CAPTAIN Study: Treatable Traits and the Outcome of Treatment with Inhaled Fluticasone Furoate/Umeclidinium/Vilanterol (FF/UMEC/VI) Versus FF/VI Therapies in Patients with Uncontrolled Asthma, a Pre-specified Subgroup Analysis

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Background

- A 'treatable traits' approach has been proposed for the treatment of asthma, in which patients are characterized by the presence of potentially modifiable disease characteristics and managed through an individualized treatment plan tailored to target these traits.[1–4]
- The discovery of simple measures of type 2 airway inflammation, one of the most influential treatable traits, has been an important catalyst for this transition towards precision medicine.[5]
- There is consistent evidence that type 2 airway inflammation is an independent predictor of the response to corticosteroids in patients with airway disease.[5]
- The Phase IIIA CAPTAIN study evaluated the use of the inhaled corticosteroid/long-acting muscarinic antagonist/long-acting β_2-agonist (ICS/LAMA/LABA) combination of fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) versus FF/VI (both administered via a single inhaler) in patients with moderate-to-severe asthma who were uncontrolled on ICS/LABA.[6] The design of CAPTAIN enables a range of clinically important comparisons to explore treatment optimization in uncontrolled asthma in the context of treatable traits.

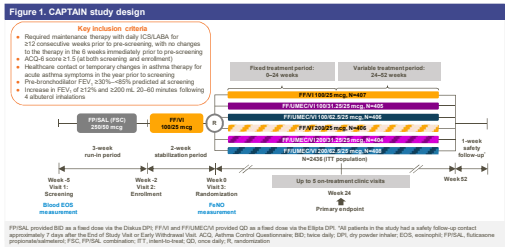
Aims

- To evaluate the influence of biomarkers of type 2 airway inflammation (baseline blood eosinophil and fractional exhaled nitric oxide (FeNO) levels) on the response to increasing ICS dose versus adding LAMA in patients with uncontrolled asthma on ICS/LABA enrolled in CAPTAIN.

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 response to increasing ICS dose versus adding LAMA, we report pre-specified comparisons of the effects of FF/VI 200/25 mcg versus FF/UMEC/VI 100/62.5/25 mcg for the following endpoints:
  - Change from baseline in trough forced expiratory volume in 1 second (FEV_1) 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
  - Fractional polynomial transformations were used to model the effect of eosinophil counts or FeNO levels on each endpoint. Models were adjusted for two transformations of the covariate and their interactions with treatment.
- In addition, we report post hoc analyses to explore whether findings from the pre-specified comparison of FF/VI 200/25 mcg versus FF/UMEC/VI 100/62.5/25 mcg were consistent when data were pooled to further evaluate the effects of doubling dose of ICS or adding a LAMA.

Figure 1. CAPTAIN study design



FF/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. *All patients in the study had a safety follow-up contact approximately 7 days after the End of Study Visit or Early Withdrawal Visit. ACQ, Asthma Control Questionnaire; BID; twice daily; DPI, dry powder inhaler; EOS, eosinophil; FF/SAL, fluticasone propionate/salmeterol; FSC, FF/SAL combination; ITT, intent-to-treat; QD, once daily; R, randomization

Results

Study population

- 2436 participants were included in the ITT population, with 406 participants in each of the FF/VI 200/25 mcg and FF/UMEC/VI 100/62.5/25 mcg treatment groups.
- Patient demographics and clinical characteristics at screening and baseline were generally similar across subgroups defined according to baseline eosinophil and FeNO levels (**Table 1**).

Pre-specified analyses

- In the ITT population, FF/UMEC/VI 100/62.5/25 mcg resulted in improvements in trough FEV_1 versus FF/VI 200/25 mcg, while FF/VI 200/25 mcg led to a numerically lower rate of moderate/severe exacerbations versus FF/UMEC/VI 100/62.5/25 mcg.
- Numerically greater improvements in clinic trough FEV_1 were observed with FF/UMEC/VI 100/62.5/25 mcg versus FF/VI 200/25 mcg across the baseline eosinophil and FeNO ranges (**Figure 2A**). The effect of FF/VI 200/25 mcg on trough FEV_1 appeared to increase with increasing baseline levels of eosinophils and FeNO.
- The effect of FF/VI 200/25 mcg on exacerbation rate was numerically greater as baseline eosinophil or FeNO levels increased (**Figure 2B**).

