Expert Review of Respiratory Medicine

ISSN: 1747-6348 (Print) 1747-6356 (Online) Journal homepage: http://www.tandfonline.com/loi/ierx20

Fluticasone furoate and vilanterol for the treatment of chronic obstructive pulmonary disease

Gaetano Caramori, Paolo Ruggeri, Paolo Casolari, Kian Fan Chung, Giuseppe Girbino & Ian M. Adcock

To cite this article: Gaetano Caramori, Paolo Ruggeri, Paolo Casolari, Kian Fan Chung, Giuseppe Girbino & Ian M. Adcock (2017): Fluticasone furoate and vilanterol for the treatment of chronic obstructive pulmonary disease, Expert Review of Respiratory Medicine, DOI: 10.1080/17476348.2017.1386564

To link to this article: http://dx.doi.org/10.1080/17476348.2017.1386564

Accepted author version posted online: 28 Sep 2017.

Submit your article to this journal

View related articles

View Crossmark data

Full Terms & Conditions of access and use can be found at
http://www.tandfonline.com/action/journalInformation?journalCode=ierx20

Download by: [Imperial College London Library] **Date:** 29 September 2017, At: 01:13

Check for updates

Publisher: Taylor & Francis

Journal: *Expert Review of Respiratory Medicine*

DOI: 10.1080/17476348.2017.1386564

Review

Fluticasone furoate and vilanterol for the treatment of chronic obstructive pulmonary disease

Gaetano Caramori[1]*, Paolo Ruggeri[1], Paolo Casolari[2], Kian Fan Chung[3], Giuseppe Girbino[1], Ian M. Adcock[3].

[1]Unità Operativa Complessa di Pneumologia, Dipartimento di Scienze Biomediche, Odontoiatriche e delle Immagini Morfologiche e Funzionali (BIOMORF) Università degli Studi di Messina, Italy.

[2]Centro Interdipartimentale per lo Studio delle Malattie Infiammatorie delle Vie Aeree e Patologie Fumo-correlate (CEMICEF; formerly Centro di Ricerca su Asma e BPCO), Sezione di Medicina Interna e Cardiorespiratoria, Università di Ferrara, Ferrara, Italy.

[3]Airways Disease Section, National Heart and Lung Institute, Royal Brompton Hospital Biomedical Research Unit, Imperial College London, UK.

*Corresponding author:
Gaetano Caramori
Unità Operativa Complessa di Pneumologia
Dipartimento di Scienze Biomediche, Odontoiatriche e delle Immagini Morfologiche e Funzionali (BIOMORF)
Università degli Studi di Messina
Piazza Pugliatti 1
98122 Messina, Italy
Phone: +39-090-2217375
E-mail: gcaramori@unime.it

Downloaded by [Imperial College London Library] at 01:13 29 September 2017

Accepted Manuscript

Abstract

Introduction: Current national and international guidelines for the management of patients with stable chronic obstructive pulmonary disease (COPD) recommend the use of inhaled long-acting bronchodilators, inhaled glucocorticoids and their combinations for maintenance treatment of moderate to severe stable COPD.

Areas covered: The role of fluticasone furoate (FF) and vilanterol (VI) once daily combination therapy for the regular treatment of patients with stable COPD is discussed in this review.

Expert commentary: The regular treatment of moderate to severe stable COPD with once daily FF/VI combination therapy is effective, as seen in in several large placebo-controlled clinical trials involving many thousands of patients. FF/VI improved lung function, decreased respiratory symptoms and deceased the number of COPD exacerbations, including COPD-related hospitalizations. FF/VI combination therapy has also been approved for this indication in most countries. The use of this combination therapy may significantly decrease the economic costs for some National Health Services.

Keywords: COPD, bronchodilators, inhaled glucocorticoids, airway inflammation, beta2-agonists.

Downloaded by [Imperial College London Library] at 01:13 29 September 2017

Accepted Manuscript

1. Introduction

Currently there are no cures for chronic obstructive pulmonary disease (COPD). The limited efficacy of current therapies for COPD indicates a pressing need to develop new treatments to prevent the progression of the disease, which consumes a significant amount of health care resources and is an important cause of mortality worldwide.

Current national and international guidelines for the management of stable COPD patients recommend the use of inhaled long-acting bronchodilators, inhaled corticosteroids (ICSs) and their combinations (usually in one single inhaler at fixed dose) for maintenance treatment of moderate to severe stable COPD [1-5].

Regular treatment of stable COPD patients with inhaled long-acting β_2-agonists (LABAs) alone produces modest increases in lung function with varying effects on health-related quality of life and reduction in symptoms. However, it is also associated with a consistent reduction in exacerbations which may help COPD patients who suffer frequent deterioration of symptoms prompting healthcare utilization [6]. In patients with stable COPD, compared with LABAs, inhaled long-acting muscarinic antagonists (LAMAs) are slightly more effective than LABAs in preventing COPD exacerbations, but there are no statistical differences between groups in overall hospitalization rates or mortality. Symptom and quality of life improvement, changes in lung function and the risk of serious adverse events are similar between the treatment groups [7].

A Cochrane review on the role of regular long term treatment with ICSs alone vs placebo in patients with stable COPD has concluded that they significantly reduce the mean rate of exacerbations and the rate of decline of quality of life. However, there was no effect on the decline in forced expiratory volume in one second (FEV_1) or on total mortality rates [8]. The incidence of pneumonia is slightly increased in patients treated with ICSs alone vs placebo in most studies, regardless of the glucocorticoid, suggesting a class effect [9,10].

LABAs and ICSs therapies alone confer similar benefits across the majority of outcomes, including the frequency of exacerbations and mortality. LABAs confer a small additional benefit in terms of improvements in lung function compared to ICSs. On the other hand, ICSs have a small advantage over LABAs in terms of health-related quality of life [11].

Several large controlled clinical trials of inhaled combination therapy with ICS and LABA in a single

Downloaded by [Imperial College London Library] at 01:13 29 September 2017

Accepted Manuscript

device in stable COPD have shown that this combination therapy is well tolerated and produces a modest, but statistically significant, reduction in the number of severe exacerbations, and improvement in FEV_1, quality of life, and respiratory symptoms in stable COPD patients [12].

In addition, the TORCH study showed a 17% relative reduction in mortality over three years for patients receiving salmeterol/fluticasone propionate although this just failed to reach significance [13]. An interesting post hoc analysis has then suggested that the benefits of ICS/LABA in TORCH are driven by salmeterol [14]. Furthermore, systematic reviews of the literature suggest that a combination of ICS and LABA reduces mortality by approximately 20%, whereas neither tiotropium nor LABA by itself modifies all-cause mortality in COPD [15]. ICS treatment is associated with a reduction in mortality rate when compared to LABAs among patients with COPD [16]. However, ICS/LABA combination therapy did not provide any additional benefit on mortality when compared to ICS monotherapy [17].

A Cochrane review concluded that combined inhaler therapy led to around a quarter fewer COPD exacerbations than were seen with placebo. Current evidence does not suggest any major differences between inhalers in terms of effects, although the evidence is not strong enough to demonstrate equivalency [12].

The development of improved LABAs has focused on once-daily agents [termed ultra-LABAs (ULABAs)], like indacaterol, olodaterol and vilanterol, that are slightly more effective in improving lung function compared with twice-daily LABAs and have a good safety profile. There are insufficient data to establish if any one ULABA is better than the others [18].

As with LABAs the development of improved ICSs has focused on once-daily agents to allow the regular treatment of the patients with stable COPD with once daily dual-therapy combined inhalers. There are many new ULABAs and once-daily ICS fixed-dose combinations under preclinical or clinical development for the treatment of stable COPD but only the fluticasone furoate/vilanterol (FF/VI) combination is approved for clinical use [19].

The previous Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (goldcopd.org) recommended ICS/LABA combination as the first-line treatment for managing stable COPD in high-risk COPD patients grades C and D. However, the updated GOLD 2017 guidance recommends LAMA/LABA over ICS/LABA [20]. In addition, following the changes in the GOLD document 2017 update, in which impaired lung function is no longer considered as a determinant of exacerbation risk, a

Downloaded by [Imperial College London Library] at 01:13 29 September 2017

Accepted Manuscript

high number of COPD patients can now be labeled as group B (low risk of exacerbations and high level of symptoms) instead of D, and hence, no longer fulfill the indication for ICS. Since long-term therapy with ICS can result in side effects, the withdrawal of this treatment should be considered in this group of patients [21]. There is often a over-prescription of ICSs in stable COPD patients, particularly in COPD grades A or B, with considerable potential for harm [22,23] but there is also often, particularly in general practice, a misdiagnosis of bronchial asthma as COPD grades A or B [24-28]. This may also explain why conflicting findings exist on the benefit of ICS withdrawal in stable COPD. For example many studies [including the Withdrawal of Inhaled Steroids during Optimized Bronchodilator Management (WISDOM) controlled clinical trial [29], the real-life study On the aPpropriaTeness of treatment In MOderate COPD patients (OPTIMO) [30] and other studies, all recently reviewed [31], have shown that ICS withdrawal did not significantly increase the overall rate of COPD exacerbation, although a clinically important increased risk of severe exacerbation was detected (relative risk >1.2). ICS withdrawal significantly impaired both lung function (-30 ml FEV_1) and quality of life [+1.24 St. George's Respiratory Questionnaire (SGRQ) units]. The time to the first exacerbation was significantly shorter in the patients who discontinued ICS [31]. Similarly the 1 year long, eFfect of Indacaterol Glycopyronium Vs Fluticasone Salmeterol on COPD Exacerbations (FLAME) [32] and the 6-months duration LANTERN [33] controlled clinical trials, both comparing LAMA/LABA vs ICS/LABA in moderate-to-severe stable COPD patients with a history of ≤1 exacerbation in the previous year, have demonstrated that the LAMA/LABA combination has fewer exacerbations, a greater improvement of FEV_1, a lower risk of pneumonia, and more frequent improvement in quality of life as measured by an increase over 4 units or more of the SGRQ. However, a very recent Cochrane Systematic Review incorporating all the studies discussed above, and many others, concluded that these data were supported by low or moderate quality evidence generated from mainly participants with moderate to severe COPD in heterogeneous trials with an observation period of less than one year [20]. This is particularly relevant because ICS discontinuation after 30 months in stable COPD can worsen lung function decline, airway hyperresponsiveness, airway inflammation and quality of life during 5-year follow-up [34,35].

This area requires carefully designed efficacy and effectiveness studies. Until and before the publication of the recently terminated large long-term IMPACT (NCT02164513) and DYNAGYTO (NCT02296138) controlled clinical trials the positioning of dual bronchodilator therapy in the treatment guidelines of stable COPD remains controversial (see for example two recent Editorials published on Lancet Respiratory Medicine by two Opinion Leaders seating in the GOLD Committee) [36,37].

COPD phenotyping can help define clusters of patients with common characteristics that relate to

Downloaded by [Imperial College London Library] at 01:13 29 September 2017

Accepted Manuscript

clinically meaningful outcomes. A very recent review, has described 7 clinically meaningful COPD phenotypes that can be identified by primary care physicians as well as specialists and that have specific management and prognostic implications: (1) asthma-COPD overlap phenotype, (2) frequent exacerbator phenotype, (3) upper lobe-predominant emphysema phenotype, (4) rapid decliner phenotype, (5) comorbid COPD phenotype, (6) physical frailty phenotype, and (7) emotional frailty phenotype [38].

