Lead team presentation
Benralizumab for treating inadequately controlled asthma

Cost effectiveness-PART 1

1st Appraisal Committee meeting (17 April 2018)

Committee A

Lead team: Rita Faria, Rachel Hobson, Sarah Parry, Pamela Rees

Assessment Group: Peninsula technology Assessment Group (PenTAG)

NICE technical team: Sana Khan, Eleanor Donegan

For public observer slides

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Key decision points

1. Should the cost-effectiveness of Benralizumab be considered for the subgroups with 3+ exacerbations OR mOCS separately or jointly?
2. If jointly, what is the most relevant estimate of proportion of patients on mOCS at treatment initiation (company 54.1% and 78.6% or ERG 41.7%)?
3. In which subgroup is mepolizumab a comparator for benralizumab?
4. Is it appropriate to generalise the relative treatment effect from the MAIC on the full MENSA/DREAM trials to the subgroup of interest?
5. What is the committee's view on the MAIC including the MUSCA trial?
6. Is the evidence compelling that reslizumab has the same clinical effectiveness and side effect profile as benralizumab?
7. Is the most appropriate weighted average of asthma-related mortality 0.01943 (company estimate based on Watson et al 2007 and Roberts et al 2013) or 0.007 per hospital admission (ERG estimate based on 2016 BTS asthma audit)?
8. What is the most plausible ICER vs standard of care, mepolizumab and reslizumab?
9. Is Benralizumab innovative?

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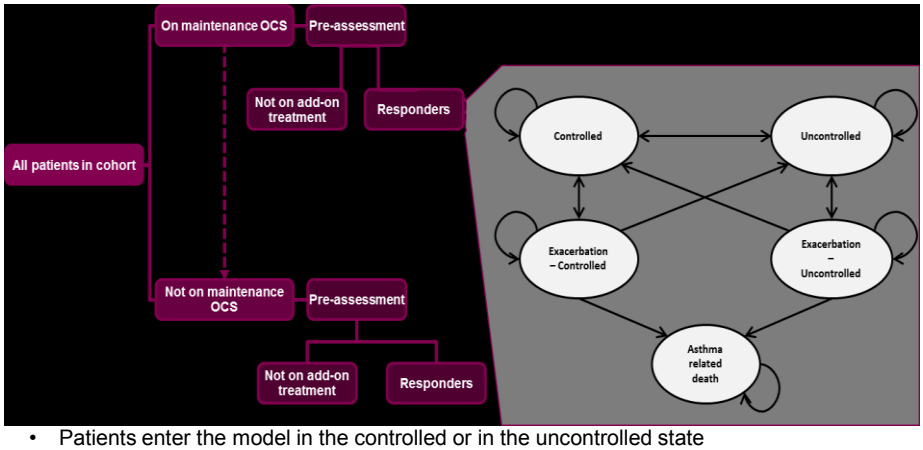
Company economic model-4 state Markov model as in the model file submitted by company



- Patients enter the model in the controlled or in the uncontrolled state
- Controlled state is defined as having an ACQ-6 score <1.5
- Exacerbations are a composite state that include OCS burst, A&E visit, and hospitalisation and includes asthma-relate death
- Type of exacerbation depends on the origin state: controlled or uncontrolled
- Patients are at risk of all cause death from all states (missing from figure above)
- Cycle length = 2 weeks

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Model details

- The model divides population into 2 subgroups but the ICER is for a blended population:
  - patients with 3+ exacerbations not on mOCS (non-mOCS)
  - and patients on mOCS aassessment of response at 52 weeks:
  - responders continue on biological drug
  - non-responders revert to SoC
- Increased efficacy for benralizumab:
  - reduces the frequency and severity of exacerbations compared with SoC
  - reduces the use of mOCS compared with SoC and with mepolizumab.
  - improves health-related quality of life (utilities) compared with SoC.
- Patients experiencing an exacerbation are at risk of asthma-related death
- Severity of exacerbations depends on if people are on biological drug or SoC
- Patients on mOCS are at risk of developing a range of long-term conditions
- Cycle length in the model is 2 weeks
- The model is in line with the NICE reference case in terms of time horizon, perspective and discount rate

