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# Why small particle fixed dose triple therapy? An excursus from COPD pathology to pharmacological treatment evolution

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***Abstract*:** Although bronchodilators are the cornerstone in chronic obstructive pulmonary disease (COPD) therapy, the treatment with a single-agent bronchodilator may not provide adequate symptoms control in COPD. The combination of drugs with different mechanisms of action may be more effective in inducing bronchodilation and preventing exacerbations, with a lower risk of side-effects in comparison with the increase of the dose of a single molecule. Several studies comparing the triple therapy with the association of long-acting ß$_2$ agonist (LABA)/inhaled corticosteroid (ICS) or long-acting muscarinic antagonist (LAMA)/LABA reported improvement of lung function and quality of life. A significant reduction in moderate/severe exacerbations has been observed with a fixed triple combination of beclometasone dipropionate (BDP), formoterol fumarate (FF) and glycopyrronium (G) in a single inhaler. The TRILOGY, TRINITY and TRIBUTE studies have provided confirming evidence for a clinical benefit of triple therapy over ICS/LABA combination treatment, LAMA monotherapy and LABA/LAMA combination, with prevention of exacerbations being a key finding. A pooled post hoc analysis of the published clinical studies involving BDP/FF/G fixed combination demonstrated a reduction in fatal events in patients treated with ICS-containing medications, with a trend of statistical significance [hazard ratio = 0.72, 95% confidence interval (CI) 0.50–1.02, $p = 0.066$], that becomes significant if we consider reduction in fatal events for non-respiratory reasons (hazard ratio = 0.65, 95% CI 0.43–0.97, $p = 0.037$). In conclusion, a fixed combination of more drugs in a single inhaler can improve long-term adherence to the therapy, reducing the risk of exacerbations and hospital resources utilization. The twice a day administration may provide a better coverage of night, particularly in COPD patients who are highly symptomatic. The inhaled extrafine formulation that allows drug deposition in both large and small – peripheral – airways, is the value added.

***Keywords:*** COPD, inhaled extrafine formulation, triple therapy

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## Introduction

With its worldwide prevalence of 9–10% in people over the age of 40,[1–4] chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality, and it is increasing especially in countries with aging population and rise in smokers' number[2]: by estimates, in 2030, COPD could become the third cause of death worldwide.[3] COPD generates a significant burden in terms of disability and impaired quality of life (QoL), as well as huge health care costs.[2]

In COPD patients, the physiological inflammatory response of the respiratory tract to chronic irritants seems to be altered and increased, maybe for genetic factors.[1] The chronic inflammation causes narrowing of the small airways and destruction of the pulmonary parenchyma, with progressive thickening of small airway walls and rising of

the resistances; the fixed obstruction leads difficult expiration and hyperinflation, with a progressive decline of $FEV_1$.[5,6]

As confirmed in the TORCH study,[7] $FEV_1$ decline is fast especially during the earliest phases of COPD, in particular, in GOLD stages II and III, compared with stage IV.[8] Smoking cessation is the cornerstone of the treatment, and it is the only intervention that can favorably impact the course of the disease: The Lung Health Study reported that patients with mild COPD who stopped smoking had a lower $FEV_1$ decline over the 5-year follow-up period, compared with patients who did not.[9] Therefore, smoking patients should be encouraged to stop and should have access to specific support programs.

Despite the recommendations on the use of drug therapy in patients with moderate to severe COPD,[1] more than 70% of patients in the Medicare population are not receiving maintenance therapy, with a clear need for improvement in the management of patients with COPD.[10] Exacerbations of the disease represent the major factors of economic burden and, depending on their severity, may require access to Emergency Departments (EDs) and hospitalization.[11–14] It is therefore necessary to define new therapeutic strategies that allow a reduction in the frequency of exacerbations. This review discusses the most appropriate treatments that can improve patients' outcome and reduce health care costs.

