PART 1 | No ACIC

NICE National Institute for Health and Care Excellence

Mepolizumab for treating severe eosinophilic asthma (review of technology appraisal guidance TA431) [ID3750]

Technical briefing

This slide set is the technical briefing for this appraisal. It has been prepared by the technical team and it is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the appraisal committee meeting and is expected reading for committee members. The submissions made by the company, consultees and nominated experts as well as the ERG report are available for committee members, and are optional reading.

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Key Issues

Clinical issues

- **Issue 1:** Is the evidence sufficient for a subgroup of adults with baseline eosinophils ≥400 cells/μl and ≥3 severe exacerbations needing corticosteroids in the previous 12 months? Can mepolizumab be recommended in the same way as TA565 and TA479?
- **Issue 2:** Does the committee accept the design and reliability of the company's indirect treatment comparison (ITC)?
- **Issue 3:** Is the committee satisfied with the evidence for similar efficacy of mepolizumab compared with comparators? (comparable efficacy assumption)

Cost comparison issues

- **Issue 1:** Is 1-year time horizon sufficient?
- **Issue 2:** How useful/cost saving is self administration?

The technologies

	Intervention	Comparators	
	Mepolizumab	**Reslizumab**	**Benralizumab**
Mechanism of action	Monoclonal antibody against anti-interleukin-5 receptor alpha. Reduces eosinophils involved in allergic response and inflammation.		
Marketing authorisation	• severe refractory eosinophilic asthma in adults, adolescents and children aged 6 years plus.	• adults with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment.	• adults patients with severe eosinophilic asthma inadequately controlled despite high-dose ICS plus long-acting β-agonists.
Formulation	• Vial (powder) • Pre-filled syringe • Pre-filled pen	• Vial (concentrate)	• Pre-filled syringe • Pre-filled pen
Administration and dose	• 100mg **SC injection** 4 weekly	• **IV infusion** 4 weekly • Dose dependent on patient body weight	• 30 mg **SC injection** 4 weekly for 3 doses, then 8 weekly

ICS: Inhaled corticosteroids; IV: Intravenous; Q4W: every four weeks; Q4W: every eight weeks; SC: Subcutaneous

Patient organisation – Asthma UK

- Urgent need for more biologic treatment options
  - For those who are ineligible or do not respond to current biologic treatment
  - 80% of those currently eligible are not receiving biologic treatment
- Biologics are only made available to specific sub-populations and widening the eligibility criteria will increase the chance of finding an effective biologic that works
  - Offers a lifeline for some people ineligible for any biologic, who have no other choice but to take oral steroids
- In effect, except for biologic treatment, patients with severe asthma uncontrolled with inhaled steroids must rely on oral steroids

"I just wish I had been put on this biologic a lot sooner"

"Being on high doses of corticosteroids for such a long time has led to all sorts of health problems from their side effects"

"After just three injections, instead of contemplating taking early retirement from the midwifery job I love, I'm actually thinking about increasing the number of hours I do"

Patient expert feedback

- Prior to mepolizumab:
  - experienced regular debilitating asthma attacks and frequent hospitalisations leading to:
    - Regular time off school and work
    - Difficulty in exercising and participation in sports
  - Antibiotics and oral corticosteroids prescribed regularly
    - Led to weight gain and high blood pressure
  - Physical and psychological pressures had negative impact on quality of life
    - Immense stress caused by severity and uncertainty of condition
- Following successful participation in a clinical trial, on mepolizumab for 5 years
  - No side-effects and self injection extremely convenient
  - No hospitalisation, no prescribed oral corticosteroids
  - Lost weight, able to exercise, and blood pressure is back to normal
- Huge need for new, safe biologic treatments in asthma community
  - New generation of biologic treatments can be potentially transformative
    - Children and young people should not have to live with disability
    - Severe asthmatics should be able to contribute fully to the economy

Clinical expert feedback

- Morbidity and mortality due to asthma is mainly related to severe disease
- Severe asthma accounts for nearly 80% of asthma healthcare costs
- Pre-biologics, high proportion of patients required long-term oral corticosteroid (OCS) associated with well-known adverse effects
- Mepolizumab is established, highly effective and safe treatment
  - The treatment could be game changing for the right patient but benefit not captured well by patient reported outcome tools in general
  - Real-world: a large multicentre international study showed 69% reduction in exacerbations and a 50% reduction in oral corticosteroid dose with mepolizumab
- Currently some inequities in treatment of severe asthma, as mepolizumab can only be used with 4 or more exacerbations in the last year
  - Beralizumab and reslizumab can be used with 3 or more provided the eosinophil count is >400 cells/mcl
- Clinical community would like access to the different anti-IL-5s to be equitable
  - With similar efficacy, treatment criteria with biologics should be standardised

