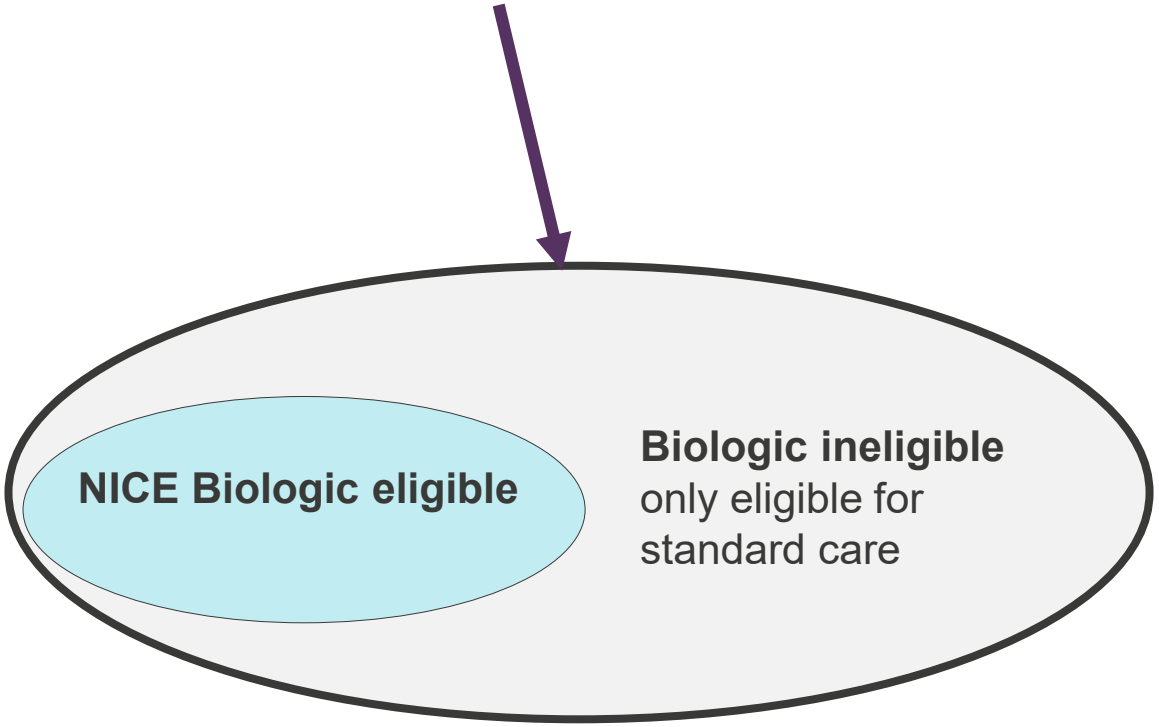
Setting of severe exacerbations: (table 79 ERG report)

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
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

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. NICE TA431, Mepolizumab - company evidence submission, Table 105, page 198
d. Bleecker et al. 2016, Appendix 14, Table 3; Segregation of A&E visit and hospitalisation assumed based on distribution reported in NICE TA565
e. Castro et al. 2015; Pooled Study 1 and 2; Segregation of A&E visit and hospitalisation assumed based on distribution in QUEST

Company's decision problem population

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



Company also presented scenarios on varying proportions of use of mOCS

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

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

[redacted]

Company's decision problem population (1)

Compared to standard of care and not on mOCS (deterministic)

