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

Poster No. 179

Hanania NA[1], Bailes Z[2], Chang S[3], Fowler A[2], Lima R[3]*, Mannino D[3†], Millard MW[4], Spahn J[3]*, Weinstein S[5], Nathan R[6]

[1]Section of Pulmonary and Critical Care Medicine, Baylor College of Medicine, Houston, TX, USA; [2]GSK, Brentford, Middlesex, UK; [3]GSK, Research Triangle Park, NC, USA; [4]Baylor Scott & White Texas Lung Center, Dallas, TX, USA; [5]Allergy and Asthma Specialists Medical Group and Research Center, Huntington Beach, CA, USA; [6]Asthma & Allergy Associates, P.C. and Research Center, Colorado Springs, CO, USA
*At time of study; †At time of study. Now at University of Kentucky, Lexington, KY, USA

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]
- Treatment with LABA or LAMA has been associated with an increased risk of cardiovascular (CV) adverse events,[9–12] which may be heightened in patients already at risk of CV events before commencing bronchodilator treatment.

Aims

- The objective of this subgroup analysis of CAPTAIN was to investigate the effects of adding UMEC 62.5 mcg to FF (100 and 200 mcg)/VI on lung function, moderate/severe exacerbation rates and asthma control according to subgroups defined by CV risk at screening.

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	Week	Period	Treatment
• ≥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	**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)
Key exclusion criteria	**Week 24** Weeks 24 to 52	**Primary endpoint** Variable treatment period	
• 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		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 (unless otherwise stated) of CAPTAIN for the overall population and for subgroups defined according to CV risk at screening.
  - CV risk was defined as ≥1 of the following: past/current arrhythmia, congestive heart failure, coronary artery disease, myocardial infarction, cerebrovascular accident, hypertension, diabetes, or hypercholesterolemia.
- 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.
- For the overall analyses of the primary and 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 and ACQ-7 total score 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

- Of the 2436 patients in the intent-to-treat (ITT) population, 1181 (48%) were at CV risk at screening.
- Baseline demographics were generally similar across the two CV risk subgroups, although the mean age was higher in the subgroup at CV risk versus the subgroup not at CV risk at screening (**Table 1**). The proportion of patients on medium-dose ICS prior to the study and baseline lung function were both lower in the subgroup at CV risk versus the subgroup not at CV risk at screening.

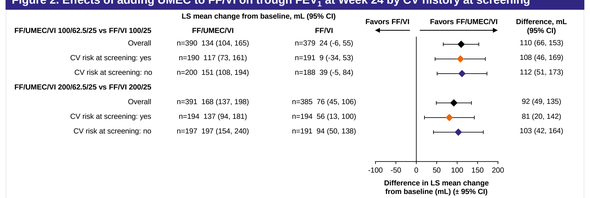
Table 1. Baseline demographics and clinical characteristics

	CV risk at screening: Yes N=1181	CV risk at screening: No N=1255	Overall (ITT) N=2436
Demographics			
Age, years, mean (SD)	59.4 (10.43)	47.3 (12.71)	53.2 (13.11)
Male, n (%)	420 (36)	502 (40)	922 (38)
BMI, kg/m^2, mean (SD)	30.9 (6.88)	27.9 (6.05)	29.4 (6.64)
Clinical characteristics			
Pre-study ICS – medium dose*, n (%)	748 (63)	873 (70)	1621 (67)
Pre-bronchodilator FEV_1†, mL, mean (SD)	n=1180 1829 (586)	n=1254 2207 (706)	n=2434 2023 (677)
ACQ-7 total score‡, mean (SD)	n=1149 2.171 (0.6930)	n=1234 2.071 (0.7072)	n=2383 2.119 (0.7020)

Data for both UMEC doses (31.25 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.
BMI, body mass index; SD, standard deviation

