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DRUG PROFILE

An overview of glycopyrrolate/eFlow® CS in COPD

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ABSTRACT

Introduction: COPD is highly prevalent in the US and globally, requiring new treatment strategies due to the high disease burden and increase in the aging population. Here, we profile the newly FDA-approved LONHALA MAGNAIR (glycopyrrolate [GLY]/eFlow® Closed System [CS]; 25 mcg twice daily), a nebulized long-acting muscarinic antagonist (LAMA) for the long-term maintenance treatment of COPD, including chronic bronchitis and/or emphysema.

Areas covered: An overview of COPD and treatment landscape, focusing on GLY/eFlow CS, reviewing the published literature pertinent to the drug/device combination is reported.

Expert commentary: GLY/eFlow CS consists of glycopyrrolate delivered via a novel electronic nebulizer and is the first nebulized LAMA to be approved by the FDA. GLY/eFlow CS has been studied in an extensive clinical development program, including phase II dose-ranging studies, two 12-week phase III studies demonstrating statistically significant and clinically important improvements in pulmonary function and patient-reported outcomes with a well-tolerated safety profile, and a 48-week phase III study highlighting the long-term safety of GLY/eFlow CS, along with long-term improvements in lung function and patient-reported outcomes. Additional studies are required to assess the impact of GLY/eFlow CS on COPD exacerbations, identify alternative uses of the eFlow CS nebulizer, and direct comparisons to other LAMAs.

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COPD; eFlow® CS; LAMA; Lonhala Magnair; nebulized glycopyrrolate

1. Overview of the market

1.1. COPD prevalence and disease burden

Chronic obstructive pulmonary disease (COPD) is characterized by persistent respiratory symptoms and airflow obstruction that is not fully reversible [1,2], as a result of airway narrowing and alveolar wall destruction due to inflammation from inhaled particulates [3]. Smoking or significant exposure to environmental inhaled particulates and air pollution are the main causes of COPD [1,2]. In 2013, in the US alone, almost 15.7 million adults had a diagnosis of COPD, with evidence of impaired lung function that may be consistent with COPD in up to 24 million [1,4,5]. COPD is currently the third leading cause of mortality in the US and the fourth globally, with 24% of the increased mortality ascribed to the aging global population, and resulting in ~3 million deaths in 2015 worldwide [1,6]. This disease represents a substantial economic and social burden, with an estimated €48 billion in the European Union in 2011 and about $50 billion annual direct and indirect costs in the United States in 2010, without taking into consideration the burden and cost of disability-adjusted life years [4,7]. This, in turn, has spurred the development of novel therapeutic agents and devices in order to improve lung function and patient quality of life.

1.2. Therapeutic landscape

Bronchodilator therapies aim to provide symptom relief, reduce the frequency and severity of exacerbations, and improve exercise tolerance and health status [1,8–11]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) report provides a guideline for the treatment of patients with COPD following assessment of patients based on 1) symptoms, as measured by the modified Medical Research Council (mMRC) questionnaire, which assesses patient dyspnea, or the COPD assessment test (CAT™), which measures health status, and 2) exacerbation risk, based on the patient's history of moderate or severe exacerbations [1]. In addition to the use of spirometry to confirm diagnosis and determine severity of airflow limitation (reported as mild to very severe), these measures allow classification of patients into four treatment groups (A, B, C, D), with tailored therapeutic approaches for each group [1]. The treatment groups, as defined by symptoms and exacerbation risk, are: A) fewer symptoms and low risk, B) more symptoms and low risk, C) fewer symptoms and high risk, and D) more symptoms and high risk [1].

Inhaled bronchodilators are central to the treatment of COPD, resulting in improvements in forced expiratory volume in 1 s (FEV_1) and other key measures of lung function, along with reductions in hyperinflation and improvements in exercise performance. In general, bronchodilators act by altering airway smooth muscle tone, with associated improvements in lung function resulting from opening of the airways and/or deflation of the lungs, rather than changes in lung elastic recoil. There are two general classes of bronchodilators, β_2-agonists and anticholinergics or muscarinic antagonists, each

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Supplemental data for this article can be accessed here

with distinct mechanisms of action [1]. β_2-agonists act by directly stimulating β_2-adrenergic receptors which relaxes airway smooth muscles, while muscarinic antagonists block parasympathetic mediated bronchoconstrictor effects of acetylcholine on the M3 muscarinic receptor of airway smooth muscle cells, reducing the effects of increased vagal tone and allowing passive muscle relaxation [1,8,12]. These classes of medications can be further categorized into short acting (usually 4–6 h) or long acting (lasting 12 or more hours) to provide short-acting β_2-agonists (SABA), short-acting muscarinic antagonists (SAMA), long-acting β_2-agonists (LABA) and long-acting muscarinic antagonists (LAMA) [1,8].