## What do we aim at when treating COPD, and how do we treat it?

The goals of COPD treatment are to stop the increase of the airflow limitation, to improve the patient's general health status and to reduce the risk of future events (such as exacerbations, hospital admissions or death).[1]

According to *Global initiative for chronic Obstructive Lung Disease* (*GOLD*), the overall severity of the disease is assessed with the combination of two aspects: symptoms evaluated with COPD Assessment Test (CAT) or dyspnea assessed with Modified British Medical Research Council (mMRC) Questionnaire, and risk of exacerbations based on past events.[1] Severity and recurrence of exacerbations are inversely related to patient QoL,[15] and are the most relevant prognostic factors for COPD, particularly if they require hospitalization.[16] The most reliable predictor for exacerbations is the number of patient's previous exacerbation episodes,[16] and it correlates with the speed of progression of lung function impairment[17,18]; frequent exacerbators have a faster $FEV_1$ decline compared with infrequent exacerbators.[19] Finally, the exacerbations have an independent negative impact on the mortality rate,[20,21] with a 1-year mortality rate of 37% in patients hospitalized for recurrent acute exacerbation.[22]

At present, there is no conclusive evidence from clinical studies that any of the available treatment for COPD is able to change long-term decline in lung function.[1] The choice of treatment should be individualized, and the cost benefit ratio assessed, on the basis of the clinical picture (i.e. severity of symptoms, blood eosinophilia, number and severity of exacerbations, possible comorbidities), as well as drug(s) availability and their cost, and ability of the patient to use the devices.[1]

A patient with COPD is characterized by a high number of comorbidities[23]: dyslipidemia/metabolic syndrome, psychiatric conditions like anxiety and depression, cardiovascular diseases (CVDs) like ischemic heart disease, heart failure and arrhythmias, cognitive impairment, lung cancer, sarcopenia/cachexia, osteoporosis and gastroesophageal reflux. In 213 patients enrolled in the CIROCO study, the prevalence of comorbidities has been found in 97.7% of patients, and 54% of them had $\geqslant$4 comorbidities.[24] Mediators of inflammation can cause sarcopenia/cachexia, osteoporosis worsening, anemia, diabetes and metabolic syndrome,[1,23] and could be responsible for the higher risk of CVDs.[25,26] The prevalence of COPD in CVD patients, as well as the prevalence of CVD in COPD, are higher than in general population.[25,27] CVDs, osteoporosis and depression/anxiety are related to poor health status and prognosis, and gastroesophageal reflux is associated with an increased risk of exacerbations.[1]

The patients with concomitant diseases need multiple and specific treatments exposing them to the risk of interactions: a retrospective study on hospitalized COPD patients found that they were prescribed an average number of six drugs at the admission and seven at the discharge.[28] Therefore, the choice of drugs with which this risk is as low as possible becomes crucial.

Cotreatments complicate patient management, and lead to poor adherence and compliance, added on the scarce adherence generally observed in COPD. Moreover, COPD patients have a higher risk of cognitive impairment compared with general population, and several authors have reported a prevalence of more than 30% in comparison with 10–12% in non-COPD patients[29,30]; this is true especially in hypoxemic patients, among whom a prevalence of 77% of cognitive impairment has been reported.[31] Also, anxiety and depression are frequently associated with COPD with a double incidence compared with patients without COPD.[32] Also, these conditions are associated with a worse prognosis, poor QoL and decrease in adherence to the treatment.[1,33]

The cornerstone of COPD therapy are inhaled bronchodilators, but this way of administration could present some further problems compared with others.

The issues of an ineffective inhalation in COPD patients include old age, airflow limitation, use of numerous devices and lack of a previous education on the inhalation technique.[34,35] Purely by way of example, many patients struggle to inhale from their device. In a retrospective analysis of 123 hospitalized patients enrolled in an acute exacerbations of Chronic Obstructive Pulmonary Disease (AECOPD), care plan was specified to study the impact of PIF (peak inspiratory flow) on readmission after hospitalization. And a suboptimal PIF (defined as PIF $\leqslant$ 60 l/min) was found in 52% of patients. A PIF of less than or equal to 60 l/min can be a problem with some dry powder inhalers.[36] Non-adherence is a frequent issue in chronic diseases, particularly in COPD.[37,38] In a retrospective study, Rolnick *et al.*[39] reported that among several chronic diseases, COPD showed the lowest degree of adherence, about 30%, compared with more than 75% for hypertension, dyslipidemia, multiple sclerosis and cancer; 62% for depression; and 51% for diabetes, but there are published more pessimistic estimations, like 16% in real-life patients found by other authors.[40] Poor adherence is associated with a worse prognosis and a lower survival rate,[41] as shown in the TORCH study, where the overall 3-year mortality resulted lower for patients with good adherence (defined as >80% use of the study medications), compared with patients with poor adherence (11.3% *versus* 26.4%).[42]

