Assessment of Peak Inspiratory Flow Rate in Patients With Chronic Obstructive Pulmonary Disease: Impact on Dose Delivery and Relationship With Response to Fluticasone Furoate/Umeclidinium/Vilanterol Triple Therapy

Poster No. 813 (A4302)

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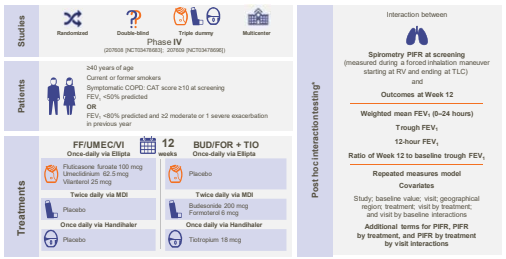
Introduction

- Concerns have been raised that patients with chronic obstructive pulmonary disease (COPD) who achieve a peak inspiratory flow rate (PIFR) <60 L/min may have suboptimal response to therapy administered via a dry powder inhaler (DPI).[1–3]
- Two clinical studies (RES113817/RES117178 [NCT01345266/NCT02076269]) have demonstrated a strong correlation between PIFR as measured by spirometry ($PIFR_{Spirometry}$) and PIFR achieved through the moderate-resistance Ellipta DPI ($PIFR_{Ellipta}$) in patients with COPD of all severities.[4] Across these studies, patients with very severe COPD had, on average, the lowest $PIFR_{Ellipta}$ values, with the lowest recorded $PIFR_{Ellipta}$ with maximal inspiratory effort ranging from 41.6 to 43.5 L/min depending on device configuration.[4,5] Subsequent in vitro data using the Electronic Lung (a breathing simulator designed for inhaler characterization) or standard test conditions (Next Generation Impactor) have demonstrated a consistent dose delivery of fluticasone furoate/umeclidinium/ vilanterol (FF/UMEC/VI) via the Ellipta DPI with $PIFR_{Ellipta}$ values ranging from 30 to 130 L/min.[5,6]
- Two recent replicate studies (207608/207609) have evaluated the efficacy and safety of FF/UMEC/VI triple therapy compared with budesonide/formoterol (BUD/FOR) plus tiotropium (TIO) therapy in patients with COPD (see Ferguson et al. Poster 806). To provide further data on PIFR and clinical outcomes, this post hoc analysis evaluated the range of $PIFR_{Spirometry}$ observed across the pooled study population and investigated the relationship between patients' $PIFR_{Spirometry}$ and study efficacy outcomes.

Methods



*Treatment populations were pooled for interaction testing of treatment with $PIFR_{Spirometry}$. CAT, COPD Assessment Test; FEV_1, forced expiratory volume in 1 second; RV, residual volume; TLC, total lung capacity

- Using COPD data from RES113817/RES117178 studies (n=60) and the relationship between two-strip $PIFR_{Ellipta}$ and $PIFR_{Spirometry}$, equations were derived to describe the relationship for both the average and 95% lower tolerance bound of $PIFR_{Ellipta}$ values from $PIFR_{Spirometry}$ data. The lower tolerance bound equation was used to predict $PIFR_{Ellipta}$ for patients in the 207608/207609 studies.
  - Lower tolerance bound ($PIFR_{Ellipta}$) = (41.8365 + 0.1314 × $PIFR_{Spirometry}$) – k_1(d) × 9.77735, where $PIFR_{Ellipta}$ is the predicted Ellipta PIFR value, and $PIFR_{Spirometry}$ is the recorded spirometry value of the patient
  - Prediction of $PIFR_{Ellipta}$ using $PIFR_{Spirometry}$ values below the observed minimum of 83.4 L/min in the RES113817/RES117178 studies was achieved by extrapolation.

Results

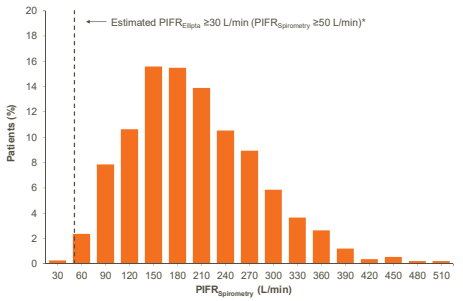
- A total of 1951 patients had spirometry values recorded at screening (**Figure 1**). Median $PIFR_{Spirometry}$ (range) was 191 L/min (28–519 L/min).
  - Of these, 1945 (99.7%) patients had a $PIFR_{Spirometry}$ ≥50 L/min, which correlates to an estimated $PIFR_{Ellipta}$ ≥30 L/min, a value shown to be adequate for appropriate dose delivery via the Ellipta DPI.[5,6]
- The pooled intent-to-treat (ITT) population comprised 1460 patients (FF/UMEC/VI n=729; BUD/FOR + TIO n=731). Baseline demographics and characteristics were similar between the two treatment arms (**Table 1**).
- No interaction between treatment and spirometry PIFR at screening was seen for any lung function endpoints (**Table 2**).
- Scatter plot graphs for weighted mean FEV_1 (0–24 hours) and trough FEV_1 are shown in **Figure 2**.

