

Spotlight on fluticasone furoate/vilanterol trifenatate for the once-daily treatment of asthma: design, development and place in therapy

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Abstract: The use of inhaled corticosteroids (ICSs) plays a key role in the treatment of asthmatic patients, and international guidelines have designated ICSs as an early maintenance therapy in controlling asthma symptoms. When asthmatic patients remain symptomatic on ICSs, one common option is to add a long-acting beta₂ agonist (LABA) to the maintenance treatment. Fixed combination inhalers that contain both an ICS and a LABA have been popular for both chronic obstructive pulmonary disease (COPD) and asthma. Historically, these inhalers have been dosed twice daily. However, currently, there is a once-daily combination therapy with the ICS fluticasone furoate (FF) and the LABA vilanterol trifenatate (VI) with indications for use in both COPD and asthma. This dry powder inhaler (DPI) comes in two doses of FF (100 or 200 µg) both combined with VI (25 µg). This article reviews the clinical trial data for FF, VI and FF/VI combination inhalers and documents the efficacy and safety of once-daily inhaled maintenance therapy by DPI in asthmatic patients.

Keywords: fluticasone furoate/vilanterol trifenatate, asthma, long-acting beta₂ agonist, inhaled corticosteroid, combined inhaler, persistent asthma, dry powder inhaler

Introduction

Asthma is an airway disease of inflammation and bronchoconstriction. Genetics and environmental factors combine to produce different asthma phenotypes and various responses to controller medications. The Global Initiative for Asthma (GINA) updated in 2016¹ is an ongoing international effort to provide a unified approach to the diagnosis and treatment of asthma. Table 1 summarizes the GINA general treatment approach to asthma that uses a stepwise function based on the severity of asthma symptoms. The table shows that inhaled corticosteroids (ICSs) play a major role as maintenance or preventative treatments in this stepwise approach to asthma. Table 2 summarizes the currently available and approved handheld inhalers by the US Food and Drug Administration (FDA) and several others not available in the USA. Fluticasone furoate (FF) is a potent corticosteroid that is dosed once daily due to its long half-life when inhaled. It was approved by the FDA as a once-daily ICS for the maintenance treatment of asthma as a dry powder inhaler (DPI) in August 2014 with the brand name Arnuity™ Ellipta® (GSK, USA).²

Controversy exists as to the role of long-acting beta₂ agonists (LABAs) in the maintenance treatment of moderate to severe asthmatics. Early clinical trials of the LABA salmeterol (SAL) noted a nonstatistically significant increase in all-cause mortality in asthmatic patients treated over 16 weeks when compared to those using

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Table 1 The 2016 stepwise approach to asthma treatment¹

| Asthma step | As-needed SABA | Low-dose ICS preferred controller | Medium/high-dose ICS/LABA | LTRA or Theo | Tiotropium | Alternative |
|-------------|----------------|-----------------------------------|---------------------------|--------------|----------------|----------------|
| Step 1 | + | + | | | | |
| Step 2 | + | + | | + | | |
| Step 3 | + ^a | + ^b | + ^b | + | | + ^c |
| Step 4 | + ^a | | + | + | + ^d | + ^e |
| Step 5 | + ^a | | + | + | + ^d | + ^f |

Notes: Adapted from GINA 2016.¹ ^aMay also include a single low-dose ICS/formoterol as a reliever medication for patients prescribed low-dose BUD/F for maintenance or low-dose BEC/F for those patients using BEC/F for maintenance. ^bPreferred step 3 maintenance for children aged 6–11 years is medium-dose ICS; adolescent/adults, low-dose ICS/LABA option. ^cMedium/high-dose ICS, low-dose ICS + LTRA, low-dose ICS + Theo are alternate options. ^dTiotropium (LAMA) by spring-driven mist (not indicated in children aged < 12 years). ^eTiotropium (LAMA) by spring-driven mist, high-dose ICS and LTRA or Theo are alternate options. ^fRefer to asthma specialist for add-on treatment options including tiotropium (LAMA), omalizumab, mepolizumab and/or oral corticosteroids.

Abbreviations: BEC/F, beclomethasone dipropionate/formoterol; BUD/F, budesonide/formoterol; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; LABA, long-acting beta₂ agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; SABA, short-acting beta₂ agonist; Theo, theophylline.

the short-acting beta₂ agonist (SABA), albuterol.³ A large 2006 clinical trial of 26,355 asthmatics named the Salmeterol Multicenter Asthma Research Trial (SMART) evaluated SAL by metered dose inhaler (MDI) compared to placebo MDI over 28 weeks.⁴ The use of ICS and leukotriene modifiers was equal in both groups (47% and 11%, respectively). The primary outcome included respiratory-related deaths or life-threatening events, and both were infrequent for the SAL group (50 patients) and placebo group (36 patients). This difference did not reach statistical significance (relative risk [RR]=1.40, 95% confidence interval [CI]=0.91–2.14). When secondary outcomes were explored, a small but significant increase in respiratory-related deaths was found in the SAL group (SAL 24 vs placebo 11; RR =2.16, 95% CI =1.06–4.41) along with specific asthma-related deaths (SAL 13 vs placebo 3; RR =4.37, 95% CI =1.25–15.4). The secondary outcome imbalances were largely related to the effects on the African-American subpopulation (20 SAL vs 5 placebo; RR =4.92, 95% CI =1.54–10.90).⁴ This study and a few others resulted in the FDA requiring a “black box” warning for all inhaled LABA agents based on the “risk” of their use in asthma.

Recent studies have called into question if there is an increase in risk to asthmatic patients treated with a combination ICS/LABA inhaler. In 2016, Peters et al⁵ studied 11,693 adult and adolescent asthmatic patients ≥12 years of age for 26 weeks. They were randomized to the ICS budesonide alone or a fixed-dose combination of budesonide and the LABA formoterol given twice daily by MDI. The budesonide/formoterol (BUD/F) combination was found to be noninferior to budesonide alone with 43 patients having a serious asthma-related event in the BUD/F group and 40 patients in the budesonide-alone-treated group (hazard ratio [HR]=1.07, 95% CI =0.70–1.65). The risk of an asthma exacerbation was

16.5% lower in the BUD/F-treated group compared to the budesonide-alone-treated group (HR =0.84, 95% CI =0.74–0.94).⁵ A similarly designed study in 11,679 asthmatic patients ≥12 years of age treated for 26 weeks also found that the combined fixed-dose fluticasone propionate (FP)/SAL did not have a significantly higher risk of serious asthma-related events and did have a 21% reduction in severe asthma exacerbations than those treated with fluticasone alone.⁶ Similarly, when a fixed combination inhaler of SAL and FP was compared to inhaled FP alone in 6,208 asthmatic children aged 4–11 years, non-inferiority for serious asthma-related events was seen (HR =1.28, 95% CI =0.73–2.27).⁷ These and other data suggest that the combination of an ICS with LABA is a safe and an effective treatment for asthma. Furthermore, the use of both an ICS and a LABA is an integral part of the GINA guidelines (Table 1) for the asthma patient at the step 3–step 5 levels.¹ Table 2 summarizes the multiple handheld inhalers available in the USA. At this time, LABA monotherapy without the simultaneous use of an ICS is still discouraged and has recently been described as “medical negligence” in children with asthma.⁸

The fixed combination of FF (100 or 200 µg) combined with the LABA vilanterol trifenate (VI; 25 µg) was approved in the USA in May 2013 for the maintenance treatment of chronic obstructive pulmonary disease (COPD) as the once-daily DPI Breo Ellipta[®] (GSK, USA). The same year, the same combination of drugs, doses and delivery system (Relvar Ellipta[®]; GSK, UK) was approved in Japan and the European Union for the treatment of asthma.⁹ Breo Ellipta (FF [100 or 200 µg]/VI [25 µg]) was approved by the FDA for the maintenance treatment of asthma in April 2015.² This article reviews the data that support the use of the fixed-dose combination of DPI FF with VI as a once-daily asthma maintenance treatment.

