Step-up to High Dose Fluticasone Furoate in Combination With Long-Acting Bronchodilator in Inadequately Controlled Asthma: The CAPTAIN Study

Poster No. 072

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Background

- Up to 50% of patients with asthma are inadequately controlled despite receiving dual therapy with an inhaled corticosteroid (ICS) and long-acting β_2-agonist (LABA).[1–5] Current guidelines for these patients recommend increasing the ICS dose in a stepwise manner.[6]
- Adding vilanterol (VI) to fluticasone furoate (FF) 100 mcg improves lung function and clinical outcomes in patients uncontrolled on ICS alone[1]; however, little evidence exists on the effect of doubling the ICS component in dual therapy.

Objective

- This analysis of the CAPTAIN study reports on the effects of doubling the FF dose in FF/VI dual therapy in patients with inadequately controlled asthma on ICS/LABA therapy.

Methods

- CAPTAIN (study 205715, NCT02924688) was a Phase IIIa, randomized, double-blind, 24–52-week, parallel-group study investigating the efficacy and safety of once-daily, single-inhaler dual therapy with FF/VI and triple therapy with FF, umeclidinium (UMEC; a long-acting muscarinic antagonist), and VI.
- Following a run-in and stabilization period on ICS/LABA, eligible patients were randomized to one of six treatment arms (all once daily via ELLIPTA dry powder inhaler) as shown in **Figure 1**.
- Patients who withdrew early from randomized treatment were encouraged to continue study participation, placed on appropriate asthma medication per the treating physician and subsequent data were included in analyses as 'post treatment'. All data collected post randomization, including 'post-treatment' were included in these analyses, with the exception of forced expiratory volume in 1 second (FEV_1) at 3 hours post treatment, which was collected on-treatment only. No multiplicity adjustments were made for data reported in this poster.

Figure 1. Study design

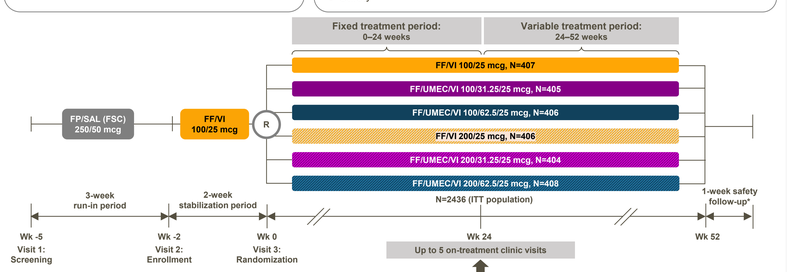
Eligible patients

- ≥18 years of age
- Pre-bronchodilator FEV_1 % predicted ≥30%–<85%
- ACQ-6 score ≥1.5
- Receiving ICS/LABA therapy (daily FP>250 mcg or equivalent)
- Documented healthcare contact or temporary change in asthma therapy for treatment of acute asthma symptoms in the year prior to screening

Primary endpoint: Trough FEV_1 CFB at Week 24

Secondary/other endpoints

- Annualized moderate (a physician-directed temporary change in maintenance treatment) or severe (requiring use of systemic corticosteroids for ≥3 days or hospitalisation requiring use of systemic corticosteroids) asthma exacerbation rates
- Time to first moderate/severe exacerbation
- FEV_1 at 3 hours post-treatment CFB at Week 24
- ACQ-7 score CFB and responders§ at Week 24
- SGRQ score CFB and responders§ at Week 24
- Safety¶



FP/SAL provided BID as a fixed-dose via the Diskus DPI; FF/VI and FF/VI/UMEC provided QD as a fixed-dose via the Ellipta DPI. *All patients in the study had a safety follow-up contact approximately 7 days after the End of Study Visit (dependent on actual transition date) or Early Withdrawal Visit; †responders were defined as patients with ≥0.5- or ≥4-point improvement from baseline in ACQ-7 and SGRQ total score, respectively; ‡safety endpoints reported here include incidence and type of adverse events (AEs), serious AEs (SAEs), and AEs of special interest (AESIs) relevant to ICS class effects; ACQ-6, Asthma Control Questionnaire-6; BID, twice daily; CFB, change from baseline; FP, fluticasone propionate; FSC, FP/salmeterol combination; ITT, intent-to-treat; QD, once daily; R, randomization; SAL, salmeterol; SGRQ, St George's Respiratory Questionnaire

