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Vilanterol trifenatate for the treatment of COPD

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ABSTRACT

Introduction: Currently the treatment of chronic obstructive pulmonary disease (COPD) has limited effectiveness and there is a need to develop new drugs. International guidelines recommend the use of long-acting bronchodilators (β2 agonists and anti-cholinergics/muscarinics), inhaled steroids and associations between these drugs in the maintenance treatment of moderate-to-severe COPD.

Area Covered: Vilanterol trifenate is a new once-daily highly selective β2-agonist available in USA and Europe in association with umeclidinium bromide (a long-acting anti-muscarnic agent) and fluticasone furoate (an inhaled corticosteroid) for the once-daily maintenance treatment of COPD. Vilanterol combined in fixed-dose treatments has been tested in numerous clinical trials involving thousands of patients.

Expert Commentary: These new once-daily formulations have the potential to improve compliance to long-term inhaled therapy. This paper will review the clinical and experimental data regarding vilanterol use in the regular treatment of COPD as well as provide a critical discussion of possible future treatment settings.

Key words: Vilanterol trifenate, umeclidinium bromide, fluticasone furoate, LABA, LAMA, COPD treatment.

1. **INTRODUCTION**

Chronic obstructive pulmonary disease (COPD) is a chronic lung disease characterized by the presence of airflow limitation and bronchial inflammation [1]. It is considered one of the diseases with greatest impact on public health and the WHO estimates that COPD will become the third leading cause of death by 2030 worldwide [2].

The main objectives of COPD treatment are the prevention of decline in respiratory function, improvement of symptoms, prevention of exacerbations and avoidance of pulmonary and extra-pulmonary complications. Treatment options depend on the stage of disease severity and the risk of exacerbation. However, the basis of therapy consists of bronchodilators and anti-inflammatory drugs administered topically [3].

The 2 main classes of long-acting bronchodilators act through different mechanisms of action: long-acting beta-2 (β2)-adrenoceptor agonists (LABA) and muscarinic receptor antagonists (LAMA). Both classes of bronchodilators are associated with improvements in symptoms, rate and severity of exacerbations and exercise tolerance [4].

The Global Obstructive Lung Disease (GOLD) International guidelines recommend classification of patients with COPD into 4 categories (A, B, C and D) in relation to airflow limitation, severity of symptoms and the risk of exacerbation (patients with more severe symptoms or at higher risk are classified as groups C or D) [1]. GOLD recommends the use of bronchodilators, LAMA or LABA, as maintenance therapy in patients with less severe symptoms; and in patients with increased symptoms combinations of fixed doses of LABA with LAMA or LABA with inhaled corticosteroids (ICS) [1]. In patients with moderate-to-severe COPD there is evidence that the combination of different classes of bronchodilators is more effective compared to using a single drug class [5].

In clinical practice, however, the prescription rate of combination drugs is very high. There is indeed the observation that adherence to treatment and compliance can be increased with combination treatments with once-daily administration [6].

Vilanterol trifenate (VIL) is a new LABA with 24 hours activity, for once-daily inhalation treatment use in association with LAMA or ICS for the treatment of COPD [7]. This paper reviews the use of VIL alone and in combination with ICS and LAMA in the treatment of COPD, and in combination with ICS for asthma. The paper will focus on VIL's pharmacokinetics and pharmcodynamics: efficacy, especially on lung function, and patient-reported outcomes such as exercise tolerance, improvement in symptoms and quality of life; and safety. Possible future treatment settings involving VIL in the treatment of COPD will also be critically discussed.

2. VILANTEROL TRIFENATE (VIL)

2.1 Mechanism of Action and Structural Characteristics

β2-adrenoceptor agonists increase airflow into the lungs via relaxation of the airways. This is achieved by the relaxing of smooth-muscle in bronchial airways through the β2-adrenoceptor G-protein coupled receptor. Activation of the β2-adrenoceptor stimulates G-protein ~~αs~~ which in turn activates adenylyl cyclase to increase intracellular levels of 3'-5'-cyclic adenosine monophosphate (cAMP). The enhanced levels of cAMP activate protein kinase A results in smooth-muscle relaxation either via an attenuation in myosin-regulatory light chain kinase activity or phosphorylation of Ca2+-dependent K+ channels [7]. Stimulation of the latter with β2-adrenoceptor agonists has also shown to be protein kinase A independent [8].

There has been continuous development of β2-adrenoceptor agonists from the late 1960s in the form of salbutamol which is short acting [9), and in the 1990s in the form of salmeterol [10] and formoterol [11] as longer acting (for at least 12 hours) bronchodilation. In order to overcome the

challenges of airways disease such as poor patient compliance either due to the frequency of dosing regimens and/or complexities of delivery, a new generation of longer acting bronchodilators (lasting 24 hours) have been developed [7, 12].

VIL is an antedrug analogue of salmeterol with a higher intrinsic activity at the β2-adrenoceptor [13]. The development of VIL was based on the modification of the salmeterol molecule to create homochiral compounds with the (R)-configuration, as the (R)-enantiomer of salmeterol is more potent.

2.2 Pharmacodynamics of VIL

Preclinical studies of VIL using radio-ligand binding and cAMP studies in recombinant assays as well as human and guinea pig tissue systems have been used to characterize its β2-adrenoceptor binding and functional properties.

Saturation binding studies report that VIL is bound either to one or two β2-adrenoceptor affinity states. Irrespective of the receptor state VIL exhibits a high affinity interaction with the β2-adrenoceptor. The affinity of VIL for the low affinity agonist state was comparable to salmeterol but significantly higher than that of formoterol and indacaterol [14].

In vitro assays of cells expressing human β-adrenoceptors, VIL was highly selective for the β2-adrenoceptor, with over 1000-fold selectivity over both β1-adrenoceptors and β3-adrenoceptors. VIL's β2-adrenoceptor selectivity was similar to salmeterol however markedly higher than formoterol, indacaterol and isoprenaline [14]. The functional potency of VIL at the β2-adrenoceptor was comparable to formoterol but markedly superior to salmeterol and indacaterol (8). Intrinsic efficacy at that β2-adrenoceptor of indacaterol and VIL were similar, however significantly greater than salmeterol and less than formoterol [14]. In fact the intrinsic activity of

VIL was lower than that of isoprenaline, the reference full β2-adrenoceptor agonist, indicating that VIL, akin to salmeterol, is a partial β2-adrenoceptor agonist.

In *ex vivo* human small airway assays, pre-contracted with histamine or carbachol, both VIL and salmeterol caused a concentration-related bronchodilation, exhibited a comparable half maximal effective concentration (EC50) and a similar efficacy (as measured by maximal percentage bronchodilation) with each spasmogen assessed [14].

In isolated guinea pig trachea, the mean onset of action for VIL was 5.8 minutes which was marginally higher than that for formoterol and indacaterol (4 minutes for both) but significantly more rapid than salmeterol with a time of onset of 15.2 minutes [14]. Human precision cut lung slices confirmed the significantly faster onset of VIL compared to salmeterol ($t_{1/2}$ 3.1 minutes versus 8.3 minutes respectively) [14].

