NICE National Institute for Health and Care Excellence

Slides for PROJECTOR

Dupilumab for severe asthma with type 2 inflammation

Chair presentation

3rd appraisal committee B meeting

Chair: Sanjeev Patel

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

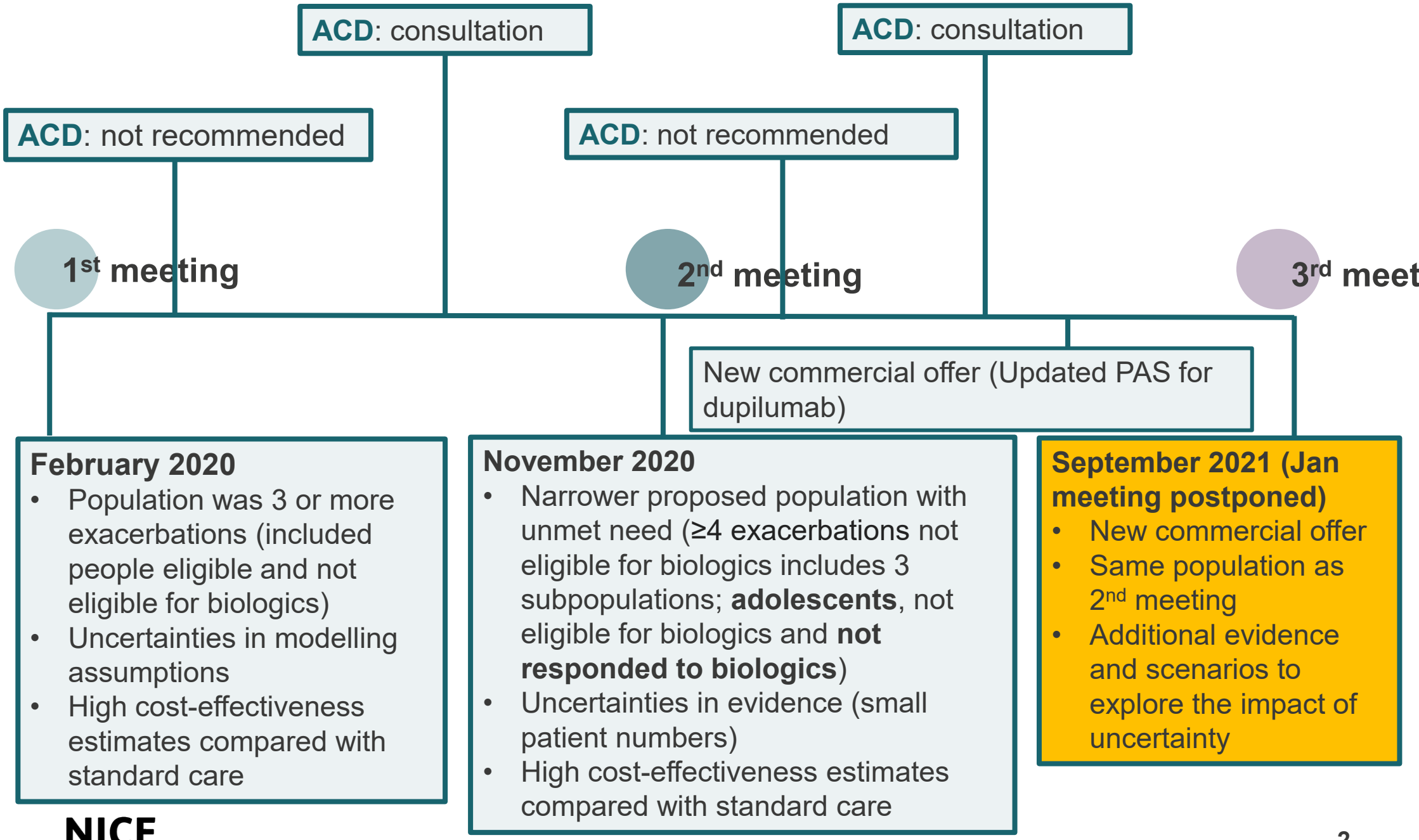
ERG: Southampton Health Technology Assessments Centre

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

Company: Sanofi Genzyme

History of appraisal

2 previous meetings



NICE

ACD, appraisal consultation document; ICER: Incremental cost-effectiveness ratio

Key issues

- **New commercial offer**
  - Is the revised ICER low enough to accept the uncertainties?
- **Supplementary evidence to support dupilumab efficacy**
  - Does evidence from QUEST and sub-group analyses support the treatment effect of dupilumab?
  - Is dupilumab as effective in people who had previously received biologic therapy?
- **Additional scenarios to address uncertainty**
  - Do the mortality rates in the model reflect current UK clinical practice?
  - Varying response rates or the relative risk of exacerbations with dupilumab vs. standard care

Appraisal Consultation Document 2 (ACD2): Dupilumab not recommended

Why committee made these recommendations

- ICER £35,968 per QALY gained vs. standard care (not cost effective)
- Very limited evidence clinical efficacy data provided for the proposed population – people aged 12 and over, with EOS≥150 and FeNo≥25 and ≥4 exacerbations not eligible /responded to biologic therapy including:
  - Aged 12-17 years (no other biologics)
  - Adults with EOS 150-299 not eligible for biologics
  - Adults with EOS ≥ 300 not responded previous biologics