We provide here an update of our previous review on the role of fluticasone furoate and vilanterol for the treatment of patients with stable COPD [39].

Downloaded by [Imperial College London Library] at 01:13 29 September 2017

Accepted Manuscript

2. Pharmacodynamics of fluticasone furoate and vilanterol

2.1 Fluticasone furoate

Functionally glucocorticoids act by suppressing airway hyperresponsiveness, reducing airway edema and the infiltration of inflammatory cells from the blood to the airway and thereby reducing the lower airway inflammatory response [40,41]. The anti-inflammatory actions of glucocorticoids occur through activation of glucocorticoid receptors (GRs), which are found in the cytoplasm of virtually all cells [40,41]. GRs are predominantly localized to the airway epithelium, alveolar macrophages and endothelium, which are, therefore, probably important sites for the anti-inflammatory action of glucocorticoids [figure 1]. Airway epithelial cells respond to various inflammatory mediators by the production of a wide range of cytokines, chemokines, and other inflammatory mediators. The GR gene encodes many protein isoforms [42]: with the major being the cytoplasmic alpha form (GRα). This binds hormone, translocates to the nucleus, and regulates gene transcription. Within the nucleus GR can bind to specific DNA elements (glucocorticoid response elements or GREs) as homodimers to control glucocorticoid-responsive genes. Several genes are upregulated by glucocorticoids, including the β_2-adrenergic receptor (β_2-AR), MAPK phosphatase (MKP1) and serum leukoprotease inhibitor (SLPI).

However, the major role of glucocorticoids appears to be gene repression [40,41]. The major anti-inflammatory action of glucocorticoids is the repression of the pro-inflammatory actions of nuclear factor kappaB (NF-κB), resulting in a reduction in inflammatory gene transcription. This requires the action of a GR monomer which either tethers to NF-κB and recruits transcriptional co-repressors or binds to negative GREs [40,41]. In addition, there are some effects on messenger ribonucleic acid (mRNA) stability. Several molecular mechanisms for the suppressive actions of activated GR on NF-κB-mediated gene transcription have been proposed. It is likely that it involves either recruitment of the

repressive co-factor histone deacetylase (HDAC)-2 to the activated deoxyribonucleic acid (DNA)-bound NF-κB complex or by modulation of RNA polymerase 2 phosphorylation and transcription re-initiation [40,41].

Oxidative stress down-regulates HDAC activity and expression and this is linked to a reduction in the repressive functions of GR. HDAC2 expression is reduced in the lung of patients with stable COPD and overexpression of HDAC2 restores glucocorticoid sensitivity in bronchoalveolar lavage (BAL) macrophages from these patients.

Fluticasone furoate (FF) (formerly drug code GW685698) is a novel enhanced-affinity synthetic trifluorinated glucocorticoid [43]. X-ray crystallography studies show that the 17-α furoate ester occupies the lipophilic 17-α pocket on the ligand binding domain of GR to a greater extent than dexamethasone and fluticasone propionate (FP), and this may account for the enhanced glucocorticoid receptor binding of FF [44]. I*n vitro* FF has a fast association and a slower dissociation rate from GR resulting in a relative receptor affinity (RRA) of 30 with reference to dexamethasone (RRA=1). This is superior to that of budesonide (RRA=8), des-ciclesonide (RRA=12), FP (RRA=18) and mometasone furoate (RRA=22) [45].

Furthermore, both FP and FF, as with budesonide, have pronounced retention (without instability or chemical modification) in human lung tissue *in vitro* [45]. As a result FF is very potent suppressor of NF-κB and a strong activator of the GRE transactivation pathway. Unlike FP, FF action is relatively resistant to oxidative stress [43,46].

FF has similar or slightly higher potency to FP and is 2-9 fold more potent than budesonide in inhibiting inflammatory cytokine production in human epithelial cells and macrophages. In addition, FF has superior effects to FP in peripheral blood mononuclear cells (PBMCs) from patients with COPD and also in U937 cells or primary bronchial epithelial cells under conditions of oxidative stress [46]. This, together with the longer GR nuclear retention seen with FF compared with FP and budesonide provides a mechanism for the 24 hours duration of action with single daily dosing [46].

Furthermore, in healthy male subjects *in vivo*, inhaled FF demonstrated prolonged absorption from the lung into the systemic circulation than inhaled FP, indicating a longer lung retention time and the potential for maintained efficacy with once-daily administration [47].

2.2 Vilanterol

Downloaded by [Imperial College London Library] at 01:13 29 September 2017

Accepted Manuscript

β_2-agonists are effective bronchodilators due primarily to their ability to relax airway smooth muscle (ASM) [48,49]. β_2-agonists act as functional antagonists and reverse bronchoconstriction irrespective of the contractile agent. This is an important property for the treatment of asthma where many bronchoconstrictor mechanisms are important. In COPD, the major mechanism of action is likely to be a reduction of cholinergic reflex bronchoconstriction.

In addition to prolonged bronchodilation, these drugs exert other β_2-agonist-mediated effects *in vitro* that may be of clinical relevance in patients with COPD [48,49].

Inhaled β_2-agonists target β_2-ARs which are members of the G protein coupled receptor (GPCR) superfamily that are expressed in high numbers (>3000) per ASM cell of the lower airways (their number increases with increasing airway generation). They are also expressed on other important target cells, including lower airways epithelium and submucosal glands, vascular smooth muscle cells, macrophages, neutrophils, lymphocytes, eosinophils, mast cells and the endothelium of the post-capillary venules [50,51] [figures 1 and 2].

β_2-agonists produce bronchodilatation by directly stimulating β_2-ARs in ASM cells, and *in vitro* relax human bronchi and lung strips (indicating an effect on peripheral airways) and *in vivo* there is a rapid decrease in airway resistance.

Ligand binding to the β_2-AR in the ASM cells results in activation of receptor-associated G-stimulatory (G_s) protein and enhanced coupling with the membrane-bound enzyme adenylyl cyclase and with calcium channels, to propagate the GPCR signaling [52]. The coupling of activated G_s and adenylyl cyclase leads to increased production of cyclic adenosine 3',5'-monophosphate (cAMP) and subsequent activation of cAMP-dependent protein kinase A (PKA), which phosphorylates several target proteins within the cell, leading to relaxation of the ASM cells [figure 2].

The molecular mechanisms by which β_2-agonists induce relaxation of ASM cells include [49,51,53]:

- Lowering of intracellular calcium ion (Ca^{2+}) concentration by active removal of Ca^{2+} from the cell and into intracellular stores. Activation of Ca^{2+}-Mg^{2+}-ATPases in the endoplasmic reticulum and plasma membrane decreases Ca^{2+} levels, thereby reducing Ca^{2+}-dependent actin-myosin interactions and leading to relaxation of ASM cells.
- An inhibitory effect on phosphoinositide (PI) hydrolysis, which leads to intracellular Ca^{2+} release

Downloaded by [Imperial College London Library] at 01:13 29 September 2017

Accepted Manuscript

- Inhibition of myosin light chain kinase (MLCK) phosphorylation and inactivation and thereby preventing myosin phosphorylation.
- Concomitant activation of myosin light chain phosphatase.
- Opening of a large conductance calcium-activated potassium channel (K_{CA}) which repolarizes the smooth muscle cell and may stimulate the sequestration of Ca^{2+} into intracellular stores.
- β_2-ARs are also directly coupled to K_{CA} via G_s so that relaxation of ASM may occur independently of an increase in cAMP.

Several of the actions of β_2-agonists are not mediated via PKA, however and these effects are transduced through other cAMP-regulated proteins [54]. Importantly, direct inhibition of PKA in human ASM cells or murine airways *ex vivo* inhibits the vast majority of the relaxant effect of the β_2-agonists, demonstrating that PKA is the principal effector of β_2-agonist-mediated ASM relaxation [55] [figure 2]. β_2-agonists may also influence gene transcription through elevation of cAMP and activation of PKA. cAMP mediates the hormonal stimulation of many genes through a conserved cAMP response element (CRE). cAMP causes translocation of the catalytic subunit of PKA to the nucleus, where it phosphorylates and activates the transcription factor cAMP response element binding protein (CREB). Activation of the β_2-AR can also lead to stimulation of the extracellular signal-regulated kinases (ERK) and p38 mitogen-activated protein kinases (MAPKs) pathways. These effects may contribute to the inhibition of ASM cell proliferation and inflammatory mediator release [48,49].

β_2-agonists may therefore cause bronchodilatation *in vivo* not only via a direct action on lower ASM, but also indirectly by inhibiting the release of bronchoconstrictor mediators from inflammatory cells and of bronchoconstrictor neurotransmitters from nerves in the lower airways. These mechanisms include [48,49]:

- Prevention of mediator release from isolated human lung mast cells (via β_2-AR).
- Attenuation of neutrophil recruitment and activation.
- Prevention of microvascular leakage and thus the development of bronchial mucosal edema.
- Weak increase in mucus secretion from submucosal glands and ion transport across airway epithelium; these effects may enhance mucociliary clearance, and therefore reverse the defective clearance found in stable COPD patients [56,57].
- Reduction of the bronchial epithelial damage caused by bacterial toxins.
- Reduction in neurotransmission in human airway cholinergic nerves by an action at pre-junctional β_2-ARs to inhibit acetylcholine release and thereby reducing cholinergic reflex bronchoconstriction [57].

Downloaded by [Imperial College London Library] at 01:13 29 September 2017

Accepted Manuscript

Although these additional effects of inhaled β_2-agonists may be relevant to the prophylactic use of these drugs against various challenges, their rapid bronchodilator action is likely attributable to a direct effect on airway smooth muscle [48,49, 53].

In the lower airways of patients with COPD, β_2-agonists may potentiate the molecular mechanism of glucocorticoid actions, with increased nuclear localization of glucocorticoid receptors (GRs) and additive or sometimes synergistic suppression of inflammatory mediator release [58]. Activated GR binding to specific GREs in concert with another transcription factor, CAAT/enhancer-binding protein alpha (C/EBPα), in ASM cells leads to optimal antiproliferative actions *via* $p21^{WAF1/Cip1}$. This mechanism been proposed to account, at least in part, for the enhanced effect of combination treatment in COPD patients [53,59].

Inhaled glucocorticoids on the other hand increase the cellular expression of β_2-AR by increasing gene transcription acting through GREs and, importantly, may regulate β_2-AR function by restoring G-protein-β_2-AR coupling and inhibiting β_2-AR down-regulation induced by inflammation, thereby preventing its desensitization [53].

Activation of the β_2-AR activates both rapid and slow negative feedback mechanisms that inhibits β_2-AR signaling. Rapid inhibition involves receptor phosphorylation and uncoupling of the β_2-AR from the G_s protein via GPCR kinases 2/3 (GRK2/3) and association of the receptor inhibitor β-arrestin-2 [60,61]. Other kinases, including PKA and PKC, can also phosphorylate the β_2-AR to promote uncoupling, without the β_2-AR necessarily being occupied by agonist.

Slower feedback mechanisms include receptor internalization, and receptor downregulation (loss of total cellular β_2-AR protein) following translocation to lysosomes for degradation [60,61].

Vilanterol trifenatate (VI) (formerly named compound 13f.triphenylacetate or GSK-642444) Is a novel ULABA that has been synthesized by incorporation of an oxygen atom at the homobenzylic position of the right-hand side phenyl ring of (*R*)-salmeterol and has suitable chemical properties for inhaled administration [62].

