

GlaxoSmithKline Inc.
5 Moore Drive
Research Triangle Park, North Carolina 27709

**BREO™ ELLIPTA™ (Fluticasone Furoate/Vilanterol Inhalation
Powder) For Treatment of
Chronic Obstructive Pulmonary Disease**

NDA 204275

FDA Advisory Committee Briefing Document

Presented to:

Pulmonary-Allergy Drugs Advisory Committee

March 7, 2013

***ADVISORY COMMITTEE BRIEFING MATERIALS:
AVAILABLE FOR PUBLIC RELEASE***

TABLE OF CONTENTS

	PAGE
ABBREVIATIONS	11
1. INTRODUCTION.....	49
2. BACKGROUND.....	49
3. RATIONALE FOR THE USE OF FF/VI IN COPD	50
4. REGULATORY HISTORY	52
5. PRODUCT DESCRIPTION	53
6. PHARMACOLOGY FINDINGS.....	54
6.1. Nonclinical Pharmacology and Toxicology	54
6.2. Clinical Pharmacology	54
6.2.1. Pharmacokinetics	55
6.2.1.1. ADME.....	55
6.2.1.2. Assessments in Special Populations	56
6.2.1.2.1. Age.....	56
6.2.1.2.2. Gender	57
6.2.1.2.3. Race.....	57
6.2.1.2.4. Renal Impairment	57
6.2.1.2.5. Hepatic Impairment.....	57
6.2.1.3. Drug Interactions	58
6.2.1.4. PK Results from Clinical Studies	58
6.2.2. Pharmacodynamics	59
6.2.2.1. Corticosteroid Effects	59
6.2.2.2. Beta ₂ -agonist Effects	59
6.2.3. Dose or Concentration/Effect Relationship.....	60
7. CLINICAL DEVELOPMENT PROGRAM	60
7.1. Selection of Doses for Phase III and Evaluation of Dose Regimen	61
7.1.1. Vilanterol Dose Selection.....	63
7.1.2. Fluticasone Furoate Dose Selection	70
7.1.3. Dose Regimen: Once-Daily Dosing.....	72
7.1.3.1. Once-Daily Dosing of Vilanterol.....	72
7.1.3.2. Once-Daily Dosing of Fluticasone Furoate	73
7.2. COPD Clinical Development Program Overview.....	74
7.3. Study Design, Efficacy Variables, and Statistical Methods of the Phase III COPD Efficacy Studies	81
7.3.1. Study Design	81
7.3.2. Efficacy Endpoints	84
7.3.3. Statistical Methods.....	85
7.3.3.1. Treatment Comparisons	85
7.3.3.2. Multiple Comparisons and Multiplicity	85
7.4. Comparison of Efficacy in the Primary Studies.....	86
7.4.1. Integration of the Primary Studies	86

7.4.2.	Demographics, Baseline Characteristics, and Patient Disposition Across the Primary Studies	86
7.4.2.1.	Demographic and Baseline Characteristics	86
7.4.2.2.	Subject Disposition	88
7.4.3.	Efficacy Results	90
7.4.3.1.	Efficacy of Vilanterol	90
7.4.3.2.	Efficacy of Fluticasone Furoate.....	92
7.4.3.3.	Efficacy of Fluticasone Furoate/Vilanterol	93
7.4.3.3.1.	Lung Function.....	94
7.4.3.3.2.	Symptomatic Endpoints	99
7.4.3.4.	Contribution of Vilanterol in the Combination	104
7.4.3.4.1.	Lung Function.....	104
7.4.3.4.2.	Symptomatic Endpoints	105
7.4.3.5.	Contribution of Fluticasone Furoate in the Combination	105
7.4.3.5.1.	Annual Rate of Moderate/Severe COPD Exacerbations (H2C102970 and H2C102871).....	105
7.4.3.5.2.	Time to First Moderate or Severe COPD Exacerbation	107
7.4.3.5.3.	Annual Rate of COPD Exacerbations Requiring Systemic/Oral Corticosteroids.....	108
7.4.3.5.4.	Lung Function.....	108
7.4.3.5.5.	Other Symptomatic Endpoints	110
7.4.3.6.	Subpopulation Analyses of the Primary/Co-Primary Endpoints in the Primary Studies.....	113
7.4.3.7.	Efficacy Results from Studies Comparing FF/VI with Marketed Products	113
7.5.	Safety Results.....	115
7.5.1.	Safety Population and Groups	118
7.5.2.	Extent of Exposure	118
7.5.3.	Adverse Events.....	119
7.5.3.1.	Overview of Adverse Events.....	120
7.5.3.2.	Common Adverse Events	121
7.5.3.3.	Deaths.....	121
7.5.3.4.	Serious Adverse Events	128
7.5.3.5.	Adverse Events Leading to Withdrawal from Investigational Product/Study	129
7.5.3.6.	Adverse Events of Special Interest (AESI).....	132
7.5.3.6.1.	Pneumonia	134
7.5.3.6.2.	Bone Disorders.....	137
7.5.4.	Cardiovascular Effects.....	138
7.5.4.1.	12-Lead Electrocardiograms.....	139
7.5.4.1.1.	Heart Rate	139
7.5.4.1.2.	QTc	139
7.5.4.2.	24-Hour Holter.....	140
7.5.4.3.	Vital Signs	141
7.5.4.4.	AEs of Special Interest: Cardiovascular Effects Category.....	141
7.5.5.	Other Safety Parameters	142
7.5.5.1.	Clinical Laboratory.....	142

7.5.5.2.	HPA-Axis Assessments	142
7.5.5.3.	Ophthalmic Evaluations	144
8.	RISK MANAGEMENT/MITIGATION PLANS	144
8.1.	Pneumonia	145
8.2.	Bone Disorders/Fractures	145
8.3.	Cardiovascular Effects	145
8.4.	Clinical Laboratory Findings.....	146
8.5.	HPA-Axis Effects	146
8.6.	Ocular Effects	146
8.7.	Rare Respiratory-Related Events Including Asthma-Related Death and Intubation	147
9.	BENEFIT-RISK ASSESSMENT	147
9.1.1.	Medical Need.....	147
9.1.2.	Therapeutic Justification	147
9.1.3.	Benefit:Risk	147
10.	OVERALL CONCLUSION	151
11.	REFERENCES.....	152
12.	APPENDICES	157
12.1.	Appendix 1: Other Efficacy Endpoints.....	158
12.2.	Appendix 2: Statistical Testing Hierarchy.....	160
12.3.	Appendix 3: Statistical Methods	162
12.4.	Appendix 4: Preferred Terms within Each of the Categories of Adverse Events of Special Interest	166

LIST OF TABLES

		PAGE
Table 1	Pharmacokinetics of FF and VI.....	16
Table 2	FF/VI COPD Clinical Development Program: Primary Studies.....	18
Table 3	ICS Contribution in ICS/LABA Combination Therapies in Subjects with COPD: FF/VI Studies and Studies of Marketed ICS/LABA Combinations – Trough FEV ₁ (mL)	24
Table 4	Overall Summary of Adverse Events (ITT Population): Integrated Study Results – 6-Month Lung Function Studies (HZC112206/HZC112207)	32
Table 5	Overall Summary of Adverse Events (ITT Population): Integrated Study Results – 1-Year Exacerbation Studies (HZC102970/HZC102871)	33
Table 6	Adverse Events with ≥3% Incidence with FF/VI 100/25 in Subjects with COPD (ITT Population): Integrated Study Results – 6-Month Lung Function Studies (HZC112206/HZC112207)	33
Table 7	Adverse Events with ≥3% Incidence with FF/VI 100/25 in Subjects in with COPD (ITT Population): Integrated Study Results – 1-Year Exacerbation Studies (/HZC102970/HZC102871).....	34
Table 8	Summary of On-Treatment Adverse Events of Special Interest (ITT Population): Integrated Study Results – 6-Month Lung Function Studies (HZC112206/HZC112207)	35
Table 9	Summary of AE of Special Interest: On-Treatment Pneumonia (ITT Population): Integrated Study Results – 6- Month Lung Function Studies (HZC112206/HZC112207).....	36
Table 10	Summary of AE of Special Interest: Pneumonia (ITT Population): Individual and Integrated Study Results – 1-Year Exacerbation Studies (HZC102970/HZC102871)	37
Table 11	Summary of Pneumonia Reports from 1-Year Studies of Marketed ICS/LABA Combinations in Subjects with COPD	38
Table 12	Bone Fractures (ITT Population): Integrated Study Results – 1-Year Exacerbation Studies (HZC102970/HZC102871).....	39
Table 13	Arrhythmias with Potential Clinical Consequences (ITT Population): Integrated Study Results – 6-Month Lung Function Studies (HZC112206/HZC112207)	42

Table 14	Cardiovascular Events: On-Treatment Cardiac-Associated AEs (ITT Population): Integrated Study Results – 6-Month Lung Function Studies (HZC112206/HZC112207)	42
Table 15	Summary of Moderate/Severe Exacerbations, Pneumonias and Total Fractures (ITT Population): Integrated Study Results – 1-Year Exacerbation Studies (HZC102970/HZC102871)	48
Table 16	Studies to Support Doses and Dose Regimen of FF and VI Evaluated in the FF/VI Phase III Clinical Development Program for COPD	62
Table 17	Analysis of Change from Baseline in Trough FEV ₁ (LOCF) on Day 29: Probability of Treatment Difference (VI versus Placebo) Being >100 mL (ITT Population) – VI Dose-Ranging Study in COPD (B2C111045)	65
Table 18	Summary of Secondary Endpoints (ITT Population): VI Dose-Ranging Study in COPD (B2C111045)	67
Table 19	FF/VI Clinical Development Program for COPD: Primary and Supporting Studies	77
Table 20	Demographic and Baseline Characteristics: Primary COPD Studies - 6-Month, Lung Function Studies (HZC112206/HZC112207 Integrated) and 1-Year Exacerbation Studies (HZC102970/HZC102871 Integrated)	87
Table 21	Summary of End of Study Record in CRF (ITT Population): Integrated Study Results - 6-Month Lung Function Studies (HZC112206 and HZC112207)	88
Table 22	Summary of End of Study Record in CRF (ITT Population): Integrated Study Results -1-Year Exacerbation Studies (HZC102970 and HZC102871)	89
Table 23	Efficacy and Safety of FF in Subjects with Asthma (HZA106827 and FFA112059)	93
Table 24	Trough and Weighted Mean FEV ₁ : Comparisons of FF 100 with Placebo (ITT Population) – Asthma Studies (HZA106827 and FFA112059)	93
Table 25	Statistical Analysis of Weighted Mean FEV ₁ (0-4 hours) (L) (ITT Population): Individual Study Results – 6-Month Lung Function Studies (HZC112206 and HZC112207)	95
Table 26	Statistical Analysis of Mean Change from Baseline in Trough FEV ₁ (L) (ITT Population): Individual Study Results – 6-Month Lung Function Studies (HZC112206 and HZC112207)	96

Table 27	Summary of Treatment Differences Versus Placebo (95% CI) for the Secondary Endpoints of Peak FEV ₁ and Time to Onset at Day 1 (ITT Population): Individual Study Results – 6-Month Lung, Function Studies (HZC112206 and HZC112207).....	98
Table 28	Diary Data Over Weeks 1-24 and CRQ-SAS-Dyspnea Data at Day 168: LS Mean Treatment Differences Versus Placebo and 95% Confidence Intervals (ITT Population) – Individual Study Results: 6-Month Lung Function Studies (HZC112206 and HZC112207).....	100
Table 29	Statistical Analysis of Weighted Mean FEV ₁ (L) Up to 24 Hours on Day 84 (ITT Population) – Individual Study Results: Supporting COPD Studies HZC113107, HZC113109 and HZC112352.....	114
Table 30	Safety Assessments Conducted in Primary COPD Studies (HZC112206/HZC112207/HZC102970/HZC102871).....	117
Table 31	Number of Subjects Treated in the COPD and Asthma Clinical Development Programs	119
Table 32	Summary of On-Treatment or Post-Treatment Fatal Adverse Events in Any Treatment Group (ITT Population): Integrated Study Results – 6-Month Lung Function Studies (HZC112206/HZC112207)	122
Table 33	Summary of On-Treatment or Post-Treatment Fatal Adverse Events in Any Treatment Group (ITT Population): Integrated Study Results – 1-Year Exacerbation Studies (HZC102970/HZC102871)	124
Table 34	Summary of On-Treatment or Post-Treatment Fatal Adverse Events in Any Treatment Group (Integrated COPD Studies)	127
Table 35	Summary of On-Treatment Serious Adverse Events (ITT Population): Integrated Study Results - 6-Month Lung Function Studies (HZC112206/HZC112207)	128
Table 36	Summary of On-Treatment Serious Adverse Events (ITT Population): Integrated Study Results – 1-Year Exacerbation Studies (HZC102970/HZC102871).....	129
Table 37	Summary of On-Treatment Adverse Events Leading to Permanent Discontinuation of Study Drug or Withdrawal from the Study (ITT Population): Integrated Study Results – 6-Month Lung Function Studies (HZC112206/HZC112207).....	131
Table 38	Summary of On-Treatment Adverse Events Leading to Permanent Discontinuation of Study Drug or Withdrawal from the Study (ITT Population): Integrated Study Results – 1 Year Exacerbation Studies (HZC102970/HZC102871).....	132

Table 39	Summary of On-Treatment Adverse Events of Special Interest (ITT Population): Integrated Results – 1-Year Exacerbation Studies (HZC102970/HZC102871)	133
Table 40	Summary of Pneumonia-Related Adverse Events (ITT Population): Integrated Study Results – 6-Month Lung Function Studies (HZC112206/HZC112207)	135
Table 41	Summary of Pneumonia-Related Adverse Events (ITT Population): Integrated Study Results – 1-Year Exacerbation Studies (HZC102970/HZC102871).....	136
Table 42	Treatment Difference (95% CI) from VI 25 for Annual Rate of On-Treatment Moderate or Severe COPD Exacerbations by BMI and GOLD Stage Sub-Groups: Integrated Study Results – 1-Year Exacerbation Studies (HZC102970/HZC102871).....	150

LIST OF FIGURES

	PAGE
Figure 1	Clinical Development Program 15
Figure 2	Least Squares Means (95%) CI in 0-4hours Weighted Mean FEV ₁ (L) (ITT Population): Integrated Study Results – 6- Month Lung Function Studies (HZC112206/HZC112207)..... 22
Figure 3	Least Squares Means (95% CI) in Change from Baseline in Trough FEV ₁ (L) (ITT Population): Integrated Study Results – 6-Month Lung Function Studies (HZC112206/HZC112207)..... 23
Figure 4	Least Squares Mean Changes from Baseline in Trough FEV ₁ (L) 95% CI) (ITT Population): Integrated Study Results – 1- Year Exacerbation Studies (HZC102970/HZC102871)..... 25
Figure 5	Treatment Differences (95% CI) for the Annual Rate of Moderate and Severe COPD Exacerbations (ITT Population): Individual and Integrated Study Results – 1-Year Exacerbation Studies (HZC102970 and HZC102871) 27
Figure 6	Kaplan-Meier Plot of Time to First On-Treatment Moderate or Severe COPD Exacerbation (ITT Population): Integrated Study Results – 1-Year Exacerbation Studies (HZC102970/HZC102871) 28
Figure 7	Treatment Differences (95% CI) in Annual Rate of COPD Exacerbations Requiring Systemic/Oral Corticosteroids (ITT Population): Integrated Study Results – 1-Year Exacerbation Studies (HZC102970/HZC102871)..... 29
Figure 8	QTcF Adjusted Mean Change from Baseline (Difference from Placebo [90% CI]) on Day 7 (Per Protocol Population) – Thorough QT Study in Healthy Subjects (HZA102936)..... 41
Figure 9	Raw Geometric Means (NMOL/L) for Serial Serum Cortisol Over Period Days 28-29 (ITT Population): Supporting VI COPD Study (HZA110946) 43
Figure 10	Box Plot of 24-Hour Urinary Cortisol Excretion Ratio to Baseline at Day 168 (Urine Cortisol Population): Integrated Study Results – 6-Month Lung Function Studies (HZA112206/HZA112207) 44
Figure 11	Adjusted Treatment Differences (95% CI) from Placebo in Change from Baseline in Trough FEV ₁ (L) at Day 29 in Subjects with COPD (ITT Population and Non-Reversible Population): VI Dose-Ranging Study in COPD (B2C111045) 64

Figure 12	Posterior Probability Distribution of the Treatment Differences in Change from Baseline in Trough FEV ₁ (L) at Day 29 (LOCF) (ITT Population): VI Dose-Ranging Study (B2C111045).....	65
Figure 13	Primary and Secondary Endpoints – Comparison of VI 25 and VI 12.5 with Placebo (ITT Population): VI Dose-Ranging Study in Asthma (B2C109575)	68
Figure 14	Empirical Distribution Function for Maximum Change from Baseline Post-Dose QTc (F) (msec): Days 1 and 28 (ITT Population) – VI Dose-Ranging Study in COPD (B2C111045)	69
Figure 15	Adjusted Treatment Differences from Placebo in Change from Baseline 0-4 Hour Maximum Pulse Rate (bpm) (ITT Population): VI Dose-Ranging Study in COPD (B2C111045)	70
Figure 16	Adjusted Treatment Differences from Placebo for Change from Baseline in Trough FEV ₁ (L) (LOCF) at Week 8 (ITT Population): FF Dose-Ranging Studies in Asthma (FFA109684, FFA109685 and FFA109687)	71
Figure 17	Adjusted Treatment Ratios for 24-Hour Urinary Cortisol Excretion (Week 8/Baseline) (Urinary Cortisol Population): FF Dose-Ranging Studies in Asthma (FFA109684, FFA109685 and FFA109687)	72
Figure 18	Adjusted Treatment Differences from Placebo in Change from Baseline FEV ₁ (L) Over Time on Day 7 (ITT Population): Supporting VI Asthma Study (HZA113310)	73
Figure 19	Adjusted Treatment Differences in Trough FEV ₁ (L) at Day 28 (ITT Population): Supporting FF Asthma Study (FFA112202).....	74
Figure 20	Efficacy of Vilanterol vs. Placebo on 0-4 Hours Weighted Mean FEV ₁ (L) (ITT Population): Individual Study Results – 6-Month Lung Function Studies (HZA112206 and HZA112207).....	91
Figure 21	Efficacy of Vilanterol vs. Placebo on Trough FEV ₁ (L) (ITT Population): Individual Study Results – 6-Month Lung Function Studies – (HZA112206 and HZA112207)	91
Figure 22	Diary Data Over Weeks 1-24 and CRQ-SAS-Dyspnea Data at Day 168: LS Mean Treatment Differences (95% CI) for FF/VI 100/25 Versus Placebo (ITT Population) – Individual Study Results: 6-Month Lung Function Studies (HZA112206 and HZA112207).....	101
Figure 23	Least Squares Means (95% CI) for IVRS Diary Mean Number of Occasions of Rescue Use (Occasions/24 hours), Four-Week Intervals (ITT Population): 1-Year Exacerbation Study (HZA102970).....	102

Figure 24	Least Squares Means (95% CI) for IVRS Diary Mean Number of Occasions of Rescue use (Occasions/24 hours), Four-Week Intervals (ITT Population): 1-Year Exacerbation Study (HZC102871).....	102
Figure 25	Least Squares Means (95% CI) for IVRS Diary Mean Number of Night-time Awakenings Due to Symptoms of COPD (occasions/24 hours), Four-Week Intervals (ITT Population): Individual Study Results – 1-Year Exacerbation Study (HZC102970).....	103
Figure 26	Least Squares Means (95% CI) for IVRS Diary Mean Number of Night-time Awakenings Due to Symptoms of COPD (occasions/24 hours), Four-Week Intervals (ITT Population): Individual Study Results – 1-Year Exacerbation Study (HZC102871).....	104
Figure 27	Treatment Differences (95% CI) for the Annual Rate of Moderate and Severe COPD Exacerbations – Frequent Exacerbators*: Integrated Study Results – 1-Year Exacerbation Studies (HZC102970/HZC102871)	107
Figure 28	Treatment Difference (95% CI) for Change from Baseline Trough FEV ₁ (L) at Day 169 (HZC112206 and HZC112207) and Day 364 (HZC102970 and HZC102871) in Subjects with COPD	109
Figure 29	Least Squares Mean Treatment Differences from VI 25 (95% CI) in IVRS Diary Mean Number of Occasions of Rescue Use (occasions/24 hours), Four-Week Intervals (ITT Population): Individual Study Results – 1-Year Exacerbation Studies (HZC102970 and HZC102871).....	110
Figure 30	Least Squares Mean Treatment Differences from VI 25 (95% CI) in IVRS Diary Mean Number of Night-time Awakenings Due to Symptoms of COPD (occasions/24 hours), Four-Week Intervals (ITT Population): Individual Study Results – 1-Year Exacerbation Studies (HZC102970 and HZC102871).....	112
Figure 31	Asthma Composite Endpoint, On-Treatment, by Study and Overall: FF/VI All Doses vs. Non-LABA All Doses	116
Figure 32	Time to First Pneumonia in Subgroups: FF/VI 100/25 vs VI 25 – Integrated Study Results: 1-Year Exacerbation Studies (HZC102970/HZC102871)	137
Figure 33	Statistical Testing Strategy: 6-Month, Lung Function Studies - HZC112206 and HZC112207	161
Figure 34	Statistical Testing Strategy: 1-Year, Exacerbation Studies - HZC102970 and HZC102871	161

ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Events of Special Interest
ANCOVA	Analysis of covariance
APSD	Aerodynamic particle size distribution
AUC ₍₀₋₂₄₎	Area under the concentration-time curve over the once-daily dosing interval
AUC _(0-t)	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration
AUC _(0-t')	Area under the concentration-time curve from zero (pre-dose) to the time of last common measurable time-point, t', within subject across treatments
BID	Twice daily
BMD	Bone mineral density
BMI	Body Mass Index
BPM	Beats per minute
BUD	Budesonide
CI	Confidence interval
CL/F	Apparent clearance following inhaled dosing
C _{max}	Maximum observed concentration
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRQ-SAS	Chronic Respiratory Disease Questionnaire – Self-Administered Standardized
CYP3A4	Cytochrome P450 3A4
DPI	Dry Powder Inhaler
ECG	Electrocardiogram
EU	European Union
FDA	Food and Drug Administration
FEV ₁	Forced expiratory volume in one second
FF	Fluticasone Furoate
FF/VI	Fluticasone Furoate/Vilanterol
FM	Formoterol
FP	Fluticasone Propionate
FVC	Forced vital capacity
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GOLD	Global Initiative for Obstructive Lung Disease
GSK	GlaxoSmithKline
HPA	Hypothalamic-pituitary-adrenal
ICH	International Conference on Harmonisation
ICS	Inhaled corticosteroid
IND	Investigational New Drug
IOP	Intraocular pressure
ITT	Intent-to-Treat
IV	Intravenous

IVRS	Interactive Voice Response System
Kg	Kilogram
LABA	Long-acting beta ₂ agonist
LLQ	Lower limit of quantification
LOCF	Last observation carried forward
LOCS III	Lens Opacities Classification System III
LogMAR	Logarithm of the angle of resolution
Mcg	Micrograms
MCID	Minimal clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligrams
NDA	New Drug Application
QD	Once daily
PD	Pharmacodynamics
PEF	Peak expiratory flow
P-gp	P-glycoprotein
PK	Pharmacokinetics
PLA	Placebo
QTci	QT interval individually corrected for heart rate
QTcF	QT interval corrected for heart rate according to Fredericia's formula
RAP	Reporting and Analysis Plan
SABA	Short-acting beta ₂ -agonist
SAE	Serious adverse event
SAL	Salmeterol
SE	Standard error
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
T _{max}	Time of occurrence of C _{max}
UC	Urinary Cortisol
URTI	Upper respiratory tract infection
US	United States
VI	Vilanterol

EXECUTIVE SUMMARY

Introduction

Airflow limitation and recurring exacerbations are the hallmarks of chronic obstructive pulmonary disease (COPD) and lead to increasing symptomatic and functional limitation and morbidity [GOLD, 2011]. Relief of reversible airflow obstruction, an important but not universal feature, in COPD has been the key target for drug therapies [FDA, 2007], though reduction of COPD exacerbations is clearly a clinically important goal.

Exacerbations can be life-threatening, are linked to co-morbid conditions and may contribute to further permanent decrements in lung function. Drugs that either prevent, or modify the severity or duration of COPD exacerbations can provide meaningful benefit to patients. As noted in the FDA Draft Guidance, reduction in chronic cough, excess sputum production, dyspnea, or other debilitating symptoms of COPD, also constitutes meaningful benefit to patients [FDA, 2007].

Product Rationale

The concomitant use of inhaled corticosteroids (ICS) and long-acting beta₂-agonists (LABA) is a well-established and recommended approach for the treatment of COPD [GOLD, 2011]. Only two inhaled ICS/LABA combination treatments, ADVAIR DISKUS® (fluticasone propionate/salmeterol) and Symbicort® (budesonide/formoterol) are approved by the FDA for treatment of COPD in the United States, and both have an indication for the treatment of airflow obstruction for a single selected dose. Only ADVAIR DISKUS also has the indication to reduce exacerbations of COPD in patients with a history of exacerbations. ADVAIR DISKUS and ADVAIR® HFA (fluticasone propionate/salmeterol), Symbicort and Dulera® (mometasone furoate/formoterol) are also indicated at multiple strengths for the treatment of asthma. All inhaled ICS/LABA combination products are dosed twice daily.

Prescription refill data suggest that patients only refill 40-50% of their ICS/LABA prescriptions annually [Delea, 2010; Hagiwara, 2010]. Thus, there is a need to improve adherence, which a once-daily alternative may provide. Indeed, it has been demonstrated that compliance with a once-daily ICS regimen is greater than with a twice-daily regimen [Price, 2010; Toy, 2011]. In a 12-week study designed to mimic the real clinical setting in subjects with mild to moderate persistent asthma, compliance with once-daily mometasone was significantly better than with twice-daily mometasone [Price, 2010]. Similarly, a retrospective study of use of inhaled medications for COPD using an administrative claims database covering 8 million people in the US, demonstrated that compliance (measured as proportion of days covered over 12 months following treatment initiation) strongly correlated with dosing frequency. Based on a sample of 55,076 COPD patients, compliance was 43.3%, 37.0%, 30.2% and 23.0% for once, twice, three times and four times daily patient cohorts, respectively [Toy, 2011].

Healthcare resource utilization costs have also been shown to be lower in patients after initiating or switching to a once-daily regimen [Toy, 2011; Guest, 2005]. In the study of

Toy and colleagues, regression analysis showed that one-year adherence correlated with healthcare resource utilization and with improved compliance leading to a net reduction in annual costs. Similarly, a case control study using the General Practice Research Database in the UK [Guest, 2005] found that switching asthma patients managed in primary care from a twice-daily to a once-daily ICS increased compliance and reduced health service costs.

The goals of pharmacologic therapy in COPD should be to reduce symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance [GOLD, 2011]. COPD exacerbations are important events associated with accelerated loss of lung function and poor health status [Wedzicha, 2007]; mortality one year after an exacerbation-related hospitalisation exceeds 20% [McGhan, 2007]. Patients who exacerbate frequently (i.e. ≥ 2 events in 1 year) may form a distinct COPD subtype [Hurst, 2010] and guidelines have identified exacerbation frequency as a key target for preventive treatment [GOLD, 2011]. Bronchodilators, such as long-acting beta₂-agonists, are central to improving lung function and managing symptoms in COPD, whereas long-term treatment with ICS added to a LABA is recommended for patients with a high risk for exacerbations [GOLD, 2011]. Specifically, an ICS combined with a LABA in COPD has been shown to be more effective than the individual components in managing stable COPD by reducing exacerbations and improving lung function and health status [GOLD, 2011; Ferguson, 2008; Calverley, 2007; Kardos, 2007; Sharafkhaneh, 2012].

In order to further improve the care of patients with COPD, GSK has developed BREO™ ELLIPTA™ as a once daily inhaled treatment for COPD for both airflow obstruction and to reduce exacerbations in patients with a history of exacerbations. BREO ELLIPTA is a novel, fixed-dose powder combination of fluticasone furoate (FF) 100 mcg, an ICS, and vilanterol (VI) 25 mcg, a LABA. Although FF is approved in the US as VERAMYST™ for intranasal administration for allergic rhinitis, neither FF nor VI is currently available as an oral inhalation product for patients with lung disease.

In a comprehensive development program (See Section 7.2 in the full Briefing Document), BREO ELLIPTA given once daily produced meaningful near- and long-term improvements in lung function in COPD patients and reduced the annual rate of moderate to severe exacerbations. These benefits were achieved with an adverse event profile that is consistent with the known effects of ICS and LABA treatment.

Therefore, a New Drug Application (NDA) was submitted in July 2012 to the Food and Drug Administration (FDA) in support of BREO ELLIPTA for the treatment of COPD, with the proposed indication as follows:

“BREO ELLIPTA is a combination inhaled corticosteroid/long-acting beta₂ adrenergic agonist (ICS/LABA) indicated for the long-term once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. BREO ELLIPTA is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations.

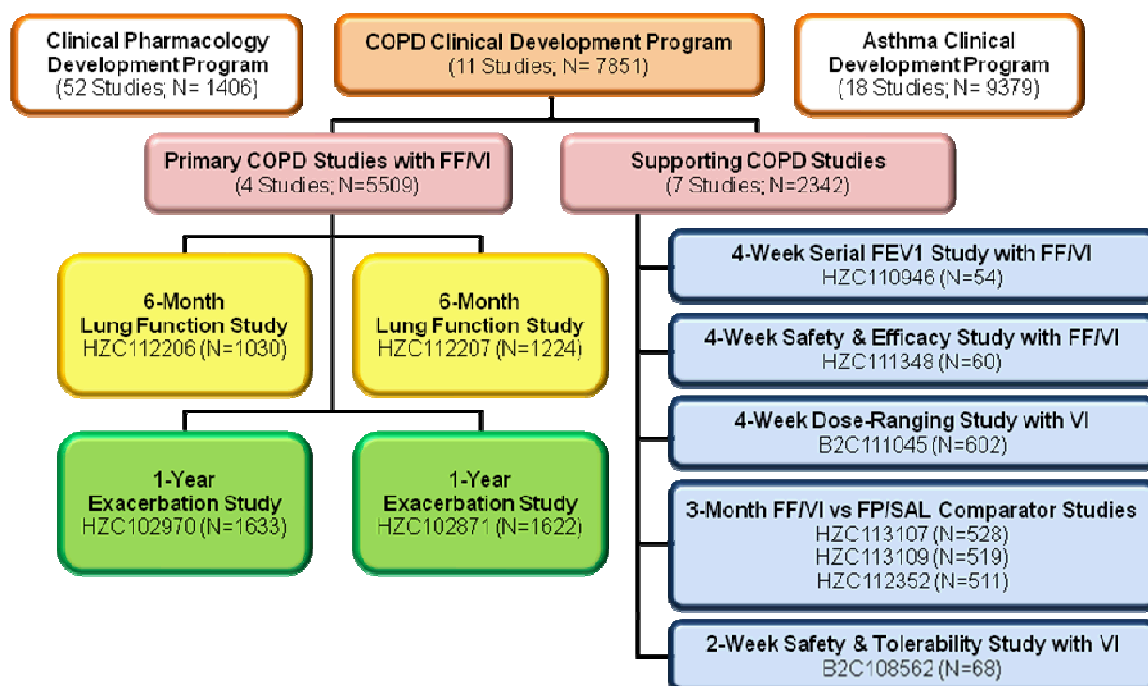
Important Limitations of Use: BREO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.”

A Phase III Clinical Development Program with FF/VI for the treatment of asthma is nearing completion.

Development Summary

The NDA for BREO ELLIPTA for the treatment of COPD is supported by a comprehensive range of nonclinical studies to support long-term clinical use, 52 Clinical Pharmacology Studies in 1,406 subjects, 11 Clinical Studies in 7,851 subjects with COPD and 18 Clinical Studies in over 9,379 subjects with asthma (Figure 1).

Figure 1 Clinical Development Program



FEV₁=forced expiratory volume in 1 second; FF=fluticasone furoate; FP=fluticasone propionate; SAL=salmeterol; VI=vilanterol

Nonclinical Summary

Nonclinical studies of FF and VI confirmed the pharmacologic effects expected with corticosteroids and beta₂-agonists, respectively (See Section 6.1 in the full Briefing Document). BREO ELLIPTA will be designated as FDA Pregnancy Category C, similar to the currently available ICS/LABA combination treatments.

Clinical Pharmacology Summary

The pharmacokinetics (PK) of FF and VI individually has been evaluated by various routes and the FF/VI combination has been evaluated by inhalation only, as the latter route is relevant for the proposed use. FF and VI have linear time-independent PK following once-daily inhaled administration of either FF or VI individually or as

combined FF/VI. Following single-dose inhaled VI administration, the plasma elimination phase half-life averaged 2.5 hours (Table 1). However, this is not representative of the duration of bronchodilation produced by VI, which is related to topical activity in the lung, where a 24-hour duration of action has been clearly demonstrated.

Table 1 Pharmacokinetics of FF and VI

	FF	VI
Oral bioavailability	<2%	<2%
Absolute bioavailability ¹	15.2%	27.3%
Mean absorption time ¹	10.5 hours	40 minutes
Time for absorption of 90% of dose ¹	35.2 hours	3.83 hours
Plasma elimination t _{1/2}	24 hours ²	2.5 hours ³
Route of elimination	Feces	Urine (70%), feces (30%)
Effect of hepatic impairment	Up to 3x increase in exposure	No change in exposure
Effect of renal impairment	No change	No change
Effect of Age	No change in COPD population	27% decrease in CL/F from age 41 years to 84 years in COPD population
Effect of gender	No change in COPD population	No change in COPD population
Race	30% higher FF AUC ₍₀₋₂₄₎ in East Asian subjects with COPD	No change in subjects with COPD

FF=fluticasone furoate; VI=vilanterol

1. FF and VI inhaled as 4 puffs of FF/VI 200/25
2. Repeat dose inhaled FF
3. Single-dose inhaled VI

As the oral bioavailability of both FF and VI is <2% (Table 1), any systemic exposure to FF or VI from the inhaled route is primarily due to absorption of the inhaled portion of the dose delivered to the lung.

Subjects with COPD had lower systemic FF exposure (C_{\max} 35% lower; AUC₍₀₋₂₄₎ 42% lower) compared with subjects with asthma. Compared with healthy subjects FF C_{\max} and AUC(0-24) was 18% and 7% lower, respectively, in subjects with asthma and 47% and 46% lower, respectively, in subjects with COPD. Neither gender nor age affected the PK of FF in subjects with COPD. Subjects with COPD also had lower VI C_{\max} (67% lower) and higher VI AUC₍₀₋₂₄₎ (24% higher) compared with healthy subjects. VI C_{\max} was 13% lower and AUC₍₀₋₂₄₎ was 57% higher in subjects with COPD compared with subjects with asthma. VI clearance (CL/F) decreased with age in subjects with COPD (Table 1).

In subjects with COPD, FF exposure was higher in subjects of East Asian origin compared with other racial groups (Table 1). Higher systemic exposure was not associated with enhanced PD effects, including safety findings, in any sub-population. Hence, no dosage adjustments are proposed based on age, gender or race, although the

proposed *Prescribing Information* for BREO ELLIPTA does recommend caution in patients with moderate or severe hepatic impairment.

FF and VI are both metabolized by CYP3A4. FF and VI systemic exposure increased modestly with co-administration of FF/VI 200/25 mcg with ketoconazole, a CYP3A4 and P-gp inhibitor. A reduction in serum cortisol was observed but there was no effect on heart rate or blood potassium. As with labelling for other ICS/LABA combinations, the proposed *Prescribing Information* for BREO ELLIPTA contains a warning regarding co-administration with strong CYP3A4 inhibitors.

The Clinical Pharmacology is described fully in the Briefing Document (Section 6.2).

Clinical Development Summary

The FF/VI COPD Clinical Development Program consisted of studies to assess the efficacy of the combination and the contribution of each component in the combination consistent with FDA 21 CFR 300.50, Combination Rule [FDA, 2012]. All efficacy endpoints were those recommended and accepted in international COPD treatment guidelines [GOLD, 2011] and in regulatory guidance.

Consistent with the FDA Draft COPD guidance [FDA, 2007], efficacy was evaluated in two pivotal COPD trials for the maintenance treatment of airflow obstruction by the co-primary endpoints of 0-4 hour weighted mean FEV₁ (i.e., measured over the first four hours after dosing) and trough FEV₁. Weighted mean FEV₁ was the primary endpoint to demonstrate the contribution of VI (the LABA component) to the combination, and trough FEV₁ was the primary endpoint to demonstrate the contribution of FF (the ICS) to the combination. Since VI is a bronchodilator that has a 24-hour duration of activity, the trough FEV₁ benefit added by FF (the ICS) at this point in time was anticipated to be modest. This is consistent with COPD trials of ADVAIR DISKUS, where the trough FEV₁ benefit added by the corticosteroid component was approximately 70 mL and Symbicort, where the trough FEV₁ benefit added by the corticosteroid component was approximately 20-40 mL.

Conversely, as expected, an ICS contributes a larger role in the combination product in reducing exacerbations in patients with COPD. Therefore, in two separate COPD exacerbation trials, the annual rate of moderate and severe COPD exacerbations in patients with a history of exacerbations was the primary endpoint to demonstrate efficacy and the contribution of FF on exacerbations.

Four of the 11 studies in the COPD Clinical Development Program were considered primary studies in the NDA (Table 2).

Table 2 FF/VI COPD Clinical Development Program: Primary Studies

Study Year Completed	Study Design	Key Inclusion Criteria	Treatment (mcg) ¹	N (ITT)	Primary Endpoint(s)
Efficacy and Safety of FF/VI; Contribution of VI to FF/VI					
HZC112206 ² 2011	R, DB, PG, PC 6 Months	<ul style="list-style-type: none"> Post bronchodilator FEV₁/FVC ratio ≤0.70 Post bronchodilator FEV₁ ≤70% predicted³ mMRC dyspnea score ≥2 	FF/VI 50/25 FF/VI 100/25 FF 100 VI 25 Placebo	206 206 206 205 207 Total = 1030	<ul style="list-style-type: none"> Weighted mean FEV₁ 0-4 hours post-dose at Day 168 Change from baseline trough FEV₁ at Day 169
HZC112207 ⁴ 2011	R, DB, PG, PC 6 Months	<ul style="list-style-type: none"> Post bronchodilator FEV₁/FVC ratio ≤0.70 Post bronchodilator FEV₁ ≤70% predicted³ mMRC dyspnea score ≥2 	FF/VI 100/25 FF/VI 200/25 FF 100 FF 200 VI 25 Placebo	204 205 204 203 203 205 Total = 1224	<ul style="list-style-type: none"> Weighted mean FEV₁ 0-4 hours post-dose at Day 168 Change from baseline trough FEV₁ at Day 169
Efficacy and Safety of FF/VI; Contribution of FF to FF/VI					
HZC102970 ⁵ 2011	R, DB, PG, AC 1 Year	<ul style="list-style-type: none"> Post bronchodilator FEV₁/FVC ratio ≤0.70 Post bronchodilator FEV₁ ≤70% predicted³ ≥1 moderate/severe exacerbation⁶ in last 12 months prior to Screening 	FF/VI 50/25 FF/VI 100/25 FF/VI 200/25 VI 25	412 403 409 409 Total = 1633	Annual rate of moderate and severe COPD exacerbations ⁶
HZC102871 ⁷ 2011	R, DB, PG, AC 1 Year	<ul style="list-style-type: none"> Post bronchodilator FEV₁/FVC ratio ≤0.70 Post bronchodilator FEV₁ ≤70% predicted³ ≥1 moderate/severe exacerbation⁶ in last 12 months prior to Screening 	FF/VI 50/25 FF/VI 100/25 FF/VI 200/25 VI 25	408 403 402 409 Total = 1622	Annual rate of moderate and severe COPD exacerbations ⁶

AC=active-controlled; DB=double-blind; FEV₁=forced expiratory volume in 1 second; FF=fluticasone furoate; FVC=forced vital capacity; ITT=Intent-to-Treat population; mMRC=Modified Research Council Dyspnea Scale; PC=placebo-controlled; PG=parallel-group; QD=once daily; R=randomized; VI=vilanterol

- All treatments administered once-daily in the morning via DPI (ELLIPTA)
- Sites who randomized subjects: 221 centers in 9 countries: Chile, Estonia, Germany, Japan, Korea, Philippines, Poland, Russian Federation and the US
- FEV₁ percent predicted calculated using NHANES III reference equations [Hankinson, 1999]
- Sites who randomized subjects: 138 centers in 8 countries: Czech Republic, Germany, Japan, Poland, Romania, Russian Federation, Ukraine and the US
- Sites who randomized subjects: 167 centers in 15 countries: Argentina, Australia, Canada, Chile, Estonia, Germany, Italy, Mexico, Netherlands, Peru, Philippines, South Africa, Sweden, UK, and the US
- Moderate: Worsening symptoms of COPD that required treatment with oral corticosteroids and/or antibiotics; Severe: Worsening symptoms of COPD that required an in-patient hospitalization
- Sites who randomized subjects: 183 centers in 15 countries: Argentina, Australia, Canada, Chile, Denmark, Germany, Italy, Mexico, Netherlands, Peru, South Africa, Spain, Sweden, UK, and the US

The four primary COPD studies included male and female subjects ≥40 years of age with a clinical history of COPD (as defined by the American Thoracic Society/European

Respiratory Society [Celli, 2004]). Subjects were required to have a current or prior history of at least 10 pack-years of cigarette smoking (a major risk factor for COPD) and the presence of at least moderate airflow limitation (Table 2). In accordance with GOLD recommendations, the degree of airflow reversibility was not an inclusion criterion. The inclusion and exclusion criteria were similar across the four studies, with the exception that in the two, 1-year exacerbation studies (HZA102970 and HZA102871), subjects were required to have had a history of ≥ 1 moderate/severe exacerbation in the previous 12 months (Table 2). In the two, 6-month, lung function studies (HZA112206 and HZA112207), subjects were excluded if they had been hospitalized due to poorly controlled COPD within 12 weeks prior to Screening and/or had poorly controlled COPD (defined as acute worsening of COPD that was managed by the subject with corticosteroids or antibiotics or that required treatment prescribed by a physician) within 6 weeks prior to Screening and/or had experienced a lower respiratory tract infection that required the use of antibiotics within 6 weeks prior to Screening. In addition, in the two, 6-month studies, subjects were required to have a score of ≥ 2 on the Modified Medical Research Council Dyspnea Scale (mMRC) prior to randomization, in order for them to be sufficiently symptomatic to have room for improvement on symptom assessments.

Detailed demographics and baseline characteristics of the subjects in the COPD Clinical Development Program are provided in the full Briefing Document (Section 7.4.2.1).

Summary of Efficacy Results

Key Finding(s):

- FF/VI 100/25 QD has been demonstrated to be an effective treatment for COPD, providing a fast onset of effect (median time of 16 minutes) after the first dose and sustained 24-hour effect with once-daily dosing. VI 25mcg provided clinically meaningful and sustained improvement in lung function and the addition of FF 100 mcg provided clinically meaningful reductions in rate of moderate or severe COPD exacerbations, time to first moderate or severe COPD exacerbation and rate of exacerbations requiring treatment with oral/systemic corticosteroids. There is a small but meaningful contribution of FF on lung function which is in the same range as for the ICS effect of other ICS/LABA combination products.
- The 100/25 strength of FF/VI provided better efficacy in subjects with COPD than FF/VI 50/25. No increased efficacy benefits were apparent for FF/VI 200/25 compared with FF/VI 100/25. FF/VI 100/25 is the strength proposed for marketing for subjects with COPD.
- The results of studies that compared FF/VI 100/25 QD with currently marketed strengths of FP/salmeterol BID were not consistent, but suggest that FF/VI QD is at least as effective as FP/salmeterol BID on improvements in lung function.
- Treatment with FF/VI 100/25 treatment provided improvements in subject-reported outcomes (rescue medication use and symptom scores) by comparison with placebo.

Inferences regarding the efficacy of FF/VI and its components are based upon multiple statistical comparisons within the various studies. Therefore, a pre-specified, step-down testing hierarchy was employed, such that within any study statistical inferences were made for the highest strength of the FF/VI combination first, followed by inferences for the lower doses if this primary test achieved statistical significance. Statistical inference stopped when a comparison was not significant and all remaining comparisons were presented descriptively only.

Data from the 6-month studies HZC112206 and HZC112207 were pooled for an integrated analysis of lung function as these studies were essentially identical in all respects except the FF/VI strengths. Similarly, data from the 1-year exacerbation studies HZC102970 and HZC102871 were pooled for integrated analyses of lung function and exacerbations. No adjustments for multiple comparisons were applied to the integrated efficacy analyses.

Although the Executive Summary primarily focuses on efficacy results for the proposed 100/25 strength, fuller details regarding the efficacy of the 50/25 and 200/25 strengths are provided elsewhere in the full Briefing Document.

All strengths of FF/VI showed clinically meaningful efficacy on 0-4 hour weighted mean FEV₁ (Figure 2) and trough FEV₁ (Figure 3) compared with placebo; treatment effects ranged between 173-214 mL and 115-144 mL for 0-4 hour weighted mean and trough FEV₁, respectively. The bronchodilator effect was rapid and sustained over the 24-hour dosing period for the entire duration of the 6-month studies.

In both 1-year, exacerbation studies, COPD exacerbations were consistently reduced by BREO ELLIPTA (FF/VI 100/25); this effect was not replicated with FF/VI 200/25 or 50/25. The weight of evidence across the four primary COPD studies, taking into account the primary/co-primary endpoints and secondary endpoints, indicated that FF/VI 100/25 was more efficacious than FF/VI 50/25, while FF/VI 200/25 conferred little additional benefit over 100/25. Therefore, FF/VI 100/25 is proposed as the recommended treatment strength for patients with COPD.

Effect of VI and Contribution of VI to FF/VI

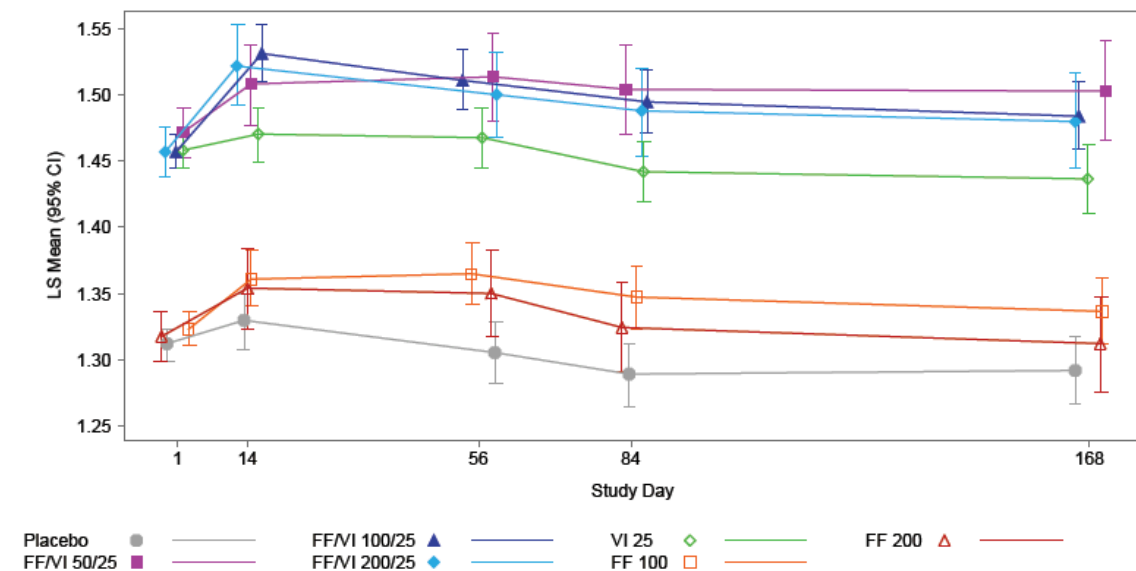
LABAs are used to treat COPD for their bronchodilatory effects, as can be measured by the 0-4 hour weighted mean FEV₁ and trough FEV₁. Both measures confirmed that VI is an effective, once-daily bronchodilator, with a rapid onset and sustained 24-hour duration of effect.

Compared with placebo, VI 25 produced rapid improvement on weighted mean FEV₁ (0-4 h) in the 6-month lung function studies HZC112206 and HZC112207, with effect sizes of 103 and 185 mL at Day 168, respectively (both p<0.001). These effects were maintained up to Day 168. Comparison of FF/VI with the respective FF alone arm at Day 168 in both studies demonstrated a similar effect size on weighted mean FEV₁ (0-4 h) ranging from 120-168 mL (all p<0.001).

Integrated analyses of studies HZC112206 and HZC112207 showed that, compared with placebo at Day 169, the FF/VI (50/25, 100/25 and 200/25) and VI 25 treatment groups showed effect sizes on weighted mean FEV₁ 0-4 h ranging from 145 to 212 mL (all p<0.001). Moreover, FF/VI 100/25 and 200/25 demonstrated effect sizes of 148 and 169 mL, respectively, at Day 168 (both p<0.001) on weighted mean FEV₁ 0-4 hours post-dose compared with the respective FF group. From Day 1 onwards, the FF/VI 100/25 and FF/VI 200/25 groups demonstrated greater improvements in weighted mean FEV₁ 0-4 h compared with the respective FF alone group (Figure 2).

These two sets of analyses confirmed that VI is effective, not only as a monotherapy, but also makes a significant contribution to the effects of the FF/VI combination on lung function.

Figure 2 Least Squares Means (95% CI) in 0-4hours Weighted Mean FEV₁ (L) (ITT Population): Integrated Study Results – 6-Month Lung Function Studies (H2C112206/H2C112207)

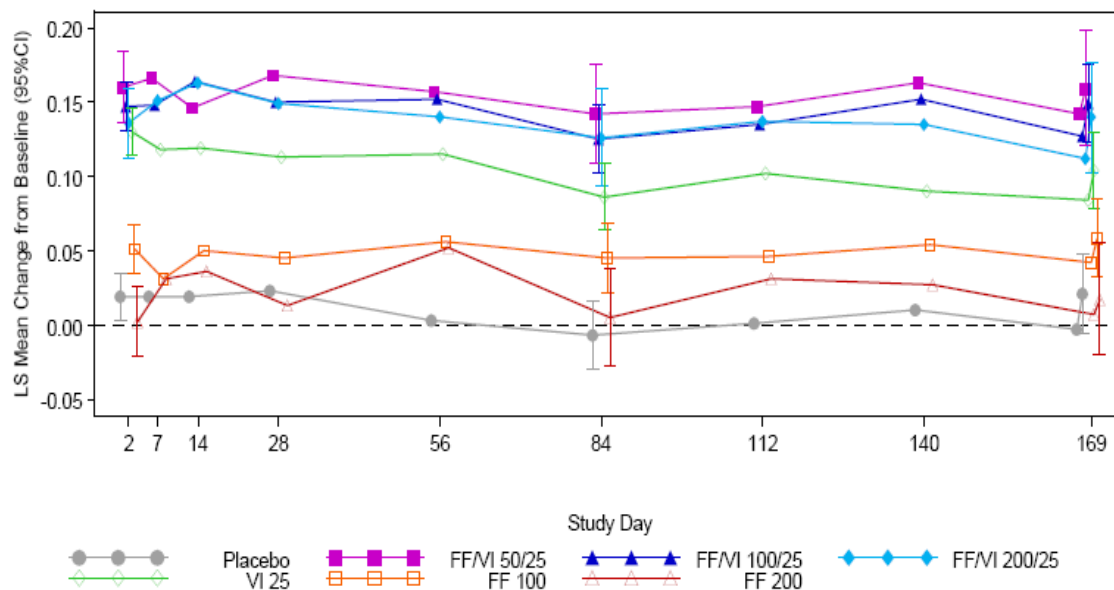


CI=confidence interval; FEV₁=forced expiratory volume in 1 second; FF=fluticasone furoate; ITT=Intent-to-Treat; VI=vilanterol

Persistence of the bronchodilatory effect with once-daily dosing of VI was initially shown in a 4-week dose-ranging study in subjects with COPD (B2C111045) and in a subsequent 1-week, crossover study that compared once- versus twice-daily dosing of VI in subjects with asthma (HZA113310). Studies H2C112206 and H2C112207 confirmed that once-daily VI dosing continued to improve trough FEV₁ in subjects with COPD up to treatment Day 169, with effect sizes of 67 mL and 100 mL compared with placebo (both $p \leq 0.017$). Similarly, all FF/VI groups consistently demonstrated greater numerical improvements from baseline in trough FEV₁ up to Day 169 compared with the placebo group and the FF and VI alone groups, supporting once-daily use of VI (Figure 3).

The primary lung function endpoints from the various studies support once-daily dosing of VI in COPD and confirm that it contributes a sustained bronchodilatory effect to the FF/VI combination. Further corroboration is provided by the secondary lung function endpoints of peak FEV₁ and time to onset of bronchodilation (defined as time to increase in FEV₁ by 100 mL from baseline).

Figure 3 Least Squares Means (95% CI) in Change from Baseline in Trough FEV₁ (L) (ITT Population): Integrated Study Results – 6-Month Lung Function Studies (HZA112206/HZA112207)



CI=confidence interval; FEV₁=forced expiratory volume in 1 second; FF=fluticasone furoate; ITT=Intent-to-Treat; VI=vilanterol

Contribution of FF to FF/VI

The FF/VI development program did not seek to establish the efficacy of FF as monotherapy in subjects with COPD, since current treatment guidelines only recommend ICS as an add-on to bronchodilator therapy [GOLD, 2011].

Effect of FF on Lung Function

The effect of FF on lung function was assessed by comparing the effects of FF/VI with VI on change from baseline in trough FEV₁ in the four primary COPD studies.

The 6-month, lung function studies (HZA112206 and HZA112207) showed statistically non-significant improvements in trough FEV₁ of 48 and 45 mL, respectively, for FF/VI 100/25 compared with VI at Day 169. However, the 46 mL improvement for this comparison in the integrated analysis of the two studies was significant ($p=0.017$) (Table 3). The magnitude of the effects on trough FEV₁ with FF/VI compared with VI is not dissimilar to that observed in previous 6-month studies of the currently approved ICS/LABA combinations (fluticasone propionate/salmeterol [FP/SAL] and budesonide/formoterol [BUD/FM]) in subjects with COPD (Table 3). In addition, in the 1-year, study of BUD/FM, the change from baseline in trough FEV₁ was 70 mL with BUD/FM compared with 40 mL with FM ($p=0.091$) [Sharafkhan, 2012].

Table 3 ICS Contribution in ICS/LABA Combination Therapies in Subjects with COPD: FF/VI Studies and Studies of Marketed ICS/LABA Combinations – Trough FEV₁ (mL)

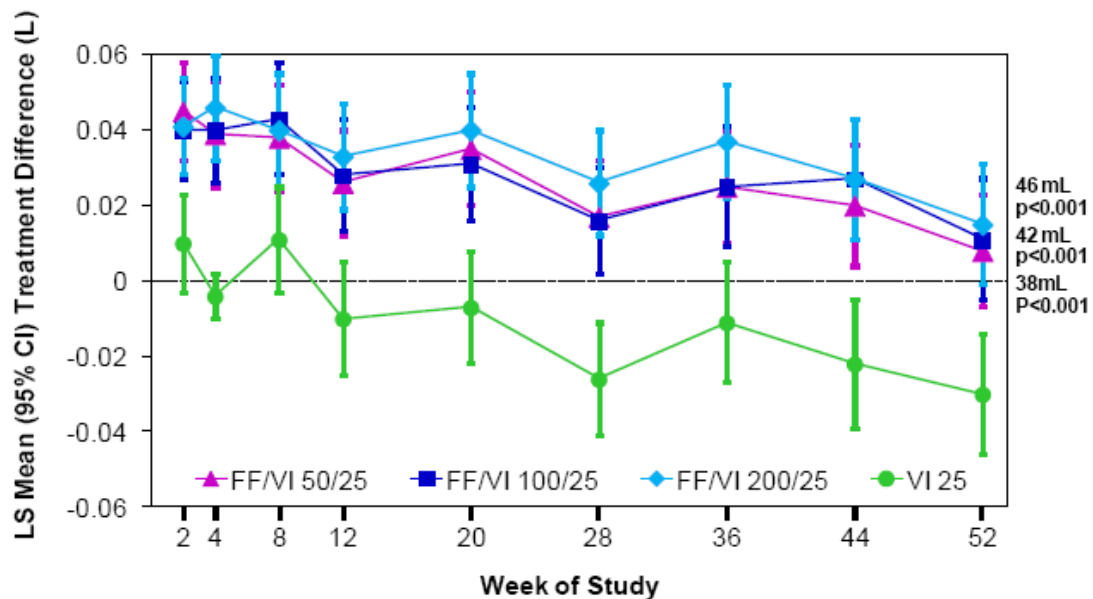
Study ¹	Treatment (mcg) Comparison	Treatment Difference in Trough (Pre-Dose) FEV ₁ , mL	95% CI	p-value
HZC112206 ² (N=1030)	FF 100/25 QD vs VI 25 QD	48 ³	-6, 102	0.082
HZC112207 ⁴ (N=1224)	FF 100/25 QD vs VI 25 QD	45 ³	-8, 97	0.093
'206/'207 Integrated (N=2254)	FF/VI 100/25 QD vs VI 25 QD	46 ³	8, 83	0.017
SFCA3007 ⁵ (N=723)	FP/SAL 250/50 BID ⁶ vs SAL 50 BID	69 ⁷	15, 123	0.012
SFCA3006 ⁸ (N=674)	FP/SAL 500/50 BID vs SAL 50 BID	67 ⁷	15, 118	0.012
SHINE ⁹ (N=1704)	BUD/FM 160/9 BID vs FM 9 BID BUD/FM 320/9 BID ⁶ vs FM 9 BID	20 ¹⁰ 40 ¹⁰	-20, 50 0, 70	NS <0.05

BID=twice daily; BUD=budesonide; CI=confidence interval; FEV₁=forced expiratory volume in 1 second; FF=fluticasone furoate; FM=formoterol; FP=fluticasone propionate; ICS=inhaled corticosteroid; LABA=long-acting beta₂-agonist; NS=not significant, QD=once daily; SAL=salmeterol; VI=vilanterol

1. All studies were 6-month, randomized, double-blind, parallel-group, placebo-controlled studies in subjects with moderate to severe COPD
2. GSK Clinical Study Register (Study sites in Chile, Estonia, Germany, Japan, Korea, Philippines, Poland, Russian Federation, and the United States)
3. Treatment difference at Treatment Day 169 (last study visit);
4. GSK Clinical Study Register (Study sites in the Czech Republic, Germany, Japan, Poland, Romania, Russian Federation, Ukraine, and the United States)
5. [Hanania](#), 2003 (Study sites in the United States only)
6. The licensed strength for treatment of COPD in the US
7. Treatment difference at Endpoint (defined as the last on-treatment post-baseline assessment excluding any data from the discontinuation visit); treatment differences were estimated and analyzed using contrasts from analysis of covariance adjusting for baseline and investigator.
8. [Mahler](#), 2002 (Study sites in the United States only)
9. [Tashkin](#), 2008 (Study sites in the United States, Czech Republic, the Netherlands, Poland, and South Africa)
10. Treatment difference in change from baseline to the average over the randomized treatment period; change from baseline was analyzed using an analysis of covariance (ANCOVA) model, adjusting for treatment, country and baseline; the analysis was adjusted using a sequential approach to hypothesis testing at the 5% significance level.

The 1-year, exacerbation studies (HZC102970 and HZC102871) also demonstrated that all three strengths of FF/VI provided sustained improvements in trough FEV₁ compared with VI 25 at all post-baseline time points over the course of the 1-year treatment period ([Figure 4](#)).

Figure 4 Least Squares Mean Changes from Baseline in Trough FEV₁ (L) 95% CI) (ITT Population): Integrated Study Results – 1-Year Exacerbation Studies (HZA102970/HZA102871)



CI=confidence interval; FEV₁=forced expiratory volume in 1 second; FF=fluticasone furoate; ITT=Intent-to-Treat; VI=vilanterol

The totality of the data confirm that there is a small contribution of FF on lung function in COPD patients that is observed early in treatment and sustained over time, and this effect is in the same range as the ICS effect seen with other ICS/LABA combination products.