Results

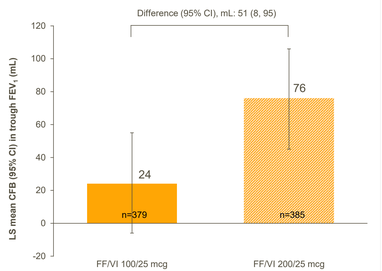
- 2436 patients were enrolled in the ITT population. Clinically meaningful improvements from baseline in mean (standard deviation) trough FEV_1 (287 [356] mL) and ACQ-7 score (-0.674 [0.705]) were seen at the end of the 3-week run-in period with FSC and 2-week stabilization period with FF/VI; improvements with FF/VI (162 [290] mL; -0.387 [0.575]) were greater than FSC (126 [307] mL; -0.283 [0.524]).
- Baseline demographics and clinical characteristics were similar between FF/VI treatment groups (**Table 1**).
- At Week 24, mean change from baseline in trough FEV_1 improved with FF/VI 200/25 mcg compared with FF/VI 100/25 mcg (**Figure 2**); improvements were also observed in clinic FEV_1 at 3 hours post treatment (treatment difference: 36 mL [95% CI: -8, 81]).
- In total, 688 patients (28%) experienced moderate/severe exacerbations over 52 weeks. FF/VI 200/25 mcg resulted in a lower rate of moderate/severe exacerbation (adjusted rate ratio [95% CI]: 0.65 [0.50, 0.85]) versus FF/VI 100/25 mcg (annualized rate FF/VI 100/25 mcg 0.87, FF/VI 200/25 mcg 0.57). Time to first moderate/severe exacerbation is shown in **Figure 3**.
  - A total of 73 and 106 severe exacerbations were reported for FF/VI 200/25 mcg and FF/VI 100/25 mcg, respectively.
- Greater improvements in ACQ-7 total score and more ACQ-7 responders at Week 24 (**Figure 4**) were seen with FF/VI 200/25 mcg compared with FF/VI 100/25 mcg. No difference in SGRQ total score and proportion of responders was observed between both treatments.
- The safety profile for both treatments was similar (**Table 2**).

Table 1. Baseline demographics and clinical characteristics (ITT population)

	FF/VI 100/25 mcg (N=407)	FF/VI 200/25 mcg (N=406)
Age, years, mean (SD)	53.3 (13.03)	53.9 (13.30)
Male, n (%)	153 (38)	154 (38)
Onset age of asthma, years, mean (SD)	32.8 (19.09)	33.2 (18.93)
BMI (kg/m²), mean (SD)	29.29 (6.08)	29.38 (6.29)
Total number of exacerbations in 12 months prior to screening, n (%)		
0	62 (15)	62 (15)
1	219 (54)	251 (62)
≥2	126 (31)	93 (23)
Former smokers, n (%)	69 (17)	69 (17)
Eosinophils at screening (10^9/L), mean (SD)*	0.327 (0.274)	0.305 (0.239)
Pre-bronchodilator FEV_1, % predicted, mean (SD) (screening)†	58.24 (13.06)	58.66 (13.20)
ACQ-6 score, mean (SD)‡ (screening)	2.48 (0.61)	2.53 (0.66)

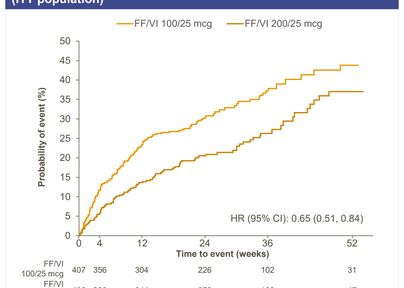
*FF/VI 100/25 mcg, n=382 and FF/VI 200/25 mcg, n=389; †FF/VI 100/25 mcg, n=402 and FF/VI 200/25 mcg, n=401; ‡FF/VI 100/25 mcg, n=406. BMI, body mass index; SD, standard deviation

Figure 2. LS mean change from baseline in clinic trough FEV_1 at Week 24 (ITT population)



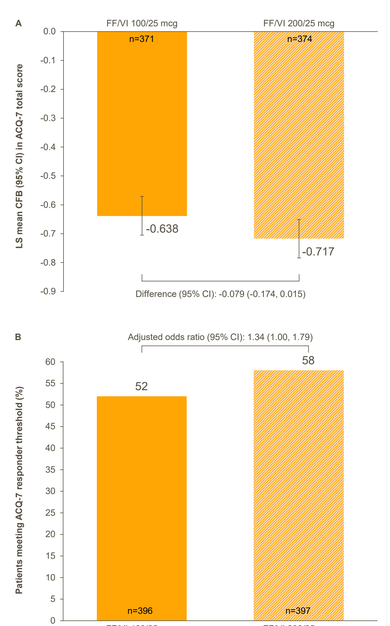
Analysis performed using mixed model repeated measures with covariates of treatment, age, sex, region, baseline value, pre-study ICS dosage at screening, and visit, interaction terms for baseline value by visit and treatment by visit. LS, least squares