Persistence and reassertion of β2-adrenoceptor agonists using *in vitro* and *ex vivo* systems demonstrated that VIL, salmeterol and indacaterol were not readily washed out of the β2-adrenoceptor and exhibited a longer persistence of action than for formoterol [14]. Importantly both VIL and salmeterol showed a significant duration of action compared to control at four hours, however only the former were shown to be significantly different from control-treated airways at 22 hours. Neither active agents demonstrated a significant level of bronchodilation at 28 hours [14].

2.3 Pharmacokinetics of VIL

In healthy humans' single oral administrations of up to 500µg of VIL was safe and well tolerated [14]. With a single oral dose of 200µg of VIL, at least 50% was orally absorbed. The primary route of elimination was via O-dealkylation to metabolites with negligible pharmacological activity, which were excreted predominantly in urine [15]. VIL represented <0.5% of total drug-related

material in plasma, demonstrating its extensive first-pass metabolism [15]. Hence, at the therapeutic inhaled dose level of 25µg, VIL is unlikely to produce marked amount of pharmacologically active metabolites that may result in any unexpected toxicity.

Ketoconozole is a potent cytochrome P450 3A4 inhibitor. To assess the effects of ketoconazole versus placebo on single doses of VIL (study 1) or in combination with fluticasone furoate (FF)(FF/VI) (study 2) in healthy individuals, Kempsford et al conducted 2 randomized, double-blind, two-way crossover studies [16]. As monotherapy VIL administration did not result in marked systemic pharmacodynamic alterations, however when combined with FF had less than a 2-fold increase in systemic exposure to FF and VIL; which may manifest the potential for AEs. Verapamil, a P-glycoprotein and moderate cytochrome P450 3A4 inhibitor has also been assessed in healthy subjects [17]. Following repeated doses of umeclidinium (a LAMA) (UMEC) monotherapy or in combination with VIL (UMEC/VIL) and verapamil on days 9-13, there was no increased systemic exposure to VIL and only a modest increase UMEC; hence unlikely to result in any meaningful drug-drug interactions. Hepatic and renal impairment can alter pharmacokinetic and pharmacodynamic properties of drugs. In patients with severe renal impairment FF/VI had no clinically important effects or tolerability on FF/VI when individually assessed [18]. Similarly, hepatic impairment has been shown to have no effects on systemic VIL exposure however in moderate and severe hepatic impairment, FF is associated with an increased systemic exposure and thus attenuated serum cortisol levels. Independently, VIL does not require any caution in patients with renal and hepatic impairment though in combination with FF may result in undesirable systemic corticosteroid effects due to FF.

In separate studies conducted by the same group on the pharmacodynamics in Japanese healthy volunteers of varying doses of monotherapy VIL (12.5, 25 and 50µg), FF (200, 400 and 800µg) and in combination (FF/VIL) (800/50µg) it was reported that there were no safety concerns or

treatment-related AEs with repeated dosing of FF and VIL and single doses of FF, VIL and FF/VIL [19]. Systemic exposure to FF and VIL increased in a dose-dependent fashion, with marked serum cortisol reductions after 7-day administration at the highest FF dose of 800µg. Although the heart rate increased with the higher VIL dose of 50µg, this was not clinically significant. When combined with FF in patients with moderate-to-severe COPD, VIL (FF/VI) compared to placebo (FF/placebo) was not associated any marked differences in weighted mean (wm) heart rate, blood glucose and potassium, vital signs or ECG/Holter changes at 28 days [20]. There were however more treatment-related adverse events (AEs) in the FF/VI group especially oral candidiasis and dysphonia.

In a single-dose healthy subject Japanese study, UMEC (500µg) and VIL (50µg) monotherapy, and in combination (UMEC/VIL) were reported to have no marked systemic exposures or tolerability issues [21].More recently an open-labeled, randomized, crossover study to assess the pharmacokinetics, safety and tolerability of 2 inhaled UMEC/VIL combinations (62.5/25 and 125/25-µg) compared to their monocomponents (UMEC - 62.5 and 125µg; VIL – 25µg) in 20 healthy Chinese subjects has been conducted [22]. Following repeat VIL dosing, time to maximum plasma concentration (tmax) was five minutes; with its accumulation at 25-66% of maximum plasma concentration (Cmax) and 17 to 43% based on AUC (0-2). No severe adverse events were reported with VIL use. Moreover no clinically important changes in vital signs, heart rate, or ECG parameters were observed irrespective of whether VIL was delivered as combination therapy or monotherapy. In a 28-day safety and tolerability double-blind, parallel group study in moderate-to-severe COPD patients UMEC/VIL was compared to placebo by Feldman et al [23]. At the end of the study (day-28), there were no differences in wm heart rates over 0-6hrs, blood pressure measurements, minimum and maximum heart rates, ECG parameters, AEs and SAEs between the

2 groups. UMEC and VIL were rapidly absorbed (mean t(max) of 6 mins) with no suggestion of accumulation over the study period.

2.4 Clinical Efficacy of VIL Monotherapy in COPD

Hanania et al conducted a phase IIb, multicentre, randomized, placebo-controlled, parallel-group 28-day dose-ranging (3, 6.25, 12.5, 25 or 50µg) study of VIL in 602 COPD patients [24]. This study assessed the dose response, efficacy, and safety of VIL. The primary endpoint was change from baseline in trough forced expiratory flow in one second (FEV_1) at the end of the 28-day treatment period. It was reported that once-daily treatment with VIL at doses ranging from 3 to 50µg for 28 days produced statistically significant, dose-dependent improvements in trough FEV_1 compared to placebo. Adjusted mean treatment differences of ≥100mL versus placebo in both trough and 0- to 24-h wm FEV_1 was consistently observed with VIL 12.5, 25 and 50µg doses, whereas a sustained 24-h duration of action was demonstrated at all doses of VIL throughout the 28-day treatment period. Bayesian analysis of trough FEV_1 demonstrated that the 25 and 50µg groups had a higher probability (92% and 99%, respectively) that the true difference versus placebo would be >100mL compared with the other VIL dosed groups. Importantly, all doses of VIL administered were associated with a low incidence of AEs/SAEs, with no suggestion of effects on blood pressure, heart rate, ECG parameters, or blood glucose and potassium levels.

In another study, single doses of inhaled VIL (25-100µg) were administered to patients with mild-to-moderate asthma and moderate-to-severe COPD, and 14 days repeated dosing to healthy controls to determine the safety, tolerability pharmacodynamics and pharmacokinetics of VIL [25]. All doses of VIL were well tolerated and the incidence and severity of adverse events were comparable to placebo. VIL administration resulted in no clinically significant abnormalities in vital signs, ECG parameters, and blood glucose or potassium levels. As expected all doses of VIL

demonstrated increases in FEV_1 from as early as five minutes of dosing, which were maintained up to 24 hours post-dose in subjects with asthma and COPD. In all subjects VIL was rapidly absorbed (healthy subjects Tmax 5 minutes; asthma and COPD subjects Tmax 10 minutes) with systemic exposure increasing in a dose-proportional manner. Marginal accumulation was noted on repeated dosing.