Effect of FF on Exacerbations

The major contribution of FF (50, 100 and 200mcg) to the FF/VI combination was evaluated in the 1-year, exacerbation studies HZA102970 and HZA102871 by measuring the effect of the combination on the annual rate of moderate and severe COPD exacerbations. Treatment with FF/VI 100/25 compared with VI 25 reduced the annual rate of moderate and severe COPD exacerbations by 21% (95% CI: 3, 36; p=0.024) and 34% (95% CI: 19, 46; nominal p<0.001), in the HZA102970 and HZA102871 studies, respectively, thereby demonstrating an important clinical benefit for the combination, as well as demonstrating the contribution of FF to FF/VI (Figure 5 – upper figures).

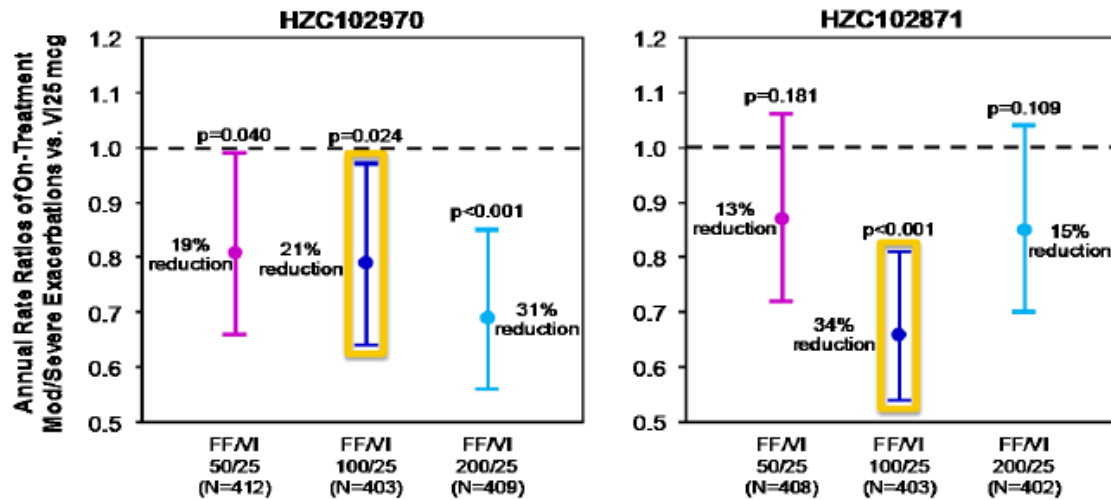
Stand-alone interpretation of study HZA102871 is confounded, however, due to results of the higher FF/VI 200/25 treatment arm. While the point estimate directionally favored benefit, there was a lack of a statistically significant difference for the comparison between the FF/VI 200/25 and VI 25 groups (15%, 95% CI: -4, 30; p=0.109) for the primary endpoint (annual rate of moderate and severe exacerbations), which prevented inferential testing of the comparison between the FF/VI 100/25 and VI 25 groups. However, the treatment effect with FF/VI 100/25 was clinically relevant in both studies

with treatment effects of 21% (95% CI: 3, 36; $p=0.024$) and 34% (95% CI: 19, 46; nominal $p<0.001$).

Moreover, **a prospectively planned** integrated analysis of the two identically designed, 1-year, exacerbation studies (HZA102970 and HZA102871) afforded a supplementary method to identify the optimal strength, and showed that FF/VI 200/25, 100/25 and 50/25 reduced the annual rate of moderate and severe exacerbations compared with VI alone by 23% (95% CI: 12, 34; $p<0.001$), 27% (95% CI: 16, 37; $p<0.001$) and 16% (95% CI: 4, 27; $p=0.014$), respectively ([Figure 5](#) – lower figure). The point estimates for the FF/VI 200/25 and FF/VI 100/25 groups suggested that the higher strength offered no incremental benefit whereas the 11% difference between the 100/25 and 50/25 strengths suggested that the lowest strength is likely to be sub-optimal. Hence, FF/VI 100/25 has been proposed as the recommended strength for the treatment of COPD.

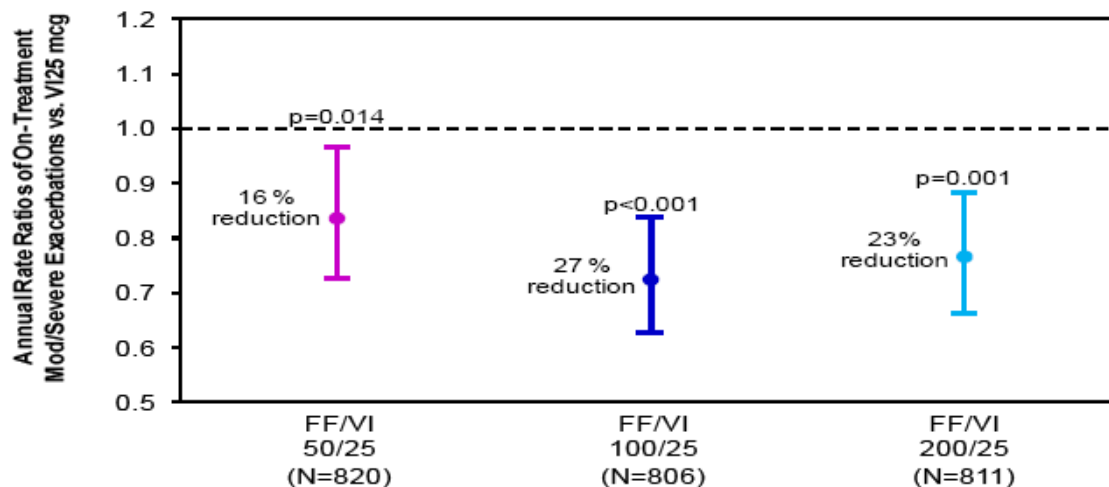
Figure 5 Treatment Differences (95% CI) for the Annual Rate of Moderate and Severe COPD Exacerbations (ITT Population): Individual and Integrated Study Results – 1-Year Exacerbation Studies (HZC102970 and HZC102871)

Individual Study Results



Annual rate for VI is 1.14 in Study HZC102970 and 1.05 in Study HZC102871

Integrated Study Results: HZC102970/HZC102871

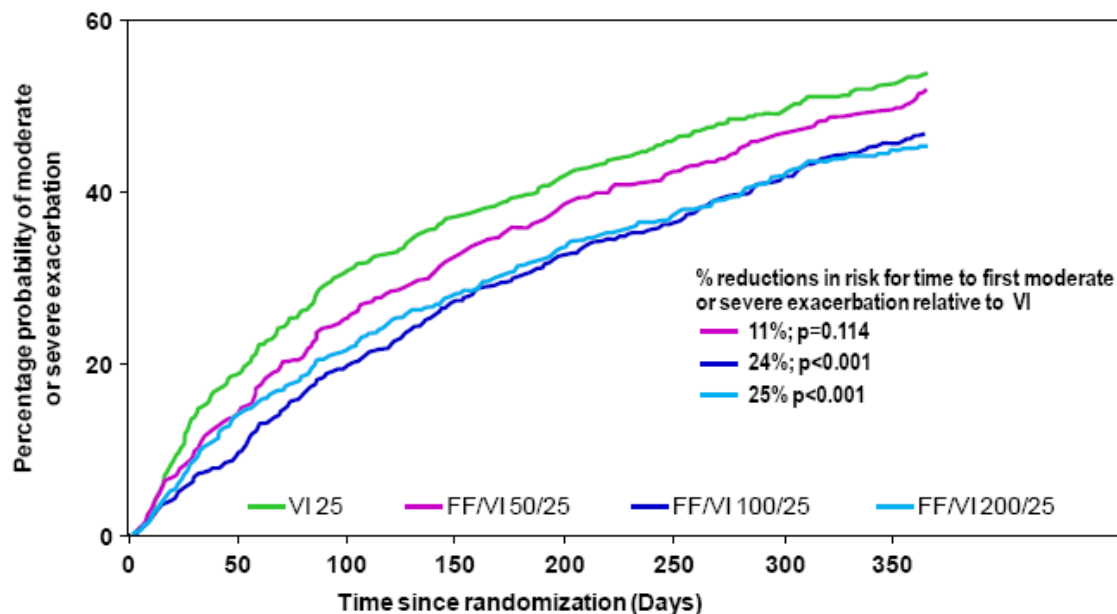


CI=confidence interval; FF=fluticasone furoate; ITT=Intent-to-Treat; VI=vilanterol

The primary endpoint analysis from the 1-year exacerbation studies and selection of the FF/VI 100/25 strength was supported by the individual and integrated analysis for the secondary endpoints of time to first moderate or severe COPD exacerbation and annual rate of COPD exacerbations requiring systemic/oral corticosteroids.

The risk of the time to first moderate or severe COPD exacerbation at any time point was reduced by 20% (95% CI: 0.66, 0.99; $p=0.036$) and 28% (95% CI: 0.59, 0.89; $p=0.002$) for FF/VI 100/25 compared with VI 25 in studies HZC102970 and HZC102871, respectively. The Kaplan-Meier plot for time to first moderate or severe exacerbation for the integrated data is depicted in Figure 6. The probability of experiencing a moderate or severe exacerbation by percentage is shown on the y-axis and the time since randomization in days is shown on the x-axis. You can appreciate the delay in exacerbations with the FF/VI 100/25 and 200/25 strengths. Specifically, the risk of the time to first moderate or severe exacerbations relative to vilanterol was significantly reduced by 24% with FF/VI 100/25 and 25% with 200/25. The risk reduction by FF/VI 100/25 compared with VI 25 for time to first moderate/severe exacerbation was 24% (95% CI: 0.66, 0.88; $p<0.001$) in the integrated analysis. Similar to the results for the primary endpoint, there was no incremental benefit in efficacy with the 200/25 strength (risk reduction of 25% compared with VI 25 (95% CI: 0.65, 0.87; $p<0.001$) over the 100/25 strength and the 50/25 strength provided sub-optimal efficacy compared with the 100/25 strength (risk reduction of 11% compared with VI 25 (95% CI: 0.78, 1.03; $p=0.114$).

Figure 6 Kaplan-Meier Plot of Time to First On-Treatment Moderate or Severe COPD Exacerbation (ITT Population): Integrated Study Results – 1-Year Exacerbation Studies (HZC102970/HZC102871)



FF=fluticasone furoate; ITT=Intent-to-Treat; VI=vilanterol

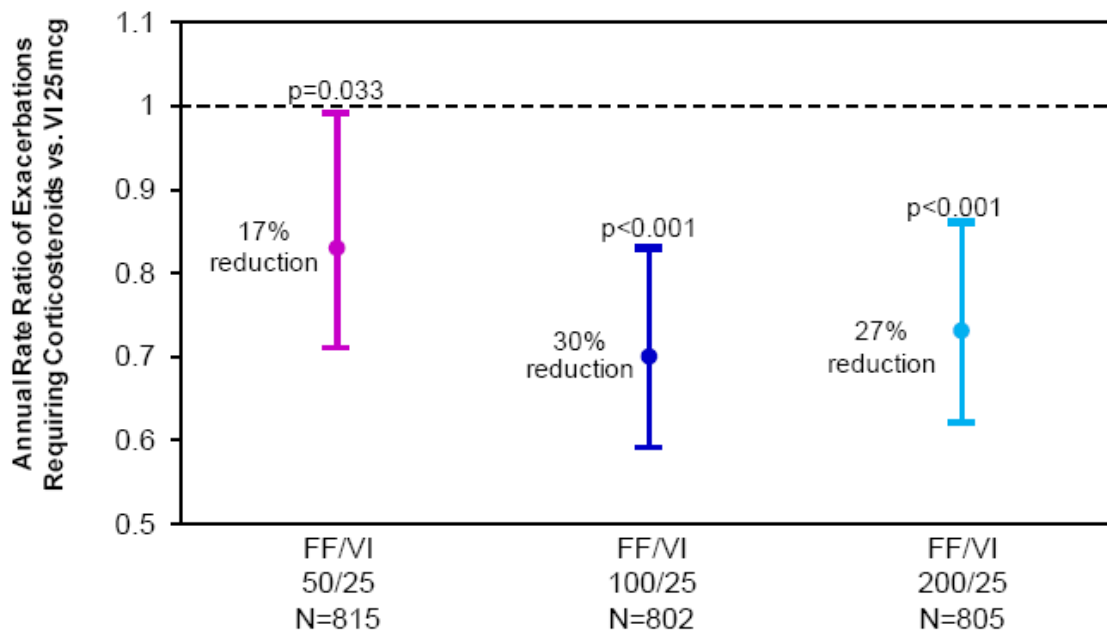
*% reductions in risk for time to first on-treatment moderate or severe COPD exacerbation for VI compared with FF/VI

The annual rate of COPD exacerbation necessitating use of systemic/oral corticosteroids at any point was reduced by 23% (95% CI: 1, 40; $p=0.041$) and 38% (95% CI: 22, 51; $p<0.001$) with FF/VI 100/25 compared with VI 25 in studies HZC102970 and HZC102871, respectively. Annual exacerbations requiring corticosteroids were reduced 27% (95% CI: 14, 38; $p<0.001$), 30% (95% CI: 17, 41; $p<0.001$) and 17% (95% CI: 1,

29; $p=0.033$), with FF/VI 200/25, 100/25 and 50/25, respectively compared with VI, in the integrated analysis (Figure 7). As with the primary endpoint, FF/VI 100/25 appeared to be the optimal dose as it provided greater efficacy than 50/25 but there was no additional incremental benefit observed with FF/VI 200/25.

Thus, the efficacy data support FF/VI 100/25 (BREO ELLIPTA) as the optimal strength to decrease the rate of moderate and severe exacerbations and to alleviate the airflow obstruction associated with COPD.

Figure 7 Treatment Differences (95% CI) in Annual Rate of COPD Exacerbations Requiring Systemic/Oral Corticosteroids (ITT Population): Integrated Study Results – 1-Year Exacerbation Studies (HZC102970/HZC102871)



CI=confidence interval; FF=fluticasone furoate; ITT=Intent-to-Treat; VI=vilanterol

Summary of Safety Results

Key Finding(s)

- The AE profile of FF/VI was generally consistent with the known class effects of an ICS/LABA combination. The data indicate that BREO ELLIPTA can be safely administered to patients with COPD.
- The cardiovascular safety profile of VI and FF/VI was broadly consistent with the known pharmacology of LABAs in patients with COPD. There was no evidence for an effect of FF/VI (or VI) on cardiovascular parameters (vital signs, ECGs and 24-Hour Holter Monitoring) or events (including cardiac arrhythmias, ischemia, heart failure and stroke). There was no evidence of QTc prolongation.
- Pneumonia is a well documented risk associated with the use of ICS in patients with COPD. An increased risk of pneumonia was observed in the FF/VI COPD Program, which was consistent with that described in the literature for other ICS/LABA combinations. The pneumonia risk appears to be primarily related to the severity of COPD (as indicated by FEV₁), the underlying health status (as reflected in BMI), as well as a history of previous pneumonia.
- There were seven pneumonia fatalities in the FF/VI 200/25 group, all of which occurred in one of the two, 1-year, exacerbation studies (HZA102871). Of these, two were at two different sites in Peru, one at a site in the United States and four at one site in the Philippines. For the latter site, compared with the other sites in the Philippines and the overall study population, the subjects were on average older, had a lower BMI and a lower Screening, post-bronchodilator percent predicted FEV₁.
- In 1-year exacerbation studies, the incidence of bone disorders was higher with FF/VI (3%) than with VI (1%); but, there was no evidence observed of a dose-related effect. Fractures customarily associated with corticosteroid use (e.g., spinal compression/thoracolumbar vertebral fractures, hip and acetabular fractures) occurred in <1% of subjects in all treatment arms.
- In subjects with COPD, there was no evidence for an effect of BREO ELLIPTA on HPA-axis (as measured by 24-hour serum or urinary cortisol excretion) or clinical chemistry or hematology.
- No clinically important ophthalmic findings were noted with FF/VI 100/25 QD in the 1-year safety study in subjects with asthma that was designed to look at potential ophthalmic effects (HZA106839). In addition, there was a low incidence of ocular events reported across the four, primary COPD studies.

The safety database for FF/VI 100/25 is comprised primarily of the four Phase IIIa primary COPD efficacy and safety trials in 5,509 subjects: two 6-month studies (HZA112206 and HZA112207) in 2,254 subjects and the two 1-year studies (HZA102970 and HZA102871) in 3,255 subjects ([Figure 1](#)). Supportive safety information is provided by 2,342 subjects in various other COPD studies, 9,379 subjects in asthma studies and 1,406 subjects in Clinical Pharmacology studies ([Figure 1](#)).

In addition to the collection of spontaneously reported adverse events, key safety concerns known to be associated with ICS and LABA use were designated *a priori* in the FF/VI program as Adverse Events of Special Interest (Refer to Section 7.5.3.6 in the full Briefing Document for more details) and were evaluated both by recording AEs and through clinical and laboratory assessments.

The Executive Summary mainly focuses on the safety data from the four primary COPD studies as these studies, along with other pertinent studies, support the proposed BREO ELLIPTA *Prescribing Information*.

GSK's plan for managing potential risks with respect to important safety findings is briefly discussed in the Risk Management/Mitigation section within the Executive Summary and more fully in the Briefing Document.

To aid the reader, data for the proposed strength of BREO ELLIPTA (FF/VI 100/25) are outlined in blue in the tables presented in the Executive Summary and in the full Briefing Document.

Adverse Events

Adverse events (AEs) were assessed in all of the COPD clinical studies. AE data from the 6-month, lung function studies (HZC112206 and HZC112207) are presented separately from the 1-year, exacerbation studies (HZC102970 and HZC102871), due to differences in study design, comparator arm, duration of study treatment, time-points of measurements and subject population.

6-Month, Lung Function Studies (HZC112206 and HZC112207)

The frequencies of any on-treatment AE, AEs leading to study drug discontinuation or withdrawal from the study, serious AEs (SAEs), and fatal events were similar between the FF/VI 100/25 and placebo groups (Table 4) in studies HZC112206 and HZC112207. Eleven subjects (<1% in all treatment arms) died during these studies. The deaths were balanced across treatment arms, including placebo, and were attributed by investigators to ongoing medical conditions. None were considered related to the study drug.

Table 4 Overall Summary of Adverse Events (ITT Population): Integrated Study Results – 6-Month Lung Function Studies (HZC112206/HZC112207)

n (%)	Placebo (N=412)	FF/VI 50/25 (N=206)	FF/VI 100/25 (N=410)	FF/VI 200/25 (N=205)	VI 25 (N=408)	FF 100 (N=410)	FF 200 (N=203)
Any on-treatment AEs	196 (48)	114 (55)	203 (50)	93 (45)	196 (48)	201 (49)	96 (47)
Any AEs leading to permanent discontinuation of study drug or withdrawal from study	39 (9)	19 (9)	36 (9)	23 (11)	40 (10)	37 (9)	15 (7)
Any on treatment SAE	21 (5)	6 (3)	23 (6)	15 (7)	31 (8)	22 (5)	10 (5)
Any on or post treatment fatal SAE	2 (<1)	2 (<1)	2 (<1)	1 (<1)	3 (<1)	1 (<1)	0

AE=adverse event; FF=fluticasone furoate; ITT=Intent-to-Treat; SAE=serious adverse event; VI=vilanterol

1-Year, Exacerbation Studies (HZC102970 and HZC102871)

Studies HZC102970 and HZC102871 included subjects with a history of moderate-severe COPD exacerbation in the past year, and as such included subjects with a higher risk of morbidity and mortality from respiratory causes due to their exacerbation history. Also, a placebo treatment arm was considered unethical in a population prone to moderate/severe COPD exacerbation. Therefore, AEs on FF/VI are compared with VI alone.

The overall incidence of any on-treatment AEs and AEs leading to study drug discontinuation or withdrawal from the study was generally similar across the FF/VI treatment groups (Table 5). The slightly higher AE rate in the FF/VI groups compared with the VI group was primarily driven by more events in the Infections and Infestations group including more reports of candidiasis. The incidence of SAEs and fatalities was similar across the treatment groups.

Fifty-three subjects (2%) died during the 1-year exacerbation studies, with a similar incidence of overall deaths across the treatment groups. The fatalities were attributed by the investigator to ongoing medical conditions. None were considered related to the study drug. The most common fatal events were those expected either in an older population of subjects (pre-existing cardiac disorders and malignancies) or those that frequently occur in subjects with COPD (COPD exacerbations and pneumonia).

Table 5 Overall Summary of Adverse Events (ITT Population): Integrated Study Results – 1-Year Exacerbation Studies (HZC102970/HZC102871)

n (%)	FF/VI 50/25 (N=820)	FF/VI 100/25 (N=806)	FF/VI 200/25 (N=811)	VI 25 (N=818)
Any on-treatment AEs	620 (76%)	621 (77%)	622 (77%)	575 (70%)
Any AEs leading to permanent discontinuation of study drug or withdrawal from study	53 (8%)	62 (8%)	61 (8%)	45 (6%)
Any on treatment SAE	136 (17%)	123 (15%)	124 (15%)	126 (15%)
Any on or post treatment fatal SAE	16 (2%)	10 (1%)	14 (2%)	13 (2%)

AE=adverse event; FF=fluticasone furoate; ITT=Intent-to-Treat; SAE=serious adverse event; VI=vilanterol

The most frequently reported AEs across the four primary COPD studies are summarized in [Table 6](#) (studies HZC112206 and HZC112207) and [Table 7](#) (studies HZC102970 and HZC102871), and are included in the Adverse Reactions section of the proposed *Prescribing Information* for BREO ELLIPTA.

Table 6 Adverse Events with ≥3% Incidence with FF/VI 100/25 in Subjects with COPD (ITT Population): Integrated Study Results – 6-Month Lung Function Studies (HZC112206/HZC112207)

Preferred Term, n (%)	Placebo (N=412)	FF/VI 50/25 (N=206)	FF/VI 100/25 (N=410)	FF/VI 200/25 (N=205)	VI 25 (N=408)	FF 100 (N=410)	FF 200 (N=203)
Nasopharyngitis	31 (8)	14 (7)	35 (9)	13 (6)	41 (10)	32 (8)	20 (10)
Headache	20 (5)	12 (6)	29 (7)	15 (7)	36 (9)	30 (7)	11 (5)
Upper respiratory tract infection	13 (3)	16 (8)	29 (7)	7 (3)	20 (5)	16 (4)	5 (2)
Oral/Oropharyngeal candidiasis ¹	9 (2)	20 (10)	22 (5)	9 (4)	9 (2)	13 (3)	13 (6)

FF=fluticasone furoate; ITT=Intent-to-Treat; VI=vilanterol

1. Term includes: oral candidiasis, oropharyngeal candidiasis, candidiasis, and oropharyngitis fungal

Table 7 Adverse Events with $\geq 3\%$ Incidence with FF/VI 100/25 in Subjects in with COPD (ITT Population): Integrated Study Results – 1-Year Exacerbation Studies (H2C102970/H2C102871)

Preferred Term, n (%)	FF/VI 50/25 (N=820)	FF/VI 100/25 (N=806)	FF/VI 200/25 (N=811)	VI 25 (N=818)
Nasopharyngitis	112 (14)	128 (16)	158 (19)	112 (14)
Upper respiratory tract infection	84 (10)	90 (11)	75 (9)	78 (10)
Oral/Oropharyngeal candidiasis ¹	110 (13)	87 (11)	88 (11)	55 (7)
Headache	61 (7)	57 (7)	67 (8)	60 (7)
Chronic obstructive pulmonary disease	53 (6)	56 (7)	53 (7)	53 (6)
Back pain	40 (5)	54 (7)	37 (5)	53 (6)
Bronchitis	41 (5)	38 (5)	47 (6)	42 (5)
Sinusitis	47 (6)	42 (5)	40 (5)	36 (4)
Pneumonia	46 (6)	49 (6)	45 (6)	23 (3)
Cough	35 (4)	31 (4)	35 (4)	34 (4)
Oropharyngeal pain	30 (4)	31 (4)	39 (5)	31 (4)
Influenza	28 (3)	27 (3)	31 (4)	27 (3)
Arthralgia	19 (2)	36 (4)	26 (3)	30 (4)
Hypertension	27 (3)	30 (4)	28 (3)	22 (3)
Pharyngitis	18 (2)	24 (3)	29 (4)	26 (3)
Diarrhoea	22 (3)	22 (3)	30 (4)	19 (2)
Oedema peripheral	21 (3)	22 (3)	12 (1)	25 (3)
Pyrexia	21 (3)	22 (3)	20 (2)	10 (1)

FF=fluticasone furoate; ITT=Intent-to-Treat; VI=vilanterol

1. Term includes: oral candidiasis, oropharyngeal candidiasis, candidiasis, and oropharyngitis fungal

Adverse Events of Special Interest (AESI)

Studies H2C112206 and H2C112207 are the most informative for assessing the AESI as these studies were placebo-controlled and included FF/VI and FF and VI monotherapy arms. There was no difference between treatment groups for any LABA-associated effects (tremor, hypertension or changes in serum potassium) (Table 8). Local corticosteroid effects (including oropharyngeal and oral candidiasis) occurred at higher incidences in the FF-containing treatment groups compared with the placebo and VI groups, although no dose response effect was apparent (Table 8). Systemic corticosteroid effects and effects on glucose were not different between treatment groups. The AESI from the 1-year exacerbation studies are presented in Section 7.5.3.6 in the full Briefing Document.

Table 8 Summary of On-Treatment Adverse Events of Special Interest (ITT Population): Integrated Study Results – 6-Month Lung Function Studies (HZC112206/HZC112207)

	Placebo N=412	FF/VI 50/25 N=206	FF/VI 100/25 N=410	FF/VI 200/25 N=205	VI 25 N=408	FF 100 N=410	FF 200 N=203
LABA-Associated Events, n (%)							
Hypertension	10 (2)	5 (2)	4 (<1)	1 (<1)	3 (<1)	8 (2)	7 (3)
Tremor ¹	1 (<1)	0	1 (<1)	0	0	1 (<1)	0
Effects on potassium	1 (<1)	0	0	1 (<1)	0	1 (<1)	0
ICS-Associated Events, n (%)							
Local steroid effects ²	15 (4)	24 (12)	27 (7)	13 (6)	14 (3)	18 (4)	17 (8)
Effects on glucose	3 (<1)	3 (1)	7 (2)	3 (1)	6 (1)	5 (1)	3 (1)
Systemic steroid effects ³	2 (<1)	2 (<1)	1 (<1)	0	1 (<1)	0	0

FF=fluticasone furoate; ICS=inhaled corticosteroid; ITT=Intent-to-Treat; LABA=long-acting beta₂-agonist; VI=vilanterol

1. Tremor: includes terms of essential tremor and tremor
2. Local steroid effects: includes terms such as candidiasis, oropharyngeal candidiasis, oral candidiasis, dysphonia, throat irritation, etc.
3. Systemic steroid effects: includes terms such as adrenal insufficiency, adrenal suppression, cortisol free urine abnormal, cortisol free urine decreased, Cushing's syndrome, hyperadrenalism, hyperadrenocorticism, hypothalamo-pituitary disorder, etc.

Pneumonia

Pneumonia is a recognized potential risk with ICS use in patients with COPD and the *Prescribing Information* for ADVAIR DISKUS and Symbicort includes a Warning regarding the increased risk of pneumonia in patients with COPD. Because this is a recognized ICS class effect, BREO ELLIPTA labelling will also include this warning.

A small number of AEs of pneumonia were reported in the 6-month, lung function studies HZC112206 and HZC112207, with no significant differences between all active treatment groups and a slightly lower incidence in the placebo group. No fatal pneumonia events were reported in either study (Table 9). Note: In accordance with the protocol, any subject who had pneumonia (presumptive diagnosed or radiographically confirmed) was to be withdrawn from the HZC112206 and HZC112207 studies.

Table 9 Summary of AE of Special Interest: On-Treatment Pneumonia (ITT Population): Integrated Study Results – 6-Month Lung Function Studies (HZC112206/HZC112207)

	Placebo	FF/VI 50/25 (N=206)	FF/VI 100/25 (N=410)	FF/VI 200/25 (N=205)	VI 25 (N=408)	FF 100 N=410	FF 200 N=203
Number of subjects (%)	(N=412)						
Any AE of Pneumonia	3 (<1)	3 (1)	6 (1)	4 (2)	7 (2)	6 (1)	3 (1)
Serious Pneumonia ¹	1 (<1)	1 (<1)	1 (<1)	3 (1)	5 (1)	3 (<1)	2 (<1)
Fatal Pneumonia	0	0	0	0	0	0	0

FF=fluticasone furoate; ITT=Intent-to-Treat; VI=vilanterol

1. Resulted in hospitalization

AEs of pneumonia (any event or serious event) were more frequent in the FF/VI groups compared with the VI 25 group in the 1-year, exacerbation studies HZC102970 and HZC102871, although there was no apparent dose-response across the three FF doses (Table 10). Two fatal pneumonia-related events were reported in study HZC102970 (one during treatment in the FF/VI 100/25 group and one post-treatment in a subject who was randomized to VI 25 during the treatment period) and 7 fatal pneumonia-related events were reported in study HZC102871 (all in the FF/VI 200/25 group). Of the seven pneumonia fatalities in the HZC102871 study, two were at two different sites in Peru, one at a site in the United States and four at one site in the Philippines. For the latter site, compared with the other sites in the Philippines and the overall study population, the subjects at this site were on average older (mean age 63.0, 63.6 and 66.2 years, respectively) had a lower BMI (mean 21.22, 26.69 and 20.39 kg/m², respectively) and a lower Screening, post-bronchodilator percent predicted FEV₁ (mean 44.9, 45.2 and 39.9%, respectively). In addition, this site reported 8 (23%) of the 35 deaths from any cause in this study; 8 of 54 (15%) subjects at this site had a fatal event compared with 2% for the overall study. There was significantly increased risk for time to death from any cause at this center compared to other centers in the Philippines (p=0.0223) and for the Philippines compared to all other countries (p=0.00004).

Table 10 Summary of AE of Special Interest: Pneumonia (ITT Population): Individual and Integrated Study Results – 1-Year Exacerbation Studies (HZC102970/HZC102871)

Number of subjects (%)	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25	VI 25
HZC102871	N=408	N=403	N=402	N=409
Any AE of Pneumonia ¹	29 (7)	25 (6)	31 (8)	16 (4)
Serious Pneumonia ^{1,2}	12 (3)	9 (2)	12 (3)	2 (<1)
Fatal Pneumonia ¹	0	0	7 ³ (2)	0
HZC102970	N=412	N=403	N=409	N=409
Any AE of Pneumonia ¹	19 (5)	26 (6)	24 (6)	11 (3)
Serious Pneumonia ^{1,2}	10 (2)	12 (3)	9 (2)	6 (1)
Fatal Pneumonia ¹	0	1 ⁴ (<1)	0	1 ⁵
871/970 Integrated	N=820	N=806	N=811	N=818
Any AE of Pneumonia ¹	48 (6)	51 (6)	55 (7)	27 (3)
Serious Pneumonia ^{1,2}	24 (3)	25 (3)	23 (3)	8 (<1)
Fatal Pneumonia ¹	0	1 ⁴ (<1)	7 ³ (<1)	1 ⁵

AE=adverse event; FF=fluticasone furoate; ITT=Intent-to-Treat; VI=vilanterol

Note: Pneumonia events were taken from the adverse events page

1. Under “pneumonia” a composite of many MedDRA terms is captured
2. Resulted in hospitalization
3. All events occurred in the HZC102871 study: three subjects at one investigative site in the Philippines, one subject at an investigative site in the US and two subjects at two investigative sites in Peru; also includes one subject who was reported as having a fatal on-treatment SAE with a preferred term of COPD but the Investigator (same site in the Philippines noted above) completed the pneumonia form in the Case Report Form page citing pneumonia at the time of death - the subject had a chest X-ray available that showed infiltrates.
4. Event occurred in the HZC102970 study at an investigative site in the US
5. One post-treatment (25 days following last dose) fatal pneumonia occurred in the HZC102970 study at an investigative site in South Africa

The incidence of AE reports of all pneumonias, SAE reports of pneumonia and fatal pneumonias observed in the BREO ELLIPTA (FF/VI 100/25) group in 1-year, exacerbation studies was similar to the incidences reported in the 1-year, exacerbation studies of the currently available ICS/LABA combinations (FP/salmeterol and budesonide/formoterol) (Table 11).

Table 11 Summary of Pneumonia Reports from 1-Year Studies of Marketed ICS/LABA Combinations in Subjects with COPD

	Studies with Fluticasone Propionate/Salmeterol (mcg) ¹		Study with Budesonide/Formoterol (mcg) ²		
	FP/SAL 250/50 BID N=788	SAL 50 BID N=791	BUD/FM 320/9 BID ³ N=407	BUD/FM 160/9 BID N=408	FM 9 BID N=403
Any AE of Pneumonia, n(%)	55 (7.0%)	25 (3.2%)	26 (6.4%)	19 (4.7)	11 (2.7%)
Serious Pneumonia, ⁴ n(%)	32 (4.1%)	18 (2.3%)	13 (3.2%)	4 (1.0%)	7 (1.7%)
Fatal Pneumonia, n (%)	1 (0.1%) ⁵	0	0	1	0

AE=adverse event; BID=twice-daily; BUD=budesonide; FM=formoterol; FP=fluticasone propionate; ICS=inhaled corticosteroid; LABA=long-acting beta₂-agonist; SAL=salmeterol; VI=vilanterol

1. [Ferguson](#), 2008; [Anzueto](#), 2009
2. [Sharafkhaneh](#), 2012
3. Approved strength in the US
4. Required hospitalization
5. Data on file: Clinical Study Report for GSK Study [SCO40043](#) [GlaxoSmithKline Document Number RM2006/00845/00]

Risk factors for pneumonia include advanced age, male gender, previous pneumonia, low body mass index (i.e., <25 kg/m²), current smoking, and severe airflow limitation (i.e., FEV₁ <50% predicted) (See Section 7.5.3.6.1 in the Full Briefing Document for more details).

Bone Disorders/Fractures

A modest increase in risk of fracture among ICS-treated patients with COPD is a recognized potential risk, though the effect is not consistent across published studies [[Lehouck](#), 2011; [Weldon](#) 2009; [Christensson](#), 2008]. Studies in adults with COPD yield varied evidence for the direct effect of ICS on bone mineral density (BMD) and fracture. The incidence of AEs related to bone disorders/fractures was recorded in the four primary COPD studies (HZA112206, HZA112207, HZA102970, and HZA102871).

In the 6-month, lung function studies (HZA112206 and HZA112207), bone disorder AEs were slightly more frequent in the FF 200 group (2%) (Study HZA112207 only) than in the other active treatment groups (0 to 1%). In the FF/VI 100/25 group, the incidence (1%) was similar to the placebo group (<1%).

In the 1-year exacerbation studies (HZA102970 and HZA102871), bone disorder AEs, the majority of which were bone fractures, were more frequent in the FF/VI groups (3%) than the VI 25 group (1%), though there was no apparent dose-response for FF. The overall frequency of bone fractures was low in all treatment groups, though higher in all FF/VI groups (2%) compared with the VI 25 group (<1%). The events occurred at a constant rate over the duration of the study. The majority of fractures were due to trauma (investigator-determined) in the FF/VI 50/25, FF/VI 100/25 and VI 25 groups, while the majority of fractures were non-traumatic in the FF/VI 200/25 group ([Table 12](#)). The majority of fractures were in the upper and lower extremities. Fractures customarily

associated with corticosteroid use (e.g., spinal compression/thoracolumbar vertebral fractures, hip and acetabular fractures) occurred in <1% of subjects in all treatment arms. Fractures affecting the pelvic region and the spine occurred sporadically across the treatment groups.

The incidence of traumatic and non-traumatic fractures is summarized separately below, to differentiate events that were less likely due to a potential treatment effect (traumatic) from those that could potentially be related to treatment (non-traumatic).

Table 12 Bone Fractures (ITT Population): Integrated Study Results – 1-Year Exacerbation Studies (HZC102970/HZC102871)

Number of fractures	FF/VI 50/25 N=820	FF/VI 100/25 N=806	FF/VI 200/25 N=811	VI 25 N=818
Total fractures	15	19	14	8
Traumatic	11	13	6	6
Non-traumatic	4	6	8	2
Upper extremities ¹	2	6	3	2
Lower extremities ²	6	3	3	1
Rib and chest	3	6	3	2
Pelvis and hip	2	1	1	1
Lumbar and thoracic spine	1	2	3	1
Other	1	1	1	1

FF=fluticasone furoate; ITT=Intent-to-Treat; VI=vilanterol

1. Shoulder, Arm, Wrist, Hand

2. Leg, Ankle, Foot/Metatarsal, Toe

Cardiovascular Effects

Cardiovascular safety assessments in the COPD Clinical Development Program included 12-lead ECG assessments (including heart rate and QTc), 24-hour Holter monitoring (sub-set of subjects), vital sign assessments (pulse rate and blood pressure) and individual AESI related to beta-adrenergic stimulation. Based on these assessments, the safety profile of VI 25 is in keeping with the known effects of the LABA class.

In the four primary COPD studies, 45 to 48% of subjects had current vascular disorders (most commonly hypertension) and 10 to 16% had current cardiac disorders (most commonly coronary artery disease). While 12-lead ECG assessments (including heart rate and QTc) and vital sign assessments (pulse rate and blood pressure) were conducted in all four primary COPD studies, the 1-year exacerbation studies (HZC102970 and HZC102871) are less informative as all patients received VI and none received placebo.

Heart rate: No clinically important effects on heart rate were observed in any study. Mean heart rate decreased from baseline in the 6-month, lung function studies (HZC112206 and HZC112207) across all treatment groups at all timepoints. Repeated measures analysis of heart rate from ECG evaluations for the integrated data showed few statistically significant differences at any timepoint for any of the active treatment groups compared with the placebo group; where statistically significant differences were noted, these differences, in the range of 1 to 2 bpm, were not considered clinically important. In

the 1-year exacerbation studies, in all treatment groups at all timepoints, mean heart rate decreased from baseline (with the exception of the change from baseline for the VI 25 treatment group at Day 196 [0.2bpm]) and ranged from -1.3 to 0.2 bpm.

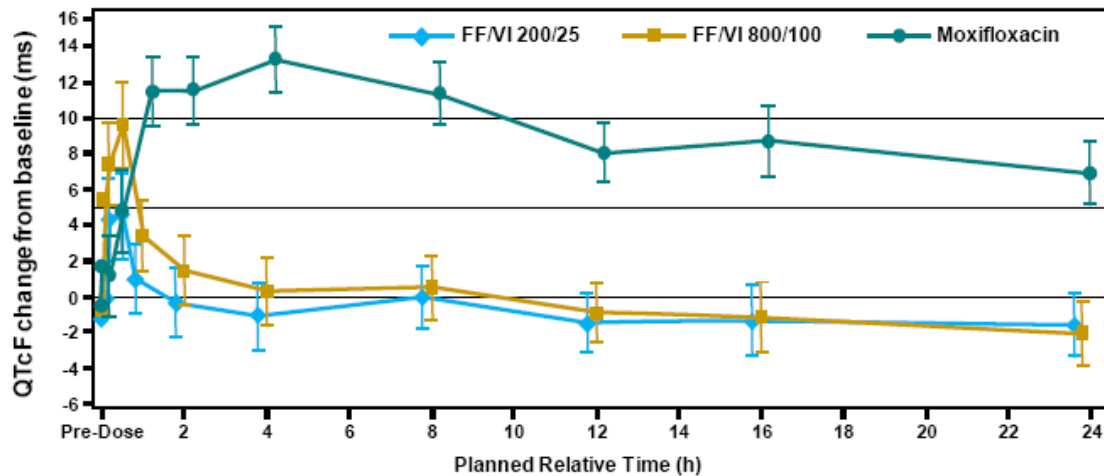
ECG Changes: Mean maximum post-baseline changes in QTc(F) at all timepoints were similar for the placebo (10.3 msec) and all active treatment (9.4 to 10.4 msec) groups in the 6-month, lung function studies (HZA112206 and HZA112207). QTc(F) changes from baseline > 30msec at any time point were similar for all active treatment groups (5-10%) versus placebo (8%). No subjects in any group had a QTc(F) > 500 msec on Day 1, 84 or 168. Mean maximum post-baseline QTc(F) changes in the 1-year, exacerbation studies (HZA102970 and HZA102871) were similar at all timepoints to those observed in the 6-month, lung function studies: 9.1 to 9.5msec across the FF/VI groups and 10.5msec in the VI 25 group. The proportion of subjects with QTc(F) changes \geq 30 msec were low and similar across all FF/VI treatment groups (3% to 5%) and the VI 25 treatment group (4% to 5%) at the Week 12, Week 28 and Week 52 post-baseline timepoints. No subjects in any group had a QTc(F) > 500 msec at Week 12, 28 or 52.

Thorough QT Study: Two thorough QTc studies were conducted. One study was conducted with FF/VI in 85 healthy subjects (Study HZA102936) and the other with FF in 40 healthy subjects (Study FFR101888). Moxifloxacin (400 mg oral single dose) was used in each study as a positive control for assay sensitivity.

Following administration of FF/VI 200/25 for 7 days in study HZA102936, all time-matched QTcF mean differences from placebo (0-24 hours) were <5 msec, with no upper 90% CI values greater than 10 msec (Figure 8). At an FF/VI dose of 800/100 for 7 days, the largest mean time-matched difference from placebo was 9.6 msec (90% CI: 7.2, 12.0), seen 30 minutes after dosing (Figure 8). This was the only time point where the upper 90% CI exceeded 10 msec. No QTcF values >450 msec were recorded at any time. There was little effect on the individually corrected QT interval (QTci) with both strengths of FF/VI: all time-matched mean differences from placebo values were less than 5 msec with no 90% CI values greater than 10 msec.

In the FFR101888 study, single dose FF 4000 mcg was not associated with an effect on QTcF: all mean time-matched differences from placebo (0-24 hour) were less than 5 msec and all 90% CIs were less than 10 msec. These data indicate that the small effect on QTcF seen with FF/VI 800/100 in study HZA102936 was attributable to the VI component.

Figure 8 QTcF Adjusted Mean Change from Baseline (Difference from Placebo [90% CI]) on Day 7 (Per Protocol Population) – Thorough QT Study in Healthy Subjects (HZA102936)



CI=confidence interval; FF=fluticasone furoate; VI=vilanterol

Cardiac arrhythmias: The 6-month, lung function studies HZC112206 and HZC112207 obtained 24-hour, 12-lead Holter monitoring in approximately half of the subjects in each treatment arm (Holter Population) at selected sites. Measurements were performed at Screening, as well as on Treatment Days 1, 84 and 168. Holter recordings included heart rate, heart rhythm, conduction intervals, and the presence of abnormal rhythm patterns. Central readers noted clinically significant abnormal ECG findings at baseline in 10 to 15% of ECGs reflecting the overall impaired health status of the COPD population.

The frequency of Holter abnormalities of potential clinical importance at any time post-randomization was similar across the VI-containing arms (13 to 15% in each of the three FF/VI combination groups and 11% for the VI 25 group) compared with the non-VI containing arms (6 to 14% for the FF monotherapy groups and 10% for the placebo group). The most frequent potentially clinically important abnormalities were ventricular arrhythmias, most commonly non-sustained ventricular tachycardia (VT) that occurred at similar incidences in the VI-containing treatment groups and the placebo group (Table 13). No sustained VTs were observed in any of the FF/VI groups or the VI 25 group. Non-sustained VTs occurred slightly more frequently across all combination groups as well as in VI and FF 100 only treated subjects when compared with placebo. Supra-ventricular arrhythmias occurred at low incidence across all groups. There were cases of sustained supra-ventricular tachycardia in the 100/25 and 200/25 arms as well as the VI and FF only groups. Atrial fibrillation and flutter were observed sporadically across groups and for atrial fibrillation slightly more frequently in FF/VI 100/25- as well as VI 25- and FF 100 only-treated subjects.

Table 13 Arrhythmias with Potential Clinical Consequences (ITT Population): Integrated Study Results – 6-Month Lung Function Studies (HZC112206/HZC112207)

Category, n (%)	Placebo N=168	FF/VI 50/25 N=98	FF/VI 100/25 N=188	FF/VI 200/25 N=98	VI 25 N=191	FF 100 N=184	FF 200 N=89
Ventricular arrhythmias, all	10 (6)	7 (7)	12 (6)	8 (8)	15 (8)	13 (7)	3 (3)
Sustained VT > 100bpm	0	0	0	0	0	0	1 (1)
Non-sustained VT	9 (5)	6 (6)	12 (6)	7 (7)	15 (8)	13 (7)	1 (1)
Supraventricular arrhythmias, all	1 (<1)	1 (1)	6 (3)	2 (2)	5 (3)	5 (3)	1 (1)
Sustained supraventricular tachycardia	0	0	3 (2)	1 (1)	1 (<1)	3 (2)	1 (1)
Atrial fibrillation	1 (<1)	0	3 (2)	1 (1)	4 (2)	4 (2)	0
Atrial flutter	0	1 (1)	0	0	0	1 (<1)	0

bpm=beats per minute; FF=fluticasone furoate; ITT=Intent-to-Treat; VI=vilanterol; VT=ventricular tachycardia

AE reports of cardiac-related events were evaluated using standardized MedDRA Queries (SMQs) groupings of terms from cardiac MedDRA System Organ Classes (SOCs) related to a defined medical condition in the cardiovascular area of interest. Cardiovascular events including arrhythmias, ischemic heart disease, cardiac failure as well as cerebrovascular disorders occurred at low and similar incidences in the active treatment groups compared with the placebo group (Table 14). The 1-year exacerbation studies (HZC102970 and HZC102871) did not provide comparative information regarding cardiovascular events, since all treatment groups contained VI 25, and indeed cardiovascular event rates were also similar across treatment arms in these studies.

Table 14 Cardiovascular Events: On-Treatment Cardiac-Associated AEs (ITT Population): Integrated Study Results – 6-Month Lung Function Studies (HZC112206/HZC112207)

Standardized MedDRA Query Category, n (%)	Placebo N=412	FF/VI 50/25 N=206	FF/VI 100/25 N=410	FF/VI 200/25 N=205	VI 25 N=408	FF 100 N=410	FF 200 N=203
Cardiac arrhythmias	30 (7)	11 (5)	22 (5)	10 (5)	20 (5)	23 (6)	16 (8)
Ischemic heart disease	4 (<1)	3 (1)	4 (<1)	1 (<1)	3 (<1)	4 (<1)	2 (<1)
Cardiac failure	3 (<1)	1 (<1)	3 (<1)	4 (2)	3 (<1)	4 (<1)	0
Cerebrovascular disorders	0	2 (<1)	4 (<1)	1 (<1)	2 (<1)	4 (<1)	0

FF=fluticasone furoate; VI=vilanterol

HPA-Axis Effects

Monitoring of HPA-axis function in subjects treated with FF/VI was important, since changes in these parameters have been reported with corticosteroids. While both 24-hour

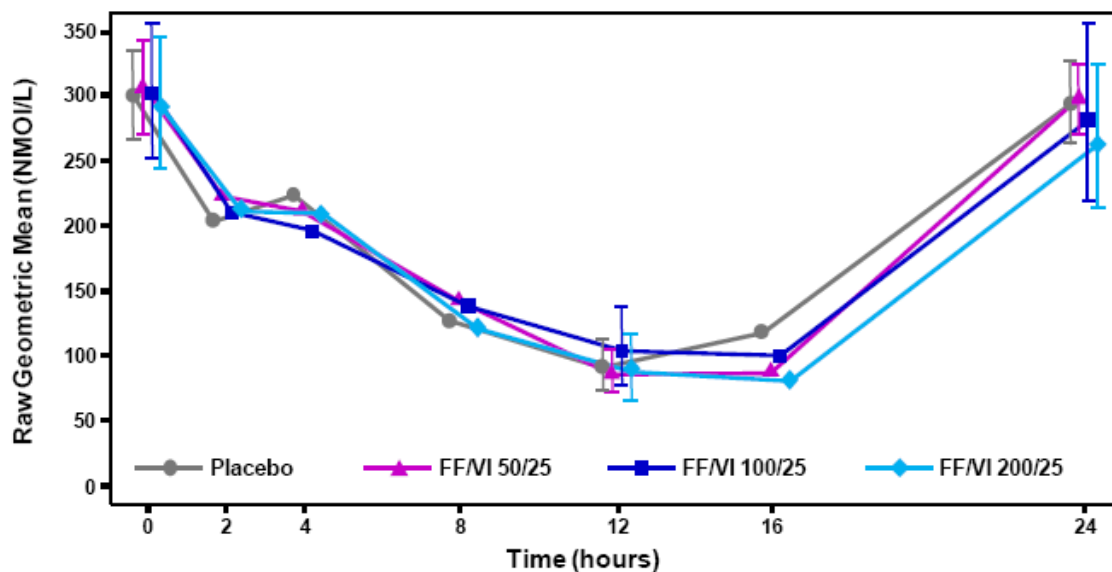
serum and 24-hour urinary cortisol excretion were evaluated in the COPD Clinical Development Program, 24-hour serum cortisol profiles are accepted as a more reliable measure of adrenal hormone secretion than 24-hour urinary hormone excretion profiles due to less variability in metabolism effects and improper collection with serum collection compared with urine collection [Bernstein, 2007].

Overall, data from subjects with COPD showed no evidence of a treatment effect on 24-hour serum or 24-hour urinary cortisol excretion. The cortisol results are consistent with the low systemic exposure to FF after inhaled dosing.

Twenty-four-hour serum cortisol was measured in subjects in the supporting, 3-way crossover, COPD study HZC110946 on Day 28 of each Treatment Period. The raw geometric mean serum cortisol levels over Days 28-29 are shown in Figure 9.

No AEs were reported that would be considered related to decreases in serum cortisol.

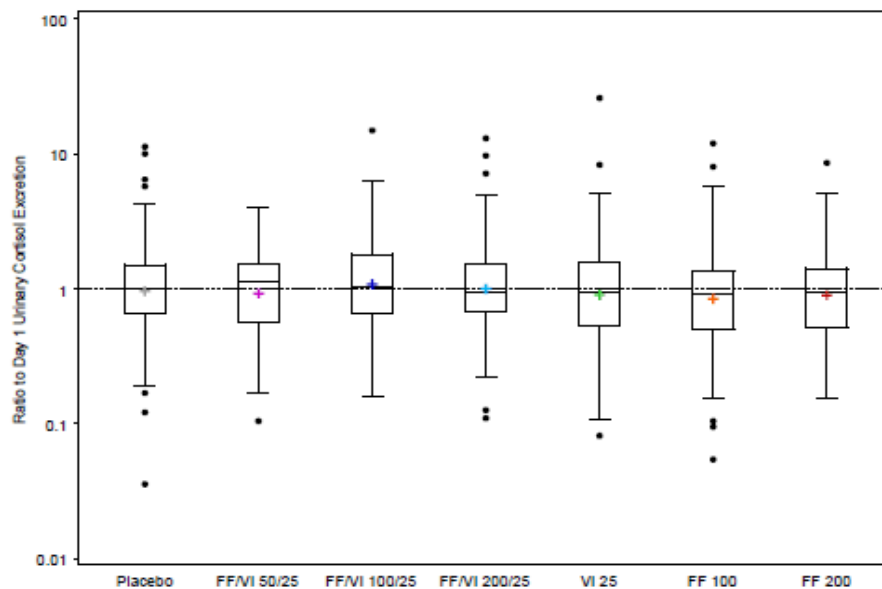
Figure 9 Raw Geometric Means (NMOL/L) for Serial Serum Cortisol Over Period Days 28-29 (ITT Population): Supporting VI COPD Study (HZC110946)



FF=fluticasone furoate; ITT-Intent-to-Treat; VI=vilanterol
Adapted from Boscia, 2012.

Twenty-four-hour urinary cortisol excretion was measured at Screening and at the end of the 6-month Treatment Period in a sub-set of subjects (approximately 100 per arm) at selected sites in two of the four, primary COPD studies, the 6-month, lung function studies (HZC112206 and HZC112207). No statistically significant differences from placebo in 24-hour urinary cortisol excretion were observed for all active treatment groups (Figure 10).

Figure 10 Box Plot of 24-Hour Urinary Cortisol Excretion Ratio to Baseline at Day 168 (Urine Cortisol Population): Integrated Study Results – 6-Month Lung Function Studies (HZA112206/HZA112207)



Note: Baseline is labelled as the Day 1 Visit. Baseline urinary cortisol is assessed from the 24-hour collection period during the Run-in period.

FF=fluticasone furoate; VI=vilanterol

The formal HPA-axis study (Study HZA106851) was conducted in subjects with asthma; because asthma patients have higher systemic FF exposure, these data can be used to support the safety of FF/VI in subjects with COPD. In this study, non-inferiority in the ratio from baseline in serum cortisol weighted mean compared with placebo was demonstrated against the predefined criterion of the lower confidence bound being >0.8 . For FF/VI 100/25, 95% CI were 0.87 to 1.12 and for FF/VI 200/25 95% CI were 0.86 to 1.10). Prednisolone 10 mg significantly reduced the ratio from baseline in serum cortisol weighted mean compared with placebo (95% CI 0.28 to 0.41), showing that the model for assessing HPA function was sufficiently sensitive to detect a drug effect.

Ocular Effects

Ocular effects, including cataracts, increased intraocular pressure (IOP) and glaucoma, have been reported with inhaled corticosteroid usage. In the TORCH safety sub-study, the background prevalence of cataracts was high in COPD patients (68.5-75.3% at Screening) [Calverley, 2007]. Because of this high background prevalence of cataracts in patients with COPD, the definitive ocular assessments were included in a long-term safety study in subjects with persistent asthma (HZA106839), as this was likely to be a less confounded population in which to assess this drug-related effect. Although conducted in subjects with asthma, these data can be used to support the safety of FF/VI in subjects with COPD, since systemic FF exposure in these subjects is lower than the exposure observed in subjects with asthma.

In the HZA106839 study, ophthalmic safety of FF/VI compared with FP 500 twice daily was evaluated. A placebo arm was not appropriate for a study of this duration. Intensive ophthalmic examinations (visual acuity [using LogMAR], LOCS III lens grades, IOP measurements, horizontal cup-to-disc ratio) were performed at Screening, Week 28 and Week 52. Subjects were excluded if they had cataracts or glaucoma at Screening. This study showed that FF/VI 100/25 and FF/VI 200/25 had no apparent ophthalmic effects compared with FP 500 twice daily.

While ophthalmic examinations were not conducted in the Phase III COPD program, ocular effects (including terms for cataracts, IOP and glaucoma) were assessed as an AESI. Ocular effects were reported in 0 to <1% of subjects across the groups in the 6-month, lung function studies (HZA112206 and HZA112207) and in ≤1% of subjects across the groups in the 1-year exacerbation studies (HZA102970 and HZA102871). Cataracts and glaucoma were reported in <1% of subjects in any treatment group. There was one report of IOP in a subject treated with FF/VI 100/25.

Sub-Group Data

The safety of FF/VI in subjects with COPD was evaluated in sub-populations based on age, gender, race, lung function reversibility, percent predicted FEV₁ (GOLD Classification), cardiovascular risk/history, BMI, smoking status, and geographic region. Although there were differences observed in the incidence of some AEs across the subgroups evaluated, the data indicate that the most frequent individual AEs were similar in the subgroups to that of the overall population. Overall, with the exception of pneumonia, there appeared to be no differences in the AE profile based on these subgroup analyses. Increases in the incidence of AEs of pneumonia for FF/VI compared with VI in the 1-year exacerbation studies (HZA102970 and HZA102871) were observed in Asian subjects, current smokers, subjects with severe COPD (GOLD III), subjects who had a prior history of pneumonia (as opposed to those with no prior history), and subjects with lower BMI (<25 kg/m², as opposed to a BMI ≥25 kg/m²). The limited data in Asian subjects makes it difficult to assess whether the risk of pneumonia is different in this racial group compared with non-Asian patients. However, the relative increase in risk of pneumonia between Caucasians and Asians appears similar.

Risk Management/Mitigation Plans

In the NDA, GSK submitted a proposed Risk Management Plan that addresses the class effects associated with ICS/LABAs as summarized in the sections that follow.

Pneumonia

Similar to the currently available ICS/LABA combinations for treatment of COPD, the “Warnings and Precautions” section of the proposed BREO ELLIPTA *Prescribing Information* includes a warning regarding an increase in the incidence of pneumonia that has been observed in subjects with COPD receiving FF/VI and guidance that physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations. This section of the proposed BREO ELLIPTA *Prescribing Information*

also includes a description of risk factors for pneumonia in patients with COPD receiving FF/VI (current smokers, patients with a history of prior pneumonia, patients with a body mass index <25 kg/m², and patients with an FEV₁ <50% predicted) and guidance that these factors should be considered when BREO ELLIPTA is prescribed, and treatment should be re-evaluated if pneumonia occurs.

Bone Disorders/Fractures

GSK plans to evaluate the incidence of bone fractures in ongoing studies and to conduct further investigations with the approved strength of FF/VI in a post-marketing setting to study the effects on BMD and the incidence of adverse event reports of fractures. The “Warnings and Precautions” section of the proposed BREO ELLIPTA *Prescribing Information* includes the class labelling warning regarding the reduction in BMD observed with long-term administration of ICS-containing products and a recommendation for the assessment of BMD prior to initiating treatment and periodically thereafter.

Cardiovascular Effects

The “Warnings and Precautions” section of the proposed BREO ELLIPTA *Prescribing Information* includes class labelling that FF/VI is to be used with caution in patients with severe cardiovascular disease. In addition, GSK is currently conducting a large, randomized, double-blind, parallel-group, placebo-controlled, clinical outcomes study in COPD patients with a history of or who are at increased risk for developing cardiovascular disease. This study is designed to determine the impact of FF/VI 100/25, and the individual components on the survival of patients with moderate airflow obstruction and either a history of cardiovascular disease or in patients >60 years of age, receiving treatment for 2 or more of the following: hypercholesterolemia, hypertension, diabetes and peripheral arterial vascular disease. Approximately 16,000 randomized subjects are planned, with approximately 4,000 subjects randomized to each of the four treatment arms. All-cause mortality is the primary endpoint. The study is an event-driven trial powered on the comparison of FF/VI vs. placebo. Secondary endpoints are decline in FEV₁ and effect on a composite cardiovascular endpoint. This study will provide further information concerning the safety of FF/VI 100/25 in this patient population.

Clinical Laboratory Findings

While there was no evidence of a treatment effect on serum glucose or potassium in the four, primary COPD studies of 6- and 12-months’ duration in subjects with COPD, the proposed BREO ELLIPTA *Prescribing Information* contains class labelling in the Warnings and Precautions section regarding beta-adrenergic agonist medicines may produce significant hypokalemia in some patients and may produce transient hyperglycemia in some patients.

HPA-Axis Effects

While no clinically relevant treatment effect was seen in 24-hour serum or 24-hour urinary cortisol in the 3 studies that evaluated HPA-axis effects in subjects with COPD,

the proposed BREO ELLIPTA *Prescribing Information* includes class labelling in the Warnings and Precautions section regarding the possibility of significant systemic absorption of inhaled corticosteroids in sensitive patients and that patients treated with BREO ELLIPTA should be observed carefully for any evidence of systemic corticosteroid effects and that particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

Ocular Effects

While no clinically important ophthalmic findings were noted in the study designed to assess any potential ocular effects and there was a low incidence of ocular events reported in the COPD Clinical Development program, the “Warnings and Precautions” section of the proposed BREO ELLIPTA *Prescribing Information* includes the class labelling warning regarding reports of glaucoma, increased intraocular pressure, and cataracts in patients with COPD following the long-term administration of ICS and advises that close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.

Benefit: Risk

The effect size of FF/VI 100/25 on reducing exacerbations in the 1-year, exacerbation studies HZC102970 (21%) and HZC102871 (34%) ([Figure 5](#)) is comparable to that observed in the 1-year exacerbation studies with ADVAIR DISKUS (FP/salmeterol 250/50 BID versus salmeterol 50 BID), 30.5% and 30.4% [[Ferguson, 2008](#); [Anzueto, 2009](#), respectively].

