Original Article

Evaluation of Potential Continuation Rules for Mepolizumab Treatment of Severe Eosinophilic Asthma

Necdet B. Gunsoy, PhD[a], Sarah M. Cockle, PhD[b], Steven W. Yancey, MSc[c], Oliver N. Keene, MSc[a], Eric S. Bradford, MD[d], Frank C. Albers, PhD[d], and Ian D. Pavord, FMedSci[e] *Middlesex and Oxford, United Kingdom; and Research Triangle Park, NC*

What is already known about this topic? The early identification of patients likely to receive long-term benefit from treatment is important to minimize unnecessary treatment, but this identification must avoid selecting less severe patients and discontinuing patients benefiting from treatment.

What does this article add to our knowledge? This analysis provides a method for assessing continuation rules that measure the impact of the rules while controlling for placebo responses. There was no evidence of a reliable rule predicting long-term exacerbation reduction from mepolizumab.

How does this study impact current management guidelines? This analysis shows no evidence that any continuation rule adds value to established initiation criteria for mepolizumab treatment, which include a history of exacerbations and appropriate blood eosinophil count in patients with severe eosinophilic asthma.

BACKGROUND: Mepolizumab significantly reduces exacerbations in patients with severe eosinophilic asthma. The early identification of patients likely to receive long-term benefit from treatment could ensure effective resource allocation.
OBJECTIVE: To assess potential continuation rules for mepolizumab in addition to initiation criteria defined as 2 or more exacerbations in the previous year and blood eosinophil counts of 150 cells/μL or more at initiation or 300 cells/μL or more in the previous year.
METHODS: This *post hoc* analysis included data from 2 randomized, double-blind, placebo-controlled studies (NCT01000506 and NCT01691521) of mepolizumab in patients with severe eosinophilic asthma (N = 1,192). Rules based on blood eosinophils, physician-rated response to treatment, FEV_1, Asthma Control Questionnaire (ACQ-5) score, and exacerbation reduction were assessed at week 16. To assess these rules, 2 key metrics accounting for the effects observed in the placebo arm were developed.
RESULTS: Patients not meeting continuation rules based on physician-rated response, FEV_1, and the ACQ-5 score still derived long-term benefit from mepolizumab. Nearly all patients failing to reduce blood eosinophils had counts of 150 cells/μL or less at baseline. For exacerbations, assessment after 16 weeks was potentially premature for predicting future exacerbations.
CONCLUSION: There was no evidence of a reliable physician-rated response, ACQ-5 score, or lung function–based continuation rule. The added value of changes in blood eosinophils at week 16 over baseline was marginal. Initiation criteria for mepolizumab treatment provide the best method for assessing patient benefit from mepolizumab treatment, and treatment continuation should be reviewed on the basis of a predefined reduction in long-term exacerbation frequency and/or oral corticosteroid dose. **(J Allergy Clin Immunol Pract 2018;6:874-82)**

Key words: *Severe asthma; Anti–IL-5; mAb; Continuation; Response*

Mepolizumab is a first-in-class anti–IL-5 mAb used as add-on therapy for the treatment of severe eosinophilic asthma. Previous studies have shown significantly reduced exacerbation rates for

[a]Clinical Statistics, GlaxoSmithKline, Stockley Park, Uxbridge, Middlesex, United Kingdom
[b]Value Evidence and Outcomes, GlaxoSmithKline, Brentford, Middlesex, United Kingdom
[c]Respiratory Therapeutic Area, GlaxoSmithKline, Research Triangle Park, NC
[d]Respiratory Medical Franchise, GlaxoSmithKline, Research Triangle Park, NC
[e]Respiratory Medicine Unit, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom
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Corresponding author: Necdet B. Gunsoy, PhD, Clinical Statistics, GSK, Stockley Park West, 1-3 Ironbridge Rd, Uxbridge, Middlesex UB11 1BT, UK. E-mail: necdet.b.gunsoy@gsk.com.
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Abbreviations used
ACQ-5- 5-item Asthma Control Questionnaire
IV- Intravenous
PARR- Placebo-adjusted rate ratio
RR- Rate ratio
RRNC- Rate ratio for noncontinuers
SC- Subcutaneous

mepolizumab compared with optimized standard of care plus placebo.[1,2]

For mAb treatments, there is a desire to identify markers that could be used as a continuation rule after treatment initiation to identify patients likely to receive benefit from ongoing treatment. This is important to ensure the benefit-risk balance in treated patients and effective allocation of limited health care resources.

The mepolizumab clinical development program endeavored to develop and validate markers that would effectively identify patients likely to respond to treatment before treatment initiation. Although several baseline characteristics were found to predict treatment benefit in Dose Ranging Efficacy And Safety with Mepolizumab in Severe Asthma (DREAM),[1] meeting specific blood eosinophil thresholds before treatment initiation was identified as the most predictive biomarker of response to mepolizumab in patients with severe eosinophilic asthma and 2 or more exacerbations in the previous 12 months despite high-dose inhaled corticosteroids and additional controller(s). Criteria of 150 cells/μL or more at initiation or 300 cells/μL or more in the previous 12 months were shown to select patients most likely to receive benefit from mepolizumab therapy. These predictive thresholds were confirmed in the subsequent Efficacy and Safety Study of Mepolizumab Adjunctive Therapy in Subjects with Severe Uncontrolled Refractory Asthma (MENSA) study.[2]

An alternative or potential adjunct to this approach is to use a posttreatment continuation rule to identify patients unlikely to receive therapeutic benefit with continued treatment. A continuation rule should ensure that patients who continue treatment are receiving benefit from the introduction of the rule beyond that observed among patients on placebo, and that patients who should stop treatment are not receiving treatment benefit compared with patients on placebo who do not meet the rule. Because the primary aim of mepolizumab treatment is to reduce the frequency of exacerbations, an evaluation of long-term treatment response should be based on exacerbations. This *post hoc* analysis assessed to what extent clinical markers and biomarkers measured 16 weeks after treatment initiation meet the criteria for an appropriate continuation rule.

METHODS

Included studies

Studies included in this analysis were DREAM (GSK/ClinicalTrials.gov identifier: MEA112997/NCT01000506)[1] and MENSA (GSK/ClinicalTrials.gov identifier: MEA115588/NCT01691521).[2] Inclusion criteria for DREAM and MENSA are summarized in this article's Online Repository at www.jaci-inpractice.org.[1,2] The rate of clinically significant exacerbations was the primary end point for both studies.