Current recommendations – based on trial populations and subgroups

	Mepolizumab (TA431)	Reslizumab (TA479)	Benralizumab (TA565)	
Population	Add-on therapy	Add-on therapy	Add-on therapy	
	as an option for treating severe refractory eosinophilic asthma			
Blood eosinophils (last 12 months)	≥300 cells/μL in the previous 12 months and	≥400 cells/μL in the previous 12 months and	≥300 cells/μL in the previous 12 months and	**≥400 cells/μL in the previous 12 months and**
Severe asthma exacerbations	≥4 needing corticosteroids in the previous 12 months	≥3 needing corticosteroids in the previous 12 months	≥4 needing corticosteroids in the previous 12 months	**≥3 needing corticosteroids in the previous 12 months**
Steroid dose requirement	Continuous OCS (at least prednisolone 5mg/day over the previous 6 months	NA	Continuous OCS (at least the equivalent of prednisolone 5mg/day over the previous 6 months	NA

ICS: Inhaled corticosteroids; NA: Not applicable; OCS: Oral corticosteroids; TA: Technology appraisal

Source: ID3750-Mepolizumab ERG Report v0.2 13.08.2020 [ACIC] Post FAC Clean – Table 1

Decision problem

	NICE scope	Company submission
Population	6 years+ with severe refractory eosinophilic asthma	**Adults** with severe refractory eosinophilic asthma with a **blood eosinophil count of ≥400 cells/µl and who have had ≥3 exacerbations in the previous 12 months**
Intervention	Mepolizumab	
Comparator(s)	• Reslizumab • Benralizumab • Optimised standard therapy without biologics	• Reslizumab • Benralizumab
Outcomes	• asthma control • incidence of clinically significant exacerbations • lung function • use of oral corticosteroids • patient and clinician evaluation of response • mortality • time to discontinuation • adverse effects of treatment • health-related quality of life	• asthma control • incidence of clinically significant exacerbations • lung function

Source: ID3750 Mepolizumab FTA Submission Document B v0.1 21.05.20 [CIC] - Table 1

Company's response to clarification:

"FTA submission only covers the adult population for the cost comparison as the comparators are currently recommended for the adult population only."

Company requests recommendation extension

- To align the recommendation for mepolizumab with benralizumab
  - **Blood eosinophil count of ≥400 cells/µl** and **≥3 exacerbations** in the previous 12 months
- Fast track appraisal route
  - Submitted cost-comparison for mepolizumab versus reslizumab and benralizumab
- Administration of three mepolizumab formulations explored
  - E.g. 100mg vial powder, 100mg pre-filled syringe, 100mg prefilled pen
    - Formulation likely to be predominantly used in practice is uncertain
    - Proportion of patients receiving the pen/syringe will self-administer is uncertain

Company's clinical effectiveness evidence

- No head to head trials available
- ITC used to compare clinical effectiveness of mepolizumab versus reslizumab and benralizumab

Clinical trials included in the ITC			
References of trial	**MPL**	**RSL**	**BRL**
MEA115588 [MENSA]	✓		
MUSCA	✓		
NCT00587288		✓	
Study 3081		✓	
Study 3082		✓	
Study 3083		✓	
Study 3084		✓	
SIROCCO			✓
CALIMA			✓