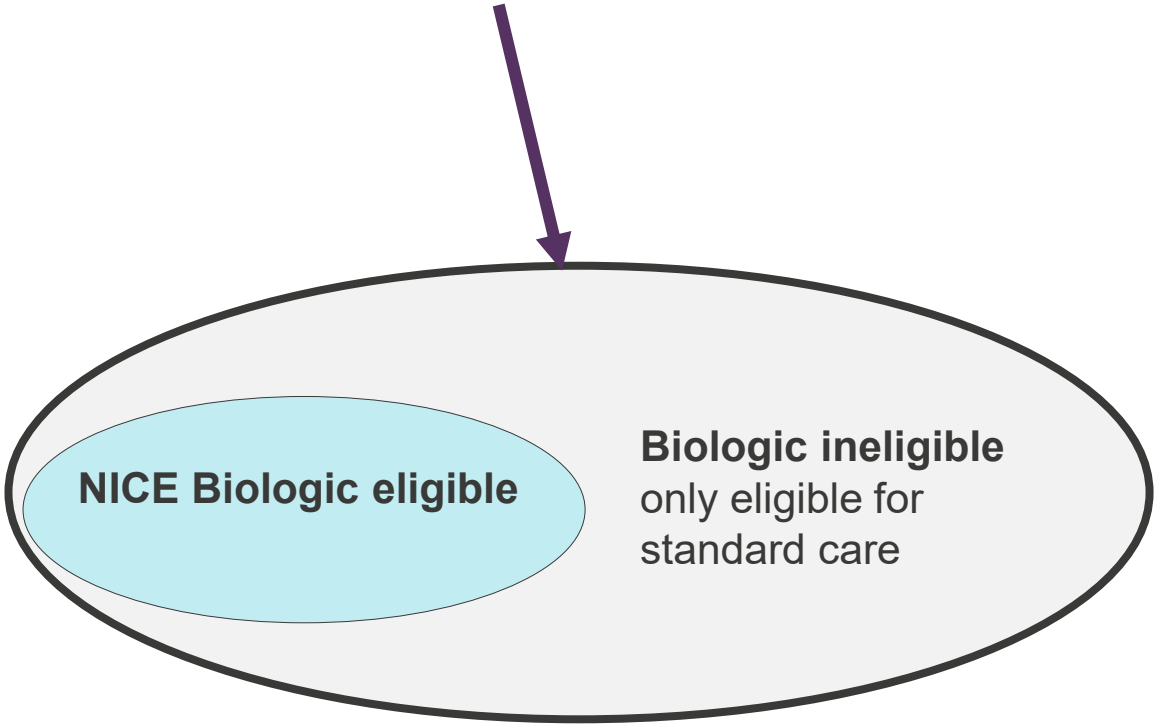
ERG preferred assumptions for base case	ICER	Change from company base case
Company's updated base case after engagement	**£34,216**	
+ Long term severe exacerbation rate: trial data multiplier=1 (company assumption = 1.35)	£46,619	+£12,403
+ Source of treatment for severe exacerbation: clinical trials (company assumption = source used in TA431 (mepolizumab appraisal)	£40,119	+£5,903
Impact of the ERG's preferred assumptions (ERG base case) on the cost-effectiveness estimate	**£55,348**	+£21,132

Abbreviations: EOS, eosinophils; FeNO, fractional concentration of exhaled nitric oxide; ICER, incremental cost-effectiveness ratio; mOCS, maintenance oral corticosteroids;

[redacted] Source: ERG post TE addendum 2 tables 2 and 5

Company's decision problem population

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



Company also presented scenarios on varying proportions of use of mOCS

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

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

[redacted]

Company's base case population (2)

Subgroup ineligible for NICE biologics vs standard care (deterministic)

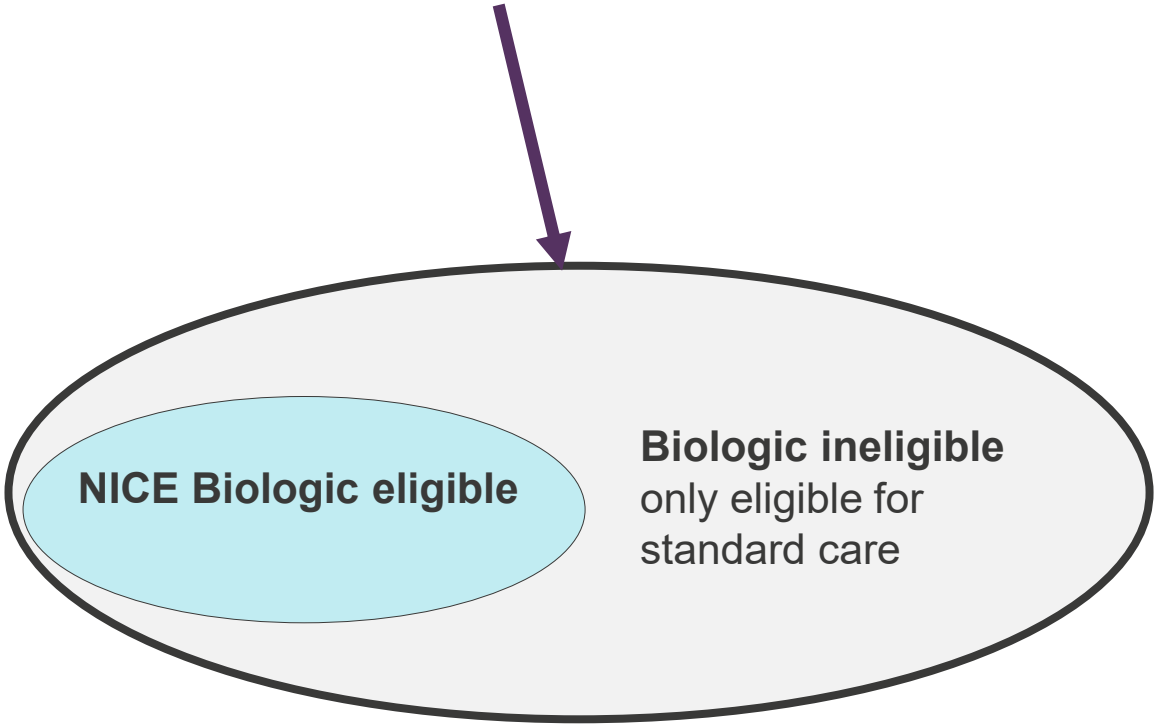
	ICERs	
Includes confidential discounted price for dupilumab	Updated company base case	ERG base case
Ineligible for biologics and no mOCS		
EOS ≥150 and <400 OR FeNO ≥25, =3 exacerbations	£56,441	£92,396
EOS ≥150 and <300 OR FeNO ≥25, ≥4 exacerbations	£43,980	£70,064
Combined	**£50,558**	**£81,676**

