CAPTAIN Study: Treatment Outcomes From Fluticasone Furoate/Umeclidinium/Vilanterol According to History of Severe Asthma Exacerbations

Poster No. P202

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Background

- The addition of a long-acting muscarinic antagonist (LAMA) to inhaled corticosteroid/long-acting β$_2$-agonist (ICS/LABA) in a single or multi-inhaler treatment has been shown to improve lung function, and potentially exacerbation rates, for patients uncontrolled on ICS/LABA with a history of severe exacerbations.[1–3]
- Previous studies have shown that frequency of asthma exacerbations and lung function decline may be related to the occurrence of prior exacerbations.[4–6]
- The Phase IIIA CAPTAIN study evaluated the efficacy and safety of once-daily fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) in comparison with FF/VI in patients with asthma inadequately controlled on medium–high dose ICS/LABA.[7] The CAPTAIN population was not enriched for severe exacerbators; however, asthma-related healthcare contact/temporary therapy change in the past year was required.
  - Results showed improved lung function and asthma control, and numerical reductions in the annualized rate of moderate/severe exacerbations with FF/UMEC/VI versus FF/VI, with no new or unexpected safety findings.[7]
- This analysis of the CAPTAIN study reports subgroup data for patients with a history of ≥1 severe exacerbation at baseline compared to those with no prior severe exacerbations and to the overall population.

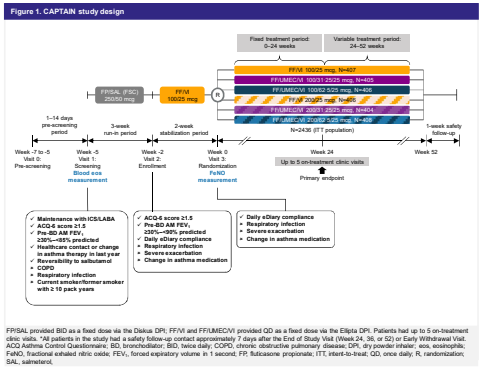
Objective

- This subgroup analysis of CAPTAIN aimed to investigate the effects of a history of severe asthma exacerbations on outcomes when adding a LAMA, increasing FF dose, or both, in patients with uncontrolled GINA-defined moderate/severe asthma despite ICS/LABA therapy.
- A subgroup analysis of the CAPTAIN study investigating the effects of FF/UMEC/VI on lung function in asthma according to age is being presented separately at this congress (Poster no. P206).

Methods

- CAPTAIN was a Phase IIIA, randomized, double-blind, 24–52-week, parallel-group study (GSK study 205715, NCT02924688). The study design is shown in **Figure 1**.

Figure 1. CAPTAIN study design



FP/SAL provided BID as a fixed dose via the Diskus DPI; FF/VI and FF/UMEC/VI provided QD as a fixed dose via the Ellipta DPI. Patients had up to 5 on-treatment clinic visits. *All patients in the study had a safety follow-up contact approximately 7 days after the End of Study Visit (Week 24, 36, or 52) or Early Withdrawal Visit. ACQ Asthma Control Questionnaire; BD, bronchodilator; BID, twice daily; COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; eos, eosinophils; FeNO, fractional exhaled nitric oxide; FEV$_1$, forced expiratory volume in 1 second; FP, fluticasone propionate; ITT, intent-to-treat; QD, once daily; R, randomization; SAL, salmeterol.

- Here we report the following endpoints by severe exacerbations in the previous year (0 vs ≥1):
  - Change from baseline in trough FEV$_1$ (primary endpoint) and FEV$_1$ 3 hours post dose at Week 24.
  - Annualized rate of moderate/severe exacerbations (Weeks 1–52; key secondary endpoint).
- The following comparisons reported here were performed post hoc:
  - All comparisons for the FEV$_1$ 3-hour post-dose data in both subgroups.
  - FF 200 mcg-containing therapies versus FF/VI 100/25 mcg for trough FEV$_1$ and annualized rate of moderate/severe exacerbations in both subgroups.
- On- and post-treatment exacerbations (over Weeks 1–52) were defined as follows:
  - Moderate: deterioration in asthma symptoms or lung function, or increased rescue bronchodilator use lasting for ≥2 days, requiring a physician-directed temporary change in maintenance treatment to prevent the exacerbation from becoming severe.
  - Severe: requiring admission to hospital or a visit to an emergency department for systemic corticosteroids, or asthma deterioration requiring systemic corticosteroid use (or doubling of the current maintenance systemic corticosteroid dose) for ≥3 days.[8,9]
- Pre-treatment exacerbations did not follow the same definitions and were instead classified based on the investigator's opinion of the available objective evidence.

