Comparison of Peak Inspiratory Flow Rate Between Clinical Trial and Real-World Populations

Poster No. P1045 (A5050)

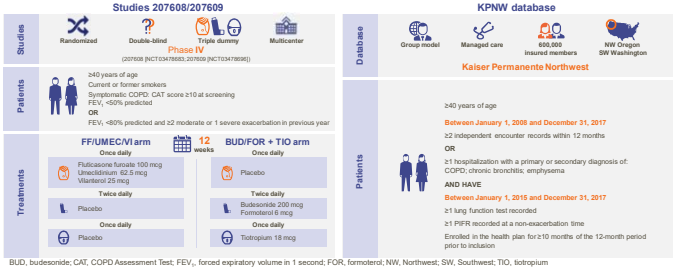
Mularski RA[1], Drummond MB[2], Jain R[3], Corbridge TC[3,4], Moretz C[3*], Zhu C-Q[5], Collison K[3], Hamilton M[6], Prime D[6*], Martin N[7,8]

[1]Kaiser Permanente Northwest Center for Health Research, Portland, OR, USA; [2]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [3]GSK, Research Triangle Park, NC, USA; [4]Feinberg School of Medicine, Northwestern University, Chicago, IL, USA; [5]GSK, Stockley Park West, Uxbridge, Middlesex, UK; [6]GSK, R&D, Ware, Hertfordshire, UK; [7]GSK, Brentford, Middlesex, UK; [8]University of Leicester, Leicester, Leicestershire, UK
*Affiliation at the time of the study

Introduction

- It is important to understand the proportion of patients with chronic obstructive pulmonary disease (COPD) who are able to achieve the peak inspiratory flow rate (PIFR) required to use a dry powder inhaler (DPI).
- 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.[1] Across these studies, patients with very severe COPD had, on average, the lowest $PIFR_{Ellipta}$ values, with the lowest recorded $PIFR_{Ellipta}$ with maximum inspiratory effort ranging from 41.6 to 43.5 L/min depending on device configuration.[1,2] 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.[2,3]
- However, in vitro and clinical trial settings are not reflective of real-world settings and as such their results may not always be applicable to clinical practice.[4] This analysis compared spirometry data from two recent replicate studies (207608/207609) (see Ferguson et al. Poster 806) against a real-world, managed care organization database (Kaiser Permanente Northwest [KPNW]) in patients with COPD.

Methods



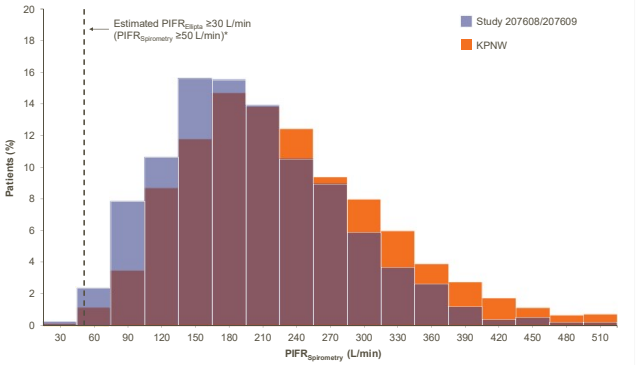
BUD, budesonide; CAT, COPD Assessment Test; FEV_1, forced expiratory volume in 1 second; FOR, formoterol; NW, Northwest; SW, Southwest; TIO, tiotropium

- $PIFR_{Spirometry}$ was measured during a forced inhalation maneuver starting at residual volume and ending at total lung capacity
- The distribution of spirometry PIFR at screening in the 207608/207609 studies was evaluated post hoc. Patients' most recent spirometry PIFR recorded during 2015–2017 was used for the KPNW cohort.
- 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

- Spirometry values were recorded in **1951** patients at screening in the pooled 207608/207609 population and **3282** patients in the KPNW population (**Figure 1**).
  - **1460** patients were included in the 207608/609 pooled intent-to-treat (ITT) population (FF/UMEC/VI n=729; BUD/FOR + TIO n=731)
- Nearly all 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.[2,3]
  - Patients with $PIFR_{Spirometry}$ ≥50 L/min: 207608/609, n=1945 (99.7%); KPNW, n=3277 (99.8%).
- Compared with the KPNW patient population, the ITT population of studies 207608/207609 (**Table 1**):
  - Was younger and had a lower body mass index (BMI)
  - Had more severe lung function deterioration
  - Had a greater proportion of current smokers, patients with a history of ≥1 moderate or severe exacerbation, and patients on dual or triple combination therapy.