Patients

Patients from the intent-to-treat populations of DREAM and MENSA were included in this *post hoc* analysis if they had a blood eosinophil count of 150 cells/μL or more at screening or 300 cells/μL or more in the past year; had continued on treatment after the week 16 visit; and had sufficient data for evaluation of a continuation rule. Patients assigned to the 100-mg subcutaneous (SC) or the 75-mg intravenous (IV) doses from either study were included in the analysis because the 2 doses give comparable pharmacokinetic exposure. Mepolizumab 75-mg IV and 100-mg SC doses were combined for analysis in MENSA.

Outcomes assessed to define continuation rules

Patients were classified according to whether they met a potential continuation rule based on values recorded at week 16, which are as follows:

1. *Blood eosinophils:* Change from baseline blood eosinophils, expressed as the ratio at week 16 and baseline, was selected because of the mechanism of action of mepolizumab. Absolute change was not considered because of dependencies with baseline count. Thresholds considered were a reduction of 20% or more, 40% or more, 60% or more, and 80% or more.
2. *Physician-rated response to treatment:* Physicians were asked to assess patients' response to treatment at week 16. The measure comprised 7 levels (significantly improved, moderately improved, mildly improved, no change, mildly worse, moderately worse, and significantly worse) and is closest to the Global Evaluation of Treatment Effectiveness, used in omalizumab studies.[3,4] The thresholds considered were moderately to significantly improved as well as any improvement (ie, mildly to significantly improved).
3. *Asthma control:* The Asthma Control Questionnaire (ACQ-5) was administered at baseline and each following visit. The minimum important difference for this questionnaire is 0.5.[5] An improvement of 0.5 or more points from baseline was therefore considered.
4. *Lung function:* Pulmonary function was evaluated at baseline and each following visit. A widely accepted threshold indicative of a meaningful improvement was not available. Therefore, thresholds considered were an improvement of 80 mL or more and 10% or more from baseline in prebronchodilator FEV_1.
5. *Exacerbations:* No change or a reduction in annualized frequency of exacerbations from baseline to week 16 compared with the previous year was considered.

Continuation rule assessment

The rate of clinically significant exacerbations after assessment (week 16) to end of study (week 32 for MENSA, week 52 for DREAM) was used as the long-term outcome to assess continuation rules.

Two measures were used to assess the performance of a potential continuation rule: the placebo-adjusted rate ratio (PARR) and the rate ratio for noncontinuers (RRNC) (Figure 1). A practical example comparing these measures to previously used measures is presented in this article's Online Repository at www.jaci-inpractice.org.

The PARR is the ratio of the effect of the continuation rule with mepolizumab compared with placebo. It provides a metric for the performance of the continuation rule among patients on mepolizumab that is adjusted for the impact of the continuation rule among patients on placebo; a value less than 1 indicates specific treatment-associated benefit (Figure 1). This placebo adjustment avoids selection of a rule that discontinues patients more likely to exacerbate regardless of treatment. A PARR of 0.8 or less was considered indicative of a potentially useful continuation rule, where patients meeting the rule show a reduction of 20% or more in

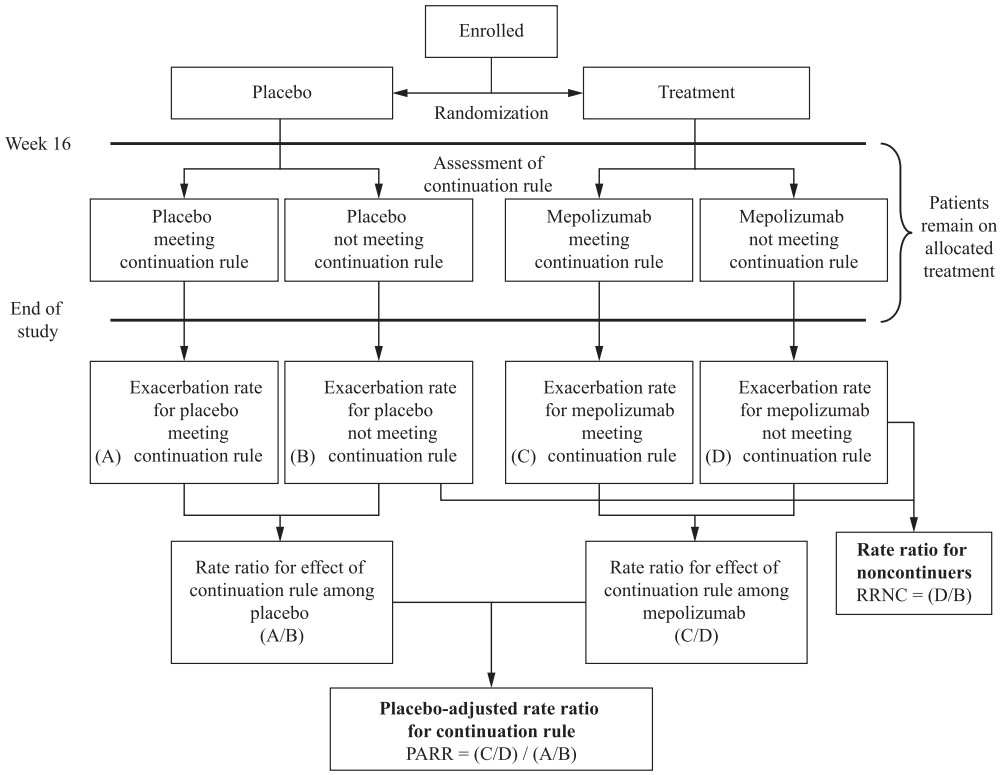

FIGURE 1. Illustration of measures to assess the performance of continuation rules using data from randomized controlled trials.

exacerbation rates after accounting for the effect among patients on placebo.

The RRNC is the ratio of exacerbation rates among patients not meeting the continuation rule on mepolizumab and placebo (Figure 1). This ratio provides an indication of whether patients on mepolizumab who would have discontinued treatment (had the continuation rule been applied) actually experience long-term benefit from treatment during the remaining study period. An RRNC of close to 1 ($\geq$0.8) was considered indicative of a potentially useful continuation rule, where patients on mepolizumab not meeting the continuation rule have similar outcomes to patients on placebo not meeting the rule and are therefore not benefiting from treatment.

Figure 2 describes the criteria used to facilitate the assessment of continuation rules. For PARR, an estimate of 0.8 or less was set as a threshold for meeting the criterion. For RRNC, this was an estimate of 0.8 or more with a 95% CI that excludes no effect (RRNC = 1).