Table 2 Major handheld inhaler therapy in asthma and COPD

| Category | Drug | Dose (μ g) | Additional drug | Dose (μ g) | Frequency | Type | Examples of brand name |
|----------------------------|---|------------------|---------------------|-----------------|-----------------------|------|-----------------------------------|
| SABA | Albuterol sulfate | 90 | None | N/A | prn, q6h | MDI | Proventil HFA [®] |
| | Albuterol sulfate | 90 | None | N/A | prn, q6h | MDI | Ventolin HFA [®] |
| | Albuterol sulfate | 90 | None | N/A | prn, q6h | MDI | ProAir HFA [®] |
| | Albuterol sulfate | 90 | None | N/A | prn, q4–6h | DPI | ProAir RespiClick [®] |
| | Albuterol sulfate (salbutamol) ^a | 100 and 200 | None | N/A | prn, q6h | DPI | Easyhaler Salbutamol [®] |
| | Levalbuterol tartrate | 45 | None | N/A | prn, q6h | MDI | Xopenex HFA [®] |
| | Formoterol fumarate ^b | 12 | None | N/A | Twice daily | DPI | Foradil [®] |
| | Formoterol fumarate ^c | 12 | None | N/A | Twice daily | DPI | Atimos Modulite [®] |
| | SAL xinafoate | 50 | None | N/A | Twice daily | DPI | Serevent Diskus [®] |
| | SAL xinafoate ^a | 25 | None | N/A | Twice daily | MDI | Neovent [®] |
| SAMA | Indacaterol maleate ^d | 75 | None | N/A | Daily | DPI | Arcapta [®] |
| | Indacaterol maleate ^c | 150 and 300 | None | N/A | Once daily | DPI | Onbrez Breezhaler [®] |
| | Olodaterol hydrochloride ^d | 2.5 | None | N/A | Daily | SDM | Striverdi Respimat [®] |
| | Ipratropium bromide ^{e,f} | 21 | None | N/A | q6h | MDI | Atrovent HFA [®] |
| | Tiotropium bromide ^d | 18 | None | N/A | Daily | DPF | Spiriva HandiHaler [®] |
| | Tiotropium bromide ^d | 2.5 | None | N/A | Daily | SDM | Spiriva Respimat [®] |
| | Tiotropium bromide | 1.25 | None | N/A | Daily | SDM | Spiriva Respimat [®] |
| | Acclidinium bromide ^d | 400 | None | N/A | Twice daily | DPI | Tudorza Pressair [®] |
| | UMEC bromide ^d | 62.5 | None | N/A | Daily | DPI | Incruse Ellipta [®] |
| | Glycopyrrolate bromide ^c | 50 | None | N/A | Daily | DPI | Seebri Breezhaler [®] |
| Combination of SABA + SAMA | Albuterol sulfate ^{e,f} | 100 | Ipratropium bromide | 30 | q6h | SDM | Combivent Respimat [®] |
| | Tiotropium bromide ^d | 2.5 | Olodaterol | 2.5 | Daily | SDM | Stiolto Respimat [®] |
| | Acclidinium bromide ^c | 400 | Formoterol | 12 | Twice daily | DPI | Duaklir Genuair [®] |
| | UMEC bromide ^d | 62.5 | VI | 25 | Daily | DPI | Anora Ellipta [®] |
| | Glycopyrrolate bromide ^d | 15.6 | Indacaterol | 27.5 | Twice daily | DPI | Ultibro Neohaler [®] |
| | Glycopyrrolate bromide ^c | 50 | Indacaterol | 110 | Daily | DPI | Ultibro Breezhaler [®] |
| | Glycopyrrolate bromide ^d | 9 | Formoterol | 4.8 | Twice daily | MDI | Bevespi Aerosphere [®] |
| | Beclomethasone dipropionate | 40 and 80 | None | N/A | Twice daily | MDI | QVAR HFA [®] |
| | Budesonide | 90 and 180 | None | N/A | Twice daily | DPI | Pulmicort Flexhaler [®] |
| | Ciclesonide | 80 and 160 | None | N/A | Twice daily | MDI | Alvesco HFA [®] |
| Combination of ICS + LABA | FP | 50, 100 and 250 | None | N/A | Twice daily | DPI | Flovent Diskus [®] |
| | FP | 44, 110 and 220 | None | N/A | Twice daily | MDI | Flovent HFA [®] |
| | FP | 100 and 200 | None | N/A | Daily | DPI | Arnuity Ellipta [®] |
| | Mometasone furoate | 110 and 220 | None | N/A | Daily and twice daily | DPI | Asmanex Twisthaler [®] |
| | Budesonide | 80 and 160 | Formoterol fumarate | 4.5 | Twice daily | MDI | Symbicort [®] |
| | Budesonide ^a | 160 and 320 | Formoterol fumarate | 4.5/9 | Twice daily | DPI | DuoResp SpiroMax [®] |
| | FP | 100, 250 and 500 | SAL xinafoate | 50 | Twice daily | DPI | Advair Diskus [®] |
| | FP | 45, 115 and 500 | SAL xinafoate | 21 | Twice daily | MDI | Advair HFA [®] |
| | FP | 100 and 200 | VI | 25 | Daily | DPI | Breo Ellipta [®] |
| | Mometasone furoate | 100 and 200 | Formoterol fumarate | 5 | Twice daily | MDI | Dulera [®] |

Notes: ^aApproved in the UK and Europe for COPD and asthmatic patients. ^bNo longer manufactured and sold in the USA but still FDA approved, still available in the UK/Europe. ^cApproved in the UK, Europe and Canada for COPD, not routinely used in asthmatic patients. ^dApproved by the FDA only for COPD, not routinely used in asthmatic patients. ^eUsed in acute exacerbations of asthma. ^fq6h, every 6 hours; prn, as needed.

Abbreviations: COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; FDA, US Food and Drug Administration; FF, fluticasone furoate; FP, fluticasone propionate; ICS, inhaled corticosteroid; LABA, long-acting beta₂ agonist; LAMA, long-acting muscarinic antagonist; MDI, metered dose inhaler; N/A, not applicable; SABA, short-acting beta₂ agonist; SAL, salmeterol; SAMA, short-acting muscarinic antagonist; SDM, spring-driven mist; UMEC, umecidinium; VI, vilanterol trifenate.