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Company model: Baseline characteristics

Characteristic	Value	Source
Benralizumab vs. SoC (base case)		
Age (years)	50.2	Pooled SIROCCO/CALIMA
% female	64.5	Pooled SIROCCO/CALIMA
% patients on mOCS at baseline	54.1	Kerkhof 2017
Benralizumab vs. Mepolizumab		
Age (years)	49.8	Pooled SIROCCO/CALIMA
% female	66.1	Pooled SIROCCO/CALIMA
% patients on mOCS at baseline	78.6	Kerkhof 2017
Benralizumab vs. Reslizumab		
Age (years)	50.2	Pooled SIROCCO/CALIMA
Weight (kg)	75.2	Pooled reslizumab trials
% female	63.3	Pooled SIROCCO/CALIMA
% patients on mOCS at baseline	0	NICE Reslizumab STA

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Company model: Proportion of responders

Drug	Value	Source
Company base case: benralizumab (vs SoC)		
Non-OCS	[redacted]	Pooled SIROCCO/CALIMA
mOCS	[redacted]	ZONDA
Benralizumab (vs Mepolizumab)		
Non-OCS (benralizumab)	[redacted]	MAIC results
mOCS (benralizumab)	[redacted]	MAIC results
Non-OCS	[redacted]	NICE mepolizumab STA
mOCS	[redacted]	Assumed equivalent to benralizumab
Benralizumab (vs Reslizumab)		
Non-OCS (benralizumab)	[redacted]	Reslizumab NICE STA
Non-OCS (reslizumab)	[redacted]	Assumed equivalent to benralizumab

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Company model: Transition probabilities

- Benralizumab compared with SoC:
  - Transition probabilities calculated from the individual level data of the trials: SIROCCO/CALIMA for non-OCS and ZONDA for mOCS
- Benralizumab compared with mepolizumab
  - Transition probabilities for benralizumab obtained from trials as above
  - Transition probabilities for mepolizumab calculated by multiplying the transition to exacerbation by 1/RR from MAIC (RR= [redacted] for non-OCS and RR=[redacted] for mOCS)
- Benralizumab compared with reslizumab
  - Transition probabilities for benralizumab obtained from trials as above
  - Reslizumab assumed to have the same clinical effectiveness as benralizumab

Company model: Reduction in severity of exacerbations

	Non-OCS		mOCS	
	Benralizumab	SoC	Benralizumab	SoC
Exacerbations from controlled state				
OCS burst	16 (100%)	25 (89.29%)	3 (100%)	21 (100%)
A&E	0	1 (3.57%)	0	0
Hospitalisation	0	2 (7.14%)	0	0
Exacerbations from uncontrolled state				
OCS burst	22(81.48%)	99(85.34%)	13(100%)	31(68.89%)
A&E	0	9(7.75%)	0	5 (11.11%)
Hospitalisation	5(18.52%)	8(6.91%)	0	9(20%)

Note: for comparisons with other biologics, the same split as benralizumab is used

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Company model: Reduction in mOCS versus SoC

Parameter	Value	Source
mOCS use at baseline	[redacted]	Kerkhof 2017
Reduction in mOCS use		
Benralizumab	[redacted]	ZONDA
SoC	[redacted]	ZONDA

In the model, the use of mOCS is associated with increased incidence of long-term conditions: Type 2 Diabetes Mellitus, Osteoporosis, Glaucoma, Cataracts, Myocardial Infarction, Heart Failure, Cerebrovascular accident, renal impairment, peptic ulcer, pneumonia.

The long-term conditions are associated with costs and disutilities in the long-term.