Statistical analysis

Analyses were performed using negative binomial regression including data on exacerbations from assessment to end of study. The log of time on treatment was included as an offset variable. The rate ratio (RR) for the effect of the continuation rule was estimated separately for each treatment group by including a covariate of meeting continuation rule. The point estimate of the PARR is the ratio of these 2 values, and the SE is the square root of the sum of variances. The RRNC was obtained in a model including all patients who did not meet the continuation rule only with covariate of treatment.

RESULTS

The intent-to-treat population comprised 616 and 576 patients in DREAM and MENSA, respectively (Table I), of whom 246 and 576 were included in the analysis (Figure 3). Demographic characteristics were similar in both studies. Patients on mepolizumab were more likely to meet the continuation rules than patients on placebo in both studies (Table II).

A summary of the assessment of continuation rules is presented in Table III. To illustrate, the assessment procedure for the 20% or more reduction from baseline blood eosinophils rule was as follows: patients on mepolizumab who met the rule had a 78% (PARR, 0.22; 95% CI, 0.10-0.50) and 27% (PARR, 0.73; 95% CI, 0.20-2.67) incremental reduction in exacerbations compared with patients on mepolizumab who did not meet the rule in excess of the corresponding reduction among patients on placebo in MENSA and DREAM, respectively (Figure 4). Patients on mepolizumab who did not meet the rule had a 75% (RRNC, 1.75; 95% CI, 0.90-3.41) increased and 21% (RRNC, 0.79; 95% CI, 0.27-2.35) decreased risk of exacerbations compared with patients on placebo who did not meet the rule in MENSA and DREAM, respectively. Criteria for a PARR less than 0.8 were met in both studies; however, criteria for an RRNC of 0.8 or more were met only in MENSA, and therefore the overall criteria for an appropriate continuation rule were not met. High levels of uncertainty may have been due to small patient numbers on mepolizumab who failed the continuation rule (24 [7%] for MENSA and 6 [5%] for DREAM; Table II).

Figure 4 presents results for continuation rules based on blood eosinophil counts. The PARR was similar across eosinophil reduction thresholds for both studies. Results for MENSA were 0.6 or less (strong evidence) for all thresholds considered. Estimates for DREAM were less than 0.8 for 2 of the 4 rules. The RRNC decreased as the reduction thresholds increased. Continuation rules based on reduction in eosinophils from

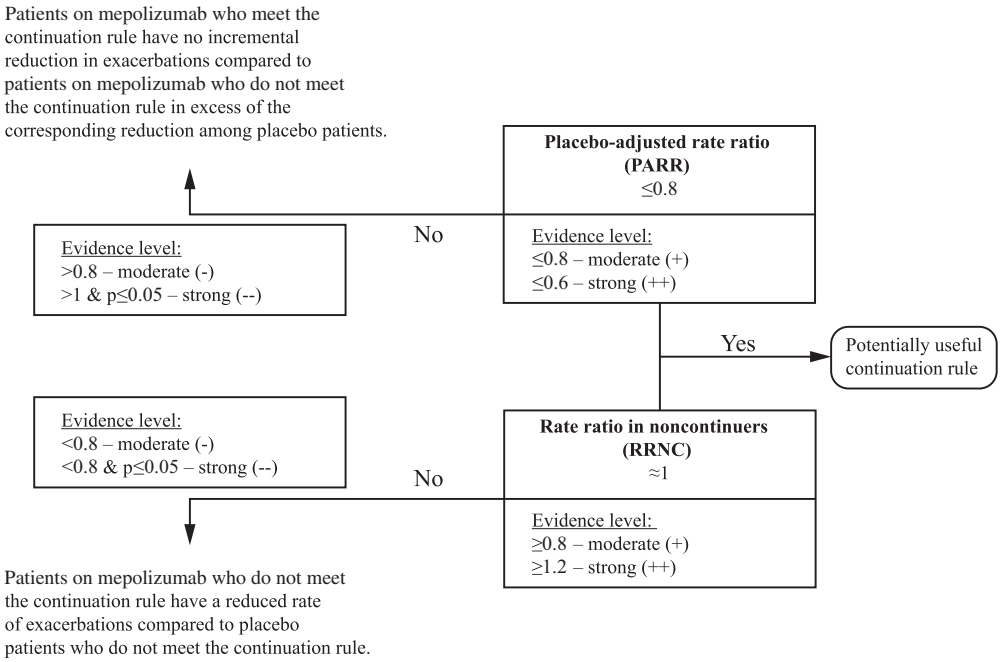

FIGURE 2. Illustration of criteria used for the assessment of continuation rules, describing thresholds for meeting each criterion, level of evidence for that criterion, and interpretation when criterion not met.

TABLE I. Baseline characteristics of patients in included studies

Characteristic	DREAM (N = 616)	MENSA (N = 576)
Sex: female, n (%)	387 (63)	328 (57)
Age (y), mean ± SD	49 ± 11	50 ± 14
Baseline blood eosinophils, geometric mean ± SD (log)	250 ± 1.03	290 ± 0.99
Patients on maintenance OCS, n (%)	188 (31)	144 (25)
Baseline ACQ-5 score, mean ± SD	2.4 ± 1.1	2.2 ± 1.2
Baseline prebronchodilator FEV_1 (mL), mean ± SD	1,880 ± 660	1,816 ± 666
Baseline percent predicted prebronchodilator FEV_1, mean ± SD	60 ± 16	61 ± 18

OCS, Oral corticosteroid.

baseline did not meet the criteria for an appropriate rule particularly because patients on mepolizumab who did not meet the reduction thresholds had a reduction in exacerbations compared with patients on placebo who did not meet the same thresholds in DREAM (Table III).

Results for continuation rules based on physician-rated response are presented in Figure 5. The criteria for PARR were not met in all cases except in MENSA for "any improvement." The RRNC was less than 0.8 in all cases, meaning that patients on mepolizumab who did not meet the continuation rule had a reduction in exacerbations compared with patients on placebo who did not meet the rule. Therefore, physician-rated response-based continuation rules did not meet the criteria for an appropriate rule.

Results for the remaining continuation rules are also shown in Figure 5. Continuation rules based on the ACQ-5 score (≥0.5-point improvement) and FEV_1 (defined as ≥80 mL or ≥10%) did not meet the criteria for useful rules because the RRNCs were less than 0.8, meaning that patients on mepolizumab who did not meet the continuation rule had reduction in exacerbations compared with patients on placebo who did not meet the rule. The rule based on exacerbation frequency (no change or a reduction from baseline to week 16 compared with the previous year) met the criteria for a potentially useful rule in DREAM but not in MENSA: the PARR was 0.60 in both studies, and the RRNC was 0.79 and 0.92 in MENSA and DREAM, respectively.

