SUPPLEMENTARY MATERIAL

Efficacy and Safety of Budesonide/Glycopyrrolate/Formoterol Fumarate Metered Dose Inhaler in Chinese Patients with COPD: A Subgroup Analysis of KRONOS

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Appendix S1 Statistical analysis

Analyses were performed in the Chinese modified intent-to-treat (mITT; all patients with post-randomization data obtained prior to treatment discontinuation), Chinese per-protocol (PP; all patients in the mITT population without any major protocol deviations), Chinese safety (all randomized patients who received ≥ 1 dose of study treatment) and Chinese rescue medication user populations (patients who had a mean baseline rescue albuterol use of ≥ 1 puff/day).

There were three treatment comparisons of interest for the Japan/China approach: budesonide/glycopyrrolate/formoterol fumarate metered dose inhaler (BGF MDI) versus budesonide/formoterol fumarate (BFF) MDI, BGF MDI versus glycopyrrolate/formoterol fumarate (GFF) MDI and BFF MDI versus budesonide/formoterol fumarate dry powder inhaler (BUD/FORM DPI). All comparisons were performed for superiority except BFF MDI versus BUD/FORM DPI, which was performed for non-inferiority.

In the Chinese mITT population, the primary efficacy estimand assumes the continuation of randomized treatments throughout the study (regardless of actual treatment adherence). The attributable estimand (effect due to the randomized treatment) accounted for treatment discontinuation. The PP estimand was used for non-inferiority analyses.

The primary endpoint was analyzed using a repeated measures linear mixed model, which included treatment, visit, treatment × visit interaction and inhaled corticosteroid use at screening as categorical covariates and baseline forced expiratory volume in 1 second, baseline eosinophil count and percent reversibility to albuterol as continuous covariates. A sensitivity analysis was performed for the primary endpoint based on a cumulative responder approach [1]. Patients with no post-baseline assessments, or who discontinued treatment for any reason, were considered non-responders in the sensitivity analysis.

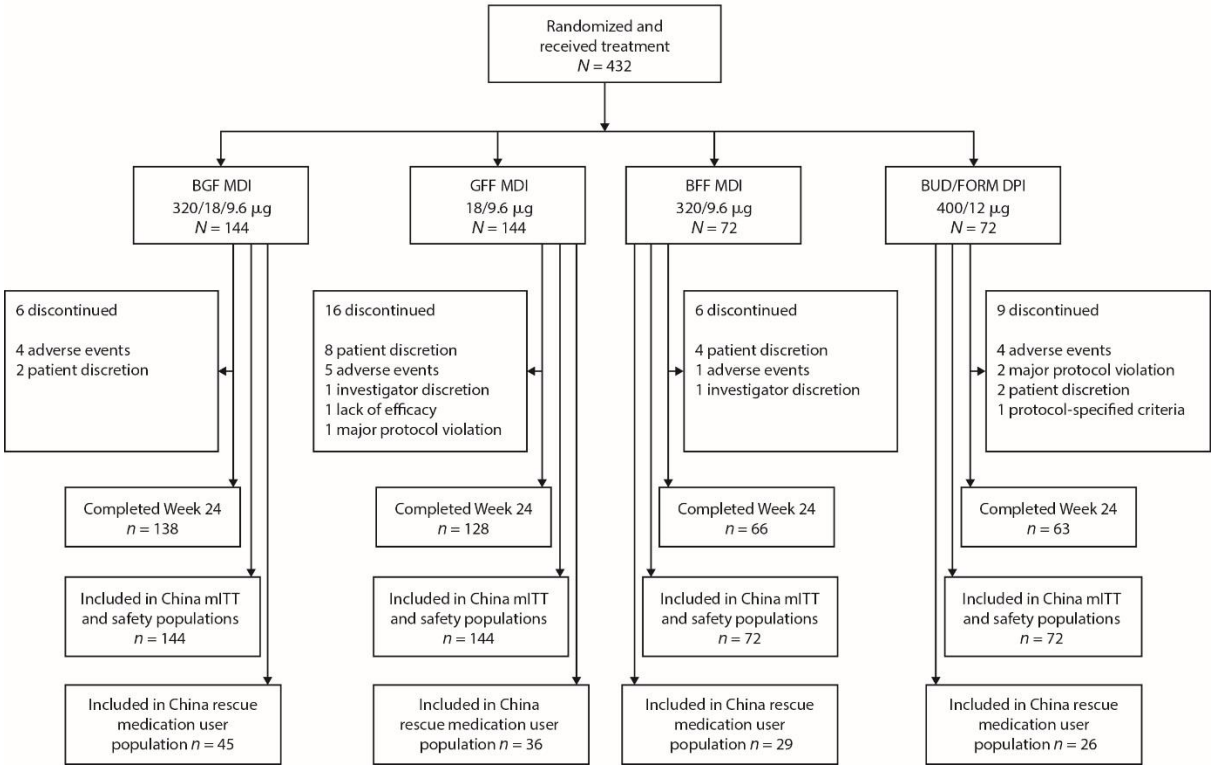
Analysis of secondary endpoints was performed using similar models to the primary endpoint, with the corresponding baseline measure as a covariate. A Cox proportional hazards model was used to analyze time to clinically important deterioration, and the rate of moderate/severe exacerbations was analyzed using a negative binomial model.