Unlike other bronchodilators, VIL is not available as a single agent and is approved for use in COPD only in a fixed-dose combinations with UMEC or FF. UMEC/VIL is orally inhaled via the dry powder inhaler (DPI) Ellipta™ which is easy to use and ensures the effective administration of a constant dose even across a range of inspiratory flows [26]. The dosage is one inhalation of UMEC/VIL 62.5/25µg once-daily equivalent to a delivered dose of 55/22µg. UMEC/VIL is approved for inhalation for the long term regular treatment of COPD in several countries including the US and EU [27,28].

In the EU, FF/VIL is indicated for symptomatic adult patients with COPD with a predicted post-bronchodilator FEV_1 <70% and an exacerbation history despite regular bronchodilator therapy [29]; and in the US for the maintenance treatment of airflow obstruction and for reducing exacerbations [30] The recommended dosage of FF/VIL is 100/25µg once-daily, with higher dosages associated with low tolerability and enhanced risk of pneumonia [31]. FF/VIL is also delivered by inhalation by the DPI ELLIPTA™.

3. UMECLIDINUM AND VILANTEROL IN COMBINATION IN THE TREATMENT OF COPD

UMECLIDINUM BROMIDE

3.1 *PHARMACOLOGY OF UMEC*

UMEC is a novel LAMA, similar to tiotropium bromide (TIO), with a strong affinity to specific receptors namely M3. UMEC is quickly absorbed (Tmax, 5–15 minutes) with slow functional reversibility. These characteristics allow a faster onset and prolonged duration of action [32]. After single or repeated dosing only 1%–2% of the total dose is excreted unchanged in the urine, and an accumulation after repeat dosing between 1.5–1.9-fold [33] In patients with COPD single and repeat doses of UMEC produced clinically relevant 24-hour lung function improvements and were well tolerated [33] . In moderate-to-severe COPD patients the efficacy of once-daily UMEC using 125, 250, and 500µg showed significantly improved FEV_1 versus placebo [34]. In a 12-week study in COPD subjects, administration of UMEC 62.5µg and 125µg improved lung function as well as breathlessness symptoms and enhanced health status [35].

As previously mentioned, LABAs act via β2-adrenoceptors, while LAMAs through anti-muscarinic/cholinergic receptors. The differing modes of actions of UMEC, a LAMA, and VIL, a LABA, in the treatment of COPD may be important, as their action via different receptors may potentially permit synergistic therapeutic benefits which may be superior to the monotherapies. This may be particularly pivotal in patients not sufficiently controlled with monotherapy bronchodilators [36].

3.2 *CLINICAL TRIALS ASSESSING SAFETY AND EFFICACY OF UMEC/VIL*

Several recent trials [23, 37-45] (collectively enrolling more than 9.000 patients with COPD) assessed the efficacy and safety of treatment with UMEC/VIL at different doses compared with placebo, the monocomponents (UMEC and VIL), and bronchodilators or anti-inflammatory treatments. The trials enrolled patients with stable COPD, mostly moderate-to-severe stage with mediam age 60 years andboth sexes satisfactorily represented (males about 68%). Notably, approximately half of the patients were active smokers and were permitted to take concomitant

ICS therapy. The duration of the studies ranged from 12 to 52 weeks (Table 1 compares the main data of the cited studies concerning UMEC/VIL; Figures 1 and 2 report results on trough FEV_1 at the end of the study of the mentioned papers).

3.2.1*CLINICAL EFFICACY OF UMEC/VIL COMBINATION THERAPY VERSUS PLACEBO IN THE REGULAR TREATMENT OF STABLE COPD*

Two 12-week double-blind randomized 12-week, crossover clinical studies specifically addressed the effects of the treatment with UMEC/VIL in COPD patients on exercise tolerance compared to placebo. [41]Endurance improvements were observed with UMEC/VIL doses (125/25µg or 62.5/25µg) compared with placebo at week12 in one study (UMEC/VIL 125/25µg: exercise endurance time (EET) difference from placebo 65.8s; p = 0.005; UMEC/VIL 62.5/25 µg: 69.4s; p = 0.003), but not in the second study where a strong placebo effect was observed making the difference with the treated group insignificant. Both studies showed trough FEV_1 improvements at week-12 for both UMEC/VIL doses.

Cardiovascular safety was specifically addressed in a 28-day randomized placebo-controlled study in moderate-to-severe COPD subjects with a high dose of UMEC/VIL of 500/25µg [23]. No significant changes in pulse rate, blood pressure, or QTc relative to placebo were observed.

Generally, compared to placebo UMEC/VIL produced significant improvement in numerous outcomes of clinical efficacy (lung function and quality of life) in COPD patients. In a 24-week double-blind, placebo-controlled, parallel-group study by Donohue et al [39] comparing placebo to UMEC/VIL 62.5/25µg the latter induced improvements in wm FEV_1 on day 168 (0.232L), rescue salbutamol use, dyspnoea index and health-related quality scales (The Shortness of Breath with Daily Activities and St. George's Respiratory Questionnaire (SGRQ)). UMEC/VIL reduced

significantly the risk of COPD exacerbations relative to placebo, showing also a safety profile comparable with placebo.

In particular the tolerability profile of UMEC/VIL tested in clinical trials [38-40,42] did not showed significant difference from placebo. The most commonly reported adverse events were headache and nasopharyngitis. The rate of typical effects due to anti-cholinergic and β2-receptor agonists associated with the use of LABAs and LAMAs was found in <3% of the cited trials.

3.2.2 *CLINICAL EFFICACY OF UMECLIDINIUM/VILANTEROL IN THE REGULAR TREATMENT OF STABLE COPD: COMPARISON WITH OTHER TREATMENTS*

Phase II and III trials of UMEC/VIL in patients with COPD were mainly comparisons of treatment at doses of 125/25µg or 62.5/25µg) compared with the mono-components: VIL 25µg [37-41,45]; UMEC 125µg or 62.5µg [31-41,45]; TIO 18µg; [38,42] or with fluticasone propionate/salmeterol (FP/SAL) 250/50µg or 500/50µg [43,44].

3.2.2.1 UMEC/VIL vs UMEC

UMEC was assessed at two different doses of 62.5µg and 125µg, with the studies reporting a significant improvement in pulmonary function ($p<0.0001$) expressed as mean change from baseline in trough FEV_1 and significantly increased percentage of patients achieving a rise of 100mL above baseline in trough FEV_1 in favour of patients taking UMEC/VIL compared to those patients treated with UMEC alone [37-39].

