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ADIS DRUG EVALUATION

Budesonide/Glycopyrronium/Formoterol: A Review in COPD

Young-A Heo[1]

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Abstract

Budesonide/glycopyrronium/formoterol (BREZTRI AEROSPHERE™; TRIXEO AEROSPHERE™) is an inhaled fixed-dose combination of the inhaled corticosteroid (ICS) budesonide, the long-acting muscarinic antagonist (LAMA) glycopyrronium bromide and the long-acting β_2-agonist (LABA) formoterol fumarate approved for the maintenance treatment of chronic obstructive pulmonary disease (COPD). It is delivered via a pressurized metered-dose Aerosphere inhaler and is formulated using co-suspension delivery technology. In two pivotal phase III trials of 24–52 weeks' duration, budesonide/glycopyrronium/formoterol reduced the rates of moderate/severe COPD exacerbations and improved lung function to a greater extent than budesonide/formoterol and/or glycopyrronium/formoterol. Budesonide/glycopyrronium/formoterol also demonstrated beneficial effects on dyspnoea, rescue medication requirements and health-related quality of life (HR-QOL), and reduced the risk of all-cause mortality. Budesonide/glycopyrronium/formoterol was generally well tolerated, with the tolerability profile being generally similar to that of the individual components. Budesonide/glycopyrronium/formoterol provides a useful and convenient option for the maintenance treatment of COPD, including for patients whose disease is inadequately controlled with dual ICS/LABA or LAMA/LABA therapy.

Plain Language Summary

Chronic obstructive pulmonary disease (COPD) is an inflammatory lung disease that is characterized by chronic airflow limitation and persistent respiratory symptoms. A step-up treatment approach combining an inhaled corticosteroid (ICS), a long-acting muscarinic antagonist (LAMA) and a long-acting β_2-agonist (LABA) may provide clinical benefits in patients with COPD whose disease is inadequately controlled by dual therapies (ICS/LABA or LAMA/LABA). Budesonide/glycopyrronium/formoterol (BREZTRI AEROSPHERE™; TRIXEO AEROSPHERE™) is a fixed-dose ICS/LAMA/LABA combination approved for the maintenance treatment of COPD. It is administered twice daily via a single pressurized metered-dose Aerosphere inhaler. Patients with moderate to very severe COPD receiving budesonide/glycopyrronium/formoterol had fewer moderate or severe COPD exacerbations and improved lung function, respiratory symptoms and quality of life compared with patients receiving ICS/LABA or LAMA/LABA therapy. The risk of death was reduced compared with that of patients receiving LAMA/LABA therapy. Budesonide/glycopyrronium/formoterol was generally well tolerated, with similar rates of adverse events to dual therapy. Budesonide/glycopyrronium/formoterol is a useful and convenient option for the maintenance treatment of COPD.

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The manuscript was reviewed by: ***S. A Antoniu***, Department of Medical Sciences II/Nursing/Palliative Care, Faculty of Medicine, Grigore T. Popa University of Medicine and Pharmacy, Iaşi, Romania; ***W. De Backer***, Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium; ***E. M. Kerwin***, Clinical Research Institute and Altitude Clinical Consulting, Medford, OR, USA.

✉ Young-A Heo
demail@springer.com

[1] Springer Nature, Private Bag 65901, Mairangi Bay, Auckland 0754, New Zealand

1 Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive inflammatory lung disease that is characterized by chronic airflow limitation and persistent respiratory symptoms (e.g. dyspnoea, sputum production and cough) [1]. Globally, COPD is associated with increasing morbidity and mortality, and poses a considerable burden on patients, caregivers and healthcare systems. The main goal of COPD treatment is to reduce symptom burden and the frequency and severity of exacerbations, while improving health-related quality of life (HR-QOL) and exercise tolerance.

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Budesonide/glycopyrronium/formoterol: (BREZTRI AEROSPHERE™; TRIXEO AEROSPHERE™) clinical considerations in COPD

Formulated as a pressurized metered-dose Aerosphere inhaler using co-suspension delivery technology.
Reduces exacerbation risk and improves lung function to a greater extent than budesonide/formoterol and/or glycopyrronium/formoterol.
Reduces the need for rescue medication and improves dyspnoea, HR-QOL and all-cause mortality rate.
Generally well tolerated.

Various pharmacological agents are available for COPD treatment, including bronchodilators (e.g. β_2-agonists, anticholinergics, methylxanthines), anti-inflammatory agents [inhaled corticosteroids (ICS)], phosphodiesterase-4 inhibitors and mucolytic agents. Inhaled bronchodilator therapy is the mainstay treatment for COPD, with long-acting formulations preferred over short-acting formulations [1].

Combining bronchodilators with different mechanisms of action, such as a long-acting β_2-agonist (LABA) and a long-acting muscarinic antagonist (LAMA), may increase the degree of bronchodilation and decrease symptoms compared with monotherapy with individual bronchodilators [1]. A step-up treatment approach combining ICS, LABA and LAMA has been shown to improve lung function and patient-reported outcomes, including exacerbation risk, in patients with moderate to very severe COPD who are symptomatic and have a history of frequent and/or severe exacerbations [1]. Additionally, using a single inhaler instead of multiple separate inhalers for delivering combination therapies may greatly improve treatment adherence and patient compliance [2].

Budesonide/glycopyrronium bromide/formoterol fumarate (BREZTRI AEROSPHERE™; TRIXEO AEROSPHERE™; hereafter referred to as budesonide/glycopyrronium/formoterol) is a fixed-dose combination (FDC) of the ICS budesonide, the LAMA glycopyrronium bromide and the LABA formoterol fumarate, administered via a pressurized metered-dose inhaler (pMDI) using Aerosphere delivery technology [3, 4]. Budesonide/glycopyrronium/formoterol is approved for the maintenance treatment of COPD in several counties, including the USA [3], those of the EU [4], China [5] and Japan [6]. This article reviews the therapeutic efficacy and tolerability of budesonide/glycopyrronium/formoterol in this indication and summarizes relevant pharmacological data.