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Company model: Reduction in mOCS versus mepolizumab

Parameter	Value	Source
mOCS use at baseline	[redacted]	Kerkhof 2017
Reduction in mOCS use		
Benralizumab	[redacted]	ZONDA
Mepolizumab	[redacted]	MAIC

In the model, the use of mOCS is associated with increased incidence of long-term conditions: Type 2 Diabetes Mellitus, Osteoporosis, Glaucoma, Cataracts, Myocardial Infarction, Heart Failure, Cerebrovascular accident, renal impairment, peptic ulcer, pneumonia.

The long-term conditions are associated with costs and disutilities in the long-term.

Company model: Other parameters and assumptions

1. Benralizumab discontinuation rate is 11.8% (pooled SIROCCO/CALIMA), and assumed the same for mepolizumab
2. 100% adherence to biological drugs.
3. Constant exacerbation rates over time
4. Treatment response sustained over time
5. The impact of adverse drug reactions is negligible

Company model: Asthma-related mortality

Parameter	Value
During OCS burst	
Age 17-44	0.05%
Age 45+	0.32%
During A&E visit	
Age 17-44	0.32%
Age 45+	2.05%
During hospital admission	
Age 18-24	0.15%
Age 25-34	0.14%
Age 35-44	0.20%
Age 45-54	0.76%
Age 55-64	2.14%
Age 65+	4.54%

- Patients experiencing exacerbations are at risk of asthma-related death
- Exacerbations assumed to last 8 weeks
- Risk of death depends on age and type of exacerbation
- Risk of death obtained from Watson et al, Roberts et al, and NRAD report

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Company model Health state utilities

- EQ-5D-5L data collected during SIROCCO and CALIMA trials and mapped to derive EQ-5D-3L utilities for the health states of the non-OCS subgroup
- AQLQ-12 collected in ZONDA and used to derive EQ-5D-3L utilities for the health states of the mOCS subgroup.
- Utilities vary by:
  - Subgroup: mOCS vs non-OCS
  - Health state: Controlled, uncontrolled, exacerbation with OCS burst, exacerbation with A&E visit, exacerbation with hospitalisaiton.
  - Treatment: Benralizumab compared with SoC (only for health states controlled and uncontrolled)
- Disutility of exacerbations lasts 8 weeks based on Golam et al. (2017). **ERG note that this is much longer than considered in previous appraisals of mepolizumab and reslizumab**

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Company model: Resource use and costs

Drug costs

- Cost of SoC sourced from trials of high dose ICS/LABA using BNF 2017 prices
- Unit cost of benralizumab reflects the cost per 8 weeks. People assumed to receive 8 doses in the first year and 6.5 doses thereafter
- Unit cost of mepolizumab reflects the cost per 4 weeks
- Cost of reslizumab based on average patient weight published in the reslizumab NICE appraisal (75.2kg) per 4 weeks

Administration costs:

- NICE appraisals for reslizumab and mepolizumab
- SoC associated with no additional drug costs

Health state unit costs

- Unit costs applied to levels of healthcare resource use estimated by WIlson et al. (2014, 2016)

AE costs:

- AEs not included in the model because of small proportions and minor differences between treatment groups (similar incidence of AEs for the placebo group (77.6%) compared with the benralizumab (74.7%) group)

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Company model: Disutilities and costs from chronic mOCS use

- mOCS use is associated with ongoing disutilities and costs due to increased incidence of long-term conditions
- Incidence obtained from OPRI study by AstraZenaca . For chronic conditions, prevalence is constant for the time horizon of the model whereas annual incidence rates used for events
- Proportion of mOCS users sourced from ZONDA
- Ten comorbidities were identified in total. A weighted average of costs by prevalence/incidence of each comorbidity was calculated for each daily dose level of mOCS. This weighted average was then multiplied by the proportion of patients on each daily dose level in order to calculate the overall cost of mOCS use for each dose level.
- Disutilities obtained from Sullivan et al (2011)

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Company model: Base case results (deterministic)

