Adv Ther (2026) 43:729–749
https://doi.org/10.1007/s12325-025-03442-x

ORIGINAL RESEARCH

Evaluating Asthma Clinical Remission with Inhaled Therapy: Post Hoc Analyses of CAPTAIN

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Received: June 20, 2025 / Accepted: November 12, 2025 / Published online: December 24, 2025

ABSTRACT

Introduction: Clinical remission (CR) is an emerging treatment goal in asthma. However, evidence showing whether CR is achievable with inhaled therapy is lacking. This post hoc analysis of CAPTAIN evaluated attainability of a composite CR endpoint with inhaled fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) or FF/VI.

Methods: CAPTAIN (GSK 205715) was a Phase IIIA, randomized, controlled, 24–52-week trial comparing once-daily single-inhaler FF/UMEC/VI versus FF/VI in adults with uncontrolled moderate-to-severe asthma despite ICS/LABA. CR was defined as a composite endpoint comprising no systemic corticosteroids, no severe exacerbations, ACQ-5 total score < 1.50, and either change from baseline in $FEV_1 \geq 0$ ml (lung function stabilization) or ≥ 100 ml (lung function optimization), assessed for patients meeting the CR endpoint at Week 24 (W24) and achieving CR at W52 with FF/UMEC/VI (100/62.5/25, 200/62.5/25 µg) versus FF/VI (100/25, 200/25 µg). Additional analyses assessed the CR endpoint at W24/W52 using ACQ-5 ≤ 0.75 and ≤ 1.00 thresholds. Adjusted odds/risk ratios for CR were calculated for W24.

Results: More patients met the CR endpoint (lung function stabilization/optimization) with FF/UMEC/VI versus FF/VI at W24 (stabilization:

Prior presentation: Some of the data reported in this manuscript have previously been presented at the 2024 American Academy of Allergy, Asthma, and Immunology Annual Meeting, Washington, DC, USA, 23–26 February 2024 (Lugogo N, et al. J Allergy Clin Immunol. 2024;153(2):Supplement AB266); American Thoracic Society 2024 International Conference, San Diego, CA, USA, 20–22 May 2024 (Oppenheimer J, et al. Am J Respir Crit Care Med. 2024;209:A5267); and European Respiratory Society Congress 2024, Vienna, Austria, 7–11 September 2024 (Oppenheimer J, et al. Eur Respir J. 2024;64(suppl 68):PA1198; Oppenheimer J, et al. Eur Respir J. 2024;64(suppl 68):PA1199).

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12325-025-03442-x.

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42–47% vs 31–36%; optimization: 31–36% vs 19–26%) and W52 (stabilization: 43–47% vs 33–34%; optimization: 30–38% vs 21–24%). Using more stringent ACQ-5 thresholds, fewer patients met the CR endpoint with ACQ ≤ 0.75 versus < 1.50 across treatment arms and timepoints. The odds and probability of meeting the CR endpoint versus not meeting the CR endpoint at W24 were greater with FF/UMEC/VI versus FF/VI, regardless of FF dose.

***Conclusion*:** The results of this post hoc analysis demonstrate that CR is achievable with inhaled therapy in moderate-to-severe asthma and is more likely with FF/UMEC/VI than FF/VI. CR should be considered an attainable treatment goal for patients with asthma, irrespective of disease severity or treatment history.

Trial Registration: ClinialTrials.gov identifier, NCT02924688.

Keywords: Clinical remission; Fluticasone furoate/vilanterol/umeclidinium; Inhalation therapy; Moderate-to-severe asthma; Single-inhaler triple therapy

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Key Summary Points

Why carry out this study?

Previous studies have demonstrated that clinical remission, generally defined as no systemic corticosteroid use, no exacerbations, symptom control, and stabilized or optimized lung function for at least 1 year, is achievable in patients with severe asthma receiving biologics.

The Global Initiative for Asthma recommends that clinical remission is a relevant treatment goal for all patients, irrespective of disease severity or treatment history.

Therefore, this post hoc analysis of the Phase IIIA CAPTAIN trial investigated the attainability of a composite clinical remission endpoint at 24 and 52 weeks with inhaled fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) and FF/VI in patients with uncontrolled moderate-to-severe asthma not yet considered for biologics.

What was learned from the study?

Clinical remission was achievable with both FF/UMEC/VI and FF/VI in uncontrolled moderate-to-severe asthma; greater treatment effects were observed with FF/UMEC/VI versus FF/VI, regardless of FF dose or asthma control and lung function threshold used.

Expectations around asthma treatment should include symptom control and stabilized or even optimized lung function, as well as elimination of exacerbations and systemic corticosteroid use, which comprise the components of clinical remission.

INTRODUCTION

Asthma is a heterogeneous respiratory disease characterized by chronic airway inflammation, variable airflow limitation, and respiratory symptoms [1], affecting approximately 262

million people worldwide [2]. Many patients experience considerable disease burden, including uncontrolled symptoms, frequent exacerbations, and impaired quality of life [3–7].

In recent decades, advances in asthma management have led to increasingly ambitious treatment goals. In the 1990s, asthma therapy was aimed at achieving and maintaining symptom control [8], leading to recommendations for stepwise pharmacologic treatment, and the use of validated measures of symptom control [9, 10]. The concept of total control also evolved and was shown to be achievable in the 2004 GOAL study, which demonstrated that more patients were able to achieve total asthma control after 1 year of treatment with inhaled corticosteroid/long-acting β_2-agonist (ICS/LABA) therapy versus ICS alone [11]. Although symptom control remains a key treatment goal, many patients continue to experience inadequate control and symptom burden despite adherence to ICS/LABA [5, 12, 13]. The introduction of targeted biologic therapies for asthma has been paradigm shifting, expanding treatment options for patients with severe asthma to allow enhanced levels of asthma control and reduced rates of exacerbations [14–17].

Clinical remission (CR) has long been considered a treatment goal in other chronic diseases, such as rheumatoid arthritis [18, 19]. However, there is currently no standardized definition of CR in asthma. Recent consensus statements and national asthma management guidelines generally recommend four key criteria for on-treatment CR assessed for at least 12 months: no systemic corticosteroid (SCS) use, no severe exacerbations, symptom control, and lung function stabilization (maintenance of existing lung function) or optimization (improvement in lung function) [1, 20–25]. In recent years, a number of studies have demonstrated that CR is achievable in patients with severe asthma receiving biologic therapy [26–31], and a recent analysis also reported achievability of CR with azithromycin in patients with persistent uncontrolled asthma [32]. Notably, although reports show that CR is attainable in patients eligible for biologics, the findings represent a subset of patients with severe asthma and a type-2 (T2) inflammatory phenotype [1, 26–28, 30], and they are therefore not generalizable to all patients with asthma. Indeed, patients with less severe asthma not eligible for biologics may be more likely to achieve components of CR [33] because of lower disease burden, reduced reliance on SCS, and less airway remodeling [33–35].

The Global Initiative for Asthma recommends that CR is a relevant treatment goal for all patients, regardless of disease severity, and highlights a need for clinical and qualitative research to determine the attainability of CR with different asthma treatments [1]. The Phase IIIA CAPTAIN study evaluated single-inhaler triple-therapy (SITT) fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) versus FF/VI in patients with uncontrolled moderate-to-severe asthma who were not required to have a history of exacerbations [36]. Improvements were seen with FF/UMEC/VI in several individual clinical endpoints, including statistically significant improvements in lung function, numerical improvements in annualized moderate/severe exacerbation rates, and nominally statistically significant improvements in symptom control (Asthma Control Questionnaire [ACQ]-7 responder rates) versus FF/VI [36]. Given the inclusion of key CR criteria within CAPTAIN, the aim of this post hoc analysis was to investigate whether CR is an achievable treatment goal with inhaled FF/UMEC/VI or FF/VI for patients with uncontrolled moderate-to-severe asthma not yet considered for biologics. We also explored the impact of different component thresholds on attainability of the CR endpoint, as well as potential indicators of CR, which may help inform future iterations of the evolving CR definition.

METHODS

Study Design

CAPTAIN (GSK study 205715/NCT02924688) was a Phase IIIA, multicenter, multinational,

randomized, double-blind, active-controlled, 24–52-week, parallel-group study (Fig. S1); full details have been reported previously [36]. After screening, patients entered a 3-week run-in period where they received twice-daily open-label fluticasone propionate (FP) plus salmeterol 250/50 µg via DISKUS dry-powder inhaler (DPI; GSK), followed by open-label FF/VI 100/25 µg via the ELLIPTA DPI (GSK) during the subsequent 2-week stabilization period. Patients were randomly assigned (1:1:1:1:1:1) to one of six treatment groups: FF/VI, 100/25 or 200/25 µg (ELLIPTA); or FF/UMEC/VI, 100/31.25/25, 100/62.5/25, 200/31.25/25, or 200/62.5/25 µg (ELLIPTA). CAPTAIN included two pre-specified treatment periods: a fixed treatment period from randomization to Week 24, followed by a variable treatment period up to Week 52 (Fig. S1). All patients completed ≥ 24 weeks of study treatment; patients who enrolled earlier during the recruitment period continued to a maximum of 52 weeks.