No significant difference in SAEs or mortality during treatment was noted comparing the treatment regimens. Subjectively, UMEC/VIL increased significantly the percentage of patients with a minimal clinically important difference (MCID) in TDI and use of rescue medications compared with UMEC monotherapy [43]. From a COPD exacebtion perspective UMEC/VIL

significantly reduced the number of patients with at least one exacerbation [44]. Also, treatment with UMEC/VIL was associated with a lower number of study withdrawals compared to UMEC monotherapy. No significant differences between the UMEC doses (62.5µg and 125µg) in combination with VIL, or monotherapy was observed.

3.2.2.2 UMEC/VIL vs VIL

Three randomized controlled trials evaluated the comparison between UMEC/VIL and VIL alone using different UMEC doses (62.5µg and 125µg) for the efficacy and safety in [37-39]. Overall, the trials showed that the mean change from baseline in trough FEV_1 increased significantly compared to VIL alone. Similar improvements in favour of UMEC/VIL in peak FEV_1 compared to VIL monotherapy were also reported [38].

Treatment differences between UMEC/VIL and VIL alone were not as distinctly defined for health-related quality outcomes measures as they were for lung function assessments [37], however UMEC/VIL showed an increased odds of achieving a TDI response than VIL monotherapy in two of the considered studies [37,38]. Only one of the cited studies [37] found a reduction in the use of albuterol in favour of UMEC/VIL treated COPD patients compared to those treated with VIL only. There were no reported differences between UMEC/VIL and VIL monotherapy in change in health-related quality scales or time to first exacerbation.

In order to clarify the differential efficacy of UMEC and VIL monotherapies compared to combined treatment, two randomized, double-blind studies enrolling 207 and 182 moderate-to-severe COPD patients were conducted [45]. All the patients were randomized to one of 6 treatment sequences in a crossover fashion and received once-daily UMEC 62.5µg, VIL 25µg, and UMEC/VIL 62.5/25µg. Using this methodology the authors could identify UMEC/VIL-induced improvements in outcome measures in patients defined as UMEC or VIL responders compared with non-responders. Non-

responders to both UMEC and VIL monotherapy achieved a significant lung function response when UMEC/VIL was administered. In these patients, response to UMEC/VIL was more than the additive effect of the monotherapies

3.2.2.3 UMEC/VIL vs tiotropium

The comparison between UMEC/VIL and TIO have been assessed in three studies [38,42]. The data report a significant improvement in change from baseline in trough FEV_1 though this was <100ml (p<0,001). The use of UMEC/VIL showed an enhancement of 0-6h wm FEV_1 and peak FEV_1 compared with TIO. Moreover UMEC/VIL significantly improved the odds of achieving an increase in FEV_1 of ≥12% or 200 ml above baseline in the 0-6h post-dose on day-1 and that of achieving an FEV_1 >100 ml above baseline at the end of treatment compared to TIO. UMEC/VIL administration significantly reduced the use of rescue albuterol compared to TIO in all the cited studies, and the SGRQ in one study [42]. No differences were observed for all the others variables including the rate of AEs, SAEs, withdrawals, deaths or COPD exacerbations.

The economic impact in the use of any therapy is important and a cost-benefit analysis undertaking is pivotal. Recently, both Punekar et al and Miravittles et al [46,47] assessed the cost-effectiveness of UMEC/VIL versus TIO monotherapy using a treatment-specific COPD economic model. The analyses suggested that UMEC/VIL can be considered a more cost-effective alternative to TIO in COPD.

3.2.2.4 UMEC/VIL vs salmeterol/fluticasone propionate (SAL/FP)

Three 12-week trials enrolling more than 2,000 patients with COPD compared UMEC/VIL 62.5/25µg once daily with SAL/FP 250/50µg twice-daily and 500/50µg twice-daily [43,44]. UMEC/VIL was associated with a significantly improved pulmonary function (mean change from

baseline in trough FEV_1) in all three trials. One study reported a reduction in rescue medication use in favour of patients treated with UMEC/VIL [44]. No differences were found in the remaining variables considered.

4. FLUTICASONE FUROATE AND VILANTEROL IN COMBINATION IN THE TREATMENT OF COPD

4.1 PHARMACOLOGY OF FLUTICASONE FUROATE (FF)

Like other ICS, FF acts primarily on a cellular level promoting the inhibition of the pro-inflammatory action of nuclear factor ƙB (NF-ƙB), reducing transcription of pro-inflammatory genes. The topical action occurs principally via alveolar macrophages, epithelial and endothelial cells culminating in an attenuation of bronchial hyperresponsiveness, airway oedema and inflammatory infiltration of lower airways [48,49]. FF is a new tri-fluorinated glucocorticoid with an enhanced glucocorticoid receptor affinity (GR); it is rapidly associated and slowly dissociated from the GR compared to dexamethasone, budesonide or mometasone [50]. FF and FP are more potent than budesonide or mometasone in the reduction of pro-inflammatory cytokine production in lung tissue [51] and the former has a prolonged duration of action allowing a once-daily dosing [52].

The different actions of ICS and LABA in the treatment of COPD, targeting different receptors suggests potential synergistic interactions, leading to enhanced clinical effects than those achieved with single agent therapy [53].

4.2 *CLINICAL TRIALS ASSESSING SAFETY AND EFFICACY OF FF/VIL*

Several recent studies enrolling more than 20000 patients have assessed the efficacy and safety treatment with FF/VIL at different doses compared with placebo [20, 54]; monocomponents (FF and VIL) and placebo [55, 56, 57]; VIL monotherapy [57]; and other bronchodilators/anti-

inflammatory treatments [58,61]. The studies enrolled adult patients with stable moderate-to-severe COPD over a period of 12-52 weeks on varying does of FF/VIL (400/25µg to 50/25µg) [58-60, 58, 59]. Three studies required a dyspnoea score of ≥2 (on a scale of 1–4) on the modified Medical Research Council dyspnoea scale (mMRC) [54-56]. (Table 2 compares the main data of the cited studies concerning FF/VIL; Figure3 reports results on trough FEV_1 at the end of the study of the mentioned papers).

4.2.1 FF/VIL Comparison with placebo only

In a phase III crossover study in 54 patients with moderate-to-severe COPD [54], all three doses of FF/VIL (200µg, 100µg and 50µg of FF, with VIL 25µg) produced a significantly higher 0-24h change from baseline in wm FEV_1 than placebo (period days 28–29): adjusted mean improvements from placebo in FEV_1 for FF/VIL were 220-236mLs ($p<0.001$) . A previous 4-week trial [20] with higher FF dose (400µg) indicated that the FF/VIL-treated group had statistically greater improvements compared with placebo in trough FEV_1 (mean difference 183 ml) and 0-4h post-dose wm FEV_1 (mean difference 236 ml). In both trials FF/VIL was well tolerated however in the trials administering the higher FF dose, an increased prevalence of oral candidosis and dysphonia were reported.