Figure 3. Time to first moderate/severe exacerbation (ITT population)



Analysis performed using a Cox proportional hazards model with covariates of treatment, age, sex, region, pre-study ICS dosage at screening, severe asthma exacerbations in the previous year (0, 1, ≥2). HR, hazard ratio

Figure 4. (A) LS mean change from baseline and (B) responder rates for ACQ-7 total score at Week 24 (ITT population)



Responder threshold is defined as an improvement (decrease) of ≥0.5 points from baseline. Analysis performed using mixed model repeated measures (for **A**) and generalized linear mixed model with a logit link function (for **B**) with covariates of treatment, age, sex, region, baseline value, pre-study ICS dosage at screening, and visit, interaction terms for baseline value by visit and treatment by visit.

Conclusions

- Clinically significant improvements from screening in trough FEV_1 and ACQ score were observed at the end of the run-in and stabilization period with FSC and FF/VI 100/25 mcg, respectively.
- Doubling the FF dose provided modest lung function improvements and a 35% reduction in annualized moderate/severe exacerbation rates. Trends for improvements in asthma control were noted and there was no increase in the risk of AEs.
- These results demonstrate the dose–response effect of FF/VI on clinical outcomes and suggest that increasing the FF dose may be a suitable treatment-escalation option for patients uncontrolled with ICS/LABA therapy.

Table 2. On-treatment AEs and AESIs relevant to ICS class effects (ITT population)

n (%)	FF/VI 100/25 mcg (N=407)	FF/VI 200/25 mcg (N=406)
Any AE	258 (63)	210 (52)
AE leading to discontinuation	11 (3)	5 (1)
Drug-related AE	21 (5)	17 (4)
SAE	25 (6)	21 (5)
AESI relevant to ICS class effects		
Decreased BMD and associated fractures	5 (1)	2 (<1)
Hyperglycemia/new-onset DM	12 (3)	8 (2)
Infective pneumonia	7 (2)	7 (2)
LRTI excluding infective pneumonia	20 (5)	25 (6)
Local steroid effects	12 (3)	17 (4)

Note: Preferred terms may have contributed to more than one special interest group. AESIs were counted in each special interest group in which they appeared.
BMD, bone mineral density; DM, diabetes mellitus; LRTI, lower respiratory tract infection

References

1. Bateman ED, et al. *Thorax* 2014;69:312–9; 2. Bernstein DI, et al. *J Asthma* 2015;52:1073–83; 3. Davis J, et al. *J Asthma* 2019;56:332–40; 4. Lee LK, et al. *J Asthma* 2018;55:208–19; 5. Sulaiman S, et al. *Eur Resp J* 2018;51:1701126; 6. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. Available at: https://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf [last accessed January 2020].

Disclosures

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- ZB, NB, DE, AF, LAL, GP, NS, and FG are employees of GSK and hold stocks or shares in GSK. SP was an employee of GSK at the time of study and owns stocks in GSK. NAH reports receiving personal fees from AstraZeneca, Boehringer Ingelheim, Genentech, Genzyme, GSK, Mylan, Novartis, Regeneron, Sanofi, Sunovion, and for serving as an advisor or consultant. He also received research support from Astra Zeneca, Boehringer Ingelheim, and GSK. HK has received research grants and served on advisory boards for Boehringer Ingelheim, GSK, and Novartis. EK is an employee of Crisor LLC Research and has served on advisory boards, speaker panels or received travel reimbursement from Amphastar, AstraZeneca, Boehringer Ingelheim, Forest, GSK, Mylan, Novartis, Pearl, Sunovion, Teva, and Theravance. EK has also conducted multicenter clinical research trials for approximately 40 pharmaceutical companies. IDP has received speaker's fees, payments for organizing education events, honoraria for attending advisory panels, sponsorship to attend international scientific meetings, research grants or payments to support FDA approval meetings from Aerocrine, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Genentech, GSK, Knopp, Merck, Novartis, Sanofi/Regeneron, and Teva.
- IDP acted as an expert witness for a patent dispute involving AstraZeneca and Teva, is a Co-patent holder for the Leicester Cough Questionnaire, and has received payments for use of the Leicester Cough Questionnaire in clinical trials from Bayer, Insmed, and Merck.
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