DISCUSSION

Mepolizumab as an add-on therapy for the treatment of severe eosinophilic asthma is aimed at reducing exacerbations and has a well-defined set of criteria for treatment initiation: a blood eosinophil count of 150 cells/μL or more at screening or 300 cells/μL or more in the past year, and 2 or more exacerbations in the previous year despite regular use of intensive anti-inflammatory and controller asthma medicines. These criteria were developed on the basis of results from DREAM and formed part of the inclusion criteria for MENSA, confirming these criteria as a useful starting rule.

The ideal patient scenario for a therapeutic intervention would be specific selection criteria with a clear prediction of clinical benefit; however, assessment of therapeutic benefit after initiation of chronic treatment is an important part of patient care. To aid physician assessment, a continuation rule for chronic-use medicines is desirable to avoid prolonged treatment in patients not receiving benefit from therapy. This is particularly salient for biological treatments because the cost of treatment is generally significantly greater than that of nonbiological treatments. However, the development of a continuation rule must be

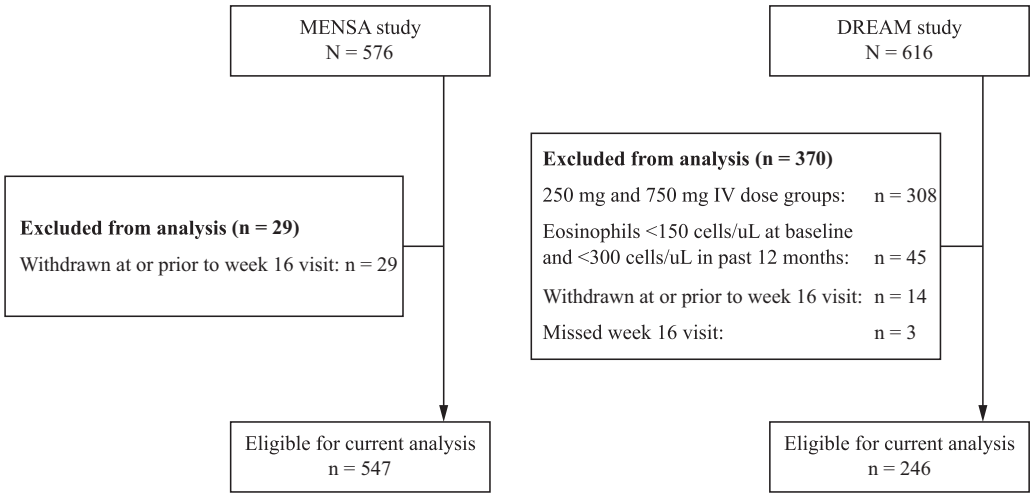

FIGURE 3. Summary of patients included in the assessment of potential continuation rules.

TABLE II. Summary of the number of patients meeting the continuation rule by study and treatment group

Assessment of continuation rule at week 16	DREAM (N = 263)				MENSA (N = 576)			
	Placebo (n = 126)		Mepolizumab (n = 120)		Placebo (n = 182)		Mepolizumab (n = 365)	
	Met, n (%)	Not met, n (%)	Met, n (%)	Not met, n (%)	Met, n (%)	Not met, n (%)	Met, n (%)	Not met, n (%)
Reduction to baseline blood eosinophils (%)								
≥20% reduction	54 (45)	65 (66)	110 (95)	6 (5)	78 (45)	95 (55)	327 (93)	24 (7)
≥40% reduction	36 (30)	83 (70)	107 (92)	9 (8)	54 (31)	119 (69)	316 (90)	35 (10)
≥60% reduction	25 (21)	94 (79)	97 (84)	19 (16)	31 (18)	142 (82)	297 (85)	54 (15)
≥80% reduction	12 (10)	107 (90)	72 (62)	44 (38)	16 (9)	157 (91)	210 (60)	141 (40)
Physician-rated response to treatment								
Moderately to significantly improved	41 (33)	85 (67)	64 (53)	56 (47)	52 (29)	128 (71)	188 (52)	177 (48)
Any improvement	76 (60)	50 (40)	88 (73)	32 (27)	106 (59)	74 (41)	282 (77)	83 (23)
ACQ-5 score								
≥0.5-point improvement	62 (52)	58 (48)	70 (60)	46 (40)	89 (51)	84 (49)	210 (61)	134 (39)
Prebronchodilator FEV_1								
≥80 mL improvement	60 (48)	66 (52)	63 (53)	57 (48)	94 (52)	88 (48)	212 (58)	153 (42)
≥10% improvement	49 (39)	77 (61)	53 (44)	67 (56)	76 (40)	106 (55)	172 (45)	193 (50)
Exacerbations from baseline to study visit								
No change or reduction from previous year	86 (68)	40 (32)	103 (86)	17 (14)	125 (69)	57 (31)	305 (84)	60 (16)

Note. Numbers do not always add up to treatment headers because of missing baseline or week 16 values.

considered carefully so that patients benefiting from treatment are not prematurely discontinued.

This *post hoc* analysis investigated potential rules assessed 16 weeks after starting treatment that could identify patients who do not benefit from treatment in terms of exacerbation reduction. The PARR assessed whether these rules identify patients receiving long-term benefit beyond what was observed among patients on placebo. The RRNC assessed whether patients who do not meet these rules still received benefit from treatment with mepolizumab when compared with patients on placebo who do not meet these rules.

Results from DREAM and MENSA were generally consistent, although some deviations emerged for rules based on eosinophils and FEV_1. The observed differences were not statistically meaningful, and any attributable differences remain unknown but could result from differences in the populations including difference in baseline oral corticosteroids use. Continuation rules based on a reduction from baseline blood eosinophils met criteria for PARR and RRNC in MENSA but not in DREAM. Blood eosinophils are a known predictor of treatment response to mepolizumab[1,2,6]; it would therefore be important to understand whether these continuation rules supplement baseline information. In MENSA, of the patients on mepolizumab with a baseline blood eosinophil count of less than 150 cells/μL, 29% (22/76) did not experience 20% or more reduction in eosinophils at week 16, compared with less than 1% (2/275) with a baseline

TABLE III. Overall summary of assessment of continuation rules by individual assessment criteria

	Assessment criteria				Potentially useful continuation rule	
	PARR		RRNC			
Continuation rule at week 16	MENSA	DREAM	MENSA	DREAM	MENSA	DREAM
Reduction in blood eosinophils (%)						
≥20% reduction	++	+	++	−	Yes	No
≥40% reduction	++	−	++	−	Yes	No
≥60% reduction	++	−	++	−	Yes	No
≥80% reduction	++	+	+	−−	Yes	No
Physician-rated response to treatment						
Moderately to significantly improved	−	−	−−	−−	No	No
Any improvement	++	+	−	−	No	No
ACQ-5 score						
≥0.5-point improvement	++	+	−	−	No	No
Prebronchodilator FEV_1						
≥80 mL improvement	++	−	−	−−	No	No
≥10% improvement	++	−	−−	−−	No	No
Exacerbations						
No change or reduction in exacerbations up to week 16	++	++	−	+	No	Yes

Note. Indicators: +, some evidence for meeting criteria; ++, strong evidence for meeting criteria; −, some evidence for not meeting criteria; −−, strong evidence for not meeting criteria.