Disease background: Subtypes of severe asthma

- **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)
- **Subtypes of asthma:**
  - Severe eosinophilic asthma
  - IgE mediate allergic asthma
  - Severe asthma with type 2 inflammation
- **Global Initiative for Asthma (GINA) defines severe asthma with Type 2 inflammation:**
  - Blood eosinophils (EOS) ≥150 cells/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)

Clinical expert noted that raised EOS and FeNO are predictors for future exacerbations (ACD 3.2)

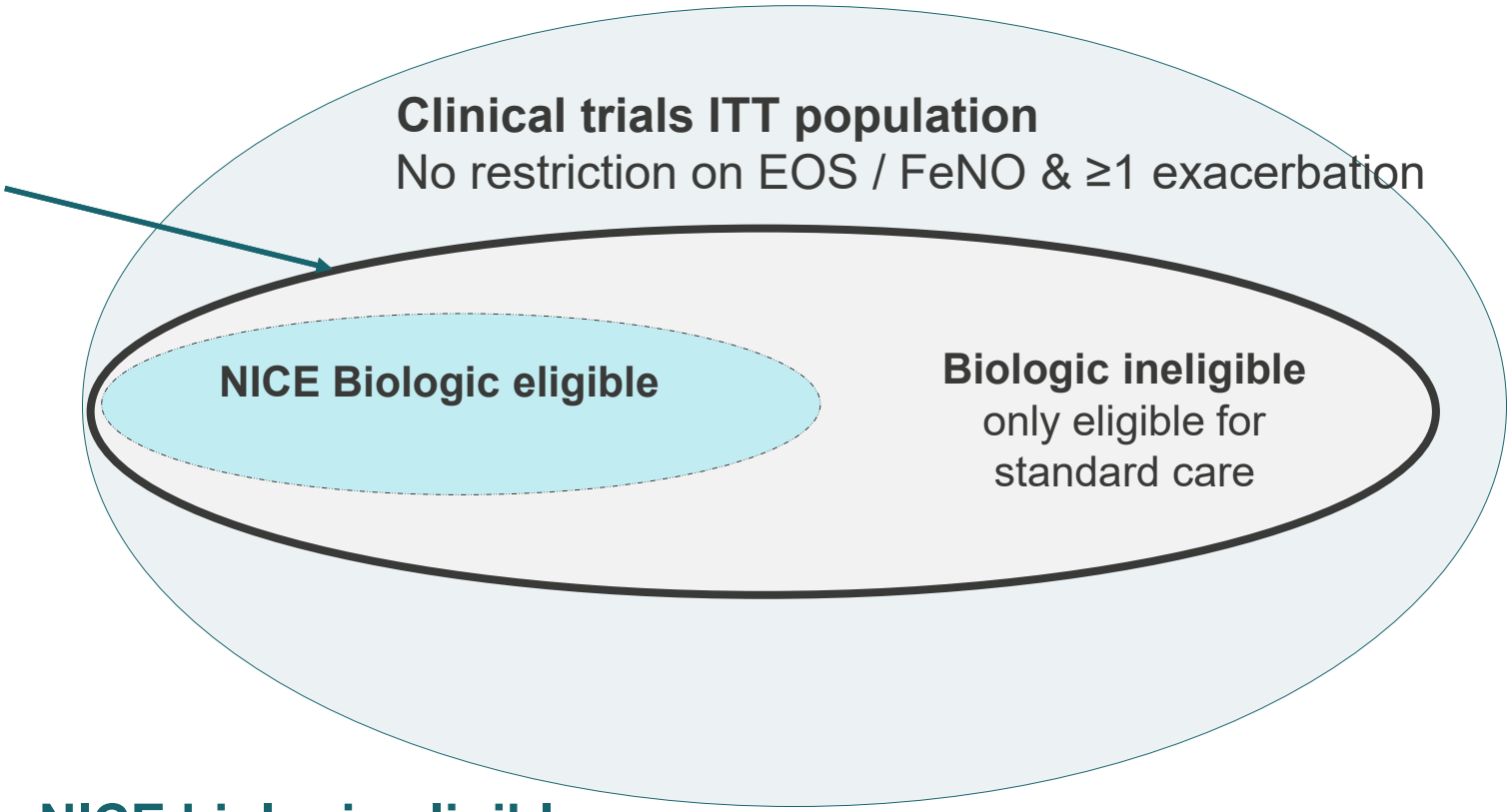
Dupilumab (Dupixent, Sanofi Genzyme)

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 type 2 inflammation characterised by raised blood eosinophils (≥ 150 cells/µl) and/or raised fractional concentration of exhaled nitric oxide (FeNO ≥ 20 parts per billion [ppb]) who are inadequately controlled with high dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment
Company's population	People aged 12 and over, with EOS≥150 and FeNo≥25 and ≥4 exacerbations not eligible / responded to biologic therapy
Administration	• Initial 400 mg dose followed by 200 mg given every other week by subcutaneous injection (people not on oral corticosteroids). • Initial 600 mg followed by 300 mg every other week by subcutaneous injection (patients on oral corticosteroids or with severe asthma and co-morbid moderate-to-severe atopic dermatitis)
Response & Stopping rule	• Response in the QUEST trial defined as at least a 50% reduction in severe asthma exacerbation rates • Stopping rule applied at 12 months considered appropriate

First committee meeting population

People eligible for biologics and not eligible for biologics

Company's decision problem population at **1st committee meeting**
EOS ≥150 cells/µl or
FeNO≥25ppb &
≥3 exacerbations