FF in asthma

The inhaled use of FF in asthma is in part based on its long half-life in the lung that allows once-daily dosing for asthma maintenance therapy.¹⁰ As given in Table 1, ICS therapy plays a major role in the current GINA guidelines. When as-needed SABAs become inadequate to control asthma symptoms, the use of low-dose ICS should be considered as early as step 1 and used through step 2 into step 3 as medium- to high-dose ICS. The 100 µg daily DPI dose of FF is considered low-dose ICS therapy for asthmatics aged 12 years and older.¹ After the addition of a LABA to low-dose ICS therapy at step 3, higher medium- or high-dose ICS therapy is recommended by the GINA guidelines for asthmatic patients that remain symptomatic. The 200 µg daily DPI dose of FF is considered a “high-dose” ICS and can be used for symptomatic step 3–5 asthmatic patients.¹

Table 3 summarizes the major clinical trials that have examined the use of FF as an ICS maintenance asthma therapy. Efficacy and safety have been verified with once-daily FF dosing in asthmatic patients in several studies. An 8-week study of 545 adolescent and adult asthmatic patients demonstrated significant (all $P \leq 0.033$) improvements with FF in pre-dose and placebo-adjusted forced expiratory volume at 1 second (FEV_1). Once-daily evening-dosed FF (400 µg) was also as effective as twice-daily dosing (200 µg) of the same total daily FF dose in improving placebo-adjusted FEV_1 (≥ 200 mL).¹¹ In this study, the morning-dosed FF (400 µg) was found to be less effective than an equal dose of FF (200 µg) given twice daily (202 mL improvement, 95% CI =96–307 vs 315 mL improvement, 95% CI =208–421 mL).¹¹ A randomized, double-blind, double-dummy and placebo-controlled study further evaluated once-daily FF (100 µg) given in the morning compared to the evening over a 2-week trial in asthmatics aged 18–70 years who required an ICS to control symptoms.¹² Inhaled FF (100 µg) daily increased 24-hour weighted mean FEV_1 relative to placebo (for AM dosing, 77 mL; 90% CI =1–152 mL and for PM dosing, 105 mL; 90% CI =29–180 mL)¹³ and found that the difference in the increase when FF was given in the morning or evening was negligible (adjusted differences, 28 mL; 90% CI =–102–45 mL).¹² A longer 24-week multicenter, double-blind, parallel-group study compared once-daily evening doses of FF (100 µg) to FF (200 µg).¹³ Both FF doses improved least-squares mean trough FEV_1 from baseline by 208 mL in the FF (100 µg) group and 284 mL in the FF (200 µg) group (treatment difference, 77 mL; 95% CI =–39–192 mL).¹³ Similar improvements were seen in rescue- and symptom-free days, morning and evening peak

Table 3 Major clinical trials with FF in asthma

| Study | Trial number | N | Drugs (µg) | Design | Results (doses in µg) |
|------------------------------|--------------|-----|--|--|---|
| Bateman et al ⁶¹ | NCT00603382 | 598 | FF (25, 50, 100 or 200) qpm or FP (100) bid or P | ≥ 12 -year-old asthmatics; MC, R, DB, DD, PC, PG, $\times 8$ weeks | A dose-response effect on FEV_1 was seen ($P < 0.001$) for FF. FF (50–200) significantly ($P < 0.05$) improved FEV_1 from baseline compared to P. FF non-inferior to FP |
| Woodcock et al ¹³ | NCT01431950 | 238 | FF (100 or 200) daily | ≥ 12 -year-old asthmatics uncontrolled on mid-high-dose ICS; MC, R, DB, PG, $\times 24$ weeks | Least-squares mean trough FEV_1 was improved from baseline for both doses of FF. No significant difference between FF (100) and FF (200). Similar rates of AEs. No clinically relevant effects on |
| Lötvall et al ⁶² | NCT01159912 | 343 | FF (100) qpm or FP (250) bid or P | ≥ 12 -year-old asthmatics uncontrolled on ICS; MC, R, DB, DD, PC, PG, $\times 24$ weeks | 24-hour urinary cortisol excretion at week 24 by either FF dose Both FF and FP significantly ($P = 0.01$) increased pre-dose evening FEV_1 compared to P at week 24. Less use of rescue medications with FF compared to P ($P < 0.001$). AEs were similar. Week 24 urinary cortisol levels were significantly reduced ($P = 0.036$) by both FF and FP compared to P |
| Busse et al ⁶³ | NCT01436110 | 347 | FF (50) qpm or FP (100) bid or P | ≥ 12 -year-old asthmatics uncontrolled by non-ICS therapy; MC, R, DB, DD, PC, PG, $\times 24$ weeks | Evening trough FEV_1 at week 24 was not significantly increased with FF (50) but increased with FP (100) bid ($P = 0.03$). No safety concerns were noted |
| O'Byrne et al ⁶⁴ | NCT01436071 | 248 | FF (50) or P qpm | ≥ 12 -year-old asthmatics; MC, R, DB, PC, PG, $\times 12$ weeks | Significant ($P = 0.012$) increase in evening trough FEV_1 with FF compared to P. Significant increase in rescue-free 24-hour periods ($P = 0.004$) with FF compared to P. Lower AEs with FF (31%) than P (38%) |

| | | | | | |
|-----------------------------------|--------------|-----|---|---|--|
| Woodcock et al ¹¹ | NCT00398645 | 646 | FF (200 or 400) qam or FF (200 or 400) qpm or FF (200) or P bid all by DPI | ≥ 12-year-old asthmatics; MC, R, DB, PC, ×8 weeks | All five FF dose groups produced significant ($P < 0.05$) increases in pre-dose FEV ₁ compared to P. No difference between qd and bid dosing. Low incidence (0%–4%) of oral candidiasis and no differences in urinary cortisol excretion. Day 28 pre-dose FEV ₁ showed non-inferiority between FF (100) bid versus FF (200) qpm. All doses of FF and FF were superior to P ($P < 0.02$). AEs were similar to P. Urinary cortisol excretion at day 28, lower for FF than for P ($P \leq 0.02$). Trough PEF improved with all doses of FF compared to P ($P \leq 0.005$). No difference in trough PEF with FF (100) qam or qpm. No serious AEs. No dose–response effect was seen across the FF doses studied. All FF doses improved PEF ($P < 0.001$) compared to P. Incidence of oral candidiasis increased compared to P with the FF (800) dose. FF (500) bid also improved PEF. Trough FEV ₁ improved with FF (100) alone but > with FF (100) + UMEC (125 or 250). FF/UMEC increased morning and evening PEF compared to FF (100) alone. AEs were similar across groups, and no laboratory parameter changes were noted. |
| Woodcock et al ⁶⁵ | NCT00766090 | 190 | All patients received bid dosing – if listed as qd – second daily dose was P. FF (100) bid or FF (200) qpm or FF (200) qpm or FF (100) bid or P bid FF (100) qam or FF (100) qpm or FF (250) qpm or P | ≥ 12-year-old asthmatics; MC, R, XO, PC, XO, ×4 weeks | |
| Medley et al ⁶⁶ | NCT01499446 | 575 | FF (200, 400, 600 or 800) qpm, FF (500) bid, P qpm | Asthmatic patients aged 16–55 years; MC, R, DB, DD, PC, PG, ×4 weeks | |
| Busse et al ⁶⁷ | NCT00063746 | 627 | FF (100) qam or FF (100) + UMEC (15.6, 31.25, 62.5, 125 or 250) qam or FF (100) + VI (25) qam | ≥ 12-year-old asthmatics uncontrolled on ICS; MC, R, DB, DD, PC, PG, ×8 weeks | |
| Lee et al ¹⁴ | NCT01573624 | 421 | FF (100, 200, 300 or 400) qpm or FF (250) bid or P bid | ≥ 18-year-old asthmatics on ICS; MC, R, DB, XO, ×2 weeks | |
| Kempsford et al ¹² | NCT01808339 | 21 | Single dose – P or FF (1,000) – 2, 14 or 26 hours or FF (1,000) – 14 or 26 hours before AmpCT | 18–70-year-old asthmatics on ICS; SC, R, DB, DD, PC, XO, ×2 weeks | FF (100) increased 24-hour weighted mean FEV ₁ . The increases for FF dosed in the AM or PM were comparable. No serious AEs were reported. |
| Bleecker et al ⁶⁸ | NCT 00603278 | 622 | FF (100, 200, 300 or 400) qpm or FF (250) bid or P bid | ≥ 12-year-old asthmatics; MC, R, DB, DD, PC, PG, ×8 weeks | Significant ($P < 0.001$) greater increase in FEV ₁ with all doses of FF and FP than P. Increases with qd FF were equal or greater than with bid FF. The 24-hour urinary cortisol levels were similar with all doses of FF, FP and P. |
| van den Berge et al ⁶⁹ | Not given | 24 | Single dose – P or FF (1,000) – 2, 14 or 26 hours or FF (1,000) – 14 or 26 hours before AmpCT | Asthmatic patients not on ICS; MC, R, DB, PC, XO | Threshold dose AmpCT increased by prior exposure to FF at 2, 14 or 26 hours compared to P. Prior FP exposure only increased AmpCT threshold at 14 hours not at 26 hours compared to P. |
| Yang et al ¹⁵ | NCT01725685 | 18 | Single dose – FF (400) or UMEC (500) or FF (400) plus UMEC (500) | 18–65-year-old healthy volunteers; SC, R, DB, XO | Plasma FF concentrations peaked at 0.5 hours alone and with combined FF/UMEC inhaler. No clinically significant AEs, vital signs or laboratory parameters. |
| Allen et al ⁷⁰ | NCT01000597 | 80 | FF (250) intravenous or FF (800) or FF (400) both by DPI | 20–59-year-old healthy Caucasian, Japanese, Korean and Chinese subjects; OL, R, XO, single and daily repeat doses ×7 days; intravenous dose ×1 only | Higher FF systemic exposures were seen in Chinese, Japanese and Korean subjects compared to Caucasian subjects. Bioavailability was higher in Asian subjects than Caucasian. Japanese had on average 22% lower serum weighted mean cortisol levels than Caucasians, Chinese or Koreans. Serum weighted mean cortisol levels were similar in Caucasians, Chinese or Koreans. Well tolerated in all groups. |