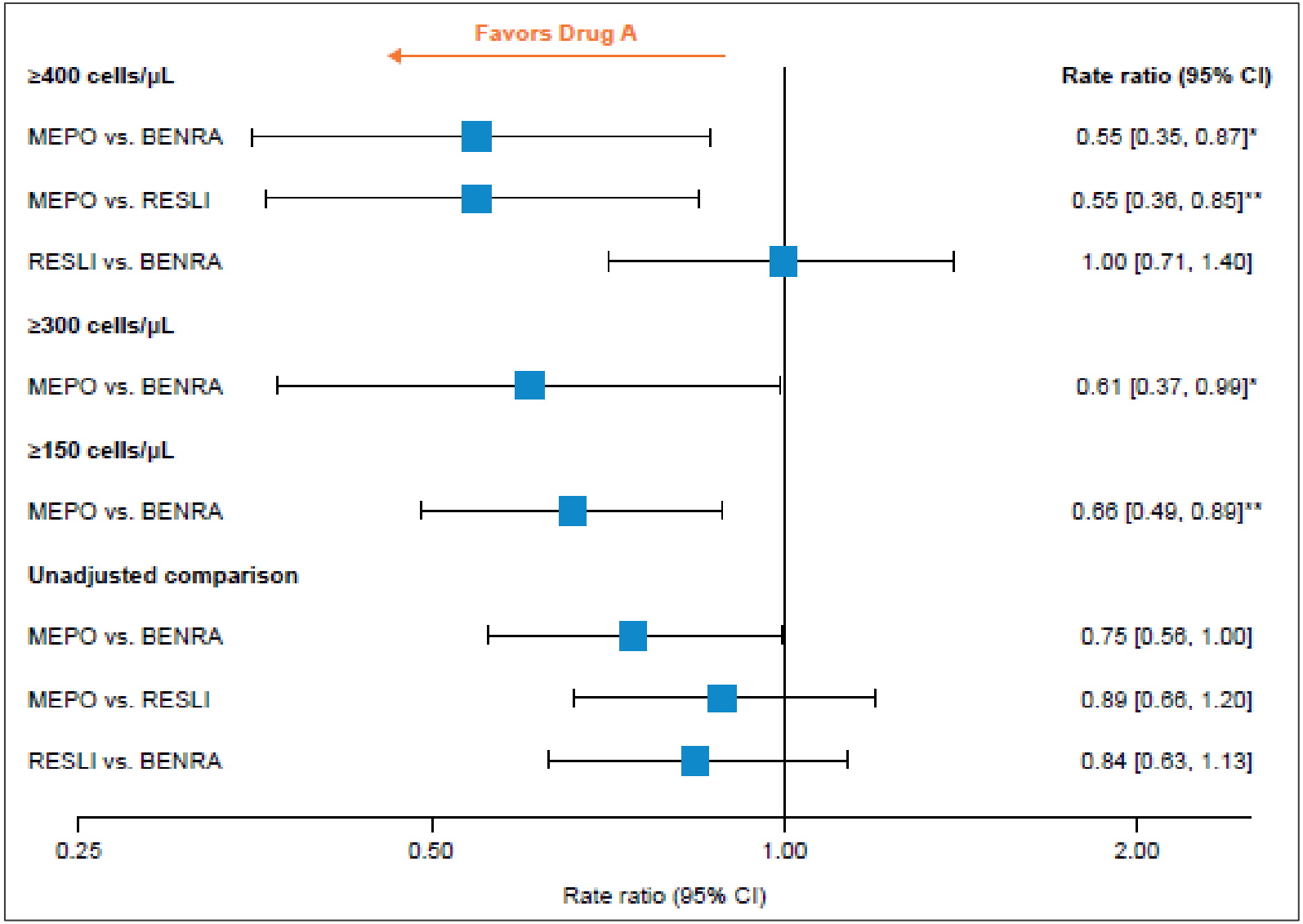
Source: ID3750 Mepolizumab FTA Submission Document B v0.1 21.05.20 [CIC] - Table 40

Analyses feasible							
Blood eosinophil count cells/μL	**≥150**	**≥300**	**≥300**	**≥300**	**≥400**	**≥400**	**≥400**
Exacerbations*	**–*** **	**–*** **	**≥3**	**≥4**	**–*** **	**≥3**	**≥4**
MPL vs BRL	✓	✓	✓	✓	✓	No data**	No data
MPL vs RSL	No data	No data	No data	No data	✓	No data**	✓
RSL vs BRL	No data	No data	No data	No data	✓	No data**	No data
MPL NICE rec				✓ TA431	Data presented	Target	
BRL NICE rec				✓ TA565		✓ TA565	
RSL NICE rec						✓ TA479	

BRL benralizumab; MPL, mepolizumab; RSL reslizumab; rec, recommendation; TA technology appraisal; vs versus
* Exacerbations needing corticosteroids in the previous 12 months; ** Data not consistently available for comparators; *** Not specified

ITC Results (1)