Results

- In the previous year, 16% and 63% of patients had ≥2 and ≥1 severe exacerbations, respectively.
- Baseline demographics were generally similar for those with and without a severe exacerbation history (**Table 1**).
- Lung function and asthma control (ACQ-7 score) were slightly poorer among those with a severe exacerbation history (**Table 1**). A higher proportion of patients with no severe exacerbation history were on medium-dose ICS at baseline than those with a severe exacerbation history.

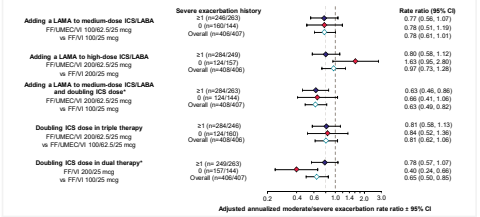
Table 1. Baseline demographics and clinical characteristics

	History of severe exacerbations		Overall (N=2436)
	≥1 (N=1544)	0 (N=892)	
Baseline demographics			
Age, years, mean (SD)	53.7 (12.9)	52.2 (13.4)	53.2 (13.1)
Male, n (%)	579 (38)	343 (38)	922 (38)
BMI (kg/m^2), mean (SD)	29.36 (6.56)	29.33 (6.79)	29.35 (6.64)
Never smoked, n (%)	1244 (81)	722 (81)	1966 (81)
Clinical characteristics			
Pre-bronchodilator FEV$_1$, mL, mean (SD)*	n= 1542 1981 (675)	n=892 2097 (675)	n=2434 2023 (677)
Percent predicted pre-dose FEV$_1$, %, mean (SD)†	n=1536 67.46 (15.20)	n=884 69.43 (13.89)	n=2420 68.18 (14.76)
Pre-dose FEV$_1$/FVC ratio, mean (SD)†	n=1536 0.65 (0.12)	n=884 0.65 (0.11)	n=2420 0.65 (0.12)
ACQ-7 score, mean (SD)†	n=1510 2.16 (0.71)	n=873 2.05 (0.68)	n=2383 2.12 (0.70)
Pre-study ICS – patients on medium dose at screening‡, n (%)	992 (64)	629 (71)	1621 (67)

N numbers include patients in 31.25 mcg UMEC-containing groups. *The last acceptable/borderline acceptable pre-dose FEV$_1$ prior to randomized treatment start date; †at randomization ‡at screening, medium dose defined as >250–≤500 mcg/day FP (or equivalent). A total of 376 (16%) and 1544 (63%) of patients had ≥2 and ≥1 severe exacerbations in the previous year, respectively. BMI, body mass index; SD, standard deviation

- Addition of UMEC 62.5 mcg to FF/VI 100/25 or 200/25 mcg was associated with improvements in trough FEV$_1$, with a possible trend for greater improvements among those without severe exacerbations with addition of UMEC 62.5 mcg to FF/VI 100/25 mcg (**Figure 2A**).
- This finding was supported by similar trends in FEV$_1$ 3 hours post dose (**Figure 2B**).

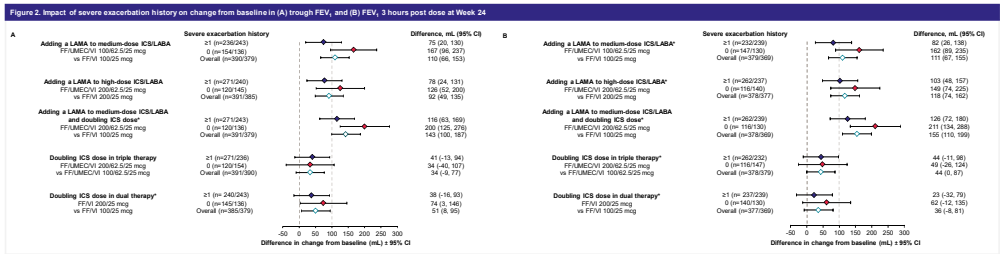
Figure 3. Impact of severe exacerbation history on annualized rate of moderate/severe exacerbations



*Comparison was performed post hoc for the ≥1 and 0 severe exacerbation history subgroups. n=number of subjects with analyzable data for each treatment (Weeks 1–52).