As previously noted, the goals of pharmacologic therapy in COPD should be to reduce symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance [[GOLD, 2011](#)]. COPD exacerbations are important events associated with the morbidity and mortality of the disease. Long-term treatment with ICS added to a LABA is recommended for patients with a high risk for exacerbations [[GOLD, 2011](#)]. ICS combined with a LABA in COPD has been shown to be more effective than the individual components in managing stable COPD by reducing exacerbations and improving lung function and health status [[GOLD, 2011](#); [Ferguson, 2008](#); [Calverley, 2007](#); [Kardos, 2007](#); [Sharafkhaneh, 2012](#)]. However, the benefit of ICS in contributing to the reduction in exacerbations must be balanced by the risks associated with the corticosteroid use. Important risks associated with ICS in general, and FF in particular are pneumonia and fractures (due to the potential effects on bone).

Shown in [Table 15](#) are the number of moderate and severe exacerbations, the number of pneumonia events and the number of fractures that occurred in each of the four treatment arms in the two, 1-year exacerbation studies (HZC102970 and HZC102871). Compared with VI 25, there were 187 fewer exacerbations with FF/VI 100/25 (i.e., 741 minus 554), in contrast with 30 more pneumonia events (i.e., 58 minus 28) and 11 more fractures (i.e., 19 minus 8); of the non-traumatic fractures, there was an excess of 4 with FF/VI 100/25 (i.e., 6 minus 2) ([Table 15](#)). These data suggest a strongly positive benefit:risk balance as it relates to the FF 100 component of BREO ELLIPTA.

Table 15 Summary of Moderate/Severe Exacerbations, Pneumonias and Total Fractures (ITT Population): Integrated Study Results – 1-Year Exacerbation Studies (HZC102970/HZC102871)

	FF/VI 50/25 N=820	FF/VI 100/25 N=806	FF/VI 200/25 N=811	VI 25 N=818
Proportion of Subjects with at Least 1 Moderate/Severe Exacerbation, n (%)	388 (47%)	338 (42%)	338 (42%)	400 (49%)
Number of Moderate/Severe Exacerbations	650	554	600	741
Proportion of Subjects with at Least 1 Pneumonia, n (%)	48 (6%)	51 (6%)	55 (7%)	27 (3%)
Number of Pneumonias	54	58	65	28
Total Fractures	15	19	14	8

FF=fluticasone furoate; ITT=Intent-to-Treat; VI=vilanterol

As discussed earlier, the incidence of AE reports of all pneumonias, SAE reports of pneumonia and fatal pneumonias observed in the BREO ELLIPTA (FF/VI 100/25) group in 1-year, exacerbation studies was similar to the incidences reported in the 1-year, exacerbation studies of the currently available ICS/LABA combinations (FP/salmeterol and budesonide/formoterol) ([Table 11](#)).

As to the VI 25 component of BREO ELLIPTA, there was no increase in cardiac-related events as classified using the standardized MedDRA Queries (SMQs) or non-sustained ventricular tachycardia ([Table 13](#)) compared with placebo ([Table 14](#)). However, there were a few more events of sustained supraventricular tachycardia and atrial fibrillation with FF/VI 100/25 and VI 25 compared with placebo. These risks are balanced by the significant improvement in lung function with BREO ELLIPTA (VI 25 component) compared with placebo and FF 100mcg ([Figure 2](#) and [Figure 3](#)). These data suggest an acceptable benefit:risk balance as it relates to the VI 25 component of BREO ELLIPTA.

BREO ELLIPTA is a once-daily ICS/LABA combination that has demonstrated clinically relevant efficacy, with improvements in both lung function and reductions in exacerbations, in clinical trials in COPD, with an acceptable safety and tolerability profile that is consistent with the ICS/LABA class. That it requires only once-daily administration may lead to improved adherence and hence, improved clinical outcomes.

Overall Conclusion

BREO ELLIPTA (fluticasone furoate/vilanterol 100/25) provides a new, safe and effective once-daily treatment option for the maintenance treatment of airflow obstruction in patients with COPD and to reduce exacerbations of COPD in patients with a history of exacerbations.

1. INTRODUCTION

Airflow limitation and recurring exacerbations are the hallmarks of chronic obstructive pulmonary disease (COPD) and lead to increasing symptomatic and functional limitation and morbidity [GOLD, 2011]. Relief of reversible airflow obstruction, an important but not universal feature, in COPD has been the key target for drug therapies [FDA, 2007], though reduction of COPD exacerbations is also an important goal.

Exacerbations can be life-threatening, are linked to co-morbid conditions and may contribute to further permanent decrements in lung function. Drugs that either prevent, or modify the severity or duration of COPD exacerbations can provide meaningful benefit to patients. As noted in the FDA Draft Guidance, reduction in chronic cough, excess sputum production, dyspnea, or other debilitating symptoms of COPD, also constitutes meaningful benefit to patients [FDA, 2007].

BREO ELLIPTA (Fluticasone Furoate/Vilanterol Inhalation Powder) is a novel, fixed-dose combination of fluticasone furoate (FF; GSK code GW685698), an inhaled corticosteroid (ICS), and vilanterol (VI; GSK code GW642444), a long-acting beta₂-agonist (LABA) that has been developed for the treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema, and to reduce exacerbations of COPD in patients with a history of exacerbations. Neither FF nor VI is currently available as an individual component for oral inhalation. However, FF is the same active component in GlaxoSmithKline's (GSK's) marketed intranasal corticosteroid (VERAMYST™), which is available in 108 countries worldwide.

FF is chemically distinct from the ICS fluticasone propionate (FP) in that the 17 α -ester of the fluticasone moiety comprises a furoate, as opposed to propionate group; this group is not cleaved from the molecule during metabolism. *In vitro*, studies of FF suggest a pharmacological profile that differs from FP and other ICS; FF exhibits greater potency in cell culture models of inflammation compared with FP and budesonide [Salter, 2007], shows greater potency compared with FP in peripheral blood mono-nuclear cells from patients with mild asthma or moderate/severe COPD and is further differentiated from FP in that cell culture assays of glucocorticoid-dependent gene expression and glucocorticoid receptor nuclear translocation indicate activity at >24 h, which is not observed with FP [Rossios, 2011].

VI is an antedrug analogue of salmeterol with a higher intrinsic activity at the beta₂ receptor than the LABA salmeterol [Procopiou, 2010]. *In vitro*, VI exhibits >1000 fold selectivity for beta₂ receptors relative to beta₁ or beta₃ receptors [Barrett, 2010], while data from human lung tissue indicate a faster onset and longer duration of action (22 hours) than salmeterol [Morrison, 2010].

2. BACKGROUND

The concomitant use of inhaled corticosteroids (ICS) and long-acting beta₂-agonists (LABA) is a well-established and recommended approach for the treatment of COPD [GOLD, 2011]. Only two inhaled ICS/LABA combination treatments, ADVAIR

DISKUS and Symbicort are approved by the FDA for treatment of COPD in the United States. Only ADVAIR DISKUS is indicated to reduce exacerbations of COPD in patients with a history of exacerbations. ADVAIR DISKUS, ADVAIR HFA, Symbicort, and Dulera are also indicated for the treatment of asthma. All inhaled ICS/LABA combination products are dosed twice daily.

GSK has developed BREO ELLIPTA as a once daily inhaled treatment for COPD. BREO ELLIPTA is a novel, fixed-dose powder combination of fluticasone furoate (FF) 100 mcg, an ICS, and vilanterol (VI) 25 mcg, a LABA. Although FF is approved in the US as VERAMYST for intranasal administration, neither FF nor VI is currently available as an oral inhalation product.

The NDA for COPD is supported by an extensive Clinical Pharmacology program consisting of 52 studies in 1,406 subjects and two separate and extensive clinical development programs, a COPD clinical development program consisting of 11 studies in 7,851 subjects with COPD and an asthma clinical development program consisting of 18 studies in over 9,379 subjects with asthma ([Figure 1](#)).

The current NDA was filed in support of the COPD indication. A Phase III Clinical Development Program with FF/VI for the treatment of asthma is nearing completion.

The COPD Clinical Development Program for BREO ELLIPTA was designed to comply with the draft FDA guidance entitled “Guidance for Industry: Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment” [[FDA](#), 2007]. As neither of the components is approved for treatment of COPD, the program aimed to demonstrate the efficacy of FF/VI and the contribution of the components. Unlike the clinical development programs for ADVAIR DISKUS and Symbicort, which simply carried forward doses that were selected from the Phase III clinical programs in patients with asthma, in the FF/VI Phase III clinical program for COPD, three doses of FF in the combination (50/25, 100/25 and 200/25mcg QD) were evaluated in the Phase III COPD Clinical Development Program to determine the appropriate dose of FF in the combination.

3. RATIONALE FOR THE USE OF FF/VI IN COPD

COPD is a common, preventable and treatable disease, characterized by persistent airflow limitation that is usually progressive and associated with an enhanced inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity [[GOLD](#), 2011]. An exacerbation is an acute event characterized by a worsening of the patient’s respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication [[GOLD](#), 2011].

More than 3 million people died of COPD in 2005, accounting for 5% of deaths globally [[WHO](#), 2012]. In 2002 COPD was the fifth leading cause of death and it is estimated to become the third leading cause of death by 2030 [[WHO](#), 2012]. As a leading cause of morbidity and mortality worldwide, COPD produces a substantial, and growing, economic and social burden [[GOLD](#), 2011], including significant healthcare costs [[Chapman](#), 2006; [Lopez](#), 2006].

The goals of pharmacologic therapy in COPD should be to reduce symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance [GOLD, 2011]. Bronchodilators, such as beta₂-agonists, are central to improving lung function and managing symptoms in COPD. Long-acting agents are convenient and more effective at producing maintained symptom relief than short-acting ones. Although long-term monotherapy treatment with ICS is not recommended, an ICS combined with a LABA in COPD has been shown to be more effective than the individual components in managing stable COPD by reducing exacerbations and improving lung function and health status [GOLD, 2011; Ferguson, 2008; Calverley, 2007; Kardos, 2007; Sharafkhaneh, 2012].

The concomitant use of inhaled corticosteroids (ICS) and long-acting beta₂-agonists (LABA) is a well-established and recommended approach for the treatment of COPD [GOLD, 2011]. Only two inhaled ICS/LABA combination treatments, ADVAIR DISKUS and Symbicort are approved by the FDA for treatment of COPD in the United States. Only ADVAIR DISKUS is indicated to reduce exacerbations of COPD in patients with a history of exacerbations. ADVAIR DISKUS and ADVAIR HFA, Symbicort and Dulera) are also indicated for the treatment of asthma. All inhaled ICS/LABA combination products are dosed twice daily.

GSK has developed BREO ELLIPTA (FF/VI 100/25) as a once daily inhaled treatment for COPD. BREO ELLIPTA is a novel, fixed-dose powder combination of fluticasone furoate (FF) 100 mcg, an ICS, and vilanterol (VI) 25 mcg, a LABA. BREO ELLIPTA will provide a new ICS/LABA treatment option, with the requirement for less frequent dosing (i.e., once-daily).

Prescription refill data suggest that patients only refill 40-50% of their ICS/LABA prescriptions annually [Delea, 2010; Hagiwara 2010]. Thus, there is a need to improve adherence, which a once-daily alternative may provide. Indeed, it has been demonstrated that compliance with a once-daily ICS regimen is greater than with a twice-daily regimen [Price, 2010; Toy, 2011]. In a 12-week study designed to mimic an actual clinical setting in subjects with mild to moderate persistent asthma, compliance with once-daily mometasone was significantly better than with twice-daily mometasone [Price, 2010]. Similarly, a retrospective study of use of inhaled medications for COPD using an administrative claims database covering 8 million people in the US, demonstrated that compliance (measured as proportion of days covered over 12 months following treatment initiation) strongly correlated with dosing frequency. Based on a sample of 55,076 COPD patients, compliance was 43.3%, 37.0%, 30.2% and 23.0% for once, twice, three times and four times daily patient cohorts, respectively [Toy, 2011].

Healthcare resource utilization costs have also been shown to be lower in patients after initiating or switching to a once-daily regimen [Toy, 2011; Guest, 2005]. In the study of Toy and colleagues, regression analysis showed that one-year adherence correlated with healthcare resource utilization and with improved compliance leading to a net reduction in annual costs. Similarly, a case control study using the General Practice Research Database in the UK [Guest, 2005] found that switching asthma patients managed in primary care from a twice-daily to a once-daily ICS increased compliance and reduced health service costs.

These data support the hypothesis that once-daily BREO ELLIPTA has the potential to improve subject compliance, and as a result, overall disease management resulting in a reduction in overall healthcare costs compared with existing twice-daily ICS/LABA.

Based upon the results of the Phase III COPD Clinical Development Program, BREO ELLIPTA has been demonstrated to be a safe and well tolerated option for patients with COPD at the recommended dose of 100/25 mcg once daily, with a safety profile consistent with the ICS/LABA class. BREO ELLIPTA has also proven to be effective treatment for COPD, providing a fast onset of effect after the first dose and sustained 24-hour effect with once-daily dosing, as measured by lung function. VI (the LABA component) provided clinically meaningful improvement in lung function and FF (the ICS component) provided clinically meaningful reductions in rate of moderate to severe COPD exacerbations, time to first moderate or severe exacerbation and rate of exacerbations requiring oral/systemic corticosteroids. BREO ELLIPTA will provide a new ICS/LABA treatment option with less frequent administration (i.e., once-daily) than the currently approved ICS/LABA treatments that require twice-daily administration. BREO will be administered via a new, easy to use, multi-dose dry powder inhaler (DPI), ELLIPTA™.

The main safety concerns with FF/VI relate to the known ICS and LABA effects. Pharmacologic class effects of ICS include bone disorders (osteoporosis, fracture, decreased bone mineral density), HPA axis effects (adrenal suppression, decreased serum cortisol, Cushing's syndrome), local oropharyngeal effects (candidiasis, hoarseness, irritation/inflammation, cough), pneumonia, and ocular effects (cataracts, increased intraocular pressure, glaucoma). Pharmacologic class effects of LABAs include cardiovascular (increased heart rate, prolonged QT interval, cardiac rhythm abnormalities, palpitations, myocardial ischemia), metabolic (low potassium, elevated glucose), and neurologic (tremor) effects. These class effects were proactively addressed in the FF/VI COPD Clinical Development Program through an evaluation of AESI as well as objective assessments of 24-hour serum cortisol, 24-hour urinary cortisol, oropharyngeal examinations, chest x-rays, pulse, heart rate, 12-lead ECGs, 24-hour Holter monitoring and biochemical bone markers.

4. REGULATORY HISTORY

Clinical development of FF commenced in 2002, followed by commencement of clinical development of VI in 2004. The first study (Phase IIa) of the FF/VI combination in patients with disease (COPD) was initiated in 2008. Since 2002, an extensive program of clinical pharmacology and clinical studies in patients with COPD and asthma has investigated the efficacy and/or safety of FF/VI (combination and monotherapy), with inhaled doses of FF monotherapy ranging from 25 to 4,000mcg, inhaled doses of VI ranging from 3 to 600mcg and inhaled doses of the FF/VI combination ranging from 50/25 to 800/100mcg.

GSK met with the FDA Division of Pulmonary and Allergy Products to discuss the FF/VI clinical development program for COPD. GSK also met with the Division to discuss the development program for asthma. The major regulatory meeting milestones were three

Pre-Investigational New Drug (IND) meetings: one for each of the individual components (04 February 2005 for FF and 31 January 2007 for VI) and one for the combination (29 April 2008); the IND for FF/VI was submitted on 23 May 2008. In addition, there were also three End-of Phase II meetings, one for the combination for COPD and two for the combination for asthma, and three Pre-New Drug Application (NDA) meetings, one for the combination for COPD and two for the combination for asthma. The pre-NDA meeting for the combination for treatment of COPD was held on 13 July 2011. On 12 July 2012, GlaxoSmithKline filed an NDA in support of FF/VI for the long-term once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema and the reduction in exacerbations in COPD patients with a history of exacerbations.

5. PRODUCT DESCRIPTION

FF/VI Inhalation Powder is delivered via a novel, single-step activation, multi-dose, dry powder inhaler (DPI) for oral inhalation, ELLIPTA™. Two, double-foil, laminate, blister strips are contained within the inhaler that provides a total of 30 doses (60 blisters). One strip contains a blend of micronized FF and lactose (excipient). The second strip contains a blend of micronized VI and magnesium stearate and lactose (excipients). When actuated, the ELLIPTA delivers the contents of a single blister simultaneously from each of the two blister strips. The drug product used in the Phase III FF/VI clinical development program for COPD was fully representative of the to-be-marketed product in terms of formulation and inhaler (ELLIPTA).



The *in vitro* pharmaceutical performance of the product has been extensively characterized and showed that the ELLIPTA delivers consistent doses within the respirable range over the lifetime of the product. In adult subjects with obstructive lung disease and severely compromised lung function (i.e., COPD with FEV₁/FVC <70% and FEV₁ <30% predicted or FEV₁ <50% predicted plus chronic respiratory failure), mean peak inspiratory flow through the DPI was 66.5 L/min (range: 43.5 to 81.0 L/min). The performance of the ELLIPTA in clinical trials was very robust as evaluated in the Phase III programs for both COPD and asthma.

6. PHARMACOLOGY FINDINGS

6.1. Nonclinical Pharmacology and Toxicology

The pharmacological, pharmacokinetic and toxicological effects of FF or VI when administered alone have been well characterized in a comprehensive range of nonclinical studies to support their long-term clinical use. Non-clinical safety assessment packages for FF and VI as single agents included safety pharmacology, repeat-dose general toxicology, genetic toxicology, carcinogenicity and reproductive toxicology studies. Combination toxicology bridging studies applicable to 'late stage' entities, in compliance with ICH M3(R2) guidance, have also been performed. The human responses to ICSs and LABAs have been extensively studied and, based on this experience and on the data derived from animal studies, the potential for adverse effects in clinical studies was monitored appropriately during the FF/VI COPD Clinical Development Program

There is no indication that either FF or VI possess any significantly greater potential for toxicity than other members of their pharmacological class when given in combination, or that the findings raise any significant safety concerns for the use in humans of FF and VI in the proposed commercial inhaled drug product. This conclusion is borne out by the clinical safety assessments in the clinical development program, which indicate that FF/VI, at the proposed dose of 100/25 mcg QD, was well tolerated in adult subjects with COPD. FF/VI is designated as Pregnancy Category C.

6.2. Clinical Pharmacology

A large Clinical Pharmacology Program consisting of 52 studies (24 evaluating FF [inhaled, oral, intravenous and cutaneous administration], 17 evaluating VI [inhaled, oral and intravenous administration] and 11 evaluating the FF/VI combination [inhaled administration] in subjects with COPD, asthma, hepatic impairment, renal impairment and in healthy subjects) provides further support for the approval of FF/VI Inhalation Powder in subjects with COPD. The Clinical Pharmacology program consisted of a variety of studies, including bioavailability studies, hepatic and renal impairment studies, drug interaction studies, healthy subject PK and initial tolerability studies, human pharmacodynamic (PD) studies, and PD and PK/PD studies in subjects with COPD and asthma. A total of 1,406 subjects were treated in the Clinical Pharmacology program.

In addition, PK samples were collected in five of the studies in the COPD Clinical Program, two of the four primary COPD studies with FF/VI (the two, 6-month, lung function studies [HZC112206 and HZC122207]), the 4-week, serial FEV₁, crossover study with FF/VI (HZC110946), the 4-week, Phase IIa, safety and efficacy study with FF/VI (HZC111348), and the Phase IIb, dose-ranging study with VI (B2C111045). Using the data from four of these studies (excluding B2C111045), a meta-analysis was conducted to characterize the FF and VI population PK, and population PK/PD profile of FF/VI and the individual components (FF and VI) administered once-daily in the morning to subjects with COPD.

Key Findings from the Clinical Pharmacology Program:

- The PK of FF and VI demonstrate linear time-independent PK following once-daily inhaled administration.
- There were no clinically relevant differences in the PK or PD of either FF or VI when administered from the DPI as FF/VI compared with administration as either FF or VI alone.
- FF systemic exposure was lower in subjects with COPD, as well as in subjects with asthma, compared with healthy subjects and was lower in subjects with COPD than in subjects with asthma.
- In subjects with COPD, VI C_{\max} was lower while $AUC_{(0-24)}$ was higher compared with healthy subjects. VI systemic exposure was lower in subjects with asthma compared with healthy subjects.
- Subjects categorized as East Asian had higher systemic exposure for FF (COPD and asthma) and VI (asthma; C_{\max} only) compared with other racial groups. However, there was no evidence that the higher systemic exposure in these populations was associated with greater PD effects.
- In subjects with COPD or asthma, there was no evidence for either age or gender to affect the PK of FF, or for gender to affect the PK of VI. In subjects with COPD, VI inhaled clearance (CL/F) was shown to decrease with age.
- In subjects with severe renal impairment, repeat administration of FF/VI 200/25 mcg did not result in significantly greater FF or VI exposure compared with healthy subjects.
- In subjects with mild, moderate or severe hepatic impairment, repeat administration of FF/VI resulted in greater FF systemic exposure (up to three-fold) and a reduction in serum cortisol by approximately one third compared with healthy subjects. There was no effect of hepatic impairment on VI systemic exposure.
- FF and VI are both eliminated mainly by CYP3A4 metabolism. Co-administration of FF/VI 200/25 mcg with the CYP3A4 and P-gp inhibitor ketoconazole showed modest increases in FF and VI systemic exposure. This was associated with a reduction in serum cortisol, but did not result in an increased effect on heart rate or blood potassium.

6.2.1. Pharmacokinetics

6.2.1.1. ADME

The absorption, distribution, metabolism and excretion of FF and VI have been studied separately after oral and intravenous (FF only) administration of radiolabelled drug. These routes were used as surrogates for the swallowed and inhaled portions of an

inhaled administration. Inhaled absorption characteristics and absolute bioavailability have been determined for FF/VI administered via DPI.

The potential for systemic PD effects resulting from absorption of the swallowed portion of the dose is low, since oral bioavailability of both FF and VI was low, on average 1.26% and <2%, respectively. Consequently, systemic exposure for both inhaled FF and VI is primarily due to absorption of the inhaled portion of the dose delivered to the lung. The absolute bioavailability for FF and VI (administered as FF/VI) was 15.2% and 27.3%, respectively. The apparent terminal phase elimination half-lives of FF and VI following inhaled FF/VI were on average, 23.7 hours and 2.47 hours, respectively. The elimination half-life of VI is not representative of the duration of bronchodilation produced by VI, which is related to topical activity in the lung where a 24-hour duration of action has been clearly demonstrated. The time for absorption of 90% of the total bioavailable dose for FF and VI was on average, 35.2 hours and 3.83 hours, respectively.

Both FF and VI are extensively distributed, with average volumes of distribution at steady-state of 661 L and 165 L, respectively. The intravenous PK of FF and VI showed high plasma clearance (on average 65.4 L/h and 108 L/h, respectively). Both FF and VI have a low association with red blood cells and high *in vitro* plasma protein binding, which are independent of concentration with average values of $\geq 99.6\%$ and 93.9%, respectively. FF was predominantly bound to albumin (96%) and α_1 -acid glycoprotein (90%).

FF and its metabolites are eliminated primarily in the feces, accounting for approximately 101% and 90% of the orally and intravenously administered dose, respectively. Urinary excretion accounted for approximately 1% and 2% of the orally and intravenously administered doses, respectively. There was no *in vivo* evidence for cleavage of the furoate moiety resulting in the formation of fluticasone. Following oral administration, VI was eliminated mainly by metabolism followed by excretion of metabolites in urine and feces (approximately 70% and 30% of the recovered radioactive dose, respectively).

6.2.1.2. Assessments in Special Populations

6.2.1.2.1. Age

The intent is for FF/VI to be used in a very wide age range to cover the COPD population. Based upon the Phase IIa, IIb and Phase III data (age studied up to 84 years), there was no evidence for age to affect the PK of FF in subjects with COPD, although for VI there was a decrease (27%) in inhaled clearance of VI (CL/F) over the observed age range of 41 to 84 years. While non-inferiority in VI AUC₍₀₋₂₄₎ was demonstrated in subjects with severe renal impairment compared with healthy subjects, the ratio of adjusted means was 1.56, consistent with a small effect of lower renal function on VI CL/F. Consequently, decreased renal function with age might contribute to the modest decrease in VI clearance seen in subjects with COPD. For an elderly subject with COPD (aged 84 years) with low bodyweight (35 kg) VI AUC₍₀₋₂₄₎ is predicted to be 35% higher than the population estimate (a subject with COPD aged 60 years and bodyweight of 70 kg), while C_{max} was unchanged. These differences in AUC₍₀₋₂₄₎ only are unlikely to be of clinical relevance as beta₂-agonist associated PD effects are known to be predominantly related to C_{max} and not to AUC₍₀₋₂₄₎.

In subjects with COPD, including the elderly, no dose modifications are proposed.

6.2.1.2.2. Gender

There was no evidence for gender to affect the PK of either FF or VI based on analyses of Phase IIa, IIb and Phase III data in subjects with COPD.

6.2.1.2.3. Race

In subjects with COPD, there was evidence from population PK analyses for greater FF systemic exposure in East Asian subjects compared with Caucasian subjects. However, the mean difference was only 30% and exposure levels in East Asian subjects at an FF dose of 200 mcg were still considerably below levels that result in cortisol suppression. Therefore, since this limited difference was not associated with an effect on the hypothalamic-pituitary-adrenal- (HPA)-axis, the findings suggest that no FF dosage adjustments are required for subjects of East Asian heritage.

There was no evidence for an effect of race on VI systemic exposure in subjects with COPD. Consequently, VI dosage adjustments are not required for subjects of East Asian heritage.

6.2.1.2.4. Renal Impairment

In subjects with severe renal impairment there was no significant increase in FF or VI systemic exposure or in any corticosteroid or beta₂-agonist class-related systemic effects compared with healthy subjects and non-inferiority for subjects with renal impairment subjects compared with healthy subjects was demonstrated (upper 90% CI for the ratio of the results of the two groups <2). This suggests that dose adjustments are not required in subjects with impaired renal function.

6.2.1.2.5. Hepatic Impairment

Following repeat dosing of FF/VI for 7 days, there was a greater FF systemic exposure (up to three-fold as measured by AUC₍₀₋₂₄₎) in subjects with moderate/severe hepatic impairment (Child-Pugh classification) compared with healthy subjects. In line with the increased FF systemic exposure, serum cortisol was reduced by approximately a third in subjects with moderate hepatic impairment after FF/VI 200/25 mcg. Although FF systemic exposure was increased in subjects with severe hepatic impairment after FF/VI 100/12.5 mcg, this was not associated with reduced serum cortisol due to the lower FF dose administered. Therefore, reduced serum cortisol would not be anticipated in COPD subjects with moderate or severe hepatic impairment. There was no effect of hepatic impairment on VI systemic exposure or beta-adrenergic systemic effects (heart rate or serum potassium) following repeat dose administration of FF/VI 200/25 mcg to subjects with mild or moderate hepatic impairment or FF/VI 100/12.5 mcg to subjects with severe hepatic impairment. Although the VI dose was 12.5 mcg in subjects with severe hepatic impairment, significant beta-adrenergic systemic PD effects would not be predicted at 25 mcg.

The “Use in Special Populations” section of the proposed *Prescribing Information* includes a recommendation to use BREO ELLIPTA with caution in patients with hepatic impairment.

6.2.1.3. Drug Interactions

The inhibition and induction potential of both FF and VI at low inhalation doses is negligible. Although FF and VI are both inhibitors and substrates of cytochrome P450 3A4 (CYP3A4), their IC₅₀ values are at least 1000-fold higher than anticipated C_{max} values in man. Consequently the risk of a PK interaction is negligible at the low inhalation doses intended for clinical use.

FF and VI are both substrates of CYP3A4 and P-glycoprotein (P-gp). Co-administration of repeat dose inhaled FF/VI (200/25 mcg) and the strong CYP3A4 and potent P-gp inhibitor ketoconazole (400 mg once daily), resulted in modest increases in mean FF AUC₍₀₋₂₄₎ and C_{max} (by 36% and 33%, respectively) and mean VI AUC_(0-∞) and C_{max} (by 65% and 22%, respectively). Co-administration did not result in an increase in beta-adrenoceptor-mediated systemic effects (maximum heart rate and minimum blood potassium), while steroid-mediated systemic effects were observed with a 27% reduction in weighted mean serum cortisol (0-24 hours).

The effect of verapamil (a potent P-gp inhibitor and moderate CYP3A4 inhibitor) on VI was studied as part of a GSK573719 (long-acting muscarinic antagonist)/VI combination development programme. Co-administration with verapamil did not affect the VI C_{max} or AUC suggesting that VI pharmacokinetics would not be significantly affected by P-gp inhibition. Since there was no significant liability for FF/VI when co-administered with ketoconazole, a strong CYP3A4 and potent P-gp inhibitor, no specific study with a P-gp inhibitor was conducted with FF/VI.

Consistent with labelling for other ICS/LABA combinations, the proposed *Prescribing Information* for BREO ELLIPTA contains a warning regarding co-administration with strong CYP 3A4 inhibitors.

6.2.1.4. PK Results from Clinical Studies

A population pharmacokinetic meta-analysis using concentration-time data from two of the four primary FF/VI COPD clinical studies (HZC112206, HZC122207) and two supporting FF/VI COPD clinical studies (HZC110946 and HZC111348), was conducted to characterize the FF and VI population PK, and population PK/PD profile of FF/VI and the individual components (FF and VI) administered once-daily in the morning to subjects with COPD. Since the dose of FF (400 mcg) in study HZC111348 was above the therapeutic range, only the data from the HZC110946, HZC112206 and HZC112207 studies were included in the FF meta-analysis. The FF population PK analysis dataset was comprised of 1,307 subjects (subjects with COPD or healthy subjects). The VI population PK analysis dataset was comprised of 1,167 subjects (subjects with COPD or healthy subjects). In the FF PK analysis, in subjects who received FF/VI 100/25 or FF 100 alone (n = 391), predicted systemic exposure to FF was a mean C_{max} of 12.0 pg/mL (95% CI: 10.9, 13.0) and an AUC₍₀₋₂₄₎ of 182.2 pg•hr/mL (95% CI: 169.6, 194.7). There was no difference in exposure to FF between the individual component and

combination treatment. In the VI PK analysis, in subjects who received VI 25 alone or in combination with FF (n = 1,091) predicted systemic exposure to VI was a mean C_{max} of 43.2 pg/mL (95% CI: 41.8, 44.6) and an AUC(0-24) of 265.7 pg•hr/mL (95% CI: 259.5, 271.9). There was no difference in exposure to VI between the individual component and combination treatment.

The systemic exposure to FF and VI was compared between subjects with COPD, healthy subjects and subjects with asthma using population pharmacokinetic analyses. In subjects with COPD the FF C_{max} and AUC₍₀₋₂₄₎ were 47% and 46% lower, respectively, than in healthy subjects. In subjects with asthma the FF C_{max} and AUC₍₀₋₂₄₎ were 18% and 7% lower, respectively, than in healthy subjects. In subjects with COPD the FF C_{max} and AUC₍₀₋₂₄₎ were 35% and 42% lower, respectively, than in subjects with asthma. In subjects with COPD the VI C_{max} and AUC₍₀₋₂₄₎ were 67% lower and 24% higher, respectively, than in healthy subjects. In subjects with asthma the VI C_{max} and AUC₍₀₋₂₄₎ were 62% and 21% lower, respectively, than in healthy subjects. In subjects with COPD the VI C_{max} and AUC₍₀₋₂₄₎ were 13% lower and 57% higher, respectively, than in subjects with asthma.

6.2.2. Pharmacodynamics

6.2.2.1. Corticosteroid Effects

Overall the Clinical Pharmacology data indicated that FF 100 mcg is not associated with clinically significant class-related corticosteroid systemic effects.

Inhaled FF at repeat doses up to 400 mcg was not consistently associated with statistically significant decreases in serum or urinary cortisol and these results were confirmed in clinical studies. At higher doses, above the therapeutic range, corticosteroid class-related decreases in serum and urine cortisol levels were observed. In line with the increased FF systemic exposure, serum cortisol was reduced by approximately a third in subjects with moderate hepatic impairment after FF/VI 200/25 mcg and a similar effect would be anticipated in subjects with severe hepatic impairment at this dose.

6.2.2.2. Beta₂-agonist Effects

Overall the Clinical Pharmacology data indicate that VI 25 mcg is not associated with clinically significant class-related beta₂-adrenoceptor systemic effects.

VI, administered either alone or as FF/VI, at doses up to 50 mcg was not associated with clinically relevant or statistically significant effects on blood potassium or blood glucose. VI 100 mcg was associated with a small decrease in blood potassium (approximately ≤0.1 mmol/L) and a small increase in blood glucose (approximately <1 mmol/L). VI at doses up to 100 mcg was not consistently associated with clinically relevant or statistically significant effects on blood pressure. Where PD effects were seen, there was no evidence of an increased effect with repeat dosing, while some effects showed signs of diminishing (i.e. showed tachyphylaxis). In the Thorough QT study, there was a lack of effect of FF/VI 200/25 on QTcF or on individually corrected QTc (QTci). There was an effect on QTcF at a single timepoint during the first hour after dosing with FF/VI 800/100

but not on QTci. Heart rate increases were detected with both FF/VI strengths investigated (200/25 and 800/100 mcg) with maximum effects seen 10 minutes after dosing.

6.2.3. Dose or Concentration/Effect Relationship

Concentration-effect analyses focused on corticosteroid and beta₂-adrenergic class related systemic effects for FF and VI. For FF, a relationship between FF AUC₍₀₋₂₄₎ and effect on 24-hour serum cortisol and 24-hour urinary cortisol excretion has been established. Based on the models, an FF AUC₍₀₋₂₄₎ of 1000 pg.h/mL would be required to reduce 24-hour serum cortisol or 24-hour urinary cortisol excretion by 20% and 17%, respectively; the proposed dose of FF (100mcg) in BREO ELLIPTA achieves a model predicted systemic exposure of FF AUC₍₀₋₂₄₎ of 181.82 pg.h/mL in subjects with COPD. For VI, the relationship between VI C_{max} and effects on both heart rate and QTcF has been established. An integrated analysis of the effects of VI dose on the QTcF interval demonstrated that administration of VI (up to 100 mcg) as either single or repeat doses resulted in very few QTcF values of potential clinical importance. The population VI dose-response relationship for trough FEV₁ determined in subjects with COPD and with asthma support the selection of a 25 mcg dose of VI in the FF/VI combination. Furthermore, these data support the FF dose of 100 mcg and the VI dose of 25 mcg as safe in BREO ELLIPTA.

7. CLINICAL DEVELOPMENT PROGRAM

This section first discusses how the doses of FF and VI doses were selected for evaluation in the Phase III COPD Clinical Development Program and then discusses the Phase III COPD Clinical Development Program, particularly the results of the four, primary COPD studies, the 6-month, lung function studies (HZA112206 and HZA112207) and the 1-year, exacerbation studies (HZA102970 and HZA102871) that form the basis of the Clinical Trials section of the proposed *Prescribing Information*. The efficacy results from the Clinical Development Program are presented first, followed by the safety results.

7.1. Selection of Doses for Phase III and Evaluation of Dose Regimen

Key Finding(s):

- Results of a dose-ranging study in subjects with COPD that evaluated a range of VI doses from 3-50mcg QD, guided the selection of VI 25 QD as the minimally effective dose of VI for evaluation in combination with FF in the Phase III COPD Clinical Development Program; results of a dose-ranging study of the same range of doses of VI in subjects with asthma supported this selection
- Results of three, dose-ranging studies in subjects with asthma that evaluated a range of doses of FF from 25-800mcg QD guided the selection of three doses of FF (50, 100 and 200mcg QD) for evaluation in the combination with VI 25mcg QD in the Phase III COPD Clinical Development Program
- Separate once- versus twice-daily studies with FF or VI demonstrated that treatment with FF 200 QD was comparable to FF 100 BID and treatment with VI 12.5 QD was comparable to VI 6.25 BID

The aim of the FF/VI Clinical Development Program for COPD was to identify doses of VI and FF that would achieve a meaningful level of clinical efficacy, for both lung function and COPD exacerbations, without compromising the safety profile. Seven Clinical Studies provided support for the doses and dose regimen of FF and VI evaluated in the FF/VI Phase III Clinical Development Program for COPD ([Table 16](#)).

A dose-ranging study of VI in subjects with COPD (B2C111045) was used to inform the choice of VI dose for study in the FF/VI Phase III Clinical Development Program for COPD. The results of this study were supported by a dose-ranging study of VI in subjects with asthma (B2C109575). No dose-ranging studies with FF monotherapy in COPD were performed, as patients with COPD demonstrate minimal bronchodilation with inhaled corticosteroids; rather, three dose-ranging studies in subjects with asthma (FFA109684, FFA109685 and FFA109687) were used to inform the choice of FF doses for study in the FF/VI Phase III program in COPD. As discussed in [Section 2](#), three doses of FF (50, 100 and 200) in the FF/VI combination were investigated in Phase III to determine the appropriate dose for use in patients with COPD.

The dosing regimen (once- versus twice-daily) of FF and VI was evaluated in two separate studies, FFA112202 and HZA113310, respectively, in subjects with asthma. As agreed with the FDA, results from these studies can be extrapolated to subjects with COPD.

Table 16 Studies to Support Doses and Dose Regimen of FF and VI Evaluated in the FF/VI Phase III Clinical Development Program for COPD

Study Year Completed	Study Design	Key Inclusion Criteria	Treatment (mcg)	N (ITT)	Primary Endpoint(s)
FF Efficacy and Safety; FF Dose-Ranging (Asthmatic Population)					
FFA109687 ¹ (Low-Dose Study) 2008	R, DB, DD, PC, PG 8 weeks	<ul style="list-style-type: none"> Pre-bronchodilator FEV₁ percent predicted 40-85% (visit between 5:00 AM and 12:00 [noon]) or 40-90% (visit between 5:00PM and 11:00PM) (NHANES III) during the Visit 1 Screening Period Reversibility of FEV₁ ≥12% and ≥200mL Using non-CS controller or SABA alone (with no ICS use ≥6 weeks) for ≥3 months preceding Visit 1 	FF 25 QD PM FF 50 QD PM FF 100 QD PM FF 200 QD PM FP 100 BID Placebo	97 100 110 95 102 94 (Total = 598)	Mean change from baseline to the end of the 8-week treatment period in trough FEV ₁
FFA109685 ² (Mid-Dose Study) 2008	R, DB, DD, PC, PG 8 weeks	<ul style="list-style-type: none"> Bullets 1 and 2 as shown for FFA109687 above Using an ICS for ≥8 weeks prior to Visit 1 and maintained on a stable dose of ICS (FP DPI ≤220mcg or equivalent for 4 weeks prior to Visit 1) 	FF 100 QD PM FF 200 QD PM FF 300 QD PM FF 400 QD PM FP 250 BID Placebo	105 101 103 99 100 107 (Total = 615)	Mean change from baseline at Week 8 in trough FEV ₁
FFA109684 ³ (High-Dose Study) 2008	R, DB, DD, PC, PG 8 weeks	<ul style="list-style-type: none"> Bullets 1 and 2 as shown for FFA109687 above Using an ICS for ≥8 weeks prior to Visit 1 and maintained on a stable dose of ICS (FP DPI >200 to ≤500mcg or equivalent) for 4 weeks prior to Visit 1) 	FF 200 QD PM FF 400 QD PM FF 600 QD PM FF 800 QDPM FP 500 BID Placebo	99 101 107 102 110 103 (Total = 622)	Mean change from baseline at Week 8 in trough FEV ₁
VI Efficacy and Safety; VI Dose-Ranging (Asthmatic Population)					
B2C109575 ⁴ 2008	R, DB, PC, PG 28 days	<ul style="list-style-type: none"> Pre-bronchodilator FEV₁ percent predicted 40-90% (NHANES III) at Visit 1 Reversibility of FEV₁ ≥12% and ≥200mL 	VI 3 QD PM ⁵ VI 6.25 QD PM ⁵ VI 12.5 QD PM ⁵ VI 25 QD PM ⁵ VI 50 QD PM ⁵ Placebo ⁵	101 101 100 101 102 102 (Total = 607)	Mean change from baseline in trough FEV ₁ at the end of the 28-day period
VI Efficacy and Safety; VI Dose-Ranging (COPD Population)					
B2C111045 ⁶ 2008	R, RD, DB, PG, PC 28 days	Post-bronchodilator FEV ₁ / FVC ratio of ≤0.70 and post-bronchodilator FEV ₁ percent predicted 35-70% (NHANES III) at screening (Visit 1)	VI 3 QD AM ⁵ VI 6.25 QD AM ⁵ VI 12.5 QD AM ⁵ VI 25 QD AM ⁵ VI 50 QD AM ⁵ Placebo ⁵	99 101 101 101 99 101 (Total = 602)	Change from baseline in trough FEV ₁ on Day 29
Once- Versus Twice-daily Dosing with FF (Asthmatic Population)					
FFA112202 ⁷ 2009	R, DB, XO 28 days	<ul style="list-style-type: none"> Pre-bronchodilator FEV₁ percent predicted 40-85% (NHANES III) at Visit 1 Reversibility of FEV₁ ≥12% and ≥200mL 	FF 200 QD PM FF 100 BID FP 200 QD PM FP 100 BID Placebo	140 142 42 43 187 (Total = 190)	Trough FEV ₁ at Day 28 of each treatment period

Study Year Completed	Study Design	Key Inclusion Criteria	Treatment (mcg)	N (ITT)	Primary Endpoint(s)
Once- Versus Twice-daily Dosing with VI (Asthmatic Population)					
HZA113310 ⁸ 2010	R, DB, PC, XO 7 days		VI 6.25 QD PM ⁵ VI 6.25 BID ⁵ VI 12.5 QD PM ⁵ VI 25 QD PM ⁵ Placebo ⁵	(Total = 75)	Mean trough FEV ₁ at the end of the 7- day treatment period

AM=morning; BID=twice-daily; CS=corticosteroid; DB=double-blind; DD=double-dummy; DPI=dry powder inhaler; FEV₁=forced expiratory volume in 1 second; FF=fluticasone furoate; FP=fluticasone propionate; ICS=inhaled corticosteroid; ITT=Intent-to-Treat population; PC=placebo-controlled; PG=parallel-group; PM=evening; QD=once-daily; R=randomized; RD=Repeat-dose; SABA=short-acting beta₂-agonist; VI=vilanterol; XO=crossover

1. Sites who randomized subjects: 108 centers in 14 countries: Bulgaria, Canada, Estonia, France, Germany, Korea, Mexico, Peru, Philippines, Poland, Russian Federation, Slovakia, Sweden, and the United States
2. Sites who randomized subjects: 98 centers in 13 countries: Canada, Estonia, Germany, Greece, Korea, Mexico, Philippines, Poland, Slovakia, Romania, Russian Federation, South Africa, and the United States
3. Sites who randomized subjects: 94 centers in 16 countries: Australia, Bulgaria, Canada, Chile, Czech Republic, Estonia, Poland, France, Germany, Mexico, Netherlands, Peru, Russian Federation, South Africa, Thailand, and the United States
4. Sites who randomized subjects: 88 centers in 16 countries: Argentina, Belgium, France, Canada, Chile, Peru, Germany, Korea, Netherlands, South Africa, Philippines, Thailand, Poland, Russian Federation, Sweden, and the United States
5. Subjects in Study B2C109575 and HZA113310 received concomitant ICS throughout study treatment; subjects in Study B2C111045 were allowed use of concomitant ICS
6. Sites who randomized subjects: 89 centers in 14 countries: Argentina, Canada, Chile, Denmark, Estonia, Germany, Korea, Mexico, Philippines, Poland, Peru, Russian Federation, Slovakia, and the United States
7. Sites who randomized subjects: 16 centers in the United States
8. Sites who randomized subjects: 9 centers in the United States

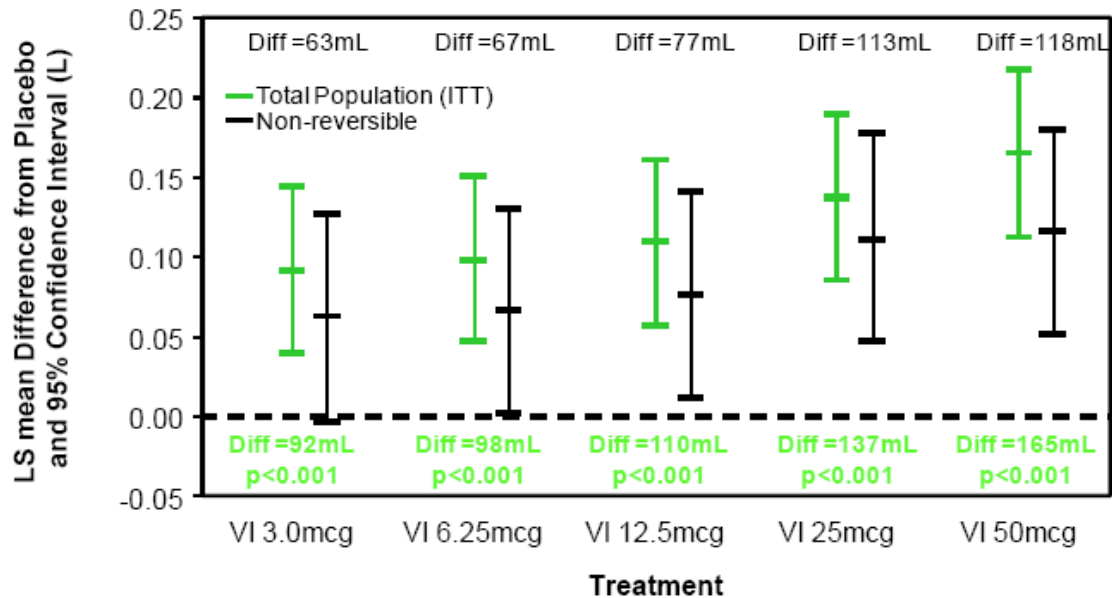
7.1.1. Vilanterol Dose Selection

The 25 mcg dose of VI was selected for testing in the Phase III COPD Clinical Development Program on the basis of results from a Phase IIb, randomized, double-blind, dose-ranging study in subjects with COPD (Study B2C111045), which tested a range of VI doses (3, 6.25, 12.5, 25 and 50 mcg once daily) (Table 16). The 25mcg dose of VI was also selected for testing in the Phase III Clinical Development Program for asthma on the basis of a separate, Phase IIb, randomized, double-blind, dose-ranging study in subjects with asthma (Study B2C109575), which tested the same range of VI doses as the COPD study. Each of the VI dose finding studies (B2C111045 and B2C109575) was 28 days in duration.

Study B2C111045 demonstrated that, based upon the primary and secondary endpoints, as well as the safety profile, 25 mcg was the appropriate dose to progress in the FF/VI combination for the Phase III COPD Clinical Development Program. Although all VI doses were statistically significantly different from placebo for the primary endpoint of trough FEV₁ (Figure 11), compared with placebo, adjusted mean treatment differences of ≥ 130 mL (the treatment difference on which the study was powered) were only observed with VI 25 and VI 50 but not with lower doses. Furthermore, the study showed an

increase in trough FEV₁ with increasing dose. The maximum effective dose was not demonstrated with the greatest efficacy seen with the 50mcg dose.

Figure 11 Adjusted Treatment Differences (95% CI) from Placebo in Change from Baseline in Trough FEV₁ (L) at Day 29 in Subjects with COPD (ITT Population and Non-Reversible Population): VI Dose-Ranging Study in COPD (B2C111045)



CI=confidence interval; Diff=difference from placebo; FEV₁=forced expiratory volume in 1 second; ITT=Intent-to-Treat Population; LS=Least Squares; VI=vilanterol

Analysis performed using ANCOVA with covariates of baseline, sex, age, smoking status (at Screening), reversibility stratum, and treatment.

Adapted from [Hanania, 2012](#)

Also, a *post-hoc* analysis based on subjects' reversibility to albuterol at Screening was conducted to further evaluate the effect of VI, since the COPD population is comprised of reversible and non-reversible subjects. This analysis demonstrated that in the non-reversible population (subjects with <12% or <200 mL change in FEV₁ after albuterol; 64% of the subjects), only subjects in the VI 25 mcg and VI 50 mcg groups achieved a clinically relevant 100 mL improvement in adjusted mean change from placebo in trough FEV₁ (mean treatment differences compared with placebo of 113 mL [95% CI: 47, 180] and 118 mL [95% CI: 52, 183], respectively) (Figure 11). Looking at the higher end of the dose range, while additional efficacy was observed with 50 compared with 25 in the reversible population as noted in the paragraph above, in the non-reversible population, there appeared to be no additional benefit conferred by the 50 dose compared with the 25 dose. Looking at the lower end of the dose range, in the VI 12.5 group, subjects in the reversible population demonstrated a clinically meaningful improvement in trough FEV₁ of 162 mL [95% CI: 76, 249] on Day 29 compared with the placebo group; however, in the non-reversible population, the response (77 mL [95% CI: 11, 143]) was less than half of that observed in the reversible population.

Additionally, an analysis was conducted to examine the change from baseline in trough FEV₁ and the probability of each treatment difference (VI vs. placebo) being > 100 mL. The value of 100 mL in trough FEV₁ was included in this analysis as it had been reported as the putative minimal clinically important difference (MCID) with bronchodilator therapy in patients with COPD [Donohue, 2004]. In further support of the 25 and 50mcg doses, this analysis demonstrated that probabilities for a >100 mL increase were more than 90% with both the 25 mcg and 50 mcg doses, but much lower (<64%) for the 3, 6.25, and 12.5 mcg doses (Table 17 and Figure 12).

Table 17 Analysis of Change from Baseline in Trough FEV₁ (LOCF) on Day 29: Probability of Treatment Difference (VI versus Placebo) Being >100 mL (ITT Population) – VI Dose-Ranging Study in COPD (B2C111045)

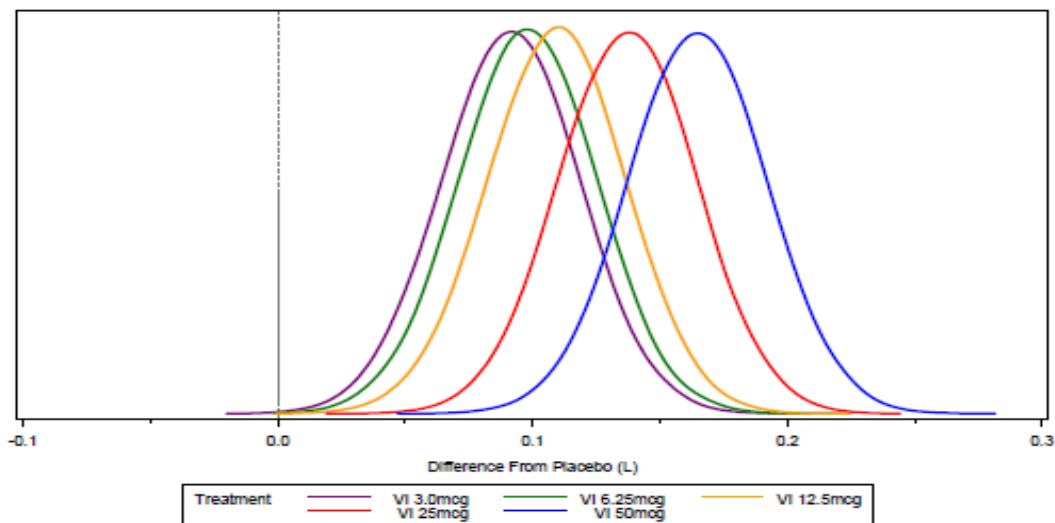
Column vs. Placebo ¹	VI				
	3 mcg N=99	6.25 mcg N=101	12.5 mcg N=101	25 mcg N=101	50 mcg N=99
n	99	100	99	99	99
Posterior Mean Difference (SD)	0.091 (0.0268)	0.098 (0.0266)	0.109 (0.0266)	0.137 (0.0266)	0.165 (0.0267)
95% Credible Interval	0.039, 0.144	0.046, 0.150	0.057, 0.161	0.085, 0.189	0.112, 0.217
Probability:					
Difference >0 L	>0.999	>0.999	>0.999	>0.999	>0.999
Difference >0.10 L	0.373	0.471	0.637	0.918	0.992
Difference >0.13 L	0.073	0.114	0.216	0.606	0.903

FEV₁=forced expiratory volume in 1 second; ITT=Intent-to-Treat; LOCF=last observation carried forward; SD=standard deviation; VI=vilanterol

1. Placebo (N=101), n=101

2. Note: Bayesian analysis using non-informative prior; analysis adjusted for baseline (pre-dose Day 1), sex, age, smoking status (at Screening), reversibility stratum, and treatment. Hanania, 2012

Figure 12 Posterior Probability Distribution of the Treatment Differences in Change from Baseline in Trough FEV₁ (L) at Day 29 (LOCF) (ITT Population): VI Dose-Ranging Study (B2C111045)



Note: Analysis adjusted for baseline (pre-dose on day 1), sex, age, smoking status (at screening), reversibility stratum and treatment.

FEV₁=forced expiratory volume in 1 second; ITT=Intent-to-Treat; LOCF=last observation carried forward; VI=vilanterol Hanania, 2012.

Consistent with the improvements in trough FEV₁, improvements with VI 25mcg were also observed across the secondary endpoints ([Table 18](#)). The adjusted mean change from baseline in weighted mean FEV₁ (0-24 hour) values on Days 1 and 28 demonstrated statistically significant ($p \leq 0.003$) differences for all five VI groups compared with the placebo group. Clinically relevant differences of ≥ 100 mL in weighted mean FEV₁ (0-24 hour) values were observed on both days at all dose levels, except for 3 mcg on Day 1. Differences of ≥ 130 mL were observed on both days only with the 25 and 50mcg doses. Log rank analyses of the time to subjects achieving a $\geq 12\%$ increase from baseline FEV₁ and time to a ≥ 100 mL increase from baseline FEV₁ over the first 4-hours post-dose on Day 1 were statistically significant for each VI dose group compared with the placebo group ($p < 0.001$) ([Table 18](#)). The median time to achieve a $\geq 12\%$ increase in FEV₁ was shortest in the 25 (18 minutes) and 50 (16 minutes) mcg groups. Similarly, the median time to achieve a ≥ 100 mL increase in FEV₁ was the shortest in the 25 and 50 mcg groups (6 minutes each) ([Table 18](#)). These results indicated that the 25 and 50 mcg doses produced the most rapid onset of effect.

Taking into account the primary and secondary endpoints, it was unclear that the differences between the VI 25 and 50 mcg doses were clinically meaningful.

Table 18 Summary of Secondary Endpoints (ITT Population): VI Dose-Ranging Study in COPD (B2C111045)

ITT Population	Placebo N=101	VI				
		3 mcg N=99	6.25 mcg N=101	12.5 mcg N=101	25 mcg N=101	50 mcg N=99
Change from Baseline in Weighted Mean FEV ₁ (0-24 Hours) – Day 1 ¹						
n	100	97	100	99	99	97
Difference vs. Placebo	---	0.057	0.104	0.120	0.150	0.174
95% CI	---	0.019, 0.095	0.066, 0.141	0.083, 0.158	0.112, 0.188	0.136, 0.212
p-value	---	0.003	<0.001	<0.001	<0.001	<0.001
Change from Baseline in Weighted Mean FEV ₁ (0-24 Hours) – Day 28 ¹						
n	84	88	91	92	92	91
Difference vs. Placebo	---	0.105	0.125	0.142	0.158	0.177
95% CI	---	0.052, 0.157	0.073, 0.177	0.090, 0.194	0.106, 0.210	0.125, 0.229
p-value	---	<0.001	<0.001	<0.001	<0.001	<0.001
Log-Rank Analysis of Time to Increase of ≥12% from Baseline FEV ₁ (0-4 hours post-dose) – Day 1 ^{2,3}						
n	101	99	101	100	100	99
No. events	27 (27)	63 (64)	73 (72)	68 (68)	81 (81)	80 (81)
No. censored	74 (73)	36 (36)	28 (28)	32 (32)	19 (19)	19 (19)
Median time (min)	NA	120	30	30	18	16
p-value	---	<0.001	<0.001	<0.001	<0.001	<0.001
Log Rank Analysis of Time to Increase of ≥100 mL from Baseline FEV ₁ (0-4 hours post-dose) – Day 1 ^{2,3}						
n	101	99	101	100	100	99
No. events	42 (42)	73 (74)	80 (79)	83 (83)	89 (89)	91 (92)
No. censored	59 (58)	26 (26)	21 (21)	17 (17)	11 (11)	8 (8)
Median time (min)	NA	32	16	16	6	6
p-value	---	<0.001	<0.001	<0.001	<0.001	<0.001

FEV₁=forced expiratory volume in 1 second; ITT=Intent-to-Treat

Analysis performed using repeated measures with covariates of baseline, sex, age, smoking status (at Screening), reversibility stratum, Day (nominal), treatment and Day by treatment and Day by baseline interactions

1. Stratified by reversibility (reversible, non-reversible)
2. If more than 50% of subjects were censored: median time to a 12% increase in FEV₁ was not defined (NA)/median time to a 100 mL increase in FEV₁ was not defined (NA)

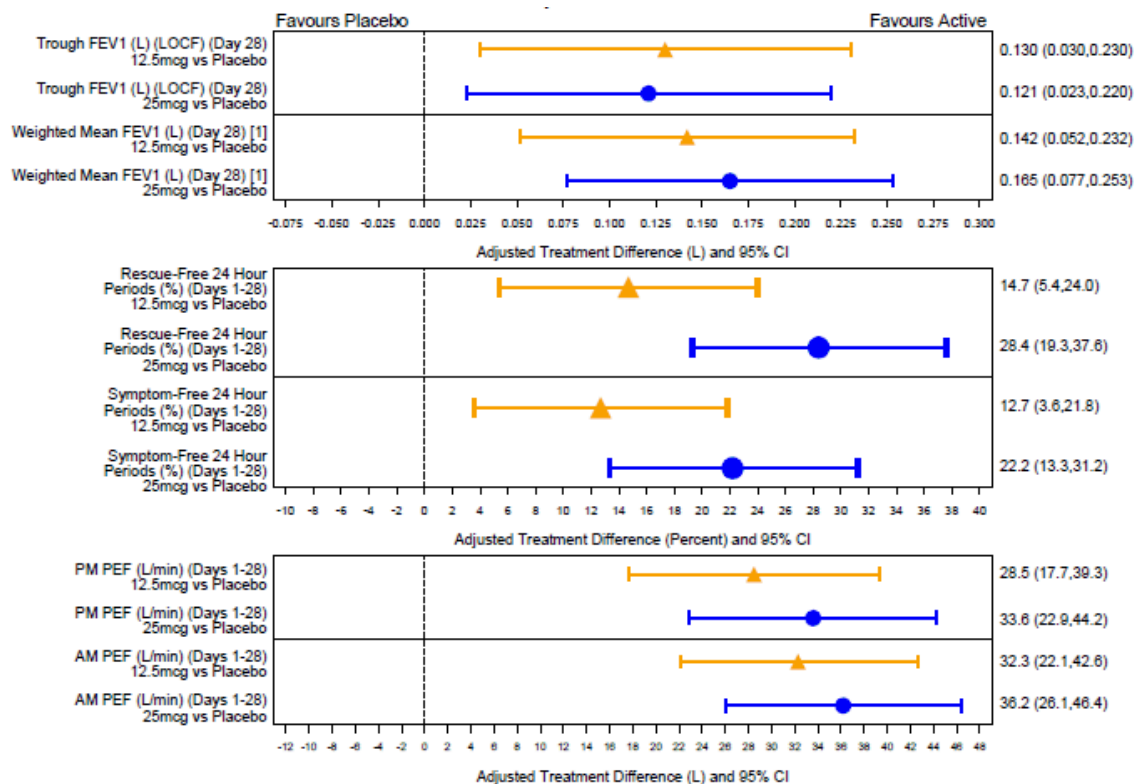
Hanania, 2012

Consistent with the improvements in the primary and secondary endpoints, improvements with VI 25mcg were also observed across the other efficacy parameters including serial FEV₁ on Days 1 and 28, AM and PM PEF and percentage of symptom- and rescue-free periods. Most of the endpoints favored the 25 mcg dose over the 12.5 mcg dose.