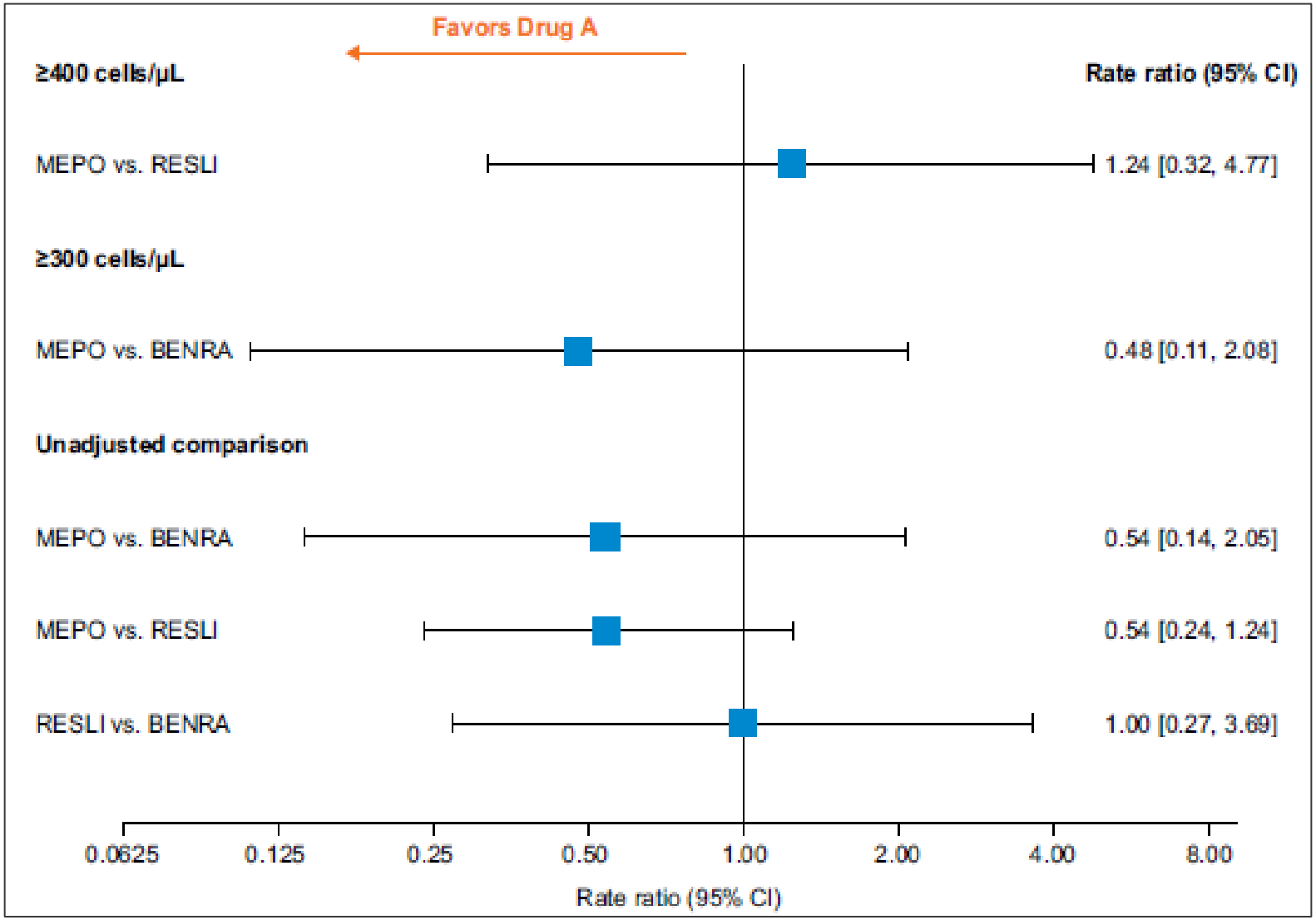
Rate of clinically significant exacerbations by baseline blood eosinophil count subgroups and in the intention to treat (ITT) population



Source: ID3750 Mepolizumab FTA Submission Document B v0.1 21.05.20 [CIC] – Figures 31

ITC Results (2)

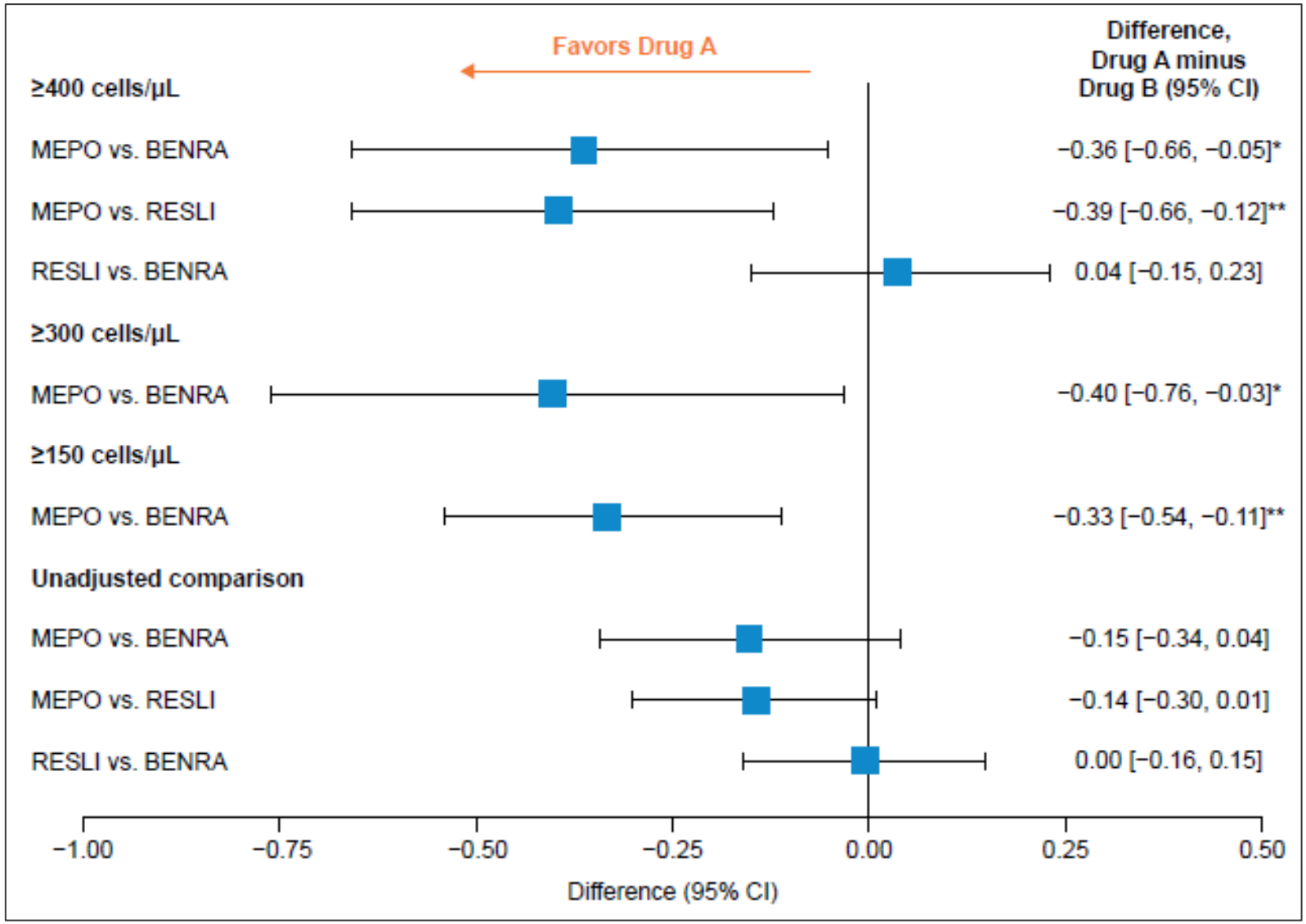
Rate of clinically significant Rate of exacerbations requiring A&E visits/hospitalisations by baseline blood eosinophil count subgroup and in the ITT population