2 Pharmacodynamic Properties

The pharmacological properties of budesonide, glycopyrronium and formoterol are well established [7, 8]. This section primarily focuses on the pharmacological properties of budesonide/glycopyrronium/formoterol, an FDC of two bronchodilators with different mechanisms of action and a glucocorticosteroid, formulated using a co-suspension delivery technology [3, 4]. Budesonide is a potent glucocorticosteroid with a rapid onset of action and demonstrates dose-dependent anti-inflammatory action in the airways. Glycopyrronium is a LAMA (anticholinergic agent) that exhibits reversible competitive inhibition of muscarinic receptors. In human airways, it inhibits the muscarinic M_3 receptor at the smooth muscle, leading to bronchodilation. Glycopyrronium dose-dependently prevents methylcholine- and acetylcholine-induced bronchoconstriction, which lasts > 12 h. Formoterol, a selective LABA with a rapid onset (1–3 min after inhalation) and long duration (> 12 h after a single dose) of action, has a higher binding selectivity to β_2- over β_1-adrenoreceptors. It rapidly relaxes bronchial smooth muscle in patients with reversible airway obstruction, with the bronchodilating effect being dose-dependent [3, 4].

Budesonide/glycopyrronium/formoterol delivered by a pressurized metered-dose Aerosphere inhaler is formulated using a co-suspension delivery technology, which creates a uniform suspension of drug crystals and porous phospholipid particles, thereby enabling simultaneous delivery of multiple drugs from one inhaler [9]. This delivery technology offers excellent dose uniformity and stability, and minimizes the potential for formulation-related drug–drug interactions in combination therapies [9].

The dose consistency, robustness and reliability of the co-suspension delivery technology used in the budesonide/glycopyrronium/formoterol pressurized metered-dose Aerosphere inhaler was demonstrated across several studies [10–12]. In patients with moderate to very severe COPD ($n = 17$), radiolabelled budesonide/glycopyrronium/formoterol administered via a co-suspension delivery technology-based pMDI was deposited efficiently in both the central and peripheral regions of the lungs, with 32.1% and 67.2% of the emitted dose detected in the lungs and in the oropharyngeal and stomach regions, respectively [11]. Radiolabelled doses of budesonide/glycopyrronium/formoterol were deposited uniformly across the lungs regardless of disease severity [11]. In addition, results from in vitro and healthy volunteer studies indicate that budesonide/glycopyrronium/formoterol pMDI formulated with co-suspension delivery technology is more forgiving for patients and less susceptible to drug delivery variability than traditional MDI formulations as it stays suspended with minimal shaking [12] and shows adequate deposition in the lungs with a short breath-hold of 3 s

[10]. To ensure proper treatment administration, budesonide/glycopyrronium/formoterol may be used with a spacer in patients with difficulty coordinating actuation with inhalation [4].

In a functional respiratory imaging study in patients with moderate to severe COPD ($n = 23$), twice-daily inhalation of budesonide/glycopyrronium/formoterol 320/18/9.6 µg and glycopyrronium/formoterol 18/9.6 µg significantly ($p < 0.0001$) increased specific image-based airway volume and reduced specific image-based airway resistance from baseline at day 29, with a higher increase in airway volume observed with budesonide/glycopyrronium/formoterol than with glycopyrronium/formoterol [least-square means (LSM) ratio 1.09; 95% CI 1.03–1.16; $p = 0.0061$] [13].

A thorough QT study was not conducted with budesonide/glycopyrronium/formoterol as budesonide is not known to prolong the QTc interval [3]. In a thorough QT study, glycopyrronium/formoterol was not associated with clinically significant effects on the QTc interval. Budesonide/glycopyrronium/formoterol had no clinically meaningful effects on cardiac rhythm in patients with COPD [3].

Given the risk of potentially additive pharmacodynamics effects and class-related adverse reactions, concomitant use of budesonide/glycopyrronium/formoterol with other LAMA- or LABA-containing products is not recommended (Sect. 5.1) [3, 4].

3 Pharmacokinetic Properties

Coadministration of budesonide, glycopyrronium and formoterol had no effect on the pharmacokinetics of the individual drugs, with the pharmacokinetic properties (including systemic exposure) of budesonide, glycopyrronium and formoterol administered via a single inhaler being comparable to those of the monocomponents administered separately [4] or as budesonide/formoterol or glycopyrronium/formoterol [3, 14].

Budesonide, glycopyrronium and formoterol exhibit linear pharmacokinetics across respective dose ranges of 80–320 µg, 18–144 µg and 2.4–38.4 µg [3]. Following inhalation of budesonide/glycopyrronium/formoterol in patients with COPD, maximum plasma concentrations were reached within 20–40 min for budesonide, 2–6 min for glycopyrronium and 20–60 min for formoterol [3, 4]. In population pharmacokinetic analyses, after repeated dosing of budesonide/glycopyrronium/formoterol, steady state is reached within ≈1–3 days and the area under the curve (AUC) from 0 to 12 h ($AUC_{0–12}$) is ≈1.3 to 1.8 times higher than after the first dose [3, 4]. At steady state, the estimated apparent volume of distribution of budesonide, glycopyrronium and formoterol is ≈1200 L, 5500 L and 2400 L, respectively. At concentrations of 1–100 nmol/L for budesonide, 2–500 nmol/L for glycopyrronium and 10–500 nmol/L for formoterol, the corresponding mean plasma protein binding is 86–87%, 43–54% and 46–58% [3, 4].

Budesonide is rapidly and extensively metabolised via CYP3A4 to metabolites of low glucocorticosteroid activity [3, 4]. Glycopyrronium is primarily metabolised by CYP2D6, but the metabolism does not play a significant role in its overall elimination, while formoterol is primarily metabolized by direct glucuronidation and *O*-demethylation (mainly by CYP2D6 and CYP2C) followed by conjugation to inactive metabolites. Secondary pathways involved in formoterol metabolism include deformylation and sulfate conjugation. The effective half-lives of budesonide, glycopyrronium and formoterol are ≈5 h, 15 h and 10 h, respectively, as derived from a population pharmacokinetics analysis. Budesonide is mainly excreted as metabolites in urine and faeces. Following intravenous administration of radiolabelled glycopyrronium, 85% of the dose was recovered in the urine within 48 h. Following simultaneous intravenous and oral administration of radiolabelled formoterol in healthy volunteers, 62 and 24% of the dose was recovered in the urine and faeces [3, 4].