Notes: References in bold are key studies; bid, twice daily; qam, daily morning; qd, once daily; qpm, daily evening.

Abbreviations: AEs, adverse events; AmpCT, adenosine 5'-monophosphate (AMP) challenge test; DB, double blind; DD, double blind; DPI, dry powder inhaler; FEV₁, forced expiratory volume in 1 second; FF, fluticasone furoate; FP, fluticasone propionate; ICS, inhaled corticosteroid; MC, multiple centers; NCT, clinical trials.gov study numbers; OL, open label; P, placebo; PC, placebo controlled; PEF, peak expiratory flow; PG, parallel group; R, randomized; SC, single center; UMEC, umecidinium; VI, vilanterol trifenate; XO, crossover.

expiratory flow (PEF) and reported adverse events with the two FF doses. The 200 µg FF-treated group was 42% more likely to have well-controlled symptoms than the 100 µg FF-treated group. There were no safety concerns, and no clinically relevant effects on 24-hour urinary cortisol levels with either of the doses of inhaled FF were found.¹³

When inhaled FF (100 µg) daily for 2 weeks was compared to FF (100 µg) combined with the long-acting muscarinic antagonist (LAMA), umeclidinium (UMEC; 15.6, 31.25, 62.5, 125 or 250 µg), in adult asthmatics, trough FEV₁ was improved with FF (100 µg) alone (by 87 mL) compared to baseline, but they increased even more when FF (100 µg) was combined with UMEC doses (141–214 mL).¹⁴ When least-squares mean change in trough FEV₁ was evaluated, statistically significant differences were seen with FF (100 µg)/UMEC (125 and 250 µg; both 55 mL, $P=0.018$) compared to FF (100 µg) alone.¹⁴ In addition, both morning and evening PEF improved more with the combination of FF with UMEC daily inhalation compared to FF alone. The FF serum concentrations peaked at half an hour when given alone, and this did not change when combined with UMEC.¹⁵ The use of daily FF given by DPI has a proven efficacy in asthmatic patients requiring an ICS for symptom control. The combination of FF with LAMA appears to increase the efficacy compared to FF alone in asthmatic patients.

The use of VI in asthma

Several new LABA agents designed for once-daily dosing are available or under study including indacaterol, olodaterol, abediterol and VI.¹⁶ Appropriate concern for the use of LABA agents alone as maintenance therapy has mandated that asthmatic subjects in most clinical studies evaluating the use of the inhaled LABA VI be currently on an ICS (Table 4). An exception is the study by Kempsford et al.¹⁷ Inhaled VI was given once daily (25–100 µg) for 14 days to healthy volunteers and once to patients with either asthma or COPD. Inhaled VI was rapidly absorbed with a median time to maximal serum concentrations of 5 minutes in healthy subjects and 10 minutes for asthma and COPD patients. All VI doses improved FEV₁ by 5 minutes and maintained increased FEV₁ up to 24 hours after inhalation in patients with asthma or COPD.¹⁷ No clinically significant adverse effects were found including evaluations of vital signs, 12-lead electrocardiogram (ECG), Holter ECG, blood glucose or potassium levels. Table 4 summarizes five placebo-controlled clinical trials in asthmatics on an ICS that evaluated inhaled VI using a DPI device lasting between 1 and 12 weeks. Doses between 3 and 50 µg daily of inhaled VI were tried, and the bronchodilator effect lasted at least 24 hours for

VI doses 12.5–50 µg.¹⁸ The efficacy and safety of once-daily VI dosing in asthmatics were established by Sterling et al¹⁹ who evaluated 72 adult (≥ 18 years old) asthmatics on an ICS with a 7-day treatment of daily inhaled VI (6.25, 12.5 and 25 µg), twice-daily inhaled VI (6.25 µg) or placebo using a DPI. The VI treatment in asthmatics resulted in a statistically significant ($P<0.001$ for all doses) increase on day 7 in trough FEV₁ and weighted mean 24-hour FEV₁ versus placebo. The differences from placebo for trough FEV₁ with once-daily VI were 94 mL (95% CI =49–140 mL), 102 mL (95% CI =57–147 mL) and 125 mL (95% CI =80–170 mL) for 6.25, 12.5 and 25 µg doses, respectively. The 6.25 µg VI twice-daily dose resulted in 140 mL (95% CI =95–185 mL) improvement in trough FEV₁ compared to placebo.¹⁹ Non-inferiority between once-daily versus twice-daily VI dosing was also shown.¹⁹

A recent large trial children aged 5–11 years ($N=456$) with persistent asthma symptoms inadequately controlled on an ICS were randomized to once-daily inhaled VI (6.25, 12.5 or 25 µg), and this was compared to placebo over 4 weeks. It demonstrated safety but failed to show an improvement from baseline in trough FEV₁ for any of the VI doses tested.²⁰ Adult asthmatic patients uncontrolled on an ICS ($N=347$) were given once-daily VI (25 µg) for 12 weeks and were compared to those given twice-daily SAL or placebo. Researchers noted the improvement in FEV₁ of 359 ± 42.9 mL with VI, 283 ± 41.9 mL with SAL and 289 ± 42.9 mL for placebo.²¹ The increase in FEV₁ was not statistically significantly different between VI and placebo. Overall, these data suggest that there is a variable response to inhaled VI in adult patients with persistent symptoms already on an ICS and even less efficacy of VI in asthmatic children on an ICS.