NICE biologic eligible
EOS≥300 cells/µl & ≥4 Ex
(mepolizumab/benralizumab)
EOS≥400 cells/µl & 3 Ex
(reslizumab/benralizumab)

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

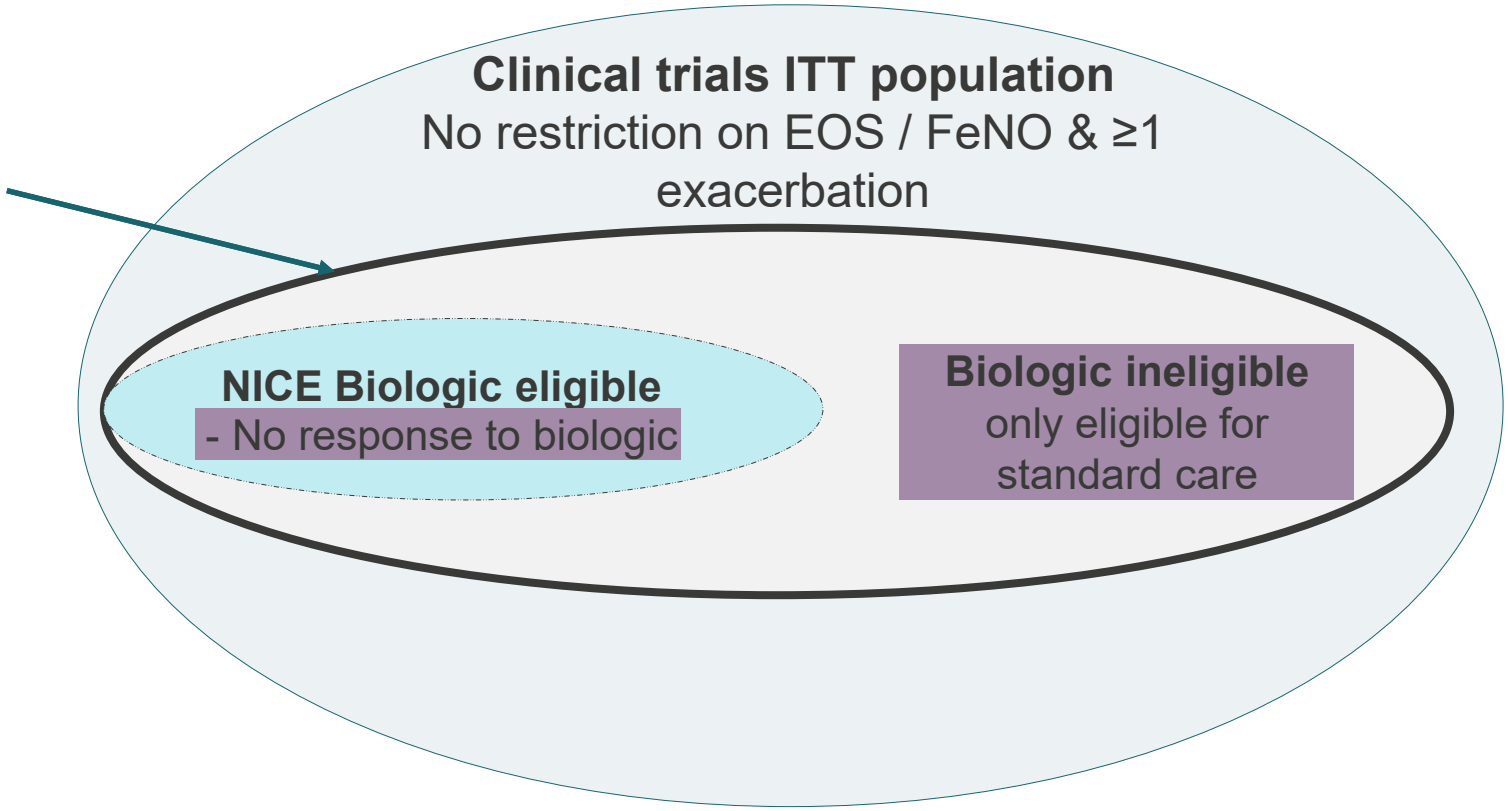
Note: QUEST included 1 patient with previous biologic treatment

Ex = exacerbations

Proposed Population – more severe /unmet need (People aged 12 and over not eligible/not responded to biologics)

Company updated the population for 2nd meeting:

Aged 12 and over, EOS ≥150cells/µ/ and FeNO≥25ppb &
≥4 exacerbations
Not eligible / responded to biologic therapy



NICE biologic eligible

EOS≥300 cells/µl & ≥4 Ex (mepolizumab/benralizumab)
EOS≥400 cells/µl & 3 Ex (reslizumab/benralizumab)