Comparator technology	Population	Inc Costs	Inc QALYs	ICER per QALY
Add-on Benralizumab vs. SOC	Base case	[redacted]	[redacted]	£34,284
Add-on benralizumab vs. Add-on mepolizumab	NICE recommended for mepolizumab	[redacted]	[redacted]	Dominant
Add-on benralizumab vs. Add-on reslizumab	NICE recommended for reslizumab	[redacted]	[redacted]	Dominant

Note: Probabilistic results give similar ICERs
ICERs are based on the benralizumab PAS price and mepolizumab and reslizumab list prices. See confidential part 2 appendix for comparisons with PAS prices
Scenario analyses showed that the results are most sensitive to including risk of asthma death from an exacerbation, equal utility /disutility across treatment arms, costs and utilities associated with mOCS

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Company model: Key sensitivity analyses

Sensitivity analysis	ICER vs SoC
Base-case	£34,284
Age at treatment initiation (50.2 years)	£41,807
Utilities independent of treatment	£38,688
Asthma mortality risk =0	£67,260
Removing the consequences of mOCS use	£36,983-£38,573

Sensitivity analyses in comparisons with mepolizumab and reslizumab had negligible impact on the ICER except:
- mepolizumab: proportion of responders on mOCS

In addition:
- PSA
- Threshold analysis on PAS price

ERG comments: strengths

- Appropriate model structure, although the way exacerbations were modelled means that it is not possible to transit between different severities of exacerbations.
- Response criteria consistent with the reslizumab appraisal (52 weeks, although it did not include annual reassessment. ICER is sensitive to response rates.
- Appropriate to apply a constant risk of treatment discontinuation.
- Method to calculate cost of SoC is reasonable.

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ERG comments: limitations (1)

- Assumption that reslizumab and benralizumab have similar effectiveness and response rates, given the different mechanism of action.
- Assumption that treatment effect is constant over time, which was not tested in the sensitivity analysis.
- Different proportion of mOCS use at baseline depending on comparator (54.1% in the SOC comparison and 78.6% in the mepolizumab comparison). ERG prefers 41.7% from Heaney et al from UK registry of adults with difficult asthma.
- Lack of clarity on patients' average age: 50.2 years (CS) vs 44.9 (ERG, based on Heaney et al). ICER is sensitive to age at treatment initiation.
- Limited robustness of transition probabilities due to small sample sizes and low exacerbation rates.
- Model assumed that patients not on mOCS in any given state were be subject to the transition probabilities, costs, and utilities associated with having received mOCS treatment if they were in the mOCS group at baseline

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ERG comments: limitations (2)

- Exclusion of the MUSCA trial from the MAIC comparing benralizumab with mepolizumab is contrary to the inclusion criteria.
  - when included in the MAIC analysis, after matching [redacted]
  - [redacted]
- Asthma-related mortality risk is overestimated.
  - Company model predicts 1.5 times higher mortality in company base case population compared to the UK general population of the same age
  - The ERG identified an asthma audit report (2016), which reported the average probability of death to be 0.0078 per hospital admission. Estimate in CS base-case is ~2.5 times higher (0.01943) for people aged 45-54 and 55-64 during hospital admission.
  - ICER sensitive to asthma-related mortality risk.

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ERG comments: limitations (3)

- Duration of disutility due to exacerbations is overestimated.
  - Method to derive 8 weeks duration is unclear.
  - NICE mepolizumab appraisal used 10-21 depending on severity.
- Reslizumab's acquisition cost was underestimated
  - ERG prefers higher average weight (83.7 Kg from Haselkorn vs 75.2 Kg from company's base-case).
  - ERG prefers that vial wastage is included.
- Drug administration costs underestimated
  - Minor impact on the ICER.
- Differences in the calculation of the health state costs, but marginal impact on ICER.