The relationship between baseline blood eosinophil count and treatment response (for lung function outcomes and the rate of moderate/severe exacerbations) was also examined via subgroup analyses and locally weighted scatter-plot smoothing. Each eosinophil subgroup was analyzed separately using the same model as the overall population analysis.

SUPPLEMENTARY REFERENCES

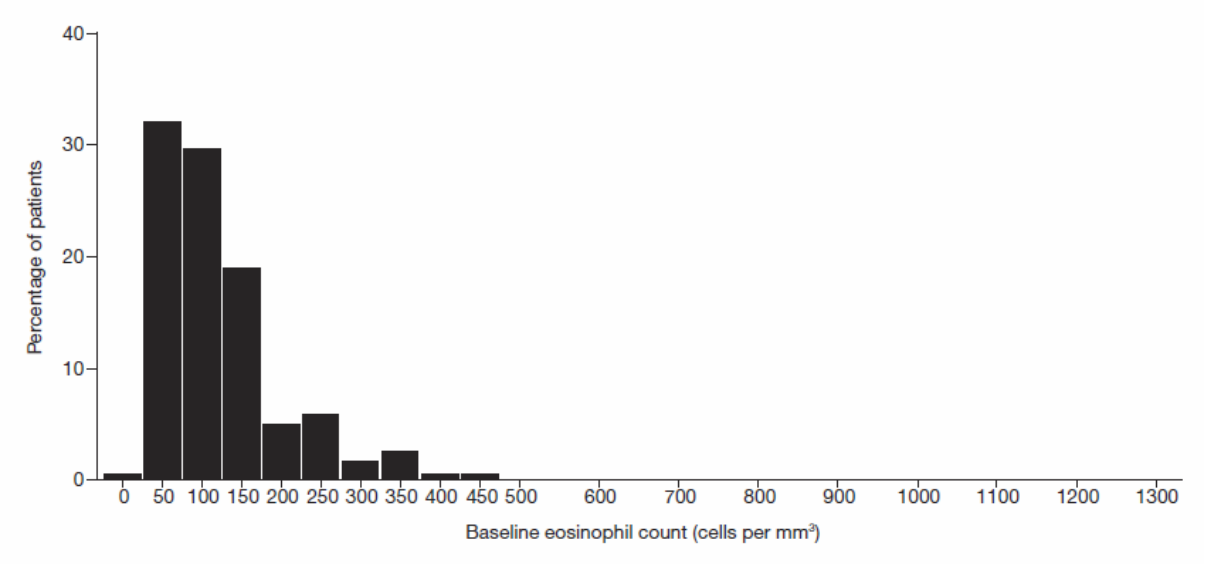
1. Farrar JT, Dworkin RH, Max MB. Use of the cumulative proportion of responders analysis graph to present pain data over a range of cut-off points: making clinical trial data more understandable. J Pain Symptom Manage. 2006;31(4):369-77.