Adherence to the prescribed regimens and medical recommendations is influenced by several factors, patient related (cognitive, emotional and psychological profile), social (support, training, drug access) and treatment related, like tolerability, dosing, method of administration and multiple treatments.[37] In COPD, as well as in asthma, there are also difficulties linked to inhaler type and inhalation technique.[38] Unintentional nonadherence plays an important role in the treatment of COPD, where a correct use of an inhaler is needed.[38] Inhaler misuse seems to increase with age and severity of obstruction.[43,44] A retrospective observational cohort study on 289,176 COPD patients showed that the use of multiple inhalers is significantly associated with a greater discontinuation rate compared with single inhaler therapy.[45,46] Many different new devices have been developed and commercialized in order to deliver new drug formulations, but their complexity contributes to the difficulty of inhalation technique, especially in elderly and poorly trained patients.[44] Remarkably, switching to a different inhaler is a key factor impacting adherence: regardless of the reasons that led to this choice, patients have to be clearly informed and must test the new inhaler.[38] From this perspective, fixed combinations of more drugs in a single inhaler can support long-term adherence to the therapy, contributing to a better outcome for the patient.[46–48] A high proportion of COPD patients are highly symptomatic during the night and when they wake up in the morning.[49] Some studies suggest a greater coverage of symptoms and respiratory function during the night with drugs administered twice a day *versus* similar drugs given once a day.[50,51] In COPD, the involvement of the peripheral airways is substantial, and it could be useful to have inhaled extrafine formulations (Mass Median Aerodynamic Diameter, MMAD $<$ 2 μm) that allow drug deposition in both large and small airways.[1,52]

### *Treatment strategies*

Although inhaled bronchodilators are the cornerstone in COPD therapy, the treatment with a single bronchodilator may not provide adequate symptoms control in COPD. The combination of drugs with different mechanisms of action may be more effective in inducing bronchodilation and preventing exacerbations, with a lower risk of side-effects in comparison with the increase of the dose of a single molecule.[1,53–55] The pharmacological

rationale for the superior clinical effect of the combination of a long-acting ß$_2$ agonist (LABA) and an inhaled corticosteroid (ICS) is that corticosteroids increase the expression of ß$_2$ receptors, counteracting their down regulation resulting from the long-term treatment; on the contrary, ß$_2$-agonists potentiate the anti-inflammatory effect of corticosteroids, reducing plasma exudation and inhibiting the release of cytokines from inflammatory cells.[56–58] From a clinical point of view, a meta-analysis on nine studies, which included 9921 randomized patients, calculated that the combination therapy of ICS/LABA allowed an overall 24% reduction in exacerbations over LABA monotherapy, and an improvement of dyspnea, symptoms, rescue medication, as well an increase of $FEV_1$, with a resulting improvement of health-related QoL.[54] We have no published clinical data on the efficacy of fixed ICS with long-acting muscarinic antagonist (LAMA) combinations, although that, conceptually, could be an excellent therapeutic alternative: in human isolated bronchi and bronchioles of passively sensitized airways, the administration of beclometasone and glycopirronium shows a synergistic interaction in preventing the reduction of cAMP caused by histamine, inducing a significant relaxation of smooth muscle.[59]

Beclometasone 17,21-dipropionate (BDP) is a pro-drug characterized by a low receptor affinity. It requires cleavage of the C-21 ester by esterase enzymes to be metabolized to 17-BMP, a highly pharmacologically active glucocorticoid with a 27-fold higher receptor affinity than BDP.[60–62] When inhaled, 97% of the BDP is rapidly transformed into 17-BMP mainly in the bronchopulmonary tissues. Only a little amount of BDP is metabolized to the active 17-BMP by liver esterases, which are much less efficient than pulmonary enzymes. For this reason, a very low amount of active metabolite is found in the systemic circulation (where it is bound for about 90% to the plasmatic proteins), with an extremely high clearance, and a distribution volume of 424 L. This confirms that the drug is mainly present in the tissues (especially in the lung) and little in the systemic circulation, with a significant reduction of the risk of systemic side-effects.[60,63] Moreover, BDP catabolism is less dependent on cytochrome P4503A (CYP3A), compared with other ICSs, such as betamethasone, budesonide, fluticasone propionate (FP), fluticasone furoate (FluF), flunisolide, mometasone and triamcinolone. This causes a lower probability of systemic side-effects from over-dosing to occur when BDP is co-administered with CYP3A45 inhibitors as recognized by the European Medicines Agency in October 2016.[63] For all these reasons, BDP could be particularly useful for COPD patients, who typically have a high number of comorbidities and, therefore, are treated with many medicines.