Abbreviations: EOS, eosinophils; FeNO, fractional concentration of exhaled nitric oxide; ICER, incremental cost-effectiveness ratio; mOCS, maintenance oral corticosteroids

[redacted] Source: Source: ERG post TE addendum 2 tables 3 and 5

Company's decision problem population

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



Company also presented scenarios on varying proportions of use of mOCS

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

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

[redacted]

Results for active comparators

All active comparator results shown in Part 2 because of commercial arrangements for them.

Technical engagement issues

Summary of technical report issues

- Issue 1: How is type 2 inflammation defined, diagnosed and treated
- Issue 2: Generalisability of the population used in the model
- Issue 3: Treatment of severe asthma caused by Type 2 inflammation (which informs the relevant comparators)
- **Issue 4: Population relevant for the base case (non mOCS, mOCS only or mixed**)
- Issue 5: Proportion of mOCS use in the mixed population
- Issue 6: Should a pooled population of different severities of asthma be used in the base case (non-mOCS) model?
- **Issue 7: Use of adjusted rates (multiplier) for severe exacerbation in the model**
- Issue 8: Discontinuation in the first 12 months?
- **Issue 9: Clinical trial vs registry data to inform the treatment setting**
- Issue 10: Utility values for controlled and uncontrolled asthma
- Issue 11: Should a consistent source of unit costs be used in the model?
- Issue 12: Should self-administration of dupilumab be assumed in the model?

Issue 4: Population relevant for the base case (non-mOCS, mOCS only or mixed)

Background	Stakeholder responses	Technical team consideration
The base case is based on non-mOCS population. Analyses is required for mOCS only and mixed population (non-mOCS & mOCS).	Provided by the company. Consultees indicate that there should be a separate population for base case split by mOCS and non-mOCS pop. Mixed population not helpful.	The base case remains in the non-mOCS population. Analyses have been provided on mixed (non-mOCS and mOCS) mOCS only population. In the mixed population, 30% on mOCS is reasonable.

Abbreviation: mOCS, maintenance oral corticosteroids

[redacted]

Issue 4: Company's decision problem population – effect of mOCS on ICERS - deterministic

Dupliumab (PAS) vs SoC	ICERS	
Percentage of patients on mOCS	Updated company base case	ERG base case
0%	£34,216	£55,348
30%	£ 40,172	£56,852
41.7%	£42,449	£57,341
100%	£ 53,441	£59,224

Abbreviations: EOS, eosinophils; FeNO, fractional concentration of exhaled nitric oxide; ICER, incremental cost-effectiveness ratio; mOCS, maintenance oral corticosteroids; SoC, standard care

Includes confidential discounted price for dupilumab

[redacted] Source: company additional analyses, ERG model

Issue 7: Use of a multiplier for rate of severe exacerbation

Background	Stakeholder responses	Technical team consideration
The company use a multiplier for the rate of severe exacerbation after the trial period in the base case and previous TAs for similar biologics do not use a multiplier.	Clinical experts and the ERG prefer using no multiplier. The company have adjusted their analysis and changed multiplier used from [redacted] to 1.35 used in TA431 (mepolizumab) for their base case (non-mOCS population) and scenario of mixed population (30% on mOCS)	As an exacerbation multiplier was not used in more recent reslizumab or benralizumab appraisals, the use of a multiplier is not considered appropriate

[redacted]

Issue 7: Impact of multiplier on ICER company's decision problem population on or off mOCS - deterministic

Source: Company additional analyses and ERG model

Dupliumab (PAS) vs SoC		ICERs	
Multiplier used		Updated company base case	ERG base case
0% mOCS	1	£46,619	£55,348
	1.35	£34,216	£40,119
30% mOCS	1	£51,059	£56,852
	1.35	£40,172	£44,638
100% mOCS	1	£59,224	£59,224
	1.35	£53,441	£53,441

Abbreviations: EOS, eosinophils; FeNO, fractional concentration of exhaled nitric oxide; ICER, incremental cost-effectiveness ratio; mOCS, maintenance oral corticosteroids; SoC, standard care.