4.2.2 FF/VIL Compared with Individual Components and Placebo

Two 24-week trials in patients with moderate-to-severe COPD assessed the efficacy of different doses of FF/VIL (100/25µg and 50/25µg) [49] and (200/25µg and 100/25µg)[56] respectively compared to its monocomponents and placebo. In the groups treated with FF/VIL the lung function (wm FEV_1 and trough FEV_1 at day-168) [56], was improved compared with placebo and FF monotherapy although in one study the improvements were not statistically significance between

FF/VIL and FF [56]. When compared with VIL alone, treatment with FF/VIL in both trials showed no significant difference for the co-primary endpoints assessed. No safety problems were signalled in the studies.

The Study to Understand Mortality and Morbidity in COPD (SUMMIT) prospectively evaluated the effect of FF/VI 100/25µg and its monocomponents compared with placebo on survival in subjects with moderate COPD (predicted FEV_1 ≥50 and ≤70%) and with a history of, or at increased risk for developing, cardiovascular disease [57]. The study enrolled more than 16.000 patients and consisted of a 4-10 day run-in period, variable treatment period until the required number of events was achieved, and a 1-week follow-up period. No significant difference was observed in terms of survival rate amongst the treatments and placebo. Mortality was 12.2% lower in the FF/VI-treated group compared to the placebo group, but was not statistically significant (p=0.137). Similarly there was no marked difference in the risk for an on-treatment cardiovascular event (a secondary end point defined as cardiovascular death, myocardial infarction, stroke, unstable angina, or transient ischemic attack); 7.4% lower with FF/VI compared to placebo (p=0.475). A lower decline in FEV_1 was observed when comparing FF/VIL-treated patients with placebo or VIL alone, and with FF 100µg compared to VIL monotherapy.

Two alike studies conducted by Dransfield et al [58] addressed the exacerbation rate between once-daily FF/VIL and VIL monotherapy in patients with moderate-to-severe COPD. In one of the studies, no significant difference in exacerbation rate was noted between the 200/25µg FF/VIL-treated group and the VIL-treated group (mean events/yr 0.90 vs 1.05; ratio 0·9). Due to the statistical hierarchy used in the study no significance could be inferred for the FF/VIL 50/25µg and 100/25µg groups, albeit that there were some differences between the 2 treatments in favour of FF/VIL. In the second study, significantly less exacerbations (moderate and severe) were observed in all FF/VIL-treated groups than in the VIL-treated group (p=0.0398 for the 50/25µg group,

p=0.0244 for the 100/25µg group, and p=0.0004 for the 200µg group). The pooled analysis reported significantly fewer exacerbations in all FF/VIL groups than in VIL monotherapy. Moreover diary dyspnoea scores, rescue medication use and night-time awakenings showed improvements from baseline with FF/VIL 100/25µg and 50/25µg than with VIL 25µg monotherapy. Compared with placebo, FF/VIL 100/25µg and 50/25µg were associated with greater improvements in health-related quality questionnaires [55,56].

4.2.3 FF/VIL Compared with Fluticasone Propionate/Salmeterol (FP/SAL)

Three 12 week studies comparing FF/VIL and FP/SAL have been conducted by Dransfield et al [59] enrolling overall 1858 patients with moderate to very severe COPD comparing FF/VIL 100/25µg once-daily with FP/SAL 250/50µg twice-daily. The results of the trials were conflicting: In Study 1, the treatment difference of 0-24h wm FEV_1 between FF/VIL and FP/SAL was statistically significant (80mL; p<0.001) while in Studies 2 and 3, the differences (29mL and 25mL respectively) were not. When the analysis was pooled an increase of 41ml which was statistically significant (p<0.001) was observed. Time to onset differences between groups was statistically significant in Study 1 (p<0.012) and the pooled data (p<0.018). The other outcomes did not showed any difference between groups (change from baseline trough FEV_1 after 12 weeks; change from baseline in FVC on day-84, the proportion of patients demonstrating a 100mL increase in FEV_1, and, in Studies 1 and 2 only, pre-dose inspiratory capacity (IC) at day-84 and rescue medication use. The frequency of AEs was similar between the treatment arms (FF/VI 27%; FP/SAL 28%). Headache and nasopharyngitis were the most frequent events, occurring in about 5% of patients in either treatment group.

In another 12-week study [60] assessing the efficacy of FF/VIL 100/25µg once-daily with FP/SAL 500/50µg twice-daily in 528 mild-to-severe COPD patients showed no significant difference

between the two study arms (22mL; p=0.282). However, a post-hoc comparison of changes in wm FEV_1 between treatment arms showed differences from 0–4h and 0–12h post-dose. FF/VIL demonstrated a mean improvement of 4.3 units compared to 3 units with FP/SAL in SGRQ scores; suggesting a modest, but statistically insignificant positive effect of FF/VIL on patient's health status.

4.2.4 FF/VIL Compared with TIO

Recently. A study using once-daily FF/VIL 100/25µg with TIO 18µg for 12 weeks in 623 subjects COPD moderate-to-severe (baseline FEV_1 47% and 50% predicted in FF/VIL and TIO groups respectively) with cardiovascular co-morbidities or at least one current cardiovascular risk factor (hypertension, hypercholesterolemia, or treated diabetes mellitus) has been conducted [61]. Changes from baseline in 24h wm FEV_1 and trough FEV_1, were similar between the treatment groups (Figure 3). Subgroup analysis on subjects with bronchial reversibility reported a greater 24h wm FEV_1 in the FF/VIL group (181mL) compared with the TIO group (110mL). Statistical hierarchy did not permit any other statistical inference for secondary endpoints. Increase in FEV_1 >100mL from baseline, trough FEV_1 at day-84, changes from baseline symptoms, rescue medication use, health-related questionnaires were similar in both groups with the exception for the individual SGRQ-C components where FF/VIL consistently had a reduced component score more than TIO, and only the FF/VIL group achieved the MCID for symptoms across all time points. More FF/VIL-treated than TIO-treated subjects experienced an AE (7 vs 4% respectively) although more TIO-treated than FF/VI-treated subjects were withdrawn from the study due to AEs (4% vs 2% respectively). Fewer subjects in the FF/VIL group (2%) experienced a COPD exacerbation than in the TIO group (4%), and pneumonia was reported in three subjects during treatment with FF/VI.

4.2.5 Triple therapy

Two 12-week, double-blind, parallel-group trials with a total of 1238 patients with moderate-to-severe COPD were conducted to assess the efficacy and safety of placebo, UMEC 62.5µg and 125µg added to 100/25µg FF/VI [62]. Although there were no safety issues, at day-85 subjects on triple therapy had statistically and clinically significant improvements in lung function compared with the group treated only with FF/VIL in patients with COPD (FF/VIL+UMEC 62.5 µg 0.124 L; FF/VIL+UMEC 125 µg 0.128 L; above placebo and FF/VIL respectively; both p<0.001). In both studies 0-6h post-dose FEV1 at day-84 and a greater odds of having an increase of FEV_1 of >100mL above baseline was clinically and statistically significant with the addition of UMEC. There were no differences in parameters of health status, COPD exacerbations and safety profiles between the two treatments. . In one of the studies the use of rescue medication was significantly reduced with UMEC addition. Overall, these findings imply clinical meaningful improvements of adding UMEC to FF/VIL in the treatment of stable COPD.