Post hoc analyses

- When all FF 100 mcg-containing treatment groups were pooled and compared with the pooled FF 200 mcg-containing treatment groups, doubling FF dose appeared to have a greater effect in patients with higher blood eosinophil and FeNO levels for both clinic trough FEV_1 (**Figure 3A**) and exacerbation rate (**Figure 3B**).
- In a further pooled analysis, addition of UMEC 62.5 mcg was associated with numerically greater improvements in trough FEV_1 across the range of baseline eosinophil/FeNO levels (**Figure 4A**), with a suggestion of a numerically greater reduction in the annualized rate of moderate/severe exacerbations at the lower range of these biomarkers (**Figure 4B**).
- An additional pooled analysis was conducted using a combined measure of baseline eosinophil and FeNO levels. The proportion of patients with a severe exacerbation was nearly three times higher in patients receiving FF 100 mcg-containing treatment in the high versus low baseline biomarker groups (**Table 2**); this relationship was not seen in patients receiving FF 200 mcg-containing treatments.
  - The low number of severe exacerbation events in the low and high combined biomarker groups may have influenced the outcomes.

Table 1. Baseline demographics and clinical characteristics for subgroups defined according to baseline eosinophil or FeNO levels (ITT population)

	EOS <150 cells/µl (N=851)	EOS ≥150 cells/µl (N=1735)	FeNO <25 ppb (N=1488)	FeNO ≥25 ppb (N=774)
Age (years), mean (SD)	53.6 (13.22)	53.1 (13.03)	52.9 (13.07)	53.7 (12.88)
Male, n (%)	334 (34)	681 (39)	533 (36)	326 (42)
Hispanic or Latino ethnicity, n (%)	48 (7)	196 (11)	143 (10)	89 (11)
BMI (kg/m^2), mean (SD)	29.6 (6.97)	29.2 (6.50)	29.5 (6.66)	28.7 (6.22)
Pre-study ICS – medium dose at screening*, n (%)	422 (65)	1170 (67)	996 (67)	509 (66)
Pre-bronchodilator FEV_1 at baseline† (L), mean (SD)	2.0 (0.65)	2.0 (0.68)	2.0 (0.65)	2.0 (0.70)
ACQ-7 score at baseline‡, mean (SD)	n=637 2.2 (0.68)	n=1697 2.1 (0.71)	n=1454 2.1 (0.69)	n=763 2.1 (0.73)

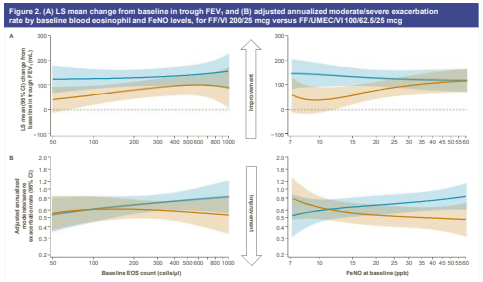
All doses are mcg. *Medium-dose defined as >250 to ≤500 mcg/day fluticasone propionate (or equivalent). †The last acceptable/borderline acceptable pre-dose FEV_1 prior to randomized treatment start date. ‡At randomization visit. BMI, body mass index; ppb, parts per billion; SD, standard deviation

Table 2. Severe exacerbations by a combined measure of type 2 inflammatory biomarkers

Pooled treatment groups	Low type 2 inflammatory biomarkers (EOS <150 cells/µl and FeNO <20 ppb) N=455	Medium type 2 inflammatory biomarkers (all other patients with an EOS and FeNO measurement) N=1674	High type 2 inflammatory biomarkers (EOS ≥300 cells/µl and FeNO >50 ppb) N=138
FF 100 mcg-containing therapies	n=194	n=836	n=67
Patients with a severe exacerbation, n (%)	24 (12%)	153 (18%)	22 (33%)
Total number of severe exacerbations	35	227	32
FF 200 mcg-containing therapies	n=211	n=838	n=71
Patients with a severe exacerbation, n (%)	29 (14%)	113 (13%)	9 (13%)
Total number of severe exacerbations	35	146	15

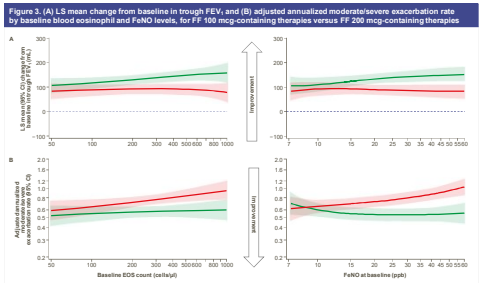
Pooled analyses were performed post hoc. FF 100 mcg-containing therapies: pooled FF/VI 100/25 mcg + FF 100 mcg/UMEC 31.25+62.5 mcg/VI. FF 200 mcg-containing therapies: pooled FF/VI 200/25 mcg + FF 200 mcg/UMEC 31.25+62.5 mcg/VI.
n= patients with analysable data for low, medium, and high type 2 inflammatory marker groups.