These data from the dose-ranging study of VI in subjects with COPD (B2C111045) were supported by dose-finding data with VI in subjects with asthma (B2C109575), from which a dose of 25 mcg was also identified as the appropriate dose for use in the treatment of asthma. Study B2C109575, in subjects with asthma receiving concomitant ICS, demonstrated that 25 mcg was the appropriate VI dose based on primary and secondary endpoints as well as the safety profile. Neither the 3 nor the 6.25 mcg doses were significantly different from placebo for the primary endpoint of mean change from baseline at Day 28 in trough FEV₁. Although once-daily treatment with VI 12.5, 25 and 50 resulted in a similar level of improvement in the primary endpoint of trough FEV₁ that was also statistically significantly greater than that observed with placebo, data for the secondary symptomatic endpoints of rescue-free and symptom-free 24-hour periods showed nearly double the effect for VI 25 compared with VI 12.5 (Figure 13; lower doses

are not shown as the results were not significantly different from placebo). Additionally, fewer than 50% of subjects treated with the 12.5 mcg dose showed an improvement from baseline in FEV₁ of at least 12% and 200 mL (a predefined improvement that is generally accepted to represent reversibility to bronchodilators [GINA, 2011]) at any timepoint across a 24-hour period at Day 28 compared with 47% to 71% at any timepoint for 25 mcg, supporting the use of a dose of VI of at least 25 mcg.

Figure 13 Primary and Secondary Endpoints – Comparison of VI 25 and VI 12.5 with Placebo (ITT Population): VI Dose-Ranging Study in Asthma (B2C109575)



AM=morning; FEV₁=forced expiratory volume in 1 second; FF=fluticasone furoate; ITT=Intent-to-Treat; ; PEF=peak expiratory flow; PM=evening; VI=vilanterol

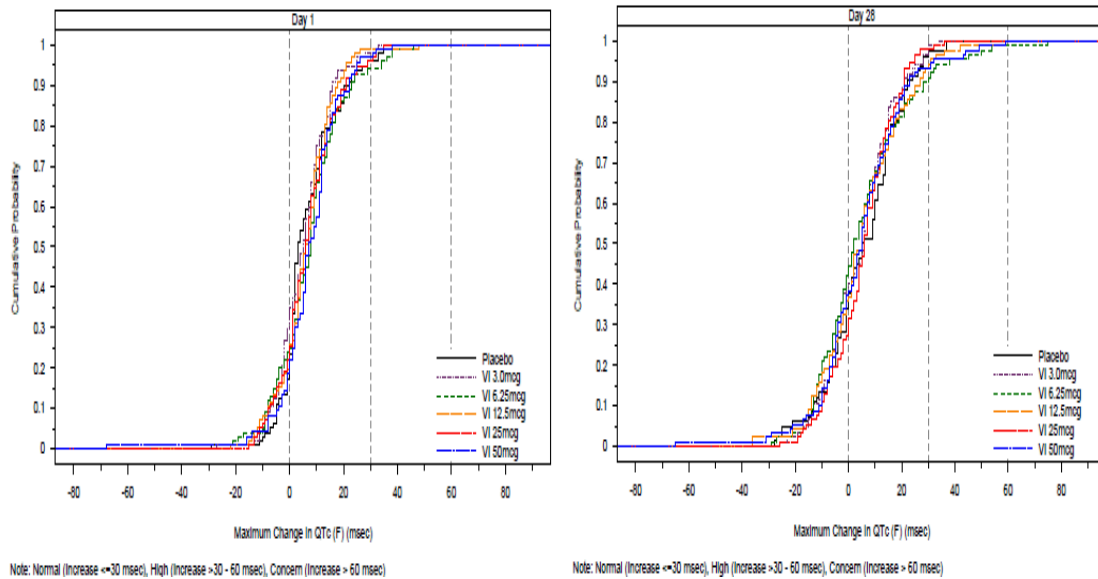
Orange = VI 12.5mcg vs Placebo; Blue = VI 25 mcg vs Placebo

In both Phase IIb, dose-ranging studies, all doses of VI tested were well-tolerated with a similar safety profile to placebo. In both the COPD (B2C111045) and asthma (B2C109575) studies, the overall incidence of AEs was similar across the VI treatment groups and was comparable with placebo. Specifically, there was no dose-related increase in the frequency of commonly reported AEs. Any changes in blood potassium or glucose levels were similar to placebo and there were no clinically relevant changes in pulse rate or QTc(F) duration in any treatment group.

In the B2C111045 study, mean maximum changes from baseline within the first four hours after dosing (i.e., 0-4 hour) QTc(F) intervals were small (≤ 8 msec on Day 1, ≤ 6

msec on Day 28) and comparable across the active treatment groups and placebo group (Figure 14).

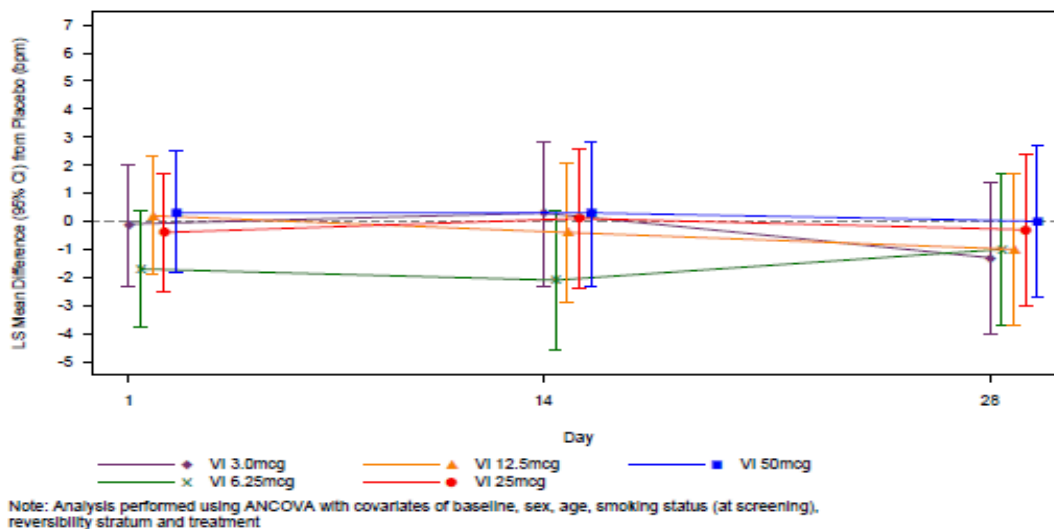
Figure 14 Empirical Distribution Function for Maximum Change from Baseline Post-Dose QTc (F) (msec): Days 1 and 28 (ITT Population) – VI Dose-Ranging Study in COPD (B2C111045)



ITT=Intent-to-Treat; VI=vilanterol

In addition, in the B2C111045 study, the adjusted mean changes from baseline in maximum pulse rates (0-4 h) on Days 1, 14 and 28 were also small and similar across the VI treatment groups (0.7 to 3.6 bpm) and comparable with the placebo group (2.3 to 3.3 bpm). Adjusted mean treatment differences between the five doses of VI and placebo ranged from -1.7 to 0.3 bpm on Day 1, -2.1 to 0.3 bpm on Day 14, and -1.3 to 0.0 bpm on Day 28; all of the confidence intervals included zero and none of the confidence intervals crossed the pre-defined 6 bpm threshold (Figure 15).

Figure 15 Adjusted Treatment Differences from Placebo in Change from Baseline 0-4 Hour Maximum Pulse Rate (bpm) (ITT Population): VI Dose-Ranging Study in COPD (B2C111045)



bpm=beats per minute; ITT=Intent-to-Treat; VI=vilanterol

Note: Analysis performed using ANCOVA with covariates of baseline, sex, age, smoking status (at screening), reversibility stratum and treatment

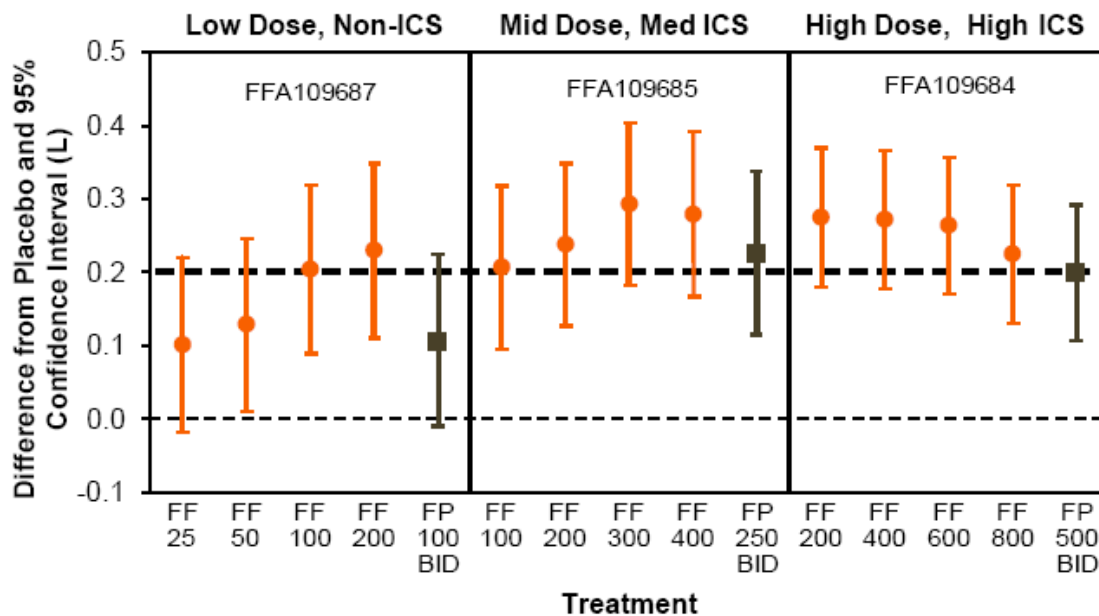
Based upon the results of the dose-ranging study B2C111045 in subjects with COPD and support from the dose-ranging study B2C109575 in subjects with asthma, 25 mcg QD was selected as the minimally effective dose of VI for evaluation in combination with FF for the overall population of subjects with COPD in the Phase III COPD Clinical Development Program.

7.1.2. Fluticasone Furoate Dose Selection

The effects of ICS in COPD patients cannot be assessed reliably in short-term studies using lung function parameters as an endpoint [Donohue, 2004]. Therefore, the results of three, Phase IIb, dose-ranging studies with FF in subjects with persistent asthma (including subjects symptomatic on short-acting beta₂-agonists [FFA109687] and medium to high doses of ICS [FFA109685 and FFA109684]) that tested a range of doses of FF (from 25 mcg to 800 mcg once daily, dosed in the evening) were used to guide the selection of doses of FF to be evaluated in the FF/VI combination in the Phase III program in subjects with COPD.

Results for different FF doses on trough FEV₁ from the three, Phase IIb, randomized, dose-ranging studies in subjects with varying severity of persistent asthma showed substantial efficacy with FF 100 and near maximal efficacy with FF 200 (Figure 16). Although efficacy was demonstrated with FF 50, the LS mean difference compared with placebo was only 129 mL.

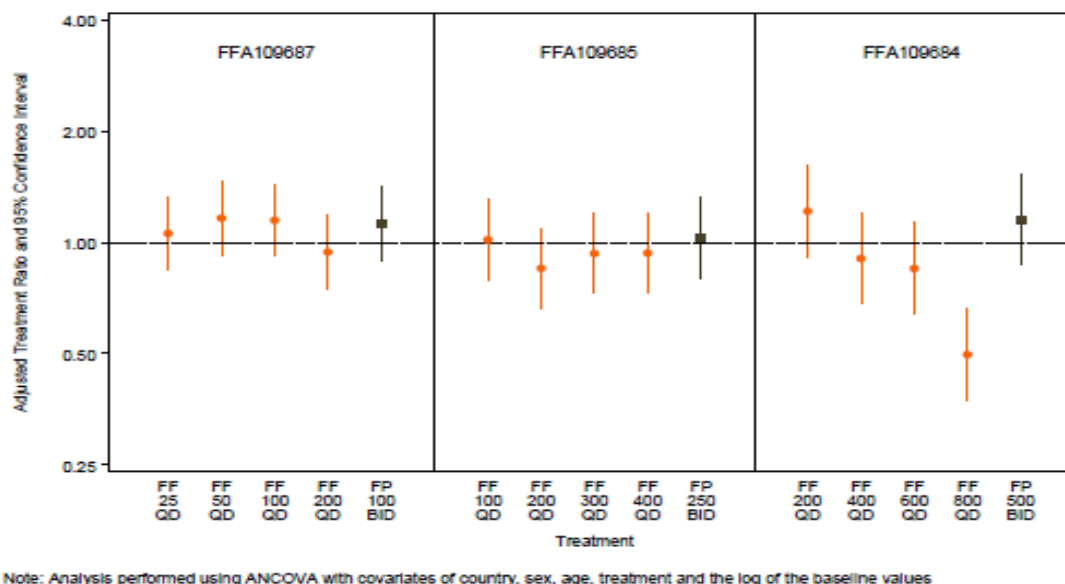
Figure 16 Adjusted Treatment Differences from Placebo for Change from Baseline in Trough FEV₁ (L) (LOCF) at Week 8 (ITT Population): FF Dose-Ranging Studies in Asthma (FFA109684, FFA109685 and FFA109687)



BID=twice daily; FEV₁=forced expiratory volume in 1 second; FF=fluticasone furoate; FP=fluticasone propionate; ICS=inhaled corticosteroid; ITT=Intent-to-Treat; LOCF=Last Observation Carried Forward; VI=vilanterol
 Note: Analysis performed using ANCOVA with covariates of baseline, country, sex, age, and treatment
 Bateman, 2012; Adapted from Bleeker, 2012; Busse, 2012

In all Phase IIb dose-ranging studies of FF in subjects with asthma, FF was well tolerated at doses up to 600 mcg, although at 800 mcg significant urinary cortisol suppression was observed (Figure 17). In the FFA109684 study (high-dose study), the 24-hour urinary cortisol excretion ratios (Week 8/Baseline) for the FF groups relative to placebo decreased as the dose of FF increased, 1.22, 0.91, 0.85, and 0.50 for the FF 200, 400, 600, and 800mcg QD PM groups, respectively. However, statistical analysis showed that across all dose groups of FF and FP 500mcg BID, only the FF 800mcg QD PM dose (0.50) was statistically ($p<0.001$) and clinically significantly different from placebo. In the FFA109685 (mid-dose study) and FFA109687 (low-dose study) studies, the 24-hour urinary cortisol excretion ratios to placebo for the FF groups (FFA109685: 0.85 to 1.02; FFA109687: 0.94 to 1.17) were similar, with no evidence of a dose response. The 24-hour urinary cortisol excretion ratios to placebo for all dosage groups of FF and FP 250mcg BID (FFA109685) and FP 100mcg BID (FFA109687) were not statistically or clinically significant.

Figure 17 Adjusted Treatment Ratios for 24-Hour Urinary Cortisol Excretion (Week 8/Baseline) (Urinary Cortisol Population): FF Dose-Ranging Studies in Asthma (FFA109684, FFA109685 and FFA109687)



BID=twice-daily; FF=fluticasone furoate; FP=fluticasone propionate; QD=once-daily

As subjects with COPD generally have a greater degree of airflow obstruction, a lesser degree of reversibility to inhaled bronchodilators, and are less responsive to the effects of ICS on lung function, it was considered that the FF 50 dose would constitute the less effective/no effect dose in subjects with COPD. Therefore, three doses of FF (50, 100 and 200 mcg) in combination with VI were included in the COPD Phase III Clinical Development Program, to define the appropriate dose(s) of FF for combination with VI in COPD patients.

7.1.3. Dose Regimen: Once-Daily Dosing

The dosing interval (once- versus twice-daily) of VI and FF was evaluated in two separate studies, HZA113310 and FFA112202, respectively, in subjects with asthma (Table 16).

7.1.3.1. Once-Daily Dosing of Vilanterol

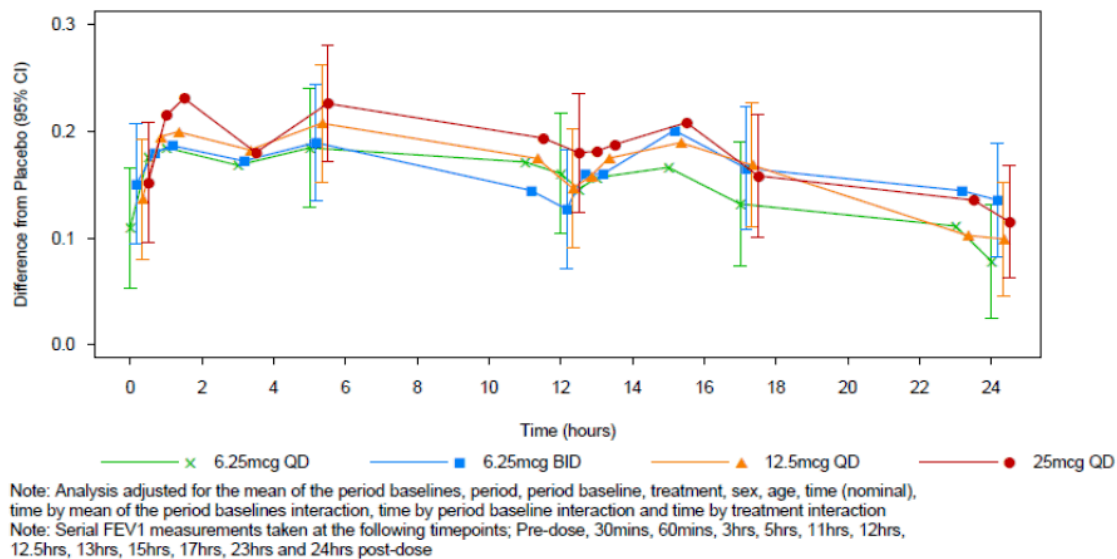
The dosing interval for VI was investigated in 75 subjects with asthma in Study HZA113310, which was designed to compare once- and twice-daily dosing for 7 days, to confirm VI is an intrinsic once-daily LABA. HZA113310 was a double-blind, placebo-controlled, crossover study that evaluated four doses of VI: 6.25 mcg once daily, 6.25 mcg twice daily, 12.5 mcg once daily, and 25 mcg once daily. As agreed with the FDA, this study was conducted in subjects with asthma as opposed to subjects with COPD, as asthma was deemed the most broncho-responsive population. The primary comparison of interest was VI 12.5 mcg once daily versus VI 6.25 mcg twice daily.

The dose of VI selected for this comparison (12.5 mcg once daily) was less than the 25 mcg dose selected for progression to Phase III in order to assure that the assessment was not made on the upper part of the dose-response curve, which could lead one to erroneously conclude that optimal dosing is once daily.

After 6 days of dosing the point estimate for trough FEV₁ for 6.25 BID and 12.5 QD only differed by 15 mL (151 and 136 mL, respectively) (Figure 18). Weighted mean FEV₁ (0-24 hour) on Day 7, which was the secondary endpoint, was also comparable between these 2 dosing regimens at 166 and 168 mL, respectively (Figure 18). Finally, at the end of 24-hour dosing, the trough FEV₁ values on day 7, the primary endpoint, were 140 and 102 mL, respectively (Figure 18). Thus, based on these 24-hour profiles as well as the small differences in FEV₁ when the same total daily dose is administered either once or twice daily, the results confirmed that VI is a once-daily LABA.

The results of this study, which studied bronchodilatation in subjects with asthma, can be extrapolated to the COPD population, as there is no reason to believe that the dosing interval of a bronchodilator should differ between subjects with asthma and subjects with COPD.

Figure 18 Adjusted Treatment Differences from Placebo in Change from Baseline FEV₁ (L) Over Time on Day 7 (ITT Population): Supporting VI Asthma Study (HZA113310)



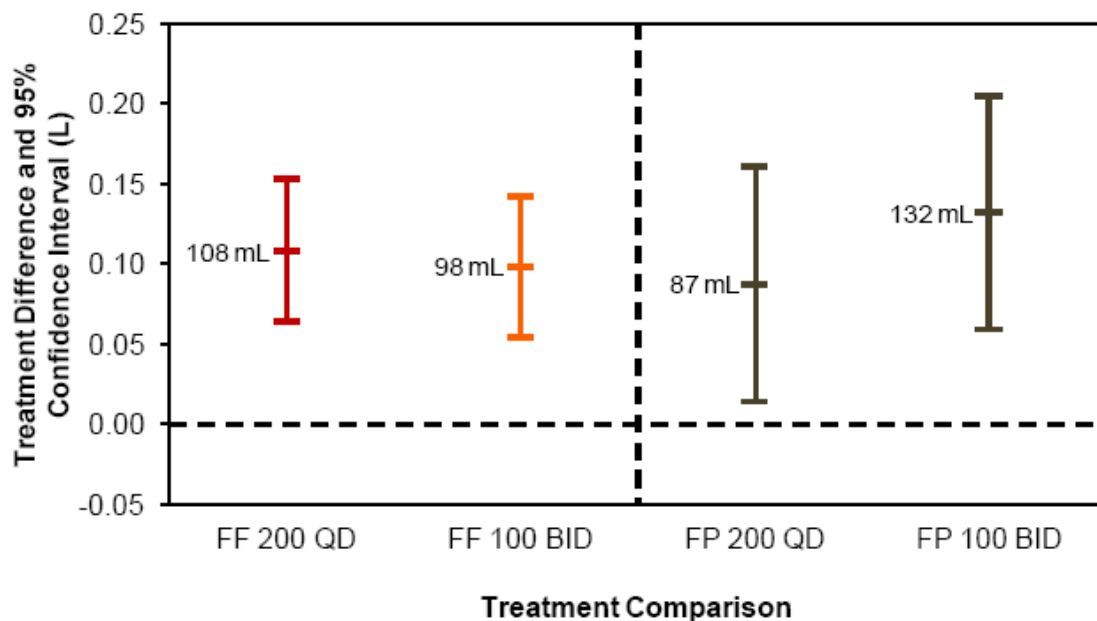
BID=twice-daily; CI=confidence interval; FEV₁=forced expiratory volume in 1 second; ITT=Intent-to-Treat; QD=once-daily; VI=vilanterol
 Adapted from [Sterling, 2012](#)

7.1.3.2. Once-Daily Dosing of Fluticasone Furoate

Study FFA112202 (performed in subjects with asthma) was designed to evaluate the comparability of once- and twice-daily dosing of FF (to confirm FF is an intrinsic once-daily ICS). Comparison of FP 100 BID with FP 200 QD was included in the study to demonstrate that efficacy of a true twice daily corticosteroid is greater than the same nominal dose administered once daily.

Results of study FFA112202 demonstrated that FF 200 once daily was comparable to FF 100 twice daily, with a treatment difference of 11 mL (95% CI: -35, 56), indicating no advantage for twice daily over once-daily dosing for the same total daily dose ([Figure 19](#)). This study had sufficient sensitivity to detect a difference between once- and twice-daily dosing, since a numerically superior improvement in FEV₁ compared with placebo was observed for the true twice-daily comparator, FP, at doses of 100 mcg twice daily compared with 200 mcg once daily. Based on these findings, FF was concluded to be a once-daily ICS.

Figure 19 Adjusted Treatment Differences in Trough FEV₁ (L) at Day 28 (ITT Population): Supporting FF Asthma Study (FFA112202)



BID=twice-daily; FEV₁=forced expiratory volume in 1 second; FF=fluticasone furoate; FP=fluticasone propionate; ITT=Intent-to-Treat; QD=once-daily
[\[Woodcock, 2011\]](#)

7.2. COPD Clinical Development Program Overview

COPD is associated with progressive airflow limitation and recurring exacerbations, both leading to symptomatic and functional limitation and increased morbidity [[GOLD](#), 2011]. As noted in the FDA Draft Guidance for Industry – Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment [[FDA](#), 2007], improvement in airflow obstruction has been the main therapeutic strategy in COPD drug development and drugs that improve airflow obstruction provide benefit through relief of reversible airflow obstruction that is an important, though not universal, feature of COPD. The guidance also discusses that COPD exacerbations can be life-threatening and have been linked to co-morbid conditions and exacerbations are believed to potentially contribute to further permanent decrements in lung function. Therefore, therapeutic drugs that modify the severity or duration of COPD exacerbations or that prevent COPD exacerbations will provide meaningful benefit to patients. Also, the FDA Draft Guidance notes that drugs

that reduce chronic cough, excess sputum production, dyspnea, or other debilitating symptoms of COPD may provide meaningful benefit to patients [FDA, 2007].

The COPD Clinical Development Program for the FF/VI combination was designed to demonstrate efficacy of FF/VI in terms of lung function parameters as well as reducing COPD exacerbations. Since FF/VI contains two components, an ICS (FF) and a LABA (VI), the FF/VI COPD Clinical Development Program was also designed to assess the efficacy of the combination and the contribution of each component in the combination studies in line with FDA 21 CFR 300.50, Combination Rule [FDA, 2012].

As noted in the FDA Draft COPD Guidance, different targets in COPD therapy can involve different endpoints, study designs, and study duration, and can likely lead to differing explicit indications. Therefore, it is important for sponsors to develop their drugs with the appropriate drug action or actions in mind [FDA, 2007]. Since FF/VI is a combination therapy, multiple endpoints were employed in the FF/VI COPD Clinical Development Program to evaluate the multiple drug actions of this class of medication. Consistent with the FDA Draft COPD guidance, for the indication for maintenance treatment of airflow obstruction, two co-primary endpoints were defined: 1) weighted mean FEV₁, to evaluate the contribution of VI (the LABA component) to the combination, and 2) pre-dose (trough) FEV₁, to evaluate the 24-hour duration of VI and the contribution of FF (the ICS) to the combination. For the indication to reduce exacerbations of COPD in patients with a history of exacerbations, the primary endpoint was the annual rate of moderate and severe COPD exacerbations. All efficacy endpoints were those recommended and accepted in international COPD treatment guidelines [GOLD, 2011] and in regulatory guidance.

As discussed in the Section 1, GSK conducted a large Clinical Development Program in subjects with COPD (Figure 1), as well as a large Clinical Development Program in subjects with asthma (Figure 1); the latter provides supportive information. A total of 17,230 subjects were treated in the COPD and Asthma Clinical Development Programs; of these subjects, 6,461 were randomized to FF/VI. The Clinical Development Program to support the approval of FF/VI in subjects with COPD consists of 11 studies in a total of 7,851 adult subjects (40 years of age and older) with COPD; nine, Phase IIa-IIIb studies with FF/VI in 7,181 subjects (Table 19), one, Phase IIb, dose-ranging study of VI in 602 subjects (B2C111045; Table 16) and one, two-week, Phase II safety and tolerability study in 68 subjects that utilized an earlier formulation of vilanterol (H-salt versus M-salt) of VI (B2C108562). Since the B2C108562 study utilized an earlier formulation of vilanterol, this study is not discussed in this Briefing Document. Of the 7,181 subjects in studies with FF/VI, 2,034 subjects were treated with FF/VI 100/25. The COPD program was conducted at investigative sites in North, Central and South America, Europe, South Africa, and Asia Pacific (Table 19).

Table 19 summarizes the nine clinical studies of FF/VI conducted in subjects with COPD. Four of these studies were considered primary studies in the NDA and form the basis of the Clinical Trials section of the proposed BREO ELLIPTA *Prescribing Information*:

- Two, 6-month, Phase IIIa, efficacy, and safety studies (HZC112206 and HZC112207) evaluated three strengths of FF/VI Inhalation Powder (50/25, [HZC112206 only] 100/25 [both studies] and 200/25 mcg [HZC112207 only] once daily) and the individual components at equivalent doses (except for FF 50 mcg) versus placebo. These studies were designed to evaluate the incremental benefit of VI (the LABA) and FF (the ICS) in the combination in treating the airflow obstruction in subjects with COPD ([Table 19](#)).
- Two, 1-year, replicate, Phase IIIa efficacy and safety studies (HZC102970 and HZC102871) evaluated three strengths of FF/VI Inhalation Powder (50/25, 100/25 and 200/25 mcg once daily) versus VI 25 alone. These studies were designed to evaluate the benefit of FF (the ICS) in the combination treatment in decreasing the annual rate of moderate/severe exacerbations in subjects with COPD and to provide long-term (i.e., at least 1-year) safety data with FF/VI ([Table 19](#)).

Six of the studies in the COPD Clinical Development Program are considered supportive studies:

- One, 1-month, Phase IIIa, crossover study (HZC110946) to evaluate the safety and efficacy of FF/VI Inhalation Powder (50/25, 100/25 and 200/25 mcg once daily) compared with placebo. The primary objective was to evaluate the 24-hour spirometric effect (FEV₁) of FF/VI Inhalation Powder at the end of the treatment period in subjects with COPD ([Table 19](#)).
- One 1 month, Phase IIa study (HZC111348) to evaluate the safety and tolerability of a single strength of FF/VI Inhalation Powder (400/25 mcg) compared with placebo administered once-daily in subjects with COPD ([Table 19](#)).

Note: Since this study evaluated a dose of FF/VI (400/25 mcg QD) that is not intended for registration, with the exception of the integrated safety results, this study and the efficacy results from this study will not be discussed further in this Briefing Document.

- Three, 3-month, Phase IIIb studies (HZC112352, HZC113107 and HZC113109) to evaluate the 24-hour spirometric effect (FEV₁) of FF/VI (100/25 mcg) once daily compared with a currently available ICS/LABA combination (fluticasone propionate/salmeterol: 500/50 mcg twice daily in HZC113107 and 250/50 mcg twice daily in HZC112352 and HZC113109) in subjects with COPD ([Table 19](#)).
- One large, 1-month, Phase IIb, dose-ranging study to evaluate the efficacy and safety of repeat doses of VI across a range of five doses from 3 mcg to 50 mcg once daily in subjects with COPD (B2C111045) ([Table 16](#)).

One other study (B2C108562) was conducted to evaluate the safety, tolerability, PD and PK of the H salt (an earlier formulation) of VI (100 and 400 mcg administered once-daily via DISKUS) compared with salmeterol (50 mcg administered twice-daily via DISKUS) and matched placebo administered for 15 days in a 68 subjects with moderate COPD (GOLD stage II) ([Figure 1](#)). These data were gathered to support future studies with VI formulations in a broader COPD population. Since this study used a formulation of vilanterol (H salt) that is different from the formulation of VI (M salt) used in the FF/VI combination, results of this study are not discussed in this Briefing Document.

Table 19 FF/VI Clinical Development Program for COPD: Primary and Supporting Studies

Study Year Completed	Study Design	Key Inclusion Criteria	Treatment (mcg) ¹	N (ITT)	Primary Endpoint(s)
PRIMARY COPD STUDIES					
<i>Efficacy and Safety of FF/VI; Contribution of VI to FF/VI</i>					
HZC112206 ² 2011	R, DB, PG, PC 6 Months	<ul style="list-style-type: none"> Post bronchodilator FEV₁/FVC ratio ≤0.70 Post bronchodilator FEV₁ ≤70% predicted³ mMRC dyspnea score ≥2 	FF/VI 50/25 FF/VI 100/25 FF 100 VI 25 Placebo	206 206 206 205 207 Total = 1030	<ul style="list-style-type: none"> Weighted mean FEV₁ 0-4hours post-dose at Day 168 Change from baseline trough FEV₁ at Day 169
HZC112207 ⁴ 2011	R, DB, PG, PC 6 Months	<ul style="list-style-type: none"> Post bronchodilator FEV₁/FVC ratio ≤0.70 Post bronchodilator FEV₁ ≤70% predicted³ mMRC dyspnea score ≥2 	FF/VI 100/25 FF/VI 200/25 FF 100 FF 200 VI 25 Placebo	204 205 204 203 203 205 Total = 1224	<ul style="list-style-type: none"> Weighted mean FEV₁ 0-4hours post-dose at Day 168 Change from baseline trough FEV₁ at Day 169
<i>Efficacy and Safety of FF/VI; Contribution of FF to FF/VI</i>					
HZC102970 ⁵ 2011	R, DB, PG, AC 1 Year	<ul style="list-style-type: none"> Post bronchodilator FEV₁/FVC ratio ≤0.70 Post bronchodilator FEV₁ ≤70% predicted³ ≥1 moderate/severe exacerbation⁶ in last 12 months prior to Screening 	FF/VI 50/25 FF/VI 100/25 FF/VI 200/25 VI 25	412 403 409 409 Total = 1633	Annual rate of moderate and severe COPD exacerbations ⁷
HZC102871 ⁷ 2011	R, DB, PG, AC 1 Year	<ul style="list-style-type: none"> Post bronchodilator FEV₁/FVC ratio ≤0.70 Post bronchodilator FEV₁ ≤70% predicted³ ≥1 moderate/severe exacerbation⁶ in last 12 months prior to Screening 	FF/VI 50/25 FF/VI 100/25 FF/VI 200/25 VI 25	408 403 402 409 Total = 1622	Annual rate of moderate and severe COPD exacerbations ⁷

SUPPORTING COPD STUDIES					
<i>Efficacy and Safety of FF/VI</i>					
HZC110946 ⁸ 2010	R, DB, IB, 3-way CO 1 Month per period	<ul style="list-style-type: none"> Post bronchodilator FEV₁/FVC ratio ≤0.70 Post bronchodilator FEV₁ ≤70% predicted³ mMRC dyspnea score ≥2 	FF/VI 50/25 FF/VI 100/25 FF/VI 200/25 Placebo	34 33 31 51 Total = 54	Time-adjusted AUC (i.e., weighted mean) for 0-24 hour serial FEV ₁ at the end of each 28-day treatment period
<i>Comparison of Efficacy and Safety of FF/VI with Marketed ICS/LABA Combination (FP/SALM)</i>					
HZC113107 ⁹ 2011	R, DB, DD, PG 3 Months	<ul style="list-style-type: none"> Post bronchodilator FEV₁/FVC ratio ≤0.70 Post bronchodilator FEV₁ ≤70% predicted³ Hospitalized or treated with OCS or antibiotics for COPD exacerbation within 3 years prior to Screening 	FF/VI 100/25 FP/SAL 500/50 BID	266 262 Total = 528	Change from baseline trough in 24-hour weighted-mean serial FEV ₁ on Day 84
HZC113109 ¹⁰ 2011	R, DB, DD, PG 3 Months	<ul style="list-style-type: none"> Post bronchodilator FEV₁/FVC ratio ≤0.70 Post bronchodilator FEV₁ ≤70% predicted³ 	FF/VI 100/25 FP/SAL 250/50 BID	260 259 Total = 519	Change from baseline trough in 24-hour weighted-mean serial FEV ₁ on Day 84
HZC112352 ¹¹ 2012	R, DB, DD, PG 3 Months	<ul style="list-style-type: none"> Post bronchodilator FEV₁/FVC ratio ≤0.70 Post bronchodilator FEV₁ ≤70% predicted³ 	FF/VI 100/25 FP/SAL 250/50 BID	259 252 Total = 511	Change from baseline trough in 24-hour weighted-mean serial FEV ₁ on Day 84
<i>Supportive Safety Data for FF/VI</i>					
HZC111348 ¹² 2008	R, DB, PG, PC 1 Month	<ul style="list-style-type: none"> Post bronchodilator FEV₁/FVC ratio ≤0.70 Post bronchodilator FEV₁ ≥40% and ≤80% 	FF/VI 400/25 Placebo	40 20 Total = 60	<ul style="list-style-type: none"> Change from baseline in weighted mean heart rate 0-4 hours post-dose at the end of the 28-day treatment period. Incidence of AEs throughout the study

AC=active-controlled; BID=twice daily; CO=crossover; DB=double-blind; DD=double-dummy; FEV₁=forced expiratory volume in 1 second; FF=fluticasone furoate; FP=fluticasone propionate; FVC=forced vital capacity; IB=incomplete block; ITT=Intent-to-Treat population; mMRC=Modified Research Council Dyspnea Scale; OCS=oral corticosteroids; PC=placebo-controlled; PG=parallel-group; QD=once daily; R=randomized; SAL=salmeterol; VI=vilanterol

1. All FF/VI treatments administered once-daily in the morning via DPI (ELLIPTA)
2. Sites who randomized subjects: 221 centers in 9 countries: Chile, Estonia, Germany, Japan, Korea, Philippines, Poland, Russian Federation and the US
3. FEV₁ percent predicted calculated using NHANES III reference equations [Hankinson, 1999]
4. Sites who randomized subjects: 138 centers in 8 countries: Czech Republic, Germany, Japan, Poland, Romania, Russian Federation, Ukraine and the US
5. Sites who randomized subjects: 167 centers in 15 countries: Argentina, Australia, Canada, Chile, Estonia, Germany, Italy, Mexico, Netherlands, Peru, Philippines, South Africa, Sweden, UK, and the US
6. Moderate: Worsening symptoms of COPD that required treatment with oral corticosteroids and/or antibiotics;
Severe: Worsening symptoms of COPD that required an in-patient hospitalization

7. Sites who randomized subjects: 183 centers in 15 countries: Argentina, Australia, Canada, Chile, Denmark, Germany, Italy, Mexico, Netherlands, Peru, South Africa, Spain, Sweden, UK, and the US
8. Sites who randomized subjects: 8 centers in the US
9. Sites who randomized subjects: 61 centers in 9 countries: Belgium, France, Germany, Italy, Philippines, Poland, Russia, Spain, and Ukraine
10. Sites who randomized subjects: 51 centers in 6 countries: Czech Republic, Germany, Poland, Romania, Russia, and the US
11. Sites who randomized subjects: 48 centers in 5 countries: Ukraine, South Africa, Spain, Italy, and the US
12. Sites who randomized subjects: 9 centers in 2 countries: Norway and Sweden

There are several aspects of the COPD Phase III Clinical Development Program on which GSK would like to elaborate, particularly with respect to the four primary COPD studies.

In the 1-year exacerbation studies (HZA102970 and HZA102871), three strengths of FF/VI (50/25, 100/25 and 200/25 QD) were evaluated in each of the studies, while, in the 6-month, lung function studies (HZA112206 and HZA112207), only the FF/VI 100/25 mcg QD strength was replicated. In the latter studies, the contribution of VI 25 was assessed by comparing the relevant combination strengths with FF 100 and FF 200; as FF 50 was considered to be a no-effect/low effect dose, it was felt that the contribution of VI did not need to be assessed with this dose. Hence, there was no FF 50 monotherapy treatment group in the HZA112206 study. The rationale for this approach is that the FF/VI 50/25 QD dose was considered to be a less effective/no effect dose. Also, the FF/VI 200/25 mcg QD strength was not replicated, since was expected to unlikely offer incremental efficacy.

While each of the 6-month lung function studies included a placebo arm, and the exacerbation studies were 1 year in duration and conducted in subjects with a prior history of COPD exacerbations, inclusion of a placebo arm was not felt to be clinically acceptable. The 1-year exacerbation studies provided 1-year safety data for the FF/VI combination (50/25, 100/25 and 200/25 strengths) and VI 25. However, since all treatment arms contained VI 25 and there was no placebo arm and/or FF monotherapy arms, the design of these studies, limits the assessment of the long-term (i.e., greater than 6 months) comparative safety of VI.

In addition to the large clinical development program in subjects with COPD, an extensive clinical development program in subjects with asthma (18 completed Phase IIb/Phase III studies) has been conducted and supports the safety profile of FF/VI (Figure 1). Of the 18 studies, nine studies are considered supportive of the product's development program for COPD. Five of the nine studies evaluated the efficacy and safety of FF as a monotherapy, two of the studies evaluated the efficacy and safety of VI on a background of marketed ICS, and one of the studies compared the safety and efficacy of FF/VI with FF 100 and placebo. The relevance of six of the asthma studies, with respect to establishing the efficacy and safety of the FF and VI monotherapies and in informing the doses selected to carry forward in the FF/VI combination in the Phase III program in subjects with COPD, are described in 7.1. Additionally, one clinical pharmacology study in subjects with asthma investigated morning versus evening dosing with FF/VI. Also, an HPA-axis study conducted in subjects with asthma (HZA105861)

(Section 7.5.5.2) and an ophthalmic safety study in subjects with asthma (HZA106839) (Section 7.5.5.3) are considered supportive for the COPD NDA.

There are a number of differences between the FF/VI COPD Clinical Development Program and the COPD Clinical Development Programs conducted for the currently marketed ICS/LABA treatments, particularly ADVAIR DISKUS, which is indicated for the maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema, and to reduce exacerbations of COPD in patients with a history of exacerbations. In particular, the Clinical Development Programs for the currently available ICS/LABA treatments for COPD simply carried forward the combination strength(s) determined for treatment of subjects with asthma, while in the FF/VI COPD Clinical Development Program, three doses of FF (50, 100 and 200 mcg QD) in combination with VI 25 QD were evaluated across the four, Phase IIIa, primary efficacy and safety studies (HZA112206, HZA112207, HZA102871, and HZA102970), to determine the appropriate dose of FF in the combination for treatment subjects with COPD. While three doses of the ICS (FF) were evaluated in the COPD Phase III program, particularly on the corticosteroid-responsive endpoint of COPD exacerbations in the 1-year exacerbation studies HZA102970 and HZA102871, as discussed in Section 7.1.1, a single dose of VI (25 mcg QD) was evaluated, since this dose was determined to be the minimally effective dose of VI in subjects with COPD (B2C111045), as well as in subjects with asthma (B2C109575).

Also, the FF/VI COPD Clinical Development Program was larger and more multi-national than the ADVAIR DISKUS COPD Clinical Development Program. For ADVAIR DISKUS, three, 6-month, studies were considered pivotal studies to support the indication for treatment of airflow obstruction (SFCA3006 [Mahler, 2002], SFCA3007 [Hanania, 2003] and FLTA3025 [GlaxoSmithKline Document Number RM2000/00031/00 FLTA3025 GSK Clinical Study Report on file]) and two, 1-year, exacerbation studies were considered pivotal studies to support the indication to reduce exacerbations of COPD in patients with a history of COPD (SCO40043 [Ferguson, 2008] and SCO100250 [Anzueto, 2009]). In the ADVAIR DISKUS COPD Clinical Development Program, a total of 2,037 subjects were treated in the 6-month studies (356 of whom were treated with FP/SAL 250/50 BID; the dose approved for treatment of COPD in the United States), and a total of 1,579 subjects were treated in the 1-year exacerbation studies (788 of whom were treated with FP/SAL 250/50 BID). In comparison, in the FF/VI COPD Clinical Development Program, a total of 2,254 subjects were treated in the 6-month, lung function studies (410 of whom were treated with FF/VI 100/25) and a total of 3,255 subjects were treated in the 1-year exacerbation studies (806 of whom were treated with FF/VI 100/25). In addition, the ADVAIR DISKUS studies were conducted solely in the United States (6-month studies) or only in North America (1-year exacerbation studies), while the FF/VI 6-month, lung function studies (HZA112206 and HZA112207) were conducted in eight to nine countries around the world (5 of the countries were the same across the two studies, including the United States) and the FF/VI 1-year, exacerbation studies (HZA102970 and HZA102871) were each conducted in 15 countries around the world (13 of the countries were the same across the studies, including the United States) (Table 19).

7.3. Study Design, Efficacy Variables, and Statistical Methods of the Phase III COPD Efficacy Studies

This section is focused on the study design, efficacy variables and statistical methods for the four, primary COPD studies, the two, 6-month, lung function studies (HZA112206 and HZA112207) and the two, 1-year, exacerbation studies (HZA102871 and HZA102970).

7.3.1. Study Design

The four, primary, COPD studies were of similar design, i.e., prospective, double-blind, randomized, parallel-group, multicenter studies that evaluated a range of strengths of FF/VI (50/25, 100/25 and 200/25mcg QD) in subjects with moderate to severe COPD (Table 19). The treatment duration was 6 months in the HZA112206 and HZA112207 studies and 1 year in the HZA102871 and HZA102970 studies. All strengths of FF/VI combination (and FF or VI individually) were administered once-daily in the morning via a DPI (ELLIPTA). The rationale for dose selection for the phase III studies is provided in Section 7.1 of this document.

Overall, for all four, primary, COPD studies (6-month, lung function studies: HZA112206 and HZA112207; 1-year, exacerbation studies: HZA102970 and HZA102871) the inclusion/exclusion criteria were defined to select patients broadly representative of the spectrum of the COPD population and were consistent with accepted clinical practice parameters and criteria set by the GOLD consensus panel. Thus, the Phase III clinical studies were conducted in the patient population in whom therapy would be appropriate [GOLD, 2011]. All four, primary studies included male and female subjects ≥ 40 years of age with a clinical history of COPD (in accordance with the definition of the American Thoracic Society/European Respiratory Society [Celli, 2004]. At the time of Screening, subjects were required to have a current or prior history of at least 10 pack-years of cigarette smoking (a major risk factor for COPD) and the presence of airflow limitation, defined by a measured post-albuterol FEV₁/forced vital capacity (FVC) ratio of ≤ 0.70 , which is in accordance with the level of airflow limitation stated in the GOLD guidelines for COPD [GOLD, 2011]. A measured post-albuterol FEV₁ of $\leq 70\%$ of predicted normal values (calculated using NHANES III reference equations [Hankinson, 1999]) was also required, ensuring that all subjects had at least moderate airflow limitation (GOLD 2). In accordance with GOLD recommendations, the degree of airflow reversibility was not an inclusion criterion.

In the two, 1-year, exacerbation studies (HZA102871 and HZA102970), subjects were also required to have had an exacerbation history of ≥ 1 moderate (defined as worsening symptoms of COPD that required treatment with oral corticosteroids and/or antibiotics) and/or severe COPD exacerbation (in-patient hospitalization) in the 12 months prior to Screening. In the two, 6-month, lung function studies (HZA112206 and HZA112207), subjects were excluded from participating in the study if they had been hospitalized due to poorly controlled COPD within 12 weeks of Screening and/or had poorly controlled COPD (defined as acute worsening of COPD that was managed by the subject with corticosteroids or antibiotics or that required treatment prescribed by a physician) within 6 weeks prior to Screening and/or had experienced a lower respiratory tract infection that

required the use of antibiotics within 6 weeks prior to Screening. Subjects in the HZC112206 and HZC112207 studies were also required to be symptomatic at screening and have a Modified Medical Research Council (mMRC) dyspnea score ≥ 2 at the screening visit.

The 6-month, lung function studies (HZC112206 and HZC112207) were designed to evaluate the efficacy and safety of three strengths of FF/VI (50/25, 100/25 and 200/25mcg QD) and the individual components versus placebo. These studies were essentially replicate studies, with the only difference between them being that the HZC112206 study included a lower strength (50/25mcg) of FF/VI Inhalation Powder, while the HZC112207 study included a higher strength (200/25 mcg) of FF/VI Inhalation Powder and the corresponding strength of FF (200mcg) as a monotherapy arm. The HZC112206 and HZC112207 studies also provided safety (including 24-hour urinary cortisol, 24-hour Holter monitoring), and PD and PK data over a 6-month treatment period. After an initial Screening Visit, eligible subjects entered a 2-week, single-blind (placebo) Run-In period to obtain baseline assessments of albuterol use and COPD symptoms and to evaluate the subjects' adherence with study treatment and procedures, diary card completion and assessment of disease stability. After completion of the Run-In period, subjects who remained eligible entered a 24-week, double-blind treatment period with a 7-day follow-up period. The use of a placebo control for up to 6 months in this study population was considered ethically acceptable given the provision of rescue medication (albuterol, a short-acting bronchodilator) and permitted use of other COPD medications (e.g., the anti-cholinergic ipratropium bromide and/or mucolytics at a stable dosage and/or oxygen for intermittent use or as ≤ 12 hours per day, in conjunction with close clinical monitoring for exacerbation of COPD symptoms. The informed consent forms described the possibility of receiving placebo and noted that alternative treatments for COPD were available. In addition, subjects were to be withdrawn from the study if they experienced an exacerbation. In the two, 1-year exacerbation studies, in addition to the medications noted above, oral corticosteroids and antibiotics (short course ≤ 14 days) were permitted for the short term treatment of COPD exacerbations.

The 1-year exacerbation studies (HZC102970 and HZC102871) were replicate studies that evaluated the efficacy and safety of the same three strengths of FF/VI (50/25, 100/25 and 200/25 mcg QD) that were evaluated across the 6-month, lung function studies versus VI alone over a 1-year treatment period. With respect to efficacy, the HZC102970 and HZC102871 studies were designed to evaluate the benefit of FF in the combination in decreasing the annual rate of moderate and severe exacerbations in subjects with COPD with a history of ≥ 1 moderate or severe COPD exacerbation in the year prior to Screening. As such, these studies included subjects with a higher risk of morbidity and mortality from respiratory causes due to their exacerbation history. A placebo treatment arm was not included in these studies, as it was considered unethical in a population prone to moderate/severe COPD exacerbation. The HZC102871 and HZC102970 studies also provided safety data over a 1-year treatment period.

After an initial Screening Visit, eligible subjects entered a 4-week, open-label, fluticasone propionate/salmeterol combination (FSC) 250/50 BID Run-In Period. The Run-In period was designed to ensure stability of disease and standardize health status before

randomization. After completion of the Run-In period, subjects who remained eligible entered a 1-year, double-blind treatment period followed by a 7-day follow-up period.

All four, primary COPD studies included exclusion criteria. A few of the key exclusion criteria included:

- Current diagnosis of asthma
- α 1-antitrypsin deficiency as the underlying cause of COPD
- Other respiratory disorders (e.g., active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, interstitial lung diseases or other active pulmonary diseases)
- Lung volume reduction surgery within the 12 months prior to Screening
- Chest X-ray (or CT scan) that revealed evidence of clinically significant abnormalities not believed to be due to the presence of COPD. In addition, in the 1-year exacerbation studies (HZC102970 and HZC102871), the presence of a parenchymal abnormality at screening, which would hinder the diagnosis of pneumonia were it to subsequently occur post-randomization (as determined by an independent radiologist), was exclusionary
- Historical or current evidence of clinically significant cardiovascular (i.e., pacemaker), neurological, psychiatric, renal, hepatic, immunological, endocrine (including uncontrolled diabetes or thyroid disease) or haematological abnormalities that were uncontrolled.
- Carcinoma that had not been in complete remission for at least 5 years. (Carcinoma in situ of the cervix, squamous cell carcinoma and basal cell carcinoma of the skin was not excluded if the subject had been considered cured within 5 years since diagnosis.)
- Long-term oxygen therapy (LTOT) or nocturnal oxygen therapy required for greater than 12 hours a day. (as needed oxygen use [i.e., ≤ 12 hours per day] was not exclusionary.
- Abnormal, clinically significant laboratory finding in any liver chemistry, biochemical, or hematology tests

Across the four, primary COPD studies, subjects were to be withdrawn from the study if they experienced a clinically important laboratory and/or 12-lead ECG finding and/or Holter finding (sub-set of subjects in the HZC112206 and HZC112207 studies). Also, in the 6-month, lung function studies, subjects were to be withdrawn from the study if they experienced a COPD exacerbation and/or pneumonia (presumptive diagnosis or radiographically confirmed), while in the 1-year studies, since COPD exacerbations formed the primary and secondary endpoints for these studies, subjects were not withdrawn from the 1-year studies if they experienced a COPD exacerbation. Unlike the 6-month studies, subjects in the 1-year studies were not withdrawn at the first experience of pneumonia.

For all four primary studies, treatment compliance was assessed via reviewing the dose counter on the ELLIPTA at each clinic visit.

Safety assessments are summarized in Section [7.5](#).

7.3.2. Efficacy Endpoints

COPD is associated with progressive airflow limitation and recurring exacerbations, both leading to symptomatic and functional limitation and increased morbidity. Therefore, the aim of the COPD Clinical Development Program was to demonstrate efficacy of FF/VI in terms of lung function parameters as well as reducing exacerbations. In addition, since FF/VI contains two components, an ICS and a LABA, the COPD Clinical Development Program was designed to assess the efficacy of the combination and the contribution of each component in the combination studies in line with 21 CFR 300.50, Combination Rule [FDA, 2012].

Lung function endpoints (weighted mean FEV₁ (0-4 h) and change from baseline in trough FEV₁) were the co-primary endpoints in the 6-month, lung function studies HZC112206 and HZC112207 (Table 2). Lung function endpoints (peak FEV₁ and time to onset in FEV₁ on Day 1) were defined as secondary endpoints and subject-reported quality of life (the Chronic Respiratory Disease Questionnaire – Self-Administered Standardized [CRQ-SAS] dyspnoea domain) and diary endpoints (COPD symptoms, rescue medication [albuterol] use and morning [AM] peak expiratory flow [PEF]) were also included as “Other” efficacy endpoints (see Appendix 1).

The primary endpoint in the 1-year, exacerbation studies HZC102970 and HZC102871 was annual rate of moderate and severe exacerbations. A moderate exacerbation was defined as worsening symptoms of COPD that required treatment with oral corticosteroids and/or antibiotics. A severe exacerbation was defined as worsening symptoms of COPD that required an in-patient hospitalization. The secondary endpoints in these studies were time to first moderate or severe exacerbation, annual rate of COPD exacerbations requiring systemic/oral corticosteroids and change from baseline in trough (pre-dose AM) FEV₁. Other efficacy endpoints, which included further lung function and symptomatic measures, are described in Appendix 1.

All efficacy endpoints were those recommended and accepted in international COPD treatment guidelines [GOLD, 2011] and in regulatory guidance. Across the four primary studies (as well as the supporting COPD studies), lung function measurements were collected using standardized spirometric equipment with centralized overreads provided by a vendor contracted by GSK. In the two, 1-year, exacerbation studies, subjects completed a daily diary using a telephone to access an interactive voice response system (IVRS), providing information on the number of night time awakenings due to COPD symptoms; use of rescue medication (albuterol), major symptoms concerning the subject’s dyspnea, sputum volume, sputum purulence (color); and minor symptoms of cough, wheeze, sore throat, colds (nasal discharge and/or nasal congestion) and fever without other cause. Subjects were instructed to complete the daily diary IVRS call in the morning, prior to taking any study medication (Run-In or double-blinded). COPD exacerbations were identified by the Investigators based upon review of the subjects’ IVRS diary (via phone contact or at a clinic visit) and his/her (the investigator’s) judgment.

7.3.3. Statistical Methods

All efficacy analyses were based on the Intent-to-Treat (ITT) Population, defined as all randomized subjects who received at least one dose of randomized, double-blind study medication during the treatment period. Appropriate statistical methods were employed for each endpoint. Details of the statistical analysis methods are described in [Appendix 3](#).

7.3.3.1. Treatment Comparisons

For the individual studies and for the integrated analyses for the four primary studies, the treatment comparisons were as follows:

	Primary Comparisons	Supportive Comparisons
6-Month Lung Function Studies (H2C112206 and H2C112207)		
Co-Primary Endpoints		
Change from Baseline Trough FEV₁ on Day 169	<ul style="list-style-type: none"> • VI vs placebo • Each FF/VI strength vs PLA • Each FF/VI strength vs VI alone 	<ul style="list-style-type: none"> • Each FF dose vs PLA • Each FF/VI strength vs the relevant FF alone dose
Weighted Mean FEV₁ Over 0-4 Hours on Day 168	<ul style="list-style-type: none"> • VI vs placebo • Each FF/VI strength vs PLA • Each FF/VI strength vs the relevant FF alone dose 	<ul style="list-style-type: none"> • Each FF dose vs PLA • Each FF/VI strength vs VI alone
Secondary and “Other” Endpoints		
	<ul style="list-style-type: none"> • Each FF/VI strength vs. PLA 	<ul style="list-style-type: none"> • VI vs. PLA • Each FF/VI strength vs. the relevant FF alone dose • Each FF/VI strength vs. VI alone • Each FF dose vs. PLA
1-Year Exacerbation Studies (H2C102970 and H2C102871)		
Primary Endpoint (Annual Rate of Moderate and Severe exacerbations) and Secondary and “Other” Endpoints	<ul style="list-style-type: none"> • Each FF/VI strength vs. VI alone 	N/A

FEV₁=forced expiratory volume in 1 second; FF=fluticasone furoate; N/A=Not Applicable; PLA=Placebo; VI=vilanterol

7.3.3.2. Multiple Comparisons and Multiplicity

Within each of the four primary studies, to account for multiplicity across treatment comparisons and key endpoints, a specific step-down testing procedure was applied, whereby inference for a test in the pre-defined hierarchy was dependent upon statistical significance having been achieved for the previous tests in the hierarchy (See [Appendix 2](#) for more details). If at any point in the hierarchy a comparison and/or endpoint did not demonstrate statistical significance, all further statistical analyses pre-specified in the hierarchy were fully described but were not inferential. Statistical significance was not achieved at all points in the hierarchy for all four of the primary studies and hence, some results were reported (including treatment difference, 95% CIs and p-values), but strictly could not be considered inferential within the individual studies. No formal multiplicity criteria were applied for the integrated analysis. To give full transparency of the data in

this Briefing Document, results from individual studies will be reported in their entirety (i.e., treatment difference, LS means, 95% confidence intervals and p-values), without reference to the strict statistical testing strategy. Looking at the data holistically across the program, the data are robust and repeated across several studies and, therefore, these findings should be afforded consideration despite the strict testing hierarchy of the individual studies.

7.4. Comparison of Efficacy in the Primary Studies

This section provides a comparison and analyses of results in the Phase III Primary Studies (6-month, lung function studies [HZC112206 and HZC112207] and the 1-year exacerbation studies [HZC102871 and HZC102970]) that assessed the efficacy of FF/VI 50/25, 100/25 and 200/25 mcg QD in patients with COPD. To aid the reader, data for the proposed strength of FF/VI (100/25) are highlighted in blue in the in-text tables throughout Section 7.4.

7.4.1. Integration of the Primary Studies

As the designs of two, 6-month, lung function studies (HZC112206 and HZC112207) were very similar, data from these two studies were integrated. Similarly, data from the two, 1-year exacerbation studies (HZC102970 and HZC102871) were integrated. No integration for efficacy of all four primary studies was performed because of the differences in the endpoints, study durations and study populations. Results are presented for the individual studies as well as results of the integrated data.

7.4.2. Demographics, Baseline Characteristics, and Patient Disposition Across the Primary Studies

7.4.2.1. Demographic and Baseline Characteristics

Of the subjects enrolled across the four, primary COPD studies, they were mostly male with a mean age between 62 to 64 years and a body mass index (BMI) of approximately 26 kg/m². In the 6 month studies, most were current smokers and the subjects overall had a mean smoking history of approximately 44 pack-years. Across the program, the subjects had on average severe airflow limitation with a mean post-bronchodilator FEV₁ of 45-48% predicted (NHANES III). Just over two-thirds of the subjects did not acutely demonstrate reversibility to inhaled albuterol ([Table 20](#)).

As discussed in [7.3.1](#), subjects in the two, 1-year exacerbation studies (HZC102871 and HZC102970) were required to have had an exacerbation history of ≥ 1 moderate/severe exacerbation in the 12 months prior to Screening, while in the two, 6-month, lung function studies (HZC112206 and HZC112207), subjects were excluded from participating in the study if they had been hospitalized due to poorly controlled COPD within 12 weeks of Screening and/or had poorly controlled COPD within 6 weeks prior to Screening and/or had experienced a lower respiratory tract infection that required the use of antibiotics within 6 weeks prior to Screening. This explains the higher incidence of COPD exacerbations in the year prior to Screening in the 1-year exacerbation studies compared with the 6-month, lung function studies.