Fig. S1 Patient disposition.



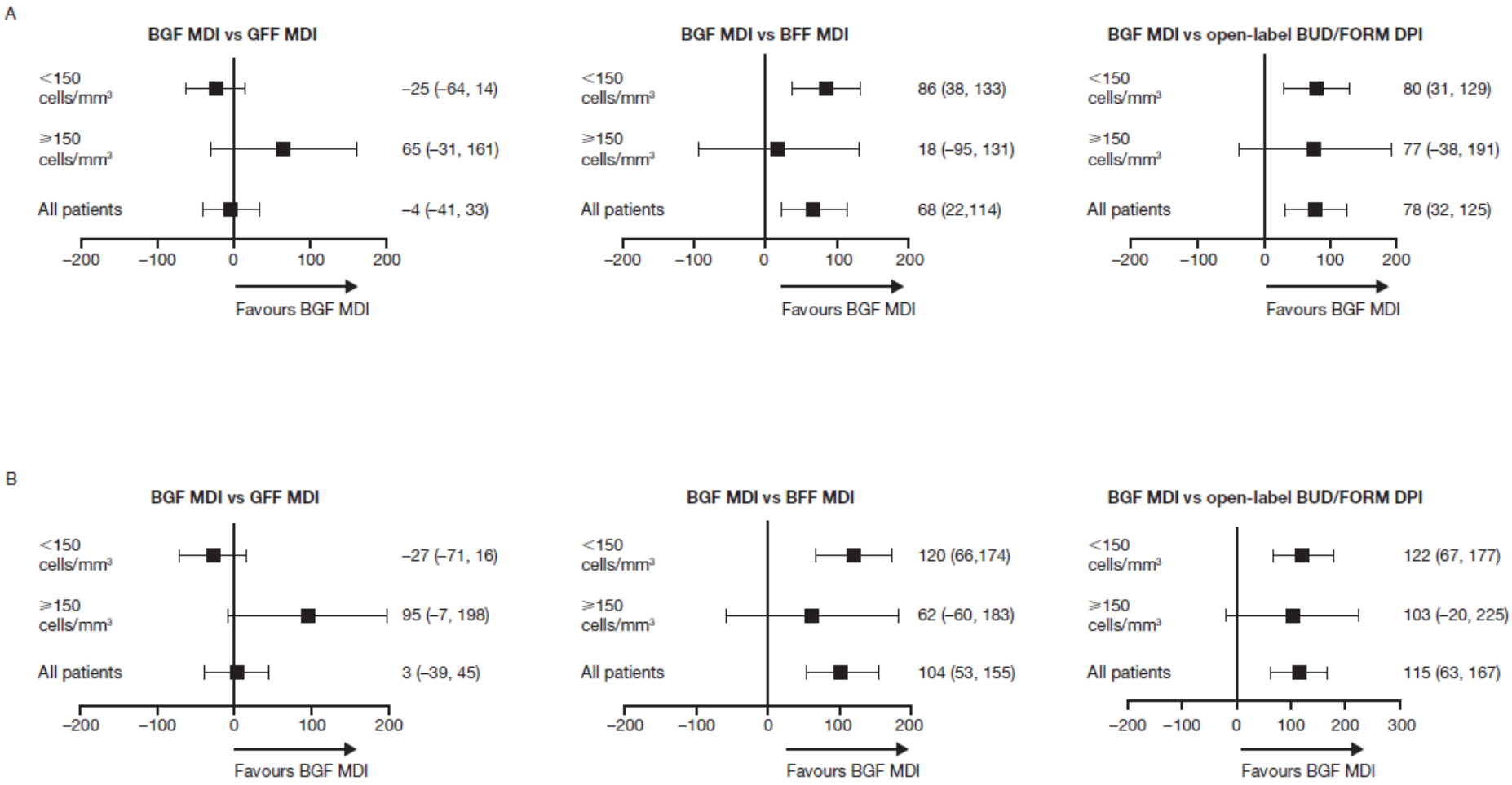
BFF, budesonide/formoterol fumarate; BGF, budesonide/glycopyrrolate/formoterol fumarate; BUD/FORM DPI, budesonide/formoterol fumarate dry powder inhaler; GFF, glycopyrrolate/formoterol fumarate; MDI, metered dose inhaler; mITT, modified intent-to-treat.