5. COMPARISON STUDIES

In the last year, interesting network meta-analyses (NMA) have investigated the relative clinical benefit of currently available LAMA/LABA and or ICS/LABA fixed-dose combinations. Huisman et al [63] compared UMEC/VI, indacaterol/glycopyrronium (QVA149), formoterol plus TIO, salmeterol plus TIO, or indacaterol plus TIO. They failed to find any significant difference in efficacy among the combination treatments on trough FEV_1, TDI score or heath-related quality related questionnaires (SGRQ), suggesting that these fixed-dose combinations had comparable efficacy. Hence, suggesting that dual bronchodilators may provide better outcomes (lung function, quality of life, symptom scores and moderate-to-severe exacerbation rates) in comparison to mono-therapies in COPD patients. Oba et al obtained similar conclusions [64].

In another meta-analysis [65] comparing LAMA/LABA (QVA149 and UMEC/VI) with LABA/ICS (salmeterol/FP) reported significantly favourable effects of LAMA/LABA on trough FEV_1, TDI, less exacerbations and less pneumonia compared to ICS/LABA.

More recently, Schlueter et al [66] published a NMA comparing the efficacy of LAMA/LABA fixed-dose formulations considering also the impact on treatment effects of COPD severity, concomitant ICS use at baseline and exacerbation history. No significant efficacy analyses were noted considering the concomitant use of ICS at baseline, the severity of COPD at baseline or the history of exacerbations, except for a favourable effect on trough FEV_1 for TIO/olodaterol 5/5 µg, QVA149 and UMEC/VIL 6.25/25 µg compared with ACL/FF 400/12µg.

The results of these meta-analyses, although relevant are not definitive to determine which treatment combination may be superior and safer in the different clinical conditions. This may be best determined by direct comparison with head-to-head randomized controlled trials.

6. EXPERT COMMENTARY

The available experimental data shows that the VIL, although not available as a single agent, has a high receptor-binding profile for the β2-receptors and improved functional potency compared to some of the other β-agonists.

Data emerging from clinical trials have shown that both in combination with FF and with UMEC [67], VIL once-daily in patients with moderate-to-severe COPD provided significant improvements in terms of lung function, but only in some cases provided benefits in COPD exacerbations rate and symptoms scores or life quality outcomes. The association LAMA and LABA (VI/UMEC) demonstrated significant improvements of lung function in moderate COPD compared with other treatments such as TIO and FP/SAL, while the association FF/VIL failed in the majority of the studies to provide a clear benefit if compared with other active treatments; less clear are the

results for other outcomes in many large randomized trials. These data taken together would suggest that VIL use in patients with COPD would benefit those who require dual bronchodilation or protection from exacerbations. To date, it is not yet clear in which COPD therapeutic step to allocate the multiple associations with VIL such as triple therapy or ICS/LABA. An important factor to be considered is that VIL has the potential to improve poor compliance to the chronic treatment of patients with COPD by its ability to be administered once-daily. Additionally the Ellipta™ delivery device enables drug delivery with minimal number of maneuvers necessary for activation, consequently reducing the risk of patient error and hopefully improving patient compliance in the real life. The device was developed to permit standardized distribution of the active compounds in the airways even in cases of poor inspiratory capacity; two characteristics particularly appreciated by patients.

7. FIVE-YEAR VIEW

The critical goal of COPD management is to decrease disease progression and mortality, and avoid exacerbations. Newly developed bronchodilators, such as VIL, have improved considerably the bronchodilatory effects as well as patient symptoms and quality of life; however current therapies including LABA and LAMA fail to substantially attenuate the critical goals of COPD management. As reported in the SUMMIT study [57] FF/VIL combination provides no mortality benefit in patients with moderate COPD and history of or risk for cardiovascular disease. Although the primary end point was not met, the study indicates a beneficial effect on lung function decline (a secondary outcome).

In the near future we expect to have some answers to still open questions about the impact of once-daily therapy on the efficacy tolerability and safety in clinical practice of the treatment of COPD. In particular, if once-daily treatment will enable greater clinical and functional stability to

patients with COPD. Effects of VIL's associations on the future treatment of COPD patients are obviously unknown particularly considering that COPD is a chronic progressive condition, and patients with COPD commonly undergo treatment changes for type of medications or dose. New trials directly comparing new LAMAs, LABAs and ICS fixed-dose combinations will be essential to assess the true advantages, or lack of, of VIL-associated therapies over others.

8. KEY ISSUES

- Vilanterol is a new high selective once-daily acting β2-agonist with a demonstrated significant bronchodilation action.
- Unlike other long-acting β2-agonists, vilanterol is not available as a single agent and is approved for use in COPD only in a fixed combinations associated with umeclidinium (dosage 62.5/25mcg once-daily) or fluticasone furoate (dosage 100/25mcg once-daily).
- Vilanterol fixed-dose combinations with fluticasone furoate represents first once-daily combination of LABA/ICS for stable COPD .
- Vilanterol in association with umeclidinium and fluticasone furoate was well tolerated and demonstrates improvements in pulmonary function, exacerbation rates and health-related quality parameters compared to placebo in the treatment of moderate-to-severe COPD
- Once-daily vilanterol in combination with umeclidinium demonstrates improvements in pulmonary function directly compared with tiotropium 18mcg once-daily and fluticasone propionate with salmeterol 250/50mcg twice-daily in the treatment of moderate-severe COPD.
- In network meta-analyses vilanterol association treatments showed equal efficacy and safety compared with other fixed-dose combinations approved for treatment of stable COPD.

Declaration of Interests

M Malerba has received sponsorship and educational grants from various pharmaceutical companies including Chiesi, Menarini, Mundipharma and Pfizer. JB Morjaria has received fees and sponsorship to attend or speak at the ERS, ATS and BTS conferences, for educational grants, and for being on the advisory boards of various pharmaceutical companies including Novartis, Boehringer Ingelheim, GlaxoSmithKline, Chiesi, MSD, Pfizer, Almirall, Teva, Napp and Astra Zeneca. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Figure 1 and 2: Trough FEV_1 values (ml) in the different treatments branches testing the efficacy of UMEC/VIL in COPD: results of the main clinical trials published.