Biologic ineligible

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

Note: QUEST included 1 patient with previous biologic treatment

Ex = exacerbations

Summary of conclusions at previous meetings

Issue raised	1st ACD meeting summary	2nd ACD meeting summary	Company's response to 2nd ACD
Population	People with severe asthma aged 12 and over EOS ≥150cells/μ/ or FeNO≥25ppb & **≥3** exacerbations - included people who are and are not eligible for biologics	New proposed population-people severe asthma aged 12 and over EOS≥150 and FeNo≥25 with **≥4** Exacerbations who are ineligible for biologics or have previously had biologic therapy". • Committee - population is suitable for decision making	No change to population. Provided supporting evidence for ACD2 population from QUEST, UK, Europe and the US
Efficacy	Uncertain in the subgroup of people who are not currently eligible for biologicals	• Uncertain efficacy in the proposed population (small patient numbers) • Uncertain efficacy in previous biologic subpopulation	Provided analyses to support dupilumab's treatment effect
Mortality rates	Searched for UK mortality, no further data available	• Modelled mortality seem overestimated • Alternative scenarios used in previous TA should be explored	• Clarification of mortality rates • Provided scenario using settings from TA431 (mepolizumab)
Long-term severe exacerbation	Not appropriate to use an exacerbation multiplier	Updated base case (no multiplier)	Base case without multiplier is conservative

ACD consultation responses

Received consultation responses from:

- Patients experts
- Professional organisations
  - Asthma UK & British Lung Foundation
  - British Thoracic Society (BTS)
  - University of Oxford
- Web comments
  - Royal College of Pathologists/Royal College of Physician
- Company – Sanofi
- GlaxoSmithKline UK Ltd
- Novartis Pharmaceuticals UK Ltd

Comments themes

- **Significant unmet need in people not eligible for biologics, but also in those eligible who did not respond to biologics**
  - "I suffer from severe eosinophilic asthma which severely disrupts my life"
  - Approximately 30% suboptimal responses to biologics
  - People not responding to biologics should have the opportunity to try dupilumab
- **Disappointed that dupilumab is not recommended**
  - Very disappointing for patients, doctors and for the pharma industry
  - Not eligible for / responding to current therapies continue to have high treatment burden
  - Likely to have a larger number of people who's disease fail to respond on biologics
- **Dupilumab is a new effective and safe treatment option**
  - Dupilumab provides the option of new treatment with a different mode of action
  - Dupilumab has a huge impact on patients with very severe disease and terrible associated morbidity. People with eczema can have flares on anti-IL5 therapy
  - Exacerbations are likely to increase over time (not regression to mean)
  - Effective in those with both an allergic and eosinophilic hybrid phenotype for which the other biologics may be least effective
- **Exacerbation multiplier was accepted by the Scottish Medicines Consortium**

Company updated value proposition

- **New commercial offer**
  - Reduced price to the NHS
- **Supplementary evidence to support dupilumab efficacy**
  - Evidence from QUEST for company's population
  - Evidence from UK, Europe and the US to address committee concerns about efficacy in people who had previously received biologic therapy
- **Additional scenarios to address uncertainty**
  - Mortality estimates using different setting TA431 (mepolizumab)
  - Varying response rates or the relative risk of exacerbations with dupilumab vs. standard care

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Cost effectiveness results

Previous and current base case with respective PAS discount

- Company updated base case include:
  - Same population as 2nd meeting
  - Company increased discount for dupilumab for 3rd meeting

Company base case	ICER (£/QALY) Simple PAS
2nd meeting base case	£35,968
3rd meeting-updated base case	**£28,156**

ICER: incremental cost-effectiveness ratio: PAS: patient access scheme; QALY: quality adjusted life years

Company updated value proposition

- New commercial offer
  - Reduced price to the NHS
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  - Varying response rates or the relative risk of exacerbations with dupilumab vs. standard care

Clinical effectiveness of dupilumab (1)

ACD: highly uncertain efficacy of dupilumab in company's population

ACD conclusion

- Small patient numbers for proposed population (post hoc analysis of QUEST)
- Clinical effectiveness of dupilumab in the company's updated base case is highly uncertain

Company ACD response: maintains dupilumab is **efficacious in company's population**

- [redacted] of 948 people (naïve to biologics) in a post-hoc analysis of QUEST had [redacted] reduction in severe asthma exacerbations vs. placebo
- Subgroup with ≥2 prior exacerbations (less severe population) from QUEST also shows [redacted] reduction in severe asthma exacerbation vs. placebo

ERG

- Confirms post-hoc analysis of data from [redacted] people in QUEST shows [redacted] reduction of severe exacerbation vs. placebo

Clinical effectiveness of dupilumab (2)