Fig. S2 Distribution of baseline eosinophil levels (China mITT population).



mITT, modified intent-to-treat.

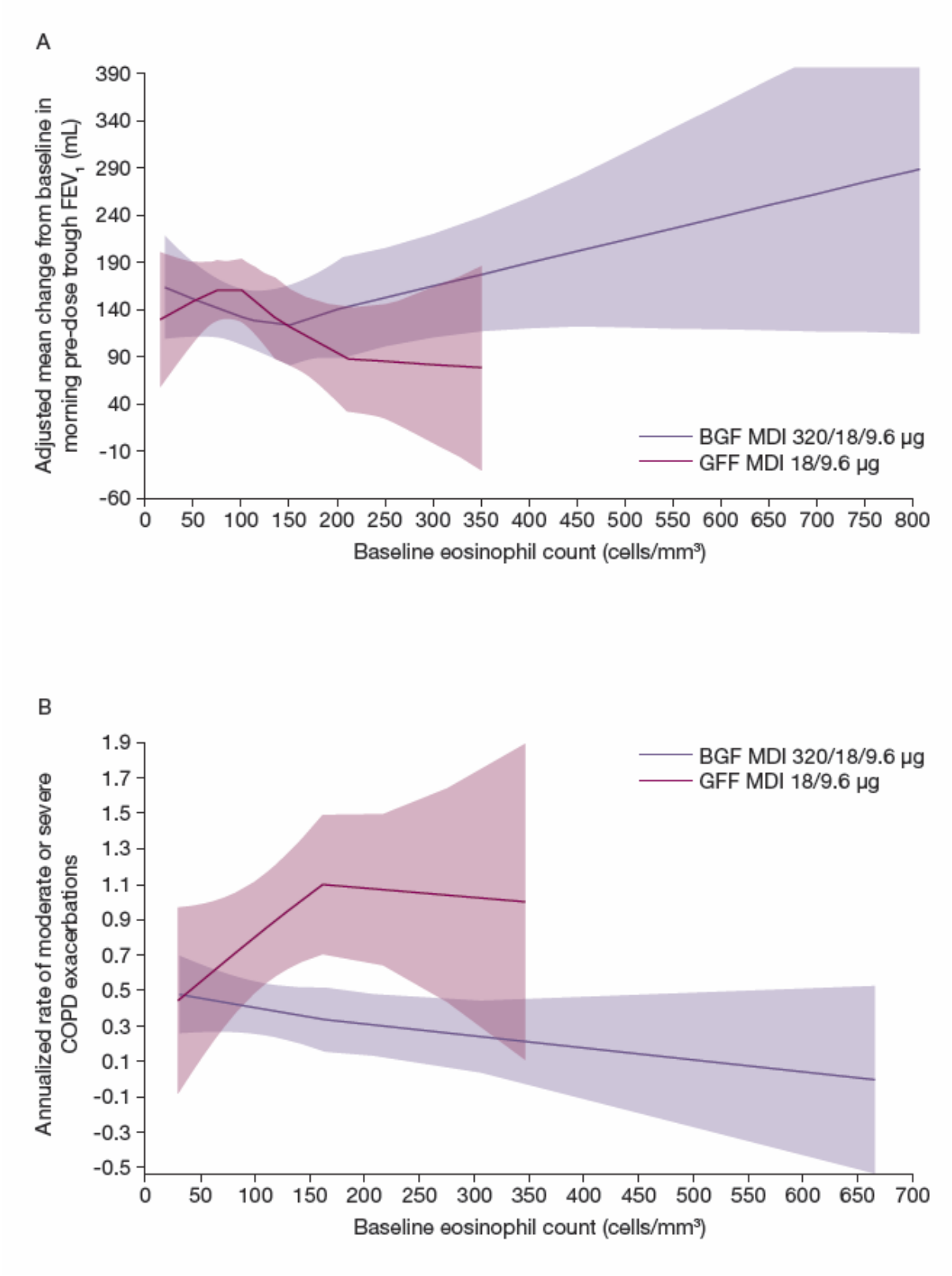
Fig. S3 Lung function responses by eosinophil subgroups (efficacy estimand; China mITT population).