The affinity of VI for the human β_2-AR is higher than formoterol, indacaterol and olodaterol but comparable with that of salmeterol and slightly lower than that of abediterol [48,63,64]. VI is a highly

Downloaded by [Imperial College London Library] at 01:13 29 September 2017

Accepted Manuscript

lipophilic molecule partitioning into cell membrane and forming depots of drug in the cell membrane, but it impossible to rule out VI binding directly to a binding site within the β_2-AR [63].

In functional activity studies, VI has similar selectivity profile as salmeterol for β_2-AR over β_1-AR and β_3-AR with over 1000-fold selectivity over both these receptors, but it has a significantly improved selectivity profile than albuterol (salbutamol), formoterol and indacaterol decreasing the risk of untoward effects due to the stimulation of the other β-ARs [48,63].

VI also has a level of intrinsic efficacy (an agonist of high intrinsic efficacy might offer advantages in clinical effectiveness over a weak partial agonist) [65] comparable to indacaterol but significantly greater than that of salmeterol. The intrinsic activity of VI is lower than that of isoprenaline, the reference full β_2-AR agonist, indicating that VI, as well as salmeterol, is a partial β_2-AR agonist. In *in vitro* cell-based studies VI has a persistence of action comparable with indacaterol and longer than that of formoterol or salmeterol [48,63].

VI, formoterol, and indacaterol have a more rapid onset of activity compared with salmeterol. In human airways preconstricted with histamine, VI has a significantly faster onset of action (3.1 min) compared with salmeterol (8.3 min) [48].

In vitro in human airways, VI also has a longer duration of action than salmeterol, still exhibiting a significant level of bronchodilation at 22 (but not 28) hours after treatment [63].

Together this results in VI having a rapid dose-dependent bronchodilation *in vivo* in healthy subjects and in patients with stable COPD, which is maintained over 24 hours [65,66]. In asthmatics patients, there is no advantage over a 24-hour period of VI twice daily versus once-daily dosing for the same total daily dose [67].

Importantly in patients with stable COPD β_2-AR gene (ADRB2) variants are not associated with the bronchodilator response to VI [68].

3. Pharmacokinetics of fluticasone furoate and vilanterol

Downloaded by [Imperial College London Library] at 01:13 29 September 2017

Accepted Manuscript

Unfortunately, for both FF and VI we only know concentrations in systemic blood. This lack of information does not allow us to understand the temporal relationship between the delivered dose and the drug concentration at the sites of action within the lungs [69].

Following intranasal administration of FF, most of the swallowed dose undergoes incomplete absorption and extensive first-pass metabolism in the liver, by the hepatic cytochrome P450 (CYP) isozyme, 3A4, resulting in negligible systemic exposure (oral bioavailability is <0.5%). At the highest recommended intranasal dosage, plasma concentrations of FF are typically not quantifiable despite the use of an highly sensitive high-performance liquid chromatography (HPLC)-mass spectroscopy(MS) assay in subjects of all ages [70]. Concomitant administration of strong CYP3A4 inhibitors, like ketoconazole, increase the plasma concentrations of both FF and VI [71].

Using pharmacokinetic studies performed in normal subjects and asthmatic patients, predictive models indicate that a FF area under the concentration-time curve over 24 h post-dose (AUC24) of 1,000 pg·h/mL would be required to reduce 24-h serum cortisol or 24-h urine cortisol excretion by 20 and 17%, respectively [72].

FF inhalation is associated with reduced serum cortisol in patients with moderate hepatic impairment [73] suggesting that caution should be exercised when prescribing FF/VI in patients with moderate or severe hepatic impairment due to a risk for unwanted systemic glucocorticoid effects associated with increased FF systemic exposure [73].

FF is not detectable in the urine of healthy subjects following intranasal dosing (<1%) and severe renal function impairment has no clinically relevant effects on the pharmacokinetic or pharmacodynamics properties or tolerability of FF/VI [70,73].

VI has a rapid turnover because it is rapidly metabolized by the human liver microsomes [62] via *O*-dealkylation to metabolites with almost absent pharmacological activity, excreted by ~70% in the urine and ~30% in the feces [74]. In healthy subjects, after a single 200 µg oral dose of VI, there is an extensive first-pass metabolism in the liver with less of the 0.5% of total dose of VI measurable in the plasma [74]. For this reason, the therapeutic inhaled dose of 25 µg of VI is unlikely to produce systemic effects. In healthy subjects verapamil, a P-glycoprotein and moderate CYP3A4 inhibitor, does not increase systemic exposure to VI [75].

Downloaded by [Imperial College London Library] at 01:13 29 September 2017

Accepted Manuscript

As a result, no dose adjustment for VI is required in patients with severe impairment of renal and/or hepatic function [73,76].

In COPD patients there are significant differences in the population pharmacokinetics of FF/VI but the magnitude of these effects on systemic exposure is not large enough to require FF/VI dosage adjustment [77,78].

4. Clinical efficacy of fluticasone furoate/vilanterol combination therapy vs placebo in the regular treatment of stable COPD

4.1 Effect on lung function, symptoms, cardiac function and exercise tolerance

Given once-daily to patients with moderate to severe stable COPD, inhaled FF/VI combination improves trough forced expiratory volume in one second (FEV_1) by more than 200 mL in two 28-day trials versus placebo [79,80]. However, a more modest increase (100-130 mL) is seen in longer 12-28-week trials [81-85]. The regular treatment of stable COPD patients with FF/VI combination decreases their symptoms, particularly dyspnea, and the use of as needed salbutamol, in 12-52-week trials [79-83,85,86].

In stable hyperinflated COPD patients, a short-term FF/VI therapy increases slightly, albeit significant, left ventricular end-diastolic, left atrial end-systolic volumes, right ventricular stroke volume, pulmonary artery pulsatility and left atrial ejection fraction but not right ventricular ejection fraction and intrinsic myocardial function [87]. There are no published studies on the effect of this therapy on exercise tolerance of stable patients with COPD. It is also unclear if the regular treatment with inhaled VI alone vs placebo improves significantly exercise endurance time in stable COPD patients [88].

4.2. Prevention of COPD exacerbations, accelerated FEV_1 decline, long-term compliance to inhaled therapy and mortality

There is no established minimal clinically important difference (MCID) for COPD exacerbations but interventions reducing exacerbations by as little as 11% appear to be regarded widely as clinically important [89].

In two trials of one-year duration, involving more than three thousand patients with stable moderate to severe COPD randomized to FF/VI or VI alone; treatment with FF/VI was associated with a slight (27%) but significant decrease (0.81 vs 1.11) in the yearly rate of moderate plus severe COPD

Downloaded by [Imperial College London Library] at 01:13 29 September 2017

Accepted Manuscript

exacerbations, the time to first moderate or severe exacerbation and the frequency of exacerbations requiring systemic glucocorticoids. There was no difference in the rate of COPD exacerbations requiring hospitalization [86].

Reductions in exacerbations with FF/VI, compared with VI alone, were 24% in patients with baseline blood eosinophil counts of ≥2-<4%, 32% for those with counts of 4-<6%, and 42% for those with eosinophil counts of ≥6%. In patients treated with VI alone, exacerbation rates increased progressively with increasing eosinophil count percentage category [90].

In the "Study to Understand Mortality and Morbidity in COPD" (SUMMIT) a multicentre, randomized, double-blind, parallel-group, placebo-controlled event-driven trial (study end date was pre-determined where approximately 1000 deaths would have occurred in the intent-to treat efficacy population, the maximum follow-up was 4 years; median study exposure was 1·8 years and was similar across all treatment groups), 16590 patients with moderate stable COPD and either a history of cardiovascular disease (CVD) or at increased risk for CVD were randomly assigned (1:1:1:1) to once-daily treatment with FF/VI (100/25 µg), FF (100 µg), VI (25 µg) or matched placebo with mortality as the primary end-point powered by the comparison of FF/VI versus placebo [91,92]. Compared with placebo, all-cause mortality was unaffected by combination therapy or FF or VI alone, whereas all treatments reduced the rate of moderate and severe COPD exacerbations [92]. Compared with placebo, FF/VI combination reduced the rate of moderate/severe COPD exacerbations by 29% and the rate of hospitalized exacerbations by 27%. These effects were similar regardless of whether the COPD patients had a history of exacerbation in the year prior to the study or an FEV_1 less than or ≥ 60% predicted [93].

In a controlled effectiveness trial (Salford Lung COPD trial) of 1-year duration conducted in 75 general practices, 2799 COPD patients≥ 40 years old, with an exacerbation in the previous 3 years, were randomized (1:1) to once-daily inhaled FF (100 µg)/vilanterol (25 µg) combination (the FF-VI group) or to usual care (the usual-care group). The primary outcome was the rate of moderate or severe exacerbations among patients who had had an exacerbation within 1 year before the trial. The rate of moderate or severe exacerbations was significantly lower, by 8.4%, with FF-VI therapy than with usual care [94]. There was no significant difference in the annual rate of COPD-related contacts to primary or secondary care. There were no significant between-group differences in the rates of the first moderate or severe exacerbation and the first severe exacerbation in the time-to-event analyses [94].

Downloaded by [Imperial College London Library] at 01:13 29 September 2017

Accepted Manuscript

There are no published studies adequately powered as the primary outcome and of sufficient duration, on the role of the effect of regular treatment of patients with stable COPD with FF/VI combination in the prevention of their accelerated FEV_1 decline.

In the SUMMIT trial (median study exposure 1·8 years), the rate of decline in FEV_1 is significantly reduced by the FF/VI combination therapy (38 mL per year vs 46 mL per year for placebo, difference 8 mL per year) with similar findings for FF (difference 8 mL per year), but not VI (difference -2 mL per year) [92].

Similarly there are no published studies using objective measures on the long-term compliance to the inhaled therapy with FF/VI combination in stable COPD patients.

4.3 Clinical efficacy of fluticasone furoate/vilanterol vs tiotropium therapy in the regular treatment of stable COPD

There are some data showing that in patients with moderate to severe stable COPD, 12 weeks treatment with FF/VI improves FEV_1 (mean ~120 mL) to the same extent as tiotropium [95].

4.4 Clinical efficacy of fluticasone furoate/vilanterol vs fluticasone propionate/salmeterol vs budesonide/formoterol combination therapy in the regular treatment of stable COPD

There are efficacy data comparing FF/VI vs fluticasone propionate/salmeterol (FP/SAL) combination in the treatment of stable COPD. In one 12-week trial weighted mean FEV_1($wmFEV_1$) (mean, 130 mL) was greater and time to 100 mL improvement shorter (median, 16 min) with FF/VI than FP/SAL (mean [wm], 108 mL; median, 28 min). Health status [St. George's Respiratory Questionnaire (SGRQ) total score] improved in both groups (FF/VI, -4.3 units; FP/SAL, -3.0 units) but these differences between treatments were not statistically significant [83].

One systematic review has suggested that FF/VI(100/25 μg) therapy has an efficacy comparable with corresponding doses of FP/SAL and budesonide/formoterol on lung function and health status outcomes. Non-inferiority on moderate/severe exacerbation rate was not demonstrated to the same degree of confidence, though observed rates are similar [96].

