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REVIEW

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Indacaterol/glycopyrronium/mometasone fixed dose combination for uncontrolled asthma

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ABSTRACT

Introduction: Asthma symptoms can be relieved through a maintenance treatment combining long-acting β_2-agonist and inhaled corticosteroids (LABA/ICS). However, for patients with inadequately controlled asthma, the LABA/ICS combination might not be sufficient, and clinical guidelines recommend the administration of inhaled long-acting muscarinic antagonists (LAMA) as an add-on therapy to better control asthma and improve lung function. For nearly two decades, the only LAMA to be approved on the market has been tiotropium.

Areas covered: We reviewed recent clinical studies evaluating the safety and efficacy of LABA/LAMA/ICS fixed dose combinations by searching the PubMed database. Molecular mechanisms and clinical data support the use of a once-daily, single-inhaler fixed dose combination of the LABA/LAMA/ICS indacaterol/glycopyrronium/mometasone (IND/GLY/MF), the first therapy combining three agents in a fixed dose approved in Europe for the treatment of uncontrolled asthma.

Expert opinion: IND/GLY/MF was superior to both IND/MF and salmeterol/fluticasone, a well-established LABA/ICS combination improving the lung function in uncontrolled asthma. Moreover, IND/GLY/MF, delivered through the Breezhaler inhaler in a single inhalation, is the first inhaled therapy prescribed alongside a digital companion, a sensor and the Propeller app, allowing for improved treatment adherence, reduced rescue inhaler usage and hospitalizations, increased patient satisfaction and asthma control.

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1. Introduction

1.1. Asthma: pathogenesis and treatment

Asthma is a disease involving chronic airway inflammation, reversible airway obstruction, bronchial hyperreactivity, and airways remodeling [1]. Asthma is characterized by a complex relationship between inflammation, which represents the central component, airway hyper-responsiveness, and remodeling. Moreover, asthma can be triggered by different stimuli and can have an early or late-onset. The clinical characteristics of individuals led to the definition of asthma phenotypes and endotypes that allowed clinicians to titrate personalized therapy targeting specific pathways [1]. Several phenotypic groups are defined by treatable or untreatable traits, measurable parameters, and risk predictors and are currently used for the stratification of asthma patients [2]. However, the definition of a phenotype does not always correlate to or give insights into the underlying pathogenic mechanisms, which are associated with the disease endotypes. We can distinguish three different endotypes in relation to the biological and inflammatory mechanisms involved: type 2 high, type 2 low, and mixed [3].

The main goal of asthma management is the reduction of individual risk factors, prevention of flares and symptoms control, assuring optimal lung functionality and management of comorbidities. The first-line therapy in all patients with persistent asthma is the treatment with low dose inhaled corticosteroids (ICS) [1]. In addition, short-acting beta agonists (SABAs) or low dose ICS-formoterol can be used as a reliever inhaler. If symptoms are difficult to control and/or lung function is declining, the combined administration of ICS and long-acting β_2 agonists (LABA) or an increased dose of ICS is required. Moreover, the recently introduced combination of LABA/ICS and long-acting muscarinic antagonists (LAMA) can be also considered for the treatment. The addition of oral corticosteroids could be considered in selected uncontrolled patients [1] affected by severe asthma (SA) [4,5]. Multiple biologics targeting the Th2 pathway should be considered as add-on treatment after analyzing SA treatable or untreatable traits, measurable parameters, and risk predictors [3].

All these interventions have shown a consistent effect on decreasing asthma exacerbations [6,7].

By screening the PubMed database, we reviewed the most recent clinical studies evaluating efficacy and safety of LABA/

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Article highlights

- Despite the available treatments, there is still a proportion of patients who suffer from uncontrolled asthma.
- The introduction of the therapies combining three agents (a corticosteroid, a LABA, and a LAMA) represents a step forward in the treatment of moderate-to-severe asthma
- The therapy combining IND/GLY/MF in a single daily fixed dose is clinically effective and safe, allowing the improvement of lung function and reduction of asthma exacerbation rate.
- The positive effect is guaranteed by the different mechanisms of action of the principles on bronchodilation and on inflammation.
- The IND/GLY/MF therapy is the first treatment that can be administered with a digital companion.
- The IND/GLY/MF once daily fixed dose increases adherence, minimizing the risk of missing doses, meeting both patients' and clinicians' satisfaction.

LAMA/ICS fixed dose combinations in asthma patients not adequately controlled.

1.2. Role of the triple therapy in the management of asthma

Although major improvements have been made in the treatment of patients with uncontrolled asthma, with an overall reduction in admissions to hospital – as documented by the GINA report – and asthma-related deaths, a considerable proportion of patients is still subjected to symptoms of uncontrolled asthma and experience exacerbations [8]. Failure in proper control of asthma means a higher economic burden and, above all, a loss of quality-adjusted life-years for a number of patients [9]. Up to 40% of the patients remain uncontrolled despite therapy with ICS alone or combined with a LABA [10]. Therefore, the need to achieve disease control has led to consider anticholinergic drugs as an option for asthma treatment.

Tiotropium soft mist inhaler was the first LAMA approved for the maintenance of asthma, and it can be used as add-on therapy in patients requiring medium-to-high dose LABA/ICS (GINA step 4–5) from 6 years of age [1]. Tiotropium Respimat modestly improves lung function and partially reduces the overall risk of severe exacerbations, and in clinical trials, it prolonged the time to first severe exacerbation (282 days vs. 226 days) when compared to placebo [11,12]. The benefit of tiotropium as an add-on therapy to a moderate-to-high dose of ICS and to LABA/ICS maintenance treatment was showed by two interesting large studies that assessed its efficacy in terms of lung function, risk of developing exacerbation and disease worsening, and its safety [13,14]. Recently, five large clinical trials on the use of fixed combination LABA/LAMA/ICS in asthma were published and added substantial knowledge on the use of the once daily therapy in asthma. The TRIMARAN study and TRIGGER trial showed that patients who received a twice daily combination of formoterol/glycopyrronium/beclomethasone had improvements in lung function (forced expiratory volume in 1 second [FEV_1]) and, to some extent, a decrease in the number of exacerbations vs beclomethasone/formoterol combination [15]. The authors found a statistically significant reduction of 15% in moderate and severe exacerbations in TRIMARAN, and a 12% decrease in TRIGGER study, which, however, was not significant. The CAPTAIN study concluded that in patients with uncontrolled moderate or severe asthma on fluticasone furoate plus vilanterol, the addition of umeclidinium improved the lung function without a significant reduction in moderate and/or severe exacerbations [16]. Two additional and recently published trials, the IRIDIUM and the ARGON studies, have demonstrated significant efficacy of the IND/GLY/MF combination in improving the lung function and other clinically relevant outcomes such as exacerbation reduction [17,18]. The IRIDIUM and ARGON studies will be described in detail below.