Age, gender, ethnicity (Asian and Western [15, 16]) and bodyweight have no clinically relevant effects on the pharmacokinetics of budesonide, glycopyrronium and formoterol [3, 4]. Budesonide/glycopyrronium/formoterol has not been formally studied in patients with kidney or hepatic impairment. No dosage adjustments of budesonide/glycopyrronium/formoterol are required in elderly patients, in patients with mild to moderate kidney impairment or in patients with mild to moderate hepatic impairment. Budesonide/glycopyrronium/formoterol should only be used in patients with severe kidney impairment, end-stage kidney disease requiring dialysis or severe hepatic impairment, if the expected benefit outweighs the potential risk. Because of the potential increase in systemic exposure of budesonide and formoterol in patients with severe hepatic impairment, monitoring for signs of increased drug exposure [3] or adverse reactions [4] is recommended in this population.

There have been no clinical drug–drug interaction studies conducted with budesonide/glycopyrronium/formoterol; however, based on in vitro studies, the potential for metabolic interactions is considered to be low [3, 4]. Because budesonide is mainly metabolised by CYP3A4, coadministration with strong CYP3A inhibitors, including itraconazole, ketoconazole, HIV protease inhibitors and cobicistat-containing products, should be used with caution [3] or avoided unless the potential benefit outweighs the increased risk of systemic corticosteroid adverse reactions (if coadministered, monitoring of such reactions is recommended) [4]. Of note, this is of limited clinical importance for short-term (1–2 weeks) treatment [3, 4]. As glycopyrronium is primarily eliminated by kidneys, concomitant use of budesonide/glycopyrronium/

formoterol with drugs that affect kidney excretion may result in drug interactions. In vitro, glycopyrronium is a substrate of OCT2 and MATE1/2K and coadministration with cimetidine (an inhibitor of OCT2 and MATE1) increased total systemic exposure of glycopyrronium by 22% and decreased glycopyrronium clearance by 23%. Coadministration of budesonide/glycopyrronium/formoterol with β-adrenergic blockers may weaken the effects of formoterol, and should be avoided unless there are no acceptable alternative treatments available. Concomitant use of budesonide/glycopyrronium/formoterol with xanthine derivatives, steroids or diuretics may potentiate the hypokalaemic effects of formoterol. Caution is required when budesonide/glycopyrronium/formoterol is coadministered with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs that are known to prolong the QTc interval [3, 4].

4 Therapeutic Efficacy

This section focuses on the efficacy of the approved dosage of inhaled budesonide/glycopyrronium/formoterol 320/18/9.6 µg twice daily (Sect. 6) in COPD patients, as evaluated in two pivotal, randomized, double-blind, active-controlled, multinational phase III trials: the 52-week ETHOS trial (NCT02465567) [17] and the 24-week KRONOS trial (NCT02497001) [18].

ETHOS and KRONOS enrolled patients aged 40–80 years with moderate to very severe COPD [defined as postbronchodilator forced expiratory volume in 1 s (FEV_1) ≥ 25% to < 65% [17] or ≥ 25% to < 80% [18] predicted normal value] [17, 18]. Patients were former (≥ 10 packs-years) or current smokers and were symptomatic [a score of ≥ 10 on the COPD assessment test (CAT)] despite receiving ≥ 2 inhaled maintenance therapies for ≥ 6 weeks prior to screening [17, 18]. Patients enrolled in ETHOS were also required to have a history of ≥ 1 moderate/severe (if FEV_1 < 50% predicted normal value) or ≥ 2 moderate or ≥ 1 severe (if FEV_1 ≥ 50% predicted normal value) COPD exacerbation(s) in the year prior to screening [17]. Key exclusion criteria included a current diagnosis of asthma or any significant respiratory diseases other than COPD, or clinically significant uncontrolled non-respiratory disease and hospitalization due to poorly controlled COPD ≤ 3 months prior to, or during, screening [17, 18].

Following a screening period (during which all patients discontinued COPD maintenance therapies, except ICS if used before screening, and received open-label ipratropium as maintenance treatment and salbutamol sulphate as rescue medication), eligible patients were randomized to receive twice daily inhalation of budesonide/glycopyrronium/formoterol 320/18/9.6 µg MDI, glycopyrronium/formoterol 18/9.6 µg MDI or budesonide/formoterol 320/9.6 µg MDI; ICS and open-label ipratropium were discontinued at the time of randomization [17, 18]. Some patients were also randomized to receive twice daily inhalation of budesonide/glycopyrronium/formoterol 160/18/9.6 µg MDI (in ETHOS) [17] and open-label budesonide/formoterol 400/12 µg dry powder inhaler (DPI; in KRONOS) [18]. Data from the budesonide/glycopyrronium/formoterol 160/18/9.6 µg treatment arm in ETHOS are not discussed further [17]. Randomization was stratified by exacerbation history, postbronchodilator FEV_1, blood eosinophil count and country in ETHOS and by reversibility to salbutamol sulphate, postbronchodilator FEV_1 and country in KRONOS [17, 18]. Following the completion of the 24-week KRONOS trial, two extension studies were conducted in subsets of patients who continued to receive randomized treatment for additional 28 weeks; the primary outcome was safety (Sect. 5.1) and efficacy outcomes were assessed as secondary endpoints in the extension studies [19, 20].