Table 20 Demographic and Baseline Characteristics: Primary COPD Studies - 6-Month, Lung Function Studies (HZC112206/HZC112207 Integrated) and 1-Year Exacerbation Studies (HZC102970/HZC102871 Integrated)

	HZC112206 & HZC112207 N=2254	HZC102970 & HZC102871 N=3255
Age (yrs): Mean (Min-Max)	62.1 (40-85)	63.7 (40-90)
Sex: Female/Male, n (%)	684 (30%)/1570 (70%)	1385 (43%)/1870 (57%)
Race, n (%)		
Caucasian	1896 (84%)	2746 (84%)
Asian	304 (13%)	168 (5%)
African American	48 (2%)	71 (2%)
Other ¹	6 (<1%)	268 (8%)
Body Mass Index (kg/m ²): Mean (Min-Max)	26.32 (13.2-63.0)	26.87 (12.4-63.2)
Current Smoker, n (%)	1222 (54%)	1439 (44%)
Smoking History-Pack Yrs: Mean (Min-Max)	44.1 (10-200)	46.2 (10-255)
Screening Lung Function		
Screening Post-Albuterol FEV ₁ , % Predicted Mean (SD)	48.1 (12.51)	45.4 (13.36)
Screening Post-Albuterol FEV ₁ (L) Mean (SD)	1.451 (0.4842)	1.285 (0.4702)
Screening Post-Bronchodilator FVC (L) Mean (SD)	3.119 (0.8854)	2.861 (0.8804)
Screening Post-Bronchodilator FEV ₁ /FVC (%) Mean (SD)	47.2 (11.29)	45.5 (11.62)
Screening Reversibility (mL)	148.3 (169.70)	140.4 (161.04)
Screening Reversibility, % of Subjects	695 (31%)	972 (30%)
In the Year Prior to Screening, n (%)		
Moderate COPD Exacerbation ²		
0	1707 (76%)	250 (8%)
≥1	547 (24%)	3005 (92%)
Severe COPD Exacerbation ³		
0	2061 (91%)	2593 (80%)
≥1	193 (9%)	662 (20%)

FEV₁=forced expiratory volume in 1 second; FVC=forced vital capacity

1. Other includes American Indian or Alaskan Native, Native Hawaiian or Other Pacific Islander, Mixed Race
2. Required oral/systemic corticosteroids and/or antibiotics but did not involve hospitalization
3. Required hospitalization

7.4.2.2. Subject Disposition

In the integrated analysis for the two, 6-month lung function studies (HZC112206 and HZC112207), the majority (71-77%) of subjects across the active treatment groups completed the treatment period, with the lowest completion rate observed in the placebo group (68%); 72% of subjects in the FF/VI 100/25 group completed the treatment period (Table 21). Withdrawals were highest in the placebo group (31%) and lowest in the FF/VI 200/25 and FF 200 groups (23% and 21%, respectively). The most common primary reason for premature withdrawal was adverse events, which occurred at a similar incidence across the groups. Lack of efficacy, as a reason for withdrawal, was slightly higher in the placebo group than in the active treatment groups and the majority of the premature withdrawals from lack of efficacy were due to COPD exacerbation. The percentages of subjects withdrawn prematurely due to other reasons were low ($\leq 6\%$) and similar across the treatment groups.

Table 21 Summary of End of Study Record in CRF (ITT Population): Integrated Study Results - 6-Month Lung Function Studies (HZC112206 and HZC112207)

	Placebo N=412	FF/VI 50/25 N=206	FF/VI 100/25 N=410	FF/VI 200/25 N=205	VI 25 N=408	FF 100 N=410	FF 200 N=203	Total N=2254
Completion Status, n (%)								
Completed ¹	284 (69)	147 (71)	295 (72)	158 (77)	303 (74)	300 (73)	160 (79)	1647 (73)
Completed Tx Pd	282 (68)	146 (71)	291 (71)	155 (76)	296 (73)	296 (72)	156 (77)	1622 (72)
Withdrawn	128 (31)	59 (29)	115 (28)	47 (23)	105 (26)	110 (27)	43 (21)	607 (27)
Primary/Sub-reason for Withdrawal, n (%)								
Adverse Event	33 (8)	17 (8)	31 (8)	19 (9)	39 (10)	35 (9)	15 (7)	189 (8)
Lack of Efficacy	32 (8)	12 (6)	20 (5)	7 (3)	26 (6)	23 (6)	6 (3)	126 (6)
Exacerbation	29 (7)	9 (4)	19 (5)	7 (3)	24 (6)	18 (4)	5 (2)	111 (5)
Protocol Deviation	10 (2)	1 (<1)	12 (3)	4 (2)	5 (1)	11 (3)	2 (<1)	45 (2)
Reached PDSC ²	18 (4)	13 (6)	24 (6)	12 (6)	15 (4)	17 (4)	7 (3)	106 (5)
SC/T ³	0	0	0	1 (<1)	0	1 (<1)	0	2 (<1)
Lost to Follow-Up	7 (2)	1 (<1)	5 (1)	1 (<1)	2 (<1)	2 (<1)	0	18 (<1)
Inv Discretion	9 (2)	5 (2)	5 (1)	1 (<1)	8 (2)	3 (<1)	6 (3)	37 (2)
Withdrew Consent	19 (5)	10 (5)	18 (4)	2 (<1)	10 (2)	18 (4)	7 (3)	84 (4)

CRF=Case Report Form; FF=fluticasone furoate; Inv=Investigator; ITT=Intent-to-Treat; Tx Pd=Treatment Period; VI=vilanterol

1. Completed the studies through the follow-up phone contact
2. PDSC=Protocol-defined stopping criteria defined stopping criteria; category included COPD exacerbation requiring treatment with other than study medication or rescue albuterol, clinically important changes in a laboratory parameter, pneumonia, clinically significant abnormality in ECG or Holter findings, predefined liver chemistry abnormalities, and pregnancy
3. SC/T=Study closed/terminated; category was used for subjects who were withdrawn from the study due to closure of the study site

In the integrated analysis for the two, 1-year, exacerbation studies (HZC102970 and HZC102871), the majority of subjects across the FF/VI groups (75-76%) completed the treatment period, with a slightly lower completion rate in the VI 25 group (71%) (Table 22). The percentages of subjects withdrawn from the study were similar across the FF/VI groups (25%) and slightly higher in the VI 25 group (29%). Similar to the 6-month, lung

function studies, the most common primary reason for premature withdrawal was adverse event, which occurred at a similar incidence across the groups. Lack of efficacy as a reason for withdrawal was slightly higher in the VI 25 group than in the FF/VI groups. The percentages of subjects withdrawn prematurely due to other reasons were low ($\leq 8\%$) and generally similar across the treatment groups.

Table 22 Summary of End of Study Record in CRF (ITT Population): Integrated Study Results -1-Year Exacerbation Studies (HZC102970 and HZC102871)

	FF/VI 50/25 N=820	FF/VI 100/25 N=806	FF/VI 200/25 N=811	VI 25 N=818	Total N=3255
Completion Status, n (%)					
Completed ¹	618 (75)	603 (75)	607 (75)	578 (71)	2406 (74)
Completed Treatment Period ²	623 (76)	607 (75)	610 (75)	580 (71)	2420 (74)
Withdrawn	202 (25)	203 (25)	204 (25)	240 (29)	849 (26)
Primary/Subreason for Withdrawal, n (%)					
Adverse Event	57 (7)	64 (8)	61 (8)	47 (6)	229 (7)
Lack of Efficacy	30 (4)	27 (3)	32 (4)	59 (7)	148 (5)
Exacerbation	18 (2)	13 (2)	20 (2)	35 (4)	86 (3)
Protocol Deviation	18 (2)	17 (2)	15 (2)	15 (2)	65 (2)
Subject Reached Protocol	27 (3)	25 (3)	19 (2)	21 (3)	92 (3)
Defined Stopping Criteria ³					
Study closed/terminated ⁴	1 (<1)	1 (<1)	0	3 (<1)	5 (<1)
Lost to Follow-Up	15 (2)	12 (1)	15 (2)	17 (2)	59 (2)
Investigator Discretion	14 (2)	15 (2)	15 (2)	14 (2)	58 (2)
Withdrew Consent	40 (5)	42 (5)	47 (6)	64 (8)	193 (6)

CRF=Case Report Form; FF=fluticasone furoate; ITT=Intent-to-Treat; VI=vilanterol

1. Completed the studies through the follow-up phone contact
2. Subjects were considered to have completed the treatment period if they attended the last clinic visit
3. Defined stopping criteria included clinically important changes in a laboratory parameter, clinically significant abnormality in ECG, predefined liver chemistry abnormalities, and pregnancy
4. Study closed/terminated was used for subjects who were withdrawn from the study due to closure of the study site.

7.4.3. Efficacy Results

Key Finding(s):

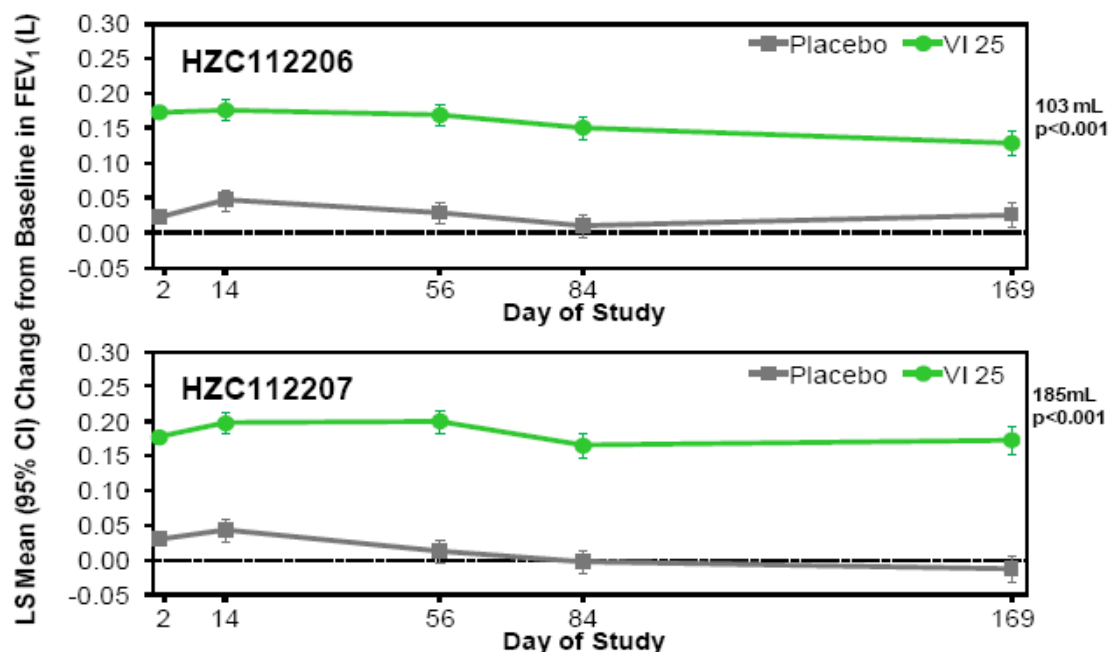
- BREO ELLIPTA has been demonstrated to be an effective treatment for COPD, providing a fast onset of effect (median time of 16 minutes) after the first dose and sustained 24-hour effect with once-daily dosing. VI 25mcg provided clinically meaningful and sustained improvement in lung function and FF 100 mcg provided clinically meaningful reductions in rate of moderate or severe COPD exacerbations, time to first moderate or severe COPD exacerbation and rate of exacerbations requiring treatment with oral/systemic corticosteroids. There is a small but meaningful contribution of FF on lung function and is in the same range as for the ICS effect of other ICS/LABA combination products.
- BREO ELLIPTA (FF/VI 100/25) provided better efficacy in subjects with COPD than FF/VI 50/25. No increased efficacy benefits were apparent for FF/VI 200/25 compared with FF/VI 100/25. FF/VI 100/25 is the strength proposed for marketing for BREO ELLIPTA in subjects with COPD.
- The results of studies that compared BREO ELLIPTA (FF/VI 100/25 QD) with currently marketed strengths of FP/salmeterol BID were not consistent, but suggest that BREO ELLIPTA is at least as effective as FP/salmeterol BID on improvements in lung function.
- Treatment with BREO ELLIPTA provided improvements in subject-reported outcomes (rescue medication use and symptom scores) by comparison with placebo.

7.4.3.1. Efficacy of Vilanterol

Persistence of the bronchodilatory effect with once daily dosing of VI in COPD patients was initially shown in the Phase IIb, 4-week dose-ranging study in COPD (B2C111045) and in a subsequent study that compared once- versus twice-daily dosing of VI in subjects with asthma (HZA113310). In addition, the B2C111045 study determined VI 25 once daily to be the appropriate dose to progress to Phase III in combination with FF (see Section 7.1.1).

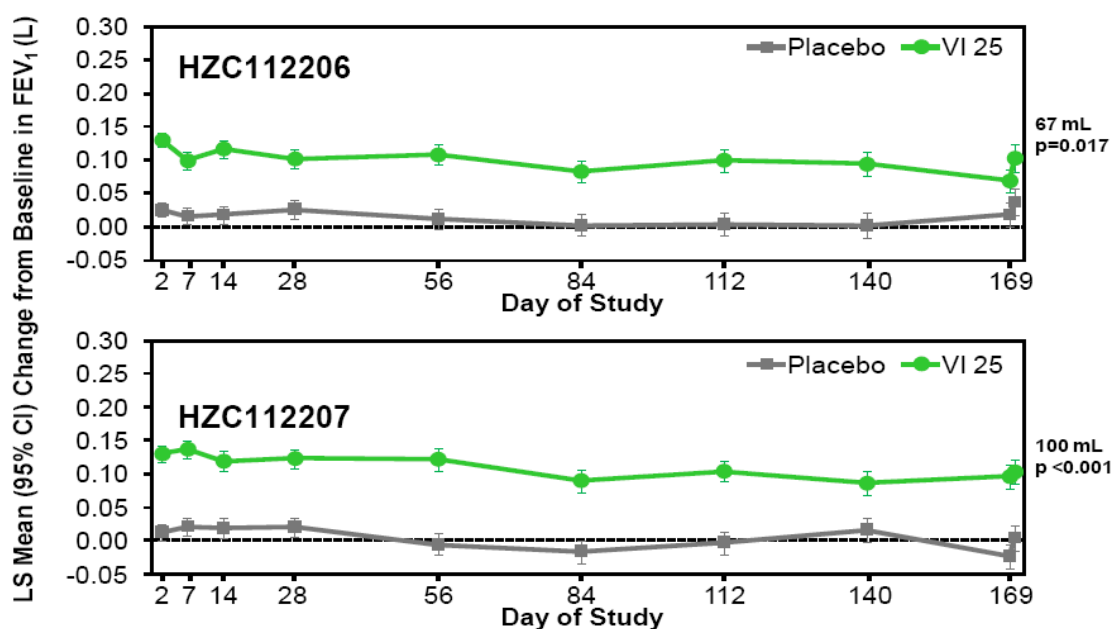
Data from both of the 6-month, lung function studies (HZA112206 and HZA112207) confirmed that once-daily VI dosing continued to improve trough FEV₁ up to treatment Day 169. Subjects in the VI 25 group demonstrated a clinically and statistically significant improvement in the co-primary endpoint weighted mean FEV₁ (0-4 h) at Day 168 (last dose of treatment) compared with the placebo group with effect sizes of 103 and 185 mL (both $p < 0.001$) (Figure 20). Similarly, for the other co-primary endpoint, trough FEV₁ at the end of treatment (Day 169), subjects in the VI 25 group demonstrated a statistically significant improvement compared with the placebo group, effect sizes of 67 and 100 mL (both $p \leq 0.017$), supporting once-daily use of VI (Figure 21).

Figure 20 Efficacy of Vilanterol vs. Placebo on 0-4 Hours Weighted Mean FEV₁ (L) (ITT Population): Individual Study Results – 6-Month Lung Function Studies (HZC112206 and HZC112207)



FEV₁=forced expiratory volume in 1 second; ITT=Intent-to-Treat; LS=Least Squares; VI=vilanterol
Adapted from [Kerwin, 2013](#) and [Martinez, 2013](#)

Figure 21 Efficacy of Vilanterol vs. Placebo on Trough FEV₁ (L) (ITT Population): Individual Study Results – 6-Month Lung Function Studies – (HZC112206 and HZC112207)



FEV₁=forced expiratory volume in 1 second; ITT=Intent-to-Treat; LS=Least Squares; VI=vilanterol
Adapted from [Kerwin, 2013](#) and [Martinez, 2013](#)

The primary lung function endpoints from the various studies support once-daily dosing of VI in COPD and confirm that it contributes a sustained bronchodilatory effect to the FF/VI combination. Further corroboration is provided by the secondary lung function endpoints of peak FEV₁ and time to onset of bronchodilation (defined as time to increase in FEV₁ by 100 mL above baseline). The VI 25 group demonstrated greater differences compared with placebo for peak FEV₁ on Treatment Day 1 and time to onset on Day 1 (Table 27). Across the two studies, after the first dose on Treatment Day 1, the difference between the VI 25 and placebo groups was 142 mL and 147 mL in the HZC112206 and HZC112207 studies, respectively. In addition, results of both studies demonstrated that VI 25 treatment provided a more rapid time to onset of bronchodilation compared with placebo, with a median (actual) time of 16-17 minutes after the first dose on Treatment Day 1 (Table 27).

7.4.3.2. Efficacy of Fluticasone Furoate

ICS therapy is positioned in treatment guidelines as an add-on to bronchodilator therapy for the treatment of COPD [GOLD, 2011]. Therefore, the COPD Clinical Development Program was not designed to demonstrate the benefit of FF monotherapy in subjects with COPD. Rather, the effectiveness of FF (compared with placebo) would be demonstrated in studies in subjects with asthma:

- Phase IIb dose ranging studies with FF monotherapy (FFA109684, FFA109685 and FFA109687) (Table 16, results summarized in 7.1.2)
- the FF monotherapy arm in the Phase III study with FF/VI (HZA106827) (Table 23)
- a Phase III study with FF monotherapy (FFA112059) (Table 23)

In the Phase IIb, asthma dose ranging studies, of 8 weeks' duration, FF doses of 100 mcg and greater were shown to be effective for the primary endpoint of trough FEV₁ (see Section 7.1.2 for further details).

Table 23 Efficacy and Safety of FF in Subjects with Asthma (HZA106827 and FFA112059)

Study Duration (Total N ¹)	Baseline Lung Function Baseline Treatment	FF/VI Strength(s) (mcg)	Components/Comparators and Doses(mcg)
Efficacy and safety of FF/VI; Efficacy and safety of FF; Contribution of VI to FF/VI			
HZA106827 12 weeks (N=609)	FEV ₁ 40-90% predicted FP 100 to 250 mcg BID or FP/salmeterol 100/50 mcg BID or equivalent	100/25 QD	Placebo FF 100 QD
Efficacy and safety of FF; Comparison of FF with a marketed ICS (FP)			
FFA112059 24 weeks (N=343)	FEV ₁ 40-90% predicted FP 50 to 250 mcg BID or equivalent	N/A	FF 100 QD FP 250 BID Placebo

BID=twice-daily; FEV₁=forced expiratory volume in 1 second; FF=fluticasone furoate; FP=fluticasone propionate;

N/A=not applicable; QD=once-daily; VI=vilanterol

Once-daily doses were administered in the evening. All studies were of randomized, double-blind and parallel group design

FEV₁ percent predicted calculated using NHANES III reference equations [Hankinson, 1999] adjusted for race

¹ Total number of subjects in ITT population

In the Phase III study HZA106827, FF 100 demonstrated efficacy versus placebo at Week 12 for the co-primary endpoints of change from baseline in trough FEV₁ and weighted mean FEV₁ (0-24 hours) and in Study FFA112059, FF 100 demonstrated significantly greater improvements in trough FEV₁ compared with placebo (Table 24).

Table 24 Trough and Weighted Mean FEV₁: Comparisons of FF 100 with Placebo (ITT Population) – Asthma Studies (HZA106827 and FFA112059)

	HZA106827	FFA112059
	FF 100 QD vs. Placebo	FF 100 QD vs. Placebo
Change from Baseline in Trough FEV₁ (mL)		
Treatment difference (95% CI)	136 (51, 222)	146 (36, 257)
p-value	0.002	0.009
Change from Baseline in Weighted Mean FEV₁ (0-24 hours) (mL)		
Treatment difference (95% CI)	186 (62, 310)	-
p-value	0.003	

CI=confidence interval; FEV₁=forced expiratory volume in 1 second; FF=fluticasone furoate; ITT=Intent-to-Treat; QD=once-daily

7.4.3.3. Efficacy of Fluticasone Furoate/Vilanterol

Since no placebo group was included in the 1-year exacerbation studies (HZC102970 and HZC102871), efficacy data for FF/VI compared with placebo are only available from the 6-month studies (HZC112206 and HZC112207).

7.4.3.3.1. Lung Function

The efficacy of FF/VI in improving lung function (weighted mean and trough FEV₁) in comparison with placebo was demonstrated. Both 6-month, lung function studies (HZC112206 and HZC112207) demonstrated that at the end of the 6-month treatment period all three strengths of FF/VI (50/25, 100/25 and 200/25 mcg once daily) provided clinically meaningful improvements in these co-primary endpoints compared with placebo ([Table 25](#) and [Figure 2](#) and [Table 26](#) and [Figure 3](#), respectively).

Table 25 Statistical Analysis of Weighted Mean FEV₁ (0-4 hours) (L) (ITT Population): Individual Study Results – 6-Month Lung Function Studies (HZC112206 and HZC112207)

Day 168	PLA	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25	VI 25	FF 100	FF 200
HZC112206	N=207	N=206	N=206		N=205	N=206	
n ¹	207	205	206		205	206	
n ²	139	146	151		144	145	
LS Mean	1.238	1.430	1.412		1.341	1.292	
LS Mean Change (SE) ³	0.026 (0.0184)	0.218 (0.0181)	0.200 (0.0179)		0.129 (0.0182)	0.080 (0.0182)	
Difference vs PLA 95% CI		0.192 (0.141, 0.243)	0.173 (0.123, 0.224)		0.103 (0.052, 0.153)	0.053 (0.003, 0.104)	
p-value		<0.001	<0.001		<0.001	0.040	
Difference vs VI 25 95% CI		0.090 (0.039, 0.140)	0.071 (0.021, 0.121)				
p-value		<0.001	0.006				
Difference vs FF 100 95% CI			0.120 (0.070, 0.170)				
p-value			<0.001				
HZC112207	N=205		N=204	N=205	N=203	N=204	N=203
n ¹	205		203	205	202	203	203
n ²	147		146	158	160	154	162
LS Mean	1.331		1.545	1.540	1.516	1.377	1.372
LS Mean Change (SE) ³	-0.012 (0.0189)		0.202 (0.0190)	0.197 (0.0184)	0.173 (0.0184)	0.034 (0.0187)	0.029 (0.0185)
Difference vs PLA 95% CI			0.214 (0.161, 0.266)	0.209 (0.157, 0.261)	0.185 (0.133, 0.237)	0.046 (-0.006, 0.098)	0.041 (-0.011, 0.093)
p-value			<0.001	<0.001	<0.001	0.085	0.123
Difference vs VI 25 95% CI			0.029 (-0.023, 0.081)	0.024 (-0.027, 0.075)			
p-value			0.274	0.357			
Difference vs FF 100 95% CI			0.168 (0.116, 0.220)				
p-value			<0.001				
Difference vs FF 200 95% CI				0.168 (0.117, 0.219)			
p-value				<0.001			

CI=confidence interval; FEV₁=forced expiratory volume in 1 second; FF=fluticasone furoate; ITT=Intent-to-Treat; LS=Least Squares; PLA=Placebo; VI=vilanterol

1. Number of subjects with analysable data for 1 or more timepoints
2. Number of subjects with analysable data at the given timepoint
3. Standard Error (SE) applies to both LS Mean and LS Mean Change

Note: Analysis performed using a Mixed Model Repeated Measures (MMRM) analysis with covariates of baseline FEV₁, smoking status (stratum), Day, geographical region, treatment, Day by baseline interaction, and Day by treatment interaction, where Day was nominal

[Kerwin, 2013](#); [Martinez, 2013](#)

Table 26 Statistical Analysis of Mean Change from Baseline in Trough FEV₁ (L) (ITT Population): Individual Study Results – 6-Month Lung Function Studies (HZC112206 and HZC112207)

Day 169	PLA	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25	VI 25	FF 100	FF 200
HZC112206	N=207	N=206	N=206		N=205	N=206	
n ¹	205	204	206		202	202	
n ²	136	144	146		143	143	
LS Mean	1.249	1.378	1.364		1.316	1.282	
LS Mean Change (SE) ³	0.037 (0.0199)	0.166 (0.0196)	0.151 (0.0194)		0.103 (0.0196)	0.070 (0.0196)	
Difference vs PLA 95% CI		0.129 (0.074, 0.184)	0.115 (0.060, 0.169)		0.067 (0.012, 0.121)	0.033 (-0.022, 0.088)	
p-value		<0.001	<0.001		0.017	0.241	
Difference vs VI 25 95% CI		0.062 (0.008, 0.117)	0.048 (-0.006, 0.102)				
p-value		0.025	0.082				
Difference vs FF 100 95% CI			0.082 (0.028, 0.136)				
p-value			0.003				
HZC112207	N=205		N=204	N=205	N=203	N=204	N=203
n ¹	202		200	204	202	202	202
n ²	142		137	153	150	148	155
LS Mean	1.347		1.492	1.479	1.447	1.392	1.356
LS Mean Change (SE) ³	0.004 (0.0189)		0.148 (0.0191)	0.135 (0.0185)	0.103 (0.0185)	0.048 (0.0187)	0.012 (0.0185)
Difference vs PLA 95% CI			0.144 (0.091, 0.197)	0.131 (0.080, 0.183)	0.100 (0.048, 0.151)	0.044 (-0.008, 0.097)	0.008 (-0.044, 0.060)
p-value			<0.001	<0.001	<0.001	0.095	0.756
Difference vs VI 25 95% CI			0.045 (-0.008, 0.097)	0.032 (-0.019, 0.083)			
p-value			0.093	0.224			
Difference vs FF 100 95% CI			0.100 (0.047, 0.152)				
p-value			<0.001				
Difference vs FF 200 95% CI				0.123 (0.072, 0.174)			
p-value				<0.001			

CI=confidence interval; FEV₁=forced expiratory volume in 1 second; FF=fluticasone furoate; ITT=Intent-to-Treat; LS=Least Squares; PLA=Placebo; VI=vilanterol

1. Number of subjects with analysable data for 1 or more timepoints
2. Number of subjects with analysable data at the given timepoint
3. Standard Error (SE) applies to both LS Mean and LS Mean Change

Note: Analysis performed using a Mixed Model Repeated Measures (MMRM) analysis with covariates of baseline FEV₁, smoking status (stratum), Day, geographical region, treatment, Day by baseline interaction, and Day by treatment interaction, where Day was nominal

Kerwin, 2013; Martinez, 2013

Secondary lung function endpoints in the two, 6-month, lung function studies (HZC112206 and HZC112207) supported the results observed with the primary endpoints and showed that all three FF/VI groups demonstrated greater differences compared with placebo for the secondary endpoints of peak FEV₁ on Treatment Day 1 and time to onset on Day 1 ([Table 27](#)). Across the two studies, after the first dose on Treatment Day 1, the difference between the FF/VI 100/25 and placebo groups was 139 mL and 152 mL in the HZC112206 and HZC112207 studies, respectively. In addition, results of both studies demonstrated that all three FF/VI treatments provide a more rapid time to onset (time to improvement from baseline of 100 mL in FEV₁) for all strengths of FF/VI compared with placebo with a median (actual) time of 16-17 minutes after the first dose on Treatment Day 1 ([Table 27](#)); in the integrated analysis, the median time to onset was 16 minutes for the FF/VI 100/25 treatment (p<0.001).

Table 27 Summary of Treatment Differences Versus Placebo (95% CI) for the Secondary Endpoints of Peak FEV₁ and Time to Onset at Day 1 (ITT Population): Individual Study Results – 6-Month Lung, Function Studies (HZC112206 and HZC112207)

Day 1	PLA	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25	VI 25	FF 100	FF 200
Peak FEV₁¹							
HZC112206	N=207	N=206	N=206		N=205	N=206	
n	207	205	206		205	206	
LS Mean	1.318	1.466	1.457		1.460	1.330	
LS Mean Change (SE) ²	0.106 (0.0098)	0.253 (0.0099)	0.245 (0.0099)		0.247 (0.0099)	0.118 (0.0099)	
Difference vs Placebo 95% CI		0.148 (0.120, 0.175)	0.139 (0.112, 0.166)		0.142 (0.114, 0.169)	0.012 (-0.015, 0.039)	
p-value		<0.001	<0.001		<0.001	0.393	
HZC112207	N=205		N=204	N=205	N=203	N=204	N=203
n	204		203	205	201	203	202
LS Mean	1.461		1.613	1.601	1.607	1.485	1.468
LS Mean Change (SE) ²	0.120 (0.0108)		0.272 (0.0109)	0.261 (0.0108)	0.267 (0.0109)	0.144 (0.0109)	0.127 (0.0109)
Difference vs Placebo 95% CI			0.152 (0.122, 0.182)	0.141 (0.111, 0.171)	0.147 (0.117, 0.177)	0.024 (-0.006, 0.055)	0.007 (-0.023, 0.037)
p-value			<0.001	<0.001	<0.001	0.111	0.635
Time to Onset (Increase in FEV₁ of ≥100 mL from Baseline³)							
HZC112206	N=207	N=206	N=206		N=205	N=206	
n	207	205	206		205	206	
Number of Events, n (%)	90 (43)	174 (85)	175 (85)		175 (85)	97 (47)	
Number Censored ⁴ , n (%)	117 (57)	31 (15)	31 (15)		30 (15)	109 (53)	
Median Time (minutes)	N/A	17	17		16	NA	
Difference vs Placebo p-value		<0.001	<0.001		<0.001	0.697	
HZC112207	N=205		N=204	N=205	N=203	N=204	N=203
n	204		203	205	201	203	202
Number of Events, n (%)	101 (50)		172 (85)	177 (86)	180 (90)	118 (58)	106 (52)
Number Censored ⁴ , n (%)	103 (50)		31 (15)	28 (14)	21 (10)	85 (42)	96 (48)
Median Time (minutes)	N/A		16	17	17	231	242
Difference vs Placebo p-value			<0.001	<0.001	<0.001	0.086	0.538

CI=confidence interval; FEV₁=forced expiratory volume in 1 second; FF=fluticasone furoate; ITT=Intent-to-Treat; LS=Least Squares; VI=vilanterol

1. Peak FEV₁ represents the maximum post-dose FEV₁ from assessments taken at 5, 15 and 30 minutes and 1, 2 and 4 hours post-dose
2. Standard error (SE) applies to both LS Mean and LS Mean Change
3. Baseline was defined as the mean of the two assessments made 30 minutes pre-dose and immediately pre-dose on Day 1
4. Censored was defined as a subject who had at least one post-dose FEV₁ on Day 1 but did not achieve a 100 mL or more increase from baseline at any scheduled time-point at which FEV₁ was assessed up to and including 4 hours. If more than 50% of subjects were censored, median time to a 100 mL increase in FEV₁ is not given.

Kerwin, 2013; Martinez, 2013

7.4.3.3.2. Symptomatic Endpoints

6-Month Lung Function Studies (H2C112206 and H2C112207)

Symptomatic benefits (in rescue medication use, nighttime awakenings and symptoms) were observed in the 6-month, lung function studies (H2C112206 and H2C112207) with all improvements in favor of FF/VI compared with placebo ([Table 28](#)). In both studies, over the 24-week treatment period, mean number of occasions of rescue medication use (occasions/24 hours) and number of nighttime awakenings requiring rescue medication use was lower in the FF/VI groups compared with the placebo groups. Similarly, LS mean cough scores, sputum scores and breathlessness scores were also lower in all of the FF/VI groups compared with the placebo group. In addition, over the 24-week treatment period, AM PEF was higher in the FF/VI groups compared with the placebo group. Results for the comparison of FF/VI 100/25 versus placebo are shown in [Figure 22](#).

Table 28 **Diary Data Over Weeks 1-24 and CRQ-SAS-Dyspnea Data at Day 168:**
LS Mean Treatment Differences Versus Placebo (95% CI) (ITT
Population) – Individual Study Results: 6-Month Lung Function
Studies (HZC112206 and HZC112207)

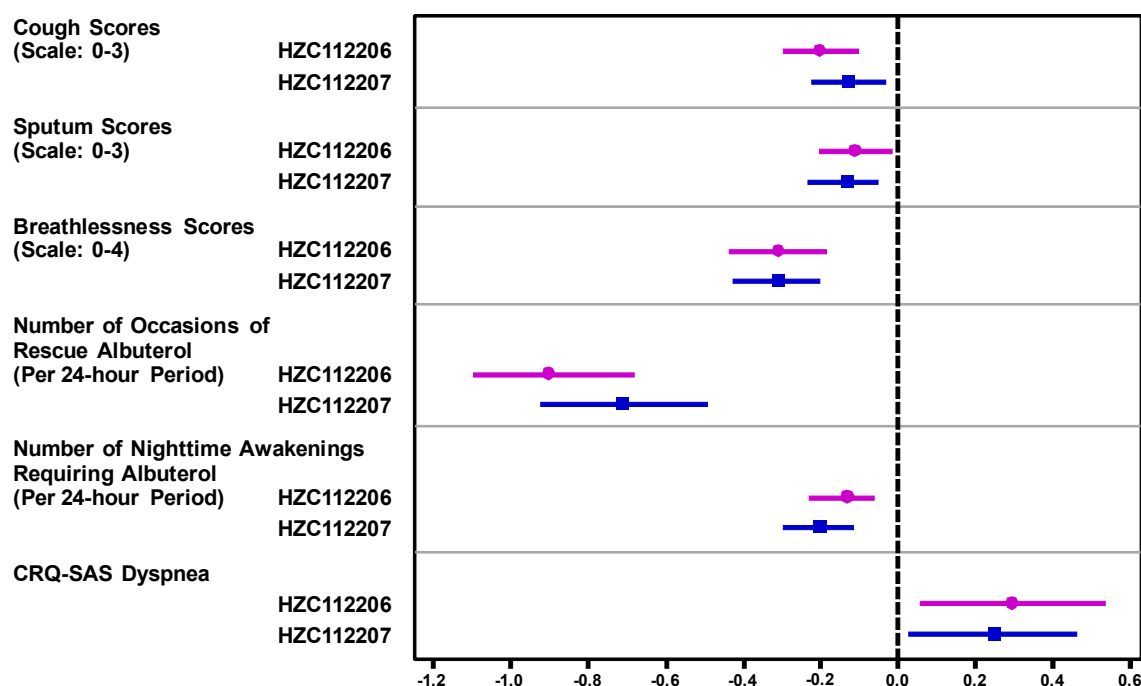
	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25	VI 25	FF 100	FF 200
Cough Scores (Scale 0-3)¹						
HZC112206	-0.21 -0.31, -0.11	-0.20 -0.29, -0.10	N/A	-0.13 -0.22, -0.03	-0.09 -0.18, 0.01	N/A
HZC112207	N/A	-0.13 -0.22, -0.03	-0.15 -0.24, -0.06	-0.07 -0.16, 0.02	-0.03 -0.12, 0.06	-0.06 -0.15, 0.04
Sputum Scores (Scale 0-3)²						
HZC112206	-0.13 -0.23, -0.04	-0.11 -0.20, -0.02	N/A	-0.05 -0.15, 0.04	-0.07 -0.17, 0.02	N/A
HZC112207	N/A	-0.14 -0.23, -0.05	-0.12 -0.20, -0.03	-0.02 -0.11, 0.06	-0.03 -0.12, 0.06	-0.07 -0.16, 0.01
Breathlessness Scores (Scale 0-4)³						
HZC112206	-0.30 -0.42, -0.18	-0.31 -0.43, -0.19	N/A	-0.19 -0.31, -0.08	-0.12 -0.24, -0.00	N/A
HZC112207	N/A	-0.31 -0.42, -0.20	-0.32 -0.43, -0.21	-0.19 -0.30, -0.08	-0.09 -0.20, 0.01	-0.13 -0.23, -0.02
Number of Occasions of Rescue Albuterol (Per 24-Hour Period)						
HZC112206	-0.72 -0.92, -0.52	-0.89 -1.09, -0.68	N/A	-0.55 -0.75, -0.34	-0.36 -0.57, -0.16	N/A
HZC112207	N/A	-0.71 -0.92, -0.49	-0.49 -0.71, -0.28	-0.43 -0.65, -0.22	-0.17 -0.39, 0.04	-0.15 -0.37, 0.06
Number of Nighttime Awakenings Requiring Albuterol (Per 24-Hour Period)						
HZC112206	-0.13 -0.21, -0.05	-0.14 -0.22, -0.06	N/A	-0.06 -0.14, 0.02	-0.06 -0.14, 0.02	N/A
HZC112207	N/A	-0.20 -0.29, -0.11	-0.15 -0.23, -0.06	-0.11 -0.20, -0.02	-0.11 -0.20, -0.02	-0.03 -0.12, 0.06
AM PEF (L/min)						
HZC112206	23.6 17.5, 29.8	25.2 19.1, 31.4	N/A	19.5 13.4, 25.7	7.5 1.4, 13.7	N/A
HZC112207	N/A	21.7 14.9, 28.6	20.1 13.3, 26.9	15.9 9.1, 22.8	9.0 2.2, 15.9	9.7 2.9, 16.5
CRQ-SAS Dyspnea⁴ – Day 168						
HZC112206	0.19 -0.05, 0.43	0.30 0.06, 0.54	N/A	0.14 -0.10, 0.38	0.06 -0.18, 0.30	N/A
HZC112207	N/A	0.24 0.02, 0.46	0.10 -0.12, 0.31	0.07 -0.14, 0.28	-0.12 -0.33, 0.10	-0.01 -0.22, 0.21

Kerwin, 2013; Martinez, 2013

AM=morning;CI=confidence interval;CRQ-SAS=Chronic Respiratory Disease Questionnaire–Self-Administered Standardized;FF=fluticasone furoate;ITT=Intent-to-Treat;N/A=not applicable;LS=Least Squares;PEF=peak expiratory flow;VI=vilanterol

1. Cough scores:0=no cough;1=mild cough (e.g., some coughing mostly in the morning);2=moderate cough (e.g., coughing in the morning and sometimes during the day);3=severe cough (coughing in the morning and throughout the day)
2. Sputum scores:0=none;1=mild sputum production (e.g., only in the morning);2=moderate sputum production (e.g., in the morning and sometimes during the day);3=severe sputum production (e.g., throughout the whole day)
3. Breathlessness scores: 0=not breathless at rest or exertion; 1=not breathless at rest, but breathless on moderate exertion (e.g., walking quickly, climbing stairs); 2=not breathless at rest, but breathless on mild exertion (e.g., walking on the level); 3=not breathless at rest, but breathless on minimal exertion (e.g., getting washed or dressed); 4=breathless at rest (e.g., sitting down reading or watching TV)
4. CRQ-SAS Dyspnea: 7-point scale, ranging from 1 (maximum impairment) to 7 (no impairment); minimal clinically important difference (MCID) = >0.5 point improvement

Figure 22 Diary Data Over Weeks 1-24 and CRQ-SAS-Dyspnea Data at Day 168: LS Mean Treatment Differences (95% CI) for FF/VI 100/25 Versus Placebo (ITT Population) – Individual Study Results: 6-Month Lung Function Studies (HZC112206 and HZC112207)



CI=confidence interval; CRQ-SAS=Chronic Respiratory Disease Questionnaire – Self-Administered Standardized; ITT=Intent-to-Treat; LS=Least Squares
Adapted from [Kerwin, 2013](#) and [Martinez, 2013](#)

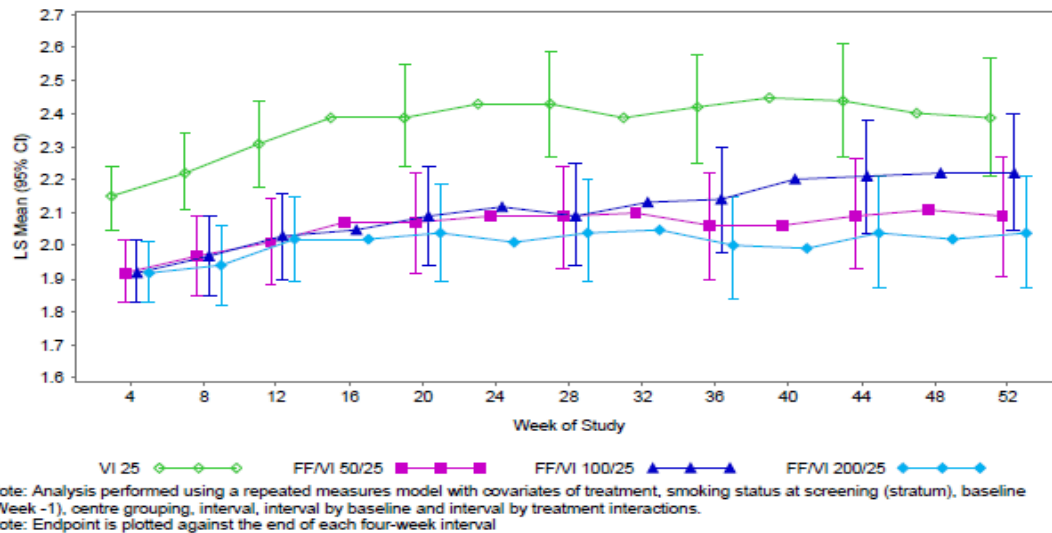
Although the LS mean change in CRQ-SAS dyspnea scores were higher for FF/VI 100/25 compared with placebo, the differences (0.30 and 0.24, for HZC112206 and HZC112207, respectively) did not meet the minimal clinically important difference (MCID of >0.5 point improvement has been established for this domain [[Schunemann, 2005](#)]). In both studies, an *a priori*-defined responder analysis (i.e., subjects who achieved the MCID for the CRQ-SAS Dyspnea Domain at the given visit) demonstrated that, at the end of the 6-month treatment period, the odds of being a responder compared with a non-responder were 2.04 times (HZC112206; 95% CI: 1.31, 3.16, $p=0.002$) and 1.67 times (HZC112207; 95% CI: 1.09, 2.57, $p=0.019$) greater for the FF/VI 100/25 groups compared with the placebo groups.

Thus, despite not achieving the MCID for the CRQ-SAS (and an unknown MCID for the endpoints measured with the diary card), it is considered that the totality of the data assessing symptomatic endpoints, especially exacerbations, and the directionality of the other symptomatic endpoints, support the efficacy of FF/VI 100/25 in ameliorating these important clinical aspects.

1-Year Exacerbation Studies (HZC102970 and HZC102871)

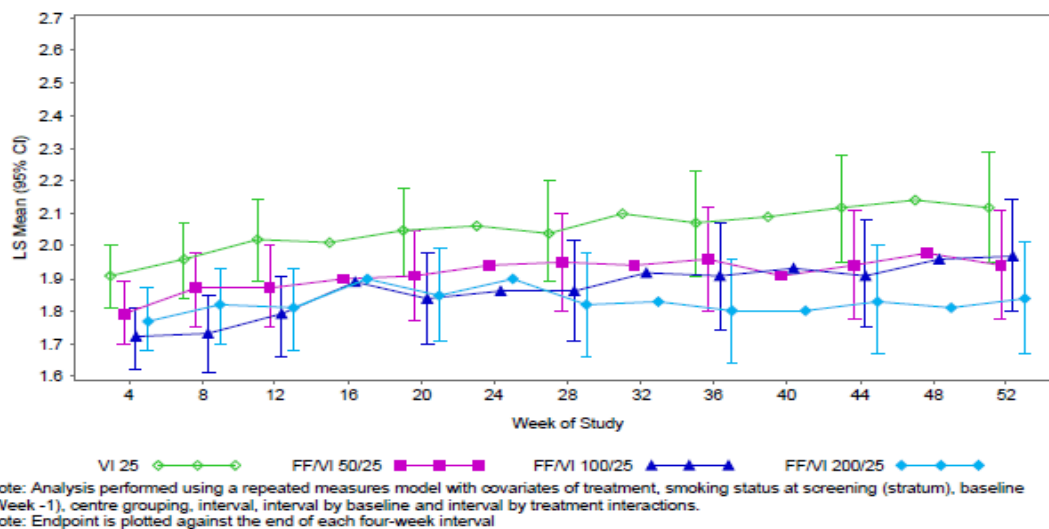
In the 1-year exacerbation studies (HZC102970 and HZC102871), over each 4-week interval during the 1-year treatment period, the mean number of occasions that rescue medication was used was consistently lower in the FF/VI groups than in the VI 25 group and this effect did not diminish over time (Figure 23 and Figure 24).

Figure 23 Least Squares Means (95% CI) for IVRS Diary Mean Number of Occasions of Rescue Use (Occasions/24 hours), Four-Week Intervals (ITT Population): 1-Year Exacerbation Study (HZC102970)



CI=confidence interval; FF=fluticasone furoate; ITT=Intent-to-Treat; IVRS=Interactive Voice Response System; VI=vilanterol

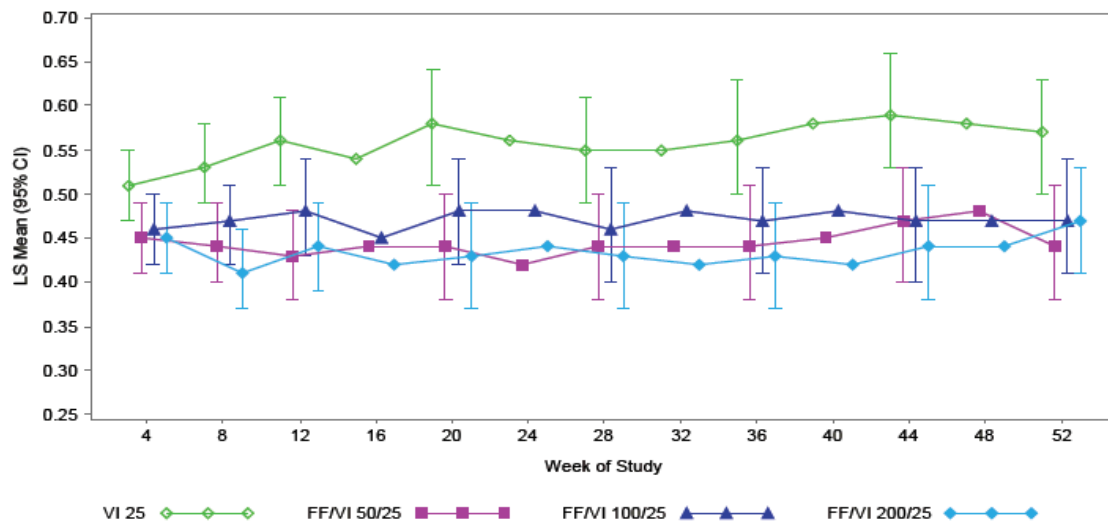
Figure 24 Least Squares Means (95% CI) for IVRS Diary Mean Number of Occasions of Rescue use (Occasions/24 hours), Four-Week Intervals (ITT Population): 1-Year Exacerbation Study (HZC102871)



CI=confidence interval; FF=fluticasone furoate; ITT=Intent-to-Treat; IVRS=Interactive Voice Response System; VI=vilanterol

In the 1-year exacerbation studies (HZA102970 and HZA102871), over each 4-week interval during the 1-year treatment period, the mean number of nighttime awakenings due to symptoms of COPD was consistently lower in the FF/VI groups than in the VI 25 group and this effect did not diminish over time (Figure 25 and Figure 26).

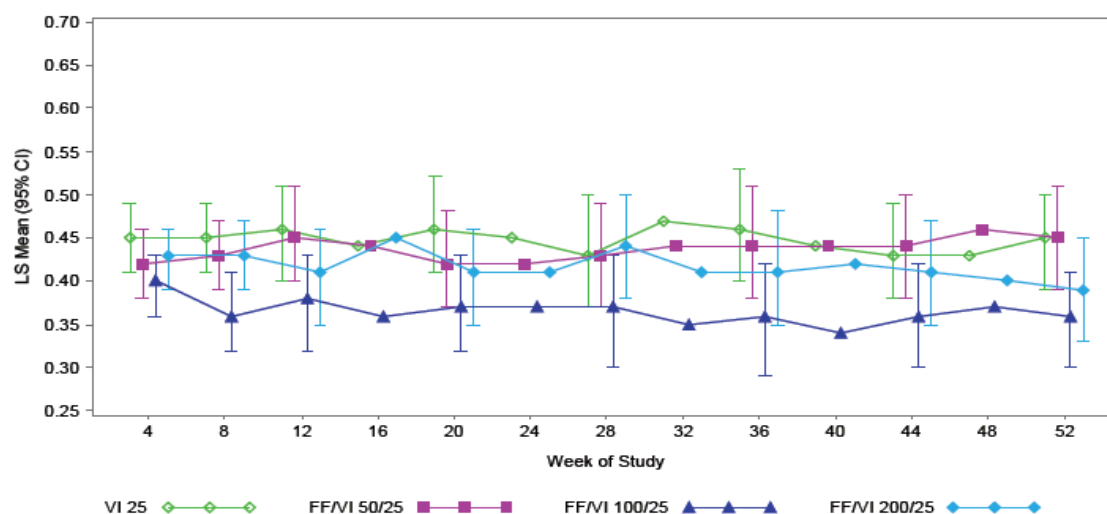
Figure 25 Least Squares Means (95% CI) for IVRS Diary Mean Number of Night-time Awakenings Due to Symptoms of COPD (occasions/24 hours), Four-Week Intervals (ITT Population): Individual Study Results – 1-Year Exacerbation Study (HZA102970)



CI=confidence interval; FF=fluticasone furoate; ITT=Intent-to-Treat; IVRS=Interactive Voice Response System; VI=vilanterol

Analysis performed using a repeated measures model with covariates of treatment, smoking status at screening (stratum), baseline (Week -1), center grouping, interval, interval by baseline, and interval by treatment interactions. Endpoint is plotted against the end of each four-week interval

Figure 26 Least Squares Means (95% CI) for IVRS Diary Mean Number of Night-time Awakenings Due to Symptoms of COPD (occasions/24 hours), Four-Week Intervals (ITT Population): Individual Study Results – 1-Year Exacerbation Study (HZC102871)



CI=confidence interval; FF=fluticasone furoate; ITT=Intent-to-Treat; IVRS=Interactive Voice Response System; VI=vilanterol

Note: Analysis as noted for Figure 25 above

7.4.3.4. Contribution of Vilanterol in the Combination

7.4.3.4.1. Lung Function

It was anticipated that the most important effects of VI on lung function would be apparent within 4 hours of dosing and thus weighted mean FEV₁ (0-4 hours) was the key lung function endpoint to demonstrate the contribution of VI to the combination in the 6-month, lung function studies HZC112206 and HZC112207. At Day 168 (the end of the 6-month treatment period), both studies demonstrated a clinically meaningful contribution of VI 25 in the combination on lung function (weighted mean FEV₁), as measured by the comparison of FF/VI with the respective FF alone group, with effect sizes of 120 and 168 mL (both p<0.001) (Figure 20), and sustained effects on lung function, as measured by the comparison with placebo, with an effect sizes of 103 and 185 mL (all p<0.001; Table 25). Integrated analyses of studies HZC112206 and HZC112207 showed that, compared with placebo at Day 168, the FF/VI (50/25, 100/25 and 200/25) and VI 25 treatment groups showed effect sizes on weighted mean FEV₁ 0-4 hours ranging from 145 to 212 mL (all p<0.001). Moreover, FF/VI 100/25 and 200/25 demonstrated effect sizes of 148 and 169 mL, respectively, at Day 168 (both p<0.001) on weighted mean FEV₁ 0-4 hours post-dose compared with the respective FF group. From Day 1 onwards, the FF/VI 100/25 and FF/VI 200/25 groups demonstrated greater improvements in weighted mean FEV₁ 0-4 hours compared with the respective FF alone group (Figure 2). Both studies also confirmed that VI made a contribution to lung function over the 24-hour dosing period based upon the results observed for trough FEV₁ (Table 26). These two sets of analyses confirmed that VI is meaningfully effective not

only in monotherapy, but also makes a significant contribution to the effects of the FF/VI combination on lung function.

Results for the secondary lung function endpoints of peak FEV₁ and time to onset (time to improvement from baseline of 100 mL in FEV₁) in the two, 6-month, lung function studies (HZA112206 and HZA112207) supported the results observed with the primary endpoints and confirmed the contribution of VI 25 in increasing FEV₁ after the first dose on Treatment Day 1 (Table 27). Across both studies, the LS mean changes from baseline in peak FEV₁ were higher for the FF/VI 100/25 group compared with the FF 100 group (Treatment differences: HZA112206 = 0.127; 95% CI: 0.100, 0.154, p<0.001; HZA112207: 0.128; 95% CI: 0.098, 0.158, p<0.001).

In addition, both 6-month, lung function studies (HZA112206 and HZA112207) demonstrated that all three FF/VI treatments and treatment with VI 25 alone provide a rapid time to onset (time to improvement from baseline of 100 mL in FEV₁), with a median (actual) time of 16-17 minutes after the first dose on Treatment Day 1 (all p versus placebo <0.001) (Table 27).

7.4.3.4.2. Symptomatic Endpoints

The contribution of VI to FF/VI for effects on exacerbations could not be evaluated since the 1-year exacerbation studies did not include an FF alone treatment arm. However, symptomatic benefits (in rescue medication use, nighttime awakenings and symptoms) were observed for FF/VI compared with FF in the 6-month studies (HZA112206 and HZA112207). The number of occasions of rescue medication use and the number of nighttime awakenings requiring rescue medication use were reduced for FF/VI 100/25 compared with FF 100 (Table 28). LS mean breathlessness scores were lower in the FF/VI 100/25 group relative to the FF 100 group in both studies; but, the contribution of VI to FF/VI was not always demonstrated for cough and sputum scores (Table 28). Although the LS mean change in CRQ-SAS dyspnoea scores were higher for FF/VI 100/25 compared with FF 100, the differences (0.24 and 0.36 for HZA112206 and HZA112207, respectively) did not meet the minimal clinically important difference [MCID] of >0.5 point improvement for this domain [Schunemann, 2005].

7.4.3.5. Contribution of Fluticasone Furoate in the Combination

7.4.3.5.1. Annual Rate of Moderate/Severe COPD Exacerbations (HZA102970 and HZA102871)

As described in the Draft COPD Guidance [FDA, 2007], COPD exacerbations can be life-threatening and have been linked to co-morbid conditions and exacerbations are believed to potentially contribute to further permanent decrements in lung function. Therefore, therapeutic drugs that modify the severity or duration of COPD exacerbations or that prevent COPD exacerbations will provide meaningful benefit to patients.

The major contribution of FF (50, 100 and 200mcg) to the FF/VI combination was evaluated in the 1-year, exacerbation studies (HZA102970 and HZA102871) by measuring the effect of the combination on the annual rate of moderate and severe COPD

exacerbations. The primary comparison of interest for this endpoint was the pair-wise comparison of each strength of FF/VI (200/25, 100/25 and 50/25) with VI 25 alone for the ITT Population. This endpoint was not assessed in the 6-month, lung function studies (HZA112206 and HZA112207), since the subjects recruited were not necessarily an exacerbating population and the protocol required subjects who experienced a moderate/severe COPD exacerbation to be withdrawn from the study.

Treatment with FF/VI 100/25 compared with VI 25 reduced the annual rate of moderate and severe COPD exacerbations by 21% (95% CI: 3, 36; $p=0.024$) and 34% (95% CI: 19, 46; nominal $p<0.001$), in the HZA102970 and HZA102871 studies, respectively, thereby demonstrating an important clinical benefit for the combination, as well as demonstrating the contribution of FF to FF/VI (Figure 5). Stand-alone interpretation of study HZA102871 is confounded because the lack of a statistically significant difference for the comparison between the FF/VI 200/25 and VI 25 groups (15%, 95% CI: -4, 30; $p=0.109$) for the primary endpoint (annual rate of moderate and severe exacerbations) prevented inferential testing of the comparison between the FF/VI 100/25 and VI 25 groups; however, as stated above, the treatment effect with FF/VI 100/25 was clinically relevant across both studies with treatment effects of 21% and 34%. Moreover, the results for FF/VI 100/25 observed in the HZA102970 and HZA102871 studies were of the magnitude observed in 1-year exacerbation studies with the currently marketed ICS/LABA treatment ADVAIR DISKUS (FP/salmeterol), in which risk reductions of 30% were observed for the mean annual rate of moderate/severe COPD exacerbations for the FP/salmeterol 250/50 BID group compared with the salmeterol 50 BID group [Ferguson, 2008; Anzueto, 2009].

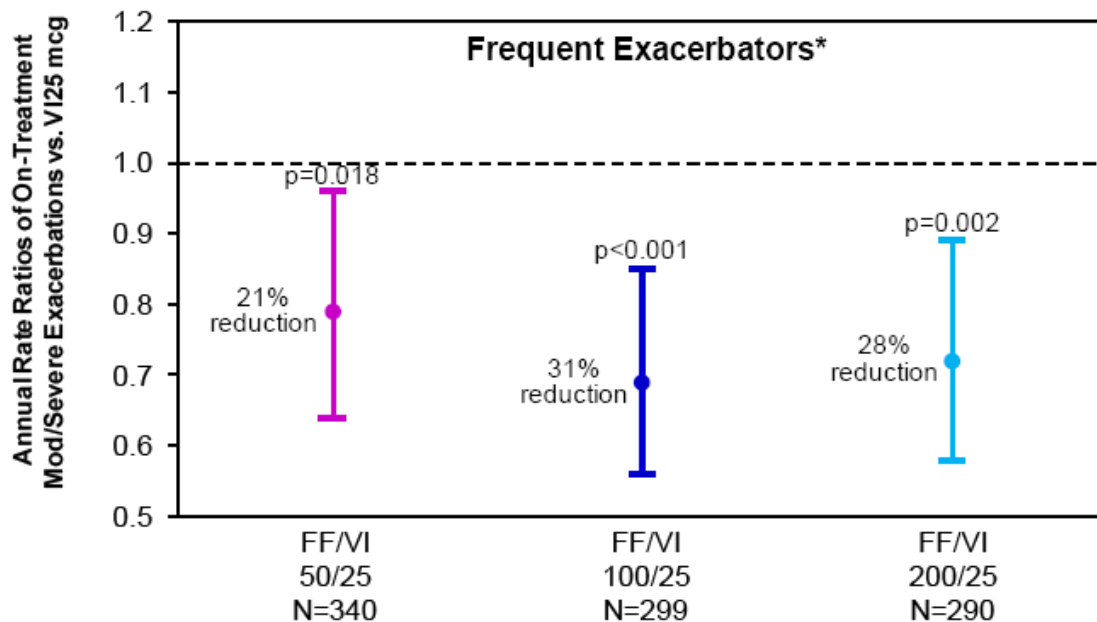
In both the HZA102970 and HZA102871 studies, a Poisson analysis of moderate and severe exacerbations (using the ITT population) confirmed the results of the negative binomial analysis (Figure 5). In the HZA102970 study, a statistically significant reduction in the annual rate of moderate and severe exacerbations was shown with a 28% (95% CI: 13, 40; $p<0.001$), 19% (95% CI: 3, 33; $p=0.023$) and 18% (95% CI: 1, 31; $p=0.037$) reduction for FF/VI 200/25, 100/25 and 50/25, respectively. In the HZA102871 study, a numerical reduction in the annual rate of moderate and severe exacerbations was shown with a 14% (95% CI: -4, 28; $p=0.116$), 31% (95% CI: 16, 43; $p<0.001$) and 12% (95% CI: -5, 27; $p=0.148$) reduction for FF/VI 200/25, 100/25 and 50/25, respectively.

Moreover, integrated analysis of the HZA102970 and HZA102871 studies afforded a supplementary method to identify the optimal strength, and showed that FF/VI 200/25, 100/25 and 50/25 reduced the annual rate of moderate and severe exacerbations by 23% (95% CI: 12, 34; $p<0.001$), 27% (95% CI: 16, 37; $p<0.001$) and 16% (95% CI: 4, 27; $p=0.014$), respectively (Figure 5). The point estimates for the FF/VI 200/25 and FF/VI 100/25 groups suggested that the higher strength offered no incremental benefit whereas the 11% difference between the 100/25 and 50/25 strengths suggested that the lowest strength is likely to be sub-optimal. Hence, FF/VI 100/25 has been proposed as the recommended strength for the treatment of COPD.

COPD exacerbations are important events associated with accelerated loss of lung function and poor health status [Wedzicha, 2007]; mortality one year after an exacerbation-related hospitalisation exceeds 20% [McGhan, 2007]. Patients who

exacerbate frequently (i.e. ≥ 2 events in 1 year) may form a distinct COPD subtype [Hurst, 2010] and guidelines have identified exacerbation frequency as a key target for preventive treatment [GOLD, 2011]. We therefore conducted a pre-defined analysis in the population of subjects who were frequent exacerbators. In this population, all strengths of FF/VI reduced the rate of moderate and severe exacerbations with the greatest reduction observed in the 100/25 group (Figure 27).

Figure 27 Treatment Differences (95% CI) for the Annual Rate of Moderate and Severe COPD Exacerbations – Frequent Exacerbators*: Integrated Study Results – 1-Year Exacerbation Studies (HZC102970/HZC102871)



CI=confidence interval; FF=fluticasone furoate; VI=vilanterol

*39% of subjects were frequent exacerbators (defined as ≥ 2 exacerbations/prior year)

7.4.3.5.2. Time to First Moderate or Severe COPD Exacerbation

The primary endpoint analysis from the 1-year exacerbation studies (HZC102970 and HZC102871) was strengthened by the individual and integrated analysis for the secondary endpoints of time to first moderate or severe COPD exacerbation and annual rate of COPD exacerbations requiring systemic/oral corticosteroids.