Source: ID3750 Mepolizumab FTA Submission Document B v0.1 21.05.20 [CIC] – Figures 32

ITC Results (3)

Change from baseline in asthma control questionnaire (ACQ) score by baseline blood eosinophil count subgroups and in the ITT population



Source: ID3750 Mepolizumab FTA Submission Document B v0.1 21.05.20 [CIC] – Figure 33

ERG review – Clinical issue 1: evidence of effectiveness in the target group

Uncertainty in the effectiveness estimate relative to benralizumab or reslizumab in target subgroup of **blood eosinophil count ≥400 cells/µl & ≥3 exacerbations in last 12 months**	• Mepolizumab vs placebo: some analyses presented (including 2 RCTs) • **Mepolizumab vs benralizumab:** No data available • **Mepolizumab vs reslizumab:** No data available • **Benralizumab vs reslizumab:** No data available
Analyses for broader subgroup of **blood eosinophil count ≥400 cells/µl** presented.	• **Does not exactly align with the subgroup with target recommendation extension** • Participants in this subgroup had at least one (reslizumab) or two (mepolizumab and benralizumab) severe exacerbations in the previous 12 months
*Analyses also presented for a more restricted subgroup of **blood eosinophil count ≥400 cells/µl & ≥4 exacerbations in last 12 months***	• **Mepolizumab vs reslizumab**

Broader subgroup is in principle closer to recommendation extension subgroup

While it was not possible to comprehensively assess this in respect of the potential modification of treatment effect, the ERG considered that it would not substantively alter the conclusion regarding similar or greater effectiveness

ERG review – Clinical Issue 2: are the ITC results acceptable?

Limitations of ITC:

- Several potentially relevant trials excluded
  - DREAM and MENSA (75 mg dose mepolizumab treatment arm)
  - ZONDA and SIRIUS do not affect final ITC results – primary outcome different
  - ERG unable to assess the effect of exclusion of the DREAM and MENSA trials– lack of information from the company
- Between study variation: length of follow-up, dosing/administration, asthma severity, blood eosinophil counts, prior exacerbations
- Mepolizumab and benralizumab: data were from a subgroup of ITT population and standard statistical significance thresholds may not apply
- OCS use was not included as an outcome
  - May introduce some uncertainty around comparable efficacy with respect to steroid sparing effect

ERG regarded that the methods used for the ITC and the interpretation of the results were broadly appropriate

Clinical issue 3 – comparable efficacy assumption

Company's conclusion

- An assumption of at least similar efficacy can be made
  - It is likely, based on the ITC, that mepolizumab may provide superior benefit in some endpoints
    - E.g. the reduction in clinically significant exacerbations and patient-reported asthma control
  - In TA565, both the committee and the ERG concluded that mepolizumab and benralizumab have similar efficacy

ERG's conclusion

- Evidence indicates that there is a low risk that mepolizumab is less effective than other available anti-IL5 treatments for severe eosinophilic asthma as recommended by NICE

Is the committee satisfied with the evidence for similar efficacy of mepolizumab compared with comparators?