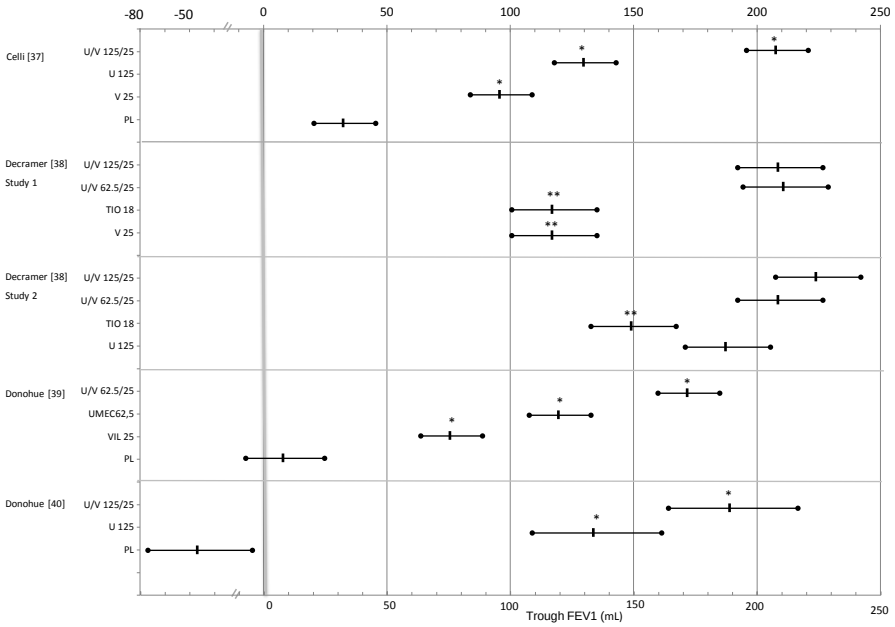

*Figure 1 : Trough FEV1 values (ml) in the different treatments branches testing the efficacy of UMEC/VIL in COPD : results of the main clinical trials published. (Continue in Figure 2) (Values expressed as LS mean changes from baseline and standard errors. *p<0.01 vs placebo,** p<0.01 vs both combined doses)*

Figure 2 : Trough FEV1 values (ml) in the different treatments branches testing the efficacy of UMEC/VIL in COPD : results of the main clinical trials published (continuation)

*(Values expressed as LS mean changes from baseline and standard errors. **p<0.01 vs placebo,* p<0.01 vs other treatment, H - not significant due to statistical Hierarchy, NR: not reported in published paper)*

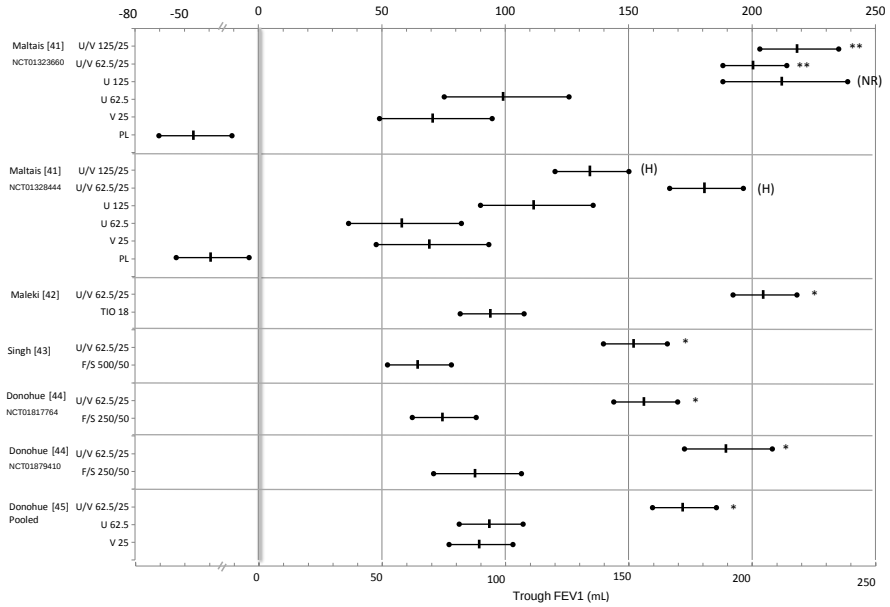

Figure 2 : Trough FEV1 values (ml) in the different treatments branches testing the efficacy of UMEC/VIL in COPD : results of the main clinical trials published (continuation)
*(Values expressed as LS mean changes from baseline and standard errors. **p<0.01 vs placebo,* p<0.01 vs other treatment, H - not significant due to statistical Hierarchy, NR: not reported in published paper)*

Figure 3: Trough FEV_1 values (ml) in the different treatments branches testing the efficacy of FF/VIL in COPD: results of the main clinical trials published.

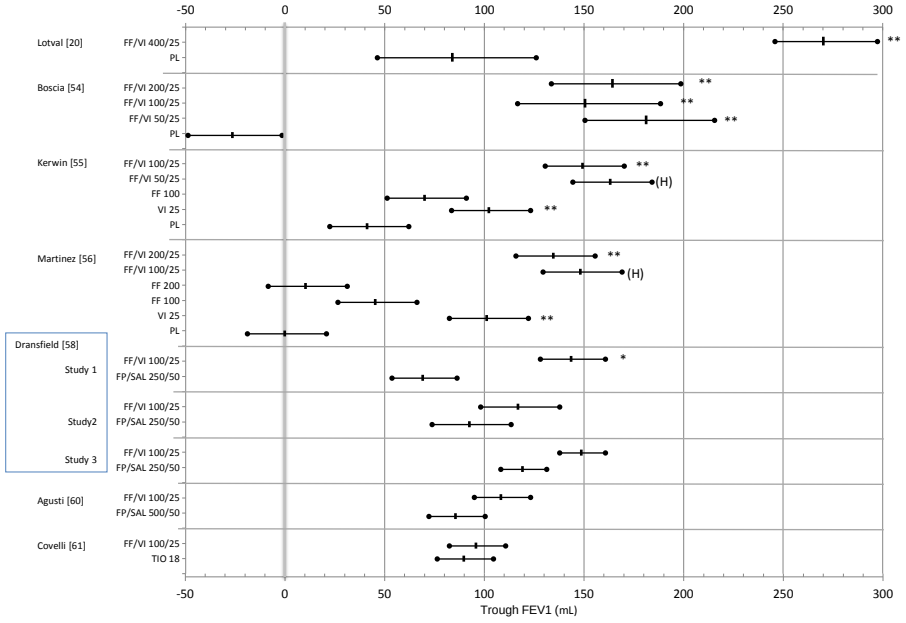

*Figure 3 : Trough FEV1 values (ml) in the different treatments branches testing the efficacy of UMEC/VIL in COPD. Results of the main clinical trials published (Values expressed as LS mean changes from baseline and standard errors. **p<0.01 vs placebo, * p<0.01 vs other treatment, H - not significant due to statistical hierarchy)*