The risk of the time to first moderate or severe COPD exacerbation at any time point was reduced by 20% ($p=0.036$) and 28% ($p=0.002$) for FF/VI 100/25 compared with VI 25 in studies HZC102970 and HZC102871, respectively. The Kaplan-Meier plot for time to first moderate or severe exacerbation for the integrated data is depicted in Figure 6. The risk reduction by FF/VI 100/25 compared with VI 25 for time to first moderate/severe exacerbation was 24% (95% CI: 12%, 34%; $p<0.001$) in the integrated analysis. Similar to the results for the primary endpoint, there was no incremental benefit in efficacy with

the 200/25 strength (risk reduction of 25% compared with VI 25 (95% CI: 13%, 35%; $p<0.001$) over the 100/25 strength and the 50/25 strength provided sub-optimal efficacy compared with the 100/25 strength (risk reduction of 11% compared with VI 25 (95% CI: -3%, 22%; $p=0.114$).

Similar to the primary endpoint, the results observed in the HZC102871 and HZC102970 studies were of the magnitude observed in 1-year exacerbation studies with the currently marketed ICS/LABA treatment ADVAIR DISKUS, in which risk reductions of 25% and 27% were observed for the time to first moderate or severe COPD exacerbation for the FP/salmeterol 250/50 BID group compared with the salmeterol 50 BID group [Ferguson, 2008; Anzueto, 2009, respectively].

7.4.3.5.3. Annual Rate of COPD Exacerbations Requiring Systemic/Oral Corticosteroids

The annual rate of COPD exacerbation necessitating use of systemic/oral corticosteroids at any point was reduced by 23% (95% CI: 1, 40; $p=0.041$) and 38% (95% CI: 22, 51; $p<0.001$) with FF/VI 100/25 compared with VI 25 in the 1-year exacerbation studies HZC102970 and HZC102871, respectively. Annual exacerbations requiring corticosteroids were reduced 27% (95% CI: 14, 38; $p<0.001$), 30% (95% CI: 17, 41; $p<0.001$) and 17% (95% CI: 1, 29; $p=0.033$), with FF/VI 200/25, 100/25 and 50/25, respectively compared with VI, in the integrated analysis (Figure 7). As with the primary endpoint, FF/VI 100/25 appeared to be the optimal strength as it provided greater efficacy than 50/25 but there was no additional incremental benefit observed with FF/VI 200/25.

7.4.3.5.4. Lung Function

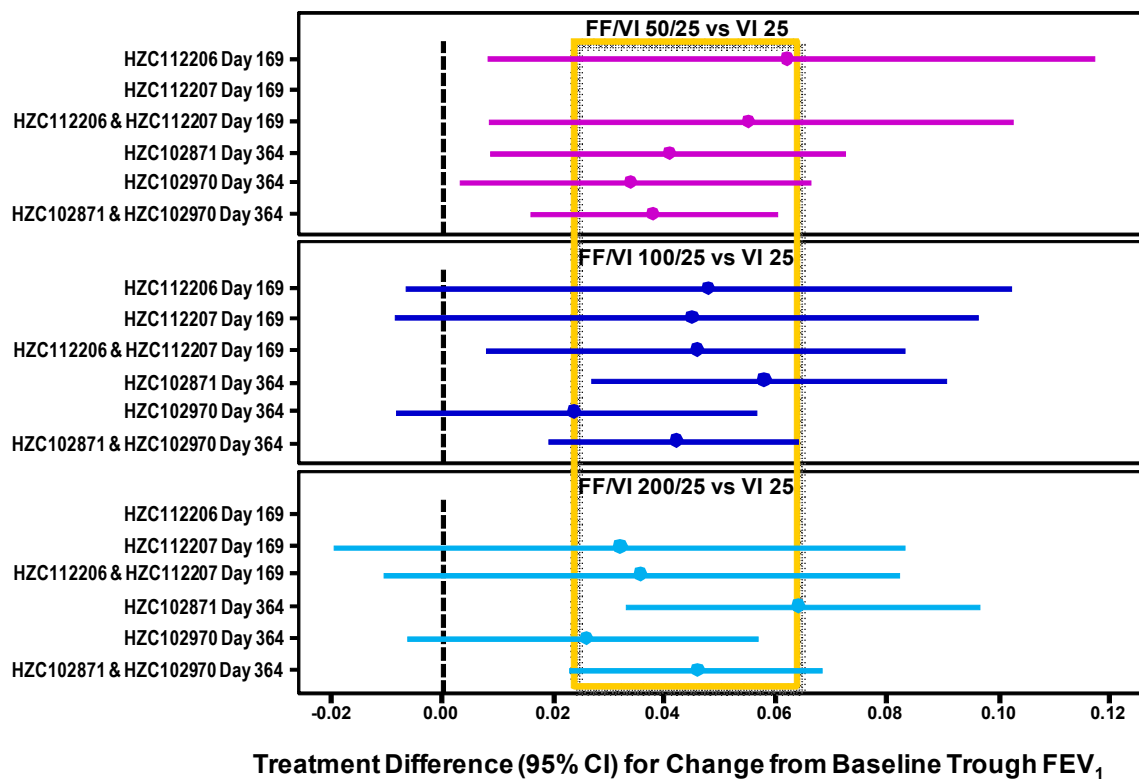
Since ICS monotherapy is not recommended for the treatment of subjects with COPD, the effectiveness of FF was evaluated in the context of the combination. The contribution of an ICS in a combination product on lung function (trough FEV₁) is relatively small. For example, compared with SAL 50 BID, treatment differences of 69mL and 67mL were observed with FP/SAL 250/50 BID and 500/50 BID, respectively. Similarly, compared with formoterol 9 BID, treatment differences of 20mL and 40mL were observed with budesonide/formoterol 160/9 BID and 320/9 BID, respectively, in subjects with COPD [Mahler, 2002; Hanania, 2003; Tashkin, 2008] (Table 3). The most important effects are those on symptomatic endpoints such as reduction in COPD exacerbations [Rabe, 2007]. Therefore, as discussed in Section 7.4.3.5.1, the FF/VI COPD clinical development program was designed to primarily evaluate the contribution of FF to FF/VI (by comparison of the latter with VI) by assessing the effect on the annual rate of moderate and severe COPD exacerbations, the primary endpoint in the two, 1-year exacerbation studies (HZC102970 and HZC102871). However, consistent with the clinical development programs for the currently available ICS/LABA combinations for COPD, the effect of FF on lung function was assessed by comparing the effects of FF/VI with VI on change from baseline in trough FEV₁ in the four primary COPD studies.

The 6-month, lung function studies (HZC112206 and HZC112207) showed statistically non-significant improvements in trough FEV₁ of 48 and 45 mL, respectively, for FF/VI 100/25 compared with VI at Day 169. However, the 46 mL improvement for this comparison in the integrated analysis of the two studies was significant ($p=0.017$) (Table

3). The magnitude of the effects on trough FEV₁ with FF/VI compared with VI is not dissimilar to that observed in previous studies of the currently approved ICS/LABA combinations (fluticasone propionate/salmeterol [FP/SAL] and budesonide/formoterol [BUD/FM]) in subjects with COPD (Table 3). The 1-year, exacerbation studies (HZC102970 and HZC102871) also demonstrated that all three strengths of FF/VI provided larger improvements in trough FEV₁ compared with VI 25 at all post-baseline time points over the course of the 1-year treatment period (Figure 4). The totality of these data demonstrate that there is a small but meaningful contribution of FF on lung function and is in the same range as for the ICS effect of other ICS/LABA combination products.

In neither the 6-month studies nor the 1-year exacerbation studies, was there evidence of a dose-response relationship for FF across the FF/VI strengths for lung function endpoints (Figure 28).

Figure 28 Treatment Difference (95% CI) for Change from Baseline Trough FEV₁ (L) at Day 169 (HZC112206 and HZC112207) and Day 364 (HZC102970 and HZC102871) in Subjects with COPD



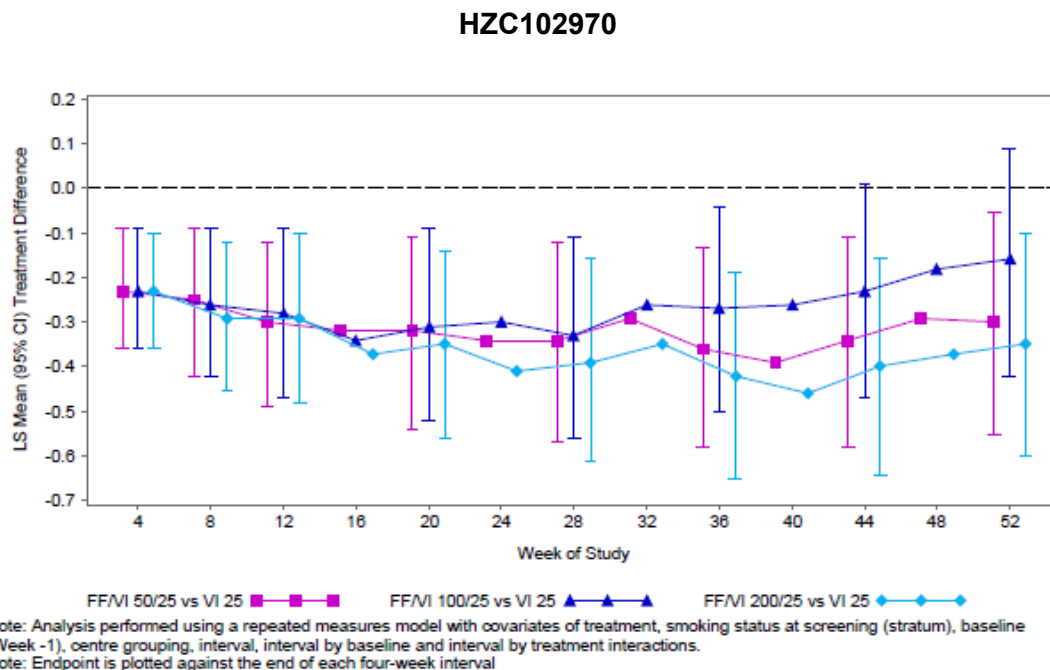
CI=confidence interval; FEV₁=forced expiratory volume in 1 second; FF=fluticasone furoate; VI=vilanterol

The 1-year exacerbation studies demonstrated that all three strengths of FF/VI provided numerical improvements in LS mean trough FEV₁ compared with VI 25 treatment alone at all post-baseline time points (Figure 4).

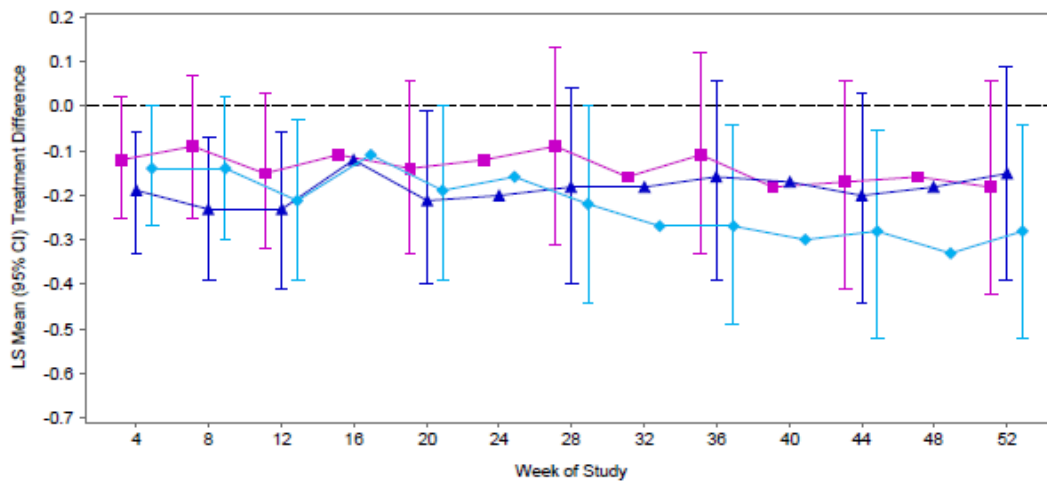
7.4.3.5.5. Other Symptomatic Endpoints

Other symptomatic contributions of FF to the combination (in rescue medication use, nighttime awakenings and symptoms) were observed. In the 1-year exacerbation studies, (HZC102970 and HZC102871) the mean number of occasions of rescue medication used (Figure 29) and the number of nighttime awakenings due to symptoms of COPD (Figure 30) were reduced in the FF/VI groups compared with the VI 25 group. Over each 4-week interval throughout the 1-year treatment period, all three FF/VI groups showed a numerical reduction in the LS mean number of occasions/24 hours of rescue use for compared with the VI 25 group, differences of -0.26 to -0.33 and -0.17 to -0.10 in the HZC102970 and HZC102871 studies, respectively. Similarly, over each 4-week interval throughout the 1-year treatment period, all three FF/VI groups showed a numerical reduction in the LS mean number of nighttime awakenings due to symptoms of COPD for compared with the VI 25 group, differences of -0.05 to -0.15 and -0.05 to -0.11 in the HZC102970 and HZC102871 studies, respectively.

Figure 29 Least Squares Mean Treatment Differences from VI 25 (95% CI) in IVRS Diary Mean Number of Occasions of Rescue Use (occasions/24 hours), Four-Week Intervals (ITT Population): Individual Study Results – 1-Year Exacerbation Studies (HZC102970 and HZC102871)



HZC102871

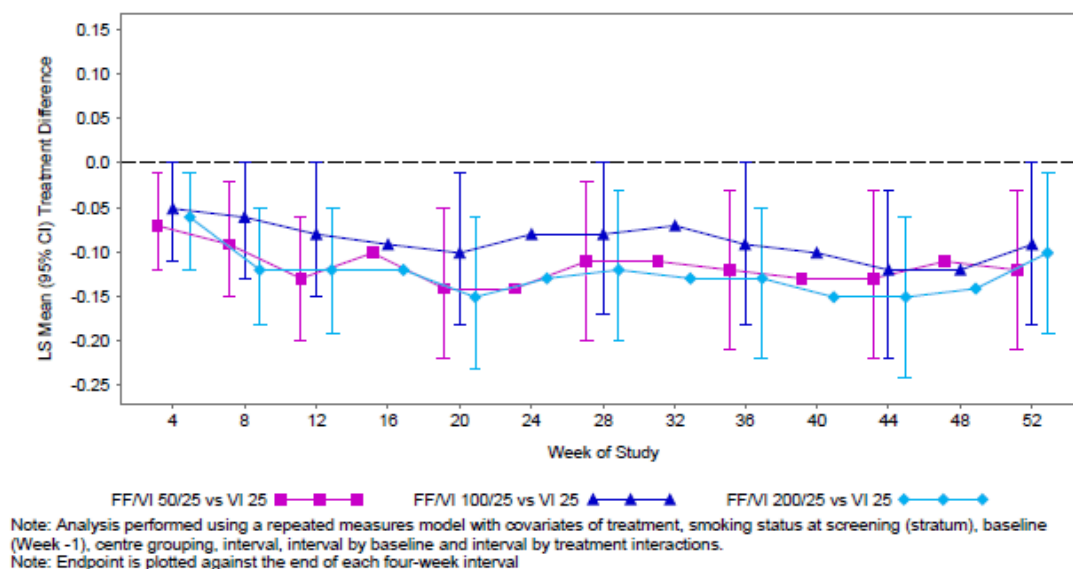


Note: Analysis performed using a repeated measures model with covariates of treatment, smoking status at screening (stratum), baseline (Week -1), centre grouping, interval, interval by baseline and interval by treatment interactions.
 Note: Endpoint is plotted against the end of each four-week interval

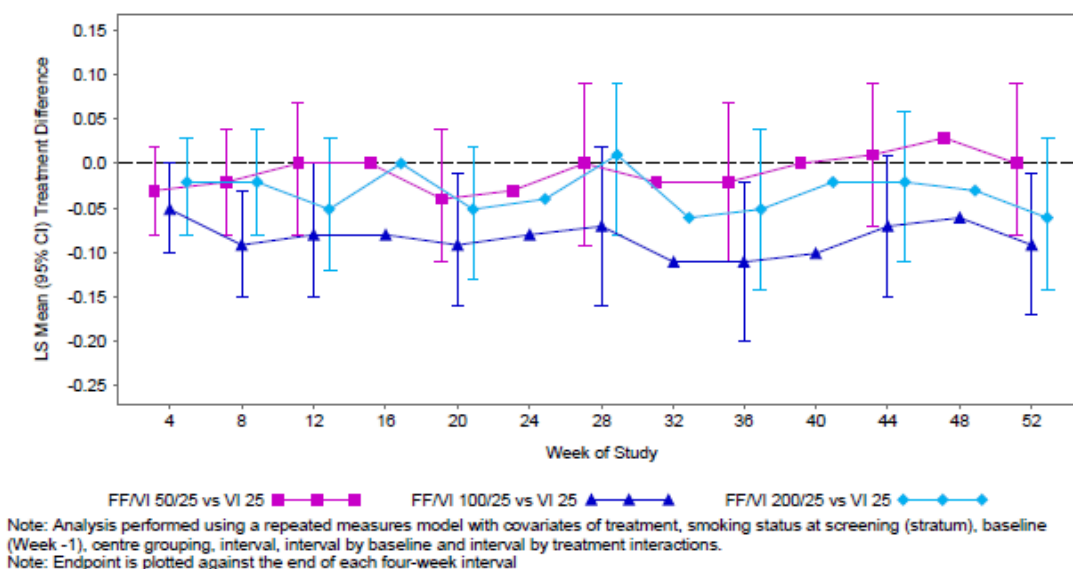
CI=confidence interval; FF=fluticasone furoate; ITT=Intent-to-Treat; IVRS=Interactive Voice Response System;
 VI=vilanterol

Figure 30 Least Squares Mean Treatment Differences from VI 25 (95% CI) in IVRS Diary Mean Number of Night-time Awakenings Due to Symptoms of COPD (occasions/24 hours), Four-Week Intervals (ITT Population): Individual Study Results – 1-Year Exacerbation Studies (HZA102970 and HZA102871)

HZA102970



HZA102871



CI=confidence interval; FF=fluticasone furoate; IVRS=Interactive Voice Response System; VI=vilanterol

Similarly, in the 6-month, lung function studies (HZA112206 and HZA112207), the number of occasions of rescue medication use and the number of nighttime awakenings

requiring rescue medication use were reduced for FF/VI 100/25 compared with VI 25 (Table 28); reductions compared with VI 25 were not observed for FF/VI 50/25 and 200/25. In both the 6-month lung function studies, LS mean breathlessness/dyspnea scores were lower in the FF/VI groups relative to the VI 25 group; but, the contribution of FF to FF/VI was not always demonstrated for cough and sputum scores (Table 28).

7.4.3.6. Subpopulation Analyses of the Primary/Co-Primary Endpoints in the Primary Studies

Effects of FF/VI treatment for the co-primary endpoints for the two, 6-month, lung function studies (weighted mean FEV₁ [0-4 hours] and trough FEV₁) and the primary endpoint for the two, 1-year exacerbation studies (annual rate of moderate and severe COPD exacerbations) were investigated for subgroups based on age, gender, race (white vs. non-white), smoking status (current vs. former smokers), percent predicted FEV₁, reversibility, cardiovascular history/risk factors, and geographical region (US vs. non-US and EU vs. non-EU) in the integrated analysis for each pair of studies.

With the exception of reversibility and cardiovascular history/risk (described below), there was no evidence of an inconsistent treatment effect for any of these subgroups (interaction tested at 10% level), with treatment differences in all subgroups directionally similar to the results for the overall population, indicating that FF/VI improved lung function and reduced the rate of moderate and severe exacerbations in the sub-populations.

A significant interaction with treatment was observed for weighted mean FEV₁ but not for trough FEV₁ in the 6-month, lung function studies (HZA112206 and HZA112207) by cardiovascular history/risk. However, both the group with a cardiovascular history/risk factors and the group without showed statistically significant reductions in weighted mean FEV₁ for all FF/VI strengths compared with placebo. A significant interaction with treatment was observed for weighted mean FEV₁ but not for trough FEV₁ in the 6-month, lung function studies by reversibility. As might be expected, the reversible subgroup demonstrated a greater magnitude of effect than the non-reversible group; however, efficacy (FF/VI compared with placebo) was demonstrated in both subgroups. A similar interaction was observed for trough FEV₁ in the 1-year exacerbation studies, with reversible subjects demonstrating a greater magnitude of effect than non-reversible subjects.

7.4.3.7. Efficacy Results from Studies Comparing FF/VI with Marketed Products

Three studies were conducted to compare the FF/VI combination with the currently marketed ICS/LABA combination of FP/salmeterol in subjects with COPD; HZA113109 and HZA112352 compared FF/VI 100/25 QD with FP/salmeterol 250/50 BID, the licensed strength for treatment of COPD in the US, and HZA113107 compared FF/VI 100/25 QD with FP/salmeterol 500/50 BID, the licensed strength for treatment of COPD in the EU.

The results of these studies were inconsistent. In Study HZA113109, subjects in the FF/VI 100/25 QD group demonstrated significantly greater change from baseline trough in 24-hour weighted mean FEV₁ (0-24 hours) compared with the lower strength of

FP/salmeterol (250/50) BID; but, Study HZC112352 was unable to replicate this result. Similarly, Study HZC113107 demonstrated no statistically significant difference between FF/VI 100/25 QD and the higher strength of FP/salmeterol (500/50) BID. These findings are perhaps not surprising given that in COPD the contribution of the corticosteroid in terms of lung function is very small, irrespective of dose. Results of these studies suggest that FF/VI 100/25 QD is at least as effective as FP/salmeterol BID on changes in lung function in subjects with COPD.

Although the statistical significance for the comparison between the FF/VI group and FP/salmeterol group varied across the three studies, all three studies demonstrated that treatment with FF/VI 100/25 QD provided consistent and clinically meaningful improvements in 24-hour weighted mean FEV₁ (as measured by the LS mean change from baseline trough FEV₁ on Treatment Day 84) of 174 mL, 142 mL and 130 mL, and in the HZC113019, HZC112352 and HZC113107 studies, respectively (Table 29).

Table 29 Statistical Analysis of Weighted Mean FEV₁ (L) Up to 24 Hours on Day 84 (ITT Population) – Individual Study Results: Supporting COPD Studies HZC113107, HZC113109 and HZC112352

Day 84	FF/VI 100/25 QD	FP/Salmeterol 250/50 BID	FP/Salmeterol 500/50 BID
HZC113109	N=260	N=259	
n	228	213	
LS Mean (SE)	1.513 (0.0153)	1.433 (0.0158)	
LS Mean Change (SE)	0.174 (0.0153)	0.094 (0.0158)	
Difference vs FP/SAL 250/50	0.080		
95% CI	(0.037, 0.124)		
p-value	<0.001		
HZC112352	N=250	N=252	
n	219	217	
LS Mean (SE)	1.475 (0.0182)	1.447 (0.0183)	
LS Mean Change (SE)	0.142 (0.0182)	0.114 (0.0183)	
Difference vs FP/SAL 250/50	0.029		
95% CI	(-0.022, 0.080)		
p-value	0.267		
HZC113107	N=266		N=262
n	224		233
LS Mean (SE)	1.417 (0.0148)		1.395 (0.0145)
LS Mean Change (SE)	0.130 (0.0148)		0.108 (0.0145)
Difference: FF/VI vs FP/SAL 500/50	0.022		
95% CI	(-0.018, 0.063)		
p-value	0.282		

FEV₁=forced expiratory volume in 1 second; FF=fluticasone furoate; FP=fluticasone propionate; ITT=Intent-to-Treat; LS=Least Squares; SAL=salmeterol; SE=standard error; VI=vilanterol
Analysis performed using ANCOVA with covariates of baseline FEV₁, reversibility stratum, smoking status (at Screening) and treatment

7.5. Safety Results

Key Finding(s)

- The AE profile of FF/VI was generally consistent with the known class effects of an ICS/LABA combination. The data indicate that BREO ELLIPTA can be safely administered to patients with COPD.
- The cardiovascular safety profile of VI and FF/VI was broadly consistent with the known pharmacology of LABAs in patients with COPD. There was no evidence for an effect of FF/VI (or VI) on cardiovascular parameters (vital signs, ECGs and 24-Hour Holter Monitoring) or events (including cardiac arrhythmias, ischemia, heart failure and stroke). There was no evidence of QTc prolongation.
- Pneumonia is a known potential risk with ICS use in patients with COPD. The incidence of AE reports of all pneumonias (including fatal and non-fatal reports) observed with BREO ELLIPTA in the 1-year, exacerbation studies was similar to the incidences reported in the 1-year, exacerbation studies of the currently available ICS/LABA combinations.
- There were seven pneumonia fatalities in the FF/VI 200/25 group, all of which occurred in one of the two, 1-year, exacerbation studies (HZC102871). Of these, two were at two different sites in Peru, one at a site in the United States and four at one site in the Philippines. For the latter site, compared with the other sites in the Philippines and the overall study population, the subjects were on average older, had a lower BMI and a lower Screening, post-bronchodilator percent predicted FEV₁.
- In 1-year exacerbation studies, the incidence of bone disorders was higher with FF/VI (3%) than with VI (1%); but, there was no evidence observed of a dose-related effect. Fractures customarily associated with corticosteroid use (e.g., spinal compression/thoracolumbar vertebral fractures, hip and acetabular fractures) occurred in <1% of subjects in all treatment arms.
- In subjects with COPD, there was no evidence for an effect of BREO ELLIPTA on HPA-axis (as measured by 24-hour serum or urinary cortisol excretion) or clinical chemistry or hematology.
- No clinically important ophthalmic findings were noted with FF/VI 100/25 QD in the 1-year safety study in subjects with asthma that was designed to look at potential ophthalmic effects (HZA106839). In addition, there was a low incidence of ocular events reported across the four, primary COPD studies.

The majority of the safety results presented in this Briefing Document are from the four primary COPD studies, the 6-month, lung function studies (HZC112206 and HZC112207) and the 1-year, exacerbation studies (HZC102970 and HZC102871). Since no additional safety findings were observed in the seven supporting COPD studies of shorter duration (i.e., 1-3 months) over what was observed in the four, primary studies, the safety results from the supporting studies are not discussed in this Briefing Document, with the exception of fatal AEs and 24-hour, serum cortisol data from the

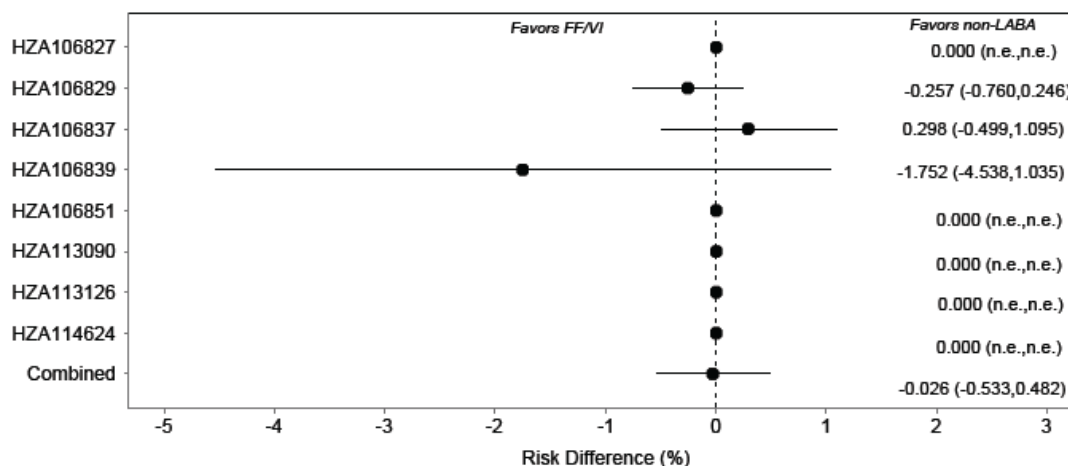
HZC110946 study and 24-hour urinary cortisol data from the HZC112352 and HZC113109 studies.

Eighteen clinical studies in subjects with asthma ([Figure 1](#)) provided data to support the safety profile of FF/VI. In addition to the safety data in subjects with COPD, 9,379 subjects were treated in the asthma clinical program, including 2,325 subjects randomized to FF/VI treatment, 1,870 of whom were randomized to FF/VI 100/25. Since no additional safety concerns were identified from the asthma data, only safety results from the asthma program that are relevant to the COPD NDA are summarized in this Briefing Document: the 24-hour serum cortisol results from the formal HPA-axis study (Study HZA106851) and the ophthalmic results from the 1-year safety study in subjects with asthma (HZA106839).

In the asthma studies included in the NDA, a total of four deaths were reported (two subjects in the FF 100 group [one occurred post-treatment], 1 subject in the FF/VI 100/25 group and 1 subject in the Placebo group). With regard to ICS/LABA class labelling and the risk for rare respiratory-related events including asthma-related death and intubation, none of these fatalities were determined to be asthma-related as adjudicated by an independent, blinded adjudication committee.

As presented in the NDA, for the composite endpoint of asthma-related hospitalizations, intubations, and deaths, there was no significant difference between the FF/VI group and the ICS group or non-LABA group ([Figure 31](#)).

Figure 31 Asthma Composite Endpoint, On-Treatment, by Study and Overall: FF/VI All Doses vs. Non-LABA All Doses



Note: For crossover studies, the first treatment period is integrated
Note: Risk difference and 95% CI based on the Mantel-Haenszel method. n.e. = not estimable
Non-LABA All Doses includes Placebo, Placebo+ICS, Placebo+OCS, FF 100, FF 200, FP 200, FP 500, FP 1000
FF/VI All Doses includes FF/VI 100/25, FF/VI 200/25
Combined estimates are stratified on study.

A broad spectrum of safety assessments were evaluated in the COPD Clinical Development Program to assess the safety of this ICS/LABA combination as shown in [Table 30](#).

Table 30 Safety Assessments Conducted in Primary COPD Studies (HZC112206/HZC112207/HZC102970/HZC102871)

	HZC112206 & HZC112207 (6-Mo, Lung Function Studies)	HZC102970 & HZC102871 (1-Yr Exacerbation Studies)
Adverse Event Assessments - All Visits	X	X
Oropharyngeal Examinations – All Visits	X	X
Blood Chemistry and Hematology (Including Serum Potassium and Glucose)		
Screening	X	X
Day 1 (Randomization – pre-dose)	N/A	X
Week 12 (pre-dose)	X ¹	X
Week 24 (pre-dose)	X ¹	N/A
Week 28 (pre-dose)	N/A	X
Week 52 (pre-dose)	N/A	X
Cortisol Assessments²		
Screening	24-hr Urine	N/A
Week 24	24-hr Urine	N/A
12-Lead ECG		
Screening	X	X
Day 1	X ³	X ⁴
Week 12	X ³	X ⁴
Week 24	X ⁴	N/A
Week 28	N/A	X ⁴
Week 52	N/A	X ⁴
24-Hr Holter Monitoring²		
Screening	X	N/A
Day 1	X	N/A
Week 12	X	N/A
Week 24	X	N/A
Vital Sign Assessments (Blood Pressure & Pulse)		
Screening	X	X
Day 1	X ³	X ⁴
Day 2	X ⁴	N/A
Week 1	X ⁴	N/A
Week 2	X ⁴	X ⁴
Week 4	X ⁴	X ⁴
Week 8	X ⁴	X ⁴
Week 12	X ³	X ⁴
Week 20	N/A	X ⁴
Week 24	X ⁴	N/A
Week 28	N/A	X ⁴
Week 36	N/A	X ⁴
Week 44	N/A	X ⁴
Week 52	N/A	X ⁴

Note: HZC112206 and HZC112207: Clinic visits at Screening, Days 1 (Randomization) and 2, Weeks 1, 2, 4, 8, 12, 16, 20, and 24 (Day 168 and Day 169); **HZC102970 and HZC102871:** Clinic visits occurred at Screening, Day 1 (Randomization) and Weeks 2, 4, 8, 12, 20, 28, 36, 44, and 52

1. Serum glucose and serum potassium conducted pre-dose and 30min post-dose
2. Conducted in a sub-set of subjects at selected sites (approximately 100 subjects per treatment arm)
3. Pre-dose and 10min post-dose
4. Pre-dose only

7.5.1. Safety Population and Groups

Intent-to-Treat Population (ITT): The ITT population, defined as all subjects who were randomized to and received at least one dose of randomized double-blind study medication in the treatment period, was the population of primary interest for all safety endpoints (except for 24-hour urinary cortisol and 24-hour Holter monitoring assessments that were conducted in a subset of subjects at selected study sites only in the two, 6-month, lung function studies: HZC112206 and HZC112207). The definition of the ITT population was consistent across the studies. The definitions of the Urinary Cortisol and Holter Populations are provided below:

Urinary Cortisol (UC) Population: The UC Population comprised a subset of subjects (approximately 100 subjects per arm) from the ITT Population for whom a 24-hour urine sample was collected and whose urine samples were not considered to have confounding factors that could have affected the interpretation of the results (e.g., low urine volume, creatinine excretion below the lower limit of threshold range, collection time <22 or >26 hours, use of a confounding medication [e.g., use of a depot, systemic, oral, parenteral, or inhaled corticosteroid within a certain timeframe prior to or during the urine collection, missing the baseline or end of treatment UC assessment]). The UC Population constituted the primary population for UC analyses.

Holter Population: The Holter population comprised a subset of subjects (approximately 100 subjects per arm) from the ITT population for whom Holter monitoring was assessed. This constituted the primary population for all Holter monitoring summaries.

In addition to evaluating the safety data for each individual study, subject-level integration of the safety data for adverse events, clinical laboratory tests (including liver function tests (LFT), glucose, potassium), 12-lead ECG, and vital sign measurements was performed for the two, 6-month, lung function studies (HZC112206 and HZC112207) and for the two, 1-year exacerbation studies (HZC102871 and HZC102970). In addition, 24-hour Holter and 24-hour urinary cortisol (UC) data were integrated for the two, 6-month, lung function studies (HZC112206 and HZC112207). With the exception of the summaries of overall Adverse Events, Serious Adverse Events, Fatal Adverse Events, Adverse Events leading to permanent discontinuation of study drug or withdrawal, Most Frequent Adverse Events, Adverse Events of Special Interest and pneumonias, safety data from Studies HZC112206 and HZC112207 were integrated separately to data from Studies HZC102871 and HZC102970, due to differences in study design, comparator arm, duration of study treatment, time-points of measurements and subject population, which could mask treatment effects if the data were combined.

7.5.2. Extent of Exposure

As shown in [Table 31](#) a total of 17,109 subjects, of whom 6,461 were treated with FF/VI, were enrolled in clinical studies in subjects with COPD or asthma. A total of 7,878 subjects with COPD were treated in the COPD Clinical Development Program. Of these, 2,034 subjects were treated with FF/VI 100/25. In the four primary COPD studies, 2,508 subjects were aged at least 65 years.

Table 31 Number of Subjects Treated in the COPD and Asthma Clinical Development Programs

	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25	FF/VI 400/25	VI	FF	All other treatments
COPD	1060	2034	1047	40	1727	613	1357
Asthma	0	1870	455	0	681	3814	2506
Total	1060	3904	1502	40	2408	4427	3863

FF=fluticasone furoate; VI=vilanterol

Notes:

Includes 10 studies in subjects with COPD and 16 studies in subjects with asthma and; does not include subjects in the COPD study B2C108562, which used an earlier formulation of VI or subjects in the two asthma studies FFA106783 and FFA20001, which used an earlier formulation of FF delivered via another dry powder inhaler (DISKUS)

Subjects in COPD crossover study HZC110946 are included for each treatment they received.

For the two asthma crossover studies FFA112202 and HZA113310 (once versus twice daily dosing studies) only the first treatment period was used

Numbers provided are not unique subjects (i.e., subjects who participated in more than one clinical study are counted more than once).

A total of 1,867 subjects were treated with the various strengths of FF/VI for at least 48 weeks; of these, 686 subjects were treated with the various strengths of FF/VI for more than 52 weeks. In addition, 381 subjects were treated with VI 25 mcg for 48 to 52 weeks and 209 subjects were treated with VI 25 mcg for more than 52 weeks. Thus, the number of subjects treated with FF/VI is considered sufficient to allow assessment of the safety of the combination product in subjects with COPD.

In addition, 1,406 subjects were treated in the 52 clinical pharmacology studies, of whom 1,351 were adults and 55 were paediatric subjects. Of the adult subjects, 333 subjects received FF/VI, 550 subjects received FF and 366 subjects received VI. The majority of these subjects were under 65 years of age with only 30 subjects aged at least 65 years.

7.5.3. Adverse Events

Adverse Events were evaluated in the seven, supporting COPD studies, the two, 4-week studies of FF/VI (HZC110946 and HZC111348), the 4-week, dose-ranging study of VI (B2C111045), the three, 3-month, FF/VI versus FP/salmeterol comparator studies (HZC112352, HZC113107 and HZC113109), and the 2-week, Phase IIa, safety and tolerability study with a previous formulation of VI (B2C108562). No additional AE findings were observed in these studies of shorter duration (≤ 3 months) over what was observed in the four, primary COPD studies of longer duration (the 6-month, lung function studies [HZC112206 and HZC112207] and the 1-year exacerbation studies [HZC102970 and HZC102871]). Therefore, the AE results from the supporting COPD studies are not summarized in this Briefing Document, with the exception of fatal AEs.

7.5.3.1. Overview of Adverse Events

Key Finding(s):

The AE profile of FF/VI was generally consistent with the known class effects of an ICS/LABA combination. The data indicate that BREO ELLIPTA can be safely administered to patients with COPD

Adverse events (AEs) were assessed in all of the COPD clinical studies. AE data from the 6-month, lung function studies (HZA112206 and HZA112207) are presented separately from the 1-year, exacerbation studies (HZA102970 and HZA102871), due to differences in study design, comparator arm, duration of study treatment, time-points of measurements and subject population.

In the 6-month, lung function studies (HZA112206 and HZA112207), the frequencies of any on-treatment AE, AEs leading to study drug discontinuation or withdrawal from the study, serious AEs (SAEs), and fatal events were similar between the FF/VI 100/25 and placebo groups ([Table 4](#)) in the 6-month, lung function studies (HZA112206 and HZA112207). Eleven subjects (<1% in all treatment arms) died during these studies. The deaths were attributed by investigators to ongoing medical conditions. None were considered related to the study drug. Further details are provided in [Section 7.5.3.3](#).

The 1-year, exacerbation studies (HZA102970 and HZA102871) included subjects with a history of moderate-severe COPD exacerbation in the year prior to Screening and, as such, included subjects with a higher risk of morbidity and mortality from respiratory causes due to their exacerbation history. Also, a placebo treatment arm was considered unethical in a population prone to moderate/severe COPD exacerbation. Therefore, AEs with FF/VI are compared with AEs with VI alone.

The overall incidence of any on-treatment AEs and AEs leading to study drug discontinuation or withdrawal from the study was generally similar across the FF/VI treatment groups ([Table 5](#)). The slightly higher AE rate in the FF/VI groups compared with the VI group was primarily driven by more events in the Infections and Infestations group including more reports of candidiasis. The incidence of SAEs and fatalities was similar across the treatment groups.

Fifty-three subjects (2%) died during the 1-year exacerbation studies, with a similar incidence of overall deaths across the treatment groups. The fatalities were attributed by the investigator to ongoing medical conditions. None were considered related to the study drug. The most common fatal events were those expected in an older population of subjects (pre-existing cardiac disorders and malignancies) or those that frequently occur in subjects with COPD (COPD, respiratory events, pneumonia). Further details are provided in [Section 7.5.3.3](#).

7.5.3.2. Common Adverse Events

Across the four, primary COPD studies, nasopharyngitis, headache, URTI, and oropharyngeal candidiasis (includes: oral candidiasis, oropharyngeal candidiasis, candidiasis, and oropharyngitis fungal) were the most frequently reported AEs. These events are summarized in [Table 6](#) (6-Month, Lung Function Studies HZC112206 and HZC112207) and [Table 7](#) (1-Year, Exacerbation Studies HZC102970 and HZC102871), and are included in the Adverse Reactions section of the proposed *Prescribing Information* for BREO ELLIPTA. These events are reported in the labelling for the current ICS/LABA treatments for COPD.

7.5.3.3. Deaths

In the 6-month, lung function studies (HZC112206 and HZC112207), 11 subjects died during the treatment or post-treatment study periods, 8 (one subject in the placebo group, three subjects in the VI 25 group and 2 in the FF/VI 50/25 group and one each in the FF/VI 100/25 and 200/25 groups) during the treatment period, and 3 (one subject in the placebo group, one subject in the FF 100 group and one subject in the FF/VI 100/25 group) during the post-treatment follow-up period ([Table 32](#)). Overall, the occurrence of on-treatment or post-treatment fatal events was low in both studies, with no remarkable differences in the incidence of fatal events across the treatment groups, with the exception that no fatal events occurred in the FF 200 group. None of the fatal events were considered related to treatment by the investigators and most were attributed to ongoing medical conditions. There were no remarkable differences in the exposure-adjusted numbers across the treatment groups; due to the small number of fatal events, these data are difficult to interpret.

Table 32 Summary of On-Treatment or Post-Treatment Fatal Adverse Events in Any Treatment Group (ITT Population): Integrated Study Results – 6-Month Lung Function Studies (H2C112206/H2C112207)

	Placebo N=412	FF/VI 50/25 N=206	FF/VI 100/25 N=410	FF/VI 200/25 N=205	VI 25 N=408	FF 100 N=410	FF 200 N=203
Subject Years	154	78	157	82	161	157	80
Preferred Term, n (%) [exposure-adjusted rate^{1,2}]							
Any Event	2 (<1) [13.0]	2 (<1) [25.6]	2 (<1) [12.7]	1 (<1) [12.2]	3 (<1) [18.6]	1 (<1) [6.4]	0 [0]
Death	0	0	1 (<1) [6.4]	0	0	0	0
Sudden cardiac death	0	0	0	0	1 (<1) [6.2]	0	0
Sudden death	1 (<1) [6.5]	0	0	0	0	0	0
Myocardial infarction	0	0	0	1 (<1) [12.2]	0	0	0
Myocardial ischaemia	1 (<1) [6.5]	0	0	0	0	0	0
Accidental poisoning	0	0	0	0	1 (<1) [6.2]	0	0
Alcohol poisoning	0	1 (<1) ³ [12.8]	0	0	0	0	0
Cerebral haemorrhage	0	1 (<1) ³ [12.8]	0	0	0	0	0
Thrombotic stroke	0	0	1 (<1) [6.4]	0	0	0	0
Gastrointestinal haemorrhage	0	1 (<1) [12.8]	0	0	0	0	0
Anaphylactic reaction	0	0	0	0	1 (<1) ⁴ [6.2]	0	0
Pulmonary embolism	0	0	0	0	0	1 (<1) [6.4]	0

FF=fluticasone furoate; ITT=Intent-to-Treat; VI=vilanterol

- Numbers represent the number of subjects with an event per 1000 subject-years of exposure; exposure-adjusted frequency is calculated as (1000 * Number of subjects with AE) divided by (Total duration of exposure in days / 365.25)
- Due to the small number of fatal events, the exposure adjusted data are difficult to interpret
- Both events occurred in the same subject
- The anaphylactic reaction in the subject in the VI 25 group was determined related to a nuclear stress test injection.

In the 1-year, exacerbation studies (H2C102970 and H2C102871), 53 subjects died during the treatment or post-treatment study periods. Forty-three subjects had fatal events that occurred during the treatment period (29 subjects in Study H2C102871 and 14 subjects in Study H2C102970), and 13 subjects had fatal events during the post-treatment period (9 in Study H2C102871 and 4 in Study H2C102970) (Table 33). It is of note that 3 of the 9 subjects with fatal events during the post-treatment period in Study H2C102871 had events that led to death that began during the on-treatment period, but the subjects' deaths occurred during the post-treatment period. It is also of note that of the 29 deaths in the H2C102871 study, 8 occurred at one site in the Philippines, and 4 of

these 8 deaths were due to pneumonia (See Section [7.5.3.6.1](#) for more details regarding pneumonia).

Overall, the occurrence of on-treatment or post-treatment fatal events was low (1% to 2%) across both of the 1-year, exacerbation studies. With the exception of the occurrence of 6 deaths due to pneumonia in the FF/VI 200/25 group (plus one subject in the FF/VI 200/25 group who was reported as having a fatal on-treatment SAE with a preferred term of COPD but the Investigator completed the pneumonia form in the Case Report Form page citing pneumonia at the time of death - the subject had a chest X-ray available that showed infiltrates - See Section [7.5.3.6.1](#)), there were no remarkable differences in the incidence of fatal events across the treatment groups. The most common fatal events were events that commonly occur in an older population of subjects (cardiac disorders that were pre-existing in this population, malignancies) or that are frequently seen in subjects with COPD (COPD exacerbations and pneumonia).

The percentages of subjects with fatal events that were cardiovascular in nature were similar across all treatment groups. While there were a higher number of subjects with fatal events that were cardiovascular in nature compared with the other Organ Classes, this is in all probability due to the more severe subject population enrolled in the 1-year exacerbation studies; differences do not appear to be driven by any particular cardiovascular event or group of events..

None of the fatal events in the 1-year exacerbation studies were considered related to treatment by the investigators. With the exception of a higher exposure-adjusted incidence of fatal pneumonia in the FF/VI 200/25 group compared with the remaining groups, (8.8 subjects with an event/1000 subject years for the FF/VI 200/25 compared to 0 to 1.5 subjects with an event/1000 subject years for the remaining treatment groups), there were no remarkable differences in the exposure-adjusted incidence across the treatment groups. The small number of fatal events makes the exposure-adjusted data difficult to interpret ([Table 33](#)).

Table 33 Summary of On-Treatment or Post-Treatment Fatal Adverse Events in Any Treatment Group (ITT Population): Integrated Study Results – 1-Year Exacerbation Studies (HZC102970/HZC102871)

	FF/VI 50/25 N=820	FF/VI 100/25 N=806	FF/VI 200/25 N=811	VI 25 N=818
Subject Years	687	676	685	661
Any Fatal Event, n (%) [exposure-adjusted rate^{1,2}]	16 (2) [23.3]	10 (1) [14.8]	14 (2) [20.5]	13 (2) [19.7]
Organ Class				
Preferred Term, n (%) [exposure-adjusted rate ^{1,2}]				
Cardiac Disorders				
Any event	5 (<1) [7.3]	4 (<1) [5.9]	3 (<1) [4.4]	5 (<1) [7.6]
Myocardial infarction	2 (<1) [2.9]	1 (<1) [1.5]	1 (<1) [1.5]	1 (<1) [1.5]
Cardiac arrest	1 (<1) [1.5]	2 (<1) [3.0]	0	0
Cardiopulmonary failure	1 (<1) [1.5]	0	0	1 (<1) [1.5]
Acute coronary syndrome	0	0	0	1 (<1) [1.5]
Acute myocardial infarction	1 (<1) [1.5]	0	0	0
Angina unstable	0	0	1 (<1) [1.5]	0
Arrhythmia	0	0	0	1 (<1) [1.5]
Cardiac failure	0	0	0	1 (<1) [1.5]
Cardiac failure congestive	0	1 (<1) [1.5]	0	0
Cardio-respiratory arrest	0	0	0	1 (<1) [1.5]
Coronary artery thrombosis	0	0	1 (<1) [1.5]	0
Respiratory, Thoracic and Mediastinal Disorders				
Any event	3 (<1) [4.4]	3 (<1) [4.4]	5 (<1) [7.3]	3 (<1) [4.5]
Chronic obstructive pulmonary disease	3 (<1) ³ [4.4]	2 (<1) [3.0]	4 (<1) [5.8]	3 (<1) [4.5]
Acute respiratory failure	0	2 (<1) ⁴ [3.0]	0	0
Respiratory failure	0	0	1 (<1) ⁵ [1.5]	0
Infections and Infestations				
Any event	1 (<1) [1.5]	1 (<1) [1.5]	6 (<1) [8.8]	3 (<1) [4.5]
Pneumonia	0	1 (<1) [1.5]	6 (<1) ⁵ [8.8]	1 (<1) [1.5]
Lower respiratory tract infection	0	0	0	1 (<1) [1.5]
Respiratory tract infection	0	0	0	1 (<1) [1.5]
Sepsis	0	0	0	1 (<1) [1.5]
Septic shock	0	0	1 (<1) [1.5]	0
Urinary tract infection bacterial	1 (<1) [1.5]	0	0	0
Neoplasms benign, malignant and unspecified				
Any event	4 (<1) [5.8]	1 (<1) [1.5]	2 (<1) [2.9]	1 (<1) [1.5]
Acute lymphocytic leukaemia	1 (<1) [1.5]	0	0	0
Diffuse large B-cell lymphoma	0	1 (<1) [1.5]	0	0
Lung squamous cell carcinoma stage unspecified	1 (<1) [1.5]	0	0	0
Metastases to bone	0	0	1 (<1) [1.5]	0
Metastases to gastrointestinal tract	1 (<1) [1.5]	0	0	0
Metastases to liver	0	0	1 (<1) [1.5]	0
Metastases to lung	0	0	1 (<1) [1.5]	0
Metastatic squamous cell carcinoma	0	0	0	1 (<1) [1.5]
Neuroendocrine tumour	1 (<1) [1.5]	0	0	0
Pancreatic carcinoma metastatic	0	0	1 (<1) [1.5]	0
Squamous cell carcinoma	1 (<1) [1.5]	0	0	0
Vascular Disorders				
Any event	1 (<1) [1.5]	1 (<1) [1.5]	1 (<1) [1.5]	1 (<1) [1.5]
Aortic aneurysm rupture	0	0	1 (<1) [1.5]	0
Arteriosclerosis	0	0	0	1 (<1) [1.5]
Hypertension	0	1 (<1) ⁴ [1.5]	0	0
Shock haemorrhagic	1 (<1) [1.5]	0	0	0
Gastrointestinal Disorders				

	FF/VI 50/25 N=820	FF/VI 100/25 N=806	FF/VI 200/25 N=811	VI 25 N=818
Any event	0	1 (<1) [1.5]	0	1 (<1) [1.5]
Abdominal pain	0	1 (<1) [1.5]	0	0
Abdominal pain lower	0	0	0	1 (<1) [1.5]
General Disorders and Administration Site Conditions				
Any event	1 (<1) [1.5]	0	0	1 (<1) [1.5]
Death	1 (<1) [1.5]	0	0	1 (<1) [1.5]
Nervous System Disorders				
Any event	2 (<1) [2.9]	0	0	0
Cerebrovascular accident	1 (<1) [1.5]	0	0	0
Loss of consciousness	1 (<1) [1.5]	0	0	0
Hepatobiliary Disorders				
Any event	0	1 (<1) [1.5]	0	0
Cholelithiasis	0	1 (<1) [1.5]	0	0
Musculoskeletal and Connective Tissue Disorders				
Any event	1 (<1) [1.5]	0	0	0
Intervertebral disc protrusion	1 (<1) ³ [1.5]	0	0	0

FF=fluticasone furoate; ITT=Intent-to-Treat; VI=vilanterol

1. Numbers represent the number of subjects with an event per 1000 subject-years of exposure; exposure-adjusted frequency is calculated as (1000 * Number of subjects with AE) divided by (Total duration of exposure in days / 365.25)

2. Due to the small number of fatal events, the exposure adjusted data are difficult to interpret

Note: Three subjects had events that began during the treatment period but the subjects died during the post-treatment period:

- Subject 068977/102558 had COPD post-treatment and intravertebral disc protrusion during the treatment period
- Subject 070244/112531 had hypertension during the post-treatment period and acute respiratory failure and COPD during the treatment period
- Subject 070244/112538 had respiratory failure during the post-treatment period and pneumonia during the treatment period

For the integrated analysis of the 11 (4 primary and 7 supporting) COPD clinical studies, overall, the incidence of fatalities was low (68 of 7,783 subjects, <1%) during the treatment or post-treatment periods. This incidence of mortality was not unexpected in a population of patients with moderate to severe COPD.

Sixty-five fatal events occurred across the seven integrated studies (11 fatal events in the 6-month, lung function studies [HZA112206 and HZA112207], 53 fatal events in the 1-year, exacerbation studies [HZA102970 and HZA102871], and one fatal event in Study B2C111045) (Table 34). In addition, three fatal events occurred in the studies comparing FF/VI versus FP/salmeterol: 1 subject died in the post-treatment period of Study HZA113107 and 2 subjects died during treatment with FP/salmeterol (one in Study HZA113109 and one in Study HZA112352).

In the seven integrated studies, fatal events occurred at similar incidences (2% or less) across all active treatment groups and the placebo group (Table 34). It is of note that the placebo exposure is from studies of shorter duration (i.e., 6-month, lung function studies and 1-month studies). In order to account for differences in exposure between the shorter and the longer term studies, incidence rates per 1000 patient years are also shown.

The percentages of subjects with fatal events that were cardiovascular in nature (including not only events in the Cardiac Disorders category, but also Vascular Disorders category, death, sudden cardiac death, sudden death, cerebral haemorrhage, cerebrovascular accident, loss of consciousness and thrombotic stroke) were similar across all treatment groups (0 to <1%). While there were a higher number of subjects with fatal events that were cardiovascular in nature across the FF/VI and VI 25 mcg groups in the 7-study integration, this is more a reflection of the study populations, (i.e., 60-62% of subjects in the 4 primary COPD studies had a history or risk of cardiovascular disease) and differences between studies (i.e., subjects in the 1-year exacerbation studies were treated for a longer duration compared with the subjects from the 6-month and 1-month studies) and the higher number of subjects enrolled in the 1-year studies compared with the number of subjects enrolled in the 6-month and 1-month studies. There was no increased incidence in exposure-adjusted fatal events that were cardiovascular in nature in the VI-containing groups (6.5 to 11.7 subjects with an event/1000 subject years) compared with placebo (12.0 subjects with an event/1000 subject years).

For the cardiac fatalities, no relevant differences were observed across the groups. Of the cardiac deaths, 7 of the 19 events were myocardial infarctions (MIs). For the respiratory deaths, 12 of the 15 events were COPD; all of these occurred in the 1-year exacerbation studies (HZC102970 and HZC102871), which recruited patients at an increased exacerbation risk compared to the shorter term placebo-controlled studies. Infection fatalities, specifically pneumonia, are discussed in Section 7.5.3.6.1. Neoplasms occurred primarily in the 1-year, exacerbation studies.

Table 34 Summary of On-Treatment or Post-Treatment Fatal Adverse Events in Any Treatment Group (Integrated COPD Studies)

Category, n (%) [exposure-adjusted rate]	Placebo N=584	FF/VI 50/25 N=1060	FF/VI 100/25 N=1249	FF/VI 200/25 N=1047	VI 25 N=1327	FF 100 N=410	FF 200 N=203
Any Fatal Event, n (%) [exposure-adjusted rate]	2 (<1) [12.0]	18 (2) [23.4]	12 (<1) [14.3]	15 (1) [19.5]	16 (1) [19.3]	1 (<1) [6.4]	0
Cardiac Disorders	1 (<1) [6.0]	5 (<1) [6.5]	4 (<1) [4.8]	4 (<1) [5.2]	5 (<1) [6.0]	0	0
Respiratory, Thoracic and Mediastinal Disorders	0	3 (<1) [3.9]	3 (<1) [3.6]	5 (<1) [6.5]	3 (<1) [3.6]	1 (<1) [6.4]	0
Infections and Infestations	0	1 (<1) [1.3]	1 (<1) [1.2]	6 (<1) [7.8]	3 (<1) [3.6]	0	0
Neoplasms benign, malignant and unspecified	0	4 (<1) [5.2]	1 (<1) [1.2]	2 (<1) [2.6]	1 (<1) [1.2]	0	0
General Disorders and Administration Site Conditions	1 (<1) [6.0]	1 (<1) [1.3]	1 (<1) [1.2]	0	2 (<1) [2.4]	0	0
Nervous System Disorders	0	3 (<1) [3.9]	1 (<1) [1.2]	0	0	0	0
Vascular Disorders	0	1 (<1) [1.3]	1 (<1) [1.2]	1 (<1) [1.3]	1 (<1) [1.2]	0	0
Gastrointestinal Disorders	0	1 (<1) [1.3]	1 (<1) [1.2]	0	1 (<1) [1.2]	0	0
Injury, Poisoning and Procedural Complications	0	1 (<1) [1.3]	0	0	1 (<1) [1.2]	0	0
Hepatobiliary Disorders	0	0	1 (<1) [1.2]	0	0	0	0
Musculoskeletal and Connective Tissue Disorders	0	1 (<1) [1.3]	0	0	0	0	0

FF=fluticasone furoate; VI=vilanterol

Studies included are HZC112206, HZC112207, HZC102871, HZC102970, HZC110946, HZC111348, B2C111045; however, no fatal AEs were reported in the HZC110946 and HZC111348 studies

1 one subject was recorded as having a fatal on-treatment SAE with a preferred term of COPD but also had the pneumonia eCRF page completed for a fatal pneumonia although no fatal AE of pneumonia was reported

Note: The VI 3, VI 6.25, VI 12.5, VI 50, and FF/VI 400/25 treatment groups are not shown due to the small number of subjects in each group. Only one fatal event was reported in these treatment groups: one subject (<1% [131.6]) in the VI 6.25 treatment group in Study B2C111045 died due to a subdural hematoma.

Note: Numbers in brackets [exposure adjusted rate] represent the number of subjects with an event per 1000 subject-years of exposure. Exposure-adjusted frequency is calculated as (1000 * Number of subjects with AE) divided by (Total duration of exposure in days / 365.25).

7.5.3.4. Serious Adverse Events

In the placebo-controlled, 6-month, lung function studies (HZA112206 and HZA112207), the incidence of on-treatment SAEs was lowest in the FF/VI 50/25 group (3%) and higher in the FF/VI 100/25, FF/VI 200/25 and the VI 25 groups (6%, 7% and 8%, respectively) than in the placebo group (5%), while the incidence of SAEs for both the FF 100 and FF 200 groups (5%) was the same as the placebo group (Table 35). COPD exacerbation was the most common SAE reported, with an incidence slightly higher in the VI 25 group (3%) compared with the remaining treatment groups (0 to 2%) and placebo (2%). Pneumonia was the next most frequent SAE, and was reported at a similar incidence across the active treatment groups and placebo (<1% to 1%). All other individual SAEs were reported by 2 subjects or fewer each with no indication of treatment differences.

Table 35 Summary of On-Treatment Serious Adverse Events (ITT Population): Integrated Study Results - 6-Month Lung Function Studies (HZA112206/HZA112207)

Organ Class, n (%)	Placebo N=412	FF/VI 50/25 N=206	FF/VI 100/25 N=410	FF/VI 200/25 N=205	VI 25 N=408	FF 100 N=410	FF 200 N=203
Any Event ¹	21 (5)	6 (3)	23 (6)	15 (7)	31 (8)	22 (5)	10 (5)
Respiratory, Thoracic and Mediastinal Disorders	8 (2)	0	9 (2)	7 (3)	12 (3)	2 (<1)	2 (<1)
Infections and Infestations	2 (<1)	1 (<1)	3 (<1)	4 (2)	6 (1)	4 (<1)	3 (1)
Cardiac Disorders	3 (<1)	1 (<1)	2 (<1)	2 (<1)	2 (<1)	2 (<1)	2 (<1)
Injury, Poisoning and Procedural Complications	3 (<1)	2 (<1)	3 (<1)	0	4 (<1)	1 (<1)	1 (<1)
Nervous System Disorders	0	2 (<1)	4 (<1)	1 (<1)	1 (<1)	4 (<1)	2 (<1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (<1)	0	1 (<1)	1 (<1)	3 (<1)	4 (<1)	0
Gastrointestinal Disorders	2 (<1)	1 (<1)	1 (<1)	1 (<1)	3 (<1)	2 (<1)	0
General Disorders and Administration Site Conditions	1 (<1)	0	0	1 (<1)	1 (<1)	1 (<1)	0
Metabolism and Nutrition Disorders	1 (<1)	0	0	0	1 (<1)	1 (<1)	1 (<1)
Musculoskeletal and Connective Tissue Disorders	0	0	1 (<1)	0	0	2 (<1)	0
Vascular Disorders	0	1 (<1)	0	0	1 (<1)	1 (<1)	0
Ear and Labyrinth Disorders	0	0	0	0	1 (<1)	1 (<1)	0
Renal and Urinary Disorders	1 (<1)	0	0	0	1 (<1)	0	0
Blood and Lymphatic System Disorders	0	0	0	0	0	1 (<1)	0
Hepatobiliary Disorders	0	0	1 (<1)	0	0	0	0
Immune System Disorders	0	0	0	0	1 (<1)	0	0

FF=fluticasone furoate; ITT=Intent-to-Treat; VI=vilanterol

- Individual subjects could have reported more than one event in each category or more than one event across multiple categories

In the 1-year, exacerbation studies (HZA102970 and HZA102871), the incidence of on-treatment SAEs was similar for all FF/VI treatment groups (15% to 17%) and for the VI 25 group (15%) (Table 36). COPD exacerbation and pneumonia were the most frequently reported SAEs. COPD exacerbation was reported with a similar incidence in the FF/VI groups (6% to 7%) compared with the VI 25 group (6%). Pneumonia was

reported at a higher incidence across the FF/VI treatment groups (3%) than in the VI 25 group (<1%); pneumonia is discussed further in Section 7.5.3.6.1. Other SAEs were reported in <1% of subjects in any treatment group.