ACD: highly uncertain efficacy of dupilumab in company's population

ACD conclusion

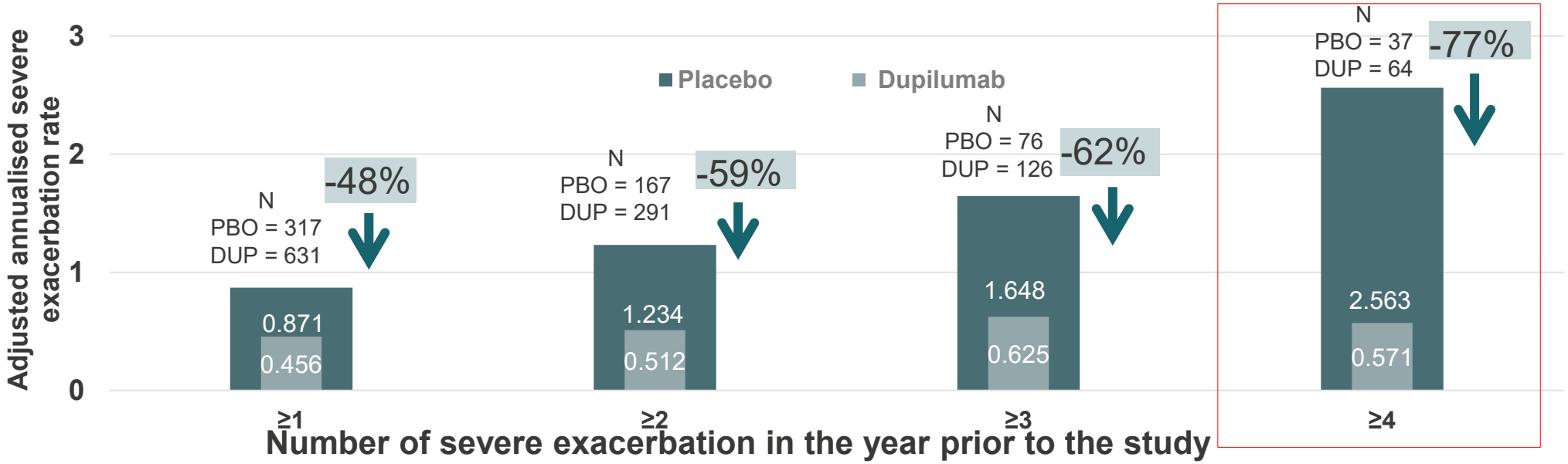
- Small patient numbers for proposed population (post hoc analysis of QUEST)
- Clinical effectiveness of dupilumab in the company's updated base case is highly uncertain

Company ACD response

- Explored subgroup analyses from QUEST to address uncertainty:
  - Treatment effect by increasing exacerbation count in 12 months prior QUEST baseline
  - Treatment effect by type 2 biomarker combinations

Clinical effectiveness of dupilumab – subgroup analysis QUEST (3)

Company: dupilumab demonstrates significant treatment effect as exacerbation rate increases



DUP: dupilumab; PBO: placebo

Source: ERG ACD response table 2

Company ACD response

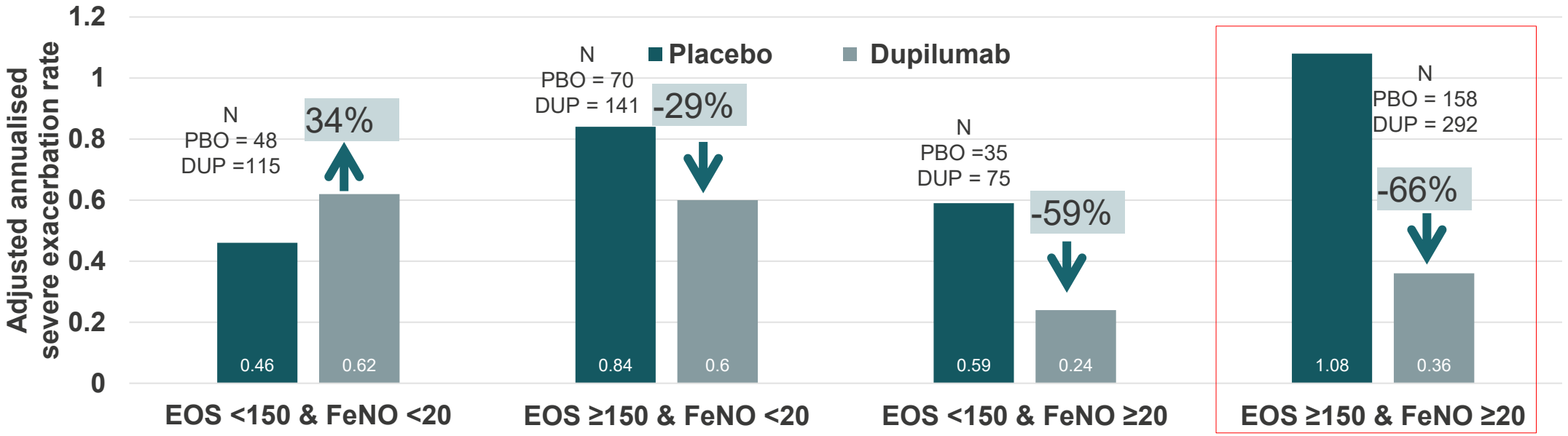
- Treatment effect maintained as the baseline historical exacerbation rate increases above 4
- Treatment effect increases from 48% reduction vs. placebo in the ≥1 exacerbation to a 77% reduction in the ≥4 exacerbations group

ERG

- Confirms dupilumab had statistically significant reduction in the severe exacerbation rate which is greatest in the subgroup with ≥4 exacerbations group

Clinical effectiveness of dupilumab – subgroup analysis QUEST (4)

Company: dupilumab demonstrates pronounced treatment effect with raised EOS and FeNO



DUP: dupilumab; PBO: placebo

Source: ERG ACD response table 3

Company ACD response

- Treatment effect greatest with raised blood EOS and FeNO (vs one or no raised biomarkers)
- Greatest reduction in adjusted annualised exacerbation rates for the subgroup with EOS ≥150 cells/μL and FeNO ≥20 ppb (this represents 48% of the QUEST trial population)

ERG

- Confirms EOS ≥150 and FeNO ≥20 had the highest adjusted annualised exacerbation rate in the placebo arm and the most pronounced treatment effect (rate reduction vs placebo 66%, p<0.001)

People with prior biological therapy – real world evidence (1)

Company: dupilumab equally effective in naïve and who had previously received biologic therapy

ACD conclusion

- Company's assumption of equal efficacy of dupilumab regardless of prior biological therapy was both optimistic and highly uncertain
- Requested scenarios with a range of alternative response rates for people who did not respond to biological therapy