The primary efficacy endpoint in ETHOS was the annualized rate of moderate or severe COPD exacerbations (Sect. 4.1) [17]. In KRONOS, the co-primary efficacy endpoints were FEV_1 AUC from 0–4 h ($AUC_{0–4}$) and the change in morning pre-dose trough FEV_1 from baseline (Sect. 4.2) over 24 weeks (EU and Canada regulatory approaches) and at week 24 (US regulatory approach) [18]. Across the trials, primary and secondary efficacy endpoints were analyzed in the modified intention-to-treat population and were tested in a combination of sequential, hierarchical and/or simultaneous approaches across comparisons to control type I error; efficacy endpoints that achieved $p < 0.05$ but either failed or were excluded from the type I error control strategy were deemed nominally significant [17, 18].

4.1 Exacerbations

In ETHOS, budesonide/glycopyrronium/formoterol significantly ($p \leq 0.0027$) reduced the model-estimated rates of annualized on-treatment moderate/severe COPD exacerbations (primary endpoint) relative to glycopyrronium/formoterol and budesonide/formoterol by 24% and 13%, respectively (Table 1) [17, 21]. These findings were supported by exacerbation data from KRONOS (Table 1) [18]. The exacerbation benefit associated with budesonide/glycopyrronium/formoterol was generally observed across all 4-week intervals of the 52-week treatment period in ETHOS (prespecified analysis [22]) and the 24-week treatment period in KRONOS (post hoc analysis [23]).

In ETHOS, budesonide/glycopyrronium/formoterol significantly ($p \leq 0.0057$) prolonged the time to first moderate/severe COPD exacerbation relative to glycopyrronium/formoterol [hazard ratio (HR) 0.88; 95% CI 0.81–0.96] and budesonide/formoterol (0.89; 0.81–0.97) [17, 21]. Similarly, in KRONOS, budesonide/glycopyrronium/formoterol

delayed the time to first moderate/severe COPD exacerbation compared with glycopyrronium/formoterol (HR 0.593; nominal $p < 0.0001$) and budesonide/formoterol (HR 0.747; $p = 0.0635$) [18].

In subgroup analyses of ETHOS and KRONOS, some of which were post hoc, budesonide/glycopyrronium/formoterol generally reduced moderate or severe COPD exacerbation rates compared with glycopyrronium/formoterol and budesonide/formoterol irrespective of sex, age, race, region, COPD exacerbation history, CAT score, prior ICS use, bronchodilator reversibility and postbronchodilator FEV_1 [3, 4, 17, 24–32]. Moreover, benefits were seen across a broad range of baseline eosinophil counts, but tended to increase as eosinophil counts increased [17, 18, 24].

4.2 Lung Function

In the spirometry sub-study of ETHOS, budesonide/glycopyrronium/formoterol significantly increased FEV_1 $AUC_{0–4}$ versus budesonide/formoterol and morning pre-dose trough FEV_1 responses versus glycopyrronium/formoterol (prespecified comparisons of interest) both over 24 weeks and at week 24 (Table 1) [3, 4, 33]. Budesonide/glycopyrronium/formoterol also provided nominally significant improvements in FEV_1 $AUC_{0–4}$ versus glycopyrronium/formoterol and morning pre-dose trough FEV_1 responses versus budesonide/formoterol, both over 24 weeks and at week 24 (statistical tests not adjusted for multiplicity in hierarchical testing plan; Table 1). Improvements in lung function with budesonide/glycopyrronium/formoterol were maintained over the 52 weeks of treatment [3, 4, 33].

Table 1 Efficacy of inhaled budesonide/glycopyrronium/formoterol in patients with moderate to very severe COPD at/over 24 or 52 weeks in the phase III ETHOS and KRONOS trials

Study treatment (μg bd) [no. of mITT pts[a]]	Annualized rate of moderate/severe exacerbations (RR for BUD/GLY/FOR vs comparator; 95% CI)[b]	FEV_1 $AUC_{0–4}$ [mL] (LSM difference for BUD/GLY/FOR vs comparator; 95% CI)[c]		LSM change from BL in morning pre-dose trough FEV_1 [mL] (LSM difference for BUD/GLY/FOR vs comparator; 95% CI)[c]	
		At wk 24	Over 24 wks	At wk 24	Over 24 wks
ETHOS [17, 21, 33]					
BUD/GLY/FOR 320/18/9.6 [2137]	1.08	NA	294	NA	129
GLY/FOR 18/9.6 [2120]	1.42 (0.76; 0.69, 0.83)**	NA (53; 29, 77)**[d]	245 (49; 31, 66)**[d]	NA (35; 12, 57)*	86 (43; 25, 60)**
BUD/FOR 320/9.6 [2131]	1.24 (0.87; 0.79, 0.95)*	NA (119; 95, 143)**	194 (99; 82, 117)**	NA (76; 54, 99)**[d]	53 (76; 58, 94)**[d]
KRONOS [18]					
BUD/GLY/FOR 320/18/9.6 [639]	0.46	292	305	124	147
GLY/FOR 18/9.6 [625]	0.95 (0.48; 0.37, 0.64)**	288 (5; −25, 34)	288 (16; −6, 38)	111 (13; −9, 36)	125 (22; 4, 39)*
BUD/FOR 320/9.6 [314][e]	0.56 (0.82; 0.58, 1.17)	177 (116; 80, 152)**	201 (104; 77, 131)**	50 (74; 47, 102)***[d]	73 (74; 52, 95)**
BUD/FOR 400/12 DPI [318]	0.55 (0.83; 0.59, 1.18)	NA	214 (91; 64, 117)**	NA	88 (59; 38, 80)**[d]

Unless otherwise stated, each formulation was administered via MDI

$AUC_{0–4}$ area under the curve from 0–4 h, *bd* twice daily, *BL* baseline, *BUD* budesonide, *CI* confidence interval, *DPI* dry powder inhaler, *FEV_1* forced expiratory volume in 1 s, *FOR* formoterol fumarate, *GLY* glycopyrronium bromide, *LSM* least squares means, *MDI* metered dose inhaler, *mITT* modified intention-to-treat, *NA* not available, *pts* patients, *RR* rate ratio, *wk(s)* week(s)