The simultaneous use of the three classes of medications in a wide patient population with uncontrolled asthma represents a step forward in the treatment of severe asthma. That LABA/LAMA/ICS combinations can assure a better management of the disease for the patients when compared to other treatments, avoiding the side-effect profile of oral corticosteroids and resulting cost-effective with comparison to biologicals. Moreover, the possibility of simplifying the inhaler regimen, through the use of a fixed dose combination of the three components, could have advantages in terms of patients' adherence and long-term compliance to treatment and reduced risks of missing doses.

2. Role of glucocorticoids in asthma

Asthma is treated with drugs blocking the underlying inflammatory mechanisms, the ones that cause the onset of clinical signs and symptoms, namely, corticosteroids [19]. ICS are the cornerstone treatment for asthma, considered a precision medicine approach as they generally act locally and have a low systemic bioavailability [20].

ICS can inhibit inflammation pathways by regulating gene transcription (either inactivating transcription factors with pro-inflammatory activity, like NF-kB, or by activating anti-inflammatory molecules such as IL-10 and adhesion molecules) or by a fast response that is not related to gene expression, i.e. acting directly on the cell membrane influencing blood flow and the function of cell membrane proteins [21].

2.1. Mometasone furoate (MF)

Various ICS are available for asthma treatment with different chemical, pharmacological, and metabolic characteristics [22]. Among them, mometasone furoate (MF), a derivative of hydrocortisone, is a topical glucocorticoid with an advantageous risk-benefit profile. It has a low oral bioavailability (around 1%) and is delivered as a dry powder, it has a long half-life and is suitable for daily dosing [23]. A daily dose of 100 µg of inhaled MF is considered as a low/medium ICS dose showing strong efficacy and tolerability [24]. MF is also widely used for treating several skin conditions such as eczema, psoriasis, and rashes with no significant effects on the

hypothalamic–pituitary–adrenal axis, having low percutaneous absorption compared to other topical corticosteroids [25].

The combination of the two inhaled molecules, a corticosteroid and a LABA, is more effective than the same dosage of MF alone in asthma symptoms control and improving the asthma related quality of life [25]. The same superiority on the lung function and other outcomes was shown in the PALLADIUM study comparing high-dose indacaterol and mometasone furoate (IND/MF 150 µg/320 µg) or medium-dose IND/MF (150 µg/160 µg) administered once daily via Breezhaler, with high-dose MF (800 µg [400 µg twice daily]) or medium-dose MF (400 µg once daily) given via Twisthaler, or high-dose salmeterol xinafoate/fluticasone propionate (SAL/FLU). One possible limitation of this study is the administration of MF with two different delivery devices, an extra variable which can interfere with the comparison of the results. These results, described in detail below, correlate with the guidelines for asthma management that support the administration of LABA/ICS as maintenance therapy in moderate and severe asthma [24].

3. Role of β_2-agonists in asthma

3.1. Indacaterol (IND)

LABA are indicated in association with ICS as the preferred maintenance treatment in asthma, leading to reduction in exacerbation risk and higher lung function [1]. Current recommendations also state that LABA are safe when used in combination with ICS, whereas they should not be used without ICS due to the increased risk of serious adverse outcomes.

A decade ago, the term ultra-LABA was coined to describe once-daily β_2-agonists and differentiate them from the known twice-daily agonists, salmeterol and formoterol. In this regard, once-daily IND was shown to provide sustained 24-h bronchodilation, a fast activity and good profiles for tolerability and safety [26]. This was the first study that demonstrated the ability of a bronchodilator to induce both a fast and a prolonged duration of action. From a patient perspective, this is what really matters, since asthmatics ask for a prompt and consistent relief of symptoms.

Studies involving IND both in vitro and in vivo have confirmed the quick onset of action and 24 h bronchodilating effect. In particular, the quick onset of action was comparable to the one of salbutamol and formoterol, and superior to salmeterol, whereas the duration of action of IND was higher than the one of salmeterol and formoterol [27]. The safety and tolerability of IND was assessed in asthma patients [28]. Over a period of 28 days, different dosages of the ultra-LABA were administered once daily and compared with placebo. IND, reported to be approved and marketed in more than 100 countries worldwide, was well tolerated, and no adverse cardiac or metabolic effects were observed. Moreover, the drug was shown to provide effective 24-h bronchodilation. In combination with MF, IND has shown improvements in lung function, symptom control and use of rescue medication, and reduction in the annual rate of exacerbations in asthmatics [29,30].

Interestingly, IND can be administered either in a maleate or in an acetate form in asthma patients, and both of the formulations resulted in effective improvement in lung function, with a safe profile, as demonstrated by a phase II study [31]. The IND acetate can be used in combination with GLY and MF in a single inhaler, increasing the acceptability of a combined once daily therapy and the potential of the patient's adherence to the treatment [31].

The PLATINUM program is the phase III clinical plan which supports the development of IND/MF and IND/GLY/MF. These investigations open the way to the use of an ultra-LABA in the treatment of asthma.

4. Role of the muscarinic receptor antagonists in asthma

Anticholinergic bronchodilators antagonize the parasympathetic system by acting on the acetylcholine receptors expressed on airway smooth muscles and lung parasympathetic nerves. There are two groups of acetylcholine receptors: nicotinic- and muscarinic- and the muscarinic subtypes M_1, M_2 and M_3 are primarily involved in the regulation of bronchoconstriction. All muscarinic receptor subtypes are widely expressed in different tissues (smooth muscles, brain, heart and the sinoatrial node, gastrointestinal tract, pupils, blood vessels and the parasympathetic nervous system). Muscarinic M_2 receptors in the heart regulate heart beating by reducing the activation of the sinus node, while the M_3 subtypes are responsible of contraction of the muscles of gastrointestinal tract, or blood vessel vasodilation [32,33]. Specifically referring to airway tract activity, M_1 receptors are widely distributed in all parasympathetic ganglia and they act by regulating cholinergic transmission. M_2 receptors are found in the prejunctional membranes of the neuromuscular junctions of airway smooth muscles and reduce acetylcholine transmission through a negative feedback. M_3 receptors are mainly expressed in smooth muscle cells in the lungs, regulating muscle contraction, while within the submucosal glands of the lung, M_3 receptors regulate mucus secretion. Thus, it is preferable that antimuscarinic bronchodilators present higher affinity for M_1 and M_3 receptors, and lower affinity for M_2 receptors [34].