Company ACD response: maintains dupilumab is as efficacious in people who had previously received a biologic as it is in biologic naive population:

- [redacted]
- Provided real-world evidence from France, Germany and the US, for people who had previously received a biologic therapy
- Concluded that all real world studies show similar efficacy of dupilumab in biologic experienced patients as those who are treatment naïve

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Dupilumab: [redacted] (2)

Company

- FOCS is not a study and there is no provision for data collection required by the NHS. There is no information on individual treatment history prior to entry into FOCS
- Eligibility criteria and people selection (including prior use of other biologics) was placed on treating clinicians registered in FOCS
- FOCS did not specify response criteria: clinicians determined response was used for people with mature data

[redacted]	
Sites	[redacted] sites signed contract • [redacted] registered people including: ○ [redacted] adult severe asthma centres or associated ○ [redacted] paediatric sites that treat adolescents
People	[redacted] - including some people never started treatment while other's treatment is on hold due to COVID-19
Data collection	Chose [redacted] centres based on highest number of people registered and earlier participation in [redacted] • [redacted] centre did not respond • [redacted] centres were too busy to provide data within time required. But noted positive results to BTS asthma Severe Asthma Group • [redacted] centres responded with their own assessment of response. ○ [redacted] were reluctant to provide assessment on all people due to a less than [redacted] month treatment period

People with prior biological therapy – real world evidence (3)

Company's real world evidence on dupilumab effectiveness

Company ACD response

- [redacted]
  - [redacted]
  - [redacted]
- [redacted]
- [redacted]

	Dupilumab population	Number of patients responding to therapy	Dupilumab responders	Total initiated
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG:

- Confirms people in [redacted] are similar to non-responder subgroup in company's population
- UK real world evidence shows that [redacted] people responded to dupilumab

Source: Company ACD response table 4

People with prior biological therapy – real world evidence (4)

Company's real world evidence on dupilumab effectiveness

	France (N=64)	Germany (N=38)	USA (N=72)
Previous therapies	Mepolizumab 17%, Omalizumab 84%	Mepolizumab 29%,reslizumab 5%, benralizumab 50% omalizumab 16%	29.2%
Baseline OCS	75.8%	64%	12.5%
Dupilumab dose	600 mg loading; 300 mg thereafter	600 mg loading; 300 mg thereafter	median 300 mg (range 200-300 mg)
Asthma control results	Median ACT score increased from 14 to 22 (p<0.001) and was >20 for 67% patients	ACT score increased by 2.9±4.6 (p<0.001) • 76% of people were responders • People with FeNO ≥ 25ppb were more likely responder as compared people with low FeNO	Mean ACT score increased from 16 to 22 (p<0.05) • 62.5% people had clinical meaningful response • 20/21 people who's treatment failed responded to dupilumab
Exacerbation rate results	Exacerbation rate reduced by 75% vs baseline • 78% of patients had ≥ 50% reduction	Annualised exacerbations decreased by a median of 0.81/y (p=0.001) vs previous antibody therapy • One patient in the non-responder group experienced an increase in exacerbations	Mean annual exacerbation frequency fell from 2.7 at baseline to 0.1

ERG

- Real world patients differ from QUEST (300mg dupilumab and, higher OCS use)
- Dupilumab likely to be effective in an unknown proportion of patients

NICE

ACT: asthma control test; OCS: oral corticosteroids

Source: ERG ACD response table 4

Does real world data from France, Germany, US reflect UK clinical practice?

People with prior biological therapy – real world evidence (5)

Company: dupilumab equally effective in naïve who had previously received biologic therapy

ACD conclusion

- Company's assumption of equal efficacy of dupilumab regardless of prior biological therapy was both optimistic and highly uncertain
- Requested scenarios with a range of alternative response rates for people who did not respond to biological therapy

Company ACD response: maintains dupilumab is as efficacious in patients who had previously received a biologic as it is in biologic naive population:

- [redacted]
- Provided evidence from France, Germany and the US, for people not responded to anti-IL-5 and /or anti-IgE treatment
- All real world studies show similar efficacy of dupilumab in biologic experienced patients as those who are treatment naïve

ERG conclusions on the UK ([redacted] and data from France, Germany and the US)

- Agreed real-world studies demonstrate improvement in asthma control and reduction exacerbations for people previously received biologics
- Highlighted people treated in real-world studies had a higher dose of dupilumab (300 mg) and a higher proportion of people received oral corticosteroids
- Agreed people previously received a biologic will respond to dupilumab but uncertain to proportion of responders due to small sample size

Company updated value proposition

- **New commercial offer**
  - Reduced price to the NHS
- **Supplementary evidence to support dupilumab efficacy**
  - Evidence from QUEST for company's population
  - Evidence from UK, Europe and the US to address committee concerns about efficacy
- **Additional scenarios to address uncertainty**
  - Mortality estimates using different setting TA431 (mepolizumab)
  - Varying response rates or the relative risk of exacerbations with dupilumab vs. standard care

ACD: *Mortality estimates used in company model may be overestimated*

Company: base-case mortality estimates reported in ACD were incorrect

ACD conclusion

- Mortality estimates are uncertain and probably overestimated in company model
- Requested alternative scenarios to explore the impact of mortality on the cost-effectiveness results