*$p < 0.05$, ** $p < 0.0001$ favouring BUD/GLY/FOR

[a]No. of mITT pts varied for FEV_1 $AUC_{0–4}$ and morning pre-dose trough FEV_1 in the spirometric sub-study of ETHOS and KRONOS at wk 24 (BUD/GLY/FOR $n = 633$ and 634, GLY/FOR $n = 588$ and 586, BUD/FOR $n = 605$ and 608 in the sub-study of ETHOS; BUD/GLY/FOR $n = 436$ and 565, GLY/FOR $n = 403$ and 522, BUD/FOR $n = 201$ and 266 in KRONOS) [3] and in the sub-study of ETHOS over 24 weeks (BUD/GLY/FOR $n = 747$, GLY/FOR $n = 779$, BUD/FOR $n = 755$) [4]

[b]Primary endpoint in ETHOS; model-estimated exacerbation rates based on the randomized treatment period (24 weeks [18] or 52 weeks [17])

[c]Co-primary endpoints in KRONOS; assessed at wk 24 for the US regulatory approach and over 24 wks for the EU and Canadian

[d]Nominal *p* value (not adjusted for multiplicity and hierarchical testing scheme)

[e]Demonstrated noninferiority to BUD/FOR DPI for co-primary endpoints [18]

In KRONOS, budesonide/glycopyrronium/formoterol significantly increased FEV_1 $AUC_{0–4}$ compared with budesonide/formoterol both over 24 weeks and at week 24 and compared with open-label budesonide/formoterol DPI over 24 weeks (prespecified comparisons of interest for co-primary endpoints; Table 1) [18]. Budesonide/glycopyrronium/formoterol also significantly increased morning pre-dose trough FEV_1 responses compared with glycopyrronium/formoterol (prespecified comparison of interest for co-primary endpoints), although only over 24 weeks but not at week 24 (Table 1). The difference in morning pre-dose trough FEV_1 responses at week 24 was nominally significant when analyzed using the attributable estimand, which accounts for missing data, suggesting that the high dropout rate in the glycopyrronium/formoterol group may have played a role in this non-significant finding. Budesonide/formoterol was noninferior to open-label budesonide/formoterol DPI for these co-primary endpoints over 24 weeks (Table 1) [18].

Moreover, budesonide/glycopyrronium/formoterol improved the lung function profile over the 12-h dosing interval in the pulmonary function test sub-study of KRONOS in patients with moderate to very severe COPD (n = 687) [34]. At week 24, budesonide/glycopyrronium/formoterol significantly ($p \leq 0.015$) improved FEV_1 $AUC_{0–12}$ from baseline relative to budesonide/formoterol and open-label budesonide/formoterol DPI (by 95 and 65 mL, respectively), with the improvement being similar to that observed with glycopyrronium/formoterol. The improvements in FEV_1 AUC were maintained throughout the 12-h dosing period in all treatment groups, albeit being greater in the first 6 h period compared with the second [34].

In subgroup analyses of ETHOS and KRONOS, some of which were post hoc, budesonide/glycopyrronium/formoterol generally improved lung function (FEV_1 $AUC_{0–4}$ and morning pre-dose trough FEV_1 responses) compared with glycopyrronium/formoterol and budesonide/formoterol irrespective of sex, age, race, COPD exacerbation history, CAT score, prior ICS use, bronchodilator reversibility and postbronchodilator FEV_1 [3, 4, 24–26, 28, 29, 32]. Patients with elevated eosinophil counts at baseline tended to benefit more with budesonide/glycopyrronium/formoterol relative to glycopyrronium/formoterol and budesonide/formoterol, with greater benefits observed in patients with baseline eosinophil counts of > 150 cells/mm^3 than those with < 150 cells/mm^3 [17, 18, 24]. Of note, budesonide/glycopyrronium/formoterol had no significant benefit over glycopyrronium/formoterol for morning pre-dose trough FEV_1 in patients with baseline eosinophil counts of < 150 cells/mm^3 in KRONOS [18].

4.3 Dyspnoea and Rescue Medications

In ETHOS, budesonide/glycopyrronium/formoterol significantly ($p < 0.0001$) improved the Transition Dyspnoea Index (TDI) focal score and improved (nominal $p < 0.0001$) Exacerbations of Chronic Pulmonary Disease Tool (EXACT) total score over 24 weeks compared with glycopyrronium/formoterol (LSM treatment differences 0.40 and −1.20) and budesonide/formoterol (0.31 and −1.06); the improvements were maintained over 52 weeks [17, 35].

In KRONOS, budesonide/glycopyrronium/formoterol significantly improved breathlessness (assessed by TDI score) over 24 weeks relative to open-label budesonide/formoterol DPI (LSM treatment difference 0.46; p = 0.0031), while a non-significant improvement seen relative to glycopyrronium/formoterol (0.18) and budesonide/formoterol (0.24) [18]. Budesonide/glycopyrronium/formoterol was also associated with improvements in COPD respiratory symptoms (assessed by RS-Total score) over 24 weeks compared with glycopyrronium/formoterol (LSM treatment difference −0.38; nominal $p = 0.043$), but not compared with budesonide/formoterol or open-label budesonide/formoterol DPI (−0.16 for both) [18].

Budesonide/glycopyrronium/formoterol also reduced the need for on-treatment rescue medication from baseline over 24 or 52 weeks [17, 35]. In ETHOS, budesonide/glycopyrronium/formoterol recipients used significantly ($p \leq 0.0002$) less rescue medication than budesonide/formoterol and glycopyrronium/formoterol recipients over 24 weeks (LSM treatment differences −0.51 and −0.37 puffs/day) and 52 weeks (−0.53 and −0.35 puffs/day) [17, 35], whereas in KRONOS, there were no statistically significant differences between the treatment groups [18].