Although the mechanisms underlying bronchial obstruction and hyper-reactivity found in asthma are multiple and complicated, the contraction of bronchial smooth muscle is the main cause of reversible airway obstruction in asthma. Therefore, cholinergic activity plays a decisive role in bronchoconstriction [34]. Additionally, patients with asthma have an increased bronchial smooth muscle tone suggesting that this is a result of an increased basal activity of the pulmonary parasympathetic cholinergic nerves, a phenomenon described as "cholinergic tone' [35]. Moreover, the non-neuronal cholinergic system of airway inflammatory cells represents a regulatory pathway which deserves further attention: indeed, potential immunomodulatory activities may influence the inflammation of obstructive respiratory diseases [36].

4.1. Glycopyrronium/ glycopyrrolate (GLY)

Among the available anticholinergics, glycopyrronium also known as glycopyrrolate (GLY) is a LAMA with a higher

selectivity for M_3 receptors, thus promoting long-lasting and selective effects. Glycopyrronium bromide acts by blocking acetylcholine-induced bronchoconstriction on airway smooth muscle cells, thus dilating the airways. Through radioligand binding studies, it was demonstrated a four times greater selectivity of GLY for human M_3 receptors compared to human M_2 receptors, as well as a rapid onset of action and a longer duration, probably attributable to prolonged concentrations of active substance in the lungs [37]. It has also been shown that differences in the affinity rate M_3/M_2 are present among different LAMAs [38].

Many studies have investigated the action of LAMAs on the degree of bronchoconstriction of the airways. For example, a Japanese study showed how SABAs with LAMAs synergistically improve the inhibition of muscarinic contraction by diminishing the sensitization to Ca^{2+} [39]. This results in less bronchoconstriction and better control of the respiratory pathology. In addition, other studies evaluating aclidinium, formoterol fumarate, GLY, and indacaterol fumarate have shown greater benefits in relaxing airway smooth muscle in isolated human bronchi.

In patients with mild to moderate asthma, GLY resulted more effective than placebo against methacholine-induced bronchoconstriction ($p < 0.002$) [40]. In the same study, each inhalation of GLY provided bronchodilation lasting for up to 30 hours. In a recent Indian study [41], the efficacy of GLY was evaluated in 53 patients with uncontrolled asthma and treated with LABA/ICS. This was an 8-week observational study in which 40 patients were treated with formoterol/budesonide plus GLY and 13 patients received only a LABA/ICS (formoterol/budesonide) combination. All patients included in the study were symptomatic and were assessed for FEV_1. At eight weeks, the group of patients treated with formoterol/budesonide plus GLY showed a significant improvement in FEV_1 compared to both baseline and the group of patients treated with the same LABA/ICS combination. Both groups showed improvements in terms of FEV_1 and asthma control test (ACT) compared to their own baselines at the start of the study.

Two additional studies have compared the effects of GLY versus (i) the muscarinic receptor antagonist tiotropium and (ii) IND on the dose-response curve to methacholine in patients with mild asthma [42,43]. In the first study, both GLY and tiotropium were administered for a week as bronchoprotective medium before the methacholine test. This study showed that tiotropium is able to guarantee a statistically significant broncho-protection against methacholine only after 24 and 72 hours, while GLY was shown to be more effective, exerting broncho-protection already 1 hour post-treatment. In the second study, GLY alone and the IND/GLY combination were able to protect against methacholine-induced bronchoconstriction already after 1 hour from the administration, and they also kept mediating broncho-protection at 24 and 48 hours [43].

In a phase II dose ranging study, GLY was administered to adult patients with either an intermittent or mild-to-moderate persistent asthma at the doses of 1.9 µg, 3.6 µg, 7.2 µg, 14.4 µg, and 28.8 µg. Results highlighted how patients experienced a significant improvement in FEV_1 from baseline without an appreciable difference between the two higher doses (14.4 µg and 28.8 µg) versus the reference drug salbutamol 50 µg [44].

Finally, a phase II/III clinical study evaluated the safety and efficacy of two doses (25 µg and 50 µg) of GLY as an add-on bronchodilator in asthmatic adult patients already treated with LABA/ICS. The patients were evaluated for an overall treatment time of 7 days and showed an improvement in lung function with both doses of GLY. The assessment of FEV_1 after one week of treatment was the primary endpoint, and the change was in the order of 89 ml significantly different from placebo. Furthermore, after one week of treatment, the change in FEV_1-peak at 4 hours post GLY administration was significantly different from placebo (173 mL with 25 µg GLY and 164 mL with 50 µg GLY, respectively) [45].

In conclusion, the data emerging from the literature suggest that not only GLY is an effective molecule, but it is also safe in the control of respiratory pathology, establishing an important bronchodilator effect in addition to LABA/ICS therapy in asthma.

5. Anti-inflammatory and bronchodilating effects of the once daily inhaled therapy

5.1. Combined actions of indacaterol (IND), glycopyrronium (GLY), and mometasone furoate (MF)

In asthmatic patients not adequately controlled by LABA/ICS coformulations, the addition of a LAMA can further decrease asthma exacerbation rate and improve lung function [11]. Within such a therapeutic context, recent phase III trials have provided very promising results about the clinical and functional effects of the fixed-dose LABA/LAMA/ICS association including IND/GLY/MF [17,18]. The pharmacological rationale underlying the combination of these three drugs is closely linked to the possibility of reciprocally potentiating their different mechanisms of action.

In particular, MF is characterized by a relatively strong in vitro potency, a powerful anti-inflammatory activity, and a high binding affinity to human glucocorticoid receptor (GR) [46,47]. Similar to all glucocorticoids (GC), MF is a liposoluble molecule that easily crosses the plasma membrane of cellular targets and interacts within the cytoplasm with GR, whose expression as GRα isoform largely prevails over the GRβ dysfunctional variant [48,49]. Following MF interaction with GR, the active ligand-receptor complex rapidly translocates into the nucleus, binding to genomic DNA at the level of regulatory nucleotide sequences named glucocorticoid response elements (GRE) (Figure 1). As a consequence, GC-inducible genes are stimulated to enhance their transcriptional activity [48], thus leading to an increased production of proteins with anti-inflammatory activity such as mitogen-activated protein kinase phosphatase-1 (MKP-1) and glucocorticoid-induced leucine zipper (GILZ) (Figure 1). MKP-1 dephosphorylates and inactivates the pro-inflammatory mitogen-activated protein kinase (MAPK) family member p38 [50,51], whereas GILZ inhibits the pro-inflammatory functions of both activator protein-1 (AP-1) and nuclear factor-kB (NF-kB) [52].