Table 1. Patient demographics and baseline characteristics (ITT population)

	FF/UMEC/VI N=729	BUD/FOR + TIO N=731
Age, years, mean (SD)	65.5 (8.0)	65.0 (8.2)
Female, n (%)	360 (49)	343 (47)
BMI, kg/m², mean (SD)	28.4 (7.1)	28.5 (7.0)
Current smoker, n (%)	356 (49)	358 (49)
Moderate COPD exacerbations in the previous 12 months, n (%)		
0	377 (52)	393 (54)
1	127 (17)	114 (16)
≥2	225 (31)	224 (31)
Severe COPD exacerbations in the previous 12 months, n (%)		
0	650 (89)	635 (87)
1	71 (10)	82 (11)
≥2	8 (1)	14 (2)
Screening lung function, mean (SD)	**n=725**	**n=730**
Post-bronchodilator FEV_1 (mL)	1152 (414.8)	1190 (420.1)
Post-bronchodilator FEV_1, % predicted	42.0 (12.2)	42.6 (12.6)
$PIFR_{Spirometry}$ at screening (L/min)	199.8 (76.8)	198.3 (80.4)
CAT score at screening, mean (SD)*	21.9 (6.4)	22.1 (6.5)
COPD medications at screening, n (%)		
ICS + LAMA + LABA	231 (32)	212 (29)
ICS + LABA	244 (33)	252 (34)
LABA + LAMA	114 (16)	109 (15)
LAMA	49 (7)	61 (8)

*FF/UMEC/VI: n=723; BUD/FOR + TIO: n=724.
BMI, body mass index; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; SD, standard deviation

Figure 1. $PIFR_{Spirometry}$ distribution at screening in the 207608/207609 studies



PIFR distribution from the 207608/207609 studies was evaluated post hoc.
*Estimation of $PIFR_{Ellipta}$ based on equation generated from RES113817/RES117178 (NCT01345266/NCT02076269), where estimations of $PIFR_{Ellipta}$ below 43.5 L/min are based on extrapolation from $PIFR_{Spirometry}$ values below the observed minimum of 83.4 L/min. Extrapolating to 50 L/min $PIFR_{Spirometry}$, there is 95% confidence that 90% of the population has at least 30 L/min $PIFR_{Ellipta}$ (lower tolerance bound).

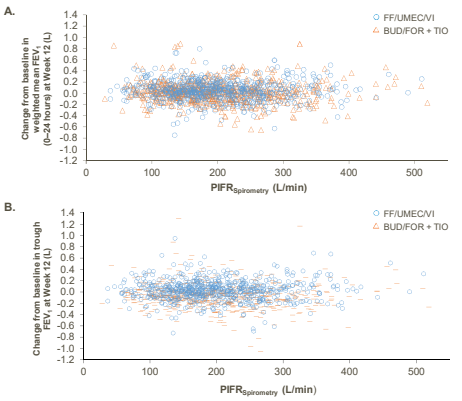
Table 2. Treatment interaction for PIFR at screening and Week 12 lung function endpoints (ITT population)

Week 12 lung function endpoint	*P*-value for interaction of treatment with PIFR at screening
Weighted mean FEV_1 (0–24 hours)	0.415
Trough FEV_1	0.091
12-hour FEV_1	0.162
Trough FEV_1 Week 12 to baseline ratio	0.275

Conclusions

- Spirometry PIFR results and corresponding predicted Ellipta PIFRs from patients screened for the 207608 and 207609 studies indicate that nearly all patients with COPD (99.7%) in these clinical trials are likely to generate a $PIFR_{Ellipta}$ ≥30 L/min, which has been shown to be adequate for consistent dose delivery of FF/UMEC/VI via the moderate-resistance Ellipta DPI.
- No decrease in treatment efficacy on lung function outcomes was seen at low PIFR values, which is consistent with previous results demonstrating flow-independent dose delivery from the Ellipta inhaler.[5,6]

Figure 2. No relationship was seen between patients' PIFR values at screening and lung function outcomes at Week 12. (A) Weighted mean FEV_1 (0–24 hours); (B) Trough FEV_1



References

1. Mahler DA. *Ann Am Thorac Soc* 2017;14:1103–7.
2. Mahler DA. *Am J Respir Crit Care Med* 2019;199:1577–9.
3. Ghosh S, et al. *J Aerosol Med Pulm Drug Deliv* 2017;30:381–7.
4. Prime D, et al. *J Aerosol Med Pulm Drug Deliv* 2015;28:486–97.
5. Hamilton M, et al. *J Aerosol Med Pulm Drug Deliv* 2015;28:498–506.
6. Prime D, et al. E1133 Presented at American College of Chest Physicians Congress, New Orleans, LA, USA, October 19–23, 2019.

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- RJ, TCC, C-QZ, KC, MH, and NM are employees of GSK and hold stocks and shares in GSK. DP was an employee of GSK at the time of the study and holds stocks and shares in GSK. MA has received speaker fees from AstraZeneca, Boehringer Ingelheim, GSK, MEDA, Orion Pharma and TEVA. MBD has received personal fees from AstraZeneca, Boehringer Ingelheim, GSK, Midmark, Mylan Theravance, and Philips, and has received research grant funding from Boehringer Ingelheim.
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