CAPTAIN was performed in accordance with the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice, and applicable country-specific regulatory requirements and received US central ethics approval from the Chesapeake Institutional Review Board (now Advarra; IRB: 00000971, IORG: 0000635). This was a multinational, multicenter study; a full list of the ethics committees that approved the study is included in Table S1. Written informed consent was obtained from all patients before participation.

Study Population

Eligible patients were ≥ 18 years of age, with uncontrolled asthma (ACQ-6 score ≥ 1.50) despite maintenance therapy with daily ICS/LABA (daily FP > 250 µg or equivalent) for ≥ 12 weeks before pre-screening. Patients had a best pre-bronchodilator morning forced expiratory volume in 1 s (FEV_1) between ≥ 30% and ≤ 85% of the predicted normal value at screening, displayed reversibility to salbutamol/albuterol, and had documented evidence of treatment for acute asthma symptoms in the year before screening. Notably, patients enrolled in CAPTAIN were not required to have had an exacerbation in the previous year. Permitted maintenance medication included SCS (≤ 5 mg/day prednisone [or equivalent dose of an alternative SCS]), provided treatment was initiated ≥ 12 weeks before Visit 1 and was stable for the 8 weeks before Visit 1.

Patients were excluded if they experienced an asthma exacerbation requiring a change in asthma maintenance therapy in the 6 weeks before screening or if they had a diagnosis of chronic obstructive pulmonary disease, had concurrent respiratory disorders including pneumonia, or were current smokers or former smokers with a smoking history of ≥ 10 pack-years. Additionally, patients who experienced a severe exacerbation during screening or the run-in period were excluded.

Study Endpoints

This post hoc analysis assessed the proportions of patients meeting a CR endpoint at Week 24 and achieving CR at Week 52 with FF/UMEC/VI (100/62.5/25 or 200/62.5/25) or FF/VI (100/25 or 200/25), as defined by a composite outcome comprising: (1) no SCS use (including all oral, intravenous, and subcutaneous steroids); (2) no severe exacerbations; (3) asthma control (ACQ-5 total score < 1.50); (4) stabilized lung function (change from baseline in trough FEV_1 ≥ 0 ml) or optimized lung function (Fig. 1). For lung function optimization, an increase in FEV_1 ≥ 100 ml was assessed to represent a clinically meaningful improvement. Baseline trough FEV_1 was defined as the last acceptable pre-dose FEV_1 measurement before treatment randomization. Severe exacerbations were defined as a hospital admission or emergency department visit due to the need for SCS, or an asthma deterioration requiring SCS use (or doubling of the current maintenance SCS dose) for ≥ 3 days. We also assessed the impact of varying asthma control thresholds on attainability of the CR endpoint at Week 24

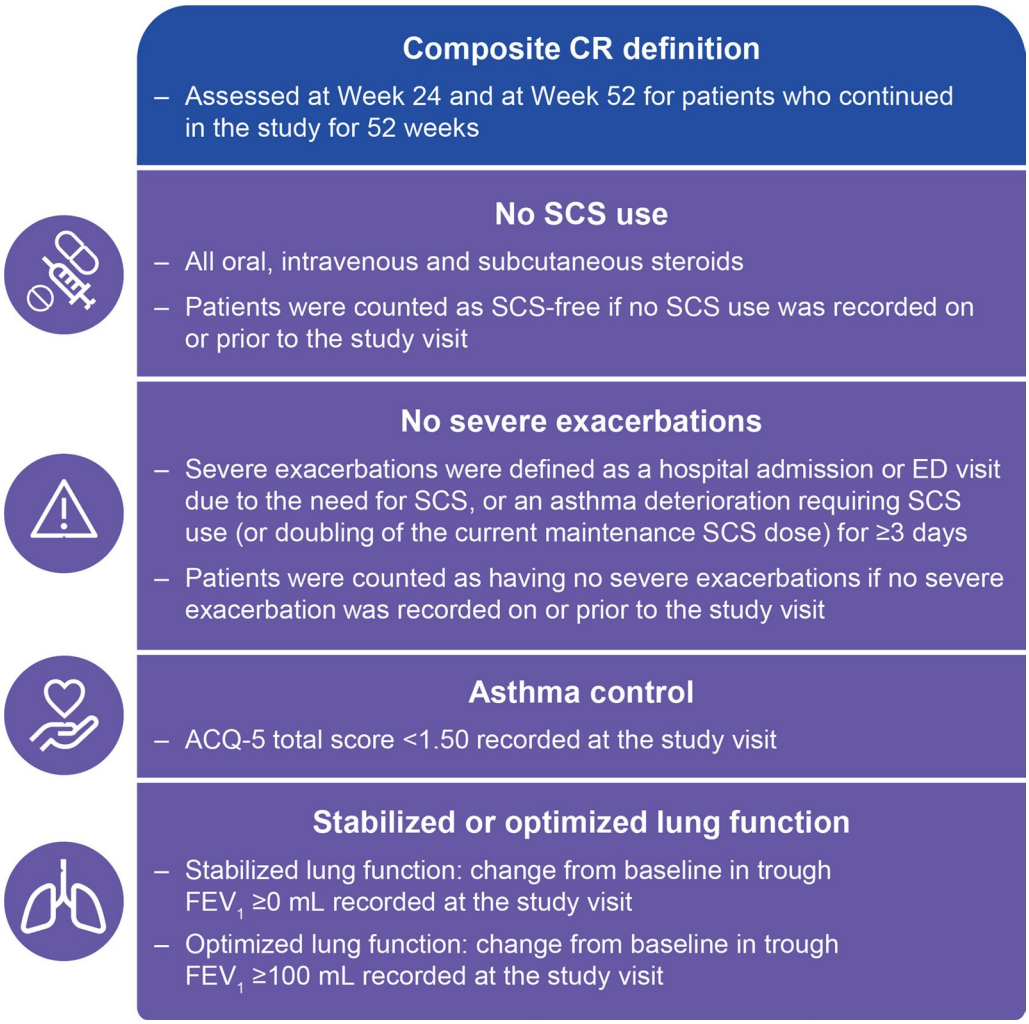


Fig. 1 Composite CR endpoint. *ACQ-5* Asthma Control Questionnaire 5-item; *CR* clinical remission; *ED* emergency department; *FEV_1* forced expiratory volume in 1 s; *SCS* systemic corticosteroid; *SD* standard deviation

and Week 52, using ACQ-5 total scores of ≤ 0.75 and ≤ 1.00.

The probability of meeting the CR endpoint at Week 24 was calculated, and risk ratios (RRs) for the following treatment comparisons were estimated: (1) addition of UMEC to FF/VI (FF/UMEC/VI 100/62.5/25 vs FF/VI 100/25 and FF/UMEC/VI 200/62.5/25 vs FF/VI 200/25); (2) doubling FF dose (FF/UMEC/VI 200/62.5/25 vs FF/VI 100/62.5/25 and FF/VI 200/25 vs FF/VI 100/25); (3) simultaneously adding UMEC and doubling FF dose (FF/UMEC/VI 200/62.5/25 vs FF/VI 100/25). Odds ratios (ORs) were also estimated to provide another measure of the association between treatment and meeting the CR endpoint. In addition, we assessed the impact of individual components of the CR endpoint on the proportion of patients meeting the CR endpoint at Week 24 or achieving CR at Week 52 with FF/UMEC/VI or FF/VI. To assess the predictive value of an early response for achieving CR, we described the proportion of patients who achieved CR at Week 52, stratified by those that did and those that did not meet the CR endpoint (lung function optimization) at Week 24. Patients who withdrew from the study, were lost to follow-up, or had missing data were considered

non-responders. Only the UMEC 62.5 treatment comparison is reported in this post hoc analysis as this is the UMEC dose selected for approved doses of FF/UMEC/VI (100/62.5/25 and 200/62.5/25) [37].