4.4 All-Cause Mortality

Budesonide/glycopyrronium/formoterol was associated with a reduced risk of mortality in patients with moderate to very severe COPD [17, 36]. In ETHOS, budesonide/glycopyrronium/formoterol reduced the risk of all-cause mortality, a type 1 error-controlled secondary endpoint, relative to glycopyrronium/formoterol (HR 0.54; 95% CI 0.34–0.87), while a non-significant risk reduction (based on the 95% CI) was observed relative to budesonide/formoterol (0.78; 0.47–1.30) [17]. These findings were consistent in an additional analysis conducted using a final retrieved vital status dataset, thereby supporting the robustness of the mortality findings (HR 0.51; 95% CI 0.33−0.80; unadjusted $p = 0.0035$ relative to glycopyrronium/formoterol and 0.72, 0.44−1.16; unadjusted $p = 0.1721$ relative to budesonide/formoterol) [36]. The reduced mortality risk observed with budesonide/glycopyrronium/formoterol versus glycopyrronium/formoterol was consistently seen when the first 30,

60 or 90 days of treatment were excluded from the analyses (HR ≤ 0.63 for all), indicating that the results were not driven by acute ICS withdrawal [36].

When the impact of budesonide/glycopyrronium/formoterol on the time to all-cause death was analysed by exacerbation history, baseline postbronchodilator FEV_1% predicted and prior triple therapy or ICS use at screening, the triple therapy demonstrated favourable mortality risk reductions over dual therapy across all subgroups, except in patients without prior ICS use at screening, possibly due to small sample size [36]. The mortality benefit of budesonide/glycopyrronium/formoterol was most prominent in patients with ≥ 2 exacerbations in the previous year or postbronchodilator FEV_1 ≥ 50% predicted (these subgroups had substantial overlap due to the inclusion criteria requirement in ETHOS) and in those with prior triple therapy or ICS use [36]. Across the treatment groups, the most common cause of death was cardiovascular-related and a reduction in cardiovascular caused deaths appeared to account for the majority of the treatment difference between budesonide/glycopyrronium/formoterol versus glycopyrronium/formoterol [36].

4.5 Other Outcomes

Budesonide/glycopyrronium/formoterol was associated with improvements from baseline in HR-QOL in ETHOS and KRONOS [17, 18]. In ETHOS, budesonide/glycopyrronium/formoterol significantly ($p \leq 0.0001$) improved St George's Respiratory Questionnaire (SGRQ) total scores relative to glycopyrronium/formoterol and budesonide/formoterol over 24 weeks (LSM treatment difference −1.62 and −1.38) and 52 weeks (−1.59 and −1.31) [17]. Furthermore, the SGRQ response rate [i.e. decrease of minimal clinically important difference (MCID) of ≥ 4 units in SGRQ total score] was significantly ($p < 0.001$) higher with budesonide/glycopyrronium/formoterol than with glycopyrronium/formoterol and budesonide/formoterol at week 24 (50.4% vs 42.6% and 44.7%) and at week 52 (44.2% vs 36.5% and 39.2%) [17, 35]. In KRONOS, budesonide/glycopyrronium/formoterol nominally significantly improved total SGRQ score over 24 weeks relative to glycopyrronium/formoterol (LSM treatment difference −1.22; nominal $p = 0.0259$), but not to budesonide/formoterol (−0.45) or open-label budesonide/formoterol DPI (−1.26) [18].

In KRONOS, at week 24, the time to clinically important deterioration (i.e. ≥ 100 mL decrease in trough FEV_1, ≥ 4 points increase in SGRQ total score, TDI focal score of ≤ −1 points or moderate/severe COPD exacerbation during the treatment period) was reduced (nominal $p \leq 0.0276$) with budesonide/glycopyrronium/formoterol versus budesonide/formoterol (HR 0.83; 95% CI 0.70–0.98) and open-label budesonide/formoterol DPI (0.81; 0.69–0.96), but the difference was not significant versus glycopyrronium/formoterol (0.88; 0.76–1.00) [18]. This endpoint was not reported in ETHOS as lung function was only assessed in a subset of patients.

5 Tolerability

Budesonide/glycopyrronium/formoterol was generally well tolerated in patients with moderate to very severe COPD in the ETHOS and KRONOS trials discussed in Sect. 4, with its safety profile being generally similar to the established safety profiles of its individual components [17, 18]. Discussion in this section focuses largely on data available from the 52-week ETHOS trial (Sect. 4) [18].

In ETHOS, treatment-emergent adverse events (TEAEs) occurred in 63.8% of 2144 budesonide/glycopyrronium/formoterol recipients, 61.7% of 2125 glycopyrronium/formoterol recipients and 64.5% of 2136 budesonide/formoterol recipients [18]. The most common (≥ 3%) TEAEs occurring more frequently in the budesonide/glycopyrronium/formoterol than glycopyrronium/formoterol and/or budesonide/formoterol groups included upper respiratory tract infection (5.7% vs 4.8% and 5.4%), pneumonia (4.6% vs 2.9% and 5.0%), back pain (3.1% vs 2.6% and 3.0%) and oral candidiasis (3.0% vs 1.1% and 2.7%) [3]. Rates of serious TEAEs (19.9% vs 20.4% and 20.6%) and treatment discontinuation due to TEAEs (5.6% vs 6.9% and 6.6%) were similar across treatment groups [18]. During the treatment period, a total of 84 deaths occurred in patients treated with budesonide/glycopyrronium/formoterol ($n = 20$), glycopyrronium/formoterol ($n = 35$) or budesonide/formoterol ($n = 29$); most deaths were due to cardiovascular and respiratory causes but majority of these cases were not considered to be treatment-related [17, 24].

The nature and incidence of TEAEs observed in KRONOS was consistent with those observed in ETHOS, with the tolerability profile of budesonide/glycopyrronium/formoterol in the Japanese [25] and Chinese [26] subpopulations being generally similar to that of the overall population in KRONOS.

5.1 Adverse Events of Special Interest

Similar to other inhaled therapies, budesonide/glycopyrronium/formoterol may produce potentially life-threatening paradoxical bronchospasm [3, 4]. If patients develop paradoxical bronchospasm, budesonide/glycopyrronium/formoterol should be discontinued immediately and substituted with alternative therapy [3, 4].