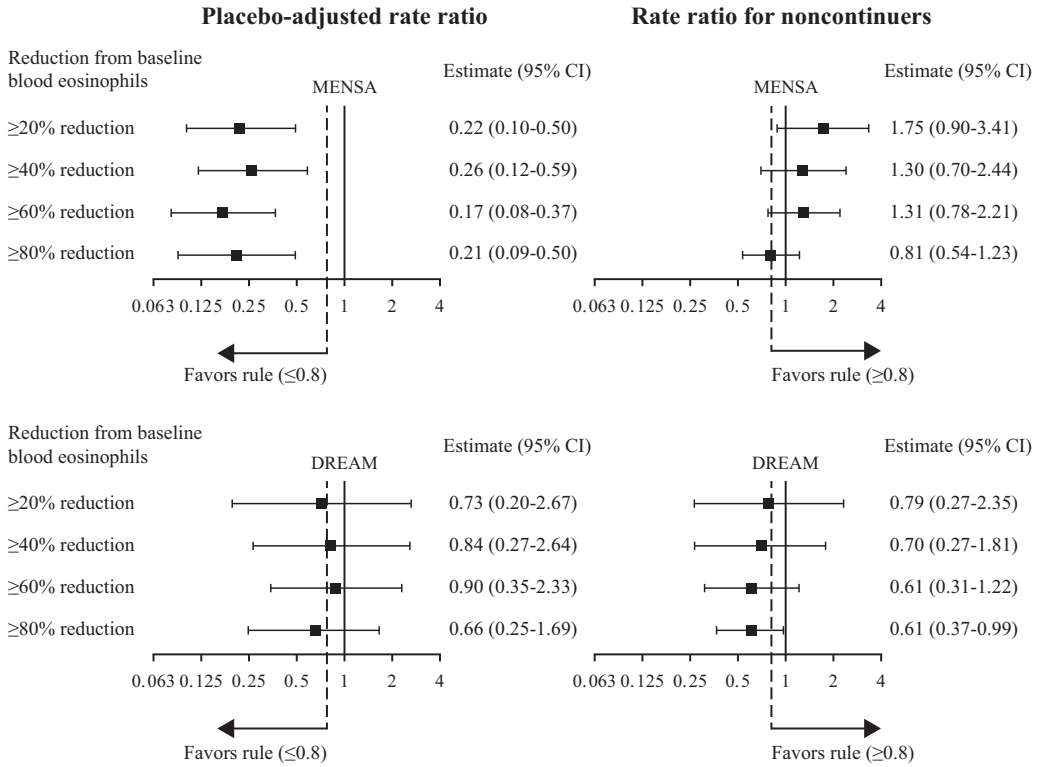

FIGURE 4. Results of the assessment of potential continuation rules based on a reduction from baseline blood eosinophils at week 16 after initiation of treatment. The PARR and the RRNC are described in the Methods section. A useful continuation rule should have a PARR of ≤0.8 and an RRNC of ≥0.8. The RRNC decreased as the threshold for reduction in eosinophils increased. All rules met the criteria on PARR and RRNC for MENSA, but not for DREAM.

blood eosinophil count of 150 cells/μL or more. A continuation rule based on eosinophil reduction is therefore unlikely to provide any added benefit for patients with a baseline blood eosinophil count of 150 cells/μL or more. In the subgroup of patients with less than 150 cells/μL, the PARR and RRNC estimates were 0.17 (95% CI, 0.05-0.55) and 1.50 (95% CI,