Company's cost-comparison analysis

Key assumptions

- 1-year model time horizon
- No costs were included other than anti-interleukin (IL) 5 treatments.
  - OCS related costs were not included in the analyses
  - Patients are seen by hospital consultants for asthma review at the same frequency across all anti-interleukin (IL) 5 treatments
  - No differences in adverse event costs
    - Safety profiles of all anti-interleukin (IL) 5 treatment are comparable
    - Recent Cochrane review found no excess serious AEs with any anti-IL-5 treatment
- Mean weight of 78 kg for the UK adult population used for costs of reslizumab

Cost of MPL vs BRL and RSL:

Administration and monitoring costs

	MPL 100 mg SC			BRL 30 mg SC		RSL 10 mg/ml IV***
Formulation	Powder for solution for injection	Pre-filled syringe or pen	Pre-filled syringe or pen: self-admin	Pre-filled syringe or pen	Pre-filled syringe or pen: self-admin	Concentration for solution infusion
Number of doses						
Year 1	13.0*	13.0*	13.0*	8.0**	8.0**	13.0*
Year 2+	13.0*	13.0*	13.0*	6.5**	6.5**	13.0*
Administration (administration/preparation/monitoring)						
Cost per dose, Doses 1 to 3	£47	£38	£38	£38	£38	£104
Cost per dose, Dose 4+	£19	£9	£0	£9	£0	£75
Administration costs Year 1	£330	£207	£113	£160	£113	£1,064
Administration costs Year 2+	£245	£122	£0	£61	£0	£979

BRL, benralizumab; IV, intravenous; MPL, mepolizumab; No, number; RSL, reslizumab; SC, subcutaneous; vs, versus
* Dose frequency every 4 weeks; ** Dose frequency every 4 weeks Doses 1 to 3 and every 8 weeks thereafter; *** Dose calculated based on mean weight 78 kg, i.e. 225 mg total dose of RSL

Company's base case – list price: MPL vs BRL and RSL: year 1

Technologies	Acquisition costs	Administration	Total costs	Incr. savings vs RSL	Incr. savings vs BRL
MPL 100mg powder vial (nurse admin.)	£10,920	£330	£11,250	£4,439	-
MPL 100mg pre-filled solution (nurse admin.)	£10,920	£207	£11,127	£4,562	-
MPL 100mg pre-filled solution (self admin. from dose 3 onwards)	£10,920	£113	£11,033	£4,656	-
RSL 10 mg/mL concentrate	£14,625	£1,064	£15,689	-	-
BRL 30 mg pre-filled (self admin.) vs MPL 100mg powder (nurse admin.)	£15,640	£113	£15,753	-	£4,503
BRL 30mg pre-filled vs MPL 100mg pre-filled (nurse admin.)	£15,640	£160	£15,800	-	£4,673
BRL 30mg pre-filled (self admin.) vs MPL 100mg pre-filled (self admin.)	£15,640	£113	£15,753	-	£4,720

BRL: Benralizumab; MPL: Mepolizumab; RSL: Reslizumab

Source: ID3750-Mepolizumab ERG Report v0.2 13.08.2020 [ACIC] Post FAC Clean – Table 11

Cost of MPL vs BRL and RSL: post year 1

Drug acquisition, administration and monitoring costs

	MPL 100 mg SC			BRL 30 mg SC		RSL 10 mg/ml IV***
Formulation	Powder for solution for injection	Pre-filled syringe or pen	Pre-filled syringe or pen: self-admin	Pre-filled syringe or pen	Pre-filled syringe or pen: self-admin	Concentration for solution infusion
Drug acquisition cost (list price)						
Cost Year 1	£10,920	£10,920	£10,920	£15,640	£15,640	£14,625
Cost Year 2	£10,920	£10,920	£10,920	£12,708*	£12,708*	£14,625
Administration (administration/preparation/monitoring)						
Admin costs Year 1	£330	£207	£113	£160	£113	£1,064
Admin costs Year 2+	£245	£122	£0	£61	£0	£979
Total costs						
Year 1	£11,250	£11,127	£11,033	£15,800	£15,753	£15,689
Year 2+	£11,165	£11,042	£10,920	£12,769*	£12,708*	£15,604

BRL, benralizumab; IV, intravenous; MPL, mepolizumab; No, number; RSL, reslizumab; SC, subcutaneous; vs, versus
* Dose frequency every 4 weeks Doses 1 to 3 and every 8 weeks thereafter for Year 2+ dose based on average of Year 2 and Year 3, 6.5 for this calculation

ERG Review – Cost comparison issue 1: Is 1-year time horizon sufficient?