Data Analyses

Endpoints were assessed in the CAPTAIN intent-to-treat (ITT) population by treatment group. Patient characteristics were collected at baseline, reported descriptively using mean and standard deviation or frequencies and percentages, and stratified by patients who did and did not meet the CR endpoint at Week 24. Proportions of patients meeting the CR endpoint at Week 24 and achieving CR at Week 52 were reported. Data at Week 52 were reported for patients who continued in the study to Week 52. Due to lower patient numbers in the Week 52 dataset, these analyses were reported descriptively. The probability (RRs, 95% confidence intervals [95% CIs]) of meeting the CR endpoint at Week 24 by treatment group was analyzed using a log-binomial model. We also reported ORs (95% CIs) for meeting the CR endpoint versus not meeting the CR endpoint at Week 24 for completeness, analyzed using a logistic model. Both RRs and ORs were adjusted for covariates of treatment, age, sex, region, and pre-study ICS dosage at screening. Additional analyses assessed patients meeting the CR endpoint at Week 24 stratified by baseline T2 inflammation status, defined here as: low T2 (combined eosinophil [EOS] < 150 cells/µl and fractional exhaled nitric oxide [FeNO] < 20 parts per billion [ppb] at baseline), high T2 (combined EOS ≥ 300 cells/µl and FeNO > 50 ppb at baseline), and intermediate T2 (all other patients with an EOS and FeNO measurement). Further details are included in the Supplementary Material.

In the pre-specified CAPTAIN analyses, a step-down closed-testing hierarchy was used to account for multiplicity across doses and efficacy endpoints, whereby inference for a test in the pre-defined hierarchy was dependent on significance having been reached for the previous tests [36]. For the study to be positive, to pass the first step of the hierarchy, significant improvements at the 0.05 level had to be observed when adding UMEC 62.5 to both FF/VI 100/25 and FF/VI 200/25 [36]. In the primary analysis of the study, the hierarchy was broken at the key secondary endpoint, and all subsequent analyses were considered descriptive and were not adjusted for multiplicity [36]. Therefore, the analyses for this post hoc exploratory analysis are also considered descriptive; *p*-values are not adjusted for multiplicity and are nominal. A non-responder imputation approach was used, where patients who discontinued the study before the Week 24 or Week 52 visit or had missing responses to any component were considered not to have met the composite CR endpoint for that visit.

RESULTS

Study Population

Data for 407 patients receiving FF/VI 100/25, 406 receiving FF/UMEC/VI 100/62.5/25, 406 receiving FF/VI 200/25, and 408 receiving FF/UMEC/VI 200/62.5/25 were included in this post hoc analysis. Of these, 87 patients receiving FF/VI 100/25, 91 receiving FF/UMEC/VI 100/62.5/25, 91 receiving FF/VI 200/25, and 91 receiving FF/UMEC/VI 200/62.5/25 continued in the study to Week 52 (Fig. 2).

Baseline demographic and clinical characteristics for the CAPTAIN ITT population (Table 1) and for the subgroup of patients that continued in the study to Week 52 (Table S2) were generally similar across groups. Additional baseline characteristics for the CAPTAIN ITT population have been reported previously [36].

Patients Meeting the CR Endpoint at Week 24 and Achieving CR at Week 52

Overall, a greater proportion of patients met the CR endpoint (no SCS use, no severe exacerbations, ACQ-5 < 1.50, lung function stabilization/optimization) with FF/UMEC/VI versus FF/VI during the study, regardless of FF dose and irrespective of the lung function component assessed (Fig. 3). Using the lung function

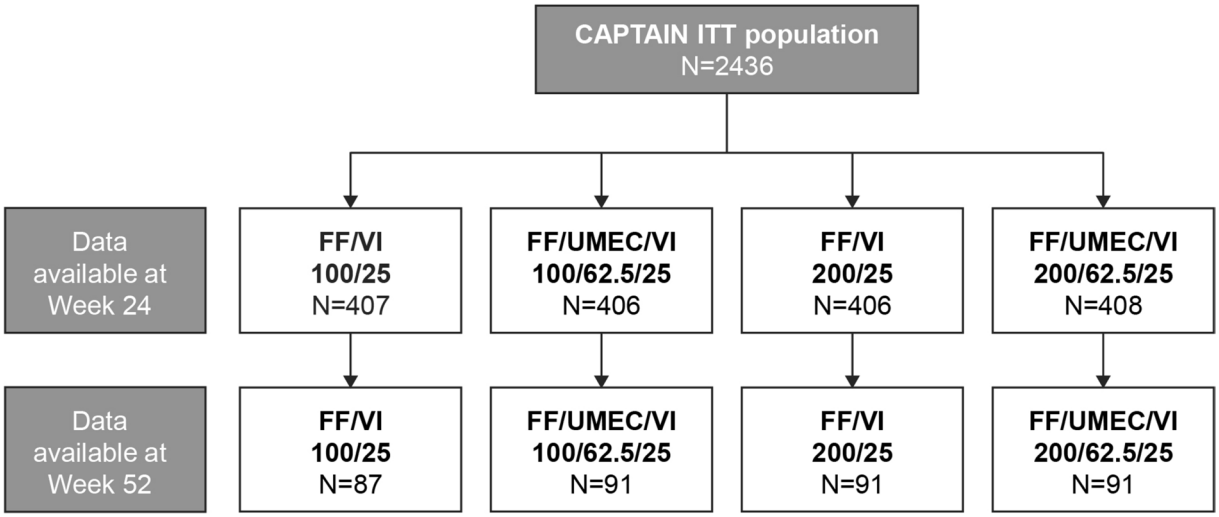


Fig. 2 Patient disposition. All doses are in μg. *FF* fluticasone furoate; *ITT* intent-to-treat; *UMEC* umeclidinium; *VI* vilanterol

stabilization criterion, 42% (n = 170/406) and 47% (n = 190/408) of patients met the CR endpoint at Week 24 with FF/UMEC/VI 100/62.5/25 or 200/62.5/25, respectively, versus 31% (n = 127/407) and 36% (n = 145/406) receiving FF/VI 100/25 or 200/25, respectively (Fig. 3a). At Week 52, 43% (n = 39/91) and 47% (n = 43/91) achieved CR with FF/UMEC/VI 100/62.5/25 or 200/62.5/25, respectively, versus 34% (n = 30/87) and 33% (n = 30/91) receiving FF/VI 100/25 or 200/25, respectively (Fig. 3b).

Using the lung function optimization criterion, 31% (n = 127/406) and 36% (n = 146/408) of patients met the CR endpoint at Week 24 with FF/UMEC/VI 100/62.5/25 or 200/62.5/25, respectively, versus 19% (n = 77/407) and 26% (n = 104/406) receiving FF/VI 100/25 or 200/25, respectively (Fig. 3a). At Week 52, 30% (n = 27/91) and 38% (n = 35/91) of patients achieved CR with FF/UMEC/VI 100/62.5/25 or 200/62.5/25, respectively, versus 21% (n = 18/87) and 24% (n = 22/91) receiving FF/VI 100/25 or 200/25, respectively (Fig. 3b).

The impact of varying asthma control thresholds on attainability of the CR endpoint (lung function optimization) is presented in Fig. 4. The proportion of patients meeting the CR endpoint decreased for all treatment groups with more stringent ACQ-5 thresholds at both Week 24 and Week 52, although more patients still met the CR endpoint with FF/UMEC/VI than with FF/VI, regardless of FF dose.

Probability and Odds of Meeting the CR Endpoint Versus not Meeting the CR Endpoint at Week 24

Using the lung function stabilization criterion, the probability of meeting the CR endpoint at Week 24 was greater when adding UMEC to FF/VI with both FF 100 and 200 doses (RR [95% CI]: 1.32 [1.10, 1.59], p=0.003; 1.30 [1.10, 1.53], p=0.002, respectively; nominally statistically significant) (Fig. 5a). The probability of meeting the CR endpoint at Week 24 was numerically increased when doubling the FF dose in both dual and triple therapy (Fig. 5b). The probability of meeting the CR endpoint at Week 24 was also greater when simultaneously doubling the FF dose and adding UMEC to FF/VI 100/25 (RR [95% CI]: 1.49 [1.24, 1.77], p<0.001; nominally statistically significant) (Fig. 5c); ORs (95% CIs) were generally aligned with RRs across all treatment comparisons (Fig. 5).