Figure 1. Distribution and range of $PIFR_{Spirometry}$ were comparable between the pooled 207608/207609 population and the KPNW population



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 1. Patient demographics and baseline characteristics

	207608/207609 (ITT population; N=1460)	KPNW (N=3282)
Age, years, mean (SD)	65.2 (8.1)	68.4 (9.9)
Female, n (%)	703 (48.2)	1533 (46.7)
BMI, kg/m², mean (SD)	28.5 (7.1)	30.1 (7.6)
Current smoker, n (%)	714 (48.9)	1198 (36.5)
COPD exacerbations in the previous 12 months, n (%)*		
0 moderate/severe	675 (46.2)	2458 (74.9)
≥1 moderate	690 (47.3)	764 (23.3)
≥1 severe	175 (12.0)	60 (1.8)
Screening lung function, mean (SD)	**n=1455**	
FEV_1 (L)	1.2 (0.4)†	1.9 (0.7)
PIFR (L/min)	**199.1** (78.6)	**230.2** (89.7)
COPD medications at screening, n (%)		
ICS + LAMA + LABA	443 (30)	602 (18)
ICS + LABA	496 (34)	409 (13)
LABA + LAMA	223 (15)	8 (0.2)
LAMA	110 (8)	1171 (36)

*As some patients in 207608/207609 recorded both moderate and severe exacerbations in the prior 12 months, the total percentage exceeds 100%; †post-bronchodilator value.
ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; SD, standard deviation

Conclusions

- Despite patients enrolled in 207608/207609 having more severe COPD than those in the KPNW database, considerable overlap between $PIFR_{Spirometry}$ values was seen between the two populations. These results suggest that patients enrolled in the 207608 and 207609 studies could generate inspiratory flow rates comparable to those observed in the real-world COPD population.
- Nearly all patients (≥99.7%) from the 207608/207609 studies and the KPNW database achieved $PIFR_{Spirometry}$ ≥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.[2,3]

References

1. Prime D, et al. *J Aerosol Med Pulm Drug Deliv* 2015;28:486–97.
2. Hamilton M, et al. *J Aerosol Med Pulm Drug Deliv* 2015;28:498–506.
3. Prime D, et al. E1133 Presented at American College of Chest Physicians Congress, New Orleans, LA, USA, October 19–23, 2019.
4. Treweek S and Zwarenstein M. *Trials* 2009;10:37.

Disclosures

- The studies were funded by GlaxoSmithKline (GSK; 207608/207609, NCT03478683/NCT03478696). Ellipta is owned by or licensed to the GSK Group of Companies; HandiHaler is a trademark of Boehringer Ingelheim International GmbH.
- RAM has received a collaborative research grant from GSK and research grants from PCORI and the COPD Foundation and served on a GSK Advisory Board in 2020. MBD has received personal fees from AstraZeneca, Boehringer Ingelheim, GSK, Midmark, Mylan Theravance, and Philips, and has received research grant funding from Boehringer Ingelheim. RJ, TCC, C-QZ, KC, MH, and NM are employees of GSK and hold stocks and shares in GSK. CM and DP were employees of GSK at the time of the study and hold stocks and shares in GSK.
- Editorial support (in the form of writing assistance, including development of the initial draft based on author direction, assembling tables and figures, collating authors' comments, grammatical editing, and referencing) was provided by Philip Chapman at Fishawack Indicia Ltd, UK, and was funded by GSK. The authors would like to thank Kevin Lief of GSK for his support with the statistical analysis.

An online version of this poster, a plain language summary and an audio recording accompanying the online poster can be accessed by scanning the QR code or via http://tago.ca/ats38

Prepared for the American Thoracic Society Annual Meeting (2020)