The pharmacodynamic rationale of LABA/LAMA combinations is their synergistic action based on the fact that the respective receptors have a different location and they relax the airway smooth muscles following separate pathways.[57,64] The $M_3$ receptors are predominant in the bronchial smooth muscles and on the mucus producing cells, their number decreases distally (from segmental to subsegmental bronchi), and they are not present in the lung parenchyma.[65,66] On the contrary, ß$_2$ receptors are located in all the bronchial tree, but in greater number distally on alveolar cells, and their stimulation induces regulation of $Na^+$, with clearance of excess fluid and inhibition of endothelial cells contraction.[67] The combined action of LABA/LAMA enhances the synthesis of cAMP in the airways smooth muscles and inhibits the release of non-neuronal acetylcholine (secreted by the bronchial epithelium),[58] resulting in a faster and more powerful relaxation of medium and small airways than the single drugs[57,58,65–67] as confirmed by a large meta-analysis.[57]

In the last decades, the use of triple therapy LABA/LAMA/ICS has been increasing,[68] and in clinical practice, triple therapy is suggested for COPD patients in all the GOLD classes.[69] A very recent publication exploring the prevalence and predictors leading to free-triple prescription in Italy accessing a national GP database reported about 21% of patients being progressively switched to triple therapy during a median follow-up of 4.5 years from the initiation of any COPD therapy. Significant factors predicting the future use of triple therapy were older age, being current or former smoker, a more severe GOLD COPD stage, and a history of previous moderate and severe exacerbations.[70]

Several studies have compared different triple therapy with the association of LABA/ICS or LAMA/LABA, unanimously reporting improvement of lung function and QoL.[71,72] The clinical benefit obtained with free-triple therapy, however, did not seem to be transferred into advantages over the exacerbation rate. The GLISTEN

study, despite the improvement in lung function and QoL, and reduction in symptoms and rescue medications, did not report any difference in exacerbation rate between the treatments.[72]

In a very recent publication by Rogliani *et al.*,[73] the synergistic interaction of BDP/formoterol fumarate (FF)/Glycopyrronium (G) fixed combination has been demonstrated *ex vivo* on human passively sensitized airways, and bronchi from COPD donors were stimulated with histamine or carbachol.

On these bases, some randomized trials explored the fixed triple therapy of BDP/FF/G compared with a LABA/ICS[74,75] or with a LABA/LAMA combination,[76,77] reporting a significant reduction in moderate/severe exacerbations without an increase of adverse events. In the TRIDENT study, the combination of BDP/FF/G showed greater improvement of the forced expiratory volume within 1 s ($FEV_1$), reduced exacerbation rate and improved health-related QoL compared with a dual fix-combination of ICS/LABA.[78]

This combination of BDP/FF/G, at the dose of 87, 5 and 9 μg, respectively, has been developed in a single inhaler, with the aim to facilitate treatment scheme and adherence.

The recommended posology is two inhalations twice daily for a total daily dose of 348, 20 and 36 μg (80 ema). It has been demonstrated that twice a day administration of respiratory drugs is more effective in stabilizing the lung function during the 24 h and in improving severity of nighttime symptoms and number of nocturnal awakenings if compared with respiratory drugs administered once a day.[50,51] In this respect, a strong correlation between sleep disorders (CASIS score) and heterogeneity of peripheral ventilation (R5-R20) was detected in COPD patients.[79]

With the particular technology of the formulation (MODULITE®) patented by Chiesi Farmaceutici S.p.A., the BDP/FF/G combination is delivered as an aerosol with extrafine particle size (MMAD $< 2$ μm), that allows homogeneous deposition of drugs in all the respiratory tract, with high deposition in the small airways.[80] Recently, lung deposition of extrafine BDP/FF/G combination compared with non-extrafine FluF/vilanterol/umeclidinium (FluF/VI/UMEC) was estimated by functional respiratory imaging.[81] Intrathoracic deposition of BDP was higher than FluF, while the two triple therapies had similar performances for both LABA and LAMA components. Peripheral deposition of all components was higher with BDP/FF/GB than FluF/VI/UMEC. Furthermore, the ratios of central to peripheral deposition for all three components of BDP/FF/GB were $<1$, indicating greater peripheral deposition, while these ratios were $>1$ for all FluF/VI/UMEC components, indicating higher central deposition. This is a further evidence of the effectiveness of extrafine combinations in reaching the whole bronchial tree, from central to peripheral airways.