Downloaded by [Imperial College London Library] at 01:13 29 September 2017

Accepted Manuscript

4.5 Clinical efficacy of fluticasone furoate/vilanterol vs umeclidinium/vilanterol vs fluticasone furoate/umeclidinium/vilanterol combination therapy in the regular treatment of stable COPD

Two large 12-week, controlled trials performed in in patients with stable COPD have shown that the addition of umeclidinium (UMEC) (62.5 µg and 125 µg) to FF/VI (100/25 µg) provides statistically significant improvements in lung function (and in quality of life in one of these studies) compared with placebo + FF/VI. This provides support for the use of triple therapy in these patients [97].

The InforMing the PAthway of COPD Treatment (IMPACT) study is a recently terminated phase 3, randomized, double-blind, three-arm, parallel-group, global (~1070 centers) study (NCT02164513) investigating the efficacy (rate of moderate and severe COPD exacerbations) and safety of FF/UMEC/VI versus FF/VI or UMEC/VI combinations over a 52-week treatment period. The study aims to recruit 10000 patients. Eligible patients are ≥40 years, with symptomatic advanced COPD [Global initiative for chronic Obstructive Lung Disease (GOLD) group D] and an exacerbation in the previous 12 months. The completion date is ~July 2017 [98] but the results have not yet published. A recent press release regarding the IMPACT study suggest that the primary endpoint of statistically significant reductions in the annual rate of on-treatment moderate to severe exacerbations for FF/VI/UMEC compared to VI/UMEC was met [99].

4.6 Clinical efficacy of fluticasone furoate/vilanterol plus tiotropium vs beclomethasone dipropionate/formoterol fumarate/glycopyrronium bromide therapy in the regular treatment of stable COPD

There is a 26-week, 2-arm, parallel group phase 3 study investigating the non-inferiority on the quality of life of the fixed combination of FF/VI plus tiotropium vs a fixed combination of beclomethasone dipropionate/formoterol fumarate/glycopyrronium bromide (CHF 5993) (NCT02467452) in ~1500 stable COPD patients. The study is terminated on January 2017 but the results have not yet published.

4.7 Anti-inflammatory effect of fluticasone furoate/vilanterol combination therapy in the regular treatment of stable COPD

Airway biopsy studies are required to evaluate whether FF/VI have a significant *in vivo* anti-inflammatory activity in the lower airways in addition to their known bronchodilator properties.

Downloaded by [Imperial College London Library] at 01:13 29 September 2017

Accepted Manuscript

5. Side effects and cost-effectiveness of fluticasone furoate/vilanterol combination therapy in the regular treatment of stable COPD

Unlike other LABAs and ULABAs, vilanterol is not available as a single agent and for the treatment of stable COPD is only marketed in a fixed combination with 100 micrograms of fluticasone furoate at a dosage of 25 micrograms of vilanterol administered in a new dry powder inhaler (DPI) (Ellipta©) incorporating a dose counter, that has little flow dependency [100].

Like other inhaled β_2-agonists VI may cause clinically significant cardiovascular effects [including increase of the pulse rate and of the systemic arterial blood pressure and prolongation of the QT interval of the electrocardiogram (ECG) corrected for the heart rate(QTc)] and therefore must be used with caution during acute coronary syndromes and in patients with cardiac arrhythmia and/or chronic heart failure. However, the safety of single and repeat VI doses up to 50 µg has been established in healthy subjects with no clinically significant abnormalities in vital signs, 12-lead ECG, Holter ECG, blood glucose or potassium and QTc observed [66,101], but some prolongation of the QTc has seen following the 100 µg VI dose after single and repeat doses in healthy subjects [66,71]. In healthy subjects there is a small effect, dependent on the plasma concentration, of repeated doses of inhaled VI on the QT interval corrected using Fridericia's correction (QTcF) [102].

In healthy Japanese subjects, no safety concerns were found following single or repeat dosing of FF, VI and FF/VI. Systemic exposure to FF and VI increases in a dose-dependent manner. In these subjects, serum cortisol level is suppressed by 97% after 7 days repeat administration of FF at a dose of 800 µg [103]. There was a slight increase in heart rate observed but only with a supratherapeutic dose of 50µg of inhaled VI [103].

Regular treatment with FF/VI combination in stable COPD patients is usually well tolerated. The adverse events reported most often in the short- and long-term clinical studies of FF/VI DPI combination therapy vs placebo in these patients include rinopharyngitis (9%), upper respiratory tract infection (7%), headache (7%) and dysphonia and oropharyngeal candidiasis (5%) [78-82,86,104]. However, in two trials of one year duration both pneumonia and bone fractures were more frequently with FF/VI combination therapy than with VI alone [86]. Although the rate of radiographically-confirmed pneumonia roughly doubled in the groups taking FF, this increase is similar to the increased pneumonia risk described previously with FP and in some studies of budesonide and mometasone [9,10,86]. In addition, the incidence of these events was very low compared with the rate of COPD exacerbations, which was ten times higher. Eight deaths from pneumonia were observed in the FF/VI

Downloaded by [Imperial College London Library] at 01:13 29 September 2017

Accepted Manuscript

combination group compared with none in the VI only group [86]. A meta-analysis has suggested that FF/VI therapy is associated with a significant 52% increase in the rate of pneumonia compared with VI monotherapy (5.3% vs. 3.5%) with no difference in the rate of pneumonia when FF/VI is compared with FF alone [105]. Likewise it has been suggested that stable COPD patients with baseline blood eosinophil counts less than 2% have more pneumonia events than those with higher blood counts [106]. However, in the largest SUMMIT trial there was no excess risks of pneumonia (5% in the placebo group, 6% in the FF/VI combination group, 5% in the FF group, and 4% in the VI group) or adverse cardiac events or composite cardiovascular events between treatment groups [92,106].

Similarly, in the Salford COPD trial there was no excess risk of pneumonia or of other serious adverse events in the FF/VI group vs the usual care group. Interestingly, there was a trend toward a higher mean number of pneumonias in the group not receiving an inhaled glucocorticoid at randomization (mean annual rate, 3.01 hospitalizations) compared to those groups on inhaled glucocorticoids (p=0.10 for the interaction of treatment with baseline maintenance therapy in the analysis across the three strata) [94].

There is an ongoing 156 week multi-center, randomized, double-blind, parallel-group study in moderate COPD patients evaluating the effect of FF on bone mineral density assessed at the total hip by comparing FF/VI treatment with VI alone treatment (NCT01957150).

There are safety data showing that the short-term treatment of stable COPD patients with FF/VI vs FP/SAL combination is equally well tolerated [91].

Current guidelines do not recommend that the new FF/VI combination be used in the treatment of COPD exacerbations.

There is no formal cost-effectiveness analysis published on the use of FF/VI combination vs other combinations in the regular treatment of patients with stable COPD.

In one Spanish simulation the treatment of stable COPD patients with FF/VI may decrease the health care costs for the Spanish National Health Service (NHS) due to the decreased rate of exacerbations compared with VI monotherapy. This resulted in an annual reduction in average health care costs to the Spanish NHS of €3,278,382 [107].

Downloaded by [Imperial College London Library] at 01:13 29 September 2017

Accepted Manuscript

6. Conclusion

The regular treatment of moderate to severe stable COPD patients with once daily FF/VI combination therapy is effective in many large controlled clinical trials involving many thousands of patients. FF/VI improves lung function, decreases respiratory symptoms and the number of COPD exacerbations, including COPD-related hospitalizations, it is usually well tolerated and has been approved for this indication in most of the countries.

7. Expert commentary

The true effectiveness achieved in clinical practice with any therapeutic intervention in patients with stable COPD is strongly influenced by the patients' inhaler technique as well as their compliance with taking the drug over many months/years [108]. Compliance should increase with once daily treatment and so a once daily combination therapy within a single inhaler should be an ideal first choice option for these patients. FF/VI represents the first once daily combination between ULABAs and inhaled glucocorticoids available for the treatment of stable COPD patients and has already shown to improve the natural history, decrease exacerbations and symptoms, but not the mortality, of the COPD patients.
The data to date indicates that FF/VI DPI once daily combination therapy is effective in improving lung function, decreasing respiratory symptoms and the number of COPD exacerbations, including COPD-related hospitalizations. Other combinations of LABAs and inhaled glucocorticoids have reported an increased risk of pneumonias in COPD patients when taken for more than 1 year. In large clinical trials and in a large "real world" effectiveness trial (Salford Lung COPD trial) of 1 year duration conducted in general practices, the combination of FF/VI is safe and reported no excess risk of pneumonia or adverse cardiac events or composite cardiovascular events.

8. Five-year view

A single simulation, with all the consequent limitations, suggest that the use of the once daily FF/VI combination therapy for the regular treatment of stable COPD patients may significantly decrease the economic costs for some National Health Services, particularly due to reduction in exacerbations. This is an increasingly important area globally but clearly requires the design and completion of appropriate studies to provide a definitive answer.

We also need additional large long-term controlled clinical trials comparing the efficacy of combination therapy with once daily FF/VI versus an once daily inhaled ultra-long acting antimuscarinic (ULAMA) alone or in combination with an inhaled ultra-long acting β2-agonist (ULABA) in COPD patients with

Downloaded by [Imperial College London Library] at 01:13 29 September 2017

Accepted Manuscript

different severities (grade B and C). In fact, there is low or moderate quality evidence, generated mainly from patients with moderate to severe COPD in heterogeneous trials with an observation period of less than one year, that treatment with ULAMA+ULABA combinations compared with ICS/LABA combinations is more effective in improving lung function, quality of life and decreasing COPD exacerbations, with a lower risk of pneumonia [20].

The large long-term controlled clinical trial IMPACT in advanced symptomatic grade D COPD patients that has been recently terminated in the 2017 will clarify the efficacy of once daily FF/VI therapy in comparison with once daily ULAMA/ULABA combination or the triple therapy with FF/VI/UMEC [98,99]. These data will aid the positioning of these treatments in the treatment guidelines of stable COPD.

There is already some evidence supporting the benefits of single inhaler triple therapy with FF/VI/UMEC compared with ICS/LABA therapy in patients with advanced COPD. The FULFIL trial has compared (double-dummy) once-daily triple therapy with FF/VI/UMEC (100 µg/25 µg/62.5 µg/; ELLIPTA®) with twice-daily budesonide/formoterol (400 µg/12 µg; Turbuhaler®) for 24 weeks in patients with severe stable COPD. In the intent-to-treat population (n =1,810) at week 24 the triple therapy was significantly better in improving lung function and reducing (35% less) moderate/severe COPD exacerbations [109].

The impact of these treatments on other distinct subphenotypes of COPD, such as those with asthma and COPD overlap (ACO) also need to be addressed.

There is also a clear need for objective data on the compliance with the long-term regular inhaled therapy in stable COPD patients with once daily FF/VI compared with other twice and once daily inhaled therapies.

The Ellipta device also has the potential to deliver additional drug along with FF/VI through the single inhaler. The most obvious candidate is the ULAMA umeclidinium that has already been added to provide a once-a-day triple inhaler. However, other candidate targets are possible, with the potential for other multiple once daily inhaled combination therapies in a single device for the regular treatment of stable COPD.

Downloaded by [Imperial College London Library] at 01:13 29 September 2017

Accepted Manuscript

Understanding of the mechanisms of glucocorticoid suppression of inflammatory genes has led to the identification of pathways that impact upon glucocorticoid function [41]. One such pathway is the phosphoinositide-3-kinase (PI3K)δ signaling pathway that is up-regulated in peripheral lung tissue of patients with stable COPD [110]. The results of the ongoing phase 2 controlled studies [NCT02130635] on the efficacy of a highly selective inhaled PI3Kδ inhibitor (GSK2269557) in patients with stable COPD are awaited with interest. This compound has already been formulated for its use in the Ellipta inhaler (NCT02691325) and if effective may represents in the future a new potential triple or quadruple once daily inhaled combination therapy together with FF/VI with or without the umeclidinium.