Among patients classified as GOLD group A, a bronchodilator, either short acting or long acting, is recommended based on its effect on dyspnea. Long-acting bronchodilators, either LABAs or LAMAs, are recommended as first-line therapy for GOLD group B patients, while the recommended first-line therapy for GOLD group C patients are LAMAs. For both GOLD groups B and C, if long-acting bronchodilator monotherapy is not sufficient and patients experience persistent symptoms or further exacerbations, the use of a combined LAMA/LABA is recommended. Combined LABA/LAMA therapy is also recommended for patients in GOLD group D, and, in case of progression and emergence of further exacerbations, an inhaled corticosteroid (ICS) can be added, to provide 'triple therapy' [1].

1.3. LAMAs

The efficacy and safety of LAMA monotherapies are well established in patients with moderate-to-severe COPD (Table 1) [1,13,14]. Clinical studies have shown that treatment with the LAMA, tiotropium (TIO), reduces the risk of exacerbations compared with no treatment or with LABAs [15,16]. The role of LABA/LAMA combinations versus LABA/ICS combinations in exacerbation reduction is under debate, with current GOLD guidelines for patients in the C and D groups recommending the use of a LABA/LAMA combination first, in part due to a potential increased risk of pneumonia in ICS-containing therapies, especially in older, more cachectic males [1,17,18]. Therefore, LAMAs are preferred to LABAs as initial therapy and LAMA/LABA combinations ahead of LABA/ICS as maintenance therapies, in GOLD classification groups A–C [1].

1.4. Devices

The devices used to deliver inhaled bronchodilators vary in their mechanisms of drug delivery and administration technique, making the choice of delivery device instrumental to optimal disease management [34,35]. Handheld devices, such as pressurized metered dose inhalers (pMDIs), dry powder inhalers (DPIs), and soft mist inhalers (SMIs) each are associated with potential risks for critical errors to be made by patients during drug delivery, leading to ineffective drug delivery and impaired treatment efficacy. Factors associated with suboptimal outcomes in some patients using handheld inhalers include: reduced peak inspiratory flows, difficulties in hand-breath coordination, physical impairments or cognitive impairments [34]. Nebulizers provide an alternative mechanism of drug delivery for patients incapable of effectively using a handheld device; improved bronchodilator drug delivery may improve clinical outcomes for these patients. Certain handheld devices may be preferable to nebulizers in patients with increased mucus and plugging as the aerosol velocity, coupled to a patient's deeper inhalation flow, may overcome resistance and blockage and allow greater drug deposition [34,36,37]. It is essential, therefore, that device choice be tailored, based on individual patient characteristics and needs [1].

2. Glycopyrrolate (GLY)/eflow® Closed System (CS)

GLY is a quaternary ammonium LAMA that has been used clinically in different formulations, combinations, and with different delivery devices in the treatment of various diseases, including COPD, for more than 50 years [38]. Nebulized GLY has been studied extensively within the Glycopyrrolate for Obstructive Lung Disease via Electronic Nebulizer (GOLDEN) clinical development program and received FDA approval in December 2017 [38–43]. Nebulized GLY is administered via the eFlow® Closed System (CS) nebulizer (PARI Pharma GmbH, Starnberg, Germany), a novel drug delivery system that provides short nebulization times, around 2–3 min, virtually silent operation, and is easily portable [44]. The eFlow CS uses a vibrating membrane to generate a gentle, soft aerosol mist of the drug solution that allows highly efficient drug uptake, with up to 88% of the nominal drug dose delivered using tidal breathing. The design of the eFlow CS device is also intended to prevent misuse and eliminate patient-introduced errors, with handset replacement required after 30 days of twice-daily use [38,44].

2.1. Dose-finding studies

Several phase II studies have been performed in order to study pharmacokinetics of nebulized GLY and determine the optimal dose for progression into the phase III studies. These phase II studies are summarized in Table 2 and discussed in more detail later.