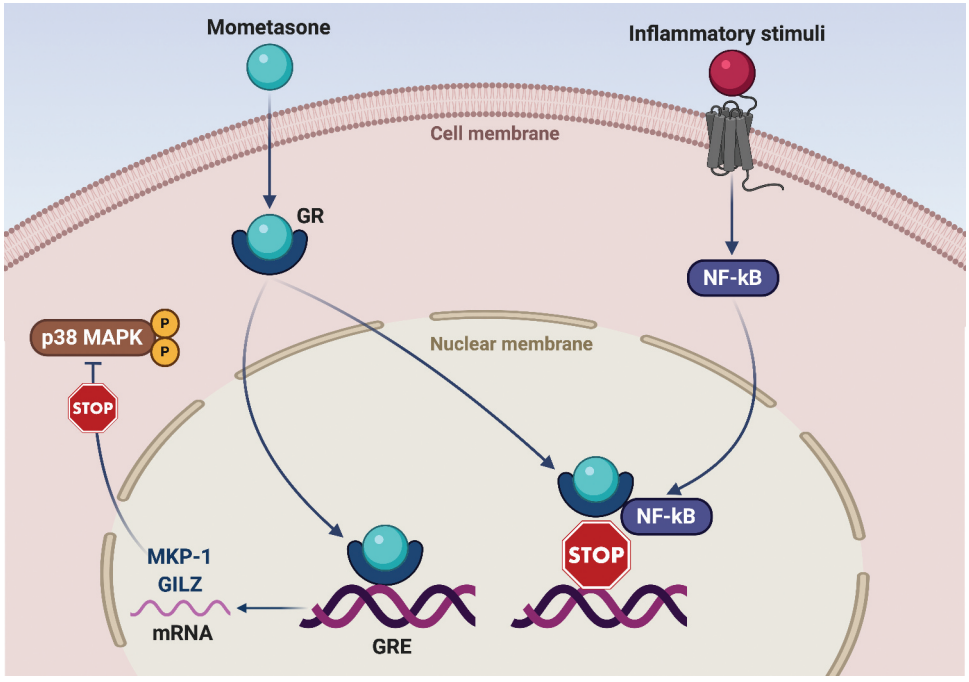

Figure 1. Molecular mechanisms underlying the therapeutic effects of mometasone furoate in asthma. Mometasone furoate is a liposoluble molecule which crosses the cell membrane and binds to the cytoplasmic glucocorticoid receptor (GR). Following mometasone binding, the activated GR migrates to the nucleus, where interacts with specific regulatory DNA sequences known as glucocorticoid response elements (GRE). GRE are located inside target genes encoding anti-inflammatory proteins such as GILZ (glucocorticoid-induced leucine zipper) and MKP-1 (mitogen-activated protein kinase phosphatase-1). The latter dephosphorylates and inactivates the pro-inflammatory p38 MAPK enzyme. Furthermore, activated GR can also bind via protein–protein interactions to the transcription factor nuclear factor-kB (NF-kB), thereby inactivating its proinflammatory functions by preventing DNA-binding.

GRE are also located inside the gene encoding for the β_2-adrenergic receptor (β_2-AR) [53,54]. Indeed, by binding to these GRE, GR activated by ICS can stimulate β_2-AR gene transcription and protein expression [55]. ICS may also increase β_2-AR number through inhibition of β_2-AR mRNA degradation [55]. Taken together, such GR-dependent mechanisms preserve a high β_2-AR cellular density, thereby preventing the risk of β_2-AR down-regulation and desensitization, possibly occurring as a consequence of patient chronic exposure to LABA [56]. In addition to enhancing β_2-AR synthesis, corticosteroids also promote β_2-AR coupling to the post-receptor signaling machinery (see below) [57,58].

Besides targeting genomic DNA, activated GR can also directly bind to NF-kB and AP-1 via protein–protein interactions (Figure 1), thus effectively neutralizing the powerful biological activities of such pro-inflammatory transcription factors. Hence, within the airways of asthmatic patients, this further mechanism contributes to GR-mediated inhibition of NF-kB/AP-1-dependent expression of cytokines and chemokines implicated in asthma pathobiology [59].

Like all β_2-AR agonists, IND induces bronchodilation by relaxing airway smooth muscle independently of the wide variety of agents eliciting bronchoconstriction, thereby acting as a functional antagonist of airway smooth muscle contraction. Hence, IND activates β_2-AR coupled to the stimulatory G protein (Gs), which in turn stimulates adenylyl cyclase (AC) that is responsible for the subsequent increase in cytosolic levels of 3′,5′-cyclic adenosine monophosphate (cAMP), the second messenger (Figure 2) [57]. IND is a potent β2-AR agonist, whose very fast and intense bronchodilating action persists for 24 hours [60]. The rapid bronchodilation afforded by IND is due to its hydrophilic moiety, which gets in contact with the β_2-AR hydrophilic pocket embedded within the seven hydrophobic transmembrane domains of the receptor [61]. The long-lasting bronchodilation induced by IND depends on the high affinity of its lipophilic tail for the structures known as ‘lipid rafts’ [62]. These lipid rafts consist of molecular domains including cholesterol and sphingolipids, which aggregate β_2-AR within the cell membrane, thus promoting their association with the signaling unit made-up of Gs and AC.

In addition to allowing airway smooth muscle relaxation, LABA-induced stimulation of β_2-AR also promotes GR nuclear translocation via activation of the post-receptor signal transduction machinery, thus potentiating the anti-inflammatory effects of corticosteroids [63]. The latter in turn facilitate β_2-AR coupling with Gs through reduction of G-protein-coupled receptor kinase-2 (GRK2) expression [58], which is responsible for β_2-AR phosphorylation and the consequent receptor-Gs uncoupling [56].

Similar to all anticholinergic bronchodilators, GLY acts through a competitive antagonism of airway muscarinic receptors [61]. In particular, GLY exerts a prompt and persistent bronchodilating action via a long-lasting blockade of the M_3 subtype of muscarinic receptors, which is mainly accountable for acetylcholine-dependent airway smooth muscle (ASM) contraction (Figure 2) [38]. Hence, M_3 competitive antagonism operated by GLY and IND-mediated functional antagonism of ASM contraction effectively cooperate to implement a reciprocal potentiation of these two different mechanisms, thereby resulting in maximization and optimization of bronchodilation [61].