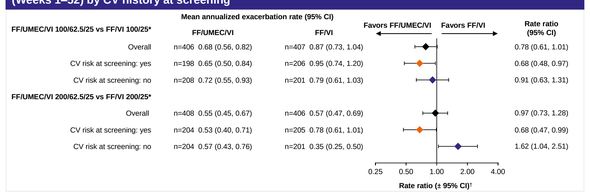
- Similar improvements in trough FEV_1 to the overall population were observed following the addition of UMEC to FF/VI 100/25 or 200/25 mcg in both CV risk subgroups (**Figure 2**).
- The addition of UMEC to FF/VI 100/25 mcg was associated with numerical reductions in the mean annualized rate of moderate/severe asthma exacerbations in both CV risk subgroups, as seen in the overall population (**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 subgroup of patients at CV risk only (**Figure 3**).
- The addition of UMEC to FF/VI 100/25 or 200/25 mcg was associated with a reduction (improvement) in ACQ-7 total score in the overall population and in the two CV risk subgroups (**Figure 4**).
- The safety profiles of the two CV risk subgroups were broadly similar (**Table 2**); however, there was a higher incidence of CV effects in the subgroup of patients at CV risk (n=14–19 [7–10%]) versus those not at CV risk (n=4–10 [2–5%]), as expected, together with a higher incidence of serious adverse events. There were no new safety signals from FF/UMEC/VI treatment in the subgroup of patients at CV risk.

Figure 2. Effects of adding UMEC to FF/VI on trough FEV_1 at Week 24 by CV history at screening



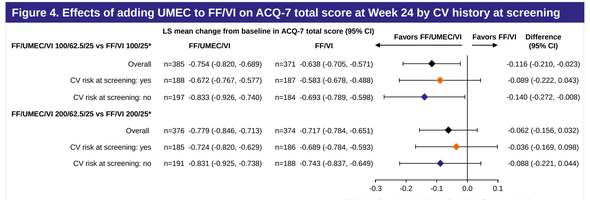
Comparisons were prespecified. n = number of patients with analyzable data at Week 24 by treatment. CI, confidence interval; LS, least squares

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



*Comparison was prespecified for the overall population and performed post hoc for the CV risk subgroups; †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 CV history at screening



*Comparison was prespecified for the overall population and performed post hoc for the CV risk subgroups. n = number of patients with analyzable data at Week 24 by treatment.

Table 2. Safety outcomes by CV risk at screening

	CV risk at screening: Yes N=1181				CV risk at screening: No N=1255			
	FF/VI 100/25 n=206	FF/UMEC/VI 100/62.5/25 n=198	FF/VI 200/25 n=205	FF/UMEC/VI 200/62.5/25 n=204	FF/VI 100/25 n=201	FF/UMEC/VI 100/62.5/25 n=208	FF/VI 200/25 n=201	FF/UMEC/VI 200/62.5/25 n=204
AEs, n (%)	142 (69)	127 (64)	119 (58)	113 (55)	116 (58)	112 (54)	91 (45)	104 (51)
AEs leading to treatment discontinuation, n (%)	7 (3)	5 (3)	3 (1)	2 (<1)	4 (2)	2 (<1)	2 (<1)	1 (<1)
Treatment-related AEs, n (%)	9 (4)	19 (10)	8 (4)	11 (5)	12 (6)	10 (5)	9 (4)	8 (4)
AESIs, n (%)								
CV effects	15 (7)	19 (10)	14 (7)	14 (7)	7 (3)	8 (4)	10 (5)	4 (2)
Supraventricular tachyarrhythmias (SMQ)	0	0	3 (1)	3 (1)	0	0	0	0
Tachyarrhythmia terms, nonspecific (SMQ)	0	0	0	0	0	0	0	0
Ventricular tachyarrhythmias (SMQ)	0	0	0	0	0	0	0	0
Infective pneumonia (SMQ)	6 (3)	3 (2)	4 (2)	1 (<1)	1 (<1)	2 (<1)	3 (1)	3 (1)
Dry mouth/drying of airway secretions (not including nasopharyngitis)*	0	1 (<1)	0	1 (<1)	1 (<1)	1 (<1)	0	0
Gastrointestinal obstruction (SMQ)*	1 (<1)	1 (<1)	0	0	0	0	0	0
LRTI excluding infective pneumonia SMQ*	10 (5)	11 (6)	17 (8)	10 (5)	10 (5)	13 (6)	8 (4)	13 (6)
SAEs, n (%)	18 (9)	15 (8)	14 (7)	16 (8)	7 (3)	8 (4)	7 (3)	5 (2)
MACE, n (%)	3 (1)	2 (1)	2 (<1)	3 (1)	2 (<1)	2 (<1)	0	0
AEs leading to death†, n (%)	0	0	1 (<1)	0	0	0	0	0