Company ACD response

- 18% 10-year mortality rate for standard of care in ACD is incorrect. The company model estimates 10-year mortality of 16.7% for standard of care and 10.1% for dupilumab
- Evidence suggests mortality estimates from company's model produces consistent results with published literature notably French severe asthma study where:
  - All-cause mortality reported was 7.1% at 3 years for mean age 61 years vs. 7.6% at 3 years when the company adjusted its model to mean starting age 61 years
- Results of company's model are robust and inappropriate to compare with TA565 (benralizumab):
  - In TA565, baseline age was 50.2 years vs [redacted] in company model
  - Lower-risk profile cohort in TA565 with only 3 exacerbations in the year prior to initiation

ERG response

- Confirms company's 16.7% 10-year mortality rates of standard care are correct
- Highlights French severe asthma study does not resolve uncertainty about generalisability of modelled mortality in NHS due to difference in the population, treatments and setting
- Accepts that there are differences in the population and assumptions of the appraisals

◉ ***Are the mortality rates in the company model appropriate?***

Company's scenario – Exacerbation settings from TA431 (mepolizumab)

Company: base case is more conservative and than previous appraisal

ACD conclusion

- Alternative methods were used in TA565 (benralizumab) to adjust for high mortality
- Explore alternative scenarios to explore the impact of the mortality on the ICER

Company ACD response

- Settings of treatment of severe exacerbations are associated with a different probability of death and impact on overall life expectancy
- Differences in model programming prevented analysis using TA565 (benralizumab) setting
- Company used settings from TA431 (mepolizumab) (8.24% inpatient and 8.24% A and E), this resulted in a lower ICER

Exacerbation (setting)	Incremental (DUP vs. SoC)		ICER
	Cost	QALYs	
Base case	XXXXX	[redacted]	**£ 28,156**
Exacerbation setting from TA431 (mepolizumab)	XXXXX	XXXX	£27,257

ERG: accepts that there are differences in the population and assumptions of the appraisals

DUP: dupilumab; ICER: incremental cost-effectiveness ratio; SoC: Standard of care: QALY: quality adjusted life years;

Source: Company ACD response table 10

People with prior biological therapy –varying treatment response rates

Reducing the 12 month response rate (non-responders) has a little effect on ICER

ACD conclusion

- Committee requested scenarios with range of alternative response rates

Company ACD response

- Explored alternative response rates by adjusting the proportion of people who responded to dupilumab at 12 months downwards and considers this as a conservative scenario

Response	Incremental (DUP vs. SoC)		ICER
	Cost	QALYs	
Base case (86.8%)	XXXXXX	XXX	**£ 28,156**
Base Case*0.9 (78.1%)	XXXXXX	XXX	£ 28,188
Base Case*0.8 (69.4%)	XXXXXX	XXX	£ 28,228
Base Case*0.7(60.7%)	XXXXXX	XXX	£ 28,278
Base Case*0.6 (52.11%)	XXXXXX	XXX	£ 28,341

ERG: does not consider realistic

- Non-responders stop dupilumab at 12 months but same QALYs as responders at 12 months
- Model not responsive to varying response rates
- At 0% response to dupilumab, the model estimates an ICER of £30,093 per QALY gained

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DUP: dupilumab; SoC: Standard of care

Source: Company ACD response table 5

People with prior biological therapy – varying rate of exacerbations

Increasing the relative risk of severe exacerbations increases the ICER

Company ACD response

- Explored an alternative approach in which the relative risk of experiencing a severe exacerbation for dupilumab versus SoC was varied
- Varied relative risk for the entire proposed population and not only for the proportion who did not respond to anti-IL-5 treatments. Considers this a conservative approach

Percentage of base case hazard ratio	Incremental (DUP vs. SoC)		ICER
	Cost	QALYs	
Base Case	XXXXXX	XXX	**£ 28,156**
100%	XXXXXX	XXX	£ 29,316
120%	XXXXXX	XXX	£ 29,849
125%	XXXXXX	XXX	£ 30,121
130%	XXXXXX	XXX	£ 30,397
250% (ERGs extreme scenario)	XXXXXX	XXX	£ 38,514

ERG: provided extreme scenario 250% increase base case hazard ratio (which represents the upper confidence interval of the based case hazard ratio). It considers this to be more reflective of the range of uncertainty in the effectiveness of dupilumab.

DUP: dupilumab 200 mg; ICER: incremental cost-effectiveness ratio; SoC: Standard of care: QALY: quality adjusted life years;

Source: Company ACD response table 6
ERG ACD response table 6

Innovation and equality

Innovation

- ACD: committee acknowledge there are additional benefits not captured in the QALY calculation (in people with comorbidities such as nasal polyps and atopic dermatitis)

Equality

- No equalities issues were identified

PART 2

Key issues

- **New commercial offer**
  - Is the revised ICER low enough to accept the uncertainties?
- **Supplementary evidence to support dupilumab efficacy**
  - Does evidence from QUEST and sub-group analyses support the treatment effect of dupilumab?
  - Is dupilumab as effective in people who have not previously responded to biologic therapy?
- **Additional scenarios to address uncertainty**
  - Do the mortality rates in the model reflect current UK clinical practice?
  - Varying response rates or the relative risk of exacerbations with dupilumab vs. standard care

Cost effectiveness results

Previous and current base case with respective PAS discount

- Company updated base case include:
  - Same population as 2nd meeting
  - Company increased discount for dupilumab for 3rd meeting