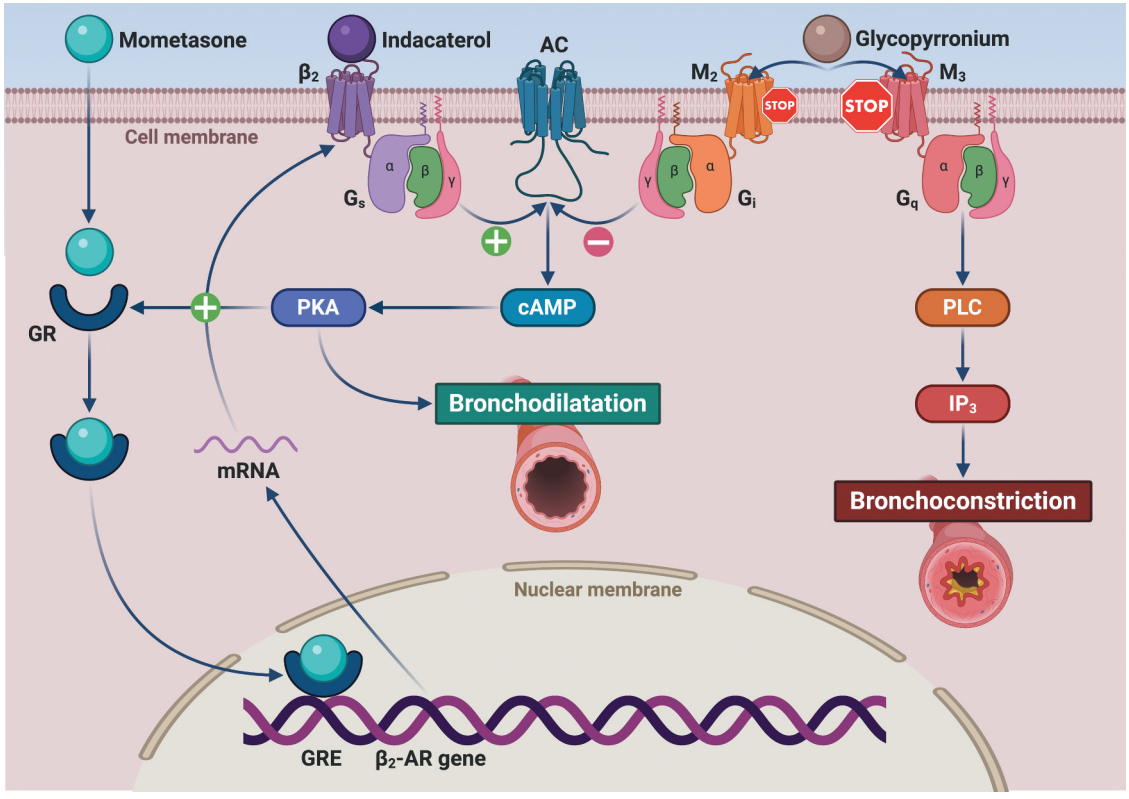

Figure 2. Molecular interactions involving the mechanisms of action of indacaterol, glycopyrronium and mometasone furoate. Indacaterol binds to the β2-adrenergic receptor (β2-AR), thus sequentially activating the stimulatory Gs protein and adenylyl cyclase (AC), which is responsible for cAMP synthesis and the subsequent activation of cAMP-dependent protein kinase A (PKA). This signaling pathway not only leads to bronchodilatation, but also promotes GR nuclear translocation, thus potentiating the pharmacologic effects of corticosteroids. The latter in turn increase β2-AR mRNA levels via GRE-dependent stimulation of β2-AR gene transcription. IND-induced bronchodilatation is synergistically potentiated by GLY through a competitive antagonism of M2 and M3 muscarinic receptors. With respect to the blockade of the M2 receptor coupled to AC inhibition operated by the inhibitory G protein (Gi), GLY occupies for a much longer time the M3 receptor, whose stimulation is the main mechanism underlying acetylcholine-induced bronchoconstriction, mediated by M3-coupling to Gq protein and phospholipase C (PLC). The latter enzyme catalyzes the generation of the intracellular second messenger inositol trisphosphate (IP3) that elicits airway smooth muscle contraction via mobilization of cytosolic calcium ions.

Moreover, IND can potentiate GLY action by inactivating the Gq protein associated with muscarinic M_3 receptors within the signaling pathway leading to acetylcholine-induced bronchoconstriction. Indeed, LABA increase the expression of the regulator of G-protein signaling 2 (RGS2) that specifically inhibits Gq activation [64]. This effect of β_2-AR agonists is further enhanced by corticosteroids [64]. Thus, through these complex mechanisms, IND and MF could amplify, at a post-receptor downstream level, GLY-induced bronchodilation resulting from upstream M_3 receptor blockade. As a consequence of the latter mechanism, GLY may in turn contribute to protect asthmatic airways from β_2-AR desensitization. In fact, GLY-dependent interruption of M_3-Gq signaling cascade inhibits Gq coupling with phospholipase C, responsible for the generation of the intracellular second messenger diacylglycerol [65]. Diacylglycerol activates protein kinase C, which not only sensitizes ASM contractile apparatus to calcium ions, but also phosphorylates both β_2-AR and Gs, thus preventing their interaction and contributing to β_2-AR desensitization [66]. Overall, the above mechanisms explain the synergistic cooperation of GLY and IND with regard to their relaxant effects, exerted on ASM and demonstrated in isolated human bronchi, pre-contracted by acetylcholine [67].

Therefore, by combining LAMA/LABA and the reciprocal potentiation of LABA/ICS mechanisms of action, IND/GLY/MF once daily therapy may provide a valuable option for inhaled treatment of asthmatic patients not adequately controlled by LABA/ICS associations.

6. PLATINUM clinical development program: clinical efficacy and safety of the once daily therapy with IND/GLY/MF

The PLATINUM clinical program includes phase III clinical studies evaluating safety and efficacy of the inhaled fixed dose combinations IND/GLY/MF and IND/MF in patients with inadequately controlled asthma [68]. The MF doses administered in the studies have been determined by bridging the doses previously approved to the new formulation taking into account pharmacokinetic and pharmacodynamic evaluation. Upon this bridging, MF 80 μg and 160 once daily (medium and high-dose) in IND/GLY/MF combination resulted similar to MF 160 μg and 320 μg once daily (medium and high dose) in the IND/MF formulation, respectively [68]. The main features of the clinical development program are summarized in Table 1.

The clinical program, which involved over 7500 patients, consisted of four clinical trials: two studies (QUARTZ and PALLADIUM) evaluating the combination IND/MF and two

Table 1. Summary of the phase III studies within PLATINUM program.