Table 1. Published studies on UMEC/VI association treatment in COPD

Papers [ref]	Treatments	Duration (weeks)	ITT pop (n)	Mean age (years)	Baseline FEV1 (%pred)	ICS %	Study type and main results
Celli [37] NCT01313637	UMEC/VIL 125/25µg UMEC 125µg VIL 25µg PL	24w	1489	62 y	48	47	*Efficacy* All active improved FEV1 vs PL and combined vs monotherapies Combined improved TDI and RM vs all Combined improved HRQLQ and ER vs PL
Decramer [38] Study 1: NCT01316900	UMEC/VIL 125/25µg UMEC/VIL 62.5/25µg TIO 18µg VIL 25µg	24w	843	63 y	47	44	*Efficacy* Both combined improved FEV1 vs TIO and VI Both combined improved RM vs TIO
Study 2: NCT01316913	UMEC/VIL 125/25µg UMEC/VIL 62.5/25µg TIO 18µg UMEC 125µg	24w	869	64 y	47	52	*Efficacy* Both combined improved FEV1 vs TIO Both combined improved RM vs TIO and UMEC
Donohue [39] NCT01313650	UMEC/VIL 62.5/25µg UMEC 62.5µg VIL 25µg PL	24w	1532	63	47	51	*Efficacy* All active improved FEV1 vs PL (greater for combined at day 168) All active Improved TDI, RM, HRQLQ vs PL Combined and UMEC reduced ER vs PL
Donohue [40] NCT01316887	UMEC/VIL 125/25µg UMEC 125µg PL	52w	562	61	54	34	*Safety* No difference in all groups for AEs All active improved FEV1 vs pl
Maltais [41] NCT01323660	UMEC/VIL 125/25µg UMEC/VIL 62.5/25µg UMEC 125µg UMEC 62.5µg VI 25µg PL	12w	348	61.6	51.3	28.2	*Exercise tolerance* Both combined improved EET vs PL Both combined improved FEV1 vs PL
NCT01328444	UMEC/VIL 125/25µg UMEC/VIL 62.5/25µg UMEC 125µg UMEC 62.5µg VI 25µg PL	12w	307	62.6	51.3	39.4	*Exercise tolerance* No difference stat for EET Both combined improved FEV1 vs PL
Maleki-Yazdi [42] NCT01777334	UMEC/VIL 62.5/25µg TIO 18µg	24w	905	62	46	50	*Comparison* Combined improved FEV1, HRQLQ and RM vs TIO
Singh [43] NCT01822899	UMEC/VIL 62.5/25µg FP/SAL 500/50µg	12w	716	62	45	51	*Comparison* UMEC/VIL improved FEV1 vs FP/SAL
Donohue [44] NCT01817764	UMEC/VIL 62.5/25µg FP/SAL 250/50µg	12w	706	63	43	48	*Comparison* UMEC/VIL improved FEV1 vs FP/SAL
NCT01879410	UMEC/VIL 62.5/25µg FP/SAL 250/50µg	12w	697	63	45	48	*Comparison* UMEC/VIL improved FEV1 and RM vs FP/SAL
Donohue [45] NCT02014480	UMEC/VIL 62.5/25µg UMEC 62.5µg VIL 25µg	2w	207	60	47	67	*Comparison* Combined Improved FEV1 vs mono, greater if mono responders
NCT01716520	UMEC/VIL 62.5/25µg UMEC 62.5µg VIL 25µg	2w	182	63	40	50	*Comparison* Combined Improved FEV1 vs mono, greater if mono responders

Table 2. Published studies on FF/VI association treatment in COPD

Abbreviations: UMEC – Umeclidinium; VI – Vilanterol; Dur – duration; ITT pop - Intention to treat population; FEV_1 - Forced expiratory flow in 1 second; pred – predicted; ICS - inhaled corticosteroids; PL – Placebo; W – weeks; Y – years; TDI - transitional dyspnoea index; RM - rescue medication; HRQLQ - health related quality of life questionnaire; ER - exacerbation rate; TIO – tiotropium; EET - exercise endurance time; FP - fluticasone propionate; SAL - salmeterol.

Papers [ref]	Treatments	Duration (weeks)	ITT pop (n)	Mean age (years)	Baseline FEV1 (% pred)	Study type and main results
Lotval [20] NCT00731822	FF/VI 400/25µg PL	4w	60	63	59	*Efficacy and safety* No differences for HR or BP, combined showed more AEs Combined improved FEV1 vs PL.
Boscia [54] NCT01072149	FF/VI 200/25µg FF/VI 100/25µg FF/VI 50/25µg PL	7w	54	58	50	*Efficacy* Alla combined improved FEV1 vs PL
Kerwin [55] NCT01053988	FF/VI 100/25µg FF/VI 50/25µg FF 100µg VI 25µg PL	24w	1030	62	42	*Efficacy* All combined improved FEV1 , HRQLQ, RM vs PL No difference for ER
Martinez [56] NCT01054885	FF/VI 200/25µg FF/VI 100/25µg FF 200µg FF 100µg VI 25µg PL	24w	1224	61	43	*Efficacy* Al combined and VI improved FEV1, HRQLQ vs PL
Dransfield [58] Study 1 NCT01323634	FF/VI 100/25µg FP/SAL 250/50µg	12w	519	61	48	*Comparison* FF/VI improved FEV1 vs FP/SAL
Study 2 NCT01323621	FF/VI 100/25µg FP/SAL 250/50µg	12w	511	61	48	*Comparison* No differences
Study 3 NCT01706328	FF/VI 100/25µg FP/SAL 250/50µg	12w	828	61	48	*Comparison* No differences
Dransfield [59] Study 1 NCT01009463	FF/VI 200/25µg FF/VI 100/25µg FF/VI 50/25µg VI 25µg	52w	1622	63	45	*Exacerbation Rate* No difference for exacerbation rate All combined improved FEV1 vs VI
Study 2 NCT01017952	FF/VI 200/25µg FF/VI 100/25µg FF/VI 50/25µg VI 25µg	52w	1633	63	45	*Exacerbation rate* All Combined showed fewer exacerbation rate vs VI All combined improved FEV1 vs VI
Agusti [60] NCT01342913	FF/VI 100/25µg FP/SAL 500/50µg	12w	528	63	47	*Comparison* No difference for FEV1 between treatments
Covelli [61] NCT01627327	FF/VI 100/25µg TIO 18µg	12w	623	62	48	*Comparison* No difference for FEV1 between treatments Combined improvements in RM, TDI, HRQLQ vs TIO* Tio improved IC and FVC vs combined* (*not statistically significant due to statistical hierarchy)

Abbreviations: FF - Fluticasone furoate; VI – Vilanterol; Dur – duration; ITT pop - Intention to treat population; FEV_1 - Forced expiratory flow in 1 second; pred – predicted; PL – Placebo; W – weeks; Y – years; HR - heart rate; BP - blood pressure; AEs - adverse events; TDI - transitional dyspnoea index; RM - rescue medications; HRQLQ - health related quality of life questionnaire; TIO – tiotropium; EET - exercise endurance time; FP - fluticasone propionate; SAL: salmeterol.