In patients with severe stable COPD, the addition to ICS/LABA of the oral PDE4 inhibitor roflumilast has some effect in reducing exacerbations and improving lung function, and this drug has been approved for the market but its use is limited by the common side effects [5]. To reduce the risk of side effects inhaled PDE4 inhibitors have been developed, including GSK256066 a potent and selective inhaled PDE4 inhibitor. This compound has already been formulated for its use in the Ellipta inhaler and appears to be safe and pharmacologically active in a phase 2 controlled study of stable COPD patients [111].

If the inhaled PDE4 inhibitors will prove to be effective in the large controlled trials of patients with stable COPD they may represent in the future a new potential triple or quadruple once daily inhaled combination therapy together with FF/VI with or without the umeclidinium and/or a selective inhaled PI3Kδ inhibitor.

Key issues

- Combinations of inhaled long-acting β_2-agonists and glucocorticoids are recommended for maintenance treatment of moderate to severe stable COPD.

- The combination in fluticasone furoate (FF) and vilanterol trifenatate (VI) in a single inhaler is the first once daily combination available on the market for the treatment of stable COPD.

- In large controlled clinical trials of moderate to severe stable COPD patients FF/VI improved lung function, decreased respiratory symptoms and the number of COPD exacerbations, including COPD-related hospitalizations.

Downloaded by [Imperial College London Library] at 01:13 29 September 2017

Accepted Manuscript

• Compliance should increase with once daily treatment and so a once daily combination therapy within a single inhaler should be an ideal first choice option for these patients.

• The use of this combination therapy may significantly decrease the economic costs for some National Health Services.

Funding

This manuscript has not funded.

Declaration of interests

Research by GC is supported by the University of Messina, Italy. GC has received in the last 48 months unrestricted educational grants and/or speaker and/or expert testimony honoraria from the pharmaceutical companies Astra-Zeneca, Boehringer-Ingelheim, GSK and Menarini that are selling FF/VI in the market (GSK and Menarini) and/or selling other drugs for the treatment of stable COPD. All these grants or honoraria were less of 5000 euro value. None of these pharmaceutical companies had any influence on the content of this review. Research by IMA and KFC is supported by the EU (IMI, project number 115010) and the MRC-ABPI COPD-MAP consortium (G1001367/1). IMA is also supported by Wellcome Trust grant 093080/Z/10/Z and by the Dunhill Medical Trust. IMA and KFC are PIs in the MRC/Asthma UK Centre for Asthma and Allergic Mechanisms and are supported by the NIHR Respiratory Disease Biomedical Research Unit at the Royal Brompton and Harefield NHS Foundation Trust and Imperial College London, UK. The views expressed in this publication are those of the authors and not necessarily those of their NHS, their National Institute for Health Research or their Hospital/Department of Health. 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.

Downloaded by [Imperial College London Library] at 01:13 29 September 2017

Accepted Manuscript

References

Papers of special interest have been highlighted as either of interest (*) or of considerable interest (**) to readers.

[1] Miravitlles M, Vogelmeier C, Roche N, et al. A review of national guidelines for management of COPD in Europe. Eur. Respir. J. 2016;47:625-637.

[2] O'Donnell DE, Hernandez P, Kaplan A, et al. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease - 2008 update - highlights for primary care. Can. Respir. J. 2008;15(sA):1A-8A.

[3] Abdool-Gaffar MS, Ambaram A, Ainslie GM, et al. COPD Working Group. Guideline for the management of chronic obstructive pulmonary disease--2011 update. S. Afr. Med. J. 2011;101:63-73.

[4] Qaseem A, Wilt TJ, Weinberger SE, et al. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. Ann. Intern. Med. 2011;155:179-191.

[5**] Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. NHLBI/WHO workshop report. Bethesda, National Heart, Lung and Blood Institute, April 2001; NIH Publication No 2701:1-100. Last update 2017. http:// http://goldcopd.org/gold-reports/ (accessibility verified on September 2017).

****An updated international guideline on the treatment of COPD.**

[6] Kew KM, Mavergames C, Walters JA. Long-acting beta2-agonists for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2013;10:CD010177.

[7] Chen WC, Huang CH, Sheu CC, et al. Long-acting beta2-agonists versus long-acting muscarinic antagonists in patients with stable COPD: a systematic review and meta-analysis of randomized controlled trials. Respirology. 2017 Jun 27. doi: 10.1111/resp.13100. [Epub ahead of print].

[8] Yang IA, Clarke MS, Sim EH, et al. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2012;7:CD002991.

[9] Arpinelli F, Caramori G, Magnoni MS. [Risk of pneumonia during long term regular treatment of stable COPD with inhaled glucocorticoids: a systematic review.] Recenti Prog. Med. 2017;108:175-182.

[10] Kew KM, Seniukovich A. Inhaled steroids and risk of pneumonia for chronic obstructive pulmonary disease. Cochrane Database Syst. Rev. 2014;3:CD010115.

[11] Spencer S, Karner C, Cates CJ, et al. Inhaled corticosteroids versus long-acting beta(2)-agonists for chronic obstructive pulmonary disease. Cochrane Database Syst. Rev. 2011;12:CD007033.

[12] Nannini LJ, Poole P, Milan SJ, et al. Combined corticosteroid and long-acting beta□-agonist in one inhaler versus placebo for chronic obstructive pulmonary disease. Cochrane Database Syst. Rev. 2013;11:CD003794.

Downloaded by [Imperial College London Library] at 01:13 29 September 2017

Accepted Manuscript

[13**] Calverley PM, Anderson JA, Celli B, et al.; TORCH investigators. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N. Engl. J. Med. 2007;356:775-789.

****The first controlled clinical trial on the long term treatment of stable COPD with ICS/LABA combination therapy with mortality as primary outcome**

[14] La Vecchia C, Fabbri LM. Prevention of death in COPD. N. Engl. J. Med. 2007;356:2211–2212.

[15] Scott DA, Woods B, Thompson JC, et al. Mortality and drug therapy in patients with chronic obstructive pulmonary disease: a network meta-analysis. BMC Pulm Med. 2015;15:145.

[16] Dong YH, Lin HH, Shau WY, et al. Comparative safety of inhaled medications in patients with chronic obstructive pulmonary disease: systematic review and mixed treatment comparison meta-analysis of randomised controlled trials. Thorax. 2013;68:48-56.

[17] Cyr MC, Beauchesne MF, Lemière C, et al. Effects of inhaled corticosteroids in monotherapy or combined with long-acting {beta}2-agonists on mortality among patients with chronic obstructive pulmonary disease. Ann. Pharmacother. 2010;44:613-622.

[18] Donohue JF, Betts KA, Du EX, et al. Comparative efficacy of long-acting β2-agonists as monotherapy for chronic obstructive pulmonary disease: a network meta-analysis. Int. J. Chron. Obstruct. Pulmon. Dis. 2017;12:367-381.

[19*] Cazzola M, Matera MG. Fixed-dose combination inhalers. Handb. Exp. Pharmacol. 2017;237:117-129.

*** An updated review on the role of fixed-dose combination of ICSs/LABAs for the treatment of stable COPD**

[20] Horita N, Goto A, Shibata Y, et al. Long-acting muscarinic antagonist (LAMA) plus long-acting beta-agonist (LABA) versus LABA plus inhaled corticosteroid (ICS) for stable chronic obstructive pulmonary disease (COPD). Cochrane. Database. Syst. Rev. 2017;2:CD012066.

[21] Harlander M, Barrecheguren M, Turel M, Miravitlles M. Should patients switched from D to B in the GOLD 2017 classification be discontinued from inhaled corticosteroids? COPD. 2017;14:465-468.

[22] Chalmers JD, Tebboth A, Gayle A, Ternouth A, Ramscar N. Determinants of initial inhaled corticosteroid use in patients with GOLD A/B COPD: a retrospective study of UK general practice. NPJ. Prim. Care. Respir. Med. 2017;27:43-51.

[23] White P, Thornton H, Pinnock H, Georgopoulou S, Booth HP. Overtreatment of COPD with inhaled corticosteroids--implications for safety and costs: cross-sectional observational study. PLoS One. 2013;8:e75221-e75230.

[24] Magnoni MS, Caminati M, Senna G, et al. Asthma under/misdiagnosis in primary care setting: an observational community-based study in Italy. Clin. Mol. Allergy 2015;13:26-30.

Downloaded by [Imperial College London Library] at 01:13 29 September 2017

Accepted Manuscript

[25] Llordés M, Jaén A, Almagro P, et al. Prevalence, risk factors and diagnostic accuracy of COPD among smokers in primary cCare. COPD. 2015;12:404-412.

[26] Miravitlles M, Andreu I, Romero Y, Sitjar S, Altés A, Anton E. Difficulties in differential diagnosis of COPD and asthma in primary care**.** Br. J. Gen. Pract. 2012;62:e68-e75.

[27] Al-Kassimi FA, Abba AA, Al-Hajjaj MS, Alhamad EH, Raddaoui E, Shaikh SA. Asthma masquerading as chronic obstructive pulmonary disease: a study of smokers fulfilling the GOLD definition of chronic obstructive pulmonary disease. Respiration. 2011;82:19-27.

[28] Marsh SE, Travers J, Weatherall M, et al. Proportional classifications of COPD phenotypes. Thorax. 2008;63:761-767.

[29] Magnussen H, Disse B, Rodriguez-Roisin R, et al; WISDOM Investigators. Withdrawal of inhaled glucocorticoids and exacerbations of COPD. N. Engl. J. Med. 2014;371:1285-1294.

[30] Rossi A, Guerriero M, Corrado A; OPTIMO/AIPO Study Group. Withdrawal of inhaled corticosteroids can be safe in COPD patients at low risk of exacerbation: a real-life study on the appropriateness of treatment in moderate COPD patients (OPTIMO). Respir. Res. 2014;15:77-88.

[31*] Calzetta L, Matera MG, Braido F, et al. Withdrawal of inhaled corticosteroids in COPD: A meta-analysis. Pulm. Pharmacol. Ther. 2017;45:148-158.

***An updated review on the effects of ICSs withdrawal in the treatment of stable COPD**

[32] Wedzicha JA, Banerji D, Chapman KR, et al; FLAME Investigators. Indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD. N. Engl. J. Med. 2016;374:2222-2234.

[33] Zhong N, Wang C, Zhou X, et al; LANTERN Investigators. LANTERN: a randomized study of QVA149 versus salmeterol/fluticasone combination in patients with COPD. Int. J. Chron. Obstruct. Pulmon. Dis. 2015;10:1015-1026.

[34] Kunz LI, Ten Hacken NH, Lapperre TS, et al; GLUCOLD Study Group. Airway inflammation in COPD after long-term withdrawal of inhaled corticosteroids. Eur. Respir. J. 2017;49: pii: 1600839. doi: 10.1183/13993003.00839-2016. Print 2017 Jan.

[35] Kunz LIZ, Postma DS, Klooster K, et al; GLUCOLD Study Group. Relapse in FEV1 decline after steroid withdrawal in COPD. Chest. 2015;148:389-396.

[36] Agustí A, Dekhuijzen PR. Maximal bronchodilation: a therapeutic target in COPD? Lancet Respir. Med. 2017;5:540-542.