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All the ICERs reported in the next slides **ONLY** include the PAS discount for benralizumab and **DO NOT** include PAS prices for the comparators mepolizumab and reslizumab

The results are therefore not representative of the true prices of the drugs- see the confidential part 2 aapendix with PAS prices cost effectiveness results

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ERG base case (1)

Item	ERG changes	Company base case
1. Asthma-related mortality	assumed ~2.5 times lower than in the company's model for some patients (BTS asthma audit 2016)	See Table 60 in ERG report
2. mOCS use at baseline	41.7% (Heaney et al., 2010) for all treatments	54.1% for SOC comparison,78.6% for the MEPO comparison
3. Administration costs of biologics	Same administration time for mepolizumab and benralizumab assumed admin cost as in reslizumab appraisal.	Monitoring time not costed; administration of MEPO takes 5 mins longer than for BEN; 55 mins for RESLI
4. Acquisition cost for reslizumab	Based on a bodyweight distribution from Haselkorn et al. and the vial-based dosing	75.2kg
5. Treatment discontinuation rate	0.0041/cycle (average across trials)	0.0048/cycle

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ERG base case (2)

	ICER for pairwise comparison of benralizumab vs		
Item	**SoC**	**Mepolizumab**	**Reslizumab**
1.Asthma-related mortality	£36,398	BEN dominates	BEN dominates
2.mOCS use at baseline	£36,531	BEN dominates	NA
3.Administration costs of biologics	£34,646	BEN dominates	BEN dominates
4.Acquisition cost for reslizumab	NA	NA	BEN dominates
5.Treatment discontinuation rate	£34,346	BEN dominates	BEN dominates
ERG base case (1+2+3+4+5)	**£39,135**	**BEN dominates**	**BEN dominates**

The CS base-case vs benralizumab was £34,284; benralizumab dominates mepolizumab and reslizumab.

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ERG base-case: key scenario analyses

Assumptions	ICER for benralizumab compared with:		
	SOC	MEPO	RESLI
ERG Base Case	£39,135	BEN dominates	BEN dominates
Set asthma-related mortality to zero	£73,560	BEN dominates	BEN dominates
mOCS use at baseline of 17% (as in Kerkhof et al. 2017)	£44,425	BEN dominates	BEN dominates

In the other scenario analyses, the ICER changed by less than £1,000/QALY.

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ERG exploratory analysis mOCS use at baseline

Technology		Total costs	Total QALYs	Inc costs	Inc QALYs	ICER
ERG'S base-case vs. SOC (0% on mOCS)	BEN	[redacted]	[redacted]	[redacted]	[redacted]	£48,883
	SOC	[redacted]	[redacted]	-	-	-
ERG'S base-case vs. SOC (100% on mOCS)	BEN	[redacted]	[redacted]	[redacted]	[redacted]	£30,278
	SOC	[redacted]	[redacted]	-	-	-
ERG'S base-case vs. mepolizumab (0% on mOCS)	BEN	[redacted]	[redacted]	[redacted]	[redacted]	£2,370,98 SW quadrant
	MEPO	[redacted]	[redacted]	-	-	-
ERG'S base-case vs. mepolizumab (100% on mOCS)	BEN	[redacted]	[redacted]	[redacted]	[redacted]	BEN dominates
	MEPO	[redacted]	[redacted]	-	-	-
ERG'S base-case vs. reslizumab (0% on mOCS)	BEN	[redacted]	[redacted]	[redacted]	[redacted]	BEN is less costly
	RESLI	[redacted]	[redacted]	-	-	-

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Innovation
Company comments

- Benralizumab results in near complete depletion of blood eosinophils within 24 hours following the first dose, which is maintained throughout the treatment period, and reduces airway mucosal eosinophils by 96% at day 84
  - mepolizumab and reslizumab indirectly reducE the activation, proliferation, and survival of eosinophils resulting in eosinophil reduction but not depletion
- Only anti eosinophilic treatment available for administration through an accessorised prefilled syringe and convenient every 8-week dosing for SC injection
  - benralizumab reduces the number of product administration visits and associated administration costs, and facilitating home administration by where needed
  - reslizumab and mepolizumab require reconstitution before administration with high associated resource use costs

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