The use of FF and VI in asthma

Pharmacodynamic, pharmacokinetic and safety data have been tested with inhaled FF/VI in several populations, including healthy Chinese and Japanese, in patients simultaneously on ketoconazole and in patients with renal and hepatic impairment.^{22–25} Stable pharmacokinetics and pharmacodynamics and no safety concerns over the use of inhaled FF/VI were found in these studies. Allergen and methacholine challenge tests were used in 27 patients randomized to inhaled FF (100 µg), VI (25 µg), FF (100 µg)/VI (25 µg) or placebo.²⁶ Using the allergen challenge to test early asthmatic response (EAR) and airway hyperresponsiveness (AHR), researchers found a decrease in FEV₁. Using the mean 0–2 hours post allergen challenge FEV₁, the least decrease was reported with the pre-challenge dosing of the

Table 4 Major clinical trials with VI in asthma

| Study | Trial number | N | Drugs (μg) | Design | Results (doses in μg) |
|------------------------------------|---|------------------|---|--|--|
| Kempford et al¹⁷ | NCT00469040; NCT00463697; NCT00519376; NCT00702910 | 36, 22 and 24 | VI (25) or VI (50) or VI (100) or P all daily and VI (25) or VI (50) or VI (100) or P single dose and VI (6.25) or VI (25) or VI (100) or P all single dose, all by DPI | Healthy subjects (36) between 18 and 55 years old, SC, PC, R, DB, PG, $\times 14$ days and persistent asthmatics (22) ≥ 18 years old, MC, R, DB, PC, XO, single dose and persistent asthmatics (24) between 18 and 55 years old, MC, R, DB, PC, XO, single dose | VI rapidly absorbed maximal concentration between 5 and 10 minutes. No significant changes in vital signs, 12-lead ECG or blood chemistry changes were noted with VI. All doses of VI resulted in increases in FEV ₁ within 5 minutes and lasted at least 24 hours |
| Lötvald et al²¹ | NCT01181895 | 347 | VI (25) daily SAL (50) bid or P, all by DPI | Adult asthmatics uncontrolled by ICS alone; MC, R, PC, DB, DD, $\times 12$ weeks | VI, SAL and P all showed substantial improvement in 24-hour weighted mean FEV ₁ after 12 weeks without statistically significant differences. Low rates of AEs compared to P The adjusted mean change from baseline in evening PEF averaged over the 4-week treatment phase showed no significant difference between VI and P. No difference was also seen in trough FEV ₁ between VI and P. VI resulted in an additional 0.6 rescue-free days and 0.7 symptom- free days per week compared to P. AEs were slightly higher with VI (28%–33%) versus P (22%) |
| Oliver et al²⁰ | NCT01573767 | 456 | VI (6.25, 12.5 or 25) or P Daily, all by DPI, all replaced their ICS with FP (100) bid during 4-week run-in phase | Children aged 5–11 years with persistent asthma on ICS; MC, R, DB, PC, PG, $\times 4$ - and 1-week follow-up | A VI dose–response effect ($P=0.037$) was seen on improving trough FEV ₁ . Statistically significant ($P\leq 0.016$) increases in mean FEV ₁ relative to P were seen for VI doses (12, 25 and 50). Prolonged bronchodilation was seen for at least 24 hours with VI All VI doses had significant ($P<0.001$) increase in weighted mean 24-hour FEV ₁ compared to P. Low incidence of AEs with VI (5%–9%) without evidence of dose dependence. P AEs were 18% |
| Lötvald et al ¹⁸ | NCT00600171 | 614 | VI (3, 6.25, 12.5, 25 or 50) or P qpm, by DPI | ≥ 12 -year-old symptomatic asthmatics on stable ICS dose; MC, R, DB, P, dose-ranging study, $\times 28$ days | Statistically significant ($P\leq 0.016$) increases in mean FEV ₁ relative to P were seen for VI doses (12, 25 and 50). Prolonged bronchodilation was seen for at least 24 hours with VI All VI doses had significant ($P<0.001$) increase in weighted mean 24-hour FEV ₁ compared to P. Low incidence of AEs with VI (5%–9%) without evidence of dose dependence. P AEs were 18% |
| Sterling et al ¹⁹ | NCT00980200 | 75 | VI (6.25) daily or VI (6.25) bid or VI (12.5) daily or VI (25) daily or P, all by DPI | ≥ 18 -year-old asthmatics on stable dose ICS; MC, R, DB, PC, XO, $\times 7$ days | Statistically significant ($P\leq 0.016$) increases in mean FEV ₁ relative to P were seen for VI doses (12, 25 and 50). Prolonged bronchodilation was seen for at least 24 hours with VI All VI doses had significant ($P<0.001$) increase in weighted mean 24-hour FEV ₁ compared to P. Low incidence of AEs with VI (5%–9%) without evidence of dose dependence. P AEs were 18% |
| Oliver et al ⁷¹ | NCT01453296 | 28 | VI (25) or P single dose and VI (25) or P daily, all by DPI | Children aged 5–11 years with persistent asthma on ICS; MC, R, DB, PC, XO, single dose then 7 days later, once-daily dosing, $\times 7$ days | All ages showed similar VI pharmacokinetics. No laboratory or ECG abnormalities. No change in PEF from day 1 to day 14 |

Notes: References in bold are key studies; bid, twice daily; qpm, daily evening.

Abbreviations: AEs, adverse events; DB, double blind; DD, double dummy; DPI, dry powder inhaler; ECG, electrocardiogram; FEV₁, forced expiratory volume in 1 second; FP, fluticasone propionate; ICS, inhaled corticosteroid; MC, multicenter; P, placebo; PC, placebo controlled; PEF, peak expiratory flow; PG, parallel group; R, randomized; SAL, salmeterol; SC, single center; VI, vilanterol trifenate; XO, crossover.

combination FF/VI inhaler (-0.614 L, 95% CI $=-0.858$ to -0.370) and the greatest decrease was after placebo inhaler (-1.091 L, 95% CI $=-1.344$ to -0.837). The methacholine challenge test was used in these patients to model late asthmatic response (LAR) and AHR at 24 hours. Weighted mean FEV₁ 4–10 hours post challenge was reduced after placebo (-466 mL, 95% CI $=-589$ to -343) but actually increased with FF (100 μg ; 18 mL, 95% CI $=-89$ to 125)

and with FF (100 μg)/VI (25 μg ; 18 mL, 95% CI $=-89$ to 124). It was also improved compared to placebo with VI (25 μg ; -298 mL, 95% CI $=-415$ to -181).²⁶ The use of the combined FF/VI provided statistically significant protection against the EAR of AHR compared to its components alone and to placebo. There was also statistically significant protection with combination FF/VI therapy when compared to placebo and VI alone against the LAR of AHR.

Cytochrome P450 3A4 (CYP3A4) is the major hepatic enzyme responsible for metabolizing FF by ester hydrolysis with the formation of the 17 beta-carboxylic acid and loss of the *S*-fluoro-methyl-carbithioate.^{24,27} FF is also believed to be a substrate for the P-glycoprotein (PgP) efflux transporter, and enterocytes may have a major metabolic effect on FF in the gastrointestinal track.²⁷ The hepatic enzyme CYP3A4 also plays a major role in the metabolism of VI by *O*-dealkylation.²⁸ It is also believed to be a substrate for PgP when in the gastrointestinal system.²⁴ Ketoconazole is a probe used to assess the potential effect of CYP3A4 metabolic inhibition, and it also has inhibitory effects on PgP.²⁴ Coadministration of repeat doses of ketoconazole 400 mg daily and inhaled VI (25 µg) alone had no pharmacodynamic or pharmacokinetic effect on VI. When 11 days of 400 mg oral ketoconazole daily was coadministered with inhaled FF (200 µg)/VI (25 µg) from days 5 to 11, no statistical or clinical effect was seen on heart rate or minimal potassium levels.²⁴ There was a 27% decrease in 24-hour weighted mean serum cortisol levels (treatment ratio =0.73, 90% CI=0.62–0.86). An increase in the FF area under the plasma concentration 0–24-hour curve by 36% with ketoconazole (90% CI =16%–59%) was reported. The area under the plasma concentration 0–24-hour VI curve increased by 65% (90% CI =38%–97%).²⁴ Table 5 summarizes the major pharmacokinetic parameters of FF and VI that allow once-daily dosing for this inhaled fixed combination medication.