- Some uncertainty as to whether a one-year time horizon is sufficient to capture the key differences in costs between treatments over time
  - Differences in dosing frequency and administration between treatments are likely to persist over time
- Conducted scenario analysis with 10-year time horizon
  - Costs not discounted

Mepolizumab 100mg remained cost saving versus both benralizumab and reslizumab

ERG Scenario: 10-year time horizon – list price: MPL vs RSL and BRL

Technologies	Acquisition costs	Administration	Total costs	Incr. savings vs RSL	Incr. savings vs BRL
MPL 100mg powder (nurse admin.)	£109,200	£2,533	£111,733	£44,391	-
MPL 100mg pre-filled solution	£109,200	£1,309	£110,509	£45,615	-
MPL 100mg pre-filled solution (self admin. from dose 3 onwards)	£109,200	£113	£109,313	£46,811	-
RSL 10 mg/mL concentrate	£146,246	£9,878	£156,124	-	-
BRL 30 mg pre-filled (self admin.) vs MPL 100mg powder (nurse admin.)	£130,985	£113	£131,098	-	£19,365
BRL 30mg pre-filled vs MPL 100mg pre-filled	£130,985	£716	£131,701	-	£21,192
BRL 30mg pre-filled (self admin.) vs MPL 100mg pre-filled (self admin.)	£130,985	£113	£131,098	-	£21,785

BRL: Benralizumab; MPL: Mepolizumab; RSL: Reslizumab

Source: ID3750-Mepolizumab ERG Report v0.2 13.08.2020 [ACIC] Post FAC Clean – Table 13

Cost comparison issue 2: self-administration Clinical advise to the ERG

- **Proportion of people self-administering**
  - Currently, 100% patients administer in home setting
    - 90% estimated to self-administer
    - 10% require nurse support – provided by company
  - People who preferred clinic contact prior to Covid-19 are now administering at home
    - Expect few patients to revert to attend clinic in the future
- **Self-administration training**
  - In clinic setting across 50% appointments
  - Patients being set-up for self-administration would require slightly longer appointments
- **Self administration follow-up/monitoring**
  - Currently, remote follow-up every 6 months
  - Prior to Covid-19 this would have been done in the clinic setting
- **Savings related to self-administration**
  - Largest impact in secondary care, specifically savings in respect of nurse and pharmacy time
    - Each nurse prescription appointment requires a small amount of consultant time
    - Savings in pharmacy time to prepare and dispense, and nurse time related to administration
  - In home setting, prescriptions are delivered by the pharmacy free of charge