When using the lung function optimization criterion, the probability of meeting the CR endpoint at Week 24 was again greater when adding UMEC to FF/VI with both FF 100 and 200 doses (RR [95% CI]: 1.60 [1.25, 2.04], p<0.001; 1.36 [1.10, 1.67], p=0.004, respectively; nominally

Table 1 Baseline demographic and clinical characteristics

	FF/VI 100/25 (*N* = 407)	FF/UMEC/VI 100/62.5/25 (*N* = 406)	FF/VI 200/25 (*N* = 406)	FF/UMEC/VI 200/62.5/25 (*N* = 408)	CAPTAIN ITT population* (*N* = 2436)
Sex, female, *n* (%)	254 (62)	248 (61)	252 (62)	258 (63)	1514 (62)
Age, years, mean (SD)	53.3 (13.03)	52.9 (13.39)	53.9 (13.30)	53.7 (12.50)	53.2 (13.11)
BMI, kg/m^2, mean (SD)	29.29 (6.08)	29.24 (6.65)	29.38 (6.29)	29.66 (6.93)	29.35 (6.64)
Asthma duration, years, mean (SD)	(*n* = 407) 20.4 (15.03)	(*n* = 406) 20.8 (15.70)	(*n* = 406) 20.7 (14.53)	(*n* = 408) 22.3 (16.15)	(*n* = 2435) 21.2 (15.31)
ACQ-5 score at screening, mean (SD)	(*n* = 406) 2.64 (0.63)	(*n* = 406) 2.66 (0.66)	(*n* = 406) 2.71 (0.69)	(*n* = 407) 2.68 (0.69)	(*n* = 2433) 2.68 (0.67)
Pre-bronchodilator FEV_1 at screening	(*n* = 402)	(*n* = 404)	(*n* = 401)	(*n* = 407)	(*n* = 2423)
L, mean (SD)	1.733 (0.5824)	1.756 (0.5979)	1.722 (0.5994)	1.732 (0.6130)	1.734 (0.5843)
% Predicted, mean (SD)	58.24 (13.061)	58.76 (12.741)	58.66 (13.196)	58.98 (13.255)	58.48 (12.787)
Severe exacerbations in the year before screening, *n* (%)					
0	144 (35)	160 (39)	157 (39)	124 (30)	892 (37)
1	198 (49)	179 (44)	196 (48)	216 (53)	1166 (48)
≥ 2	65 (16)	67 (17)	53 (13)	68 (17)	378 (16)
SCS use at screening/during run-in,† *n* (%)	2 (< 1)	3 (< 1)	5 (1)	4 (< 1)	28 (1)

All doses are in µg

BMI body mass index; *ACQ-5* Asthma Control Questionnaire 5-item; *FEV_1* forced expiratory volume in 1 s; *FF* fluticasone furoate; *ITT* intent-to-treat; *SCS* systemic corticosteroid; *SD* standard deviation; *UMEC* umeclidinium; *VI* vilanterol

*The CAPTAIN ITT population includes data from UMEC 31.25 µg treatment arms; †including systemic, oral, parenteral, and intra-articular corticosteroids

statistically significant) (Fig. 5a). The probability of meeting the CR endpoint at Week 24 was nominally statistically significantly greater when doubling the FF dose in dual therapy (RR [95% CI]: 1.37 [1.06, 1.77], $p = 0.017$) and numerically increased when doubling the FF dose in triple therapy (Fig. 5b). The probability of meeting the CR endpoint at Week 24 was greater when simultaneously doubling the FF dose and adding UMEC to FF/VI 100/25 (RR [95% CI]: 1.86 [1.47, 2.36], $p < 0.001$; nominally statistically significant) (Fig. 5c). Similar results were seen with ORs across treatment comparisons (Fig. 5).

Predictive Value of Meeting the CR Endpoint at Week 24 for Achieving CR at Week 52

The predictive value of an early response at Week 24 for achieving CR at Week 52 was assessed in the subset of patients who

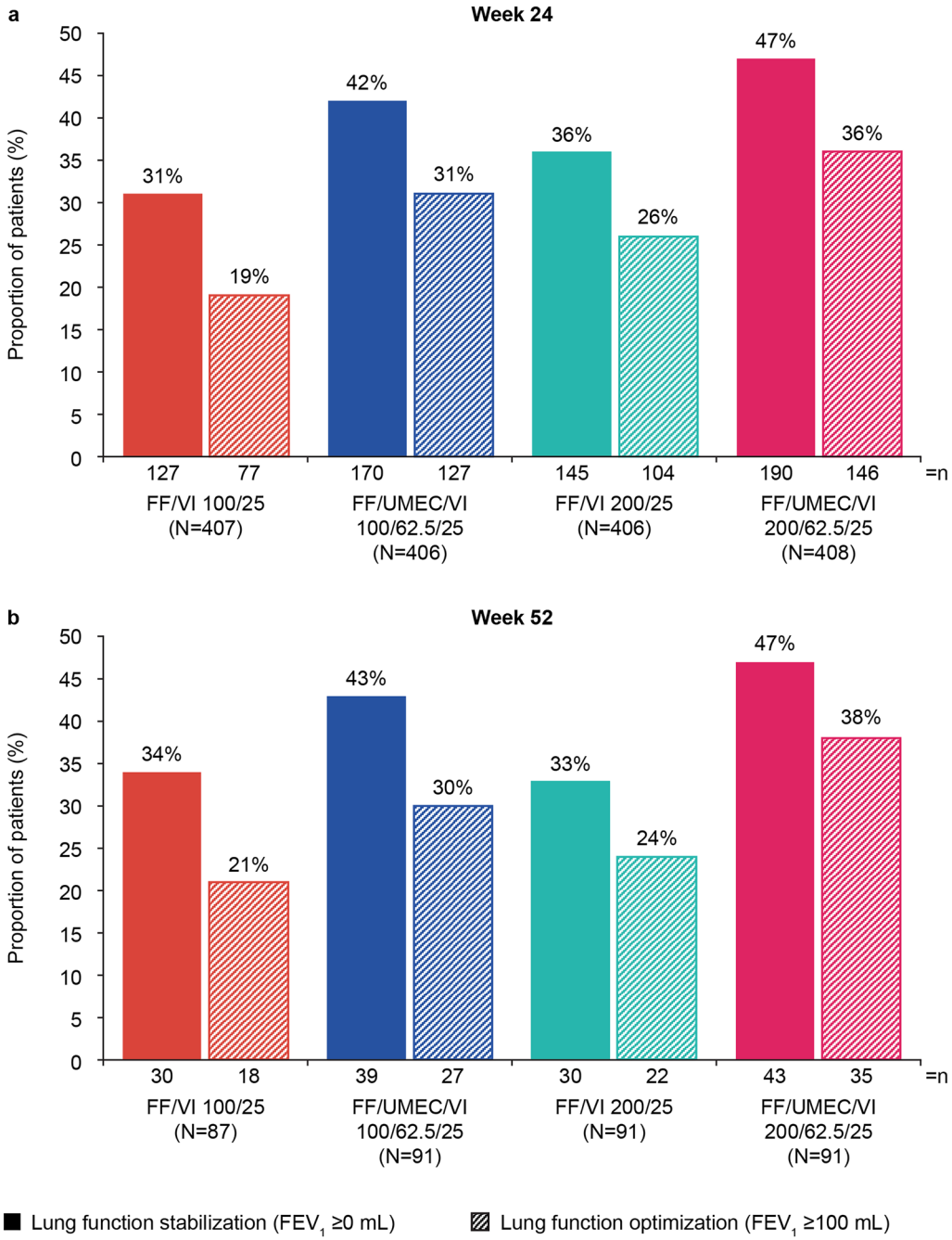
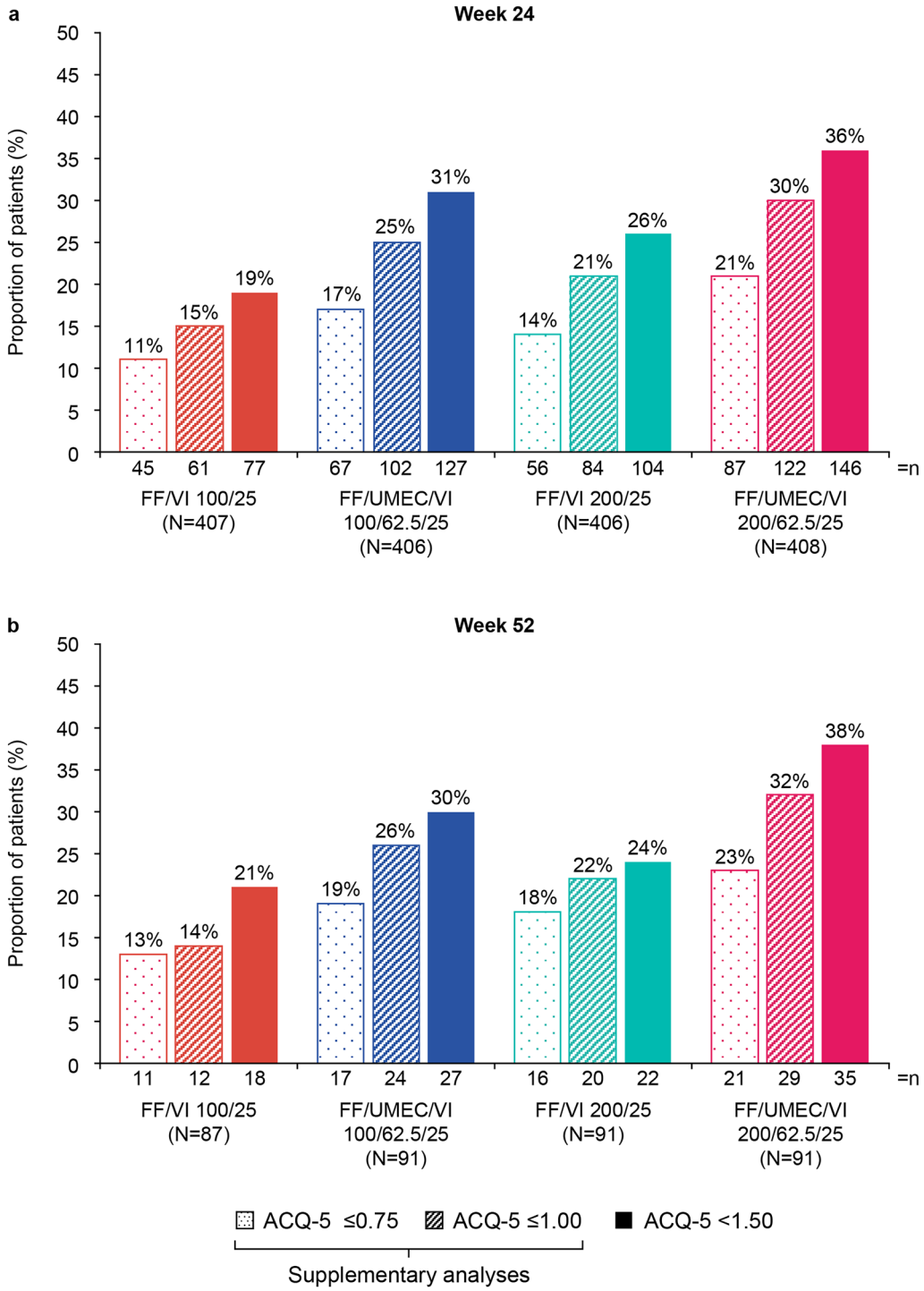


