CAPTAIN: Effects of Body Mass Index (BMI) on Response to Triple Therapy in Patients With Inadequately Controlled Asthma on Inhaled Corticosteroids/Long-acting β_2-agonists (ICS/LABA)

Poster No. 176

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*At the time of the study

Background

- Approximately 30–50% of patients with asthma remain uncontrolled, despite adherence to inhaled corticosteroid/long-acting β_2-agonist (ICS/LABA) therapy.[1–4]
- The addition of a long-acting muscarinic antagonist (LAMA) to ICS/LABA therapy has been shown to improve lung function and reduce exacerbation rates in patients with asthma.[5–7]
- 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.
  - Results showed improved lung function, symptoms 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.[8]
- Several studies have suggested that obesity is associated with reduced lung function, poor asthma control and worsening of symptoms.[9,10]

Aims

- The objective of this prespecified subgroup analysis of CAPTAIN was to evaluate the influence of obesity on lung function, moderate/severe exacerbation rates and asthma control following the addition of UMEC 62.5 mcg to FF (100 and 200 mcg)/VI 25 mcg.

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**.

Figure 1. CAPTAIN study design

Key inclusion criteria

- ≥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

Key exclusion criteria

- Patients with COPD or other respiratory disorders, including pneumonia and pneumonia risk factors
- Current smokers and former smokers with a smoking history of ≥10 pack years

Week	Period	Treatment
Week -5 Weeks -5 to -2	**Visit 1: Screening** 3-week run-in period	FP/SAL 250/50 mcg
Week -2 Weeks -2 to 0	**Visit 2: Enrollment** 2-week stabilization period	FF/VI 100/25 mcg
Week 0 Weeks 0 to 24	**Visit 3: Randomization** Fixed treatment period	FF/VI 100/25 mcg (N=407) FF/UMEC/VI 100/31.25/25 mcg (N=405) FF/UMEC/VI 100/62.5/25 mcg (N=406) FF/VI 200/25 mcg (N=406) FF/UMEC/VI 200/31.25/25 mcg (N=404) FF/UMEC/VI 200/62.5/25 mcg (N=408)
Week 24 Weeks 24 to 52	**Primary endpoint** Variable treatment period	
	1-week safety follow-up*	

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; BID, twice daily; COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; FEV_1, forced expiratory volume in 1 second; FP, fluticasone propionate; QD, once daily; SAL, salmeterol

- Here we report prespecified analyses of CAPTAIN for the overall population and for subgroups defined according to BMI: <30 (non-obese) versus ≥30 kg/m^2 (obese).[11]
- Endpoints reported here are:
  - Change from baseline in trough FEV_1 at Week 24 (primary endpoint) analyzed using a mixed-model repeated measures (MMRM) model.
  - Annualized rate of moderate/severe asthma exacerbations (Weeks 1–52; key secondary endpoint) analyzed using a negative binomial model.
  - Change from baseline in ACQ-7 total score at Week 24 analyzed using a MMRM model.
  - Percentage of ACQ-7 responders at Week 24 analyzed using a generalized linear mixed model with a logit link function.
- For the overall analyses of the primary and key secondary endpoints, a step-down closed-testing hierarchy was used to account for multiplicity across endpoints and UMEC doses.
  - The overall analyses of moderate/severe asthma exacerbation rate, ACQ-7 total score, and ACQ-7 response presented here were not adjusted for multiplicity.
  - All subgroup analyses presented here were not adjusted for multiplicity.
  - Data for UMEC 62.5 mcg only are shown here.

Results

- A total of 2436 participants were included in the overall intent-to-treat (ITT) population. There were higher proportions of female patients (70%) and patients on high-dose ICS prior to the study (38%) in the obese subgroup compared with the non-obese subgroup (**Table 1**). Baseline lung function was also lower among patients in the obese subgroup.

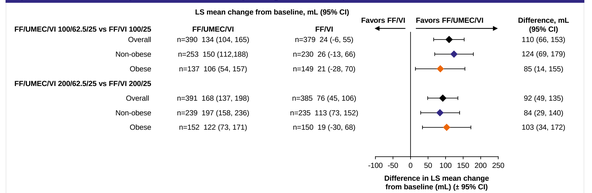
Table 1. Baseline demographics and clinical characteristics

	Non-obese (BMI <30 kg/m^2) N=1500 (62%)	Obese (BMI ≥30 kg/m^2) N=936 (38%)	Overall (ITT) N=2436
Demographics			
Age, years, mean (SD)	53.2 (13.65)	53.1 (12.22)	53.2 (13.11)
Male, n (%)	642 (43)	280 (30)	922 (38)
BMI, kg/m^2, mean (SD)	25.3 (2.94)	35.8 (5.71)	29.4 (6.64)
Clinical characteristics			
Pre-study ICS dose– medium dose*, n (%)	1039 (69)	582 (62)	1621 (67)
FEV_1, mL, mean (SD)†	n=1500 2069 (701)	n=934 1951 (632)	n=2434 2023 (677)
ACQ-7 score‡, mean (SD)	n=1473 2.053 (0.6939)	n=910 2.228 (0.7020)	n=2383 2.119 (0.7020)