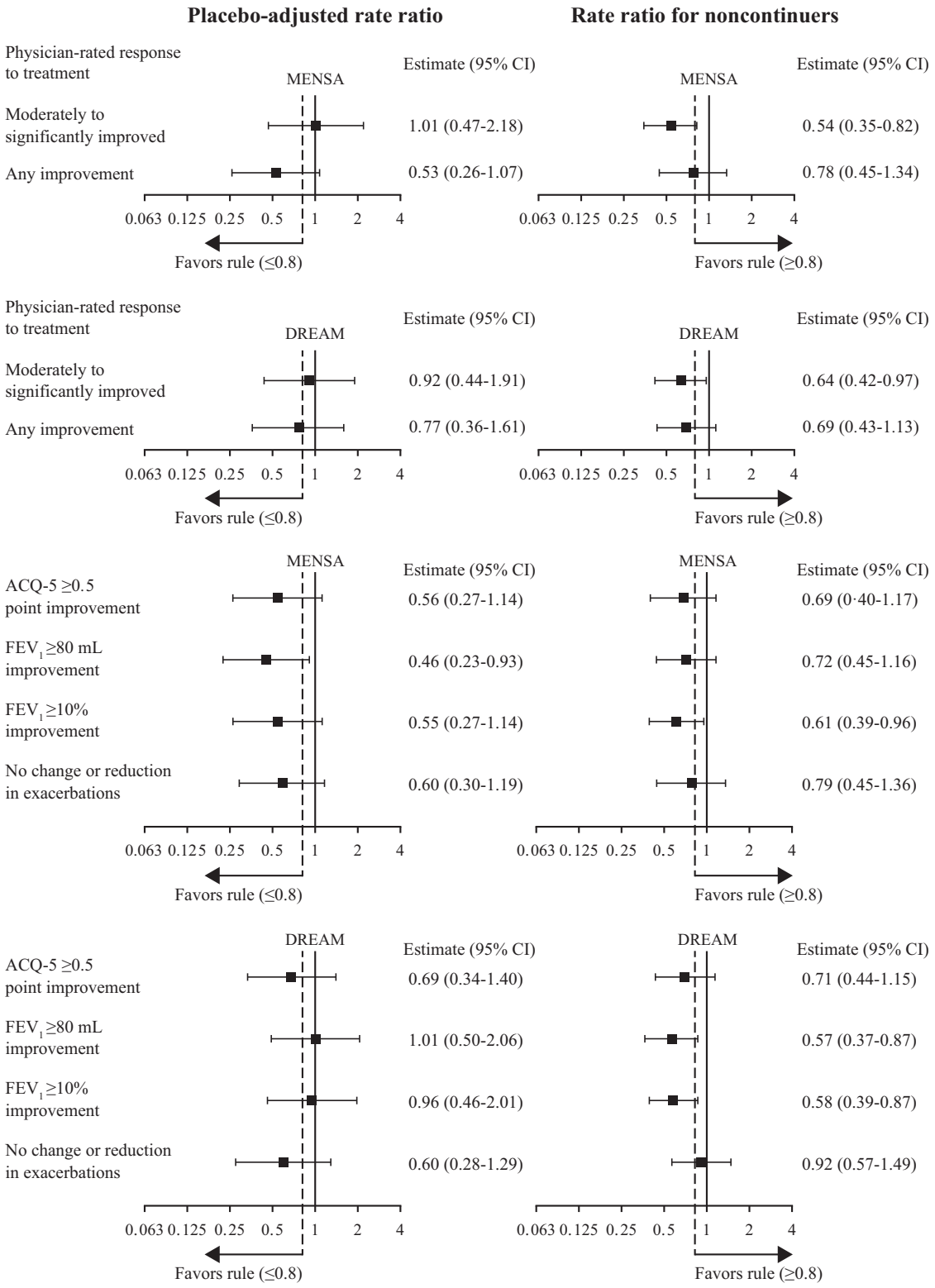

FIGURE 5. Results of the assessment of potential continuation rules based on additional measures at week 16 after initiation of treatment. The PARR and the RRNC are described in the Methods section. A useful continuation rule should have a PARR of ≤0.8 and an RRNC of ≥0.8. Criteria for PARR and RRNC were met for "no change or reduction in exacerbations" in MENSA.

0.68-3.34), respectively, indicative of a potentially useful continuation rule. However, such a rule would not be very useful in practice, because only a small number of patients would have a blood eosinophil count of less than 150 cells/μL at treatment initiation, and an even smaller number would fail to reduce eosinophils.

Previous studies have shown that absolute eosinophil counts of more than 300 cells/μL or 400 cells/μL are associated with an increased risk of exacerbations[7-9]; therefore, a potential rule based on reducing counts to less than such levels may be considered informative. However, absolute cutoffs do not take account of eosinophil counts at initiation and can therefore be unfair to patients with very high eosinophils. Because these patients are likely those who could benefit most from a reduction in eosinophils, relative reductions were used. Results based on absolute cutoff at 150 cells/μL and 300 cells/μL are presented in this article's Online Repository at www.jaci-inpractice.org. An analysis at thresholds of 300 cells/μL or more could not be performed because only 5 out of a total of 511 (<1%) patients on mepolizumab had absolute counts of more than 300 cells/μL at week 16. For the 150 cells/μL threshold, results were inconsistent between studies, with results suggesting a potentially useful rule in MENSA and a potentially detrimental rule in DREAM. Therefore, a continuation rule based on achieving a specific threshold of blood eosinophils was not supported by this analysis.

Continuation rules based on physician-rated response did not identify patients who would benefit in terms of future exacerbation reduction. Patients on mepolizumab who met the rule were at a similar risk of exacerbations compared with patients on mepolizumab who did not meet the rule, when compared with the corresponding effect among patients on placebo; patients on mepolizumab who did not meet the rules had a significantly reduced risk of exacerbations compared with patients on placebo who did not meet the rules. However, physician-rated response may capture other treatment effects, such as impacts on quality of life.

In both studies, patients on mepolizumab who did not achieve an improvement of 0.5 or more points in the ACQ-5 score had a considerable reduction in exacerbations compared with patients with placebo who did not meet the rule (31% [RRNC, 0.69] and 29% [RRNC, 0.71] in MENSA and DREAM, respectively). Therefore, the ACQ-5, despite its potential for predicting short-term exacerbations,[10] does not appear to predict exacerbations in the longer term.

Two rules were based on change in FEV_1: 80 mL or more and 10% or more improvement. The RRNC criterion was not met for either analysis; patients on mepolizumab who did not meet the rule had a substantial reduction in exacerbations compared with patients on placebo who did not meet the rule. Therefore, changes in lung function may not be predictive of future exacerbation reduction, because patients on mepolizumab without meaningful improvements in lung function appeared to experience considerable reduction in exacerbations. Existing guidelines suggest that changes of less than 8% or less than 150 mL are likely to be within measurement variability; therefore, thresholds chosen in this analysis may be considered insufficient.[11] However, these thresholds may not be applicable to patients with severe asthma on optimized therapy, where smaller measurement variability could be expected.

Mepolizumab has consistently shown reduced exacerbation rates[1,2,12]; therefore, response should be assessed on the basis of exacerbations. Having no change or a reduction in exacerbations from baseline to week 16 compared with the previous year met criteria for PARR and RRNC in MENSA. The 16-week time point for the assessment of the continuation rule was likely insufficient for the assessment of long-term exacerbation reduction. A longer period of exposure might be more predictive of future exacerbation reduction; therefore, an assessment 1 year after treatment may be more appropriate. Compared with the evaluation of asthma symptoms and lung function, the assessment of exacerbations is a paradigm shift in the evaluation of biological treatment responses in patients with severe asthma.

Most commonly used measures for assessing continuation rules are not appropriate because they do not take account of the impact of the continuation rule among patients on placebo.[4,13-15] Failure to account for this can lead to the identification of rules that select only patients with less severe disease or with reduced exacerbation risk regardless of treatment and exclude patients with more severe disease who are greatly benefiting from treatment.[14] For example, suppose patients were selected for continued treatment on the basis of whether the physician rated the patient as moderately or significantly improved compared with baseline at week 16. For patients who would stop treatment according to this rule, the MENSA and DREAM trials show 46% and 36% reductions, respectively, in exacerbation rate for mepolizumab compared with placebo in this group; clearly such patients would benefit considerably from continued treatment. The PARR and RRNC account for effects observed in patients on placebo and are therefore an appropriate combination of measures to assess the usefulness of continuation rules.