Includes confidential discount price of dupilumab

Note: all other assumptions are the company and ERG preferred

[redacted]

Issue 7: Impact of multiplier on ICER in biologic ineligible population on or off mOCS - deterministic

Source: Company additional analyses and ERG model

Dupliumab (PAS) vs SoC		ICERs	
Multiplier used		Updated company base case	ERG base case
0% mOCS	1	£66,976	£81,676
	1.35	£50,558	£61,192
100% mOCS*	1	£80,132	£80,132
	1.35	£77,972	£ 77,972

* Estimated by ERG, assuming XXX9xx/152) mOCS patients meet mepolizumab criteria
Abbreviations: EOS, eosinophils; FeNO, fractional concentration of exhaled nitric oxide; ICER, incremental cost-effectiveness ratio; mOCS, maintenance oral corticosteroids; SoC, standard care.
Includes confidential discount price of dupilumab

Note: all other assumptions are the company and ERG preferred

Source: ERG model

[redacted]

Issue 9: Source used to inform treatment settings for severe exacerbations

Background	Stakeholder responses	Technical team consideration
To estimate the numbers treated for severe exacerbation in secondary care the company uses a registry, however the ERG highlight that the estimate is higher than that used in previous TA for asthma.	The company state that QUEST trial data is not an accurate or representative source of data on exacerbation setting for UK patients Clinical experts state that trial data is a better source, however as the numbers a low they should be used in caution The ERG consider the trial data to be a better source because the definitions of severe exacerbation events will be consistent with the clinical data used in the model	The technical team considers the trial data to be a better source for similar reason to the ERG and experts

Issue 9: Impact of source to inform treatment settings for severe exacerbations on ICERs company's decision problem population on or off mOCS – deterministic

Dupilumab (PAS) vs SoC		ICERs	
Source used		Updated company base case	ERG base case
0% mOCS	O'Neill et al (2015)	£31,692	£43,549
	QUEST Clinical Trial settings	£40,119	£55,348
	TA431	£34,216	£46,619
30% mOCS	O'Neill et al (2015)	£37,029	£47,258
	QUEST Clinical Trial settings	£44,638	£56,852
	TA431	£40,172	£51,059
100% mOCS	O'Neill et al (2015)	£48,126	£53,692
	QUEST Clinical Trial settings	£53,441	£59,224
	TA431	£53,441	£59,224

Abbreviations: EOS, eosinophils; FeNO, fractional concentration of exhaled nitric oxide; ICER, incremental cost-effectiveness ratio; mOCS, maintenance oral corticosteroids; SoC, standard care.

Includes confidential discount price for dupilumab

Note: all other assumptions are the company and ERG preferred

[redacted] Source: Company additional analyses and ERG model

Issue 9: Impact of source to inform treatment settings for severe exacerbations on ICERs in biologic ineligible population on or off mOCS – deterministic

Dupilumab (PAS) vs SoC		ICERs	
Source used		Updated company base case	ERG base case
0% mOCS	O'Neill et al (2015)	£46,107	£61,230
	QUEST Clinical Trial settings	£61,192	£81,676
	TA431	£50,558	£66,976
100% mOCS*	O'Neill et al (2015)	£71,468	£74,538
	QUEST Clinical Trial settings	£77,972	£80,132
	TA431	£77,972	£80,132

*Estimated by ERG, assuming [redacted] (xx/152) mOCS patients meet mepolizumab criteriabreviations: EOS, eosinophils; FeNO, fractional concentration of exhaled nitric oxide; ICER, incremental cost-effectiveness ratio; mOCS, maintenance oral corticosteroids; SoC, standard care.

Includes confidential discount price for dupilumab

Note: all other assumptions are the company and ERG preferred

[redacted] Source: Company additional analyses and ERG model

Additional areas of uncertainty

Issue	Why issue is important	Impact on ICER
There are many limitations in the ITC approaches.	For results comparing dupilumab with IL-5 biologics, NICE will need to interpret with caution.	Unknown
The model used to assess trial data from VENTURE does not include the moderate exacerbation health state (no data was available for this health state).	This is not consistent with the company's base case 4 health state model.	Unknown
The outcomes loss of asthma control (LOAC) event and severe exacerbation events seem to be overlapping, based on the definition provided for each	This may introduce double counting. Footnotes to table 10 of the company submission gave definitions which overlap (see Table 15 and p48/49 of ERG report):	Unknown
No long-term efficacy and safety data beyond trial period (52 weeks).	Long-term severe exacerbation rate would be useful if the data was available rather than being based on assumptions	Unknown

Innovation

Company's position

Due to the distinct interleukin (IL)-4 and IL-13 pathways, dupilumab targets a different patient population compared to current biologic therapies.

Innovative because it targets a different patient population to the other current biological therapies (although, as noted there is some overlap between the different patient populations)

Have all the health benefits been captured in the QALY?

[redacted]

Equalities

- No equalities issues were identified.

[redacted]