Finally, the use of an extrafine solution results in lower but equivalent dose of ICS and, consequently, in lower systemic exposure to ICS compared with the aerosol inhalation of the same ICS, but delivered by non-extrafine formulation.[82,83]

The BDP/FF/G fixed extrafine combination has been developed in COPD through an extensive program that has included about 8000 patients worldwide. After the pharmacokinetic and dose-finding studies, three large trials have been conducted, two in phase III (TRILOGY and TRINITY) and one in phase IIIB (TRIBUTE). The two phase III studies TRILOGY and TRINITY[74,84] evaluated the safety and efficacy of extrafine BDP/FF/G *versus* an BDP/FF combination (in TRILOGY study), and *versus* tiotropium monotherapy and an extemporary triple combination of BDP/FF plus tiotropium (in TRINITY study). The studies had very similar inclusion criteria: symptomatic patients with CAT $\geq 10$, Baseline Dyspnea Index $\geq 10$ (in TRILOGY), $FEV_1 < 50\%$ and $FEV_1/FVC < 0.7$ post bronchodilators, a COPD diagnosis $\geq 12$ month prior the screening and at least one moderate exacerbation within 12 months before screening. The duration of the treatment was 52 weeks for both studies, and this has been considered by regulatory agencies as the most appropriate period to properly evaluate the efficacy of the therapies.[80] The fixed triple therapy resulted superior to single agent and double combination, in increasing $FEV_1$ and in reducing the exacerbation adjusted annual rate, and in both studies, a statistically significant and clinically relevant reduction of St George's Respiratory Questionnaire (SGRQ) total score has been observed for the BDP/FF/G group *versus* the comparators.[74,84]

In summary, TRILOGY has been the first long-term study comparing the triple therapy ICS/LABA/LAMA in only one inhalator with the corresponding fixed combination ICS/LABA. The triple therapy has shown a better bronchodilator activity over the whole length of the study, a statistically significant reduction of moderate/severe exacerbations, a longer time to first exacerbation and a greater improvement of health-related QoL, in patients with severe/very severe COPD and a history of exacerbations.[74] TRINITY study has shown that the triple therapy BDP/FF/G is superior to tiotropium in decreasing the rate of moderate/severe exacerbations and improving the pre-dose $FEV_1$ and QoL *versus* baseline and, as expected, is not inferior than BDP/FF + tiotropium.[84] Surprisingly, in the subgroup of frequent exacerbators (⩾2 exacerbations in the year prior to the study), the fixed triple combination reduced the number of exacerbations with a clinically and statistically significant difference compared with the open triple combination.[80] This result could be due to the greater peripheral activity of the fixed combination, which differs from the open one, due to the LAMA component, that is, in extrafine formulation. Indeed, a correlation is known between peripheral obstruction and frequency of exacerbations in COPD patients.[85] Moreover, a better synergistic effect can be hypothesized when three active principles are delivered simultaneously in a unique formulation, but this should be proved in specific experimental settings.

The TRIBUTE study has compared extrafine BDP/FF/G (87 μg/5 μg/9 μg) twice a day *versus* one inhalation of IND/GLY (indacaterol/glycopyrronium) (85 μg/43 μg) a day in COPD patients with severe airflow obstruction, post-bronchodilator $FEV_1 < 50\%$, post-bronchodilator $FEV_1/FVC < 0.7$, at least one moderate or severe exacerbation in the previous year. This is certainly a cornerstone study, testing once and for all the benefits of ICS therapy in COPD. The study showed that BDP/FF/G is significantly more effective than IND/GLY in reducing the rate of moderate-to-severe exacerbations ($p = 0.043$) without increasing neither the number of adverse events (64% *versus* 67%) nor the risk of pneumonia (4% each).[76] The increased risk of pneumonia linked to use of ICS in COPD patients is well known[86,87] even if no randomized controlled trials (RCT) found an increase of overall and pneumonia mortality, resulting even reduced in observational trials.[87,88] Although the TORCH study recorded an alarming 19.6% pneumonia percentage in 3 years, a post hoc analysis has found that the risk factors for pneumonia were age > 55 years, $FEV_1 < 50\%$, previous exacerbations, higher dyspnea score and BMI < 25,[89] suggesting that the principal risk factor could be the severity of COPD and not the ICS use. These results have been confirmed by a recent meta-analysis focused on the effect of triple therapy on exacerbation rate.[90]