Fig. 3 Proportion of patients meeting the CR endpoint at Week 24 (**a**) and achieving CR at Week 52 (**b**) with FF/VI or FF/UMEC/VI. This was a post hoc exploratory analysis. All doses are in µg. Data at Week 52 were reported for patients who continued in the study for 52 weeks. Solid bars represent the CR endpoint (no SCS use, no severe exacerbations, ACQ-5 < 1.50, and stabilized or optimized lung function), including the lung function stabilization component; hatched bars represent the CR endpoint including the lung function optimization component. *ACQ-5* Asthma Control Questionnaire 5-item; *CR* clinical remission; *FEV_1* forced expiratory volume in 1 s; *FF* fluticasone furoate; *SCS* systemic corticosteroid; *UMEC* umeclidinium; *VI* vilanterol


a
Week 24
Proportion of patients (%)
50
45
40
35
30
25
20
15
10
5
0
11%
15%
19%
17%
25%
31%
14%
21%
26%
21%
30%
36%
45 61 77
67 102 127
56 84 104
87 122 146
=n
FF/VI 100/25 (N=407)
FF/UMEC/VI 100/62.5/25 (N=406)
FF/VI 200/25 (N=406)
FF/UMEC/VI 200/62.5/25 (N=408)
b
Week 52
Proportion of patients (%)
13%
14%
21%
19%
26%
30%
18%
22%
24%
23%
32%
38%
11 12 18
17 24 27
16 20 22
21 29 35
=n
FF/VI 100/25 (N=87)
FF/UMEC/VI 100/62.5/25 (N=91)
FF/VI 200/25 (N=91)
FF/UMEC/VI 200/62.5/25 (N=91)
ACQ-5 ≤0.75
ACQ-5 ≤1.00
ACQ-5 <1.50
Supplementary analyses

◂**Fig. 4** Impact of varying ACQ thresholds on the proportion of patients meeting the CR endpoint at Week 24 (**a**) and achieving CR at Week 52 (**b**) with FF/VI or FF/UMEC/VI. This was a post hoc exploratory analysis. All doses are in μg. Data at Week 52 were reported for patients who continued in the study for 52 weeks. Data represent the 4-component CR endpoint including lung function optimization and varying ACQ-5 thresholds: dotted bars represent ACQ-5 ≤ 0.75; hatched bars represent ACQ-5 ≤ 1.00; solid bars represent ACQ-5 < 1.50. *ACQ-5* Asthma Control Questionnaire 5-item; *CR* clinical remission; *FF* fluticasone furoate; *UMEC* umeclidinium; *VI* vilanterol

continued for the duration of the study, using the lung function optimization criterion. For all treatment groups, a greater proportion of patients who met the CR endpoint at Week 24 also achieved CR at Week 52 compared with those who did not meet the CR endpoint at Week 24 (Fig. 6). Specifically, among patients treated with FF/UMEC/VI 100/62.5/25 (49% [*n* = 45/91]) or 200/62.5/25 (37% [*n* = 34/91]) who met the CR endpoint at Week 24, 44% (*n* = 20/45) and 68% (*n* = 23/34), respectively, went on to achieve CR at Week 52. In comparison, among those who did not meet the CR endpoint at Week 24 with FF/UMEC/VI 100/62.5/25 (51% [*n* = 46/91]) and 200/62.5/25 (63% [*n* = 57/91]), only 15% (*n* = 7/46) and 21% (*n* = 12/57), respectively, achieved CR at Week 52. Similar results were observed for FF/VI 100/25 and 200/25 (Fig. 6).

Impact of Each Component of CR

The proportions of patients who were SCS-free and/or had no severe exacerbations were generally similar with either FF/UMEC/VI or FF/VI at Week 24 (79–84%) and Week 52 (69–76%), regardless of FF dose (Fig. 7). The components of asthma control and lung function had the greatest impact on attainability of CR. The proportions of patients who were SCS-free, had no severe exacerbations, and had an ACQ-5 total score < 1.50 at Week 24 were generally similar across treatment groups (53–60%), although increases were seen with FF/UMEC/VI (59%) versus FF/VI (48–51%) at Week 52 (Fig. 7). Greater proportions of patients met the CR endpoint at Week 24 (42–47% vs 31–36%) and achieved CR at Week 52 (43–47% vs 33–34%) with FF/UMEC/VI versus FF/VI when using the lung function stabilization criterion (no SCS use, no severe exacerbations, ACQ-5 total score < 1.50, and change from baseline in trough FEV_1 ≥ 0 ml), regardless of FF dose (Fig. 7). The lung function optimization criterion (change from baseline in trough FEV_1 ≥ 100 ml) resulted in lower proportions of patients meeting the composite CR endpoint for all treatment groups. However, a similar pattern was observed in terms of treatment difference between FF/UMEC/VI and FF/VI, with greater proportions of patients meeting the CR endpoint at Week 24 (31–36% vs 19–26%) and achieving CR at Week 52 (30–38% vs 21–24%) with FF/UMEC/VI versus FF/VI (Fig. 7).

Baseline Characteristics of Patients Who Met and Did Not Meet the CR Endpoint at Week 24

Across treatment groups, patients who met the CR endpoint at Week 24 versus those who did not were generally younger and had a better ACQ-5 score and pre-dose FEV_1, lower body mass index (BMI), and a shorter asthma duration at baseline; fewer patients experienced ≥ 2 severe exacerbations in the year before screening (Table S3). However, these differences were small, and results are descriptive only. There were also some inconsistencies: baseline BMI in the FF/VI 100/25 group and baseline pre-dose FEV_1 in the FF/UMEC/VI 200/62.5/25 group were similar between those who did and did not meet the CR endpoint at Week 24; in the FF/UMEC/VI 100/62.5/25 group, patients who met the CR endpoint at Week 24 had a longer asthma duration than those who did not. In addition, in patients treated with FF/VI 200/25 or FF/UMEC/VI 200/62.5/25, a greater proportion who met the CR endpoint at Week 24 had high baseline EOS (> 300 cells/μl) or FeNO (> 50 ppb) levels than those who did not meet the CR endpoint at Week 24; no notable