Key Issues – recap

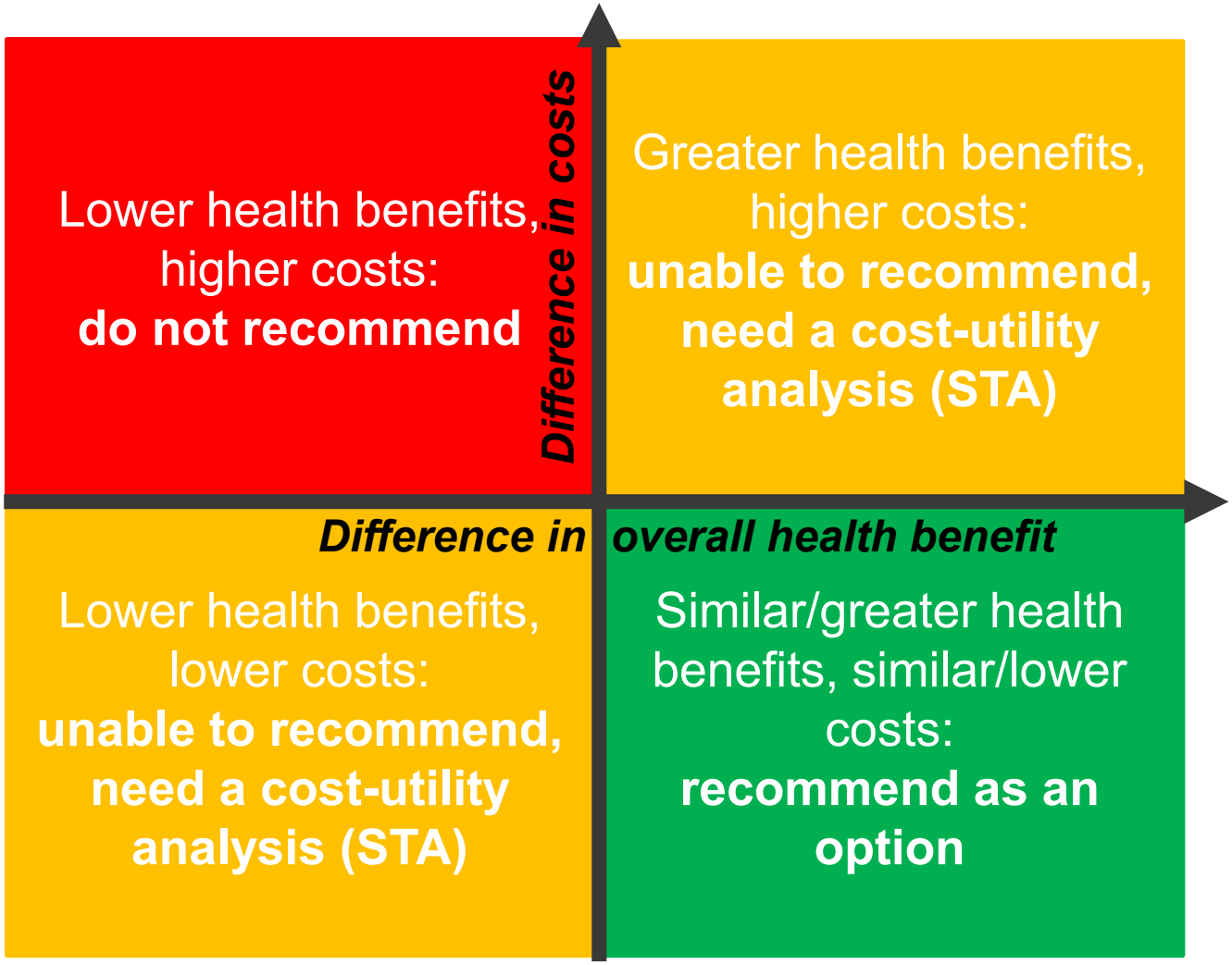
Clinical issues

- **Issue 1:** Is the evidence sufficient for a subgroup of adults with baseline eosinophils ≥400 cells/μl and ≥3 severe exacerbations needing corticosteroids in the previous 12 months? Can mepolizumab be recommended in the same way as TA565 and TA479?
- **Issue 2:** Does the committee accept the design and reliability of the company's indirect treatment comparison (ITC)?
- **Issue 3:** Is the committee satisfied with the evidence for similar efficacy of mepolizumab compared with comparators? (comparable efficacy assumption)

Cost comparison issues

- **Issue 1:** Is 1-year time horizon sufficient?
- **Issue 2:** How useful/cost saving is self administration?

Potential recommendations: cost comparison



Cost of mepolizumab vs benralizumab and reslizumab: using list price post year 1

Difference by MPL formulation vs BRL formulation and RSL in Year 1 and Year 2+

	BRL prefilled		BRL self-admin		RSL	
	Year 1	Year 2	Year 1	Year 2	Year 1	Year 2
MPL vs	−£4,551*	−£1,604*	−£4,503*	−£1,543*	−£4,439*	−£4,439*
MPL prefilled vs	−£4,673*	−£1,726*	NA	−£1,665*	−£4,562*	−£4,562*
MPL self-admin vs	NA	NA	−£4,720*	−£1,788*	−£4,656*	−£4,684*

BRL, benralizumab; MPL, mepolizumab; RSL, reslizumab; vs, versus
* Denotes incremental savings with mepolizumab

NICE

ERG Review – OCS related healthcare costs

- Clinical advice to ERG: patients who do not respond to anti-IL-5 treatments are likely to require treatment with a low dose of OCS indefinitely, resulting in healthcare costs associated with adverse effects.
  - OCS related healthcare costs excluded and OCS not included as an outcome.
  - ERG scenario analysis: 20% of mepolizumab patients incur costs associated with continuous OCS use.
    - Assumes that mepolizumab was less effective than both comparators for OCS reduction.
    - Estimated annual OCS cost to be £58
    - Assumed these patients incur intensive resource use costs associated with OCS treatment (£4,533)

Mepolizumab 100mg remained cost saving versus both benralizumab and reslizumab

ERG Scenario: OCS related costs – list price

Technologies	Acquisition costs	Admin. costs	OCS related costs	Total costs	Incr. savings vs RSL	Incr. savings vs BRL
MPL 100mg powder (nurse admin.)	£10,920	£330	£918	£12,168	£3,521	-
MPL 100mg pre-filled solution	£10,920	£207	£918	£12,045	£3,643	-
MPL 100mg pre-filled solution (self admin. from dose 3 onwards)	£10,920	£113	£918	£11,951	£3,738	-
RSL 10 mg/mL concentrate	£14,625	£1,064	£0	£15,689	-	-
BRL 30 mg pre-filled (self admin.) vs MPL 100mg powder (nurse admin.)	£15,640	£113	£0	£15,753	-	£3,585
BRL 30mg pre-filled vs MPL 100mg pre-filled	£15,640	£160	£0	£15,800	-	£3,755
BRL 30mg pre-filled (self admin.) vs MPL 100mg pre-filled (self admin.)	£15,640	£113	£0	£15,753	-	£3,802

BRL: Benralizumab; MPL: Mepolizumab; OCS: Oral corticosteroids RSL: Reslizumab

Source: ID3750-Mepolizumab ERG Report v0.2 13.08.2020 [ACIC] Post FAC Clean – Table 15