	IRIDIUM [18]	ARGON [17]	QUARTZ [70]	PALLADIUM [71]
Population	3092 symptomatic patients, despite treatment with medium or high doses of LABA/ICS.	1426 symptomatic patients, despite treatment with medium or high doses of LABA/ICS.	802 adult and adolescent symptomatic patients, despite treatment with ICS low dose.	2216 symptomatic patients, despite treatment with medium or high doses of ICS, or low doses of LABA/ICS.
Drugs, doses and frequency	Medium-dose or high-dose MF/IND/GLY (80 µg, 150 µg, 50 µg; 160 µg, 150 µg, 50 µg) or MF/IND (160 µg, 150 µg; 320 µg, 150 µg) once daily or high-dose fluticasone-salmeterol (FLU/SAL; 500 µg, 50 µg) twice daily	IND/GLY/MF high- (150/50/160 µg) or medium-dose (150/50/80 µg) once daily or SAL/FLU high-dose (50/500 µg) twice daily+ tiotropium 5 µg once daily	Low-dose IND/MF 150/80 µg once daily or MF 200 µg once daily	High-dose MF/IND (320 µg, 150 µg) or medium-dose MF/IND (160 µg, 150 µg) once daily; high-dose MF (800 µg [400 µg twice daily]) or medium-dose MF (400 µg once daily); or high-dose fluticasone propionate-salmeterol xinafoate (FLU/SAL; 500 µg, 50 µg) twice daily.
Study duration	52 weeks.	24 weeks.	12 weeks.	52 weeks.
Age	18–75 years.	>18 years.	≥12 and <_75 (64 adolescents, aged ≥12 to <18 years).	12–75 years
Primary outcome	Superiority of either medium or high dose of IND/GLY/MF over the corresponding dosages of IND/MF at week 26 of treatment in terms of trough FEV_1.	Non-inferiority of either medium or high dose of IND/GLY/MF to SAL/FLU high dose (twice daily) + Tiotropium 5 µg (once daily) at week 24 of the treatment, in terms of AQLQ.	Superiority of IND/MF over MF (both low dose) in terms of trough FEV_1 after 12 weeks of treatment.	Superiority of IND/MF medium and high doses over correspondent doses of MF in terms of trough FEV_1 after 26 weeks.
Secondary outcome	Superiority of either medium or high dose of IND/GLY/MF over the corresponding dosages of IND/MF at week 26 of treatment in terms of ACQ-7.	Change from baseline in AQLQ, ACQ-7, trough FEV_1, FVC, $FEF_{25-75\%}$ of FVC ($FEF_{25-75\%}$) after 24 weeks.	Superiority of IND/MF over MF in terms of ACQ-7 after 12 weeks of treatment.	Superiority in the combination doses of IND/MF over the combination doses of MF in terms of ACQ-7 after 26 weeks.
Additional outcomes	PEF, reliever drug, exacerbations, comparison to high doses of SAL/FLU.	SGRQ and PEF after 24 weeks.	ACQ-7 of morning and evening PEF, AQLQ, reliever drug use, total daily symptom score, nighttime awakenings and number of exacerbations at 12 weeks of treatment.	Trough FEV_1, ACQ-7 at 52 weeks, PEF, reliever drug, exacerbations, comparison with high doses of SAL/FLU.

Abbreviations. ACQ-7: 7-item Asthma Control Questionnaire, AQLQ: Asthma Quality of Life Questionnaire; FEV_1: forced expiratory volume in 1 second, $FEF_{25-75\%}$of FVC: forced expiratory flow at 25–75% of forced vital capacity, FLU: fluticasone, FVC: forced vital capacity, LABA: long acting β2-agonist, PEF: peak expiratory flow, IND: indacaterol, GLY: glycopyrronium, MF: mometasone, SAL: salmeterol, SGRQ: St George's Respiratory Questionnaire.

studies (IRIDIUM and ARGON) for the IND/GLY/MF combination. All aforementioned studies have been completed and published.

Overall, the administration of multiple inhaled doses of IND, GLY and MF, alone or combined, resulted to be safe and tolerated by the patients.

In addition, no relevant pharmacokinetic interaction between IND, GLY, and MF was reported when compounds were given in combination –IND/GLY/MF– [69].

6.1. QUARTZ and PALLADIUM studies

The QUARTZ study is a 12-weeks multicenter, randomized, double-blind, double-dummy and parallel-group phase III study aiming at assessing the efficacy and safety of once daily IND/MF low-dose (150/80 μg) administered via Breezhaler versus a fixed once daily MF dose (200 μg) administered via Twisthaler in adult and adolescent (age range: 12–75 years) patients with asthma not adequately controlled [70].

The primary outcome of the study was to show superiority of low-dose IND/MF to MF in terms of trough FEV_1 after 12 weeks of treatment.

At 12 weeks, low-dose IND/MF significantly improved trough FEV_1 and the Asthma Control Questionnaire (ACQ-7) versus MF, as well as all other secondary endpoints, thus supporting the use of the once daily low-dose of IND/MF for adult and adolescent patients with uncontrolled asthma.

The PALLADIUM study is a 52-week, double-blind, triple-dummy, parallel-group, phase III study, having the aim of verifying the efficacy and safety of high-dose IND/MF (150/320 μg) or IND/MF medium-dose (150/160 μg), administered once daily via Breezhaler versus MF monotherapy high-dose (800 μg total, in a twice daily administration of 400 μg) or MF medium-dose (400 μg) single daily dose via Twisthaler, in patients (≥12 – < 75 years of age) with inadequately controlled asthma [71].

The primary endpoint was improvement in trough FEV_1 from baseline at 26 weeks, while the secondary outcome was the assessment of patients' quality of life by ACQ-7.

Both medium- and high-dose IND/MF were superior in improving trough FEV_1 over corresponding MF doses at 26 weeks. Moreover, the once-daily administration of high-dose IND/MF was able to elicit similar improvements to twice-daily high-dose SAL/FLU in trough FEV_1 at 26 weeks, and significant improvements at week 52. The same improvements were observed on peak expiratory flow (PEF) and percentage of rescue medication free days.

The PALLADIUM study demonstrates that once-daily fixed-dose of IND/MF improves lung function over MF monotherapy over the course of 26 weeks and that the IND/MF combination is non-inferior to the twice-daily combination of SAL/FLU, showing also significant benefits in patients' quality of life, thus providing a novel option in the management of asthma.

6.2. IRIDIUM and ARGON studies

The IRIDIUM study is a 52-week, multicenter, randomized, double-blind study in which the enrolled patients were diagnosed for asthma for at least 1 year before screening [18]. In spite of a therapy with medium- or high-dose LABA/ICS, the individuals presented both symptomatic asthma and at least one exacerbation episode occurred in the previous year. Patients were randomized (1:1:1:1:1) to receive IND/GLY/MF medium-dose (either 15, 50, or 80 μg; n = 620 patients), IND/GLY/MF high-dose (150, 50,160 μg; n = 619), IND/MF medium-dose (150;160 μg; n = 617), high-dose (150;320 μg; n = 618) once daily via Breezhaler, or high-dose SAL/FLU (50;500 μg; n = 618) twice daily via Diskus.

The primary outcome was the change from baseline in trough FEV_1 after 26 weeks of the once-daily treatment with either dose of IND/GLY/MF, compared to the respective dose of IND/MF. Trough FEV_1 is the parameter of choice as recommended by the EMA guidelines, while the 26-week time point was chosen based on the pharmacokinetics and pharmacodynamics of the drugs, which reach a steady state by 4 weeks.

At week 26, trough FEV_1 resulted in improvement with both medium-dose IND/GLY/MF and high-dose IND/GLY/MF, which were superior versus corresponding doses of IND/MF (medium-dose IND/GLY/MF: treatment difference [Δ] 76 mL [95% CI 41–111]; $p < 0.001$; high-dose IND/GLY/MF: Δ 65 mL [31–99]; $p < 0.001$).