- In the overall population, adding UMEC 62.5 mcg to FF/VI 100/25 mcg but not 200/25 mcg improved the annualized moderate/severe exacerbation rate (**Figure 3**). When adding a LAMA or doubling ICS dose, rate ratios for subjects with severe exacerbation history were generally consistent with the overall results. Less consistency with the overall results was observed for subjects with no severe exacerbation history.
- For patients with a severe exacerbation history, the annualized moderate/severe exacerbation rate improved from 0.93 to 0.72 when adding UMEC 62.5 mcg to FF/VI 100/25 mcg or doubling FF dose. There was a further improvement to 0.58 with simultaneous step-up (**Table 2**). Similar patterns were seen in the overall population and no severe exacerbation history subgroups when adding UMEC, but simultaneous step up did not improve the moderate/severe exacerbation rate any more than doubling FF dose in these groups.
- Doubling ICS dose improved all outcomes reported here regardless of exacerbation history (**Figure 2 & 3**).

Figure 2. Impact of severe exacerbation history on change from baseline in (A) trough FEV$_1$ and (B) FEV$_1$ 3 hours post dose at Week 24



*Comparison was performed post hoc for the ≥1 and 0 severe exacerbation history subgroups. n = number of patients with analyzable data at Week 24 for each treatment. CI, confidence interval

Table 2. Treatment outcomes by history of severe exacerbations

	Treatment groups	FF/VI 100/25 mcg	FF/UMEC/VI 100/62.5/25 mcg	FF/VI 200/25 mcg	FF/UMEC/VI 200/62.5/25 mcg
Severe exacerbation history ≥1	Trough FEV$_1$, at Week 24 — Patients with analyzable data at Week 24 (n)	243	236	240	271
	Trough FEV$_1$, at Week 24 — LS mean CFB, mL (95% CI)	37 (-1, 76)	112 (73, 151)	76 (37, 114)	153 (117, 190)
	FEV$_1$ 3 hours post dose at Week 24 — Patients with analyzable data at Week 24 (n)	239	232	237	262
	FEV$_1$ 3 hours post dose at Week 24 — LS mean CFB, mL (95% CI)	152 (113, 191)	234 (194, 274)	175 (136, 215)	278 (241, 315)
	Annualized rate of moderate/severe exacerbations — n	263	246	249	284
	Annualized rate of moderate/severe exacerbations — Mean rate (95% CI)	0.93 (0.75, 1.15)	0.72 (0.57, 0.91)	0.72 (0.57, 0.91)	0.58 (0.46, 0.74)
Severe exacerbation history = 0	Trough FEV$_1$, at Week 24 — Patients with analyzable data at Week 24 (n)	136	154	145	120
	Trough FEV$_1$, at Week 24 — LS mean CFB, mL (95% CI)	1 (-50, 53)	188 (119, 216)	75 (26, 125)	202 (146, 257)
	FEV$_1$ 3 hours post dose at Week 24 — Patients with analyzable data at Week 24 (n)	130	147	140	116
	FEV$_1$ 3 hours post dose at Week 24 — LS mean CFB, mL (95% CI)	94 (41, 147)	256 (206, 306)	156 (105, 207)	306 (249, 362)
	Annualized rate of moderate/severe exacerbations — n	144	160	157	124
	Annualized rate of moderate/severe exacerbations — Mean rate (95% CI)	0.82 (0.61, 1.11)	0.64 (0.47, 0.87)	0.33 (0.22, 0.49)	0.54 (0.37, 0.78)
Overall population	Trough FEV$_1$, at Week 24 — Patients with analyzable data at Week 24 (n)	379	390	385	391
	Trough FEV$_1$, at Week 24 — LS mean CFB, mL (95% CI)	24 (-6, 55)	134 (104, 165)	76 (45, 106)	168 (137, 198)
	FEV$_1$ 3 hours post dose at Week 24 — Patients with analyzable data at Week 24 (n)	369	379	377	378
	FEV$_1$ 3 hours post dose at Week 24 — LS mean CFB, mL (95% CI)	132 (100, 163)	243 (212, 274)	168 (137, 199)	286 (255, 317)
	Annualized rate of moderate/severe exacerbations — n	407	406	406	408
	Annualized rate of moderate/severe exacerbations — Mean rate (95% CI)	0.87 (0.73, 1.04)	0.68 (0.56, 0.82)	0.57 (0.47, 0.69)	0.55 (0.45, 0.67)