Change from baseline in morning pre-dose trough FEV_1, mL (A) and FEV_1 $AUC_{0–4}$ (B), both over Weeks 12–24. Error bars represent 95% confidence intervals.

$AUC_{0–4}$, area under the curve from 0–4 hours; BFF, budesonide/formoterol fumarate; BGF, budesonide/glycopyrrolate/formoterol fumarate; BUD/FORM DPI, budesonide/formoterol dry powder inhaler; FEV_1, forced expiratory volume in 1 second; GFF, glycopyrrolate/formoterol fumarate; MDI, metered dose inhaler; mITT, modified intent-to-treat.

Fig. S4 Lung function responses and exacerbation rates by baseline eosinophil count (efficacy estimand; China mITT population)



Banded LOESS modeling by baseline eosinophil count for change from baseline in morning pre-dose trough FEV_1 (A) and annualized rate of moderate/severe COPD exacerbations (B)

Banded areas represent 95% confidence intervals

BGF, budesonide/glycopyrrolate/formoterol fumarate; GFF, glycopyrrolate/formoterol fumarate; LOESS, locally weighted scatter-plot smoothing; MDI, metered dose inhaler; mITT, modified intent-to-treat

Table S1 Non-inferiority comparisons of BFF MDI with BUD/FORM DPI (PP estimand; over Weeks 12–24 unless otherwise indicated)

	China PP population	***Global PP population***
	BFF MDI (*n* = 72) vs BUD/FORM DPI (*n* = 72)	**BFF MDI (*n* = 314) vs BUD/FORM DPI (*n* = 318)**
Primary endpoint		
Change from baseline in morning pre-dose trough FEV_1, mL	10 (–45, 66)	–11 (–39, 17)
Secondary endpoints		
Change from baseline in morning pre-dose trough FEV_1, mL (over 24 weeks)	14 (–38, 66)	–10 (–36, 16)
FEV_1 $AUC_{0–4}$, mL	8 (–54, 70)	–13 (–50, 24)
Peak change from baseline in FEV_1 within 4 h post-dosing, mL	4 (–62, 69)	–16 (–54, 22)
TDI focal score	1.01 (0.29, 1.74)	0.29 (–0.11, 0.69)
Change from baseline in SGRQ total score	–0.39 (–3.96, 3.17)	–0.60 (–2.34, 1.14)
Change from baseline in average daily rescue medication use, puffs/day (over 24 weeks)[a]	0.44 (–0.31, 1.19)	0.49 (0.00, 0.98)
Time to CID (over 24 weeks), HR (95% CI)	0.70 (0.44, 1.10)	0.98 (0.81 to 1.19)

Data are LSM difference (95% CI) unless otherwise indicated. Non-inferiority margins (based on 2-sided 95% CIs in the global PP population) were as follows: lower bounds of –50 mL (trough FEV_1), –75 mL (post-dose FEV_1 measures), and –0.75 (TDI focal score); upper bounds of 3.0 (SGRQ score), 0.75 (rescue medication use), and 1.1 (time to first CID). No non-inferiority margin was pre-specified for the rate of moderate/severe exacerbations since the study was not powered for this analysis

[a]Assessed in the rescue medication user populations

$AUC_{0–4}$, area under the curve from 0 to 4 hours; BFF, budesonide/formoterol fumarate; BUD/FORM DPI, budesonide/formoterol fumarate dry powder inhaler; CI, confidence interval; CID, clinically important deterioration; FEV_1, forced expiratory volume in 1 second; HR, hazard ratio; LSM, least squares mean; MDI, metered dose inhaler; PP, per-protocol; SGRQ, St George's Respiratory Questionnaire; TDI, Transition Dyspnea Index