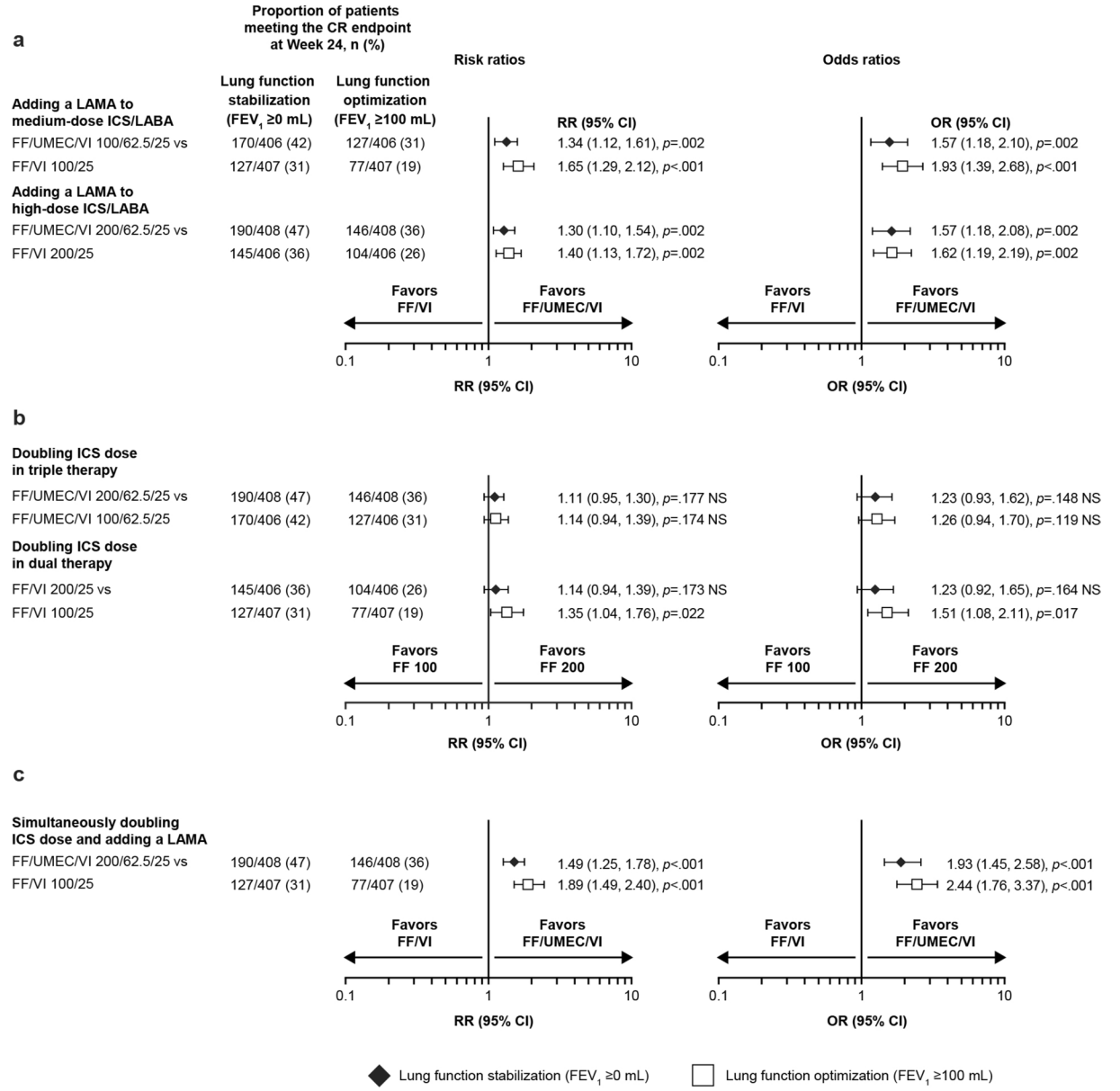


Fig. 5 Risk ratios and odds ratios for meeting the CR endpoint at Week 24 after adding UMEC to FF/VI (**a**), doubling ICS dose (**b**), and simultaneously adding UMEC and doubling ICS dose (**c**). This was a post hoc exploratory analysis; p values were not adjusted for multiplicity. All doses are in µg. The composite CR endpoint was defined as no SCS use, no severe exacerbations, ACQ-5 < 1.50, and stabilized or optimized lung function. *ACQ-5* Asthma Control Questionnaire 5-item; *CI* confidence interval; *CR* clinical remission; *FEV_1* forced expiratory volume in 1 s; *FF* fluticasone furoate; *ICS* inhaled corticosteroid; *LABA* long-acting β_2-agonist; *LAMA* long-acting muscarinic antagonist; *NS* not significant; *OR* odds ratio; *RR* risk ratio; *SCS* systemic corticosteroid; *UMEC* umeclidinium; *VI* vilanterol

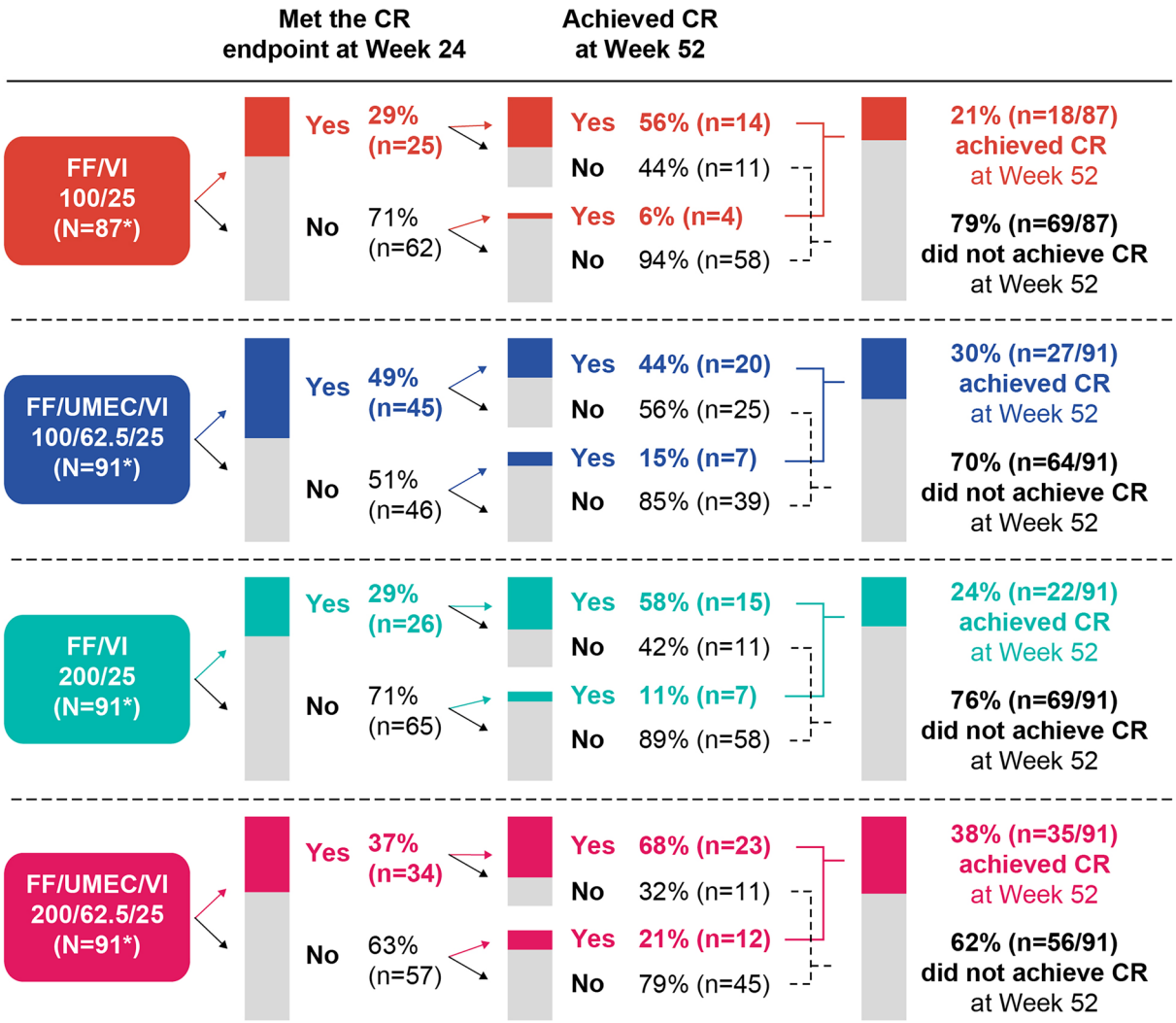


Fig. 6 Proportion of patients who achieved CR at Week 52 and who did or did not meet the CR endpoint at Week 24, with FF/VI or FF/UMEC/VI. *For patients with data available at Week 52. This was a post hoc exploratory analysis. All doses are in μg. The composite CR endpoint was defined as no SCS use, no severe exacerbations, ACQ-5 < 1.50, and optimized lung function. *ACQ-5* Asthma Control Questionnaire 5-item; *CR* clinical remission; *FF* fluticasone furoate; *SCS* systemic corticosteroid; *UMEC* umeclidinium; *VI* vilanterol

differences were seen for FF/VI 100/25 and FF/UMEC/VI 100/62.5/25 (Table S3).

