

CAPTAIN Study: Simultaneous Step-up to High Dose Fluticasone Furoate and Addition of Umeclidinium for the Treatment of Inadequately Controlled Asthma

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Background

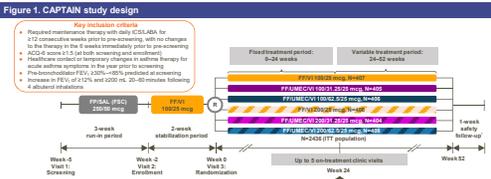
- Despite adherence to inhaled corticosteroid (ICS)/long-acting β_2 -agonist (LABA) therapy, $\geq 30\%$ of patients with asthma remain symptomatic and poorly controlled.^{1,4}
- Approximately 10%–25% of Global Initiative for Asthma Step 3 or higher patients experience an exacerbation within a 1-year period.^{5,6}
- Addition of a long-acting muscarinic antagonist (LAMA) to ICS/LABA therapy improves lung function and reduces exacerbation rates in patients with asthma.^{7,8}
- Single-inhaler triple therapy with the ICS/LAMA/LABA combination of fluticasone furoate/umeclidinium/vilanterol (FF/UMECVI) is approved as a once-daily treatment for chronic obstructive pulmonary disease (COPD), but previously no studies had investigated its use in patients with asthma.
- The Phase IIIA CAPTAIN clinical study in Asthma Patients receiving Triple therapy in A single Inhaler study was designed to evaluate the efficacy and safety of once-daily FF/UMECVI in comparison with FFVI (both administered via a single inhaler) in patients with asthma inadequately controlled on ICS/LABA.
 - Results showed improved lung function and numerical reductions in the annualized rate of moderate/severe exacerbation with FF/UMECVI versus FFVI, with no new or unexpected safety findings.⁹

Aims

- To report data from the CAPTAIN study on the effects of simultaneously doubling ICS dose and adding LAMA on lung function, moderate/severe exacerbations, and symptom control in patients with asthma inadequately controlled on ICS/LABA.

Methods

- CAPTAIN was a Phase IIIA, randomized, 24–52-week, parallel-group study (GSK study 205715, NCT02924688). The study design is shown in Figure 1.
- To assess the impact of simultaneously doubling ICS dose and adding LAMA, we report treatment differences for FFVI 200/25 mcg, FF/UMECVI 200/62.5/25 mcg, and FF/UMECVI 200/62.5/25 mcg versus FFVI 100/25 mcg for the following endpoints:
 - Change from baseline in trough forced expiratory volume in 1 second (FEV₁) at Week 24 (primary endpoint), analyzed using a mixed model repeated measures model
 - Annualized rate of moderate/severe asthma exacerbations (key secondary endpoint), analyzed using a negative binomial model
 - Proportion of Asthma Control Questionnaire (ACQ-7) responders (response defined as a decrease [improvement] from baseline of ≥ 0.5 units) at Week 24
 - Proportion of St. George's Respiratory Questionnaire (SGRQ) responders (response defined as a decrease [improvement] from baseline of ≥ 4 units) at Week 24
- For all analyses reported, P-values were not adjusted for multiplicity.



FF/VI, fluticasone furoate/VI; FF/UMECVI, fluticasone furoate/umeclidinium/vilanterol. *FF/VI 100/25 mcg was the control group. All doses are mcg. LS, least squares. P-values were not adjusted for multiplicity. Baseline values were last value prior to randomization. n=patients with analyzable data. All doses are mcg. LS, least squares.

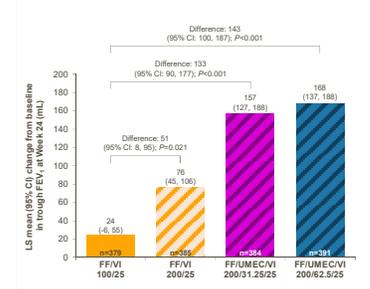
Results

- 2436 participants were included in the intent-to-treat (ITT) population.
- Patient demographics and clinical characteristics at screening and baseline were generally similar across treatment arms (Table 1). Notably, the population was not enriched for frequent exacerbators.
- Effects of simultaneously doubling FF dose and adding UMEC led to the greatest improvement overall (Figure 2).
 - There was a 143 mL (95% confidence interval [CI]: 100, 187) greater change from baseline in trough FEV₁ with FF/UMECVI 200/62.5/25 mcg versus FFVI 100/25 mcg at Week 24.
- Doubling FF dose led to numerical reductions in the annualized rate of moderate/severe exacerbations versus FFVI 100/25 mcg, while the effect of simultaneously adding UMEC was minimal (Figure 3).
 - The adjusted odds ratio for ACQ-7 response was 1.71 (95% CI: 1.27, 2.30) for FF/UMECVI 200/62.5/25 mcg versus FFVI 100/25 mcg.
- The SGRQ responder analysis demonstrated high levels of response across all groups; however, there was no clear indication of differences between treatments (Figure 5).