Company base case	ICER (£/QALY) Simple PAS
2nd meeting base case	£35,968
3rd meeting-updated base case	**£28,156**

NICE

ICER: incremental cost-effectiveness ratio: PAS: patient access scheme; QALY: quality adjusted life years

Back up slides

Additional company's scenario analyses

To address remaining uncertainty, the company provided additional scenarios:

- Varying mortality risks for hospitalised exacerbation in people aged 55-64 years
- Using exacerbation settings from TA431 (mepolizumab)
- Long-term exacerbation rates
- Scenario analyses with discount rate at 1.5%

Company's scenario – varying mortality risks

Company ACD response:

- Used methodology for deriving mortality estimates based on TA565 (benralizumab)
- Provides a correction to mortality rate for 55 to 64 year-old patients admitted to hospital due to a severe exacerbation from 1.81% to 0.85%

Varying mortality risks for hospitalised exacerbations	Incremental (DUP vs. SoC)		ICER
	Cost	QALYs	
Base Case (1.81%)	XXXXXX	XXX	**£ 28,156**
Revised mortality in aged 55-64 years (0.8568%)	XXXXXX	XXX	£28,929

ERG

- Confirms company's correction increase the ICER from £28,156 to £28,929 per QALY gained

NICE DUP: dupilumab; ICER: incremental cost-effectiveness ratio; SoC: Standard of care: QALY: quality adjusted life years;

Source: Company ACD response table 9

Company's additional scenario – Long-term exacerbation rates (1)

Company ACD response

- Highlights the limitations of QUEST trial protocol underestimated severe exacerbations
- Presented scenarios using multiplier to inflate the severe exacerbations in both arms after the end of QUEST follow up
- Baseline and in-trial exacerbation rates are lower than clinical practice
- Considers dupilumab cost-effective than the existing base case result

Scenario (value of long-term multiplier)	Multiplier	Incremental (DUP vs. SoC)		ICER
		Cost	QALYs	
Base case	[redacted]	[redacted]	[redacted]	£ 28,156
Lifting 28-day restriction	[redacted]	[redacted]	[redacted]	£ 25,784
Exacerbation-free run in period	[redacted]	[redacted]	[redacted]	£ 21,033
Adjustments for both QUEST protocol restriction	[redacted]	[redacted]	[redacted]	£19,678

ERG

- Were able to replicate the company's results

NICE ◉ ***Should an exacerbation multiplier be accepted?***

DUP: dupilumab`; ICER: incremental cost-effectiveness ratio; SoC: Standard of care: QALY: quality adjusted life years;

Source: Company ACD response table 11

Company's additional scenario – Long-term exacerbation rates (2)

Company ACD response

- Presented a range of scenarios with multipliers calibrated to achieved defined long-term average exacerbation rates

Scenario (calibrated long-term multiplier)	Standard care AER	Incremental (DUP vs. SoC)		ICER
		Cost	QALYs	
Base case (1)	XXX	XXXXXX	XXX	**£ 28,156**
AER 3.5 (1.063)	XXX	XXXXXX	XXX	£ 26,793
AER 3.8 (1.145)	XXX	XXXXXX	XXX	£ 25,226
AER 4 (1.198)	XXX	XXXXXX	XXX	£ 24,303
AER 4.3 (1.278)	XXX	XXXXXX	XXX	£ 23,060
AER 4.5 (1.331)	XXX	XXXXXX	XXX	£ 22,319

ERG

- Were able to replicate the company's results

DUP: dupilumab; ICER: incremental cost-effectiveness ratio; SoC: Standard of care: QALY: quality adjusted life years;

Should an exacerbation multiplier be accepted?

Source: Company ACD response table 13

Company's scenario – adjusting discount rates to 1.5%

- 3.5% discounting rates recommended by the HM Treasury Green Book is not applicable to health economic evaluations in its entirety
- Company: wealth effect of 2% is not applicable because the value of health does not decline as real incomes rise
- As such presented scenario analysis at 1.5% discount rate

Discount rate	Incremental (DUP vs. SoC)		ICER
	Cost	QALYs	
Base Case (3.5%)	XXXXXX	XXX	**£ 28,156**
1.5%	XXXXXX	XXX	£24,482

ERG:

- Confirmed 1.5% discount rate of scenario analysis ICER of £24,482 per QALY gained

NICE DUP: dupilumab; ICER: incremental cost-effectiveness ratio; SoC: Standard of care: QALY: quality adjusted life years

Source: Company ACD response table 14

History of the appraisal

- **First committee meeting (February 2020)** - Dupilumab not recommended within its marketing authorisation
  - ACD sent out for consultation April 2020 - Topic paused due to covid-19
- **Second meeting November 2020** - Company submitted revised base case
  - Narrower population (people not eligible for biologics or not responded to biologics)
  - removed asthma exacerbation multiplier
  - explored other sources for asthma exacerbations treatment settings
  - explored different ways of mortality modelling
  - Updated PAS
  - ICER £35,968 per QALY gained vs. standard care not cost effective use of NHS resources
  - **Conclusion: not recommended** - Committee concerned about high mortality rates and assumption of dupilumab response rates in people not responding to other biologics
  - **Conclusion:** Committee concerned about the high mortality rates and assumption on dupilumab response rates in people who have not responded to other biologics
- **Third meeting September 2021**– Company submitted further scenarios to explore impact of remaining uncertainty and updated PAS