A number of analyses aiming to assess continuation rules for omalizumab[3,14] and reslizumab[13] have also been published. Results for ACQ and FEV_1 reported for reslizumab were similar to those observed in this analysis.[13] Reductions in exacerbation rates for reslizumab compared with placebo were seen among patients who at week 16 failed to achieve increases of 100 mL in FEV_1 or improve the ACQ-6 score by 0.5 points. Because patients on reslizumab without meaningful improvement in lung function or the ACQ-6 score experience clinically relevant reductions in exacerbations, the use of lung function and ACQ-6 score changes at 16 weeks are not effective continuation criteria for predicting future exacerbation reduction, despite the suggestion by the authors.

Two published analyses assessing potential continuation rules for omalizumab in patients with severe allergic asthma concluded that physician's overall assessment (Global Evaluation of Treatment Effectiveness) following a course of treatment best discriminated treatment outcomes,[4] and that it was an accurate predictor of response to omalizumab.[14] In the first analysis, the conclusions were based on a comparison of exacerbation rates in patients treated with omalizumab who met the continuation rule and patients treated with omalizumab who did not meet the rule and on another comparison of patients treated with omalizumab who met the continuation rule with all patients on placebo. Both comparisons yielded a more favorable rate of exacerbations for patients who met the rule.[4] These comparisons are not suitable for assessing the usefulness of a continuation rule: a comparison of treated patients who meet and do not meet the continuation rule simply indicates that the rule has selected patients who exacerbate less, and it provides no indication of whether any additional treatment benefit exists. An improved comparison against all patients on placebo merely proves that a subset of

patients that exacerbate less was selected, but provides no indication as to the usefulness or benefit of the continuation rule. In the second analysis, the conclusions were based on favorable estimates shown on a comparison of patients treated with omalizumab who met the continuation rule to patients on placebo meeting the continuation rule and to patients treated with omalizumab who did not meet the continuation rule.[14] However, this analysis did not assess the benefit of treatment among patients treated with omalizumab who did not meet the continuation rule, and also did not assess the extent at which the reduction in exacerbations among patients treated with omalizumab who met the continuation rule surpasses the reduction in exacerbations among patients on placebo who met the continuation rule. Information provided in both these studies was not relevant for the assessment of the usefulness of a continuation rule. Misinterpretation of these results may adversely impact more severe patients who could be wrongfully discontinued from treatment.

There were limitations to this analysis. First, the studies included were not of optimal design for deriving continuation rules, because patients continued on treatment throughout; there was no group that started mepolizumab and then discontinued treatment. Studies also had limited follow-up; longer follow-up would provide a clearer understanding of the long-term predictability of continuation rules and reduce uncertainties. Second, only a small number of patients on mepolizumab did not meet the continuation rules, particularly for reduction from baseline blood eosinophils. This also meant that it was not possible to explore subgroups. Third, the rules were assessed on exacerbations, because this is the primary aim of mepolizumab treatment; different end points might lead to different conclusions. Finally, this analysis assessed the added value provided by the continuation rules in patients selected on the basis of established starting criteria; results in an unselected population may differ.

CONCLUSIONS

On the basis of this *post hoc* analysis of DREAM and MENSA, there is no evidence for a reliable data-driven continuation rule based on short-term measures that distinguishes between a group of patients with enhanced benefit and one not benefiting from mepolizumab treatment in terms of exacerbation reduction. This analysis suggests that the combination of clinical (history of exacerbations despite previous intensive asthma therapy) and blood (blood eosinophil count) markers, identified through the clinical development program, effectively identifies patients most likely to reduce exacerbations in response to mepolizumab treatment. These criteria create a useful starting rule, which mitigates the utility of any subsequent continuation rule. In addition, stricter starting criteria, such as those specified by reimbursement bodies or payers, can further mitigate the potential utility of continuation rules, because these will be met by a larger proportion of patients. The principle of effective starting rules will continue to emerge with personalized treatment approaches, which will use patient markers to identify and target treatments to those likely to respond. Thereafter, decisions about continuation of treatment should perhaps be based on achieving a predefined reduction in longer term exacerbation frequency and/or oral corticosteroid dose; failure to achieve this should prompt a reevaluation of the role of eosinophilic airway inflammation in the pathogenesis of the patients' events and a new treatment approach.

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SUPPLEMENTARY MATERIALS

Additional information on included studies

The DREAM study included 4 arms: patients were randomly allocated to 1 of 3 different mepolizumab IV doses (75 mg, 250 mg, or 750 mg), or matched placebo for 52 weeks. The MENSA study included 3 arms: patients were randomly allocated to 1 of 2 different mepolizumab doses (75 mg IV or 100 mg SC), or matched placebo for 32 weeks in a double-dummy design.

In brief, DREAM required patients to have a history of at least 2 exacerbations requiring systemic corticosteroid treatment in the previous year, and evidence of eosinophilic inflammation at study entry or within the previous year, determined through either a peripheral blood eosinophil count of 300 cells/μL or more, sputum eosinophil counts of more than 3%, fractional exhaled nitric oxide value of 50 parts per billion or more, or a prompt deterioration in asthma control after 25% or less reduction in regular maintenance inhaled corticosteroids or oral corticosteroids. For MENSA, patients were also required to have at least 2 exacerbations requiring systemic corticosteroid treatment in the previous year; an eosinophilic phenotype was defined as a blood eosinophil count of 150 cells/μL or more at screening or 300 cells/μL or more at any point in the previous year.

The rate of clinically significant exacerbations was the primary end point for both studies. Clinically significant exacerbations were defined as worsening of asthma that required the use of systemic corticosteroids and/or emergency room visits and/or hospitalization. Exacerbations reported from the start of treatment until completion of study or up to withdrawal (but $\leq$4 weeks after the last dose of study medication) were included in the analysis. Exacerbations separated by less than 7 days were considered a continuation of the same exacerbation. Hospitalization included intubation and admittance to an intensive care unit.

Issues associated with commonly used measures for assessing the performance of continuation rules

The example herein (see Tables E1 and E2) illustrates commonly used measures for assessing the performance of continuation rules and the new measures developed in this study: the PARR quantifies the incremental difference in the risk of exacerbations in treated patients who meet the continuation rule compared with treated patients who do not meet the continuation rule in excess of the corresponding reduction among patients on placebo. The RRNC is the difference in the risk of exacerbations in treated patients who do not meet the continuation rule compared with patients with placebo who do not meet the continuation rule.

Data are presented in Table E1 on the rate of exacerbations among patients on treatment and on placebo separately for all patients in the arm, for patients meeting or not meeting the continuation rule. Exacerbation rates were 50% lower among treated patients when compared with patients on placebo (1.00/2.00 = 0.50). Exacerbation rates among patients meeting the continuation rule were lower than among patients not meeting the continuation rule.