Table 36 Summary of On-Treatment Serious Adverse Events (ITT Population): Integrated Study Results – 1-Year Exacerbation Studies (H2C102970/H2C102871)

Organ Class, n (%)	FF/VI 50/25 N=820	FF/VI 100/25 N=806	FF/VI 200/25 N=811	VI 25 N=818
Any Event ¹	136 (17)	123 (15)	124 (15)	126 (15)
Respiratory, Thoracic and Mediastinal Disorders	59 (7)	63 (8)	59 (7)	60 (7)
Infections and Infestations	35 (4)	43 (5)	37 (5)	20 (2)
Cardiac Disorders	14 (2)	17 (2)	10 (1)	16 (2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	13 (2)	7 (<1)	15 (2)	10 (1)
Gastrointestinal Disorders	10 (1)	6 (<1)	10 (1)	8 (<1)
Nervous System Disorders	6 (<1)	6 (<1)	6 (<1)	8 (<1)
Injury, Poisoning and Procedural Complications	9 (1)	4 (<1)	4 (<1)	4 (<1)
Vascular Disorders	3 (<1)	3 (<1)	5 (<1)	5 (<1)
Musculoskeletal and Connective Tissue Disorders	3 (<1)	1 (<1)	4 (<1)	6 (<1)
General Disorders and Administration Site Conditions	4 (<1)	3 (<1)	1 (<1)	3 (<1)
Hepatobiliary Disorders	2 (<1)	5 (<1)	0	4 (<1)
Metabolism and Nutrition Disorders	3 (<1)	3 (<1)	2 (<1)	3 (<1)
Renal and Urinary Disorders	4 (<1)	1 (<1)	1 (<1)	3 (<1)
Blood and Lymphatic System Disorders	0	3 (<1)	1 (<1)	1 (<1)
Anaemia	0	3 (<1)	1 (<1)	1 (<1)
Psychiatric Disorders	0	2 (<1)	1 (<1)	1 (<1)
Reproductive System and Breast Disorders	0	0	0	4 (<1)
Benign prostatic hyperplasia	0	0	0	3 (<1)
Endocrine Disorders	0	1 (<1)	1 (<1)	0
Eye Disorders	0	1 (<1)	1 (<1)	0
Immune System Disorders	2 (<1)	0	0	0
Investigations	0	2 (<1)	0	0
Skin and Subcutaneous Tissue Disorders	0	2 (<1)	0	0
Ear and Labyrinth Disorders	1 (<1)	0	0	0

FF=fluticasone furoate; ITT=Intent-to-Treat; VI=vilanterol

1. Individual subjects could have reported more than one event in each category or more than one event across multiple categories

A total of 10 SAEs were reported across the supporting studies H2C110946, H2C111348 and B2C111045, of which 5 occurred during treatment (one [ulcerative colitis] during treatment with FF/VI 400/25 in Study H2C111348 and four during treatment with VI 3 to 12.5 mcg in Study B2C111045). In the three studies comparing FF/VI with FP/salmeterol, the incidence of on-treatment SAEs was low ($\leq 3\%$ in any treatment group) and, in general, the types of SAEs reported were similar for the two treatments.

7.5.3.5. Adverse Events Leading to Withdrawal from Investigational Product/Study

In subjects with COPD, the number of withdrawals due to AEs was low and no pattern was discernible in the types of AEs that led to withdrawal. In the integrated summary for the 6-month, lung function studies (H2C112206 and H2C112207), the incidence of AEs

leading to permanent discontinuation of study drug or withdrawal was similar across all active treatment groups (9% to 11%) and the placebo group (9%), with the exception of a slightly lower incidence in the FF 200 group (7%) ([Table 37](#)). The Infections and Infestations category had the highest incidence of AEs reported as leading to permanent discontinuation of study drug or withdrawal from the study (3% to 4% across all active treatment groups compared with 3% in placebo). Within this category, pneumonia, upper respiratory tract infection and lower respiratory tract infection were the most common events, and the incidence of these events were similar (0 to 2%) across all active treatment groups and placebo. The Cardiac Disorders category had the second highest incidence of AEs leading to permanent discontinuation of study drug or withdrawal from the study (2% to 4% in the active treatment groups compared with 3% in placebo). The most common events within this category were ventricular tachycardia and ventricular extrasystoles; these events occurred at similar incidences (0 to $\leq 1\%$) across the treatment groups. The Respiratory, thoracic and mediastinal disorders category had the third highest incidence of AEs leading to permanent discontinuation of study drug or withdrawal from the study (0 to 3% in the active treatment groups compared with 2% in the placebo group); COPD exacerbation was the most common event in this category, with a similar or lower incidence in the active treatment groups (0-2%) compared with the placebo group (2%). The remaining AEs occurred a low incidence (0- $<1\%$) within each treatment group.

Table 37 Summary of On-Treatment Adverse Events Leading to Permanent Discontinuation of Study Drug or Withdrawal from the Study (ITT Population): Integrated Study Results – 6-Month Lung Function Studies (HZC112206/HZC112207)

Organ Class, n (%)	Placebo N=412	FF/VI 50/25 N=206	FF/VI 100/25 N=410	FF/VI 200/25 N=205	VI 25 N=408	FF 100 N=410	FF 200 N=203
Any Event ¹	39 (9)	19 (9)	36 (9)	23 (11)	40 (10)	37 (9)	15 (7)
Infections and Infestations	11 (3)	7 (3)	16 (4)	9 (4)	12 (3)	13 (3)	8 (4)
Cardiac Disorders	12 (3)	8 (4)	11 (3)	7 (3)	10 (2)	14 (3)	4 (2)
Respiratory, Thoracic and Mediastinal Disorders	9 (2)	0	8 (2)	6 (3)	9 (2)	5 (1)	2 (<1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (<1)	0	1 (<1)	0	3 (<1)	3 (<1)	0
Nervous System Disorders	1 (<1)	2 (<1)	2 (<1)	1 (<1)	2 (<1)	1 (<1)	0
Gastrointestinal Disorders	2 (<1)	2 (<1)	0	0	1 (<1)	1 (<1)	1 (<1)
General Disorders and Administration Site Conditions	1 (<1)	1 (<1)	0	0	3 (<1)	0	0
Injury, Poisoning and Procedural Complications	0	1 (<1)	0	0	4 (<1)	0	0
Psychiatric Disorders	2 (<1)	0	0	0	1 (<1)	0	1 (<1)
Investigations	1 (<1)	0	1 (<1)	0	0	1 (<1)	0
Musculoskeletal and Connective Tissue Disorders	1 (<1)	0	0	0	1 (<1)	0	0
Blood and Lymphatic System Disorders	0	0	0	0	0	1 (<1)	0
Ear and Labyrinth Disorders	0	0	0	0	0	1 (<1)	0
Eye Disorders	1 (<1)	0	0	0	0	0	0
Immune System Disorders	0	0	0	0	1 (<1)	0	0
Metabolism and Nutrition Disorders	0	0	0	0	0	0	1 (<1)
Skin and Subcutaneous Tissue Disorders	0	0	1 (<1)	0	0	0	0
Vascular Disorders	0	0	0	0	1 (<1)	0	0

FF=fluticasone furoate; ITT=Intent-to-Treat; VI=vilanterol

- Individual subjects could have reported more than one event in each category or more than one event across multiple categories

In the integrated summary for the 1-year, exacerbation studies (HZC102970 and HZC102871), the incidence of AEs leading to permanent discontinuation of study drug or withdrawal from the study was similar across all FF/VI treatment groups (6% to 8%) and the VI 25 treatment group (6%) (Table 38). The Respiratory, Thoracic and Mediastinal disorders category had the highest incidence of AEs leading to permanent discontinuation of study drug or withdrawal from the study, with COPD exacerbation being the most common event: 1% to 2% in the FF/VI treatment groups compared with 1% in the VI 25 group. The remaining AEs in this category occurred at a low incidence (0-<1%) within each treatment group. The Cardiac Disorders category had the second highest incidence of AEs leading to permanent discontinuation of study drug or withdrawal from the study (1% to 2% in the FF/VI treatment groups compared with <1% in VI 25 group); all individual AEs in this category occurred at an incidence of <1% in all treatment groups. Atrial fibrillation and myocardial infarction were the most common events in this category and occurred at similar incidences across the treatment groups. The Infections and Infestations category had the next highest incidence of AEs reported as leading to permanent discontinuation of study drug or withdrawal from the study (<1% to 2% in the FF/VI groups compared with <1% in the VI 25 group; all individual AEs in this category

occurred at an incidence of <1% in all treatment groups. Within this category, pneumonia was the most frequent event and occurred in 3 (<1%), 5 (<1%) and 8 (<1%) subjects in the FF/VI 50/25, 100/25 and 200/25 groups, respectively, compared with 3 subjects (<1%) in the VI 25 group.

Table 38 Summary of On-Treatment Adverse Events Leading to Permanent Discontinuation of Study Drug or Withdrawal from the Study (ITT Population): Integrated Study Results – 1 Year Exacerbation Studies (HZC102970/HZC102871)

Organ Class, n (%)	FF/VI 50/25 N=820	FF/VI 100/25 N=806	FF/VI 200/25 N=811	VI 25 N=818
Any Event	53 (6)	62 (8)	61 (8)	45 (6)
Respiratory, Thoracic and Mediastinal Disorders	17 (2)	21 (3)	18 (2)	17 (2)
Cardiac Disorders	12 (1)	14 (2)	11 (1)	8 (<1)
Infections and Infestations	6 (<1)	12 (1)	18 (2)	7 (<1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9 (1)	6 (<1)	12 (1)	8 (<1)
Nervous System Disorders	3 (<1)	4 (<1)	2 (<1)	5 (<1)
Gastrointestinal Disorders	1 (<1)	1 (<1)	4 (<1)	3 (<1)
General Disorders and Administration Site Conditions	3 (<1)	3 (<1)	1 (<1)	2 (<1)
Psychiatric Disorders	2 (<1)	1 (<1)	1 (<1)	2 (<1)
Skin and Subcutaneous Tissue Disorders	1 (<1)	2 (<1)	0	1 (<1)
Vascular Disorders	1 (<1)	0	2 (<1)	1 (<1)
Hepatobiliary Disorders	1 (<1)	2 (<1)	0	0
Investigations	2 (<1)	1 (<1)	0	0
Musculoskeletal and Connective Tissue Disorders	0	2 (<1)	0	1 (<1)
Metabolism and Nutrition Disorders	0	0	2 (<1)	0
Blood and Lymphatic System Disorders	0	1 (<1)	0	0
Eye Disorders	0	0	1 (<1)	0
Injury, Poisoning and Procedural Complications	0	1 (<1)	0	0
Renal and Urinary Disorders	0	0	1 (<1)	0

FF=fluticasone furoate; ITT=Intent-to-Treat; VI=vilanterol

1. Individual subjects could have reported more than one event in each category or more than one event across multiple categories

7.5.3.6. Adverse Events of Special Interest (AESI)

Based on the known pharmacology and side effect profile of corticosteroids and beta₂-agonists, AESIs were defined *a priori* as cardiovascular effects, effects on glucose, effects on potassium, tremor, hypersensitivity, bone disorders, local steroid effects (e.g., oral candidiasis, hoarseness), ocular effects, pneumonia and lower respiratory tract infection (LRTI), and systemic corticosteroid effects (e.g., HPA axis). All AE (MedDRA) preferred terms that related to these AE groups were specifically evaluated. [Appendix 4](#) provides the selected preferred terms within each of the categories of AESI.

The 6-month, lung function studies (HZC112206 and HZC112207) are the most informative for assessing the AESI as these studies were placebo-controlled and included FF/VI and FF and VI monotherapy arms. There was no difference between treatment groups for any LABA-associated effects (tremor, hypertension or changes in serum potassium) ([Table 8](#)). Local corticosteroid effects (including oropharyngeal and oral

candidiasis) occurred at higher incidences in the FF-containing treatment groups compared with the placebo and VI groups, though no dose response effect was apparent (Table 8). Systemic corticosteroid effects and effects on glucose were not different between treatment groups.

Consistent with the AESI profile observed in the 6-month , lung function studies, in the 1-year exacerbation studies (HZC102970 and HZC102871) there was no difference between treatment groups for any LABA-associated effects (tremor, hypertension or changes in serum potassium). Local corticosteroid effects (including oropharyngeal and oral candidiasis) occurred at higher incidences in the FF-containing treatment groups compared with the VI 25 group, though no dose response effect was apparent, and there was no difference in effects of glucose across the treatment groups (Table 39). No systemic corticosteroid effects were reported in any of the treatment groups.

Table 39 Summary of On-Treatment Adverse Events of Special Interest (ITT Population): Integrated Results – 1-Year Exacerbation Studies (HZC102970/HZC102871)

	FF/VI 50/25 N=820	FF/VI 100/25 N=806	FF/VI 200/25 N=811	VI 25 N=818
LABA-Associated Events, n (%)				
Hypertension	32 (4)	36 (4)	36 (4)	25 (3)
Tremor ¹	1 (<1)	2 (<1)	2 (<1)	3 (<1)
Effects on potassium	5 (<1)	1 (<1)	2 (<1)	8 (<1)
ICS-Associated Events, n (%)				
Local steroid effects ²	142 (17)	121 (15)	140 (17)	96 (12)
Effects on glucose	18 (2)	15 (2)	22 (3)	14 (2)
Systemic steroid effects ³	0	0	0	0

FF=fluticasone furoate; ICS=inhaled corticosteroid; ITT=Intent-to-Treat; LABA=long-acting beta₂-agonist; VI=vilanterol

1. Tremor: includes terms of essential tremor and tremor
2. Local steroid effects: includes terms such as candidiasis, oropharyngeal candidiasis, oral candidiasis, dysphonia, throat irritation, etc.
3. Systemic steroid effects: includes terms such as adrenal insufficiency, adrenal suppression, cortisol free urine abnormal, cortisol free urine decreased, Cushing's syndrome, hyperadrenalism, hyperadrenocorticism, hypothalamo-pituitary disorder, etc.

In the Phase IIIb supporting studies comparing FF/VI 100/25 with either FP/salmeterol 250/50 (HZC113109, and HZC112352) or FP/salmeterol 500/50 (HZC113107), the incidence of local corticosteroid effects was lower in the FF/VI 100/25 groups (1% to 4%) compared with the FP/salmeterol groups (4% to 8%).

7.5.3.6.1. *Pneumonia*

Pneumonia is a well documented risk associated with the use of ICS in patients with COPD. An increased risk of pneumonia was observed in the FF/VI COPD Program, which was consistent with what has been described in the literature for other ICS/LABA combinations. The pneumonia risk appears to be primarily related to the severity of COPD (as indicated by FEV₁), the underlying health status (as reflected in BMI), as well as a history of previous pneumonia.

As repeatedly shown in clinical trials, patients with COPD are at an increased risk of developing pneumonia [Mannino, 2009]. Patients with severe COPD have an even greater risk of developing pneumonia. Once hospitalized, these COPD patients suffer from a higher in-hospital mortality, not only from the pneumonia but also from other co-morbidities [Holguin, 2005]. It is also well documented that COPD patients treated with an ICS/LABA combination, in order to reduce COPD exacerbations, show an increased incidence of pneumonia when compared to patients not receiving an ICS. This has been described in multiple studies and meta-analyses [Calverley, 2007; Sharafkhaneh, 2012; Doherty, 2012; Drummond, 2008]. However, in most of these studies, the data regarding pneumonias are limited, since pneumonias were only collected as adverse events, with no *a priori* definition, no detailed clinical assessments and no requirement for chest X-ray confirmation. In contrast, in the FF/VI COPD Clinical Development Program, GSK took a more rigorous approach to better understand and characterize the pneumonia risk associated with the use of ICS in patients with COPD. In particular, the protocols for the 1-year, exacerbation studies (HZC102970 and HZC102871) included an *a priori* guidance of what should be classified as pneumonia and required chest X-ray confirmation within 48 hours of diagnosis for all suspected pneumonias, with the chest X-rays over-read by an independent radiologist from a central vendor to confirm the presence of new radiographic findings compatible with pneumonia. In addition, Investigators were asked to record details of all suspected pneumonias on a specific pneumonia form and on the AE/SAE form in the CRF. The protocols for the 6-month, lung function studies (HZC112206 and HZC112207) advised Investigators that all suspected cases of pneumonia should be considered for radiographic confirmation within 48 hours of diagnosis and to report all diagnoses of pneumonia (radiographically confirmed or unconfirmed) as an AE/SAE and to record the chest X-ray results on a form in the CRF. Thus, we were able to obtain more robust data describing pneumonias.

In the two, 6-month, lung function studies (HZC112206 and HZC112207), a total of 32 subjects developed pneumonia (recorded as an AE/SAE). The incidence of pneumonia was low (<1% to 2% of subjects) across the groups (Table 40). The event rate of pneumonia was higher in all active treatment groups, including the VI 25 group, compared with the placebo group. For 16 of the 32 events, the pneumonias were serious, with the highest incidences in the VI 200/25 and VI 25 groups. No pneumonia fatalities were reported. Note: subjects were to be withdrawn from the HZC112206 and HZC112207 studies if pneumonia (presumptive diagnosis or radiographically confirmed) occurred.

Table 40 Summary of Pneumonia-Related Adverse Events (ITT Population): Integrated Study Results – 6-Month Lung Function Studies (HZA112206/HZA112207)

	Placebo N=412	FF/VI 50/25 N=206	FF/VI 100/25 N=410	FF/VI 200/25 N=205	VI 25 N=408	FF 100 N=410	FF 200 N=203
Subjects with Pneumonia¹, n (%)	3 (<1)	3 (1)	6 (1)	4 (2)	7 (2)	6 (1)	3 (1)
Event rate ²	19.5	38.3	38.1	48.7	43.4	38.2	37.6
Subjects with Serious Pneumonia^{1,3}, n(%)	1 (<1)	1 (<1)	1 (<1)	3 (1)	5 (1)	3 (<1)	2 (<1)
Event rate ²	6.5	12.8	6.4	36.5	31.0	19.1	25.1
Subjects with Fatal Pneumonia¹, n (%)	0	0	0	0	0	0	0

FF=fluticasone furoate; ITT=Intent-to-Treat; VI=vilanterol

Note: Pneumonia events were taken from the adverse event pages only.

1. Under "pneumonia" a composite of many MedDRA preferred terms is captured
2. Within each category, event rate is calculated as (1000 * Number of events of pneumonia) divided by (Total duration of exposure in days / 365.25)
3. Required hospitalization

In the 1 year exacerbation studies (HZA102970 and HZA102871), in a more severely affected COPD population with a history of COPD exacerbations, and due to the longer duration of the exacerbation trials, more pneumonias were reported overall. An increased incidence of pneumonia was observed in the FF/VI groups (range 6 to 7%) compared with the VI 25 group (3%), with no apparent FF dose-related trend (Table 41). Chest X-rays, which were performed in 81 to 93% of the pneumonia events, showed compatible infiltrates in 50 to 62% of the events for which an X-ray was obtained. A total of nine fatal cases with pneumonia were reported during the 1-year exacerbation studies. Two fatal pneumonia-related events were reported in study HZA102970 (one during treatment in the FF/VI 100/25 group and one post-treatment in a subject who was randomized to VI 25 during the treatment period) and 7 fatal pneumonia-related events were reported in study HZA102871 (all in the FF/VI 200/25 group). Of the seven fatalities in the HZA102871 study, two were at two different sites in Peru, one at a site in the United States and four at one site in the Philippines. For the latter site, compared with the other sites in the Philippines and the overall study population, the subjects were on average older (mean age 63.0, 63.6 and 66.2 years, respectively) had a lower BMI (mean BMI 21.22, 26.69 and 20.39 kg/m², respectively) and a lower Screening, post-bronchodilator percent predicted FEV₁ (mean 44.9, 45.2 and 39.9%, respectively). In addition, this site reported 8 (23%) of the 35 deaths from any cause in this study; 8 of 54 (15%) subjects at this site had a fatal event compared with 2% for the overall study. There was significantly increased risk for time to death from any cause at this center compared to other centers in the Philippines (p=0.0223) and for the Philippines compared to all other countries (p=0.00004). None of the subjects with fatal pneumonia had received either the pneumococcal or influenza vaccine.

Table 41 Summary of Pneumonia-Related Adverse Events (ITT Population): Integrated Study Results – 1-Year Exacerbation Studies (HZC102970/HZC102871)

	FF/VI 50/25 N=820	FF/VI 100/25 N=806	FF/VI 200/25 N=811	VI 25 N=818
Subjects with pneumonia¹, n (%)	48 (6)	51 (6)	55 (7)	27 (3)
Event rate ²	78.6	85.7	94.9	42.3
Subjects with Serious Pneumonia^{1,3}, n (%)	24 (3)	25 (3)	23 (3)	8 (<1)
Event rate ²	37.8	42.9	35.1	12.1
Subjects with Fatal Pneumonia¹, n (%)	0	1 ⁴ (<1)	7 ⁵ (<1)	1 ⁶
Event rate ²	0	1.5	10.2	0

FF=fluticasone furoate; ITT=Intent-to-Treat; VI=vilanterol

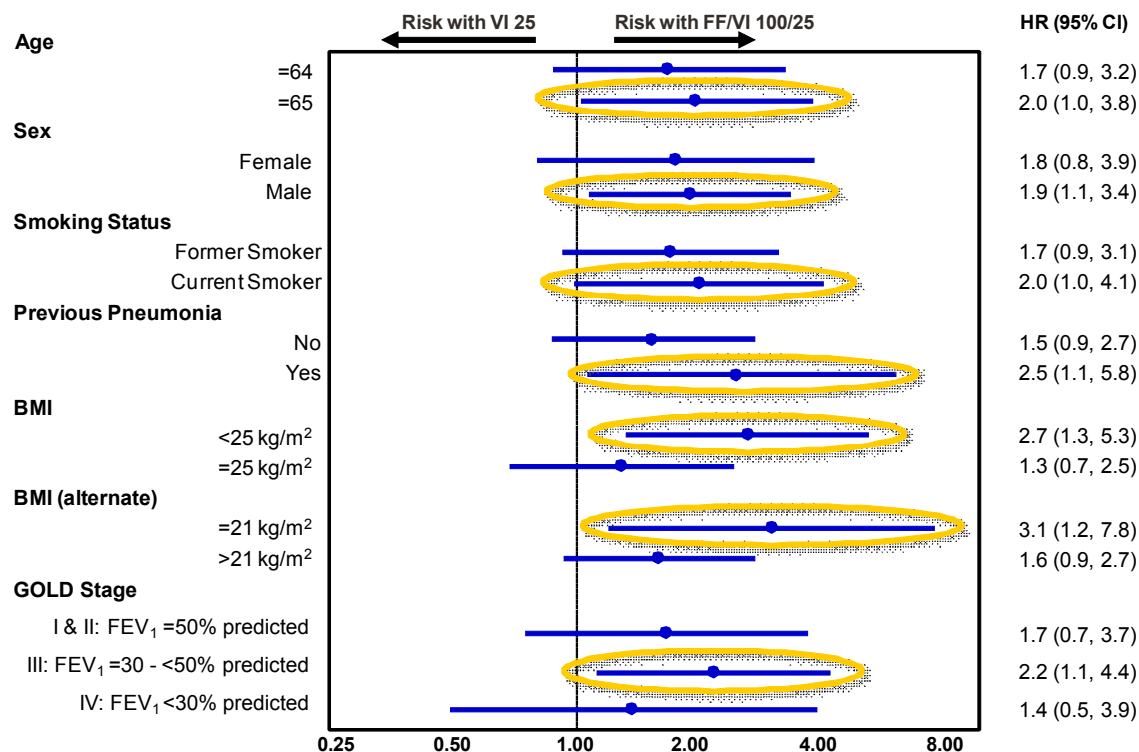
Note: Pneumonia events were taken from the adverse event pages

1. Under “pneumonia” a composite of many MedDRA preferred terms is captured
2. Within each category, event rate is calculated as (1000 * Number of events of pneumonia) divided by (Total duration of exposure in days / 365.25)
3. Resulted in hospitalization
4. Event occurred in the HZC102970 study at an investigative site in the US
5. All events occurred in the HZC102871 study: three subjects at one investigative site in the Philippines, one subject at an investigative site in the US and two subjects at two investigative sites in Peru; also includes one subject who was reported as having a fatal on-treatment SAE with a preferred term of COPD but the Investigator (same site in the Philippines noted above) completed the pneumonia form in the Case Report Form page citing pneumonia at the time of death - the subject had a chest X-ray available that showed infiltrates.
6. One post-treatment (25 days following last dose) fatal pneumonia occurred in the HZC102970 study at an investigative site in South Africa

In order to clarify whether certain patients are at increased risk to develop pneumonia, the pneumonia adverse events of the 1-year, exacerbation studies (HZC102970 and HZC102871) were analyzed by subgroup factors. As expected and as described for other ICSs in the literature, elderly patients as well as men showed a trend towards an elevated risk of time to first pneumonia on FF/VI 100/25 compared with VI ([Figure 32](#)). Also current smokers, patients with a history of previous pneumonia, patients with a low BMI (<25 kg/m²), and a lower predicted FEV₁ value (<50% of predicted) carried a higher risk for developing pneumonia on FF/VI. These data are reflected in the proposed *Prescribing Information* for BREO ELLIPTA and are the same as those demonstrated in other large COPD studies with ICS, specifically the TORCH trial [[Crim, 2009](#)].

Note: The most severe group (FEV₁ <30% of predicted) comprised only 15% of the patients. Therefore it is difficult to draw meaningful conclusions in this sub-group.

Figure 32 Time to First Pneumonia in Subgroups: FF/VI 100/25 vs VI 25 – Integrated Study Results: 1-Year Exacerbation Studies (HZC102970/HZC102871)



BMI=body mass index; CI=confidence interval; FEV₁=forced expiratory volume in 1 second; FF=fluticasone furoate; HR=hazard ratio; VI=vilanterol

7.5.3.6.2. Bone Disorders

Key Finding(s):

In 1-year exacerbation studies, the incidence of bone disorders was higher with FF/VI (3%) than with VI (1%); but, there was no evidence observed of a dose-related effect. Fractures customarily associated with corticosteroid use (e.g., spinal compression/thoracolumbar vertebral fractures, hip and acetabular fractures) occurred in <1% of subjects in all treatment arms.

A modest increase in risk of fracture among ICS-treated patients with COPD is a known potential risk, though this observation is not consistent across published studies [Lehouck, 2011; Weldon, 2009; Christensson, 2008]. Studies in adults with COPD yield varied evidence for the direct effect of ICS on bone mineral density (BMD) and fracture. The incidence of AEs related to bone disorders/fractures was recorded in the four primary COPD studies (HZC112206, HZC112207, HZC102970, and HZC102871).

In the 6-month, lung function studies (HZA112206 and HZA112207), bone disorder AEs were slightly more frequent in the FF 200 group (2%) (study HZA112207 only) than in the other active treatment groups (0 to 1%). Specifically, in the FF/VI 100/25 group, the incidence (1%) was similar to the placebo group (<1%). In the 1-year, exacerbation studies (HZA102970 and HZA102871), bone disorder AEs, the majority of which were bone fractures, were more frequent in the FF/VI groups (3%) than the VI 25 group (1%), though there was no apparent dose-response for FF. The overall frequency of bone fractures was low in all treatment groups, though higher in all FF/VI groups (2%) compared with the VI 25 group (<1%). The events occurred at a constant rate over the duration of the study. The majority of fractures were due to trauma (investigator-determined) in the FF/VI 50/25, FF/VI 100/25 and VI 25 groups, while the majority of fractures were non-traumatic in the FF/VI 200/25 group (Table 12). The majority of fractures were in the upper and lower extremities. Fractures customarily associated with corticosteroid use (e.g., spinal compression/thoracolumbar vertebral fractures, hip and acetabular fractures) occurred in <1% of subjects in all treatment arms. Fractures affecting the pelvic region and the spine occurred sporadically across the treatment groups.

Biochemical markers of bone resorption (carboxy terminal cross-linking telopeptide of bone collagen [CTX]) and bone formation (osteocalcin) were evaluated during Study HZA102871. No consistent changes were noted at the end of the study compared with baseline or across the treatment groups for CTX. There was a statistically significant decrease (9%) in serum osteocalcin with FF/VI 200/25 relative to VI 25. The relationship with fracture risk is unclear, although it is noteworthy that there were more exacerbations requiring treatment with oral corticosteroids in the VI 25 than the FF/VI groups.

7.5.4. Cardiovascular Effects

Key Finding(s):

The cardiovascular safety profile of VI and FF/VI was broadly consistent with the known pharmacology of LABAs in patients with COPD. There was no evidence for an effect of FF/VI (or VI) on cardiovascular parameters (vital signs, ECGs and Holter Monitoring) or events (including cardiac arrhythmias, ischemia, heart failure and stroke). There was no evidence of QTc prolongation.

Inhaled beta₂-agonists are associated with cardiovascular effects including tachycardia, arrhythmias and QT prolongation. Therefore, the COPD Clinical Development Program included a broad array of assessments to evaluate potential cardiovascular effects with FF/VI, including 12-lead ECG assessments (including heart rate and QTc), 24-hour Holter monitoring (subset of subjects in the 6-month, lung function studies: HZA112206 and HZA112207) and vital sign assessments (pulse rate and blood pressure) (Table 30) and evaluation of adverse events of special interest categorized as cardiovascular effects.

In addition, two thorough QT studies were conducted, one study of FF/VI in healthy subjects (HZA102936) and one study with FF in healthy subjects (FFR101888).

COPD patients could be considered to be more at risk for cardiovascular effects than asthma patients since they have more cardiovascular co-morbidities. Indeed, in the four primary COPD studies (6-month lung function studies: HZC112206 and HZC112207; 1-year exacerbation studies: HZC102871 and HZC102970), 45 to 48% of subjects had current vascular disorders (most commonly hypertension) and 10 to 16% had current cardiac disorders (most commonly coronary artery disease). While 12-lead ECG assessments (including heart rate and QTc) and vital sign assessments (pulse rate and blood pressure) were conducted in all four of the primary COPD studies ([Table 30](#)), since all subjects in the two, 1-year, COPD exacerbation studies received VI 25 and there was no placebo, it is difficult to make conclusions about the cardiovascular effects of VI 25 from these studies.

7.5.4.1. 12-Lead Electrocardiograms

7.5.4.1.1. Heart Rate

No clinically important effects on heart rate were observed in either of the 6-month, lung function studies (HZC112206 and HZC112207). Mean heart rate decreased from baseline across all treatment groups at all timepoints. Repeated measures analysis of heart rate from ECG evaluations for the integrated data showed few statistically significant differences at any timepoint for any of the active treatment groups compared with the placebo group; where statistically significant differences were noted, these differences, in the range of 1 to 2 bpm, were not considered clinically important. In the 1-year exacerbation studies (HZC102970 and HZC102871), in all treatment groups at all timepoints, mean heart rate decreased from baseline (with the exception of the change from baseline for the VI 25 treatment group at Day 196 [0.2bpm]) and ranged from -1.3 to 0.2 bpm.

In the Thorough QTc study conducted in healthy subjects (Study HZA102936), ECG heart rate increases were observed at both FF/VI strengths with maximum effects noted 10 minutes after dosing. Maximum heart rate (0-4 hours) mean difference from placebo [90% CI] was 3.9 bpm [2.7, 5.1] and 12.4 bpm [11.2, 13.6] following administration of FF/VI 200/25 and 800/100 mcg, respectively.

The effects on heart-rate were transient within the first half-hour after dosing and appeared to be associated with C_{max} for VI. There was no evidence of an insidious increase in resting heart-rate at trough over time with chronic dosing, and the transient increases post-dose were not considered to be clinically relevant at the intended marketed dose of VI of 25 mcg.

7.5.4.1.2. QTc

In the 6-month, lung function studies (HZC112206 and HZC112207), mean maximum post-baseline changes in QTc(F) at all timepoints were similar for the placebo (10.3 msec) and all active treatment (9.4 to 10.4 msec) groups. QTc(F) changes from baseline > 30msec at any time point were similar for all active treatment groups (5-10%) versus

placebo (8%). No subjects in any group had a QTc(F) > 500 msec on Day 1, 84 or 168. Mean maximum post-baseline QTc(F) changes in the 1-year, exacerbation studies (HZC102970 and HZC102871) were similar at all timepoints to those observed in the 6-month, lung function studies: 9.1 to 9.5 msec across the FF/VI groups and 10.5 msec in the VI 25 group. The proportion of subjects with QTc(F) changes ≥ 30 msec were low and similar across all FF/VI treatment groups (3% to 5%) and the VI 25 treatment group (4% to 5%) at the Week 12, Week 28 and Week 52 post-baseline timepoints. No subjects in any group had a QTc(F) > 500 msec at Week 12, 28 or 52.

Two thorough QTc studies were conducted. One study was conducted with FF/VI in 85 healthy subjects (Study HZA102936) and the other with FF in 40 healthy subjects (FFR101888). Moxifloxacin (400 mg single oral dose) was used in each study as a positive control for assay sensitivity.

Following administration of FF/VI 200/25 for 7 days in Study HZA102936 all time-matched QTcF mean differences from placebo (0-24 hours) were <5 msec, with no upper 90% CI values greater than 10 msec (Figure 8). At an FF/VI dose of 800/100 for 7 days the largest mean time-matched difference from placebo was 9.6 msec (90% CI: 7.2, 12.0), observed 30 minutes after dosing (Figure 8). This was the only time point where the upper 90% CI exceeded 10 msec. No QTcF values >450 msec were recorded at any time. There was little effect on the individually corrected QT interval (QTci) with either strength of FF/VI: all time-matched mean differences from placebo values were less than 5 msec with no 90% CI values greater than 10 msec.

In the FFR101888 study, single dose FF 4000 mcg was not associated with an effect on QTcF: all mean time-matched differences from placebo (0-24 hour) were less than 5 msec and all 90% CIs were less than 10 msec. These data indicate that the small effect on QTcF seen with FF/VI 800/100 in study HZA102936 was attributable to the VI component.

7.5.4.2. 24-Hour Holter

Twenty-four-hour, 12-lead, Holter monitoring was performed in the 6-month, lung function studies (HZC112206 and HZC112207) that included placebo. The Holter monitoring was conducted in approximately half of the subjects in each treatment arm at selected sites. Measurements were performed at Screening, as well as on Treatment Days 1, 84 and 168 (Table 30). Holter recordings included heart rate, heart rhythm, conduction intervals, and the presence of abnormal rhythm patterns. The Holter Population (see definition in Section 7.5.1) was the primary population for the analysis of 24-hour Holter data.

Central readers noted clinically significant abnormal ECG findings at baseline in 10 to 15% of ECGs, reflecting the overall impaired health status of the COPD population. The frequency of Holter abnormalities of potential clinical importance at any time post-randomization was similar across the VI-containing arms (13 to 15% in each of the three FF/VI combination groups and 11% for the VI 25 group) compared with the non-VI containing arms (6 to 14% for the FF monotherapy groups and 10% for the placebo group). The most frequent potentially clinically important abnormalities were ventricular arrhythmias, most commonly non-sustained ventricular tachycardia (VT) that occurred at

similar incidences in the VI-containing treatment groups and the placebo group (Table 13). No sustained VTs were observed in any of the FF/VI groups or the VI 25 group. Non-sustained VTs occurred slightly more frequently across all combination groups, as well as the VI 25 and FF 100 groups, when compared with placebo. Supra-ventricular arrhythmias occurred at low incidence across all groups. There were cases of sustained supra-ventricular tachycardia in the FF/VI 100/25 and 200/25 arms as well as the VI 25 and FF groups. Atrial fibrillation and flutter were observed sporadically across groups; atrial fibrillation occurred slightly more frequently in FF/VI 100/25, VI 25 and FF 100 groups (Table 13).

7.5.4.3. Vital Signs

Vital signs were assessed in the four primary COPD studies (6-month, lung function studies: HZC112206 and HZC112207; 1-year exacerbation studies: HZC102970 and HZC102871) as shown in Table 30.

Overall, in the 6-month, lung function studies there was little change in pulse rate or systolic or diastolic blood pressures over the treatment period, and changes from baseline were similar for the active treatment groups and placebo and for the FF/VI combination groups and the individual component groups. Changes in pulse rate were small in all treatment groups (i.e., LS mean changes ranged from a decrease of <3 beats/minute to an increase of <1 beat/minute) and changes in blood pressure were also small in all treatment groups (i.e., all LS mean changes were decreases of <3 mmHg for systolic blood pressure and ≤ 2.3 mmHg for diastolic blood pressure). Similarly in the 1 year exacerbation studies, there was little change in pulse rate or systolic or diastolic blood pressures over the treatment period, and changes from baseline were similar for the FF/VI groups and the VI 25 group. Changes in mean pulse rate and blood pressure were small in all treatment groups. It should be noted that since all treatments in the 1-year studies included VI, it is difficult to assess LABA-related effects.

Thus, changes in vital signs data were small and similar across the treatment groups, with no clinically remarkable differences across the treatment groups.

7.5.4.4. AEs of Special Interest: Cardiovascular Effects Category

AE reports of cardiac-related events were evaluated using standardized MedDRA Queries (SMQs) groupings of terms from cardiac MedDRA System Organ Classes (SOCs) related to a defined medical condition in the cardiovascular area of interest. In the 6-month, lung function studies, cardiovascular events including arrhythmias, ischemic heart disease, cardiac failure as well as cerebrovascular events occurred at low and similar incidences in the active treatment groups compared with the placebo group (Table 14). The 1-year exacerbation studies (HZC102970 and HZC102871) did not provide comparative information regarding cardiovascular events, since all treatment groups contained VI 25, and indeed cardiovascular event rates were also similar across treatment arms in these studies.

In the three, supporting COPD studies comparing FF/VI 100/25 with FP/salmeterol, cardiovascular AEs of special interest occurred in 3%, 2%, and 2% of subjects treated with FF/VI 100/25 and <1%, 3% and <1% of subjects treated with FP/salmeterol for

studies HZC113107 (FP/salmeterol 500/50 BID) and HZC113109 and HZC112352 (FP/salmeterol 250/50 BID), respectively. The cardiovascular AEs reported included chest pain, hypertension, palpitations, atrial fibrillation, and tachycardia.

7.5.5. Other Safety Parameters

Other safety parameters including clinical chemistry (including glucose and potassium assessment), HPA-axis assessments and ophthalmic evaluations were conducted to assess the safety of FF/VI.

7.5.5.1. Clinical Laboratory

Key Finding(s):

In subjects with COPD, there was no evidence for an effect of FF/VI 100/25 QD on clinical chemistry or hematology.

Hypokalemia and hyperglycaemia are known pharmacological effects with beta₂ – agonists and/or corticosteroid treatments (hyperglycemia only) and are generally related to systemic exposure. Therefore, effects on glucose and potassium were monitored specifically in the COPD Clinical Development Program, including the four primary COPD studies (the two, 6-month, lung function studies [HZC112206 and HZC112207] and the two, 1-year, exacerbation studies [HZC102970 and HZC102871]) as shown in [Table 30](#).

Based on the review of shifts with respect to the normal reference range for hematology and clinical chemistry analytes, there was no indication from the laboratory evaluations of an effect on glucose or potassium with inhaled FF/VI or the individual components (FF and VI) in the COPD studies.

Overall, no FF/VI- or VI-associated changes in liver function tests of potential clinical concern were observed in the COPD Clinical Development Program. The few episodes of liver abnormalities were generally transient or confounded by concurrent medical problems or concomitant medications.

7.5.5.2. HPA-Axis Assessments

Key Finding(s):

Overall, data from subjects with COPD and asthma showed no evidence of a treatment effect with FF/VI 100/25 QD on HPA-axis, as measured by 24-hour serum or urinary cortisol excretion.

Monitoring of HPA-axis function in subjects treated with FF/VI was important, since changes in these parameters have been reported with corticosteroids. While both 24-hour serum and 24-hour urinary cortisol excretion were evaluated in the COPD Clinical

Development Program, 24-hour serum cortisol profiles are accepted as a more reliable measure of adrenal hormone secretion than 24-hour urinary hormone excretion profiles due to less variability in metabolism effects and improper collection with serum collection compared with urine collection [[Bernstein 2007](#)].

Twenty-four-hour serum cortisol was measured on Day 28 of each Treatment Period in subjects in the supporting, 3-way crossover, COPD study HZC110946. Twenty-four-hour urinary cortisol excretion was measured at Screening and at the end of the Treatment Period in a sub-set of approximately 100 subjects per arm at selected sites in two of the four, primary COPD studies, the 6-month, lung function studies (HZC112206 and HZC112207), and at Screening and at the end of the 3-month Treatment Period in two of the three, supporting FF/VI 100/25 versus FP/salmeterol 250/50 COPD comparator studies (HZC113109 and HZC112352). In addition, a formal HPA-axis study was conducted in subjects with asthma (Study HZA106851).

Overall, data from subjects with COPD showed no evidence of a treatment effect on 24-hour serum or 24-hour urinary cortisol excretion. The cortisol results are consistent with the low systemic exposure to FF after inhaled dosing. In the HZC110946 study, the raw geometric mean serum cortisol levels over Days 28-29 are shown in [Figure 9](#). No AEs were reported that would be considered related to decreases in serum cortisol. In the HZC112206 and HZC112207 studies, no statistically significant differences from placebo in 24-hour urinary cortisol excretion were observed with any of the active treatment groups ([Figure 10](#))

Also, Studies HZC113109 and HZC112352 showed no statistically significant differences in 24-hour urinary cortisol excretion between the FF/VI 100/25 QD and FP/salmeterol 250/50 BID groups. The LS geometric mean ratios to baseline were close to 1 for both the FF/VI 100/25 QD and FP/salmeterol 250/50 BID groups in both studies (HZC113109: 1.08 and 0.90, respectively; HZC112352: 1.12 and 1.01, respectively). For both studies, the statistical analysis did not show a statistically significant difference for the FF/VI 100/25 and FP/salmeterol 250/50 BD treatment group comparison (HZC113109: ratio of FF/VI to FP/salmeterol: 1.203, $p=0.070$; HZC112352: ratio of FF/VI to FP/salmeterol: 1.019, $p=0.301$). These data suggest that FF/VI 100/25 QD does not have a greater effect on the HPA-axis than FP/Salmeterol 250/50 BID.

Although the formal HPA-axis study (Study HZA106851) was conducted in subjects with asthma, these data can be used to support the safety of FF/VI in subjects with COPD, since systemic FF exposure in these subjects is lower than the exposure observed in subjects with asthma. In this study, non-inferiority in the ratio from baseline in serum cortisol weighted mean compared with placebo was demonstrated against the predefined criterion of the lower confidence bound being >0.8 . For FF/VI 100/25, 95% CI were 0.87 to 1.12 and for FF/VI 200/25 95% CI were 0.86 to 1.10). Prednisolone 10 mg significantly reduced the ratio from baseline in serum cortisol weighted mean compared with placebo (95% CI 0.28 to 0.41), showing that the model for assessing HPA function was sufficiently sensitive to detect a drug effect.

7.5.5.3. Ophthalmic Evaluations

Key Finding(s):

No clinically important ophthalmic findings were noted with FF/VI 100/25 QD in the 1-year safety study in subjects with asthma that was designed to look at potential ophthalmic effects (HZA106839). In addition, there was a low incidence of ocular events reported across the four, primary COPD studies.

Ocular effects, including cataracts, increased intraocular pressure (IOP) and glaucoma, have been reported with corticosteroid usage. Moreover, as the COPD population is elderly, ocular changes are more likely to be prevalent in this group. For example, in the TORCH safety sub-study, the background prevalence of cataracts was high in COPD patients (68.5-75.3% at Screening) [Calverley, 2007]. Because of this high background prevalence of cataracts in patients with COPD, the definitive ocular assessments were included in the 1-year safety study in subjects with asthma (HZA106839), as this was likely to be a less confounded population in which to assess this drug-related effect. Although conducted in subjects with asthma, these data can be used to support the safety of FF/VI in subjects with COPD, since systemic FF exposure in these subjects is approximately lower than the exposure observed in subjects with asthma.

In the HZA106839 study, ophthalmic safety of FF/VI compared with FP 500 twice daily was evaluated in a year-long study in persistent asthmatics. A placebo arm was not appropriate for a study of this duration. Intensive ophthalmic examinations (visual acuity [using LogMAR], LOCS III lens grades, IOP measurements, horizontal cup-to-disc ratio) were performed at Screening, Week 28 and Week 52. Subjects were excluded if they had cataracts or glaucoma at Screening. This study showed that FF/VI 100/25 QD and FF/VI 200/25 QD had no apparent ophthalmic effects. The effects detected while on FF/VI were similar to those observed with FP 500 twice daily.

While ophthalmic examinations were not conducted in the Phase III COPD program, ocular effects (including cataracts) were assessed as an AE of special interest in the four, primary COPD studies. AE reports of ocular effects were reported in 0 to <1% of subjects across the groups in the 6-month, lung function studies (HZA112206 and HZA112207) and in ≤1% of subjects across the groups in the 1-year exacerbation studies (HZA102871 and HZA102970). Cataracts and glaucoma were reported in <1% of subjects in any treatment group across these four studies. There was one report of increased intraocular pressure in a subject treated with FF/VI 100/25.

8. RISK MANAGEMENT/MITIGATION PLANS

In the NDA, GSK submitted a proposed Risk Management Plan that addresses the class effects associated with ICS/LABAs as summarized in the sections that follow.

8.1. Pneumonia

Similar to the currently available ICS/LABA combinations for treatment of COPD, the “Warnings and Precautions” section of the proposed BREO ELLIPTA *Prescribing Information* includes a warning regarding an increase in the incidence of pneumonia that has been observed in subjects with COPD receiving FF/VI and guidance that physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations. This section of the proposed BREO ELLIPTA *Prescribing Information* also includes a description of risk factors for pneumonia in patients with COPD receiving FF/VI (current smokers, patients with a history of prior pneumonia, patients with a body mass index <25 kg/m², and patients with an FEV₁ <50% predicted) and guidance that these factors should be considered when BREO ELLIPTA is prescribed, and treatment should be re-evaluated if pneumonia occurs.

8.2. Bone Disorders/Fractures

As discussed in Section 7.5.3.6.2, bone disorders, and in particular fractures, were reported more frequently with FF/VI than VI. However, fractures customarily associated with corticosteroid use (e.g., spinal compression/thoracolumbar vertebral fractures, hip and acetabular fractures) occurred in <1% of subjects in all treatment arms. The Phase III studies were not designed to address the effect of FF/VI on bone mineral density and decreased bone mineral density in COPD patients is multi-factorial in nature (e.g. advanced age, immobility, diet) and potentially exacerbated from systemic absorption of inhaled corticosteroids as well as the use of systemic corticosteroids to treat exacerbations. Nevertheless, the potential pharmacological effect on bone with the inhaled corticosteroid FF remains and, as such, GSK plans to evaluate the incidence of bone fractures in ongoing studies and to conduct further investigations with the approved dose of FF/VI in a post-marketing setting to study the effects on BMD and the incidence of adverse event reports of fractures. The “Warnings and Precautions” section of the proposed BREO ELLIPTA *Prescribing Information* includes the class labelling warning regarding the reduction in BMD observed with long-term administration of ICS-containing products and a recommendation for the assessment of BMD prior to initiating treatment and periodically thereafter.

8.3. Cardiovascular Effects

Despite the risks of cardiovascular disease in patients with COPD, FF/VI does not appear to increase the risk of cardiovascular events compared with non-VI containing therapies. In particular, there was no increase in fatal events which could be possibly cardiovascular in nature for VI-containing arms compared with non-VI containing arms. Furthermore, there was a similar efficacy and safety profile in subjects with and without cardiovascular history or risk factors. Thus, a favorable benefit:risk profile remains for COPD patients with and without underlying cardiovascular disease. Nevertheless, the “Warnings and Precautions” section of the proposed BREO ELLIPTA *Prescribing Information* includes class labelling that FF/VI is to be used with caution in patients with severe cardiovascular disease. In addition, GSK is currently conducting a large, randomized, double-blind,

parallel-group, placebo-controlled, clinical outcomes study in COPD patients with a history of or who are at increased risk for developing cardiovascular disease. This study is designed to determine the impact of FF/VI 100/25, and the individual components on the survival of patients with moderate airflow obstruction and either a history of cardiovascular disease or in patients >60 years of age, receiving treatment for 2 or more of the following: hypercholesterolemia, hypertension, diabetes and peripheral arterial vascular disease. Approximately 16,000 randomized subjects are planned, with approximately 4,000 subjects randomized to each of the four treatment arms. All-cause mortality is the primary endpoint. The study is an event-driven trial powered on the comparison of FF/VI vs. placebo. Secondary endpoints are decline in forced expiratory volume in 1 second (FEV₁) and effect on a composite cardiovascular endpoint. This study will provide further information concerning the safety of FF/VI 100/25 in this patient population.

8.4. Clinical Laboratory Findings

While in the four, primary COPD studies of 6- and 12-month's duration in subjects with COPD, there was no evidence of a treatment effect on serum glucose or potassium (Section 7.5.5.1), the proposed BREO ELLIPTA *Prescribing Information* contains class labelling in the Warnings and Precautions section regarding beta-adrenergic agonist medicines may produce significant hypokalemia in some patients and may produce transient hyperglycemia in some patients.

8.5. HPA-Axis Effects

As discussed in Section 7.5.5.2, while no clinically relevant treatment effect was seen in 24-hour serum or 24-hour urinary cortisol in the 3 studies that evaluated HPA-axis effects in subjects with COPD, the proposed BREO ELLIPTA *Prescribing Information* includes class labelling in the Warnings and Precautions section regarding the possibility of significant systemic absorption of inhaled corticosteroids in sensitive patients and that patients treated with BREO ELLIPTA should be observed carefully for any evidence of systemic corticosteroid effects and that particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

8.6. Ocular Effects

While no clinically important ophthalmic findings were noted in the study designed to assess any potential ocular effects and there was a low incidence of ocular events reported in the COPD Clinical Development program (Section 7.5.5.3), the “Warnings and Precautions” section of the proposed BREO ELLIPTA *Prescribing Information* includes the class labelling warning regarding reports of glaucoma, increased intraocular pressure, and cataracts in patients with COPD following the long-term administration of ICS and advises that close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.

8.7. Rare Respiratory-Related Events Including Asthma-Related Death and Intubation

Safety assessments from studies in adults with asthma using a LABA in single component presentations have been associated with an increased risk for rare respiratory-related events including asthma-related death and intubation [Nelson, 2006]. This risk was evaluated in the FF/VI Clinical Development Program in asthma and the results showed that there was no increased risk of serious asthma-related events for subjects receiving FF/VI compared with those not receiving a LABA. While the current NDA was submitted for the COPD indication, the proposed BREO ELLIPTA *Prescribing Information* includes the class labelling Boxed Warning regarding the risk of asthma-related death observed in a placebo-controlled trial with another LABA (salmeterol).

9. BENEFIT-RISK ASSESSMENT

FF/VI is a once-daily ICS/LABA combination that has demonstrated clinically relevant efficacy in clinical trials in COPD, with an acceptable safety and tolerability profile. Goals in the management of COPD include alleviation of airflow obstruction and symptoms, and reducing exacerbations. Exacerbations, and in particular severe exacerbations, may contribute to COPD morbidity and mortality.

9.1.1. Medical Need

The concomitant use of ICS and LABA is a well-established and recommended approach for the treatment of COPD [GOLD, 2011].

9.1.2. Therapeutic Justification

Only two inhaled ICS/LABA combination treatments, ADVAIR DISKUS and Symbicort are approved by the FDA for treatment of COPD in the United States. Of the ICS/LABA combination products, only ADVAIR DISKUS is indicated to reduce exacerbations of COPD in patients with a history of exacerbations. Both of these treatments need to be administered twice daily. Data with marketed products suggests that compliance improves with less frequent administration and therefore a once-daily treatment may improve compliance, which could lead to improvements in disease control and reductions in healthcare resource utilization costs.

9.1.3. Benefit:Risk

The effect size of FF/VI 100/25 on reducing exacerbations in the 1-year, exacerbation studies HZC102970 (21%) and HZC102871 (34%) (Figure 5) is comparable to that observed in the 1-year exacerbation studies with ADVAIR DISKUS (FP/salmeterol 250/50 BID versus salmeterol 50 BID), 30.5% and 30.4% [Ferguson, 2008; Anzueto, 2009, respectively].

As previously noted, the goals of pharmacologic therapy in COPD should be to reduce symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance [GOLD, 2011]. COPD exacerbations are important events

associated with the morbidity and mortality of the disease. Long-term treatment with ICS added to a LABA is recommended for patients with a high risk for exacerbations [GOLD, 2011]. ICS combined with a LABA in COPD has been shown to be more effective than the individual components in managing stable COPD by reducing exacerbations and improving lung function and health status [GOLD, 2011; Ferguson, 2008; Calverley, 2007; Kardos, 2007; Sharafkhaneh, 2012]. However, the benefit of ICS in contributing to the reduction in exacerbations must be balanced by the risks associated with the corticosteroid use. Important risks associated with ICS in general and FF in particular are pneumonia and fractures (due to the effects on bone).

Shown in Table 15 are the number of moderate and severe exacerbations, the number of pneumonia events and the number of fractures that occurred in each of the four treatment arms in the two, 1-year exacerbation studies (HZA102970 and HZA102871). Compared with VI 25, there were 187 fewer exacerbations with FF/VI 100/25 (i.e., 741 minus 554), in contrast with 30 more pneumonia events (i.e., 58 minus 28) and 11 more fractures (i.e., 19 minus 8); of the non-traumatic fractures, there was an excess of 4 with FF/VI 100/25 (i.e., 6 minus 2) (Table 15). These data suggest a strongly positive benefit:risk balance as it relates to the FF 100 component of BREO ELLIPTA.

As with BREO ELLIPTA, in the two, 1-year exacerbation studies with FP/salmeterol, the overall incidence of pneumonia and the incidence of SAEs of pneumonia were higher in the FP/salmeterol 250/50 mcg BID group compared with the salmeterol 50 mcg BID group (Table 11) [Ferguson, 2008; Anzueto, 2009]. Similarly, in the 1-year exacerbation study with budesonide/formoterol, the overall incidence of pneumonia was higher in both of the budesonide/formoterol groups (320/9 mcg BID [the approved strength in the US] and 160/9 mcg BID) compared with the formoterol 9 mcg BID group (Table 11) [Sharafkhaneh, 2012]. In the budesonide/formoterol study, compared with the formoterol 9 mcg BID group, the incidence of SAEs of pneumonia was higher in the budesonide/formoterol 320/9 mcg BID group and lower in the budesonide/formoterol 160/9 mcg BID group. Similar to BREO ELLIPTA, across both FP/salmeterol studies, one subject in the FP/salmeterol 250/50 mcg BID group experienced fatal pneumonia and in the budesonide/formoterol study, one subject in the budesonide/formoterol 160/9 mcg BID group experienced fatal pneumonia during the treatment period Table 11. The risk of pneumonia is included in the proposed BREO ELLIPTA *Prescribing Information* and as an identified risk proposed Risk Management Plan.

In order to clarify whether certain patients are at increased risk to develop pneumonia, the pneumonia adverse events of the 1-year, exacerbation studies (HZA102970 and HZA102871) were analyzed by subgroup factors. As expected and as described for other ICSs in the literature, elderly patients as well as men showed a trend towards an elevated risk of time to first pneumonia (Figure 32). Also current smokers, patients with a history of previous pneumonia, patients with a low BMI ($<25 \text{ kg/m}^2$), and a lower predicted FEV₁ value ($<50\%$ of predicted) carried a higher risk for developing pneumonia with FF/VI treatment compared with VI 25 treatment. These data are reflected in the proposed *Prescribing Information* for BREO ELLIPTA and are the same as those demonstrated in other large COPD studies with ICS, specifically the TORCH trial [Crim, 2009].

The relationship between exacerbation reduction and BMI and severity of airflow obstruction in COPD was examined as shown in [Table 42](#). In the sub-group with BMI $>21 \text{ kg/m}^2$, compared with the VI 25 group, all three FF/VI groups demonstrated significantly greater reductions in the annual rate of moderate or severe exacerbations, with the greatest reduction observed in the FF/VI 100/25 group (27%). In the sub-group with BMI $\leq 21 \text{ kg/m}^2$, compared with the VI 25 group, all three FF/VI groups demonstrated numerical reductions in moderate or severe exacerbations; however, the differences were not statistically significant. The FF/VI 100/25 group demonstrated the greatest reduction (32%), which approached statistical significance ($p=0.056$). With respect to the GOLD Stage sub-groups, compared with the VI 25 group, only the FF/VI 100/25 group demonstrated a significantly greater reduction in the annual rate of moderate or severe exacerbations across all three GOLD Stage sub-groups, with subjects in the GOLD Stage III and IV sub-groups demonstrating the greatest reductions, 26% and 43%, respectively ([Table 42](#)).

Table 42 Treatment Difference (95% CI) from VI 25 for Annual Rate of On-Treatment Moderate or Severe COPD Exacerbations by BMI and GOLD Stage Sub-Groups: Integrated Study Results – 1-Year Exacerbation Studies (HZC102970/HZC102871)

	FF/VI 50/25 N=820	FF/VI 100/25 N=806	FF/VI 200/25 N=811	VI 25 N=818
On-Treatment Moderate or Severe COPD Exacerbations by BMI Subgroup¹				
BMI ≤21 kg/m², n	111	97	127	126
LS Mean Annual Rate	0.84	0.69	0.92	1.01
Column vs VI 25 Ratio 95% CI p-value	0.82 (0.57, 1.20) 0.312	0.68 (0.46, 1.01) 0.056	0.91 (0.63, 1.29) 0.586	
Percent Reduction 95% CI	18 (-20, 43)	32 (-1, 54)	9 (-29, 37)	
BMI >21 kg/m², n	704	704	677	681
LS Mean Annual Rate	0.95	0.82	0.84	1.12
Column vs VI 25 Ratio 95% CI p-value	0.84 (0.72, 0.98) 0.027	0.73 (0.62, 0.85) <0.001	0.74 (0.63, 0.87) <0.001	
Percent Reduction 95% CI	16 (2, 28)	27 (15, 38)	26 (13, 37)	
On-Treatment Moderate or Severe COPD Exacerbations by GOLD Stage²				
I & II: FEV₁ ≥50% of Predicted,³ n	324	325	305	304
LS Mean Annual Rate	1.00	0.86	0.73	1.11
Column vs VI 25 Ratio 95% CI p-value	0.90 (0.71, 1.15) 0.397	0.78 (0.61, 0.99) 0.042	0.66 (0.51, 0.85) 0.002	
Percent Reduction 95% CI	10 (-15, 29)	22 (1, 39)	34 (15, 49)	
III: FEV₁ ≥30 to <50% of Predicted	364	362	375	380
LS Mean Annual Rate	0.91	0.78	0.91	1.05
Column vs VI 25 Ratio 95% CI p-value	0.87 (0.70, 1.06) 0.169	0.74 (0.60, 0.92) 0.006	0.87 (0.71, 1.06) 0.167	
Percent Reduction 95% CI	13 (-6, 30)	26 (8, 40)	13 (-6, 29)	
IV: FEV₁ <30% of Predicted, n	120	109	121	118
LS Mean Annual Rate	0.91	0.78	0.91	1.36
Column vs VI 25 Ratio 95% CI p-value	0.67 (0.48, 0.94) 0.019	0.57 (0.40, 0.81) 0.002	0.67 (0.48, 0.94) 0.019	
Percent Reduction 95% CI	33 (6, 52)	43 (19, 60)	33 (6, 52)	

BMI=body mass index; CI=confidence interval; FEV₁=forced expiratory volume in 1 second; FF=fluticasone furoate; GOLD= Global Initiative for Obstructive Lung Disease; LS=Least Squares; VI=vilanterol

1. Note: Analysis performed using a negative binomial regression model with covariates of study, treatment, smoking status at screening, baseline disease severity (pre-dose Day 1 % predicted FEV₁), BMI subgroup, region and treatment by BMI subgroup interaction, with logarithm of time on treatment as an offset variable.
2. Note: Analysis performed using a negative binomial regression model with covariates of study, treatment, smoking status at screening, baseline disease severity (pre-dose Day 1 % predicted FEV₁), GOLD classification, region and treatment by GOLD classification interaction, with logarithm of time on treatment as an offset variable
3. GOLD categories I and II combined for the purposes of analysis

As to the VI 25 component of BREO ELLIPTA, there was no increase in cardiac-related events as classified using the standardized MedDRA Queries (SMQs) or non-sustained ventricular tachycardia compared with placebo ([Table 13](#)). However, there were a few more events of sustained supraventricular tachycardia and atrial fibrillation with FF/VI 100/25 and VI 25 compared with placebo. These risks are balanced by the significant improvement in lung function with BREO ELLIPTA (VI 25 component) compared with placebo and FF 100mcg ([Figure 2](#) and [Figure 3](#)). These data suggest an acceptable benefit:risk balance as it relates to the VI 25 component of BREO ELLIPTA.