Like other muscarinic antagonists and β_2-agonists, budesonide/glycopyrronium/formoterol may potentially produce clinically significant cardiovascular effects, including increased pulse rate, increased blood pressure,

electrocardiographic changes and cardiac arrhythmias [3, 4]. In addition, budesonide/glycopyrronium/formoterol may cause serious hypokalaemia, which can potentially lead to adverse cardiovascular effects. Budesonide/glycopyrronium/formoterol should be used with caution in patients with cardiovascular disorders (e.g. unstable ischemic heart disease, cardiac arrhythmias), convulsive disorders or thyrotoxicosis, in patients who are unusually responsive to β_2-agonists and in those with known or suspected QT interval prolongation or who are receiving medications known to affect the QT interval [3, 4]. In ETHOS and KRONOS, the incidence of confirmed major adverse cardiovascular events was low and similar across the budesonide/glycopyrronium/formoterol, glycopyrronium/formoterol, and budesonide/formoterol groups [37], with no clinically meaningful differences seen in vital signs and electrocardiogram findings [17, 18]. Moreover, in a 24-h Holter monitoring sub-study of the ETHOS trial ($n = 721$), changes from baseline in 24-h heart rate, day-time heart rate, night-time heart rate and 24-h minimum heart rate were small and showed no meaningful differences across treatment groups [37].

Budesonide/glycopyrronium/formoterol, like other β_2-agonist-containing products, may aggravate preexising diabetes mellitus (transient hyperglycaemia observed with inhalation of high doses of β_2-agonists) and ketoacidosis [3, 4]. Therefore, blood glucose level monitoring following the initiation of budesonide/glycopyrronium/formoterol in patients with diabetes is recommended in the EU [4].

As with other anticholinergic medications, budesonide/glycopyrronium/formoterol should be used with caution in patients with urinary retention or narrow-angle glaucoma and should be discontinued if signs or symptoms of acute narrow-angle glaucoma develop [3, 4].

The use of ICS may increase the risk of pneumonia [3, 4]. In ETHOS, the time to the first confirmed pneumonia event was shorter in patients treated with ICS-containing therapy (i.e. budesonide/glycopyrronium/formoterol and budesonide/formoterol) than those treated with non-ICS-containing therapy (i.e. glycopyrronium/formoterol), with the incidence of serious confirmed pneumonia events also being higher (unadjusted $p < 0.05$) with ICS-containing therapy than with non-ICS-containing therapy (2.4–3.0% vs 1.3%) [18]. In addition, long-term use of ICS may increase the risk of systemic corticosteroid adverse events [e.g. Cushing's syndrome, decrease in bone mineral density (BMD), cataract and glaucoma] [3, 4]. In a 28-week extension study of KRONOS in patients with moderate to very severe COPD ($n = 456$), budesonide/glycopyrronium/formoterol and budesonide/formoterol (both ICS-containing therapies) were non-inferior to glycopyrronium/formoterol (non-ICS-containing therapy) with respect to primary BMD and ophthalmological safety endpoints [20]. Across the treatment groups, no clinically meaningful differences in the changes from baseline in BMD and ophthalmological safety endpoints were observed and the incidence of bone- and ocular-related TEAEs was low (≤ 3.1% incidence each group) [20]. It is recommended to assess BMD before and during treatment with budesonide/glycopyrronium/formoterol and a referral to ophthalmology should be considered if ocular symptoms develop [3, 4].

6 Dosage and Administration

Inhaled budesonide/glycopyrronium/formoterol is approved for the maintenance treatment of COPD in adults in the USA [3], and the maintenance treatment of moderate to severe COPD in adults not adequately controlled with a combination of an ICS and a LABA or a combination of a LABA and LAMA therapy in the EU [4]. The recommended dosage of budesonide/glycopyrronium/formoterol is 320/18/9.6 μg twice daily in the morning and in the evening [3, 4]. Each actuation from the inhaler delivers 160 μg of budesonide, 9 μg of glycopyrronium bromide (glycopyrrolate [3]) equivalent to 7.2 μg of glycopyrronium and 5 μg of formoterol fumarate dihydrate (4.8 μg of formoterol fumarate [3]) [3, 4].

Budesonide/glycopyrronium/formoterol is not indicated for the relief of acute bronchospasm (i.e. as a rescue medication) or for the treatment of asthma [3, 4]. Patients are recommended to rinse their mouths with water without swallowing after inhalation to reduce the risk of oropharyngeal candidiasis [3, 4]. Local prescribing information should be consulted for further details regarding administration, contraindications, potential drug interactions, warnings and precautions, and use in special patient populations.

7 Place of Budesonide/Glycopyrronium/Formoterol in the Management of COPD

Management strategies in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines include pharmacological and non-pharmacological interventions, with all patients (if applicable) strongly encouraged to quit smoking [1]. In patients with COPD, pharmacological treatment decisions should be individualized based on several factors, including the severity of symptoms, risk of exacerbations, co-existing comorbidities, drug availability, side-effect profile and costs, and patient preference and the ability to properly use inhaler devices [1].

The GOLD guidelines recommend a single bronchodilator therapy as the initial pharmacological option in patients with COPD, with patients with more severe symptoms or higher risk of exacerbations and/or blood eosinophil counts of ≥ 300 cells/mm^3 usually requiring a dual combination therapy with a LAMA plus LABA or ICS plus LABA [1].

Available evidence suggests that escalating to triple combination therapy with ICS, LAMA and LABA may provide clinical and mortality benefits in COPD patients with persistent exacerbations, persistent breathlessness and/or exercise limitation, despite receiving dual ICS/LABA or LAMA/LABA therapy [1]. To avoid the need for multiple inhalers with different techniques and/or different dosing regimens, several single inhalers containing FDCs of ICS, LAMA and LABA have been developed [38]. One such combination is budesonide/glycopyrronium/formoterol. Glycopyrronium and formoterol induce relaxation of airway smooth muscle via two different mechanisms of action, while budesonide reduces inflammation in the airways (Sect. 2).