Head-to-head studies comparing the triple extrafine combination with a non-extrafine triple combination are not available, but we can have some indications from studies of the double combination. As reported by Calverley *et al.*, extrafine BDP/FF is not inferior to a non-extrafine ICS/LABA combination (budesonide/formoterol DPI) in terms of $FEV_1$, but superior in improving predose FVC from baseline to the end of the study, that confirm the greater activity in the peripheral lung district.[92] Patients who were treated with extrafine formulation had significantly greater improvement in the 6 min walking test (6-MWT), which exceeded the threshold for clinical significance (37 m).[91] In the FUTURE study on patients with moderate to severe COPD, the mean $FEV_1$ $AUC_{0\text{-}30min}$ was greater in the extrafine BDP/FF group, compared with the non-extrafine (fluticasone/salmeterol) group, with a faster start of action on day 1 and at the week 12, confirming the more rapid onset of action of formoterol than salmeterol. Moreover, a clinically significant improvement of QoL, greater than 4-unit minimal clinically important difference (MCID) was observed only with extrafine BDP/FF.[92] Another study reported similar results, with a greater efficacy in reducing several measures of hyperinflation (residual volume, total lung capacity and functional residual capacity) compared with FP/salmeterol (FP/S).[93] This trial showed that patients treated with extrafine BDP/F experienced a statistically significant improvement in transition dyspnea index (TDI) total score from baseline, which exceeded the threshold for clinical relevance (+1 points) demonstrating that the clinical benefit observed can be reached using a low dose of ICS.[93]

Only a little amount of BDP is metabolized to the active 17-BMP by liver esterases, which are much less efficient than pulmonary enzymes (Figure 1).

Considering the new revision of the GOLD document 2020,[94] the possibility to step-up to triple in

case of the recurrence of one exacerbation in patients under maintenance therapy with LABA/LAMA or ICS/LABA has been considered also in a sub-analysis of the three studies. The subgroup of patients with one moderate exacerbation in the previous 12 months represented 55.1%, 49.2% and 63.3% of the overall population in TRILOGY, TRINITY and TRIBUTE, respectively. There were no substantial differences between groups in baseline demographics or disease characteristics, either within or among the three studies. The majority of patients (82.0% overall) included in the analyses had severe airflow limitation ($FEV_1$ 30–50% predicted).

The effect of BDP/FF/G on moderate-to-severe exacerbations was consistent across the three studies, with a 23% reduction *versus* BDP/FF (TRILOGY), a 22% reduction *versus* tiotropium (TRINITY), and a 23% reduction *versus* IND/GLY (TRIBUTE).[95]

In line with a recent meta-analysis that considers BDP associated with a non-statistically significant increased risk of pneumonia,[96] in the three pivotal studies, TRILOGY, TRINITY and TRIBUTE, the greater reduction of exacerbations events compared with BDP/F, TIO and IND/GLY was not associated with an increased risk of pneumonia. In the pooled analysis of TRILOGY and TRINITY safety data, the rate of pneumonia (2.9%) resulted lower, compared with the FLAME study, that was performed to indagate efficacy and safety of IND/GLY compared with FP/S (3.2% in IND/GLY group and 4.8% in FP/S group).[97] To complete these figures, in the TRIBUTE study, the incidence of pneumonia was not increased with the addition of BDP to LAMA/LABA.[76] Also, for patient with only one exacerbation occurred in the previous year, safety resulted consistently similar to the comparator drugs. This lower risk of pneumonia has been shown for other ICS extrafine formulations too, and it is probably due to the already commented optimized dose or to the lower lipophilicity of BDP compared with other ICS that results in shorter lung retention and, in turn, less local immunosuppression in the presence of impaired mucociliar clearance and altered lung microbiome, typical of COPD patients.[98,99]

The assessment of the risk–benefit ratio, through the analysis of the three studies, has shown that