Effect of T2 Inflammation Status on Meeting the CR Endpoint at Week 24

In patients with either low or intermediate T2 status, a greater proportion of patients met the CR endpoint at Week 24 with FF/UMEC/VI versus FF/VI, regardless of FF dose (Fig. S2). Doubling the FF dose resulted in a greater treatment response in patients with a high T2 status: 38% of patients met the CR endpoint at Week 24 with FF/VI 200/25 versus 24% with FF/VI 100/25 and 23% with FF/UMEC/VI 100/62.5/25; however, 61% of patients met the CR endpoint at Week 24 with FF/UMEC/VI 200/62.5/25 (Fig. S2). Pooled analyses were broadly supportive of these results: the effect of increasing FF dose on meeting the CR endpoint at Week 24 was greatest in

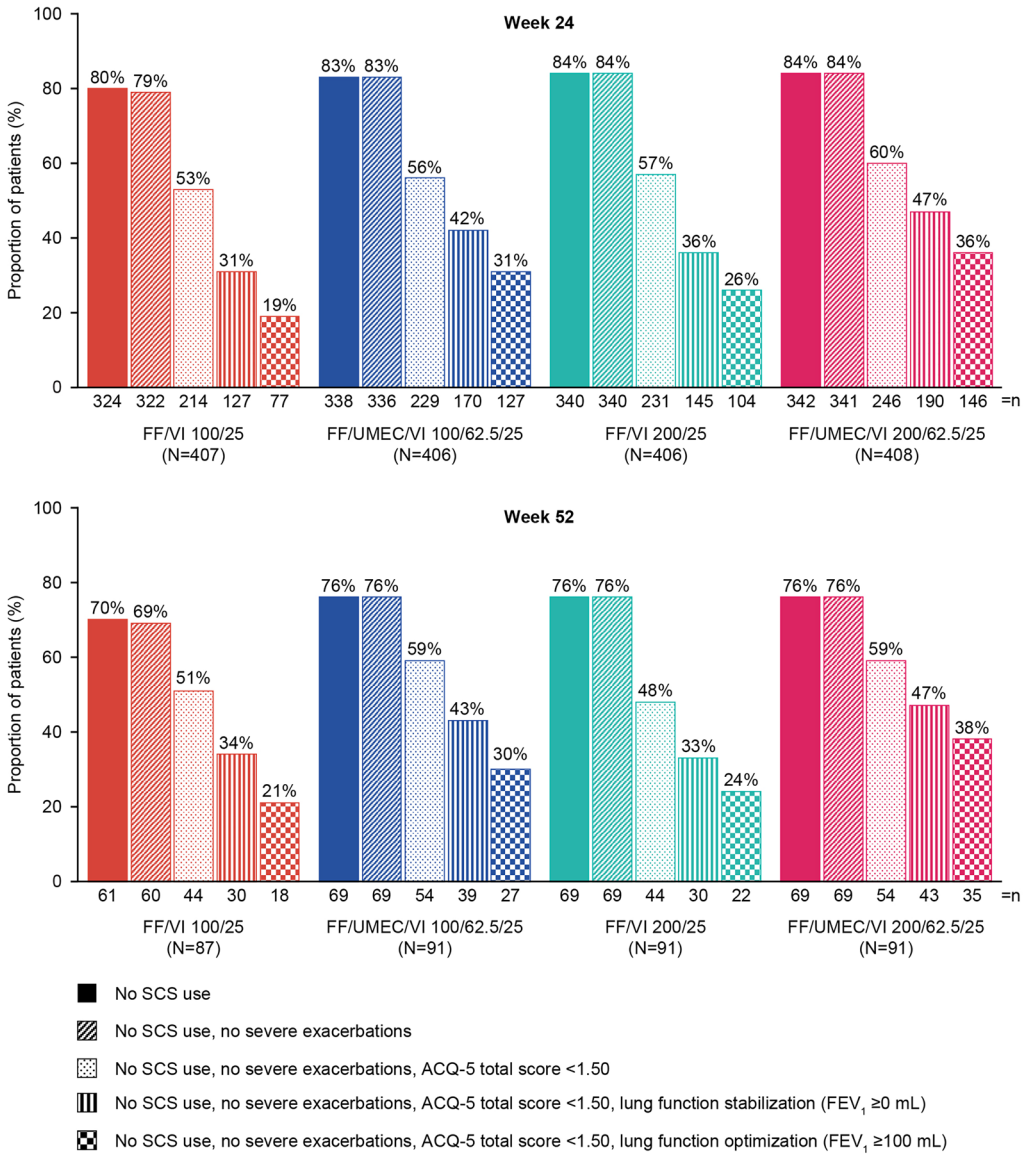


Fig. 7 Impact of each component of the CR definition on the proportion of patients meeting the CR endpoint at Week 24 and achieving CR at Week 52 with FF/VI or FF/UMEC/VI. This was a post hoc exploratory analysis. All doses are in µg. Data at Week 52 were reported for patients who continued in the study for 52 weeks. *ACQ-5* Asthma Control Questionnaire 5-item; *CR* clinical remission; *FEV_1* forced expiratory volume in 1 s; *FF* fluticasone furoate; *SCS* systemic corticosteroid; *UMEC* umeclidinium; *VI* vilanterol

patients with a high T2 status, with minimal differences in low and intermediate T2 subgroups, whereas adding UMEC to FF/VI increased the probability of meeting the CR endpoint regardless of T2 status (Figs. S3 and S4). Of note, results from T2 subgroup analyses should be interpreted with caution because of the low patient numbers in low T2 and high T2 subgroups.

DISCUSSION

The results of this post hoc analysis show, for the first time to our knowledge, that CR is achievable with both FF/UMEC/VI and FF/VI inhaled therapy for patients with asthma previously uncontrolled on ICS/LABA but who

have not yet been considered for biologic therapy. A greater proportion of patients met the CR endpoint at Week 24 and achieved CR at Week 52 with FF/UMEC/VI than FF/VI (FF 100 or 200 µg), and the probability of meeting the CR endpoint at Week 24 was greater with FF/UMEC/VI versus FF/VI, irrespective of FF dose and lung function threshold used.

Recently, data have emerged showing that CR is achievable for patients treated with inhaled therapy alone and for those with less severe asthma [33, 38–40]. However, these studies have limitations in the size [39] and selection [40] of the patient population, selection of interventions [33, 38], and definition of endpoints [38]. In contrast, the current post hoc analysis evaluated asthma CR using robust data from the CAPTAIN clinical trial, including a defined ITT population of 2436 patients with uncontrolled moderate-to-severe asthma, not required to have a history of exacerbations, and who were stabilized on FF/VI prior to treatment randomization to either FF/UMEC/VI or FF/VI. We also evaluated a 4-component definition of CR, in line with the current literature, comprising no SCS use, no severe exacerbations, asthma control, and stabilized or optimized lung function [1, 21, 22], and demonstrate the attainability of CR with both FF/UMEC/VI and FF/VI.

When assessing the impact of individual components, we found that most patients had no SCS use and no severe exacerbations, with similar results across treatment groups. This finding is not altogether surprising, given that patients enrolled in CAPTAIN were not required to have experienced an exacerbation in the year prior. Instead, we found that symptom control and lung function were the components that most impacted attainability of the CR endpoint. Despite this, over half of patients across treatment groups had symptom control (ACQ-5 < 1.50) at Week 24. Interestingly, in the overall population there were only minor differences in treatment effect between FF/UMEC/VI and high-dose FF/VI at Week 24, whereas in the subgroup that continued to Week 52, more patients achieved CR using the ACQ-5 < 1.50 threshold with FF/UMEC/VI than FF/VI, regardless of FF dose. This may suggest short-term benefits in symptom control from increasing ICS dose versus longer-term benefits from adding a long-acting muscarinic antagonist (LAMA) to ICS/LABA. When including lung function, irrespective of the stabilization/optimization definition used, a greater proportion of patients met the CR endpoint at Week 24 or achieved CR at Week 52 with FF/UMEC/VI versus FF/VI. These results may be expected from the addition of a second bronchodilator. Indeed, results from Phase III trials have demonstrated that ICS/LAMA/LABA triple therapy improves lung function and symptom control versus ICS/LABA dual therapy in patients with uncontrolled asthma [36, 41, 42]. In addition, a recent medical imaging study found that in patients with uncontrolled asthma despite previous ICS/LABA therapy, initiating FF/UMEC/VI led to improvements in lung function and a reduction in small airways dysfunction [43], emphasizing the added benefit of LAMA for improving patient outcomes.

Despite the greater treatment effect with FF/UMEC/VI compared with FF/VI, a subset of patients did not meet the CR endpoint at Week 24 or achieve CR at Week 52 with either therapy. It is unclear why the CR composite endpoint appeared out of reach of these patients; indeed, the high proportions meeting individual components indicate that many patients still responded to treatment. These findings highlight that CR remains an ambitious and challenging treatment goal, particularly given the multifactorial nature of assessment. As such, identifying characteristics associated with CR may help improve achievability by allowing personalization of treatment. In this post hoc analysis, we found that patients who met the CR endpoint at Week 24 were generally younger, had fewer severe exacerbations in the year prior, and had better asthma control and lung function, a lower BMI, and shorter asthma duration at baseline than those who did not meet the CR endpoint at Week 24. Although these findings are descriptive, and were inconsistent across treatment groups, they broadly align with those from other studies in patients with mild-to-moderate and severe asthma [33, 35].