CFB, change from baseline; LS, least squares

Conclusions

- For patients uncontrolled on ICS/LABA, the addition of UMEC was associated with improved lung function, with a possible trend for greater improvements among those without a history of severe exacerbations.
- Doubling FF dose was associated with improved lung function and exacerbation rate regardless of prior severe exacerbations.
  - Additional analyses of the CAPTAIN study presented elsewhere[7] have shown that the effects of doubling FF dose on exacerbations appear to be more pronounced in patients with raised biomarkers of type 2 airway inflammation.
- When treating patients with one or more baseline severe exacerbations, simultaneously adding UMEC and doubling FF dose appeared to be most successful, leading to greater reductions in annualized moderate/severe exacerbation rates versus adding UMEC or increasing FF dose alone.
- The availability of FF/UMEC/VI with medium and high FF doses may help patients with uncontrolled asthma achieve better asthma control utilizing a once-daily single-inhaler therapy.

Disclosures

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- Ellipta and Diskus are owned by or licensed to the GSK Group of Companies.
- Figure 1 was reprinted from *The Lancet Respiratory Medicine*, Lee LA et al., Efficacy and safety of once-daily single-inhaler triple therapy (FF/UMEC/VI) versus FF/VI in patients with inadequately controlled asthma (CAPTAIN): a double-blind, randomised, phase 3A trial [Epub ahead of print], Copyright (2020), with permission from Elsevier.
- On behalf of all authors, an audio recording of this poster was prepared by John Oppenheimer, who did not receive any payment for this recording.
- JO: has served on adjudication committees/data and safety monitoring boards for AstraZeneca, GSK, Novartis, and Sanofi/Regeneron, and has received grants/personal fees from GSK. IDP is an employee of the University of Oxford. He has received research grants, speaker fees, fees for advisory boards and travel expenses for attending international meetings/advisory boards from Chiesi and Afferent. He has received speaker's honoraria, travel expenses and honoraria for attending advisory boards from AstraZeneca, Boehringer Ingelheim, GSK, and Teva. IDP: has also received speakerfees/fees for advisory boards from Circassia,Knopp, Merck, Mundipharma, Novartis, Roche/Genentech, and Sanofi/Regeneron. WB: reports grants from NIH-NIAID, consulting fees from AstraZeneca, Novartis, GSK, Genentech, Sanofi, Regeneron, Boston Scientific (Data Safety Monitoring Board), and Elsevier (royalties). PW: is an employee of Allergy, Asthma & Immunology Center, SC, The Clinical Research Center of Southern Illinois, LLC, and TIO Food Therapies, PLLC and has served on advisory boards, speaker panels, and/or received speaker honoraria and travel reimbursement from Genentech, AstraZeneca, Regeneron/Sanofi, GSK, Merck, and Teva. He has served as an investigator and conducted multicenter clinical research trials for approximately 20 pharmaceutical companies over the past 15 years. NJ has received speaker's honoraria and honoraria for advisory boards from Regeneron, Sanofi-Genzyme, AstraZeneca, Novartis, Optinose, Pfizer, Merz, and Allakos. AZ and AF: are employees of and own stocks and shares in GSK. DM: was an employee of GSK at the time of the study, and owns stocks and shares in the company. GB has received speaker's fees from and served on advisory boards for AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, and Teva. He has served on advisory boards for Sanofi. 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, Cipla, Chiesi, Forest, GSK, Mylan, Novartis, Pearl, Sunovion, Teva, and Theravance. He has also conducted multicenter clinical research trials for approximately 40 pharmaceutical companies.

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CAPTAIN TRIAL

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