The first method presented (Table E2) is a comparison of patients on treatment meeting the continuation rule with all patients on placebo, which yields a considerable improvement in the RR from 0.50 to 0.38. These results might be interpreted as an improvement in the reduction in exacerbations from 50% (RR = 0.50) in all patients to 62% (RR = 0.38) when introducing the continuation rule. However, this comparison merely reflects the fact that the patients on treatment selected on the basis of the continuation rule have lower exacerbation rates than all patients on treatment, and it provides no information on the benefit or usefulness of the continuation rule.

The second method presented (Table E2) is a comparison of patients on treatment meeting the continuation rule with (1) patients on placebo meeting the continuation rule and (2) patients on treatment not meeting the continuation rule. Both these comparisons show results in favor of the continuation rule whereby patients on treatment meeting the continuation rule have lower exacerbation rates than patients on placebo meeting the continuation rule and patients on treatment not meeting the continuation rule. One might interpret these results as suggestive of a useful continuation rule; however, the comparisons do not provide information on (1) the benefit observed among patients on treatment who do not meet the continuation rule or (2) the extent at which the benefit observed among patients on treatment who meet the continuation rule surpasses the benefit observed among patients on placebo who meet the continuation rule.

Finally, the measures proposed in this study are considered (Table E2). The PARR, which accounts for the effect of the continuation rule among patients on placebo, was 1.09, indicating that the continuation rule is not providing additional benefit. The RR for noncontinuers is 0.43, indicating that patients on treatment who do not meet the rule have a 57% reduction in exacerbations compared with patients on placebo who do not meet the rule. Adopting this rule in practice would continue patients on treatment without providing any additional benefit and removing patients from treatment who were experiencing substantial benefit. These measures therefore suggest that the continuation rule is not appropriate.

This example highlights that the choice of comparisons can have an impact on the interpretation of results and on the conclusions as to whether a continuation rule is useful. Interpreting a continuation rule as useful when in fact correct comparisons would have shown it as inappropriate can have devastating impacts on patients who may be incorrectly withheld from treatment because of the application of the continuation rule in clinical practice.

Potential continuation rules based on absolute eosinophils thresholds

Table E3 presents the number and proportion of patients with eosinophil counts of less than the thresholds of 150 and 300 cells/μL at week 16. Overall, 14 (12%) and 24 (7%) patients failed to reduce eosinophil counts to less than the threshold of 150 cells/μL at week 16. However, 5 (<1%) patients in total had eosinophil counts of more than 300 cells/μL, meaning that most patients (33 of 38) who failed to reach the 150 cells/μL cutoff had eosinophil counts between 150 and 300 cells/μL.

Statistical analysis could not be conducted for the 300 cells/μL cutoff because too few patients were available for analysis in the mepolizumab treatment arm who did not meet the continuation rule. Results for the 150 cells/μL threshold are presented in Table E4.

The continuation rule based on an absolute count of 150 cells/μL was identified as potentially useful according to PARR and RRNC criteria in MENSA but not in DREAM. Results

from DREAM suggest that the continuation rule is inappropriate, because patients who failed to reach 150 cells/μL on mepolizumab have a considerable reduction in exacerbations compared with patients who failed to reach 150 cells/μL on placebo. The PARR of 1.56 also suggests that the continuation rule has a detrimental impact overall, leading to a 56% increase in exacerbations beyond effects observed in placebo, through the introduction of the rule.

The continuation rules for 20% relative reduction in eosinophils and absolute threshold of 150 cells/μL had similar proportions of patients who did not meet the rule in both studies. However, there were much larger discrepancies in the results between DREAM and MENSA with absolute thresholds compared with relative reductions. This could potentially be attributable to small differences in baseline blood eosinophils between the 2 studies, which are accounted for through the use of relative reductions, but not absolute thresholds. These results also suggest that the use of relative reductions may be more appropriate in a clinical setting, where potential continuation rules applied on an individual basis may be much more suitable using relative reductions because they take appropriate account for counts at initiation.

TABLE E1. Example data to illustrate common methods used for assessing continuation rules

Rate of exacerbations	Placebo	Treatment
All patients	2.00	1.00
Meeting continuation rule	1.60	0.75
Not meeting continuation rule	2.80	1.20

TABLE E2. Common methods for assessing the performance of continuation rules using example data

Rate ratio	Treatment
Main result: Treatment/placebo	1.00/2.00 = 0.50
Method 1: Comparison against all placebo	
Treatment meeting continuation rule/placebo	0.75/2.00 = 0.38
Method 2: Comparison against patients on placebo meeting continuation rule and patients on treatment not meeting continuation rule	
Treatment meeting continuation rule/placebo meeting continuation rule	0.75/1.60 = 0.47
Treatment meeting continuation rule/treatment not meeting continuation rule	0.75/1.20 = 0.63
Methods presented in this article:	
PARR	(0.75/1.20)/(1.60/2.80) = 1.09
RRNC	1.20/2.80 = 0.43

TABLE E3. Summary of the number of patients meeting continuation rules based on absolute eosinophil counts by study and treatment group

Assessment of continuation rule at week 16	DREAM (N = 263)				MENSA (N = 576)			
	Placebo (n = 126)		Mepolizumab (n = 120)		Placebo (n = 182)		Mepolizumab (n = 365)	
	Met, n (%)	Not met, n (%)	Met, n (%)	Not met, n (%)	Met, n (%)	Not met, n (%)	Met, n (%)	Not met, n (%)
Absolute eosinophil count								
≤150 cells/μL	28 (24)	91 (76)	102 (88)	14 (12)	40 (23)	135 (77)	332 (93)	24 (7)
≤300 cells/μL	59 (50)	60 (50)	114 (98)	2 (2)	84 (48)	91 (52)	353 (99)	3 (<1)

TABLE E4. Summary of the number of patients meeting continuation rules based on absolute eosinophil counts by study and treatment group

Assessment of continuation rule at week 16	DREAM (N = 263) (95% CI)	MENSA (N = 576) (95% CI)
PARR (target ≤0.8)	1.56 (0.54-4.52)	0.41 (0.16-1.05)
RRNC (target ≈1.0)	0.46 (0.20-1.03)	1.02 (0.48-2.16)
Assessment for PARR	−	++
Assessment for RRNC	−	+
Potentially useful	No	Yes

Note. Indicators: +, some evidence for meeting criteria; ++, strong evidence for meeting criteria; −, some evidence for not meeting criteria.