The IRIDIUM study has been the first clinical study employing IND/GLY/MF to evaluate the once daily dosing of the IND/GLY/MF combination and to demonstrate that the addition of the GLY –a LAMA– to a medium- or high-dose IND/MF combination significantly ameliorates trough FEV_1 over 26 weeks.

Moreover, from as early as 2 weeks and throughout the entire 52 weeks of treatment, both medium and high IND/GLY/MF doses proved to be superior in improving lung function in patients with inadequately controlled asthma as compared to high-dose SAL/FLU (medium dose IND/GLY/MF: treatment difference Δ 99 mL [64–133]; $p < 0.001$; high dose IND/GLY/MF: treatment difference Δ 119 mL [72–154]; $p < 0.001$), a benchmark LABA/ICS combination. Despite an overall non-significant reduction of exacerbation rate of IND/GLY/MF vs MF/IND, the IND/GLY/MF once daily therapy was correlated to a 36% reduction in moderate-to-severe exacerbations and a 42% reduction in severe exacerbations compared to high-dose SAL/FLU. Importantly, because IND/GLY/MF therapy is combined in a single inhaler, its once-daily dosing offers a strategy that can potentially enhance adherence to treatment, thus improving disease control.

The number of adverse events resulted similar among the groups.

The ARGON study is a 24-week, multicenter, randomized, parallel-group, open-label, active-controlled, non-inferiority phase IIIb study in patients with uncontrolled asthma [17]. Criteria for patient inclusion were presence of asthma as diagnosed as early as six months prior to screening, being symptomatic despite treatment with medium- or high-doses of LABA/ICS and having a history of one or more asthma exacerbations. Patients were randomized (1:1:1) to IND/GLY/MF medium-dose (n = 474 patients) or IND/GLY/MF high-dose (n = 476) or concurrent administration of twice-daily SAL/FLU high-dose (50/500 μg) + tiotropium (5 μg, once-daily; n = 475) for 24 weeks.

The primary outcome was to evaluate the non-inferiority of both medium- and high-dose IND/GLY/MF administered via Breezhaler, compared to SAL/FLU twice daily via Diskus +

tiotropium via Respimat after 24 weeks of treatment, by the Asthma Quality of Life Questionnaire (AQLQ).

At 24 weeks, the non-inferiority of either IND/GLY/MF medium- or high-dose to SAL/FLU high-dose + tiotropium was demonstrated by AQLQ score (least square mean treatment difference [Δ]: −0.038 and 0.073 form medium- and high-dose, respectively; both $p < 0.001$). With the high-dose, IND/GLY/MF ameliorated ACQ-7 (Δ: −0.124; $p = 0.004$), trough FEV_1 (Δ: 96 mL; $p < 0.001$), PEF ([Δ: 9.56 L/min; $p = 0.005$] for the morning, [Δ: 9.15 L/min; $p = 0.006$] for the evening) and St. George's Respiratory Questionnaire SGRQ (Δ: −2.00; $p = 0.04$) compared to SAL/FLU high dose + tiotropium. Specifically, improvements in trough FEV_1 were detectable as early as 8 weeks from the beginning of the treatment and were maintained throughout the entire duration of the study. Comparable results were found for medium-dose of IND/GLY/MF and high dose of SAL/FLU + tiotropium, with the benefit of employing a lower steroid dose.

Of note, the TRIGGER phase III trial reported no difference in pre-dose FEV_1 between formoterol/beclomethasone/GLY (FF/BDP/GLY, high-dose, twice daily) versus FF/BDP (high-dose, twice daily) +tiotropium (−45 mL; $p = 0.13$; at week 26).

In the ARGON study, exacerbation rates (mild, moderate and severe) were comparable between both IND/GLY/MF doses and twice daily SAL/FLU high-dose + tiotropium once daily.

Recently, two metanalyses have been published evaluating single inhaler triple therapy and its comparison to dual inhaler therapy [72,73]. It appears clear from current evidence that some patients may benefit differently from once daily triple therapy or biologic therapy, according to their phenotype, though the specific patient characteristics on which basing the choice is yet unknown [72] Similarly, the choice of high ICS treatment is still reasonable and further studies are needed to understand whether high-dose single inhaler triple therapy might be an alternative choice to avoid maintenance therapy with systemic corticosteroids [72].

7. Breezhaler and propeller sensor

IND/GLY/MF is delivered through the Breezhaler inhaler, a single dose DPI that allows confirmation of the inhaled dose via three feedback mechanisms (auditory, taste, and visual). The Breezhaler inhaler is approved for the use of long-term maintenance treatments for COPD and asthma. Unlike during randomized clinical trials, where patients are thoroughly instructed on the correct use of inhalers, in clinical practice errors made during inhalation are frequent, and some studies suggest a link between these errors and symptom control. The study by Molimard and colleagues in COPD patients found a correlation between critical errors and severe COPD exacerbations, highlighting the fact that device-handling errors could have an impact on clinical outcomes [74]. In the same study, the use of the Breezhaler inhaler was related to a lower percentage of both device-dependent errors and critical errors compared to other inhalers evaluated [74]. A subsequent analysis, The Real-life Experience and Accuracy of inhaLer use (REAL) survey, assessed the patients' level of training in the correct use of the inhaler, factors affecting adherence to treatment and ease of use of the commercially available inhalers (Breezhaler, Ellipta, Genuair or Respimat) [34]. The REAL survey showed a greater adherence to therapy and a greater likelihood of administering the correct dose of a given drug through Breezhaler compared to other inhalers, also avoiding the risk of under or overdosing.

The above-mentioned studies concern the use of Breezhaler in patients with COPD, therefore, further studies addressing the correct use of Breezhaler in asthma are needed to expand our knowledge of real clinical practice.

7.1. Propeller sensor for Breezhaler and Propeller app

Adherence to therapy in respiratory diseases is very low, and it is a recurrent problem in asthma therapy [75]. It has been estimated that between 30–70% of asthma patients do not adhere to their treatment [76,77], and that as much as 50% of patients are unable to correctly use their inhaler, despite having received training [78].

Poor adherence, especially in severe asthma cases can contribute to substantial worsening of the disease. Asthma patients are often asked to comply with treatments that require medications to be taken at different dosages, under different times, with different kinds of inhalers, all factors that could contribute to poor adherence. Adherence to any given therapy has been shown to improve when the dosing frequency is reduced (e.g. once daily) and when reinforcing visits are increased [79]. In this sense, the management of uncontrolled asthma through the use of the single-inhaler fixed dose combination of IND/GLY/MF could prove beneficial in enhancing patients' adherence, as it reduces the administration frequency to once daily. Moreover, the IND/GLY/MF therapy is the first inhaled therapy that can be prescribed alongside a digital companion (Propeller Health, USA). Propeller is a digital health platform for patients with asthma and COPD. The patient easily attaches the sensor to the Breezhaler device, and the sensor communicates with the smartphone app via Bluetooth. Through the use of the app the patient can obtain inhalation confirmation, reminders at appropriate time (when medication is needed), and access to objective data (e.g. reports of medication use and trends) to better support therapeutic decisions. This is optional and IND/GLY/MF therapy can be prescribed to patients also without the sensor, if not needed or useful.