| | FFVI 100/25 (N=487) | FFVI 200/25 (N=486) | FF/UMECVI 200/62.5/25 (N=484) | FF/UMECVI 200/62.5/25 (N=488) | Total (N=2436) |
|--|-----------------------|-----------------------|-------------------------------|-------------------------------|------------------------|
| Age, years, mean (SD) | 53.3 (13.03) | 53.9 (13.30) | 53.5 (13.12) | 53.7 (12.90) | 53.2 (13.14) |
| Male, n (%) | 153 (38) | 154 (38) | 164 (41) | 150 (37) | 622 (38) |
| BMI (kg/m ²), mean (SD) | 29.3 (6.08) | 29.4 (6.29) | 29.4 (7.07) | 29.7 (6.53) | 29.4 (6.64) |
| Total number of exacerbations in 12 months prior to screening, n (%) | | | | | |
| 0 | 62 (15) | 62 (15) | 66 (16) | 45 (12) | 254 (15) |
| 1 | 219 (54) | 251 (62) | 224 (55) | 235 (58) | 1398 (57) |
| 2 | 126 (31) | 93 (23) | 114 (28) | 125 (31) | 662 (28) |
| Former smokers, n (%) | 69 (17) | 69 (17) | 80 (20) | 93 (23) | 476 (19) |
| Pre-bronchodilator FEV ₁ , % predicted screening, mean (SD) | n=402 58.2 (13.03) | n=401 58.7 (13.20) | n=404 57.4 (12.70) | n=406 58.98 (13.26) | n=1618 58.6 (13.29) |
| Mean reversibility to salbutamol at screening, % mean (SD) | n=402 28.5 (18.07) | n=403 29.1 (18.29) | n=403 30.0 (18.08) | n=406 29.88 (18.45) | n=1618 29.9 (18.12) |
| ACQ-7 score at screening, mean (SD) | n=401 2.8 (0.59) | n=404 2.8 (0.63) | n=401 2.8 (0.60) | n=401 2.8 (0.61) | n=1618 2.8 (0.61) |

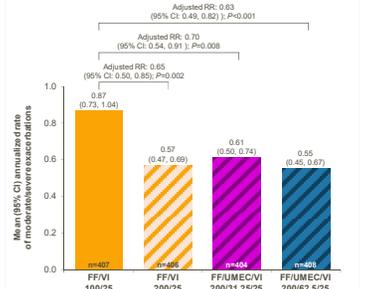
n=patients with analyzable data. All doses are mcg. BMI, body mass index; SD, standard deviation

Figure 2. LS mean change from baseline in trough FEV₁ at Week 24



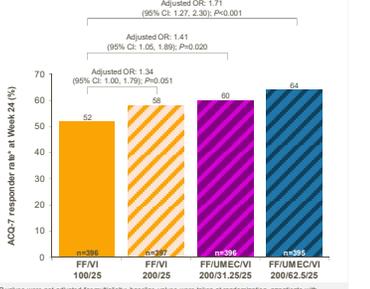
P-values were not adjusted for multiplicity. Baseline values were last value prior to randomization. n=patients with analyzable data. All doses are mcg. LS, least squares.

Figure 3. Mean annualized rate of moderate/severe exacerbations



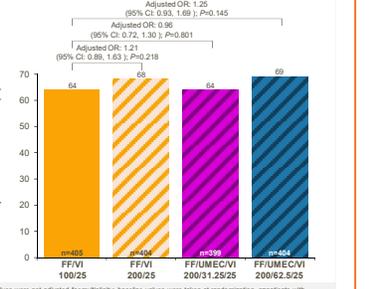
P-values were not adjusted for multiplicity. All doses are mcg. RR, rate ratio.

Figure 4. ACQ-7 responder rate at Week 24



P-values were not adjusted for multiplicity; baseline values were taken at randomization. n=patients with analyzable data at Week 24. All doses are mcg. *Patients reaching a responder threshold of ≥ 0.5 -points (the MCD) [improvement from baseline, MCD, minimal clinically important difference, OR, odds ratio]

Figure 5. SGRQ responder rate at Week 24



P-values were not adjusted for multiplicity; baseline values were taken at randomization. n=patients with analyzable data at Week 24. All doses are mcg. *Patients reaching a responder threshold of ≥ 4 -points (the MCD) [improvement from baseline, MCD, minimal clinically important difference, OR, odds ratio]

References

- Salzman I, et al. Eur Respir J. 2018;51:1701126.
- Balaban DJ, et al. J Allergy Clin Immunol. 2019;143:1073-83.
- Chaves I, et al. J Allergy Clin Immunol. 2019;143:1073-83.
- Lee LA, et al. J Allergy Clin Immunol. 2019;143:1073-83.
- Pavord ID, et al. J Allergy Clin Immunol. 2020;145(2 Suppl):A841.
- Suzuki RV, et al. BMC Pulm Med. 2017;17:74.
- Zeilger RS, et al. J Allergy Clin Immunol Pract. 2014;2:741-50.
- Vitchovsk J, et al. Lancet. 2019;393:1937-49.
- Katagiri AK, et al. J Exp Med. 2019;211:1198-207.
- Pavord ID, et al. J Allergy Clin Immunol. 2020;145(2 Suppl):A841.
- Pavord ID, et al. Am J Respir Crit Care Med. 2020;201:A6247.

Disclosures

- This study was funded by GlaxoSmithKline (GSK; study 205715/NCT02924688).
- Dr. AP, Dr. DC, Dr. NB, and Dr. WF are employees of GSK and hold stocks or shares in GSK. LAA is an employee of GSK and holds stocks or shares in GSK. LAA has received research grants and served on advisory boards for AstraZeneca, GSK, and Novartis. Dr. Lee has received research grants and served on advisory boards for AstraZeneca, GSK, and Novartis. Dr. Lee has received research grants and served on advisory boards for AstraZeneca, GSK, and Novartis. Dr. Lee has received research grants and served on advisory boards for AstraZeneca, GSK, and Novartis. Dr. Lee has received research grants and served on advisory boards for AstraZeneca, GSK, and Novartis.

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