Once-daily mometasone/indacaterol fixed-dose combination versus twice-daily fluticasone/salmeterol in patients with inadequately controlled asthma: Pooled analysis from PALLADIUM and IRIDIUM studies

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Table S1: Definition of asthma exacerbations and models used for the statistical analysis

Moderate exacerbation	Moderate exacerbations were defined as the occurrence of two or more of the following: (i) progressive increase of at least one asthma symptom, lasting at least 2 consecutive days (ii) increased use of "rescue" short-acting β_2-agonist (SABA) on 2 out of any 3 consecutive days or night-time awakenings requiring SABA use on at least 2 out of any 3 consecutive nights (iii) deterioration in lung function lasting ≥2 days but usually not severe enough to warrant systemic corticosteroids (SCS) for more than 2 days or hospitalisation. This deterioration would be defined by: • 20% decrease in forced expiratory volume in 1 second (FEV_1) from baseline value Or • ⩾ 20% decrease in morning or evening peak expiratory flow (PEF) from baseline on 2 out of any 3 consecutive days compared to baseline. Or • < 60% of PEF compared to baseline
Mild exacerbation	Mild exacerbations were defined as occurance of one of the following: (i) deterioration of at least one asthma symptom (ii) increased use of "rescue" SABA (iii) deterioration in lung function lasting ≥2 days but usually not severe enough to warrant SCS or hospitalisation. This deterioration would be defined by:

	• 20% decrease in FEV_1 from baseline value Or • ≥ 20% decrease in morning or evening PEF from baseline on 2 out of any 3 consecutive days compared to baseline. Or • < 60% of PEF compared to baseline
Statistical analysis	• Asthma exacerbations starting after the first dose and not later than one day after the date of last dose were included in the analyses of efficacy. The annual rates of asthma exacerbations were analysed using a generalised linear model assuming the negative binomial distribution including study, treatment, region and history of asthma exacerbations in the 12 months prior to screening (Yes/No) as fixed-effect factors, and age, FEV_1 prior to inhalation and FEV_1 15 to 30 min post-inhalation of salbutamol/albuterol as covariates. The log exposure in years was included as an offset variable in the model. The estimated rate ratio along with two-sided 95% confidence interval (CI) and corresponding *P* values are provided. Time-to-event variables was analysed using a Cox regression model stratified by study that included treatment as fixed-effect factor, and region, history of asthma exacerbations in the 12 months prior to screening (Yes/No), age, FEV_1 prior to inhalation and FEV_1 15 to 30 min post-inhalation of salbutamol/albuterol as covariates. For treatment comparisons, the estimated adjusted hazard ratios are provided along with the associated two-sided 95% CI and corresponding *P*-value.

	• Trough FEV_1 at Week 26, was analysed using a mixed model for repeated measures (MMRM) on the full analysis set (FAS). FAS included all patients who were assigned a randomisation number who received at least one dose of study medication. Patients were analysed according to the treatment they were assigned to at randomisation. The model contained treatment, study, region, visit, and treatment-by-visit interaction as fixed effects with age, baseline FEV_1 measurement, baseline-by-visit interaction, FEV_1 prior to inhalation and FEV_1 within 15 to 30 min post-inhalation of salbutamol/albuterol (components of SABA reversibility) as covariates, and center nested within region as a random effect. Each between-treatment comparison was performed using the least squares (LS) mean difference based on the treatment main effect and the coefficient for the treatment-by-visit interaction factor corresponding to Week 26. The estimated LS mean treatment difference is presented along with the associated SE, 95% CI (2-sided), and p-value (2-sided). Similar analyses were performed for ACQ-7 at Weeks 4, 12, 26, and 52. • PEF was measured twice a day for the entire duration of the study. At each time point, the patient was instructed to perform 3 consecutive maneuvers. Mean morning/evening PEF were summarised at 4-weekly (28 days) intervals. Separate ANCOVA was performed to evaluate treatment differences in the change from baseline in mean morning/evening PEF during the first 26 weeks, and during the whole 52 weeks of double-blind treatment. The model contained study, treatment, study-by-treatment interaction, and region as fixed effect factors with center nested within region as a random effect, and age, baseline morning/evening PEF, FEV_1 prior to inhalation and FEV_1 within 15 to 30 min post-inhalation of salbutamol/albuterol (components of