The efficacy of budesonide/glycopyrronium/formoterol was established in the phase III ETHOS and KRONOS trials in patients with moderate to very severe COPD (Sect. 4). Budesonide/glycopyrronium/formoterol significantly reduced the annualized moderate/severe COPD exacerbation rate over 52 weeks compared with glycopyrronium/formoterol and budesonide/formoterol in ETHOS, while in the 24-week KRONOS study, there was a significant difference for budesonide/glycopyrronium/formoterol versus glycopyrronium/formoterol and a numerical difference versus budesonide/formoterol (Sect. 4.1). Budesonide/glycopyrronium/formoterol also improved lung function to a greater extent than dual LAMA/LABA and/or ICS/LABA therapy over 24 weeks, with the improvement in lung function maintained throughout the 12-h dosing period (Sect. 4.2). In addition, budesonide/glycopyrronium/formoterol improved dyspnoea and reduced the need for rescue medication (Sect. 4.3), improved HR-QOL to a clinically meaningful extent and delayed the time to clinically important deterioration (Sect. 4.5).

Exacerbation and lung function benefits associated with budesonide/glycopyrronium/formoterol were seen regardless of various demographic and background factors, such as sex, age, race, COPD exacerbation history, CAT score, prior ICS use, bronchodilator reversibility and postbronchodilator FEV_1 (Sects. 4.1 and 4.2). Moreover, the beneficial effects of budesonide/glycopyrronium/formoterol were seen across a broad range of baseline eosinophil counts, with patients experiencing a more prominent treatment benefit as eosinophil counts increased [17, 18, 24]. Of note, although increasing treatment effect of ICS-containing regimens, such as ICS/LAMA/LABA and ICS/LABA therapy, has been suggested with higher blood eosinophil counts, the exact mechanism for this benefit in COPD patients remains unclear [1].

A potential mortality benefit with inhaled triple combination therapy in patients with COPD has been suggested [1]. In ETHOS, budesonide/glycopyrronium/formoterol reduced the risk of all-cause mortality, a type I error-controlled secondary endpoint, relative to glycopyrronium/formoterol, while a non-significant risk reduction was observed relative to budesonide/formoterol (Sect. 4.4). Although the study was not specifically designed to assess the impact of ICS or LAMA withdrawal, the mortality benefit observed in the study did not appear to be due to an acute ICS withdrawal effect [36]. Furthermore, a reduction in cardiovascular-related deaths appeared to account for the majority of the mortality difference between budesonide/glycopyrronium/formoterol versus glycopyrronium/formoterol; more studies are warranted to further characterize the mechanism of this effect [36].

Budesonide/glycopyrronium/formoterol was generally well tolerated in trials of up to 52 weeks' duration in patients with moderate to very severe COPD, with the tolerability profile of budesonide/glycopyrronium/formoterol being generally similar to the established safety profiles of its individual components (Sect. 5). The most common TEAEs were respiratory in nature. Budesonide/glycopyrronium/formoterol was not associated with clinically meaningful effects on cardiovascular parameters [17, 18] and the incidence of pneumonia was similar to that reported with other ICS-containing therapy, but higher than with non-ICS-containing therapy (Sect. 5.1) [17, 38]. Moreover, the effects of budesonide/glycopyrronium/formoterol on BMD and ocular safety were noninferior to non-ICS-containing therapy [20].

Results of systematic reviews and/or meta-analyses comparing the efficacy of inhaled triple ICS/LAMA/LABA therapy versus inhaled dual ICS/LABA or LAMA/LABA therapy for the treatment of COPD have indicated that inhaled triple ICS/LAMA/LABA therapy provides the greatest benefit in reducing the risk of exacerbations and improving lung function [38–40]. In addition, in network meta-analyses, the efficacy of budesonide/glycopyrronium/formoterol was comparable to that of other ICS/LAMA/LABA fixed-dose or open combination therapies in reducing exacerbation rates and improving lung function and COPD symptoms in patients with moderate to very severe COPD [41, 42].

COPD is associated with a substantial economic and societal burden [1]. A semi-Markov modelling using ETHOS data indicates that, over a lifetime, budesonide/glycopyrronium/formoterol triple therapy may reduce exacerbation-related costs relative to dual therapy in patients with moderate to very severe COPD [43]. In addition, based on ETHOS data, the model-estimated quality-adjusted life years (QALYs) gained with budesonide/glycopyrronium/formoterol in patients with moderate to very severe COPD was higher than with glycopyrronium/formoterol and/or budesonide/formoterol (8.13 vs 7.82 and 7.42 QALYs) [44], with the analysis based on KRONOS data being generally similar (6.85 vs 6.41 and 6.47 QALYs) [45]. Furthermore, a simplified regimen using a single inhaler to deliver triple therapy may increase cost-effectiveness and decrease healthcare resource utilization [2].

In conclusion, budesonide/glycopyrronium/formoterol is effective and generally well tolerated in patients with moderate to very severe COPD. Therefore, budesonide/glycopyrronium/formoterol provides a useful and convenient option for the maintenance treatment of COPD, including for those whose disease is inadequately controlled with dual ICS/LABA or LAMA/LABA therapy.

Data Selection Budesonide/Glycopyrronium/Formoterol: 185 records identified	
Duplicates removed	50
Excluded during initial screening (e.g. press releases; news reports; not relevant drug/indication; preclinical study; reviews; case reports; not randomized trial)	67
Excluded during writing (e.g. reviews; duplicate data; small patient number; nonrandomized/phase I/II trials)	23
Cited efficacy/tolerability articles	21
Cited articles not efficacy/tolerability	24
Search Strategy: EMBASE, MEDLINE and PubMed from 1946 to present. Clinical trial registries/databases and websites were also searched for relevant data. Key words were budesonide/glycopyrronium/formoterol, Trixeo Aerosphere, BREZTRI AEROSPHERE, COPD. Records were limited to those in English language. Searches last updated 17 June 2021	

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