Figure 2. (A) LS mean change from baseline in trough FEV_1 and (B) adjusted annualized moderate/severe exacerbation rate by baseline blood eosinophil and FeNO levels, for FF/VI 200/25 mcg versus FF/UMEC/VI 100/62.5/25 mcg



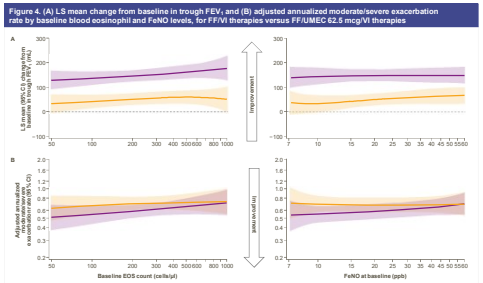
Results are presented on a log-transformed scale. FP transformations were used to model the effects of blood EOS and FeNO levels on the endpoint. For trough FEV_1, baseline value is the last acceptable/borderline acceptable pre-dose FEV_1 prior to randomized treatment start date. CI, confidence interval; FP, fractional polynomial; LS, least squares

Figure 3. (A) LS mean change from baseline in trough FEV_1 and (B) adjusted annualized moderate/severe exacerbation rate by baseline blood eosinophil and FeNO levels, for FF 100 mcg-containing therapies versus FF 200 mcg-containing therapies



Pooled analyses were performed post-hoc. Best fitting FP models from 36 pre-defined models are presented.

Figure 4. (A) LS mean change from baseline in trough FEV_1 and (B) adjusted annualized moderate/severe exacerbation rate by baseline blood eosinophil and FeNO levels, for FF/VI therapies versus FF/UMEC 62.5 mcg/VI therapies



Pooled analyses were performed post hoc. Best fitting FP models from 36 pre-defined models are presented.

Conclusions

- The addition of UMEC improved trough FEV_1 independently of baseline blood eosinophil and FeNO levels.
- The effect of increasing the dose of FF on trough FEV_1 and moderate/severe exacerbations was numerically greater with increasing blood eosinophil counts and FeNO levels.
- This relationship was particularly noteworthy for the combined measure of blood eosinophils and FeNO and severe exacerbations, suggesting that raised biomarkers of type 2 inflammation are a marker of increased risk of severe exacerbations and an increased likelihood of a response to more intensive corticosteroid treatment.
- The size of the subgroups and variability in data limit our ability to draw definitive conclusions. Inconsistencies in the effect of adding UMEC in the unpooled analysis of moderate/severe exacerbations may have implications on the validity of pooling the data; as such, the pooled comparisons of the effect of adding UMEC require further research.
- A precision medicine approach targeting treatment according to desired outcome and type 2 biomarker status might lead to more effective and economic use of inhaled treatments.
- CAPTAIN is the first large-scale asthma study to indicate that a treatable trait-based approach adds value to decision making for inhaled therapies for patients with uncontrolled asthma.

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Disclosures

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AF, NB, and EP are employees of GSK and hold stocks or shares in GSK. LAL was an employee of GSK and holds stocks or shares in GSK. BH was an employee of GSK and holds stocks or shares in GSK; he is currently an employee of Veramed UK, which is contracted by GSK. 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; acted as an expert witness for a patent dispute involving AstraZeneca and Teva; co-patent holder for the Leicester Cough Questionnaire, and received payments for use of the Leicester Cough Questionnaire in clinical trials from Bayer, Insmed, and Merck. HKA has received research grants and served on advisory boards for Boehringer Ingelheim, GSK, and Novartis. AP has received research grants and personal fees from Chiesi, GSK, and Teva, and personal fees from AstraZeneca, Boehringer Ingelheim, Menarini, Merck Sharp & Dohme, Mundipharma, Novartis, Sanofi, and Zambon. JO has participated in adjudication or data and safety monitoring boards for AstraZeneca, GSK, Novartis, and Sanofi.
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