[37] Vestbo J, Woodcock A. Clinical trial research in focus: time to reflect on the design of exacerbation trials in COPD. Lancet Respir. Med. 2017;5:466-468.

[38] Mirza S, Benzo R. Chronic obstructive pulmonary disease phenotypes: implications for care. Mayo Clin. Proc. 2017;92:1104-1112.

[19] Caramori G, Chung KF, Adcock IM. Profile of fluticasone furoate/vilanterol dry powder inhaler combination therapy as a potential treatment for COPD. Int. J. Chron. Obstruct. Pulmon. Dis. 2014;9:249-256.

Downloaded by [Imperial College London Library] at 01:13 29 September 2017

Accepted Manuscript

[40**] Adcock IM, Mumby S. Glucocorticoids. Handb. Exp. Pharmacol. 2016. 2017;237:171-196.

** **An updated review on the molecular mechanisms of action of glucocorticoids in lung diseases, including COPD.**

[41**] Barnes PJ. Glucocorticosteroids. Handb. Exp. Pharmacol. 2017;237:93-115.

** **An updated review on the molecular mechanisms of action of glucocorticoids in lung diseases, including COPD.**

[42**] Ramamoorthy S, Cidlowski JA. Corticosteroids: mechanisms of action in health and disease. Rheum. Dis. Clin. North Am. 2016;42:15-31.

* **An updated review on the mechanisms of action of glucocorticoids from a worldwide expert**

[43] Salter M, Biggadike K, Matthews JL, et al. Pharmacological properties of the enhanced-affinity glucocorticoid fluticasone furoate in vitro and in an in vivo model of respiratory inflammatory disease. Am. J. Physiol. Lung Cell. Mol. Physiol. 2007;293:L660-667.

[44] Biggadike K, Bledsoe RK, Hassell AM, et al. X-ray crystal structure of the novel enhanced-affinity glucocorticoid agonist fluticasone furoate in the glucocorticoid receptor-ligand binding domain. J. Med. Chem. 2008;51:3349-3352.

[45] Valotis A, Högger P. Human receptor kinetics and lung tissue retention of the enhanced-affinity glucocorticoid fluticasone furoate. Respir. Res. 2007;8:54.

[46] Rossios C, To Y, To M, et al. Long-acting fluticasone furoate has a superior pharmacological profile to fluticasone propionate in human respiratory cells. Eur. J. Pharmacol. 2011;670:244-251.

[47] Allen A, Bal J, Cheesbrough A, et al. Pharmacokinetics and pharmacodynamics of intravenous and inhaled fluticasone furoate in healthy Caucasian and East Asian subjects. Br. J. Clin. Pharmacol. 2014;77:808-820.

[48] Cazzola M, Page CP, Calzetta L, et al. Pharmacology and therapeutics of bronchodilators. Pharmacol Rev. 2012;64:450-504.

[49] Cazzola M, Page CP, Rogliani P, et al. β2-agonist therapy in lung disease. Am. J. Respir. Crit. Care Med. 2013;187:690-696.

[50] Barnes PJ. Distribution of receptor targets in the lung. Proc. Am. Thorac. Soc. 2004;1:345-351.

[51] Caramori G, Adcock IM, Chung KF. Drugs for airway diseases. In: Nijkamp FP, Parnham MJ, editors. Principles of immunopharmacology. London: Springer Verlag, 4th edition; 2018. In press.

[52] Bang I, Choi HJ. Structural features of β2 adrenergic receptor: crystal structures and beyond. Mol. Cells. 2015;38:105-111.

[53] Chung KF, Caramori G, Adcock IM. Inhaled corticosteroids as combination therapy with beta-adrenergic agonists in airways disease: present and future. Eur. J. Clin. Pharmacol. 2009;65:853-871.

Downloaded by [Imperial College London Library] at 01:13 29 September 2017

Accepted Manuscript

[54] Zieba BJ, Artamonov MV, Jin L, et al. The cAMP-responsive Rap1 guanine nucleotide exchange factor, Epac, induces smooth muscle relaxation by down-regulation of RhoA activity. J. Biol. Chem. 2011;286:16681-16692.

[55] Morgan SJ, Deshpande DA, Tiegs BC, et al. β-Agonist-mediated relaxation of airway smooth muscle is protein kinase A-dependent. J. Biol. Chem. 2014;289:23065-23074.

[56] Raju SV, Solomon GM, Dransfield MT, et al. Acquired cystic fibrosis transmembrane conductance regulator dysfunction in chronic bronchitis and other diseases of mucus clearance. Clin. Chest. Med. 2016;37:147-158.

[57] Johnson M, Rennard S. Alternative mechanisms for long-acting beta(2)-adrenergic agonists in COPD. Chest. 2001;120:258-270.

[58] Haque R, Hakim A, Moodley T, et al. Inhaled long-acting β2 agonists enhance glucocorticoid receptor nuclear translocation and efficacy in sputum macrophages in COPD. J. Allergy. Clin. Immunol. 2013;132:1166-1173.

[59] Roth M, Johnson PR, Rüdiger JJ, et al. Interaction between glucocorticoids and beta2 agonists on bronchial airway smooth muscle cells through synchronised cellular signalling. Lancet. 2002;360:1293-1299.

[60**] Pera T, Penn RB. Bronchoprotection and bronchorelaxation in asthma: New targets, and new ways to target the old ones. Pharmacol. Ther. 2016;164:82-96.
** **An updated review on the molecular mechanisms of action of β_2-agonists.**

[61] Walker JK, DeFea KA. Role for β-arrestin in mediating paradoxical β2AR and PAR2 signaling in asthma. Curr. Opin. Pharmacol. 2014;16:142-147.

[62] Procopiou PA, Barrett VJ, Bevan NJ, et al. Synthesis and structure-activity relationships of long-acting beta2 adrenergic receptor agonists incorporating metabolic inactivation: an antedrug approach. J. Med. Chem. 2010;53:4522-4530.

[63] Slack RJ, Barrett VJ, Morrison VS, et al. In vitro pharmacological characterization of vilanterol, a novel long-acting β2-adrenoceptor agonist with 24-hour duration of action. J. Pharmacol. Exp. Ther. 2013;344:218-230.

[64] Aparici M, Gavaldà A, Ramos I, et al. In vitro and in vivo preclinical profile of abediterol (LAS100977), an inhaled long-acting β2-adrenoceptor agonist, compared with indacaterol, olodaterol and vilanterol. Eur. J. Pharmacol. 2016;770:61-69.

[65] Hanania NA, Sharafkhaneh A, Barber R, et al. Beta-agonist intrinsic efficacy: measurement and clinical significance. Am. J. Respir. Crit. Care. Med. 2002;165:1353-1358.

[66] Kempsford R, Norris V, Siederer S. Vilanterol trifenatate, a novel inhaled long-acting beta2 adrenoceptor agonist, is well tolerated in healthy subjects and demonstrates prolonged bronchodilation in subjects with asthma and COPD. Pulm. Pharmacol. Ther. 2013;26:256-264.

[67] Sterling R, Lim J, Frith L, et al. Efficacy and optimal dosing interval of the long-acting beta agonist, vilanterol, in persistent asthma: a randomised trial. Respir. Med. 2012;106:1110-1115.

Downloaded by [Imperial College London Library] at 01:13 29 September 2017

Accepted Manuscript

[68] Condreay L, Huang L, Harris E, et al. Genetic effects on treatment response of umeclidinium/vilanterol in chronic obstructive pulmonary disease. Respir. Med. 2016;114:123-126.

[69] Calzetta L, Rinaldi B, Cazzola M, et al. Pharmacodynamic and pharmacokinetic assessment of fluticasone furoate + vilanterol for the treatment of asthma. Expert. Opin. Drug. Metab. Toxicol. 2016;12:813-22.

[70] Kumar R, Kumar D, Parakh A. Fluticasone furoate: a new intranasal corticosteroid. J. Postgrad. Med. 2012;58:79-83.

[71] Kempsford R, Allen A, Bal J, et al. The effect of ketoconazole on the pharmacokinetics and pharmacodynamics of inhaled fluticasone furoate and vilanterol trifenatate in healthy subjects. Br. J. Clin. Pharmacol. 2013;75:1478-1487.

[72] Allen A, Bareille PJ, Rousell VM. Fluticasone furoate, a novel inhaled corticosteroid, demonstrates prolonged lung absorption kinetics in man compared with inhaled fluticasone propionate. Clin. Pharmacokinet. 2013;52:37-42.

[73] Allen A, Davis A, Hardes K, et al. Influence of renal and hepatic impairment on the pharmacokinetic and pharmacodynamic properties and tolerability of fluticasone furoate and vilanterol in combination. Clin. Ther. 2012;34:2316-2332.

[74] Harrell AW, Siederer SK, Bal J, et al. Metabolism and disposition of vilanterol, a long-acting β(2)-adrenoceptor agonist for inhalation use in humans. Drug. Metab. Dispos. 2013;41:89-100.

[75] Mehta R, Kelleher D, Preece A, et al. Effect of verapamil on systemic exposure and safety of umeclidinium and vilanterol: a randomized and open-label study. Int. J. Chron. Obstruct. Pulmon. Dis. 2013;8:159-167.

[76] Mehta R, Hardes K, Brealey N, et al. Effect of severe renal impairment on umeclidinium and umeclidinium/vilanterol pharmacokinetics and safety: a single-blind, nonrandomized study. Int. J. Chron. Obstruct. Pulmon. Dis. 2014;10:15-23.

[77] Chen X, Zheng X, Jiang J, et al. Pharmacodynamics and pharmacokinetics of fluticasone furoate/vilanterol in healthy Chinese subjects. Pharmacotherapy. 2015;35:586-599.

[78] Siederer S, Allen A, Yang S. Population pharmacokinetics of inhaled fluticasone furoate and vilanterol in subjects with chronic obstructive pulmonary disease. Eur. J. Drug. Metab. Pharmacokinet. 2016;41:743-758.

[79] Boscia JA, Pudi KK, Zvarich MT, et al. Effect of once-daily fluticasone furoate/vilanterol on 24-hour pulmonary function in patients with chronic obstructive pulmonary disease: a randomized, three-way, incomplete block, crossover study. Clin. Ther. 2012;34:1655-1666.

[80] Lötvall J, Bakke PS, Bjermer L, et al. Efficacy and safety of 4 weeks' treatment with combined fluticasone furoate/vilanterol in a single inhaler given once daily in COPD: a placebo-controlled randomised trial. BMJ. Open. 2012;2:e000370.

[81] Kerwin EM, Scott-Wilson C, Sanford L, et al. A randomised trial of fluticasone furoate/vilanterol (50/25 μg; 100/25 μg) on lung function in COPD. Respir. Med. 2013;107:560-569.

Downloaded by [Imperial College London Library] at 01:13 29 September 2017

Accepted Manuscript

[82] Martinez FJ, Boscia J, Feldman G, et al. Fluticasone furoate/vilanterol (100/25; 200/25 µg) improves lung function in COPD: a randomised trial. Respir Med. 2013;107:550-559.

[83] Agustí A, de Teresa L, De Backer W, et al. A comparison of the efficacy and safety of once-daily fluticasone furoate/vilanterol with twice-daily fluticasone propionate/salmeterol in moderate to very severe COPD. Eur. Respir. J. 2014;43:763-772.