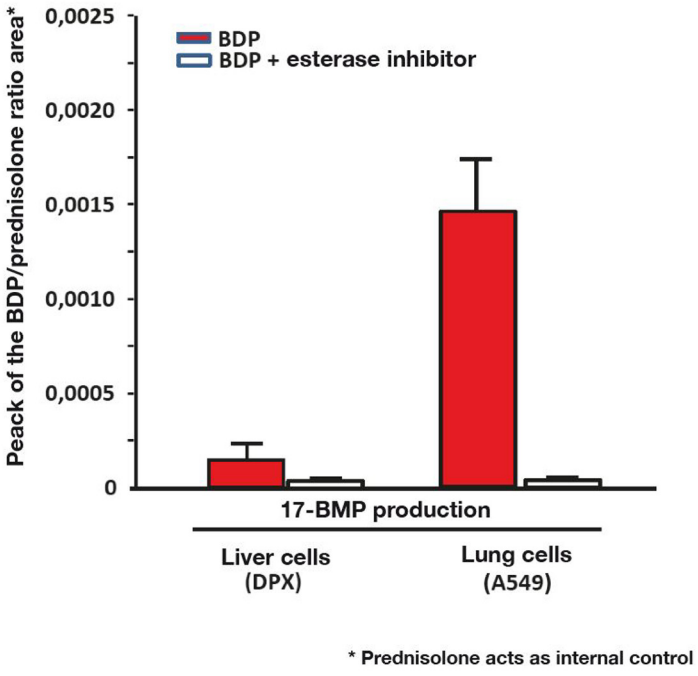


**Figure 1.** Metabolization of BDP to 17-BMP in liver and lung cells.

the number of events of pneumonia has been very low compared with the number of avoided exacerbations.[74,76,84] The benefit (exacerbation reduction)/risk (pneumonia increase) balance was 30 and 60 times in favor of BDP/FF/G, compared with TIO (rate of avoided exacerbations 0.11 events/patient/year *versus* rate of pneumonia increments of 0.0036 events/patient/year in the group with ICS) and IND/GLY (rate of avoided exacerbations 0.09 events/patient/year *versus* rate of pneumonia increments of 0.0015 events/patient/year in the group with ICS), respectively (Figure 2).[76,80,84,100]

We calculated the relative risk (RR) of having a pneumonia event in patients treated with generical triple ICS/LABA/LAMA combinations and with BDP/FF/G fixed combination compared with LABA/LAMA treatment. Comparing ICS/LABA/LAMA with LABA/LAMA, the RR is 1.63 [95% confidence interval (CI) 1.34–1.99, $p < 0.0001$], comparing the BDP/FF/G fixed combination with IND/GLY, the RR is 1.04 (95% CI 0.62–1.75, $p \leqslant 0.88$), which means no risk observed with the extrafine triple combination. Data are taken from Zheng *et al.*,[90] and processed with 'MedCalc® easy-to-use statistical software'.