Here below, we summarize some clinical evidence regarding the use of this innovative digital system in asthma patients.

Improved Medication Adherence: in a six-month randomized study including 125 adults with asthma, patients using a Propeller's asthma platform had higher adherence than those in the control group [80]. Propeller consistently provides higher levels of medication adherence [81], which may lead to a reduced risk of asthma exacerbations [82].

Reduced Need of Rescue Inhaler Use: The Propeller platform is also accompanied by reductions in rescue inhaler use as demonstrated by several studies [83,84]. A pragmatic controlled study aiming to measure real-world effectiveness of the Propeller platform demonstrated that the system significantly

decreased SABA use, increased SABA-free days, and improved ACT scores [84]. By improving medication adherence and reducing rescue inhaler use, the sensor and app associated with IND/GLY/MF Breezhaler may provide patients with enhanced asthma control, longer time without symptoms and a better quality of life.

Reduced Healthcare Utilization: The Propeller use allows better adherence and therefore better asthma control. This can be translated into reduced patients' hospitalizations and emergency department (ED) visits, meaning decreased healthcare costs. During a study lasting 12 months, there was a general reduction in both ED visits and ED visits and hospitalizations (reduced by 53% and 57%, respectively) with a digital health intervention consisting in the administration of SABA with the Propeller [85]. There is therefore good indication to speculate a plausible similar result with the use of the monitored IND/GLY/MF inhaler.

Patient Satisfaction: Participants of a randomized controlled study (a total of 89 subjects, adults and children with asthma) completed a satisfaction survey at the end of the trial. The results of the survey showed 79% of the patients being 'very satisfied' with the use of the device, and 20% being 'somewhat satisfied' [86]. Moreover, 93% were satisfied with the reports generated, 90% reported that the information collected by the sensor was useful to knowing more about their asthma condition, and 72% expressed their interest in continuing to use the sensor and platform even after the end of the study [86].

This digital solution represents an innovation in the asthma treatment and has the potential to improve treatment adherence and efficiency by introducing a simple and effective tool able to support the patients in the self-management of their own condition. Moreover, monitoring asthma therapy adherence is fundamental to healthcare professionals in order to share decisions with the patient and to tailor their treatments. Thus, the introduction of a supporting digital system would translate into better monitoring progress of the disease in asthma patients by healthcare professionals and in a general optimization of the resources.

As confirmation, recently EMA gave a significant award to IND/GLY/MF Breezhaler for the 'Outstanding contributions to public health' as the only product approved in 2020 that represent significant progress in the asthma therapeutic area as 'the first asthma once daily combination therapy that includes an optional electronic sensor to collect data on the use of the inhaler by the patient' [87].

8. Conclusions

The management of asthma aims to efficiently control clinical symptoms, reduce individual risk factors and comorbidities, and assure patients an improved quality of life.

The introduction of IND/GLY/MF once daily therapy represents a step forward in the treatment of severe asthma. The evaluation of the results of phase III clinical trials supports both the clinical efficacy on lung function, exacerbation reduction, and the safety of the once daily therapy.

The IND/GLY/MF once daily therapy administered with Breezhaler and Propeller sensor is the first asthma treatment that is supported by a digital companion, allowing patients' self-management of their condition, thus resulting in better adherence and improved monitoring of the disease, meeting the satisfaction of both the patients and the healthcare professionals.

9. Expert opinion

The introduction in clinical practice of a single fixed dose inhaled combination including the three principles LABA/LAMA/ICS represents a valuable advance in the management of asthma in a wide percentage of moderate-to-severe patients. In this regard, the potential benefits of the IND/GLY/MF inhaled formulation include both improvement of lung function and reduction of the asthma exacerbation rate. Therefore, it is likely that these therapeutic effects can be achieved by patients with not adequately controlled asthma. Indeed, the different mechanisms of action of GLY and IND guarantee a maximal bronchodilation resulting from the competitive antagonism of muscarinic receptors, induced by GLY, optimally combined with the bronchodilation implemented by IND. In addition, IND and MF reciprocally integrate their respective pharmacological actions. Indeed, IND improves the anti-inflammatory effects of MF, which in turn potentiates the bronchodilation induced by IND.

The practical advantages arising from the adoption of a single daily fixed dose of IND/GLY/MF, demonstrated by recent trials included within the PLATINUM study program, are as follows:

- An effective therapy that can simultaneously target lung functions and exacerbation rate will help to better treat the patients, reducing hospitalizations, and emergency treatments.
- Providing a better control of asthma would also allow a decreased health economic burden to the health care system and society, relieving the pressure on hospitals particularly crucial in the current health emergency situation.
- The IND/GLY/MF combination can play a competitive role vs alternative step-up option, considering both the side-effect profile challenge of systemic oral corticosteroids and the cost/availability/management challenges that come with the use of biological treatments.
- An effective and safe treatment administered once daily for asthma management could be a valuable option for a cutting-edge management of moderate to severe asthma, allowing to increase adherence to recommended doses of prescribed treatments.
- Improvement of symptoms' control means the increased quality of life for a large percentage of patients (up to 40% that remain uncontrolled despite usual therapy with ICS alone or combined with a LABA).
- The administration of a unique dose by means of a handy and dose confirming inhaler can help to increase patient independence and ability to manage his/her own treatment.
- Increased patient engagement and self-management would allow an increment in adherence to therapy while minimizing the risk of missing doses, particularly

when the use of IND/GLY/MF will be supported by the optional digital sensor

On the basis of these considerations, it can be inferred that once daily fixed drug combination could represent an improvement in key areas of asthmatic patient treatment. One additional positive aspect is the presence of a dedicated app that can increase patients' engagement to asthma management and assist in the control of the dosage administration. This technological support can provide a valuable option in modern medicine.

Therefore, inhaled triple LABA/LAMA/ICS combinations and particularly IND/GLY/MF provide a real possibility, for moderate-to-severe asthmatic patients, to achieve the main goals of asthma treatment. Among the positive outcomes of this triple therapeutic approach, prevention of asthma exacerbations, as well as better improvements in lung function and overall quality of life, can be considered the most important results of LABA/LAMA/ICS treatment.

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P. Morini, A. Rizzi, and O. Bonavita declare to be Novartis employees. S. Andaloro is a former Novartis employee, employed during the drafting of the manuscript. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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