n = patients with analyzable data. *Special interest groups related to LAMA; †on-treatment fatal AE reported for one patient treated with FF/VI 200/25 mcg (circulatory collapse, not considered drug-related by the investigator). AE, adverse event; AESI, adverse event of special interest; LRTI, lower respiratory tract infection; MACE, major adverse cardiovascular event; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event; SMQ, standardized MedDRA queries

Conclusions

- Improvements in lung function (trough FEV_1) and asthma control (ACQ-7 total score) occurred following the addition of UMEC to either dose of FF/VI irrespective of CV risk at screening.
- 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 both in patients at CV risk and in patients who were not at CV risk at screening, as seen in the overall population. The addition of UMEC to FF/VI 200/25 mcg was associated with a numerical reduction in the rate of moderate/severe asthma exacerbations in the subgroup of patients at CV risk only; the lack of consistency for this treatment comparison is likely due to variability in the data.
- There were no new safety signals from FF/UMEC/VI treatment in the subgroup at CV risk at screening.
- Based on the totality of data presented, FF/UMEC/VI triple therapy is an effective treatment option with a favorable benefit–risk profile in patients whose asthma is inadequately controlled on ICS/LABA, irrespective of baseline CV risk.

References

1. Bernstein DI, et al. *J Asthma* 2015;52:1073–83.
2. Lee LK, et al. *J Asthma* 2018;55:208–19.
3. Sulaiman I, et al. *Eur Respir J* 2018;51:1701126.
4. Davis J, et al. *J Asthma* 2019;56:332–40.
5. Virchow JC, et al. *Lancet* 2019;394:1737–49.
6. Kerstjens HAM, et al. *N Engl J Med* 2012;367:1198–207.
7. Kerstjens HAM, et al. *Lancet Respir Med* 2020;8:1000–12.
8. Lee LA, et al. *Lancet Respir Med* 2021;9:69–84.
9. Almazura AA, et al. *Thorax* 2019;74:Suppl 2, P236.
10. Salpeter SR, et al. *Chest* 2004;125:2309–21.
11. Rogliani P, et al. *Expert Opin Pharmacother* 2019;20:737–50.
12. Singh S, et al. *JAMA* 2008;300:1439–50.

Disclosures

This study was funded by GlaxoSmithKline (GSK study 205715, NCT02924688). ELLIPTA and DISKUS are owned by or licensed to the GSK Group of Companies.

On behalf of all authors, an audio recording of this poster was prepared by Nicola Hanania, who did not receive any payment for this recording.

ZB, SC and AF are employees of GSK and hold stocks/shares in GSK. RL, DM and JS were employees of GSK at the time of the study and hold stocks/shares in GSK. NAH received personal fees from AstraZeneca, Genentech, GSK, Mylan, Sanofi, Regeneron, Amgen, and Teva and research support from Boehringer Ingelheim, GSK, Novartis, Sanofi Genzyme, and Genentech. MWM received personal fees from AstraZeneca, GSK, and Boehringer Ingelheim, and research support from AstraZeneca, GSK, and Boehringer Ingelheim. SW received research grants from AstraZeneca, Boehringer Ingelheim, GSK, and Teva. RN received speaker's fees and honoraria for advisory boards for GSK and Boehringer Ingelheim. MWM co-authored the abstract but was unable to review or approve the poster at this current time. JS co-authored the abstract and contributed to poster development but was unable to approve the final poster.

Editorial support in the form of preparation of the first draft based on input from all authors, and collation and incorporation of author feedback to develop subsequent drafts, was provided by Anne Errichelli, DPhil, of Fishawack Indicia Ltd., UK, part of Fishawack Health, and was funded by GSK.

Scan the QR code or go to http://bago.ca/aaaai_1 to access a downloadable version of this poster and the associated audio recording

Prepared for the American Academy of Allergy Asthma & Immunology Annual Meeting 2021