[84] Bollmeier SG, Prosser TR. Combination of fluticasone furoate and vilanterol for the treatment of chronic obstructive pulmonary disease. Ann. Pharmacother. 2014;48:250-257.

[85] Zheng J, de Guia T, Wang-Jairaj J, et al. Efficacy and safety of fluticasone furoate/vilanterol (50/25 mcg; 100/25 mcg; 200/25 mcg) in Asian patients with chronic obstructive pulmonary disease: a randomized placebo-controlled trial. Curr. Med. Res. Opin. 2015;31:1191-1200.

[86] Dransfield MT, Bourbeau J, Jones PW, et al. Once-daily inhaled fluticasone furoate and vilanterol versus vilanterol only for prevention of exacerbations of COPD: two replicate double-blind, parallel-group, randomised controlled trials. Lancet. Respir. Med. 2013;1:210-222.

[87] Stone IS, Barnes NC, James WY, et al. Lung deflation and cardiovascular structure and function in chronic obstructive pulmonary disease. A randomized controlled trial. Am. J. Respir. Crit. Care. Med. 2016;193:717-726.

[88] Maltais F, Singh S, Donald AC, et al. Effects of a combination of umeclidinium/vilanterol on exercise endurance in patients with chronic obstructive pulmonary disease: two randomized, double-blind clinical trials. Ther. Adv Respir Dis. 2014;8:169-181.

[89] Chapman KR, Bergeron C, Bhutani M, et al. Do we know the minimal clinically important difference (MCID) for COPD exacerbations? COPD. 2013;10:243-249.

[90] Pascoe S, Locantore N, Dransfield MT, et al. Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials. Lancet. Respir. Med. 2015;3:435-442.

[91] Vestbo J, Anderson J, Brook RD, et al. The Study to Understand Mortality and Morbidity in COPD (SUMMIT) study protocol. Eur. Respir. J. 2013;41:1017-1022.

[92**] Vestbo J, Anderson JA, Brook RD, et al; SUMMIT Investigators. Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. Lancet. 2016;387:1817-1826.

** **A large controlled clinical trial of FF/VI in the long term treatment of stable COPD with mortality as primary outcome.**

[93] Martinez FJ, Vestbo J, Anderson JA, et al; SUMMIT Investigators. Effect of fluticasone furoate and vilanterol on exacerbations of COPD in patients with moderate airflow obstruction. Am. J .Respir. Crit. Care. Med. 2017;195:881-888.

Downloaded by [Imperial College London Library] at 01:13 29 September 2017

Accepted Manuscript

[94**] Vestbo J, Leather D, Diar Bakerly N, et al; Salford Lung Study Investigators. Effectiveness of fluticasone furoate-vilanterol for COPD in clinical practice. N. Engl. J. Med. 2016;375:1253-1260. Please also read the comments on N. Engl. J. Med. 2016;375:2605-2607 and Dal-Ré R. Could phase 3 medicine trials be tagged as pragmatic? A case study: The Salford COPD trial. J. Eval. Clin. Pract. 2017 Jul 7. doi: 10.1111/jep.12796. [Epub ahead of print].

** **The first real life study of FF/VI in the long term treatment of stable COPD in general practice.**

[95] Covelli H, Pek B, Schenkenberger I, et al. Efficacy and safety of fluticasone furoate/vilanterol or tiotropium in subjects with COPD at cardiovascular risk. Int. J. Chron. Obstruct. Pulmon. Dis. 2015;11:1-12.

[96] Stynes G, Svedsater H, Wex J, et al. Once-daily fluticasone furoate/vilanterol 100/25 mcg versus twice daily combination therapies in COPD - mixed treatment comparisons of clinical efficacy. Respir. Res. 2015;16:25.

[97] Siler TM, Kerwin E, Sousa AR, et al. Efficacy and safety of umeclidinium added to fluticasone furoate/vilanterol in chronic obstructive pulmonary disease: Results of two randomized studies. Respir. Med. 2015;109:1155-1163.

[98**] Pascoe SJ, Lipson DA, Locantore N, et al. A phase III randomised controlled trial of single-dose triple therapy in COPD: the IMPACT protocol. Eur. Respir. J. 2016;48:320-330.

** **A large recently terminated controlled clinical trial of FF/VI in the long term treatment of advanced stable COPD in comparison with UMEC/VI and triple therapy with FF/UMEC/VI.**

[99] https://www.gsk.com/en-gb/media/press-releases/gsk-and-innoviva-report-positive-headline-results-from-impact-study-showing-single-inhaler-triple-therapy-trelegy-ellipta-reduced-copd-exacerbations/

[100] Hamilton M, Leggett R, Pang C, et al. In vitro dosing performance of the ELLIPTA® dry powder inhaler using asthma and COPD patient inhalation profiles replicated with the electronic lung (eLung™). J. Aerosol. Med. Pulm. Drug. Deliv. 2015;28:498-506.

[101] Kelleher DL, Mehta RS, Jean-Francois BM, et al. Safety, tolerability, pharmacodynamics and pharmacokinetics of umeclidinium and vilanterol alone and in combination: a randomized crossover trial. PLoS. One. 2012;7:e50716.

[102] Mehta R, Green M, Patel B, et al. Concentration-QT analysis of the randomized, placebo- and moxifloxacin-controlled thorough QT study of umeclidinium monotherapy and umeclidinium/vilanterol combination in healthy subjects. J. Pharmacokinet. Pharmacodyn. 2016;43:153-164.

[103] Nakahara N, Wakamatsu A, Kempsford R, et al. The safety, pharmacokinetics and pharmacodynamics of a combination of fluticasone furoate and vilanterol in healthy Japanese subjects. Int. J. Clin. Pharmacol. Ther. 2013;51:660-671.

[104] Hussar DA, Ahmad A. Vilanterol trifenatate/fluticasone furoate, lomitapide mesylate, and mipomersen sodium. J Am Pharm Assoc (2003). 2013;53:662-670.

[105] Rodrigo GJ, Neffen H. A systematic review with meta-analysis of fluticasone furoate/vilanterol combination for the treatment of stable COPD. Pulm. Pharmacol. Ther. 2017;42:1-6.

Downloaded by [Imperial College London Library] at 01:13 29 September 2017

Accepted Manuscript

[106] Pavord ID, Lettis S, Anzueto A, et al. Blood eosinophil count and pneumonia risk in patients with chronic obstructive pulmonary disease: a patient-level meta-analysis. Lancet Respir. Med. 2016;4:731-741.

[107] Mayoralas S, Huerta A, Parrondo J, et al. Monte-Carlo simulation to estimate the health care costs avoided with fluticasone furoate/vilanterol due to exacerbation rate reduction in spanish COPD patients. Value. Health. 2014;17:A603 (abstract).

[108] Fromer L, Goodwin E, Walsh J. Customizing inhaled therapy to meet the needs of COPD patients. Postgrad. Med. 2010;122:83-93.

[109] Lipson DA, Barnacle H, Birk R, et al. FULFIL Trial: Once-daily triple therapy in patients with chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care. Med. 2017;196:438-446.

[110] Marwick JA, Caramori G, Mazzoni F, et al. A role for phosphoinositol 3-kinase delta in the impairment of glucocorticoid responsiveness in patients with chronic obstructive pulmonary disease. J. Allergy. Clin. Immunol. 2010;125:1146-1153.

[111] Watz H, Mistry SJ, Lazaar AL; IPC101939 investigators. Safety and tolerability of the inhaled phosphodiesterase 4 inhibitor GSK256066 in moderate COPD. Pulm. Pharmacol. Ther. 2013;26:588-595.

Table of abbreviations:
AC: adenylyl cyclase
ACO: asthma and COPD overlap
ADRB2: β_2-AR gene
ASM: airway smooth muscle cell
ATP: adenosine triphosphate
AUC24: concentration-time curve over 24 h post-dose
β_2-ARs: β_2-adrenergic receptors
BAL: bronchoalveolar lavage
Ca^{2+}: intracellular calcium ion
cAMP: cyclic 3'5'adenosine monophosphate+
COPD: chronic obstructive pulmonary disease
CBP: CREB binding protein
C/EBPα: CAAT/enhancer-binding protein alpha
CRE: cAMP response element
CREB: cAMP response element binding protein
CVD: cardiovascular disease
CYP: cytochrome P450
DNA: deoxyribonucleic acid
DPI: dry powder inhaler
ERK: extracellular signal-regulated kinases
FEV_1: forced expiratory volume in one second
FF: fluticasone furoate
FF/VI: fluticasone furoate/vilanterol
FP: fluticasone propionate

Downloaded by [Imperial College London Library] at 01:13 29 September 2017

Accepted Manuscript

FP/SAL: fluticasone propionate/salmeterol
GPCR: G protein coupled receptor
GR: glucocorticoid receptors
GRα: glucocorticoid receptor isoform alpha
GRβ: glucocorticoid receptor isoform beta
GREs: glucocorticoid response elements
GRK: G protein-coupled receptor kinase
GRK2/3: G protein coupled receptor kinases 2/3
HDAC-2: histone deacetylase 2
HPLC: high-performance liquid chromatography
ICSs: inhaled corticosteroids
IMPACT: InforMing the PAthway of COPD Treatment
LABAs: long-acting β_2-agonists
LAMAs: long-acting muscarinic antagonists
MAPK: mitogen-activated protein kinase
MCID: minimal clinically important difference
MKP1: MAPK phosphatase
MLCK: myosin light chain kinase
mRNA: messenger ribonucleic acid
MS: mass spectroscopy
NF-κB: nuclear factor kappaB
NHS: National Health Service
PBMCs: peripheral blood mononuclear cells
PI: phosphoinositide
PI3Kδ: phosphoinositide-3-kinase isoform delta
PKA: cAMP-dependent protein kinase A
PKC: protein kinase C
QTc: corrected QT
QTcF: QT interval corrected using Fridericia's correction
RRA: relative receptor affinity
SGRQ: St. George's Respiratory Questionnaire
SUMMIT: Study to Understand Mortality and Morbidity in COPD
ULABAs: ultra-long-acting β_2-agonists
ULAMA: ultra-long acting antimuscarinic
VI: vilanterol
$wmFEV_1$: weighted mean FEV_1

Downloaded by [Imperial College London Library] at 01:13 29 September 2017

Accepted Manuscript

Table 1

Table of abbreviations:
AC: adenylyl cyclase
ACO: asthma and COPD overlap
ADRB2: β_2-AR gene
ASM: airway smooth muscle cell
ATP: adenosine triphosphate
AUC24: concentration-time curve over 24 h post-dose
β_2-ARs: β_2-adrenergic receptors
BAL: bronchoalveolar lavage
Ca^{2+}: intracellular calcium ion
cAMP: cyclic 3'5'adenosine monophosphate+
COPD: chronic obstructive pulmonary disease
CBP: CREB binding protein
C/EBPα: CAAT/enhancer-binding protein alpha
CRE: cAMP response element
CREB: cAMP response element binding protein
CVD: cardiovascular disease
CYP: cytochrome P450
DNA: deoxyribonucleic acid
DPI: dry powder inhaler
ERK: extracellular signal-regulated kinases
FEV_1: forced expiratory volume in one second
FF: fluticasone furoate
FF/VI: fluticasone furoate/vilanterol
FP: fluticasone propionate
FP/SAL: fluticasone propionate/salmeterol
GPCR: G protein coupled receptor
GR: glucocorticoid receptors
GRα: glucocorticoid receptor isoform alpha
GRβ: glucocorticoid receptor isoform beta
GREs: glucocorticoid response elements
GRK: G protein-coupled receptor kinase
GRK2/3: G protein coupled receptor kinases 2/3
HDAC-2: histone deacetylase 2
HPLC: high-performance liquid chromatography
ICSs: inhaled corticosteroids
IMPACT: InforMing the PAthway of COPD Treatment
LABAs: long-acting β_2-agonists
LAMAs: long-acting muscarinic antagonists
MAPK: mitogen-activated protein kinase
MCID: minimal clinically important difference
MKP1: MAPK phosphatase
MLCK: myosin light chain kinase
mRNA: messenger ribonucleic acid
MS: mass spectroscopy
NF-κB: nuclear factor kappaB
NHS: National Health Service
PBMCs: peripheral blood mononuclear cells
PI: phosphoinositide