BREO ELLIPTA is a once-daily ICS/LABA combination that has demonstrated clinically relevant efficacy, with improvements in both lung function and reductions in exacerbations, in clinical trials in COPD, with an acceptable safety and tolerability profile that is consistent with the ICS/LABA class. That it requires only once-daily administration may lead to improved adherence and hence, improved clinical outcomes.

10. OVERALL CONCLUSION

BREO ELLIPTA (fluticasone furoate/vilanterol) 100/25 provides a new, safe and effective once-daily treatment option for the maintenance treatment of airflow obstruction in patients with COPD and to reduce exacerbations of COPD in patients with a history of exacerbations in a new and easy to use device, ELLIPTA.

11. REFERENCES

- Anzueto A, Ferguson GT, Feldman G, Chinsky K, Seibert A, Emmett A, Knobil K, O'Dell D, Kalberg C, Crater G. Effect of fluticasone propionate/salmeterol (250/50) on COPD exacerbations and impact on patient outcomes. *COPD*. 2009; 6(5):320-9.
- Barrett VJ, Emmons A, Ford AJ, et al. In vitro pharmacological characterisation of GW642444, a novel long acting b2-agonist (LABA) using human recombinant b1/2/3 adrenoceptor CAMP Assays. *Am J Respir Crit Care Med*. 2010;181:A4451.
- Bateman ED, Bleecker ER, Lotvall J, Woodcock A, Forth R, Medley H, Davis AM, Jacques L, Haumann B, Busse WW. Dose effect of once-daily fluticasone furoate in persistent asthma: a randomized trial. *Respir Med*. 2012;106(5):642-50.
- Bernstein DI, Allen DB. Evaluation of tests of hypothalamic-pituitary-adrenal axis function used to measure effects of inhaled corticosteroids. *Ann Allergy Asthma Immunol*. 2007;98(2):118–27.
- Bleecker ER, Bateman ED, Busse WW, Woodcock A, Frith L, House KW, Jacques L, Davis AM, Haumann B, Lötval J. Once-daily fluticasone furoate is efficacious in patients with symptomatic asthma on low-dose inhaled corticosteroids. *Ann Allergy Asthma Immunol*. 2012;109(5):353-58.
- Boscia JA, Pudi KK, Zvarich MT, Sanford L, Siederer SK, Crim C. Effect of once-daily fluticasone furoate/vilanterol on 24-hour pulmonary function in patients with chronic obstructive pulmonary disease: a randomized, three-way, incomplete block, crossover study. *Clin Ther*. 2012; 34(8):1655–66.
- Busse WW, Bleecker ER, Bateman ED, Lötval J, Forth R, Davis AM, Jacques L, Haumann B, Woodcock. Fluticasone furoate demonstrates efficacy in patients with asthma symptomatic on medium doses of inhaled corticosteroid therapy: an 8-week, randomised, placebo-controlled trial. *Thorax*. 2012;67(1):35-41.
- Calverley PMA, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Eng J Med*. 2007;356(8):775-89.
- Celli BR, MacNee W. Standards of the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Resp J*. 2004;23:932-46.
- Chapman KR, Mannino DM, Soriano JB, Vermeire PA, Buist AS, Thun MJ, Connell C. Epidemiology and costs of chronic obstructive pulmonary disease. *Eur Respir J*. 2006;27:188-207.
- Christensson C; Thorén A, Lindberg B. Safety of inhaled budesonide: clinical manifestations of systemic corticosteroid-related adverse effects. *Drug Safety*. 2008;31(11):965-988.

Crim C, Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, et al. Pneumonia risk in COPD patients receiving inhaled corticosteroids alone or in combination: TORCH study results. *Eur Respir J*. 2009; 34(3):641-7.

Delea TE, Hagiwara M, Stempel DA, Stanford RH. Adding salmeterol to fluticasone propionate of increasing the dose of fluticasone propionate in patients with asthma. *Allergy Asthma Proc*. 2010;31:211-18.

Doherty DE, Tashkin DP, Kerwin E, Knorr BA, Shekar T, Banerjee S, Staudinger H. Effects of mometasone furoate/formoterol fumarate fixed-dose combination formulation on chronic obstructive pulmonary disease (COPD): results from a 52-week Phase III trial in subjects with moderate-to-very severe COPD. *Int J COPD*. 2012;7:57-71.

Drummond MB, Dasenbrook EC, Pitz MW, Murphy DJ, Fan E. Inhaled corticosteroids in patients with stable chronic obstructive pulmonary disease: a systematic review and meta-analysis. *JAMA*. 2008;300(20):2407-2416.

Food and Drug Administration (FDA) Code of Federal Regulations Title 21 Food and Drugs – Chapter I Food and Drug Administration Department of Health and Human Services Subchapter D – Drugs for Human Use Part 300 General Subpart B – Combination Products Section. 300.50 - Fixed-combination prescription drugs for humans. (21CFR300.50). 2012;
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=300.50>

FDA Guidance. Guidance for Industry Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). November 2007.

Ferguson GT, Anzueto A, Fei R, Emmett A, Knobil K, Kalberg C. Effect of fluticasone propionate/salmeterol (250/50 mcg) or salmeterol (50 mcg) on COPD exacerbations. *Resp Med*. 2008;102:1099-1108.

GlaxoSmithKline Document Number RM2000/00031/00. Clinical Study Report for FLTA3025. A randomized, double-blind, parallel-group, comparative trial of inhaled fluticasone propionate 250mcg BID, 500mcg BID, and placebo BID via the DISKUS in subjects with Chronic Obstructive Pulmonary Disease (COPD).

GlaxoSmithKline Document Number RM2006/00845/00. Clinical Study Report for SCO40043. A randomized, double-blind, parallel-group, 52-week study to compare the effect of fluticasone propionate/salmeterol DISKUS 250/50mcg BID with salmeterol DISKUS 50mcg BID on the annual rate of moderate/severe exacerbations in subjects with Chronic Obstructive Pulmonary Disease (COPD).

Global Initiative for Asthma (GINA). From the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2011. Available from www.ginasthma.org.

Global Initiative for Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease. Global Initiative for Obstructive Lung Disease (GOLD) 2011. Available from www.goldcopd.org.

Guest JF, Davie AM, Ruiz FJ, et al. Switching asthma patients to a once-daily inhaled steroid improves compliance and reduces healthcare costs. *Primary Care Respiratory Journal* 2005;14:88-98.

Hagiwara M, Delea TE, Stanford RH, Stempel DA. Stepping down to fluticasone propionate or a lower dose of fluticasone propionate/salmeterol combination in asthma patients recently initiating combination therapy. *Allergy Asthma Proc.* 2010;31:203-210.

Hanania NA, Feldman G, Zachgo W, Shim JJ, Crim C, Sanford L, Lettis S, Barnhart F, Haumann B. The efficacy and safety of the novel long-acting β_2 agonist vilanterol in patients with COPD: a randomized placebo-controlled trial. *Chest.* 2012;142(1):119-27.

Hanania N, Darken P, Horstman D, Reisner C, Lee B, Davis S, Shah T. The efficacy and safety of fluticasone propionate (250 μ g)/salmeterol (50 μ g) combined in the diskus inhaler for the treatment of COPD. *Chest.* 2003;124:834-43.

Hankinson JL, Odencrantz JR, Feden KB. Spirometric Reference Values from a Sample of the General US Population. *Am J Respir Crit Care Med* 1999;159:179-187.

Holguin F, Folch E, Redd SC et al. Comorbidity and Mortality in COPD Related Hospitalizations in the United States, 1979 to 2001. *Chest* 2005;128:2005-11.

Hurst JR, Vestbo J, Anzueto A, Locantore N, et. al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med.* 2010;363:1128-38.

Kardos P, Wencker M, Glaab T. Impact of salmeterol/fluticasone propionate versus salmeterol on exacerbations in severe chronic obstructive pulmonary disease. *Am J Resp Crit Care Med.* 2007;175:144-149.

Kerwin EM, Scott-Wilson C, Sanford L, Rennard S, Agusti A, Barnes N, Crim C. A randomised trial of fluticasone furoate/vilanterol (50/25 mg; 100/25 mg) on lung function in COPD. *Resp Med.* 2013 (in press).

Lehouck A, Boonen S, Decramer M, Janssens W. COPD, bone metabolism, and osteoporosis. *Chest.* 2011;139(3):648-57.

Lopez AD, Shibuya K, Rao C, Mathers CD, Hansell AL, Held LS, Schmid V, Buist S. Chronic obstructive pulmonary disease: current burden and future projections. *Eur Respir J.* 2006;27:397-412.

Mahler DA, Wire P, Horstman D, Chang C-N, Yates J, Fischer T, Shah T. Effectiveness of fluticasone propionate and salmeterol combination delivered via the diskus device in the treatment of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2002;166:1084-91.

- Mannino DM, Davis KJ, Kiri VA. Chronic obstructive pulmonary disease and hospitalizations for pneumonia in a US cohort. *Respir Med.* 2009;103(2):224-9.
- Martinez FJ, Boscia J, Feldman G, Scott-Wilson C, Kilbride S, Fabbri L, Crim C, Calverley Peter MA. Fluticasone furoate/vilanterol (100/25; 200/25 mg) improves lung function in COPD: A randomised trial. *Resp Med.* 2013 (in press).
- McGhan R, Radcliff T, Fish R, Sutherland ER, Welsh C, Make B. Predictors of rehospitalization and death after a severe exacerbation of COPD. *Chest.* 2007; 132(6):1748-55.
- Morrison V, Sturton G, Barrett V, et al. Pharmacological characterisation of GW642444, a long-acting β_2 -agonist (LABA) with rapid onset and long duration, on isolated large and small human airways. *Am J Respir Crit Care Med* 2010;181:A4453.
- Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM, the SMART Study Group. The salmeterol multicenter asthma research trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *CHEST.* 2006;129(1):15-26.
- Price D, Robertson A, Bullen K, et al. Improved adherence with once-daily versus twice-daily dosing of mometasone furoate administered via a dry powder inhaler: a randomized open-label study. *BMD Pulmonary Medicine.* 2010;10(1):1-9.
- Procopiou PA, Barrett VJ, Bevan NJ. Synthesis and structure-activity relationships of long-acting beta2 adrenergic receptor agonists incorporating metabolic inactivation: an antedrug approach. *J Med Chem.* 2010;53:4522e30.
- Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2007;176: 532-55.
- Rossios C, To Y, To M, et al. Long-acting fluticasone furoate has a superior pharmacological profile to fluticasone propionate in human respiratory cells. *Eur J Pharmacol.* 2011;670:244e51.
- Salter M, Biggadike K, Matthews JL, et al. Pharmacological properties of the enhanced-affinity glucocorticoid fluticasone furoate in vitro and in an in vivo model of respiratory inflammatory disease. *Am J Physiol Lung Cell Mol Physiol.* 2007;293:L660e7.
- Schunemann H, Goldstein R, Mador J, McKim D, Stahl E, Griffith L, Puhan M, Grant BJB, Austin P, Collins R, Guyatt GH. A randomized controlled trial to evaluate the selfadministered standardized CRQ. *Eur Respir J.* 2005;25(1):31-40.
- Sharafkhaneh A, Southard JG, Goldman M, Uryniak T, Ubaldo JM. Effect of budesonide/formoterol pMDI on COPD exacerbations: a double-blind, randomized study. *Resp Med.* 2012;106:257-68.

Sterling R, Lim J, Frith L, Snowise NG, Jacques L, Haumann B. Efficacy and optimal dosing interval of the long-acting beta₂ agonist, vilanterol, in persistent asthma: a randomised trial. *Respir Med*. 2012;106(8):1110-5.

Tashkin DP, Rennard SI, Martin P, et al. Efficacy and safety of budesonide and formoterol in one pressurized metered-dose inhaler in patients with moderate to very severe chronic obstructive pulmonary disease. *Drugs*. 2008;68(14):1975-2000.

Toy EL, Beaulieu NU, McHale JM, et al. Treatment of COPD: Relationships between daily dosing frequency, adherence, resource use, and costs. *Respiratory Medicine* 2011;105:435-441.

Wedzicha JA, Seemungal TA. COPD exacerbations: defining their cause and prevention. *Lancet*. 2007; 370:786-96.

Weldon D. The effects of corticosteroids on bone growth and bone density. *Ann Allergy Asthma Immunol*. 2009;103:3-11.

WHO. Chronic Obstructive Pulmonary Disease (COPD). Burden of COPD. WHO 2012.

Woodcock A, Bleecker ER, Busse WW, Lötvall J, Snowise NG, Frith L, Jacques L, Haumann B, Bateman ED. Fluticasone furoate: once-daily evening treatment versus twice-daily treatment in moderate asthma. *Respir Res*. 2011;12(1): 160.

12. APPENDICES

12.1. Appendix 1: Other Efficacy Endpoints

6-Month, Lung Function Studies (HZC112206 and HZC112207)

- Time to 12% change from baseline in FEV₁ on Treatment Day 1
- Weighted mean FEV₁ 0-4 hours post-dose on Treatment Days 1, 14, 56 and 84
- Change from baseline in trough FEV₁ on Treatment Days 2, 7, 14, 28, 56, 84, 112, and 140
- Percentage of symptom-free 24-hour periods and rescue-free 24-hour periods during each week of treatment and over the entire 24-week Treatment Period #
- Symptom scores (breathlessness, cough and sputum production) averaged over each week and over the entire 24-week Treatment Period #
- Number of occasions rescue albuterol/salbutamol used during a 24-hour period averaged over each week and over the entire 24-week Treatment Period
- Percentage of nights with no night-time awakenings requiring albuterol/salbutamol during each week of treatment and over the entire 24-week Treatment Period
- Number of night-time awakenings requiring albuterol/salbutamol averaged over each week of treatment and over the entire 24-week Treatment Period
- Mean AM PEF averaged over each week of treatment and over the entire 24-week Treatment Period
- CRQ-SAS other domains (fatigue, emotional function and mastery) ## and total score

1-Year Exacerbation Studies (HZC102970 and HZC102871)

- Annual rate of severe exacerbations
- Annual rate of all exacerbations (mild, moderate, severe)
- Time to onset of multiple moderate and severe exacerbations
- Change from baseline in trough FEV₁ at Visits 3-10
- Number of night-time awakenings due to symptoms of COPD averaged over each 4-week treatment interval and over the entire 52-week Treatment Period

- Percentage of nights with no night-time awakenings due to symptoms of COPD averaged over each 4 week treatment interval and over the entire 52-week Treatment Period
- Number of occasions rescue albuterol/salbutamol used during a 24-hour period averaged over each 4 week treatment interval and over the entire 52-week Treatment Period
- Percentage of rescue free 24-hour periods during each 4 week treatment interval and over the entire 52-week Treatment Period
- Mean dyspnoea score averaged over each 4 week treatment interval and over the entire 52-week Treatment Period
- Percentage of 24-hour periods with increased sputum during each 4 week treatment interval and over the entire 52-week Treatment Period
- Percentage of 24-hour periods with increase in yellow/green sputum color during each 4-weektreatment interval and over the entire 52-week treatment period
- Healthcare utilization

12.2. Appendix 2: Statistical Testing Hierarchy

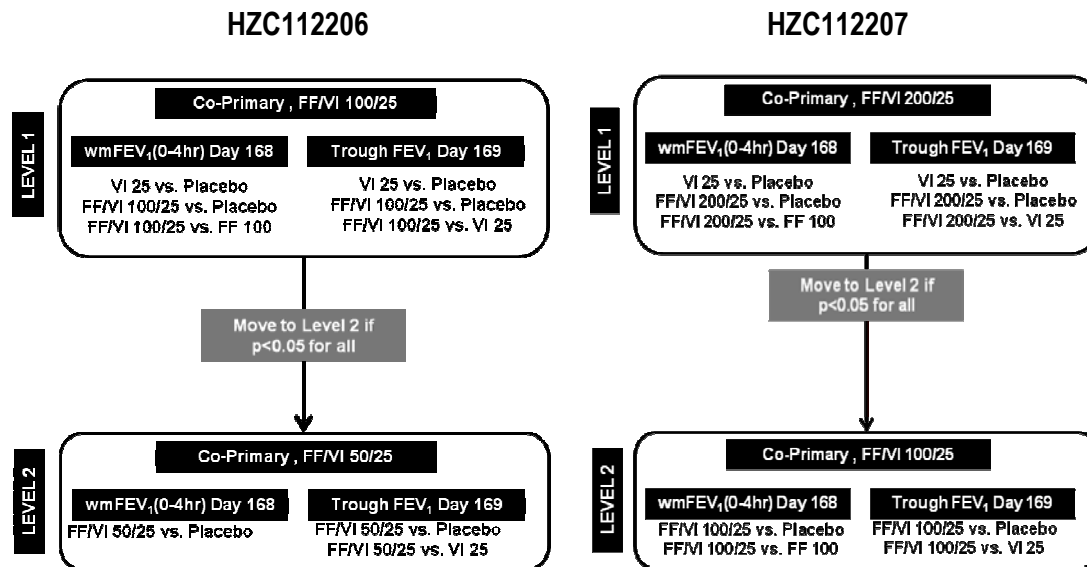
As shown in [Table 2](#), the four primary COPD studies included 4-6 treatment arms, the 6-month studies (HZC112206 and HZC112207) included two primary endpoints and the 1-year, exacerbation studies (HZC102871 and HZC102970) had one primary endpoint. As a consequence, there were a number of treatment comparisons of primary interest across a number of endpoints. So, in order to account for these multiple comparisons, a specific step-down testing procedure was applied *a priori* for the statistical analyses of the efficacy data in each of the four studies. In this hierarchy, treatment comparisons for the highest strength of FF/VI in the given study were evaluated for statistical significance and, if achieved, the secondary endpoints were then tested as well as the primary endpoint for the next lower strength of FF/VI in the study. If at any point in the hierarchy a comparison and/or endpoint did not demonstrate statistical significance, all further statistical analyses pre-specified in the hierarchy were fully described but are not strictly inferential.

Specifically, if the defined treatment comparisons for the higher FF/VI combination dose demonstrate statistical significance at the 5% level on the primary efficacy endpoints, then inference could be made for the defined treatment comparisons for the lower combination dose for the primary efficacy endpoints ([Figure 33](#) and [Figure 34](#)).

In addition, for a given FF/VI combination dose, the secondary endpoints were nested under the primary endpoints. If the defined treatment comparisons for the higher FF/VI combination dose demonstrated statistical significance at the 5% level on the primary efficacy endpoints, then inferences relating to the secondary endpoints for the higher combination dose were made; the same strategy was applied for the lower combination dose.

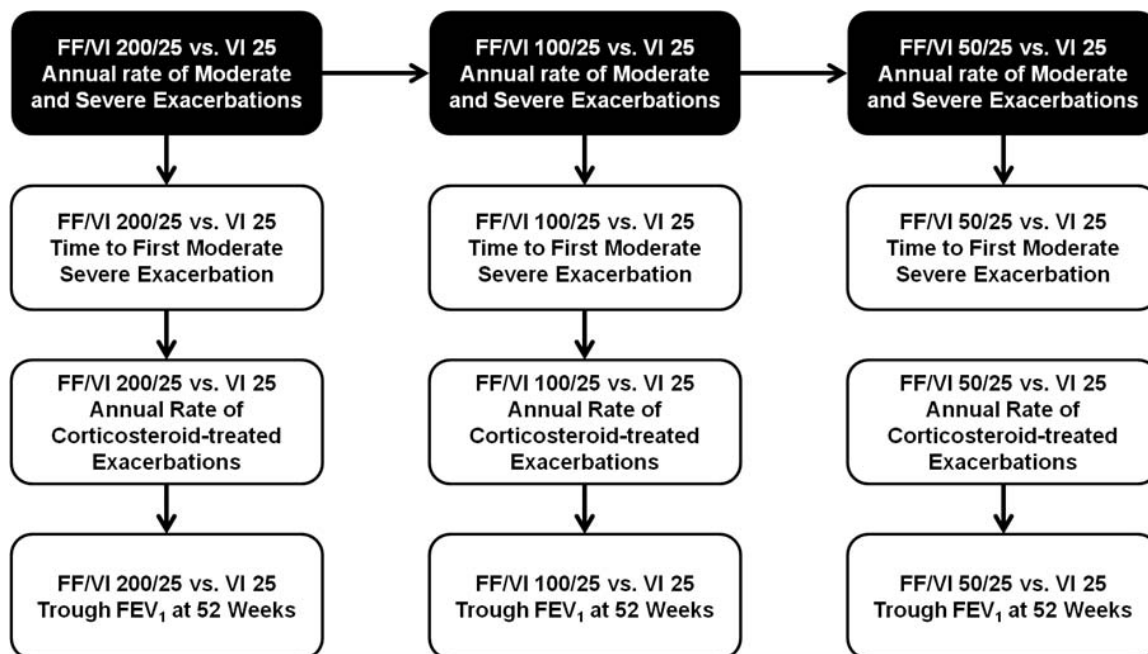
No further multiplicity adjustments were applied.

Figure 33 Statistical Testing Strategy: 6-Month, Lung Function Studies - HZC112206 and HZC112207



FEV₁=forced expiratory volume in 1 second; FF=fluticasone furoate; VI=vilanterol; wm=weighted mean

Figure 34 Statistical Testing Strategy: 1-Year, Exacerbation Studies - HZC102970 and HZC102871



FEV₁=forced expiratory volume in 1 second; FF=fluticasone furoate; VI=vilanterol; wm=weighted mean

12.3. Appendix 3: Statistical Methods

Primary/Co-Primary Efficacy Endpoints

Lung Function

Weighted Mean FEV₁ 0-4hrs Post-Dose

Weighted mean (WM) FEV₁ 0-4 hours was one of the two, co-primary endpoints in the two, 6-month, lung function studies (HZC112206 and HZC112207). This endpoint was not measured in HZC102871 or HZC102970.

WM FEV₁ 0-4 hours post-dose on Day 168 was analyzed using a repeated measures model. The primary analysis was performed using Mixed Model Repeated Measures analysis (MMRM) with covariates of study (integrated analysis only), baseline FEV₁, smoking status (stratum), Day, geographical region, treatment, Day by baseline interaction and Day by treatment interaction, where Day was nominal (and therefore equivalent to fitting Visit). The model used all available WM 0-4 hours FEV₁ values recorded on Days 1, 14, 56, 84, and 168. Missing data were not directly imputed in this analysis; however, all non-missing data for a subject were used within the analysis to estimate the treatment effect for WM 0-4 hours FEV₁ on Day 168. Two models were fitted; one with a response variable of WM 0-4 hours FEV₁, and one with a response variable of change from baseline WM 0-4 hours FEV₁.

For the integrated data, treatment comparisons were also provided for each level of each categorical subgroup at Screening (i.e., gender [male/female], age [≤ 64 , 65+], race [African American/African Heritage, American Indian or Alaskan Native, Asian, Native Hawaiian or other Pacific Islander, White, Mixed Race], smoking status [current or former smoker], geographical region, reversibility [reversible or not reversible], percent predicted FEV₁, cardiovascular history/risk). Cardiovascular history or risk was defined as the subject having had at least one of the following past or current medical conditions at screening: coronary artery disease, myocardial infarction, arrhythmia, congestive heart failure, hypertension, cerebrovascular accident, diabetes, or hypercholesterolemia. For each subgroup, these were obtained by fitting an additional model with terms for the subgroup (if not already included as a main effect in the primary model), subgroup by treatment interaction and subgroup by treatment by day interaction. From this model, estimates for each treatment comparison along with 95% CIs were obtained for the primary time point for each level of the subgroup.

Trough FEV₁

Change from baseline in trough FEV₁ on Day 169 was the other co-primary endpoint for the two, 6-month, lung function studies (HZC112206 and HZC112207). Trough FEV₁ was defined as the mean of the values obtained 23 and 24 hours after dosing on the previous day. If one of the two paired assessments was missing then trough FEV₁ was defined as the single 23 or 24 hour assessment. Baseline FEV₁ was defined as the mean of the two assessments made 30 minutes pre-dose and immediately pre-dose on Day 1.

For all other endpoints, the baseline value was taken as the value at the end of the Run-In Period.

Trough FEV₁ was analyzed using a repeated measures model. The primary analysis was performed using the same MMRM model as described for WM 0-4 hours FEV₁ above. All available trough FEV₁ values, recorded at each clinic visit, were used in the analysis. Missing data were not directly imputed but the correlation between visits for all subjects was used to adjust the estimate of treatment effect. The subgroup analyses were performed and presented as for the WM FEV₁, except that the trough FEV₁ was measured on Day 169 rather than Day 168.

Change from baseline in trough FEV₁ at 12 months (Visit 11) was a secondary endpoint in the two, 1-year exacerbation studies (HZC102871 and HZC102970). This endpoint was summarised and analyzed using the same methodology described for the two, 6-month, lung function studies (HZC112206 and HZC112207) as described above.

Annual Rate of Moderate and Severe Exacerbations

Annual rate of moderate and severe exacerbations was the primary endpoint for the two, 1-year, exacerbation studies (HZC102871 and HZC102970). This endpoint was not measured in two, 6-month, lung function studies (HZC112206 and HZC112207), as subjects were to be withdrawn if they experienced a moderate or severe exacerbation.

The primary endpoint of the annual rate of moderate and severe exacerbations was analysed using a generalized linear model, assuming the Negative Binomial distribution. The response variable was the number of recorded, on-treatment, moderate and severe exacerbations experienced per subject. The explanatory variables were study (integrated analysis only), treatment group, smoking status at screening (stratification variable), baseline disease severity (as %-predicted FEV₁) and geographical region. The model also included the logarithm of time on treatment per subject (derived from exposure start and stop) as an offset variable.

A supportive analysis was also performed whereby the number of moderate/severe exacerbations were analysed using a Poisson regression model with deviance overdispersion correction. The response variable and the explanatory variables were as defined for the Negative Binomial model. The model also included the logarithm of time on treatment per subject (derived from exposure start and stop) as an offset variable.

Note: The time to onset of multiple moderate and severe exacerbations was defined as an “other” endpoint and was analysed using the Andersen-Gill model for recurrent events [Andersen, 1982]. For the integrated data, for each of the categorical subgroups defined earlier in this section, a separate additional negative binomial model was fitted with terms for the subgroup (if not already included as a main effect in the primary model) and treatment by subgroup interaction. From this model, point estimates and 95% CIs for treatment differences for each level of the subgroup were obtained.

Secondary Efficacy Endpoints

Peak FEV₁

Peak FEV₁ on Day 1 was a secondary endpoint in the two, 6-month, lung function studies (HZA112206 and HZA112207). This endpoint was not measured in the two, 1-year exacerbation studies (HZA102871 and HZA102970). This endpoint was analysed using an analysis of covariance (ANCOVA) model with covariates of study (integrated analysis only), baseline FEV₁, smoking status, geographical region and treatment. Two models were fitted; one with a response variable of 0-4hrs peak FEV₁, and one with a response variable of change from baseline 0-4hrs peak FEV₁.

Time to time to ≥ 100 mL increase from baseline in FEV₁ on Day 1

Time to time to ≥ 100 mL increase from baseline in FEV₁ on Day 1 was a secondary endpoint in the two, 6-month, lung function studies (HZA112206 and HZA112207). This endpoint was not measured in the two, 1-year exacerbation studies (HZA102871 and HZA102970). This endpoint was analysed using the log-rank test, stratified for study (integrated analysis only) and smoking status. For this analysis, actual times of FEV₁ results were used. The p-values for the treatment comparisons were presented.

CRQ-SAS Dyspnea Domain

The CRQ-SAS dyspnea domain was an “Other” endpoint in the two, 6-month, lung function studies (HZA112206 and HZA112207). This endpoint was not evaluated in the two, 1-year exacerbation studies (HZA102871 and HZA102970).

The CRQ-SAS dyspnea domain was analysed using the same repeated measures model as for the co-primary endpoints, with the covariates of study (integrated analysis only), baseline dyspnea score, smoking status, Day, geographical region, treatment, Day by baseline interaction and Day by treatment interaction, where Day is nominal. The model used all available dyspnea domain scores on Days 28, 56, 84 and 168.

Time to First Moderate or Severe Exacerbation

Time to first moderate or severe exacerbation was a secondary endpoint in the two, 1-year exacerbation studies (HZA102871 and HZA102970). The analysis for the individual and integrated studies was performed using a Cox’s proportional hazards model. Only on-treatment exacerbations falling into Quarters 1-4 were used in the analysis. For the integrated analysis, the model was stratified by study (to allow for a different baseline hazard in the two studies) and included covariates for treatment group, smoking status at screening, baseline disease severity (as % predicted FEV₁) and geographical region. Hazard ratios for each combination dose against VI alone, with associated p-values and 95% CIs were presented.

In addition, Kaplan-Meier survivor functions were obtained for each treatment group separately using PROC LIFETEST with a TIME statement. The survivor functions for the four treatment groups were plotted on the same graph. The probability of having a moderate or severe exacerbation at weeks 13, 26, 39 and 52 (i.e., at the end of each pre-

defined time period from above) for each treatment group was presented, as well as the associated 95% CIs; these estimates were obtained from PROC LIFETEST.

In the two, 6-month, lung function studies (HZC112206 and HZC112207), moderate and severe exacerbations were recorded as a Safety Endpoint. However, analysis of time to first moderate/severe exacerbation was performed for the integrated data from these studies using the method described above for HZC102871/HZC102970 studies combined.

Annual Rate of Exacerbations Requiring Systemic/Oral Corticosteroids

The annual rate of exacerbations requiring systemic/oral corticosteroids was a secondary endpoint in the two, 1-year exacerbation studies (HZC102871 and HZC102970). This endpoint was not measured in the two, 6-month, lung function studies (HZC112206 and HZC112207) as subjects were required to be withdrawn if they reported a moderate or severe exacerbation.

In the individual and integrated analysis for the HZC102871 and HZC102970 studies, the number of on-treatment exacerbations requiring treatment with systemic/oral corticosteroids was calculated for each subject as the number of mild, moderate and severe exacerbations recorded on the exacerbations page of the eCRF which were marked as requiring treatment with systemic/oral corticosteroids. Note, per protocol, it was not possible to have a mild exacerbation that required systemic/oral corticosteroids. The annual rate of on-treatment exacerbations requiring systemic/oral corticosteroids was analyzed using a generalized linear model, assuming the Negative Binomial distribution.

12.4. Appendix 4: Preferred Terms within Each of the Categories of Adverse Events of Special Interest

Special Interest Group	Special Interest Subgroup	MedDRA Preferred Term Text
Bone disorders		Acetabulum fracture
Bone disorders		Ankle fracture
Bone disorders		Bone decalcification
Bone disorders		Bone density abnormal
Bone disorders		Bone density decreased
Bone disorders		Bone disorder
Bone disorders		Bone formation decreased
Bone disorders		Bone fragmentation
Bone disorders		Bone loss
Bone disorders		Cervical vertebral fracture
Bone disorders		Clavicle fracture
Bone disorders		Closed fracture manipulation
Bone disorders		Comminuted fracture
Bone disorders		Complicated fracture
Bone disorders		Compression fracture
Bone disorders		Epiphyseal fracture
Bone disorders		External fixation of fracture
Bone disorders		Facial bones fracture
Bone disorders		Femoral neck fracture
Bone disorders		Femur fracture
Bone disorders		Fibula fracture
Bone disorders		Foot fracture
Bone disorders		Forearm fracture
Bone disorders		Fracture
Bone disorders		Fracture delayed union
Bone disorders		Fracture displacement
Bone disorders		Fracture reduction
Bone disorders		Fractured coccyx
Bone disorders		Fractured ischium
Bone disorders		Fractured sacrum
Bone disorders		Fractured skull depressed
Bone disorders		Greenstick fracture
Bone disorders		Hand fracture
Bone disorders		Hip fracture
Bone disorders		Humerus fracture
Bone disorders		Ilium fracture
Bone disorders		Impacted fracture
Bone disorders		Internal fixation of fracture
Bone disorders		Internal fixation of spine
Bone disorders		Jaw fracture
Bone disorders		Lower limb fracture
Bone disorders		Lumbar vertebral fracture
Bone disorders		Multiple fractures
Bone disorders		Open fracture
Bone disorders		Open reduction of fracture

Special Interest Group	Special Interest Subgroup	MedDRA Preferred Term Text
Bone disorders		Osteocalcin decreased
Bone disorders		Osteonecrosis
Bone disorders		Osteonecrosis of jaw
Bone disorders		Osteopenia
Bone disorders		Osteoporosis
Bone disorders		Osteoporosis postmenopausal
Bone disorders		Osteoporotic fracture
Bone disorders		Osteosynthesis
Bone disorders		Patella fracture
Bone disorders		Pathological fracture
Bone disorders		Pelvic fracture
Bone disorders		Post-traumatic osteoporosis
Bone disorders		Pubis fracture
Bone disorders		Radius fracture
Bone disorders		Resorption bone increased
Bone disorders		Rib fracture
Bone disorders		Scapula fracture
Bone disorders		Senile osteoporosis
Bone disorders		Skeletal injury
Bone disorders		Skull fracture
Bone disorders		Skull fractured base
Bone disorders		Spinal compression fracture
Bone disorders		Spinal fracture
Bone disorders		Sternal fracture
Bone disorders		Stress fracture
Bone disorders		Thoracic vertebral fracture
Bone disorders		Tibia fracture
Bone disorders		Torus fracture
Bone disorders		Traumatic fracture
Bone disorders		Ulna fracture
Bone disorders		Upper limb fracture
Bone disorders		Vertebral wedging
Bone disorders		Wrist fracture
Cardiovascular effects	Acquired Long QT	Electrocardiogram QT interval abnormal
Cardiovascular effects	Acquired Long QT	Electrocardiogram QT prolonged
Cardiovascular effects	Acquired Long QT	Long QT syndrome
Cardiovascular effects	Acquired Long QT	Long QT syndrome congenital
Cardiovascular effects	Acquired Long QT	Torsade de pointes
Cardiovascular effects	Cardiac Arrhythmia	Accelerated idioventricular rhythm
Cardiovascular effects	Cardiac Arrhythmia	Agonal rhythm
Cardiovascular effects	Cardiac Arrhythmia	Anomalous atrioventricular excitation
Cardiovascular effects	Cardiac Arrhythmia	Arrhythmia
Cardiovascular effects	Cardiac Arrhythmia	Arrhythmia supraventricular
Cardiovascular effects	Cardiac Arrhythmia	Atrial fibrillation
Cardiovascular effects	Cardiac Arrhythmia	Atrial flutter
Cardiovascular effects	Cardiac Arrhythmia	Atrial parasystole
Cardiovascular effects	Cardiac Arrhythmia	Atrial tachycardia
Cardiovascular effects	Cardiac Arrhythmia	Atrioventricular extrasystoles
Cardiovascular effects	Cardiac Arrhythmia	Bradyarrhythmia

Special Interest Group	Special Interest Subgroup	MedDRA Preferred Term Text
Cardiovascular effects	Cardiac Arrhythmia	Bradycardia
Cardiovascular effects	Cardiac Arrhythmia	Cardiac arrest
Cardiovascular effects	Cardiac Arrhythmia	Cardiac fibrillation
Cardiovascular effects	Cardiac Arrhythmia	Cardiac flutter
Cardiovascular effects	Cardiac Arrhythmia	Cardio-respiratory arrest
Cardiovascular effects	Cardiac Arrhythmia	Cardiotoxicity
Cardiovascular effects	Cardiac Arrhythmia	Electrocardiogram R on T phenomenon
Cardiovascular effects	Cardiac Arrhythmia	Extrasystoles
Cardiovascular effects	Cardiac Arrhythmia	Heart rate abnormal
Cardiovascular effects	Cardiac Arrhythmia	Heart rate increased
Cardiovascular effects	Cardiac Arrhythmia	Heart rate irregular
Cardiovascular effects	Cardiac Arrhythmia	Loss of consciousness
Cardiovascular effects	Cardiac Arrhythmia	Nodal arrhythmia
Cardiovascular effects	Cardiac Arrhythmia	Nodal rhythm
Cardiovascular effects	Cardiac Arrhythmia	Palpitations
Cardiovascular effects	Cardiac Arrhythmia	Paroxysmal arrhythmia
Cardiovascular effects	Cardiac Arrhythmia	Postural orthostatic tachycardia syndrome
Cardiovascular effects	Cardiac Arrhythmia	Presyncope
Cardiovascular effects	Cardiac Arrhythmia	Pulseless electrical activity
Cardiovascular effects	Cardiac Arrhythmia	Rhythm idioventricular
Cardiovascular effects	Cardiac Arrhythmia	Sick sinus syndrome
Cardiovascular effects	Cardiac Arrhythmia	Sinus arrest
Cardiovascular effects	Cardiac Arrhythmia	Sinus bradycardia
Cardiovascular effects	Cardiac Arrhythmia	Sinus tachycardia
Cardiovascular effects	Cardiac Arrhythmia	Supraventricular extrasystoles
Cardiovascular effects	Cardiac Arrhythmia	Supraventricular tachyarrhythmia
Cardiovascular effects	Cardiac Arrhythmia	Supraventricular tachycardia
Cardiovascular effects	Cardiac Arrhythmia	Syncope
Cardiovascular effects	Cardiac Arrhythmia	Tachyarrhythmia
Cardiovascular effects	Cardiac Arrhythmia	Tachycardia
Cardiovascular effects	Cardiac Arrhythmia	Tachycardia paroxysmal
Cardiovascular effects	Cardiac Arrhythmia	Ventricular arrhythmia
Cardiovascular effects	Cardiac Arrhythmia	Ventricular asystole
Cardiovascular effects	Cardiac Arrhythmia	Ventricular dyssynchrony
Cardiovascular effects	Cardiac Arrhythmia	Ventricular extrasystoles
Cardiovascular effects	Cardiac Arrhythmia	Ventricular fibrillation
Cardiovascular effects	Cardiac Arrhythmia	Ventricular flutter
Cardiovascular effects	Cardiac Arrhythmia	Ventricular parasystole
Cardiovascular effects	Cardiac Arrhythmia	Ventricular pre-excitation
Cardiovascular effects	Cardiac Arrhythmia	Ventricular tachyarrhythmia
Cardiovascular effects	Cardiac Arrhythmia	Ventricular tachycardia
Cardiovascular effects	Cardiac Arrhythmia	Wandering pacemaker
Cardiovascular effects	Cardiac Failure	Acute left ventricular failure
Cardiovascular effects	Cardiac Failure	Acute right ventricular failure
Cardiovascular effects	Cardiac Failure	Cardiac asthma
Cardiovascular effects	Cardiac Failure	Cardiac failure
Cardiovascular effects	Cardiac Failure	Cardiac failure acute
Cardiovascular effects	Cardiac Failure	Cardiac failure chronic
Cardiovascular effects	Cardiac Failure	Cardiac failure congestive

Special Interest Group	Special Interest Subgroup	MedDRA Preferred Term Text
Cardiovascular effects	Cardiac Failure	Cardiac failure high output
Cardiovascular effects	Cardiac Failure	Cardiac output decreased
Cardiovascular effects	Cardiac Failure	Cardiac ventriculogram left abnormal
Cardiovascular effects	Cardiac Failure	Cardio-respiratory distress
Cardiovascular effects	Cardiac Failure	Cardiogenic shock
Cardiovascular effects	Cardiac Failure	Cardiopulmonary failure
Cardiovascular effects	Cardiac Failure	Cardiorenal syndrome
Cardiovascular effects	Cardiac Failure	Cardiothoracic ratio increased
Cardiovascular effects	Cardiac Failure	Cardiovascular insufficiency
Cardiovascular effects	Cardiac Failure	Chronic left ventricular failure
Cardiovascular effects	Cardiac Failure	Chronic right ventricular failure
Cardiovascular effects	Cardiac Failure	Cor pulmonale
Cardiovascular effects	Cardiac Failure	Cor pulmonale acute
Cardiovascular effects	Cardiac Failure	Cor pulmonale chronic
Cardiovascular effects	Cardiac Failure	Echocardiogram abnormal
Cardiovascular effects	Cardiac Failure	Echography abnormal
Cardiovascular effects	Cardiac Failure	Ejection fraction abnormal
Cardiovascular effects	Cardiac Failure	Ejection fraction decreased
Cardiovascular effects	Cardiac Failure	Gallop rhythm present
Cardiovascular effects	Cardiac Failure	Hepatojugular reflux
Cardiovascular effects	Cardiac Failure	Left ventricular failure
Cardiovascular effects	Cardiac Failure	Oedema due to cardiac disease
Cardiovascular effects	Cardiac Failure	Oedema peripheral
Cardiovascular effects	Cardiac Failure	Right ventricular failure
Cardiovascular effects	Cardiac Failure	Stroke volume decreased
Cardiovascular effects	Cardiac Failure	Ventricular failure
Cardiovascular effects	Cardiac Ischaemia	Acute coronary syndrome
Cardiovascular effects	Cardiac Ischaemia	Acute myocardial infarction
Cardiovascular effects	Cardiac Ischaemia	Angina pectoris
Cardiovascular effects	Cardiac Ischaemia	Angina unstable
Cardiovascular effects	Cardiac Ischaemia	Arteriospasm coronary
Cardiovascular effects	Cardiac Ischaemia	Blood creatine phosphokinase MB abnormal
Cardiovascular effects	Cardiac Ischaemia	Blood creatine phosphokinase MB increased
Cardiovascular effects	Cardiac Ischaemia	Cardiac enzymes increased
Cardiovascular effects	Cardiac Ischaemia	Cardiac stress test abnormal
Cardiovascular effects	Cardiac Ischaemia	Chest discomfort
Cardiovascular effects	Cardiac Ischaemia	Chest pain
Cardiovascular effects	Cardiac Ischaemia	Coronary artery disease
Cardiovascular effects	Cardiac Ischaemia	Coronary artery insufficiency
Cardiovascular effects	Cardiac Ischaemia	Coronary artery stenosis
Cardiovascular effects	Cardiac Ischaemia	ECG signs of myocardial ischaemia
Cardiovascular effects	Cardiac Ischaemia	Electrocardiogram ST segment abnormal
Cardiovascular effects	Cardiac Ischaemia	Electrocardiogram ST segment depression
Cardiovascular effects	Cardiac Ischaemia	Electrocardiogram ST segment elevation
Cardiovascular effects	Cardiac Ischaemia	Electrocardiogram ST-T change
Cardiovascular effects	Cardiac Ischaemia	Electrocardiogram ST-T segment abnormal
Cardiovascular effects	Cardiac Ischaemia	Electrocardiogram ST-T segment depression

Special Interest Group	Special Interest Subgroup	MedDRA Preferred Term Text
Cardiovascular effects	Cardiac Ischaemia	Electrocardiogram ST-T segment elevation
Cardiovascular effects	Cardiac Ischaemia	Electrocardiogram U-wave abnormality
Cardiovascular effects	Cardiac Ischaemia	Electrocardiogram U-wave biphasic
Cardiovascular effects	Cardiac Ischaemia	Microvascular angina
Cardiovascular effects	Cardiac Ischaemia	Myocardial infarction
Cardiovascular effects	Cardiac Ischaemia	Myocardial ischaemia
Cardiovascular effects	Cardiac Ischaemia	Papillary muscle infarction
Cardiovascular effects	Cardiac Ischaemia	Postinfarction angina
Cardiovascular effects	Cardiac Ischaemia	Prinzmetal angina
Cardiovascular effects	Cardiac Ischaemia	Silent myocardial infarction
Cardiovascular effects	Cardiac Ischaemia	Stress echocardiogram abnormal
Cardiovascular effects	Cardiac Ischaemia	Subendocardial ischaemia
Cardiovascular effects	Cardiac Ischaemia	Troponin I increased
Cardiovascular effects	Cardiac Ischaemia	Troponin T increased
Cardiovascular effects	Cardiac Ischaemia	Troponin increased
Cardiovascular effects	Hypertension	Blood pressure abnormal
Cardiovascular effects	Hypertension	Blood pressure ambulatory abnormal
Cardiovascular effects	Hypertension	Blood pressure ambulatory increased
Cardiovascular effects	Hypertension	Blood pressure diastolic abnormal
Cardiovascular effects	Hypertension	Blood pressure diastolic increased
Cardiovascular effects	Hypertension	Blood pressure increased
Cardiovascular effects	Hypertension	Blood pressure orthostatic abnormal
Cardiovascular effects	Hypertension	Blood pressure orthostatic increased
Cardiovascular effects	Hypertension	Blood pressure systolic abnormal
Cardiovascular effects	Hypertension	Blood pressure systolic increased
Cardiovascular effects	Hypertension	Essential hypertension
Cardiovascular effects	Hypertension	Hypertension
Cardiovascular effects	Hypertension	Hypertensive nephropathy
Cardiovascular effects	Hypertension	Labile hypertension
Cardiovascular effects	Hypertension	Malignant hypertensive heart disease
Cardiovascular effects	Hypertension	Mean arterial pressure increased
Cardiovascular effects	Hypertension	Orthostatic hypertension
Cardiovascular effects	Hypertension	Secondary hypertension
Cardiovascular effects	Hypertension	Systolic hypertension
Cardiovascular effects	Sudden Death	Cardiac death
Cardiovascular effects	Sudden Death	Sudden cardiac death
Cardiovascular effects	Sudden Death	Sudden death
Effects on glucose		Blood glucose abnormal
Effects on glucose		Blood glucose fluctuation
Effects on glucose		Blood glucose increased
Effects on glucose		Carbohydrate tolerance decreased
Effects on glucose		Diabetes mellitus
Effects on glucose		Diabetes mellitus inadequate control
Effects on glucose		Gestational diabetes
Effects on glucose		Glucose tolerance decreased
Effects on glucose		Glucose tolerance impaired
Effects on glucose		Glucose tolerance impaired in pregnancy
Effects on glucose		Glucose tolerance test abnormal
Effects on glucose		Glycosuria

Special Interest Group	Special Interest Subgroup	MedDRA Preferred Term Text
Effects on glucose		Glycosuria during pregnancy
Effects on glucose		Glycosylated haemoglobin increased
Effects on glucose		Hyperglycaemia
Effects on glucose		Impaired fasting glucose
Effects on glucose		Increased insulin requirement
Effects on glucose		Insulin resistant diabetes
Effects on glucose		Insulin-requiring type 2 diabetes mellitus
Effects on glucose		Type 1 diabetes mellitus
Effects on glucose		Type 2 diabetes mellitus
Effects on potassium		Blood potassium abnormal
Effects on potassium		Blood potassium decreased
Effects on potassium		Hypokalaemia
Effects on potassium		Hypokalaemic syndrome
Hypersensitivity		Allergic oedema
Hypersensitivity		Anaphylactic reaction
Hypersensitivity		Anaphylactic shock
Hypersensitivity		Anaphylactoid reaction
Hypersensitivity		Anaphylactoid shock
Hypersensitivity		Angioedema
Hypersensitivity		Circulatory collapse
Hypersensitivity		Circumoral oedema
Hypersensitivity		Dermatitis allergic
Hypersensitivity		Documented hypersensitivity to administered drug
Hypersensitivity		Drug eruption
Hypersensitivity		Drug hypersensitivity
Hypersensitivity		Drug rash with eosinophilia and systemic symptoms
Hypersensitivity		Erythema
Hypersensitivity		Exfoliative rash
Hypersensitivity		Eye swelling
Hypersensitivity		Eyelid oedema
Hypersensitivity		Eyelids pruritus
Hypersensitivity		Face oedema
Hypersensitivity		Fixed eruption
Hypersensitivity		Flushing
Hypersensitivity		Generalised erythema
Hypersensitivity		Generalised oedema
Hypersensitivity		Gingival oedema
Hypersensitivity		Gingival swelling
Hypersensitivity		Haemorrhagic urticaria
Hypersensitivity		Hypersensitivity
Hypersensitivity		Idiopathic urticaria
Hypersensitivity		Laryngeal oedema
Hypersensitivity		Lip oedema
Hypersensitivity		Lip pruritus
Hypersensitivity		Lip swelling
Hypersensitivity		Localised oedema
Hypersensitivity		Milk allergy

Special Interest Group	Special Interest Subgroup	MedDRA Preferred Term Text
Hypersensitivity		Mucocutaneous rash
Hypersensitivity		Oedema
Hypersensitivity		Oedema mouth
Hypersensitivity		Orbital oedema
Hypersensitivity		Palatal oedema
Hypersensitivity		Palmar erythema
Hypersensitivity		Periorbital oedema
Hypersensitivity		Pharyngeal oedema
Hypersensitivity		Plantar erythema
Hypersensitivity		Pruritus
Hypersensitivity		Pruritus allergic
Hypersensitivity		Pruritus generalised
Hypersensitivity		Rash
Hypersensitivity		Rash erythematous
Hypersensitivity		Rash follicular
Hypersensitivity		Rash generalised
Hypersensitivity		Rash macular
Hypersensitivity		Rash maculo-papular
Hypersensitivity		Rash maculovesicular
Hypersensitivity		Rash morbilliform
Hypersensitivity		Rash papular
Hypersensitivity		Rash papulosquamous
Hypersensitivity		Rash pruritic
Hypersensitivity		Rash rubelliform
Hypersensitivity		Rash scarlatiniform
Hypersensitivity		Rash vesicular
Hypersensitivity		Reaction to drug excipients
Hypersensitivity		Reticular erythematous mucinosis
Hypersensitivity		Swelling face
Hypersensitivity		Swollen tongue
Hypersensitivity		Tongue oedema
Hypersensitivity		Tongue pruritus
Hypersensitivity		Toxic skin eruption
Hypersensitivity		Type I hypersensitivity
Hypersensitivity		Type II hypersensitivity
Hypersensitivity		Type III immune complex mediated reaction
Hypersensitivity		Type IV hypersensitivity reaction
Hypersensitivity		Urticaria
Hypersensitivity		Urticaria aquagenic
Hypersensitivity		Urticaria cholinergic
Hypersensitivity		Urticaria chronic
Hypersensitivity		Urticaria contact
Hypersensitivity		Urticaria papular
Hypersensitivity		Urticaria physical
Hypersensitivity		Urticaria pigmentosa
Hypersensitivity		Urticaria pressure
Hypersensitivity		Urticaria thermal
Hypersensitivity		Urticaria vesiculosa
Hypersensitivity		Urticaria vibratory

Special Interest Group	Special Interest Subgroup	MedDRA Preferred Term Text
LRTI excluding pneumonia		Acute pulmonary histoplasmosis
LRTI excluding pneumonia		Aspergilloma
LRTI excluding pneumonia		Aspergillosis
LRTI excluding pneumonia		Bacterial tracheitis
LRTI excluding pneumonia		Bronchiolitis
LRTI excluding pneumonia		Bronchitis
LRTI excluding pneumonia		Bronchitis bacterial
LRTI excluding pneumonia		Bronchitis fungal
LRTI excluding pneumonia		Bronchitis haemophilus
LRTI excluding pneumonia		Bronchitis moraxella
LRTI excluding pneumonia		Bronchitis pneumococcal
LRTI excluding pneumonia		Bronchitis viral
LRTI excluding pneumonia		Bronchopulmonary aspergillosis
LRTI excluding pneumonia		Chronic pulmonary histoplasmosis
LRTI excluding pneumonia		Enterobacter tracheobronchitis
LRTI excluding pneumonia		Fibrinous bronchitis
LRTI excluding pneumonia		Fungal tracheitis
LRTI excluding pneumonia		Hantavirus pulmonary infection
LRTI excluding pneumonia		Infective exacerbation of chronic obstructive airways disease
LRTI excluding pneumonia		Legionella infection
LRTI excluding pneumonia		Lower respiratory tract infection
LRTI excluding pneumonia		Lower respiratory tract infection bacterial
LRTI excluding pneumonia		Lower respiratory tract infection fungal
LRTI excluding pneumonia		Lower respiratory tract infection viral
LRTI excluding pneumonia		Lung abscess

Special Interest Group	Special Interest Subgroup	MedDRA Preferred Term Text
LRTI excluding pneumonia		Necrotising bronchiolitis
LRTI excluding pneumonia		Pleural infection
LRTI excluding pneumonia		Pleural infection bacterial
LRTI excluding pneumonia		Pseudomonas bronchitis
LRTI excluding pneumonia		Pulmonary echinococcosis
LRTI excluding pneumonia		Pulmonary mycosis
LRTI excluding pneumonia		Pulmonary mycotoxicosis
LRTI excluding pneumonia		Pulmonary sepsis
LRTI excluding pneumonia		Pulmonary trichosporonosis
LRTI excluding pneumonia		Pyopneumothorax
LRTI excluding pneumonia		Respiratory moniliasis
LRTI excluding pneumonia		Respiratory syncytial virus bronchiolitis
LRTI excluding pneumonia		Respiratory syncytial virus bronchitis
LRTI excluding pneumonia		Respiratory tract infection bacterial
LRTI excluding pneumonia		Rhinotracheitis
LRTI excluding pneumonia		Sinobronchitis
LRTI excluding pneumonia		Tracheitis
LRTI excluding pneumonia		Tracheitis obstructive
LRTI excluding pneumonia		Tracheobronchitis
LRTI excluding pneumonia		Tracheobronchitis mycoplasmal
LRTI excluding pneumonia		Tracheobronchitis viral
LRTI excluding pneumonia		Viral tracheitis
Local steroid effects		Candida test positive
Local steroid effects		Candidiasis
Local steroid effects		Dysphonia
Local steroid effects		Mucocutaneous candidiasis
Local steroid effects		Oral candidiasis
Local steroid effects		Oral fungal infection

Special Interest Group	Special Interest Subgroup	MedDRA Preferred Term Text
Local steroid effects		Oropharyngeal candidiasis
Local steroid effects		Oropharyngeal pain
Local steroid effects		Oropharyngitis fungal
Local steroid effects		Throat irritation
Local steroid effects		Tonsillitis fungal
Ocular effects		Angle closure glaucoma
Ocular effects		Atopic cataract
Ocular effects		Borderline glaucoma
Ocular effects		Cataract
Ocular effects		Cataract cortical
Ocular effects		Cataract nuclear
Ocular effects		Cataract operation
Ocular effects		Cataract subcapsular
Ocular effects		Eye pain
Ocular effects		Glaucoma
Ocular effects		Glaucoma drug therapy
Ocular effects		Glaucoma surgery
Ocular effects		Glaucomatocyclitic crises
Ocular effects		Glaucomatous optic disc atrophy
Ocular effects		Intraocular lens extraction
Ocular effects		Intraocular pressure increased
Ocular effects		Intraocular pressure test abnormal
Ocular effects		Lens discolouration
Ocular effects		Lens disorder
Ocular effects		Lenticular opacities
Ocular effects		Normal tension glaucoma
Ocular effects		Ocular hypertension
Ocular effects		Ocular toxicity
Ocular effects		Open angle glaucoma
Ocular effects		Phacolytic glaucoma
Ocular effects		Pigmentary glaucoma
Ocular effects		Toxic cataract
Pneumonia		Atypical mycobacterial pneumonia
Pneumonia		Bronchopneumonia
Pneumonia		Bronchopneumopathy
Pneumonia		Candida pneumonia
Pneumonia		Enterobacter pneumonia
Pneumonia		Infectious pleural effusion
Pneumonia		Legionella test positive
Pneumonia		Lobar pneumonia
Pneumonia		Lung consolidation
Pneumonia		Lung infection
Pneumonia		Lung infection pseudomonal
Pneumonia		Miliary pneumonia
Pneumonia		Mycobacterium test positive
Pneumonia		Organising pneumonia
Pneumonia		Pneumocystis jiroveci pneumonia
Pneumonia		Pneumonia
Pneumonia		Pneumonia adenoviral

Special Interest Group	Special Interest Subgroup	MedDRA Preferred Term Text
Pneumonia		Pneumonia bacterial
Pneumonia		Pneumonia blastomyces
Pneumonia		Pneumonia bordetella
Pneumonia		Pneumonia chlamydia
Pneumonia		Pneumonia cryptococcal
Pneumonia		Pneumonia cytomegaloviral
Pneumonia		Pneumonia escherichia
Pneumonia		Pneumonia fungal
Pneumonia		Pneumonia haemophilus
Pneumonia		Pneumonia helminthic
Pneumonia		Pneumonia herpes viral
Pneumonia		Pneumonia influenzal
Pneumonia		Pneumonia klebsiella
Pneumonia		Pneumonia legionella
Pneumonia		Pneumonia measles
Pneumonia		Pneumonia moraxella
Pneumonia		Pneumonia mycoplasmal
Pneumonia		Pneumonia necrotising
Pneumonia		Pneumonia parainfluenzae viral
Pneumonia		Pneumonia pneumococcal
Pneumonia		Pneumonia primary atypical
Pneumonia		Pneumonia respiratory syncytial viral
Pneumonia		Pneumonia salmonella
Pneumonia		Pneumonia staphylococcal
Pneumonia		Pneumonia streptococcal
Pneumonia		Pneumonia toxoplasmal
Pneumonia		Pneumonia tularaemia
Pneumonia		Pneumonia viral
Pneumonia		Pneumonitis
Pneumonia		Pulmonary tuberculosis
Pneumonia		Tuberculosis
Systemic steroid effects		ACTH stimulation test abnormal
Systemic steroid effects		Addison's disease
Systemic steroid effects		Adrenal atrophy
Systemic steroid effects		Adrenal insufficiency
Systemic steroid effects		Adrenal suppression
Systemic steroid effects		Adrenocortical insufficiency acute
Systemic steroid effects		Blood corticosterone abnormal
Systemic steroid effects		Blood corticosterone decreased
Systemic steroid effects		Blood corticotrophin abnormal
Systemic steroid effects		Blood corticotrophin decreased
Systemic steroid effects		Blood cortisol abnormal
Systemic steroid effects		Blood cortisol decreased
Systemic steroid effects		Cortisol free urine abnormal
Systemic steroid effects		Cortisol free urine decreased
Systemic steroid effects		Cushing's syndrome
Systemic steroid effects		Cushingoid
Systemic steroid effects		Dexamethasone suppression test negative
Systemic steroid effects		Dexamethasone suppression test positive

Special Interest Group	Special Interest Subgroup	MedDRA Preferred Term Text
Systemic steroid effects		Glucocorticoids decreased
Systemic steroid effects		Hydroxycorticosteroids urine abnormal
Systemic steroid effects		Hydroxycorticosteroids urine decreased
Systemic steroid effects		Hyperadrenalism
Systemic steroid effects		Hyperadrenocorticism
Systemic steroid effects		Hypercorticism
Systemic steroid effects		Hypothalamo-pituitary disorder
Systemic steroid effects		Secondary adrenocortical insufficiency
Systemic steroid effects		Steroid withdrawal syndrome
Tremor		Essential tremor
Tremor		Tremor