	SABA reversibility) as covariates. LS means and associated 95% CIs were presented for treatments and treatment differences. Additionally, the mean morning/evening PEF were summarised by 4-weekly (28-days) intervals and analysed using a similar MMRM as specified for the FEV_1 analysis with baseline FEV_1 value replaced with the appropriate baseline PEF. • The mean daily number of puffs of rescue medication used were calculated for each patient over the first 26 weeks, over the whole 52 weeks of double-blind treatment, and over 4 weekly intervals and analysed using the same ANCOVA and MMRM as used for analysis of PEF with baseline PEF value replaced with the appropriate baseline mean number of puffs of rescue medication. This analysis was also performed for morning and evening rescue medication use. The percentage of 'rescue medication-free days' are summarised by treatment and analysed in the same way as described for the number of puffs of rescue medication use with baseline mean number of puffs replaced with the baseline percentage of rescue medication-free days as a covariate. Percentage of days with no daytime symptoms, percentage of nights with no night-time awakenings, percentage of mornings with no symptoms on awakening, percentage of asthma symptom-free days, mean daytime asthma symptom score, and mean total daily symptom score during Weeks 1–26 and 1–52 were analysed using the same ANCOVA model as specified for PEF with appropriate baseline values. Percentage of days with no daytime symptoms, percentage of nights with no night-time awakenings, percentage of mornings with no symptoms on awakening, percentage of asthma symptom-free days, mean daytime asthma symptom scores, and mean total daily symptom scores were also summarised at 4-weekly intervals and

	analysed using a similar MMRM as specified for the FEV_1 analysis but including the appropriate visits and baseline as covariates. Subgroup analyses were conducted for trough FEV_1 at Week 26 using similar MMRMs as used for through FEV_1, with the appropriate interaction term in the models and additional covariate as a fixed effect if necessary for the FAS to explore the treatment effect in subgroups as specified in the main article. Subgroup analyses were also conducted for the annual rate of asthma exacerbations using similar generalised linear models with appropriate additions. All safety evaluations were based on the safety set, which consisted of all patients who received at least one dose of study medication. The number and percentage of patients who reported treatment-emergent adverse events were summarised.

Table S2: Change in asthma symptoms score with high-dose MF/IND versus high-dose FLU/SAL at Week 52

Treatment	Baseline raw mean	Change from baseline LS mean (SE)	Comparison	Treatment difference LS mean (95% CI); *P*-value
Mean daytime asthma symptom score				
High-dose MF/IND	0.85 (n=892)	−0.37(0.015)	High-dose MF/IND vs High-dose FLU/SAL	−0.04 (−0.08 to 0.00); 0·077
High-dose FLU/SAL	0.86 (n=902)	−0.33 (0.015)		
Mean total daily symptom score				
High-dose MF/IND	2.11 (n=856)	−0.97 (0.037)	High-dose MF/IND vs High-dose FLU/SAL	−0.12 (−0.23 to −0.02); 0.022
High-dose FLU/SAL	2.11(n=863)	−0.85 (0.037)		
Percentage of asthma symptom-free days				
High-dose MF/IND	15.3 (n=856)	30.1 (1.29)	High-dose MF/IND vs High-dose FLU/SAL	3.6 (0.0 to 7.2); 0.048
High-dose FLU/SAL	14.6 (n=863)	26.5 (1.29)		

Percentage of days with no daytime symptoms				
High-dose MF/IND	18.0 (n=892)	29.4 (1.28)	High-dose MF/IND vs High-dose FLU/SAL	3.3 (−0.2 to 6.9); 0·065
High-dose FLU/SAL	16.7 (n=902)	26.1 (1.27)		
Percentage of mornings with no symptoms on awakening				
High-dose MF/IND	38.2 (n=894)	24.9 (1.23)	High-dose MF/IND vs High-dose FLU/SAL	5.4 (2.0 to 8.8); 0.002
High-dose FLU/SAL	37.7 (n=908)	19.5 (1.22)		
Percentage of nights with no night-time awakenings				
High-dose MF/IND	63.7 (n=894)	19.4 (0.96)	High-dose MF/IND vs High-dose FLU/SAL	1.9 (−0.8 to 4.5); 0.171
High-dose FLU/SAL	63.4 (n=908)	17.6 (0.96)		

Participants received high-dose MF/IND (320/150 µg) o.d.; or high-dose FLU/SAL (500/50 µg) b.i.d.

n, number of patients analysed

b.i.d., twice-daily; FLU/SAL, fluticasone propionate/ salmeterol xinafoate; MF/IND, mometasone furoate/indacaterol acetate; o.d., once-daily

Table S3: Change in rescue medication use with high-dose MF/IND q.d. versus high-dose FLU/SAL b.i.d. at Week 52