Recent research in severe asthma populations has shown that the odds of CR with biologic therapy are higher in patients with high T2 asthma [44, 45]. Although we assessed a patient population with less severe asthma, not yet considered for biologics, we also evaluated the impact of T2 inflammation status on CR with inhaled therapy. We found that when increasing FF dose, patients with high T2 inflammation were more likely to meet the CR endpoint at Week 24, with little effect in patients with low T2 inflammation. In contrast, adding UMEC to FF/VI increased the probability of meeting the CR endpoint at Week 24 versus FF/VI alone, regardless of T2 status. Moreover, patients who met the CR endpoint at Week 24 with high-dose FF/UMEC/VI or FF/VI had higher baseline EOS and FeNO levels than those who did not meet the CR endpoint at Week 24. Early optimization of treatment based on T2 phenotype may therefore help patients achieve CR: in patients with moderate-to-severe asthma and low T2 inflammation, addition of a LAMA to ICS/LABA may improve rates of CR, whereas in those with high T2 inflammation, increasing ICS dose in dual or triple therapy could be considered.

The results of this post hoc analysis also showed that patients meeting the CR endpoint at Week 24 were more likely to achieve CR at Week 52 than those who did not meet the CR endpoint at Week 24, regardless of treatment. This suggests that there may be predictive value in assessing the components of CR at an earlier timepoint, as an indicator of long-term success in achieving CR. Healthcare providers might therefore consider implementing regular assessments of CR components earlier in the treatment process to proactively manage patients and target CR as a treatment goal. Furthermore, earlier optimization of treatment may increase the ability of patients to meet CR components at earlier timepoints and in turn maintain this as CR at 52 weeks [46, 47]. Indeed, in patients with severe asthma treated with biologics, a shorter asthma duration prior to treatment initiation is associated with greater odds of remission [34].

Although CR represents an aspirational treatment goal for patients with asthma, some refinements are still required regarding the component criteria. Thus far, SCS-/OCS-free and exacerbation-free criteria are consistently applied across CR definitions, reflecting the objectivity of assessment and the clear benefits of freedom from exacerbations and SCS use [48–52]. However, despite the importance of maintaining lung function to long-term asthma management [53], there has been considerable variability in lung function criteria used to assess CR in asthma, with some studies mandating either lung function stabilization or optimization and others omitting lung function as a component entirely [54, 55]. We assessed lung function optimization alongside stabilization, in line with recommendations from expert consensus statements on CR [21, 22], and found that the lung function component had the greatest impact on attainability of CR in this population. Interestingly, the greater treatment effect of FF/UMEC/VI versus FF/VI remained, irrespective of which lung function threshold was assessed, suggesting that the addition of UMEC offers clinical benefits for both stabilizing and optimizing lung function in the right patients. In keeping with the aim to refine and standardize the CR definition, our results suggest that lung function stabilization could be considered the minimum benchmark for CR, particularly in patients aiming to prevent decline, such as those with long-standing asthma who experience persistent airway obstruction [44, 47]. For those with less airway dysfunction, optimization could then be explored as a further threshold in CR.

Asthma control has previously been assessed cross-sectionally via the ACT and ACQ [26, 28–31, 55, 56], but as with lung function, specific assessment criteria for CR have yet to be robustly defined. We assessed symptom control using an ACQ-5 score of < 1.50, in line with previous studies [28, 31, 55, 56], as well as exploring more stringent thresholds of ≤ 0.75 and ≤ 1.00 [57]. As expected, fewer patients met the composite CR endpoint with ACQ-5 ≤ 0.75 than ACQ-5 < 1.50. However, the difference between FF/UMEC/VI and FF/VI was still evident even at the most stringent ACQ-5 threshold. Further research is needed to define the optimal thresholds and timeline for assessment of symptom control in CR. However, as the definition of CR evolves,

the results of this post hoc analysis may help inform discussions about the impact of different component thresholds to ensure that CR is a relevant and achievable goal for all patients.

Limitations associated with this analysis include those typically associated with post hoc analyses; care must be taken when interpreting data because the analysis may not be powered to optimally answer the study's questions. A limitation of CAPTAIN for this post hoc exploratory analysis was the 24-week fixed treatment period and optional continuation to Week 52; consequently, a relatively low number of patients contributed to the Week 52 dataset. To mitigate this, we report data for the composite CR endpoint at both Week 24 and Week 52. Assessment of a 24-week CR endpoint may lead to overestimation of the rate of remission, as there may be fewer exacerbations versus the 52-week period. However, the CAPTAIN population included patients with moderate-to-severe asthma who were not required to have a history of exacerbations, thereby reducing this risk of bias. Furthermore, descriptive data at Week 24 and Week 52 showed consistent treatment effects from FF/UMEC/VI and FF/VI therapies, with more patients attaining the CR endpoint at both timepoints with triple versus dual therapy, regardless of ICS dose.

CONCLUSIONS

This post hoc analysis showed that in patients with uncontrolled moderate-to-severe asthma not yet considered for biologics, a greater proportion achieved CR with FF/UMEC/VI versus FF/VI alone, regardless of FF dose. Our findings suggest that meeting a CR endpoint at 24 weeks may be indicative of CR at 52 weeks, regardless of dual or triple therapy, underscoring the importance of early assessment and treatment optimization to achieve CR. Collectively, these findings indicate that CR should be considered an ambitious but attainable treatment goal for patients with uncontrolled asthma, irrespective of disease severity and current therapy.

ACKNOWLEDGEMENTS

We thank the participants of the CAPTAIN study. Permission for use of the Asthma Control Questionnaire was acquired, and we thank the respective rights holders.

Medical Writing/Editorial Assistance. Editorial support (in the form of writing assistance, including preparation of the draft manuscript under the direction and guidance of the authors, collating, and incorporating authors' comments for each draft, assembling tables and figures, grammatical editing, and referencing) was provided by Ben Usher, PhD, of Fishawack Indicia Ltd, UK, part of Avalere Health, and was funded by GSK.

Author Contributions. All authors were involved in the preparation and review of the manuscript and approved the final version to be submitted. All authors take complete responsibility for the integrity of the data and accuracy of the data analysis. John Oppenheimer, Ian D Pavord, Tom Corbridge, Steven Gould, Mohamed Hamouda, Peter Howarth, Emmeline Burrows, Alison Moore, Stephen G Noorduyn, David Slade, Stephen Weng, and Njira Lugogo contributed to the data interpretation. Jodie Crawford contributed to the data analysis and interpretation.

Funding. This study was funded by GSK (Study 205715; NCT02924688). GSK-affiliated authors had a role in study design, data analysis, data interpretation, and writing of the report, and GSK funded the journals rapid service and open access fees.

Data Availability. The datasets generated during and/or analyzed during the current study are available at https://clinicalstudydatarequest.com/Posting.aspx?ID=20767. Please refer to GSK weblink to access GSK's data sharing policies and as applicable seek anonymized subject level data via the link https://www.gsk-studyregister.com/en/.

Declarations

Conflicts of Interest. John Oppenheimer has served on adjudication committees or data and safety monitoring boards for AstraZeneca, GSK, Novartis, and Sanofi-Regeneron; received consultancy fees from AstraZeneca, GSK, and Sanofi; and received grants and personal fees from GSK. Ian D Pavord 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, GSK, Knopp, Merck, Novartis, Roche-Genentech, Sanofi-Regeneron, and Teva; acted as an expert witness for a patent dispute involving AstraZeneca and Teva; is a 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. Tom Corbridge, Jodie Crawford, Steven Gould, Mohamed Hamouda, Peter Howarth, Emmeline Burrows, Alison Moore, Stephen G Noorduyn, David Slade, and Stephen Weng are employed by GSK and hold financial equities in GSK. Stephen G Noorduyn is a PhD candidate at McMaster University, Hamilton, ON, Canada. Njira Lugogo has received consulting fees from Amgen, AstraZeneca, Avillion, Genentech, GSK, Niox, Novartis, Regeneron, Sanofi, and Teva; honoraria for non-speaker's bureau presentations from GSK and AstraZeneca; and travel support from AstraZeneca; her institution received research support from Amgen, AstraZeneca, Avillion, Evidera, Genentech, Gossamer Bio, GSK, Janssen, Novartis, Regeneron, Sanofi, and Teva. She is an honorary faculty member of the Observational and Pragmatic Research Institute (OPRI) but does not receive compensation for this role.

Ethics Approval. CAPTAIN was performed in accordance with the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice, and applicable country-specific regulatory requirements, and received United States central ethics approval from the Chesapeake Institutional Review Board (now Advarra; IRB: 00000971, IORG: 0000635). This was a multinational, multicenter study; a full list of the ethics committees that approved the study are included in Table S1. Written informed consent was obtained from all patients before participation.

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