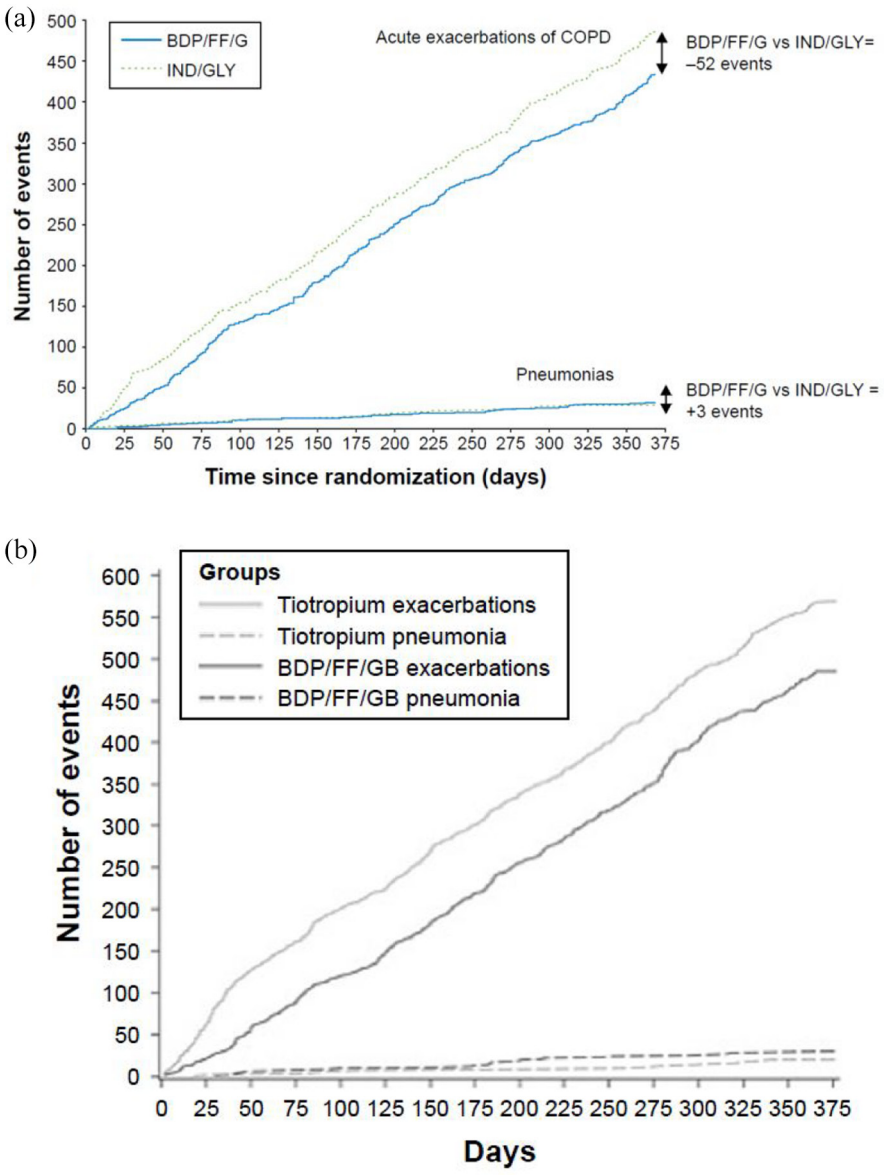


**Figure 2.** Frequency plot considering days in the study *versus* cumulative number of events (COPD moderate/severe exacerbations and pneumonias) in the studies comparing BDP/FF/G *versus* IND/GLY (a) and Tiotropium (b).

### What do RCTs on COPD treatments with extrafine triple combination teach us?

The protocol and the inclusion/exclusion criteria of the TRILOGY, TRINITY and TRIBUTE studies have been thought to include realistic samples of COPD patients: the studies included patients with one or more exacerbations in the previous year, a severe or very severe degree of obstruction, and most of the enrolled patients (more than 80%) had at least one concomitant disease. The analysis of subgroups indicated the efficacy of BDP/FF/G in reducing exacerbations *versus* comparators both in patients with one exacerbation, and in patients with two or more exacerbations in the previous year.[80,94] It showed efficacy in reducing exacerbations, irrespective of the frequency of events in the previous year; this is in contrast with GOLD recommendations, that assign COPD initial therapy according to the frequency of exacerbations in the previous year; however, as far as we know, these indications are not supported by published data. Anyway, the

GOLD document's recent revision suggests the opportunity to use triple therapy in case of a new exacerbation episode in patients being treated by dual combinations. Despite the high severity of obstruction and high prevalence of comorbidities in the enrolled patients of the mentioned studies, there was not, in principle, an increase of cardiovascular or other adverse events in both groups, as a confirmation of the relative safety of the inhaled drugs used in COPD therapy.[74,76,84] At this time, there are evidences derived about the effect of ICS-base treatments on mortality in COPD patients.[101,102] Along this line, note that a pooled post hoc analysis of the published clinical studies involving BDP/FF/G fixed combination was performed, demonstrating a reduction in fatal events in patients treated with ICS-containing medications, with a trend of statistical significance (hazard ratio = 0.72, 95% CI 0.50–1.02, $p = 0.066$), that becomes significant if we consider reduction in fatal events for non-respiratory reasons (hazard ratio = 0.65, 95% CI 0.43–0.97, $p = 0.037$).[103,104]

In conclusion, a fixed combination of three drugs in a single inhaler can improve long-term adherence to the therapy, reducing the risk of exacerbations and hospital resources utilization. The twice a day administration may provide a better coverage at night, particularly in highly symptomatic COPD patients. The inhaled extrafine formulation that allows drug deposition in both large and small – peripheral – airways, is the added value.

## Author contributions

**Fulvio Braido:** Conceptualization; Investigation; Writing – original draft.

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**Nicola Scichilone:** Conceptualization; Investigation; Writing – original draft.

## Conflict of interest statement

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