Table 6 summarizes the major clinical trials evaluating pharmacokinetics, safety and efficacy of FF/VI given by DPI in asthmatic patients. Large randomized double-blind clinical trials have shown improved FEV₁ and PEF measures by treatment with FF/VI compared to placebo or the same or better measures with active control agents such as inhaled FP and FP with the LABA SAL twice daily.^{29–36} These clinical trials lasted from 2 to 52 weeks and evaluated efficacy and safety. Two trials each of 12-week duration have confirmed the efficacy of FF (100–200 µg)/VI (25 µg) given daily by DPI in Asian asthmatic patients compared to placebo³⁷ and

compared to the active comparator FP using PEF measures of efficacy.³⁸

An observational study from Italian National Health Service data used propensity score matching on baseline covariates of gender, age, FEV₁ and comorbidities on 40 adult asthmatic patients. They were treated with FF (100 µg)/VI (25 µg) by DPI once daily or beclomethasone dipropionate/formoterol (BEC/F) inhalation twice daily.³⁹ The BEC/F-treated group had 0.28 (±0.12) days of hospitalization, and those treated with FF/VI had 0.08 (±0.04) days of hospitalization ($P=0.09$) during the 12-week analysis period. Both the number of physician visits and the number of specialist visits were statistically reduced in the FF/VI-treated group compared to the BEC/F-treated group.³⁹ Another small comparison study (N=30) in Japan evaluated BUD (160 µg)/F (4.5 µg) two puffs twice daily and one additional inhalation as needed of BUD/F each day versus FF (100 µg)/VI (25 µg) by DPI daily over 4 weeks in asthmatics ≥20 years who required an ICS.⁴⁰ Both drug combinations showed statistically significant ($P<0.001$) improvement in the asthma control questionnaire during the 4 weeks with greater improvement in the scores with the BUD/F-treated group. Both groups also showed decreases ($P<0.001$) in fractional exhaled nitric oxide (FeNO) from baseline to week 4 with the levels in the BUD/F group reduced greater ($P<0.001$) than the FF/VI-treated group. The use of a fixed-dose ICS/LABA as a rescue medication in this study goes against historical dogma of using SABA agents as rescue medication in asthma but is in the GINA guidelines (Table 1). In addition, direct comparisons between different combinations of ICS/LABA beg the question of dosage equivalence. In this study, perhaps the comparator should have been FF (200 µg)/VI (25 µg) as a high-dose ICS as opposed to the low-dose FF (100 µg)/VI (25 µg) combination.

The asthma–COPD overlap syndrome (ACOS) is an asthma phenotype that shares features of both asthma and traditional COPD.^{1,41} A small (N=16) open-label, randomized, crossover study of patients with ACOS in Japan compared

Table 5 Pharmacokinetics of FF and VI

| Drug | Mean absorption time (IN) (hours) | Absolute bioavailability (IN) (%) | t _{max} (IN) (hours) | t _{1/2} beta (hours) | VD (IN) (L) |
|------|-----------------------------------|-----------------------------------|--|--|---------------|
| FF | 10.53 (8.52–13.01) | 6.3–18.4; 15.2 (12.6–18.4) | 1.0 (0.08–4.00) to 0.08 (0.08–1.50) | 23.7 (20.8–26.9) (IN); 15.4 (13.1–18.2) (IV) | 661 (546–800) |
| VI | 0.659 (0.286–1.517) | 10–12; 27.3 (21.6–34.6) | 0.150 (0.08–0.17) to 0.100 (0.08–0.18) | 2.47 (1.65–3.70) (IN); 2.40 (1.65–3.48) (IV) | 165 (129–211) |

Notes: Data are mean (90% CI); t_{max}, time to maximum observed concentration (inhaled); t_{1/2} beta, terminal elimination half-life. Data from.^{10,70,72,73}

Abbreviations: CI, confidence interval; FF, fluticasone furoate; IN, inhaled dose; IV, intravenous dose; L, liters; VD, volume of distribution at steady state; VI, vilanterol trifenate.

Table 6 Major clinical trials with FF/VI in asthma

| Study | Trial number | N | Drugs (μg) | Design | Results (doses in μg) |
|-------------------------------|-----------------------------|-------|---|--|--|
| Allen et al ²⁴ | NCT01086410 | 185 | FF (100)/VI (25) or FF (200)/VI (25) or P by DPI or P by DPI plus 10 mg Pred oral last 7 days | 12–65-year-old asthmatic patients; MC, R, PC, DB, PG, DD, all daily doses $\times 6$ weeks | No differences (non-inferior) in 24-hour weighted mean serum or urinary cortisol levels between FF/VI at either dose and P. Pred substantially reduced 24-hour weighted mean serum cortisol compared to P |
| Woodcock et al ²⁶ | NCT01147848 | 806 | FF (100)/VI (25) qpm or FF (250)/SAL (50) bid by DPI | ≥ 12 -year-old asthmatic patients on stable ICS; MC, R, DB, DD, PG, $\times 24$ weeks | Significant improvement from baseline seen in 0–24-hour weighted mean FEV ₁ after 24-week treatment with both FF/VI qpm or FP/SAL bid. No difference in asthma control measures or exacerbations |
| Busse et al ³⁴ | NCT01018186 | 503 | FF (100)/VI (25) qpm or FF (200)/VI (25) qpm or FP (500) bid by DPI | ≥ 12 -year-old asthmatic patients on ICS; MC, R, DB, DD, PG, $\times 52$ weeks | Exacerbation rates were FF (100)/VI (25) (1%), FF (200)/VI (25) (3%) and FP (500) (3%) during the study. Statistically significant ($P \leq 0.006$) cortisol suppression seen with FP compared to both FF/VI doses at weeks 12 and 28 but not at week 52. No clinically important glucose, potassium, ECG or ophthalmic changes were noted |
| O'Byrne et al ³² | NCT01134042 | 586 | FF (200)/VI (25) qpm or FF (200) qpm or FP (500) bid by DPI | ≥ 12 -year-old asthmatic patients on ICS; MC, R, DB, DD, PG, $\times 24$ weeks | FF/VI significantly ($P < 0.001$) improved both trough and weighted mean (0–24 hours) FEV ₁ compared to both FF and FP alone. AEs were similar between groups |
| Bateman et al ³¹ | NCT01086384 | 2,019 | FF (100)/VI (25) or FF (100) daily qpm by DPI | ≥ 12 -year-old asthmatic patients on ICS; MC, R, DB, PG, $\times 24$ –78 weeks | FF/VI compared to FF alone delayed onset of first severe asthma experience exacerbation ($P \leq 0.05$). Significantly ($P < 0.001$) greater trough FEV ₁ improvement with FF/VI than FF alone. Both were well tolerated with similar AEs |
| Bernstein et al ²⁹ | NCT01686633 | 1,039 | FF (100) or FF (100)/VI (25) or FF (200)/VI (25) qpm daily by DPI | ≥ 12 -year-old asthmatic patients on ICS; MC, R, DB, stratified, PG, $\times 12$ weeks | Weighted mean FEV ₁ (0–24 hours) was significantly ($P < 0.01$) increased by both doses of FF/VI compared to FF alone. Trough FEV ₁ percentage of rescue-free 24-hour periods and morning/evening PEF were also improved. Small numerical improvements occurred with FF (200)/VI (25) compared to FF (100)/VI (25). All treatments were well tolerated |
| Kempford et al ³⁵ | NCT01287065 | 26 | FF (100)/VI (25) qpm or FF (100)/VI (25) qam or P by DPI | 18–70-year-old asthmatic patients on stable ICS; SC, R, DB, PC, XO, daily dose of FF/VI given qam or qpm with P given the opposite qam/qpm or P given bid $\times 14$ days | Both, morning and evening FF/VI, increased weighted mean FEV ₁ . Both dosing times produced comparable improvements in lung function |
| Allen et al ²⁵ | NCT01266941 and NCT01266980 | 35 | FF (200)/VI (25) or FF (100)/VI (25) by DPI | Two studies, OL, PG, daily doses in: 1) mild to moderate hepatic impaired patients or healthy matched patients, all daily dose $\times 7$ days; 2) severe renal impaired (CrCl < 30 mL/min) patients or healthy matched patients, all daily dose $\times 7$ days | No effect on VI maximal concentrations or area under the concentration curve for 24 hours in liver or renal impaired patients. No difference in heart rate, serum potassium or 24 hour serum cortisol levels seen |