Treatment	Baseline raw mean	Change from baseline LS mean (SE)	Comparison	Treatment difference LS mean (95% CI); *P*-value
Mean daily number of puffs of rescue medication				
High-dose MF/IND	1.83 (n=921)	−0.95 (0.045)	High-dose MF/IND vs High-dose FLU/SAL	−0.05 (−0.17 to 0.08); 0·473
High-dose FLU/SAL	1.73 (n=932)	−0.90 (0.045)		
Mean daytime number of puffs of rescue medication				
High-dose MF/IND	1.07 (n=892)	−0.54 (0.027)	High-dose MF/IND vs High-dose FLU/SAL	0.00 (−0.08 to 0.07); 0.910
High-dose FLU/SAL	1.01 (n=902)	−0.53 (0.027)		
Mean night-time number of puffs of rescue medication				
High-dose MF/IND	0.74 (n=894)	−0.39 (0.022)	High-dose MF/IND vs High-dose FLU/SAL	−0.04 (−0.10 to 0.02); 0·215
High-dose FLU/SAL	0.70 (n=908)	−0.35 (0.022)		

Percentage of rescue medication free days				
High-dose MF/IND	40.8 (n=877)	30.4 (1.12)	High-dose MF/IND vs High-dose FLU/SAL	3.2 (0.1 to 6.3); 0.044
High-dose FLU/SAL	43.2 (n=895)	27.3 (1.11)		

Participants received high-dose MF/IND (320/150 µg) o.d.; or high-dose FLU/SAL (500/50 µg) b.i.d.

n, number of patients analysed

b.i.d., twice-daily; FLU/SAL, fluticasone propionate/ salmeterol xinafoate; MF/IND, mometasone furoate/indacaterol acetate; o.d., once-daily

Table S4: Patients with AEs (at least 1.0%) by preferred term and SAEs occurring in high-dose MF/IND q.d. and high-dose FLU/SAL b.i.d. groups

Preferred term	**High-dose MF/IND (320/150 µg) o.d. N=1056**	**High-dose FLU/SAL (500/50 µg) b.i.d N=1062**
AEs, n (%)		
Patients with at least one AE	740 (70.1)	777 (73.2)
Asthma	369 (34.9)	446 (42.0)
Nasopharyngitis	123 (11.6)	130 (12.2)
Upper respiratory tract infection	74 (7.0)	90 (8.5)
Headache	50 (4.7)	47 (4.4)
Bronchitis	66 (6.3)	72 (6.8)
Back pain	27 (2.6)	22 (2.1)
Respiratory tract infection viral	21 (2.0)	35 (3.3)
Influenza	35 (3.3)	40 (3.8)
Hypertension	24 (2.3)	29 (2.7)
Pharyngitis	30 (2.8)	34 (3.2)
Rhinitis	27 (2.6)	20 (1.9)

Viral upper respiratory tract infection	45 (4.3)	68 (6.4)
Cough	19 (1.8)	23 (2.2)
Oropharyngeal pain	21 (2.0)	16 (1.5)
Rhinitis allergic	14 (1.3)	27 (2.5)
Dysphonia	18 (1.7)	16 (1.5)
Viral infection	12 (1.1)	11 (1.0)
Gastroenteritis	12 (1.1)	12 (1.1)
Diarrhea	11 (1.0)	18 (1.7)
Upper respiratory tract infection bacterial	32 (3.0)	37 (3.5)
Sinusitis	13 (1.2)	19 (1.8)
Arthralgia	10 (0.9)	15 (1.4)
Contusion	10 (0.9)	8 (0.8)
Respiratory tract infection	11 (1.0)	17 (1.6)
Blood pressure increased	3 (0.3)	3 (0.3)
Lower respiratory tract infection	17 (1.6)	30 (2.8)
Pyrexia	16 (1.5)	19 (1.8)
Toothache	14 (1.3)	3 (0.3)
Urinary tract infection	14 (1.3)	21 (2.0)

Abdominal pain upper	11 (1.0)	7 (0.7)
Acute sinusitis	8 (0.8)	13 (1.2)
Pneumonia	5 (0.5)	12 (1.1)
Urticaria	5 (0.5)	11 (1.0)
Gastroesophageal reflux disease	13 (1.2)	10 (0.9)
Dizziness	8 (0.8)	3 (0.3)
Oral candidiasis	6 (0.6)	13 (1.2)
Gastritis	3 (0.3)	12 (1.1)
Laryngitis	9 (0.9)	13 (1.2)

A patient with multiple AEs with the same preferred term is counted only once for that preferred term. Only AEs reported whilst on study drug or within 7 days of the last dose (within 30 days for SAEs) are included.

N, number of patients

AE, adverse event; b.i.d., twice-daily; FLU/SAL, fluticasone propionate/salmeterol xinafoate; MF/IND, mometasone furoate/indacaterol acetate; o.d., once-daily