Downloaded by [Imperial College London Library] at 01:13 29 September 2017

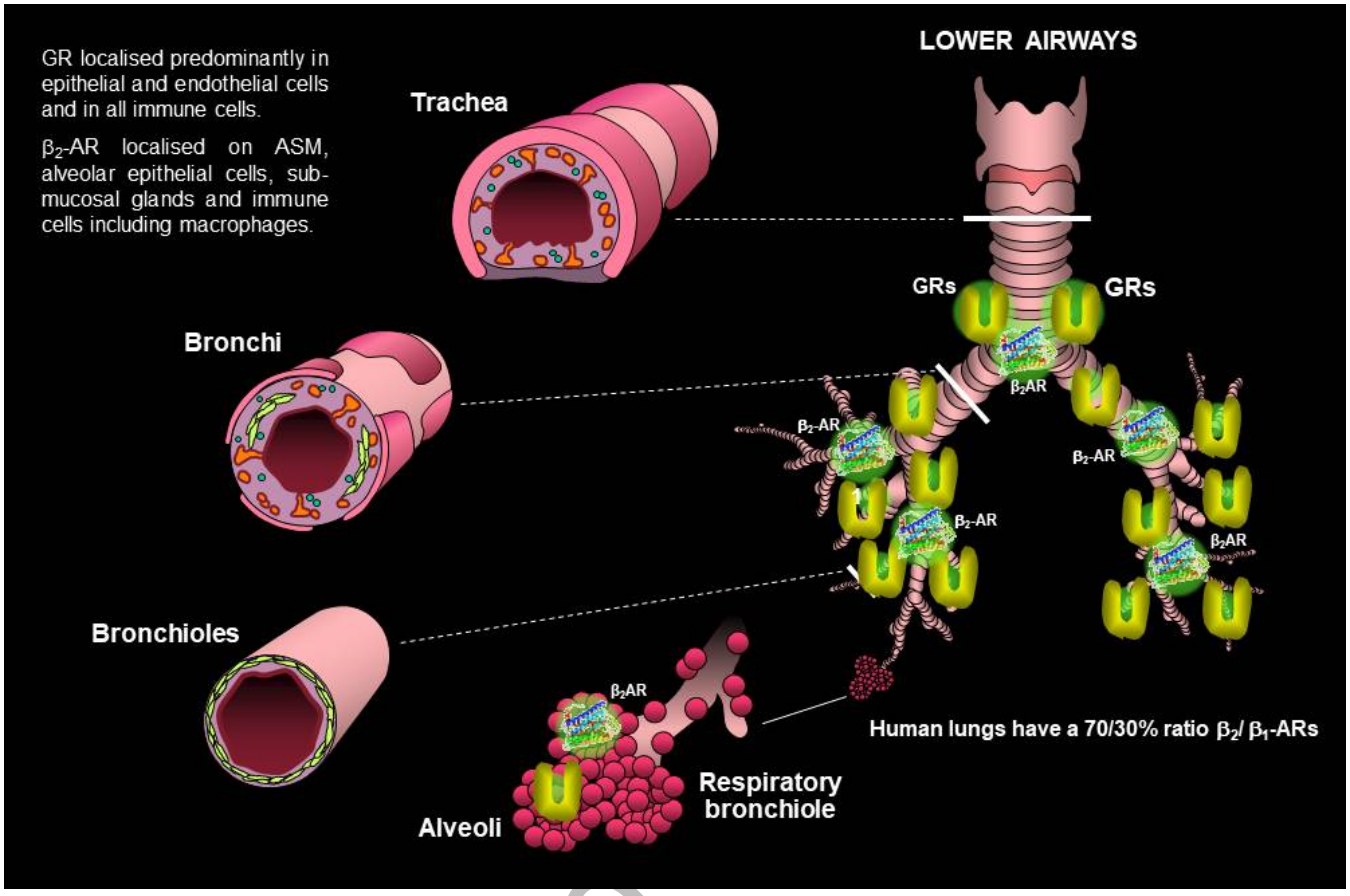
Accepted Manuscript

PI3Kδ: phosphoinositide-3-kinase isoform delta
PKA: cAMP-dependent protein kinase A
PKC: protein kinase C
QTc: corrected QT
QTcF: QT interval corrected using Fridericia's correction
RRA: relative receptor affinity
SGRQ: St. George's Respiratory Questionnaire
SUMMIT: Study to Understand Mortality and Morbidity in COPD
ULABAs: ultra-long-acting β_2-agonists
ULAMA: ultra-long acting antimuscarinic
VI: vilanterol
wmFEV_1: weighted mean FEV_1

Downloaded by [Imperial College London Library] at 01:13 29 September 2017

Accepted Manuscript

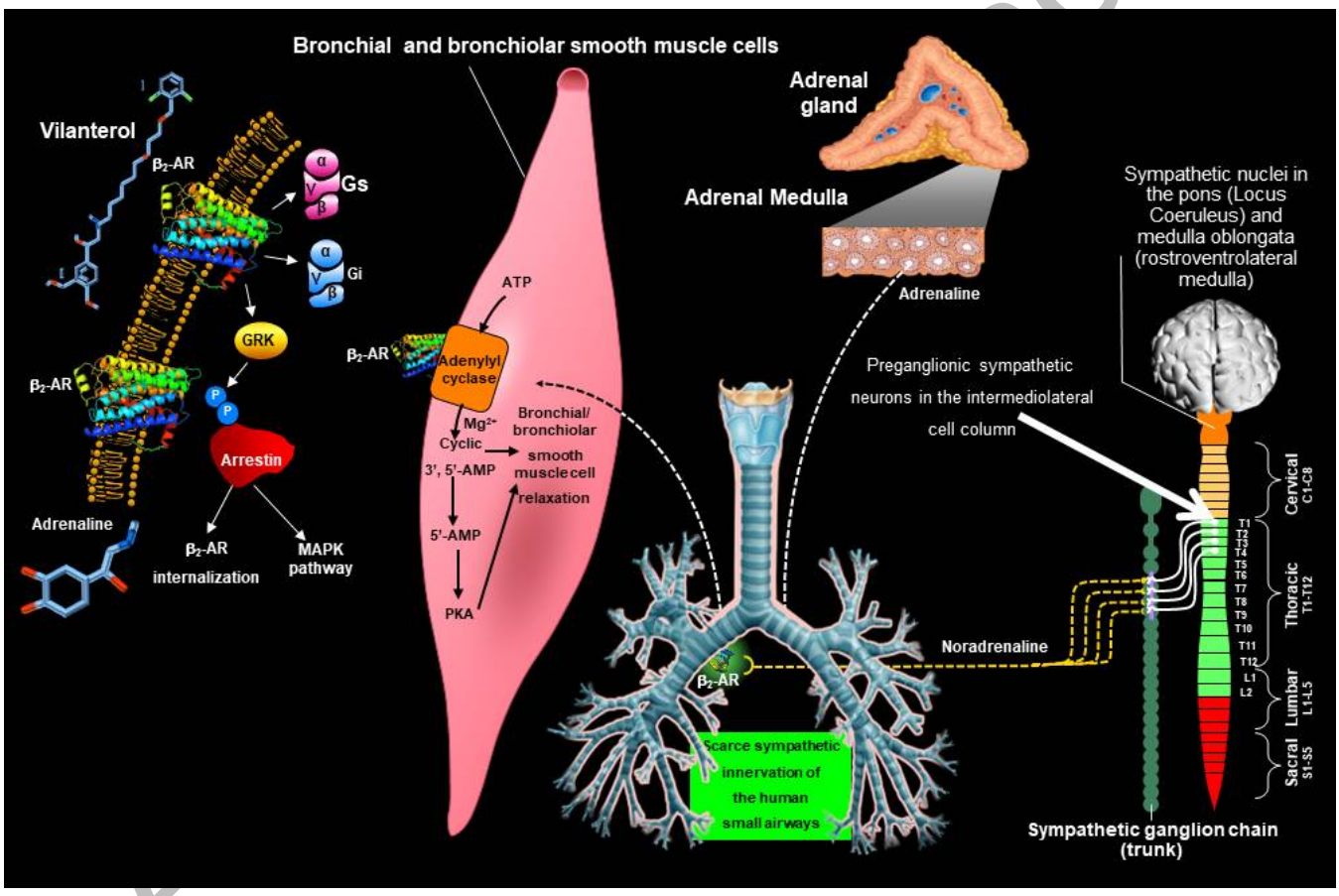
Figure 1: Glucocorticoid receptors (GRs) and beta-2-adrenergic receptors (beta-2-ARs) are widely distributed in both the structural and inflammatory cells of the lower airways of normal subjects and patients with stable COPD. ASM=airway smooth muscle cells.



Downloaded by [Imperial College London Library] at 01:13 29 September 2017

Accepted

Figure 2: Summary of the adrenergic/noradrenergic pathways in the lower airways and of the molecular mechanism of action of inhaled beta-2-agonists (including vilanterol) on bronchial and bronchiolar smooth muscle cells. The central sympathetic nuclei located in the brain stem [pons (locus coeruleus) and medulla oblongata (rostroventrolateral medulla)] modulate the activity of the sympathetic preganglionic neurons of the spinal cord. Motor efferent sympathetic preganglionic nerve fibers originate in the sympathetic preganglionic neurons located in the intermediolateral cell column of the first four thoracic metamers of the spinal cord and terminate into the sympathetic ganglionic chain at the level of the trunk where modulate the activity of the sympathetic postganglionic neurons. The motor efferent sympathetic postganglionic nerve fibers innervate mainly the central lower airways, whereas there is scarce sympathetic innervation in the human small airways. Their activation causes bronchodilation by releasing the neurotransmitter noradrenaline that stimulates the beta-2-adrenergic receptors (beta-2-ARs) (so termed because are also activated by the adrenaline released in the blood by the medullary portion of the adrenal glands) located on the cell membrane of the bronchial and bronchiolar smooth muscle cells. Ligand binding of adrenaline or noradrenaline to the beta-2-ARs results in activation of receptor-associated G-stimulatory (Gs) proteins and enhanced coupling with the enzyme adenylyl cyclase (AC) and stimulation of the G protein-coupled receptor kinase (GRK). The coupling of activated Gs and adenylyl cyclase leads to increased production of cyclic 3'5'adenosine monophosphate (cAMP) and subsequent activation of cAMP-dependent protein kinase A (PKA), which then phosphorylates several target proteins which result in relaxation of the smooth muscle cell. ATP=adenosine triphosphate. MAPK=mitogen-activated protein kinase. For a more detailed explanation of the molecular mechanisms of action of beta-2-agonists please refer to the text.



Downloaded by [Imperial College London Library] at 01:13 29 September 2017