(Continued)

Table 6 (Continued)

| Study | Trial number | N | Drugs (μg) | Design | Results (doses in μg) |
|------------------------------|---------------------------------------|---------------|--|---|--|
| Oliver et al ²⁵ | NCT01128569 | 52 | FF (100) or FF (100)/VI (25) or P by DPI | 18–65-year-old asthmatics; MC, R, DB, PC, XO, daily dose $\times 28$ days | Weighted mean FEV ₁ for the 2-hour post-allergen challenge was improved by FF and FF/VI compared to P. No difference was seen between FF and FF/VI |
| Kempford et al ²⁴ | NCT01165125 and NCT00866515 | 20 and 18 | 1) Keto 400 mg or P oral daily $\times 6$ days on day 5 VI (25) $\times 1$ dose by DPI and 2) Keto 400 mg or P oral daily $\times 11$ days with FF (200)/VI (25) daily days 4–11 by DPI | 18–52-year-old healthy subjects; SC, R, DB, XO, all doses were daily | Oral Keto is known as CYP3A4 and Pgp inhibitors. No major effect of Keto on VI pharmacodynamics was seen. Maximal levels and area under the curve (0–24 hours) were increased approximately twofold by Keto on FF (36%) and VI (65%). No effect on maximal heart rate or minimal potassium levels was seen when Keto was given with FF/VI. A 27% decrease in 24-hour weighted mean serum cortisol levels was noted |
| Nakahara et al ²³ | NCT00625196; NCT00964249; NCT00972673 | 48, 32 and 16 | FF (200, 400 or 800) or P and VI (12.5 or 25) and FF (800) or VI (50) or FF (800)/VI (50) by DPI | Healthy adult Japanese males, single dose; then 4-day washout; then daily dose days 5–11 (7 days) and single dose daily $\times 7$ days and single dose | Peak serum concentrations of FF and VI were up to two times higher compared to single doses. No clinically significant difference in VI or FF levels when administered together compared to alone. Repeat doses of FF affected weighted mean (0–24 hours) serum cortisol with FF (200, 400 and 800) resulting in respective reductions from placebo of 32%, 38% and 97% respectively. No safety concerns were seen |
| Oliver et al ²⁶ | NCT01128595 | 26 | FF (100) or VI (25) or FF (100)/VI (25) or P by DPI | 18–65-year-old asthmatic patients; MC, R, DB, PC, XO, daily dose qam $\times 21$ days; allergen challenge test and MCT | Treatment with FF, VI or FF/VI all reduced the early decrease in FEV ₁ with allergen challenge test 0–2 hours and 24 hours compared to P on day 21. Same protection was seen with MCT for FF, VI or FF/VI on day 22 |
| Oliver et al ³³ | None given | 26 | FF (100)/VI (25) or FF (100) daily by DPI | 5–11-year-old patients with mild asthma controlled by ICS, R, DB, XO, stratified by age, $\times 14$ days | No difference was seen in primary outcomes including AEs, laboratory measures, heart rate, blood pressure, PEF or ECG between FF/VI and FF |
| Bleecker et al ³⁰ | NCT01165138 | 609 | FF (100)/VI (25) or FF (100) or P all daily qpm by DPI | ≥ 12 -year-old asthmatic patients; MC, R, DB, PG, $\times 12$ weeks | Both FF/VI and FF significantly ($P < 0.003$) increased trough and weighted mean (0–24 hours) FEV ₁ compared to P. No statistical difference between FF/VI and FF in FEV ₁ . The percentage of rescue inhaler-free 24-hour periods 10.6% greater with FF/VI than FF alone and 19.3% greater with FF/VI than P |
| Lin et al ³⁸ | NCT10498653 | 309 | FF (200)/VI (25) qpm or FP (500) bid by DPI | ≥ 12 -year-old asthmatic patients from the People's Republic of China, South Korea and the Philippines; MC, R, DB, DD, PG, $\times 12$ weeks | Significantly greater change from baseline on evening PEF by FF/VI compared to FP ($P < 0.001$). No difference in AEs |
| Chen et al ²² | NCT01711463 | 16 | FF (50)/VI (25) or FF (100)/VI (25) or FF (200)/VI (25) or P qam daily by DPI | 18–45-year-old healthy Chinese subjects; SC, R, DB, PC, XO, $\times 7$ days | Reductions compared to P in weighted mean serum cortisol (0–24 hour) levels for day 7 were seen for FF (100)/VI (25) and FF (200)/VI (25) compared to P. FF/VI was safe and well tolerated |
| Lin et al ³⁷ | NCT01498679 | 307 | FF (100)/VI (25) or P daily all by DPI | ≥ 12 -year-old patients with Asian ancestry and asthmatics on ICS; MC, R, DB, PC, PG, $\times 12$ weeks | Significant ($P < 0.001$) improvement in change from baseline for FF/VI versus P in evening PEF. Greater percentage of symptom-free 24-hour periods with FF/VI than P. ADEs were 35% for FF/VI and 31% for P |

| | | | | | |
|-------------------------------|------------|-----|--|--|--|
| Hozawa et al ⁴⁰ | None given | 30 | BUD (320)/F (9) bid plus as-needed BUD (160)/F (4.5) or FF (100)/VI (25) qpm plus as-needed procaterol, all by DPI | ≥20-year-old Japanese asthmatics on ICS; SC, R, OL, ×4 weeks | BUD/F and FF/VI both showed improvement in airway inflammation, FEV ₁ , resonance frequency exhaled nitric oxide and asthma control scores, but FF/VI improvement seemed to plateau, while BUD/F did not. The use of a single as-needed dose of BUD/F was well tolerated |
| Dal Negro et al ³⁹ | None given | 117 | BEC (100)/F (6) bid or FF (92)/VI (22) daily, all by DPI | Adult asthmatic patients; observational, retrospective with propensity score matching, ×12 weeks | The number of relapses per patient was 0.53 (±0.12) for the BEC/F treatment group and 0.28 (±0.07) for the FF/VI group ($P=0.12$). Less hospitalizations ($P=0.11$), specialist visits ($P<0.001$) and general physician visits ($P<0.001$) were seen in the FF/VI group compared to the BEC/F-treated group. The mean cost of hospitalizations per patient was less but not significant for the FF/VI group |
| Ishiura et al ⁴² | None given | 16 | FF (200)/VI (25) qam or FP (500)/SAL (50) bid, all by DPI | Adult 59–87-year-old Japanese patients with ACOS; OL, R, XO, ×12 weeks | The trough FEV ₁ was significantly ($P<0.01$) higher after FF/VI than at baseline. No significant change in FEV ₁ was seen with FP/SAL treatment. Each spirometry parameter was significantly ($P<0.05$) higher after FF/VI treatment than values found with FP/SAL |

Notes: References in bold are key studies; bid, twice daily; qam, daily morning; qpm, daily evening.