Data for both UMEC doses (31.25 mcg and 62.5 mcg) are included; *At screening; medium dose defined as >250 to ≤500 mcg/day FP (or equivalent); †the last acceptable/borderline acceptable pre-dose FEV_1 prior to randomized treatment start date; ‡at randomization. SD, standard deviation

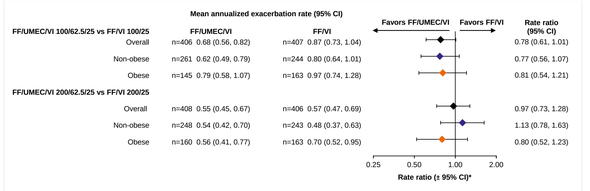
- Similar improvements in trough FEV_1 to the overall population were observed in both BMI subgroups following the addition of UMEC to FF/VI 100/25 mcg (mL, [95% {confidence interval} CI]: 110 [66, 153] in overall, 124 [69, 179] in non-obese and 85 [14, 155] in obese) or 200/25 mcg (mL, [95% CI]: 92 [49, 135] in overall, 84 [29, 140] in non-obese and 103 [34, 172] in obese) (**Figure 2**).
- As in the overall population, mean annualized exacerbation rates were numerically lower in both subgroups (rate ratios [95% CI] 0.78 [0.61, 1.01] for overall, 0.77 [0.56, 1.07] for non-obese and 0.81 [0.54, 1.21]) for obese) when UMEC was added to FF/VI 100/25 mcg (**Figure 3).** For the FF 200 mcg dose comparisons, the addition of UMEC was associated with a numerical reduction in the mean annualized rate of moderate/severe asthma exacerbations in the obese subgroup only (**Figure 3).**
- The addition of UMEC to FF/VI 100/25 mcg or 200/25 mcg was associated with a reduction (improvement) in ACQ-7 total score in the overall population and both BMI subgroups (**Figure 4**).
- For ACQ-7 response, trends were seen favoring addition of UMEC to FF/VI 100/25 mcg or 200/25 mcg in the overall population and across both BMI subgroups (**Figure 5**).

Figure 2. Effects of adding UMEC to FF/VI on trough FEV_1 at Week 24, by baseline BMI



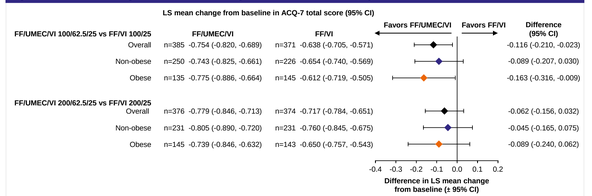
n = number of patients with analyzable data at Week 24 by treatment. LS, least squares

Figure 3. Effects of adding UMEC to FF/VI on annualized rate of moderate/severe exacerbations (Weeks 1–52) by baseline BMI



*Note: the x-axis is on a log scale. n = number of patients with analyzable data by treatment.

Figure 4. Effects of adding UMEC to FF/VI on ACQ-7 total score at Week 24, by baseline BMI

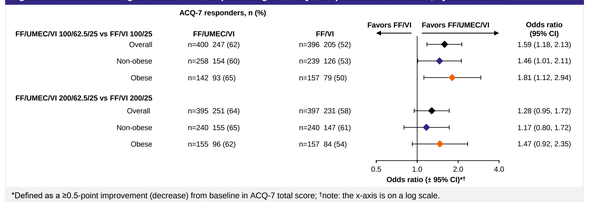


n = number of patients with analyzable data at Week 24 by treatment.

Conclusions

- Improvements in trough FEV_1, ACQ-7 total score and ACQ-7 response were observed with the addition of UMEC to either dose of FF/VI in both the obese and non-obese subgroups.
  - It should be noted that the number of patients in the obese subgroup was smaller than in the non-obese subgroup.
- The addition of UMEC to FF/VI 100/25 mcg was associated with numerical reductions in the mean annualized rate of moderate/severe asthma exacerbations in both BMI subgroups, as seen in the overall population. The addition of UMEC to FF/VI 200/25 mcg was associated with a numerical reduction in the mean annualized rate of moderate/severe asthma exacerbations in the obese subgroup only.
- Despite studies indicating that obesity may impact overall asthma control and symptoms, findings from this analysis indicate that the response to FF/UMEC/VI was largely consistent with the overall population, suggesting that obesity does not alter treatment response to FF/UMEC/VI.

Figure 5. Effects of adding UMEC to FF/VI on percentage of ACQ-7 responders* at Week 24, by baseline BMI



*Defined as a ≥0.5-point improvement (decrease) from baseline in ACQ-7 total score; †note: the x-axis is on a log scale.
n = number of patients with analyzable data at Week 24 by treatment.

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