Mepolizumab for Eosinophilic Chronic Obstructive Pulmonary Disease (COPD): A Meta-Analysis of METREX and METREO Patient-Reported Outcomes, Response to Therapy and Lung Function

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Rationale: METREX and METREO explored the use of mepolizumab in patients with exacerbating COPD and an eosinophilic phenotype. This pre-specified meta-analysis combining data from both these trials aimed to further assess the effect of mepolizumab on patient-reported outcomes, response to therapy and lung function. Methods: METREX and METREO were Phase III, placebo-controlled, randomized, double-blind, multicenter trials enrolling patients (aged ≥40 years) with COPD, and a history of ≥2 moderate/≥1 severe exacerbations in the prior year, despite inhaled corticosteroid (ICS)-based triple maintenance therapy. Patients received subcutaneous mepolizumab (100mg [METREX], 100 or 300mg [METREO]) every 4 weeks for 52 weeks, in addition to triple therapy, consisting of ICS, a long-acting β2-agonist and a long-acting muscarinic-receptor antagonist. This pre-specified meta-analysis was performed in patients from the modified intent-to-treat populations of METREX and METREO (with an eosinophilic phenotype: blood eosinophil counts ≥150 cells/μL [screening] or ≥300 cells/μL [prior year]). Two treatment comparisons: mepolizumab 100mg versus placebo and mepolizumab all-doses (100 and 300mg) versus placebo, were performed. Endpoints included the change from baseline in St George's Respiratory Questionnaire (SGRQ) and COPD Assessment Test (CAT) scores, proportion of SGRQ and CAT (post-hoc) responders (patients with ≥4-point and ≥2-point score improvement from baseline, respectively), patient- and clinician-rated response to therapy and pre-bronchodilator forced expiratory volume in 1s, all at Week 52. Results: 1136 patients were included in the meta-analysis (mepolizumab 100mg: N=456; mepolizumab 300mg: N=225, placebo: N=455), with 95% meeting the criteria for GOLD Group D. Mepolizumab 100mg versus placebo treatment resulted in numerical improvements in all endpoints at Week 52, with statistically significant differences reported for CAT and clinician-rated responses to therapy (Table). Similar results to mepolizumab 100mg were observed in the mepolizumab all-doses group. Conclusions: Patient-reported outcomes can complement the assessment of benefits provided by therapeutic interventions. In this meta-analysis, mepolizumab versus placebo-treated patients were significantly more likely to demonstrate clinically important improvements in CAT score and to be in a higher treatment-response improvement category based on an objective

clinician assessment. Mepolizumab versus placebo-treated patients were more likely to report clinically important improvements in SGRQ score and rate themselves as being in a higher treatment-response improvement category (not significant). Meaningful improvements in lung function were not reported. These results are supportive of mepolizumab reducing aspects of disease burden, alongside the previously demonstrated reduction in moderate/severe exacerbations, in a subgroup of patients with COPD and an eosinophilic phenotype. Funding: GSK ([117113/NCT02105961; 117106/NCT02105948])

Table: Summary of endpoints at Weeks 12, 24, 36, and 52*

Study endpoint	Week			
	12	24	36	52
SGRQ score change from baseline, difference mepo 100mg vs placebo (95% CI)	-1.5 (-3.1, 0.0)	-3.4 (-5.2, -1.6)	-0.5 (-2.3, 1.3)	-0.7 (-2.7, 1.3) p=0.486
CAT score change from baseline, difference mepo 100mg vs placebo (95% CI)	-1.8 (-2.6, -1.1)	-2.1 (-3.0, -1.3)	-0.4 (-1.3, 0.4)	-0.9 (-1.8, 0.0) p=0.039
SGRQ responders, OR, mepo 100mg vs placebo (95% CI)	1.37 (1.04, 1.79)	1.60 (1.22, 2.11)	1.27 (0.97, 1.67)	1.23 (0.94, 1.61) p=0.138
CAT responders, OR, mepo 100mg vs placebo (95% CI)	1.93 (1.44, 2.57)	2.02 (1.52, 2.69)	1.42 (1.07, 1.87)	1.39 (1.04, 1.85) p=0.024
Patient-rated response to therapy, OR, mepo 100mg vs placebo (95% CI)	-	-	-	1.26 (0.97, 1.63) p=0.077
Clinician-rated response to therapy, OR, mepo 100mg vs placebo (95% CI)	-	-	-	1.41 (1.09, 1.83) p=0.008
Pre-bronchodilator FEV_1 Difference mepo 100mg vs placebo, (95% CI)	31 (1, 60)	20 (-13, 52)	15 (-18, 47)	5 (-28, 38) p=0.764

CI, confidence interval; CAT, COPD assessment test; FEV_1, forced expiratory volume in 1s; Mepo, mepolizumab; OR, odds ratio; SGRQ, St George's Respiratory Questionnaire;
*A limited number of timepoints are shown. SGRQ scores were assessed at baseline and Weeks 12, 24, 36 and 52; CAT scores were assessed every 4 weeks from baseline until Week 52; Patient- and clinician-rated response to therapy were assessed at Weeks 8, 20, 32, 44 and 52; Pre-bronchodilator FEV_1 was assessed at Weeks 4, 12, 24, 36, 48 and 52.

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