Abbreviations: ACOS, asthma-COPD overlap syndrome; ADE, adverse drug event; AEs, adverse events; BEC/F, beclomethasone dipropionate/formoterol; BUD/F, budesonide/formoterol; COPD, chronic obstructive pulmonary disease; CYP, cytochrome P450; DB, double blind; DD, double dummy; DPI, dry powder inhaler; ECG, electrocardiogram; FEV₁, forced expiratory volume in 1 second; FF, fluticasone furoate; FP, fluticasone propionate; ICS, inhaled corticosteroid; Keto, ketoconazole; MC, multicenter; MCT, methacholine challenge test; OL, open label; PC, placebo controlled; PEF, peak expiratory flow; PG, parallel group; Pgp, P-glycoprotein; Pred, prednisolone; R, randomized; SAL, salmeterol; SC, single center; VI, vilanterol trifenatate; XO, crossover.

once-daily FF (200 µg)/VI (25 µg) versus FP (500 µg)/SAL (50 µg) twice daily for 4-week treatment periods.⁴² The mean value of FEV₁ was 1.33 L (±1.29) during the run-in period, 138 L (±0.39) after the FP/SAL treatment and 1.47 (±0.38) L after the FF/VI treatment. The mean value of FEV₁ was significantly ($P<0.01$) greater in the FF/VI treatment group compared to the run-in period in these patients with ACOS. Although a small trial of short duration, it is one of the few pharmacological trials in patients with ACOS and the only randomized trial evaluating the FF/VI combination inhaler in patients with ACOS phenotype.

A large pragmatic study evaluating FF (100 or 200 µg)/VI (25 µg) inhaler use versus existing asthma maintenance therapies is ongoing. The Salford Lung Study is a randomized and controlled trial started before FF/VI inhalers were approved for asthma treatment. It utilizes the Salford electronic medical record to give near real-time data collection and monitoring of safety data at 66 primary care sites in and around Salford and South Manchester, England.⁴³ The data from this study when available will complement the more standard double-blind, randomized, controlled trials evaluating real-world efficacy and obtaining risk/benefit information on inhaled FF/VI.

When East Asian patients were compared to non-East Asian patients from the large randomized, double-blind, multicenter clinical trials in a prespecified subgroup analysis, both FF (100 or 200 µg)/VI (25 µg) dose combinations were as effective in improving FEV₁ compared to placebo as in non-East Asian patients.⁴⁴ A systematic review with meta-analysis of seven published trials (N=5,668) evaluating inhaled FF/VI in asthmatic patients was recently performed.⁴⁵ The combination therapy of FF (100 or 200 µg)/VI (25 µg) daily increased trough FEV₁ in asthmatics treated longer than 8 weeks compared to either FP twice daily or FF daily alone. Three of the seven trials compared FF (100 or 200 µg)/VI (25 µg) doses to FF (100 µg) once daily and showed a significant ($P\leq 0.001$) increase in trough FEV₁ of 90 mL (95% CI =60–120 mL) with the combination inhaler compared to FF alone.⁴⁵

Medication adherence with inhalers

Medication adherence or following the medication plan is a significant problem and factor in the treatment of chronic diseases.⁴⁶ Dosing frequency has a major effect on the rate of nonadherence of medication in chronic diseases.⁴⁷ When medications are given twice daily compared to once daily, the adherence rates were significantly lower, with regimen adherence reduced by 13.1% and timing adherence reduced

by 26.7% compared to once daily.⁴⁷ The adherence rates fall 23.1% for regimen adherence and 54.2% for timing adherence when medications are given four times daily compared to daily dosing. Nonadherence to treatment is associated with poor baseline asthma control.^{48,49} The nonadherence rates among asthmatic patients range between 30% and 70%, and because of this the assessment of medication adherence is a critical part of evaluating the difficult to treat asthma patient.^{50,51} Integrated and innovative approaches to patients are needed to improve medication adherence in difficult asthmatic patients.⁵² Once-daily medications and the combination of an ICS with a LABA in a single inhaler are associated with improved medication adherence compared to that of an ICS alone.^{53,54} Better medication adherence must be addressed and will improve health outcomes and asthma disease control.^{55,56}

In addition to being a daily combination dosing asthma maintenance medication, Breo Ellipta (GSK) utilizes the Ellipta delivery system. The Ellipta dry powder system (GSK, UK and Japan) has been shown to be easy to use and preferred over the Breezhaler (Novartis Pharma UK, Japan) in device-naïve Japanese volunteers.⁵⁷ When semi-structured, in-depth, qualitative interviews were conducted on asthma and COPD patients after using Ellipta (GSK, Germany) dry powder inhalation systems, the Ellipta device was associated with the highest patient satisfaction and preference.⁵⁸ Patient preference for the Ellipta device was also demonstrated in 287 COPD patients randomized to the Ellipta or Diskus DPIs.⁵⁹ The Ellipta device was significantly preferred ($P < 0.001$) over the Diskus device in all categories. Overall inhaler preference was 67% for the Ellipta device and 31% for the Diskus.⁵⁹ Once-daily dosing with the FF/VI Ellipta device and its high patient preference are also likely to contribute to improved asthma medication adherence.

To date, a large amount of clinical trial data exists supporting the efficacy and safety of the use of inhaled FF/VI by DPI for asthma maintenance treatment. The combination ICS/LABA of FF/VI fits well into the GINA guidelines starting as early as step 3.¹ Studies looking at a fixed-dose triple-combination inhaler with FF, VI and the LAMA UMEC are ongoing in healthy volunteers, being developed for COPD indication and could be evaluated in asthmatic patients.⁶⁰

Conclusion

The DPI inhaler, FF/VI, is a fixed combination of two strengths of FF (100 or 200 µg) both with VI (25 µg) used as a maintenance treatment in asthmatic patients not controlled on just an ICS therapy alone. The doses of FF cover low- and high-dose ICS categories and fit nicely into the current GINA

asthma treatment guidelines. Clinical trials have focused on each of the components of the combination inhaler. Efficacy and safety were demonstrated with inhaled FF in asthmatic patients. Similarly, efficacy and safety were demonstrated in clinical trials in adolescent and adult asthmatic patients on an ICS with adding inhaled VI but not in children aged 5–11 years. The data supporting the combined use of FF/VI in asthmatic patients requiring ICS are strong and document its efficacy and safety in long-term, large and randomized clinical trials in adolescents and adults. Pharmacokinetics and pharmacodynamics have been well studied and have demonstrated limited clinically important drug interactions (eg, ketoconazole) and minimal alterations from renal and liver impairments. Limited efficacy data with inhaled FF/VI exist for asthmatic children (<12 years). Further studies on asthmatic children and various asthma phenotypes such as patients with ACOS are needed to better understand the full spectrum of the use of inhaled fixed combination FF/VI in the maintenance treatment of asthma.

Disclosure

The authors report no conflicts of interest in this work.

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