Soluble GLY in the eFlow nebulizer was first studied in a phase II, randomized, double-blind, placebo-controlled, six-period crossover study, with subjects receiving a single dose, ranging from 12.5–400 mcg of nebulized GLY or placebo in order to assess efficacy and tolerability, as well as plasma pharmacokinetics in a subset of subjects [43]. All single doses of nebulized GLY were well tolerated. The mean delivery time for all doses was less than 2 min. Nebulized GLY was rapidly absorbed, with peak plasma levels occurring within 15–30 min of dose administration, and a dose-proportional maximal serum concentration (C_{max}). The elimination half-life ($t_{1/2}$) was 1.10–1.15 h for the 0–1-hour interval and 2.30–7.45 h for the 0–12-hour interval, following administration of 50, 100, 200, or 400 mcg doses [43]. In addition, all doses induced a rapid, dose-dependent response within 5 min in FEV_1, with clinically significant improvements starting at 50 mcg dose and higher; the response followed the normal circadian rhythm over 24 h. This study confirmed the efficacy and safety of the GLY/eFlow CS drug-device combination in patients with moderate-to-severe COPD.

Table 1. Summary of the efficacy outcomes for LAMA monotherapies in selected trials.

Drug	Dose	Delivery device	Pivotal trial	Trial duration	Efficacy outcomes
Aclidinium bromide	200/400 mcg b.i.d.	Dry powder inhaler	ACCORD I [19]	12 weeks	• Mean change from baseline in trough FEV_1 of 0.086 and 0.124 L for 200 and 400 mcg b.i.d., respectively
			ACCORD II [20]	12 weeks	• Mean change from baseline in trough FEV_1 of 0.051 and 0.072 L for 200 and 400 mcg b.i.d., respectively • Mean change from baseline in SGRQ total score of –6.0 and • –5.4 for 200 and 400 mcg b.i.d., respectively
			ACCLAIM/COPD I and I [21]	52 weeks	200 mcg q.d. • Placebo-adjusted mean changes from baseline in trough FEV_1 at 12 and 28 weeks were 0.061 and 0.067 L for ACCLAIM/COPD I and 0.063 and 0.059 L for ACCLAIM/COPD II ($p < 0.001$ compared to placebo for both studies) • At 52 weeks, mean change from baseline in SGRQ total score was –4.63 units and –3.49 units for ACCLAIM/COPD I and ACCLAIM/COPD II, respectively
			LAS-MD-35 [22]	52 weeks	400 mcg b.i.d. • Mean change from baseline in trough FEV_1 of 0.072 L • Mean change from baseline in SGRQ total score of –5.2 units
Tiotropium	18 mcg q.d.	HandiHaler	Combined analysis of two 6-month studies [23]	24 weeks	• Mean change from baseline in trough FEV_1 of 0.120 L • Mean change from baseline in SGRQ total score of –4.2 units
			Combined analysis of two 1-year studies [24]	1 year	• Mean change from baseline in trough FEV_1 of 0.110–0.130 L • ($p < 0.01$ compared to placebo) • Mean improvement from baseline in SGRQ total score was significantly greater than placebo ($p < 0.05$)
			UPLIFT [25]	4 years	• Placebo-adjusted mean change from baseline in FEV_1 of 0.087–0.103 L before bronchodilation and 0.047–0.065 L after bronchodilation ($p < 0.001$ compared to placebo) • Mean change from baseline in SGRQ total score ranged from • −2.3 to −3.3 units ($p < 0.001$ compared to placebo)
Glycopyrrolate	15.6 mcg b.i.d.	Neohaler®	GEM 1 [26]	12 weeks	• Superior change from baseline in FEV_1 $AUC_{0\text{-}12h}$ compared to placebo (LSM treatment difference 0.139 L ($p < 0.001$) • Placebo-adjusted LSM change from baseline in SGRQ total score of –2.8 units ($p = 0.016$ compared to placebo)
			GEM 2 [27]	12 weeks	• Superior change from baseline in FEV_1 $AUC_{0\text{-}12h}$ compared to placebo (LSM treatment difference 0.123 L ($p < 0.001$) • Placebo-adjusted LSM change from baseline in SGRQ total score of –5.2 units
			GEM 3 [28]	52 weeks	• LSM change from baseline of FEV_1 was 0.056 L, and was similar to that observed with indacaterol ($p = 0.902$)
Umeclidinium bromide	62.5 mcg q.d.	ELLIPTA™ dry powder inhaler	NCT02207829 [29]	12 weeks	• Mean change from baseline in FEV_1 of 0.147 L, which was greater than the change observed with TIO ($p < 0.001$) • Mean change from baseline of SGRQ total score of –6.03, which was similar to that observed with TIO ($p = 0.571$)
			NCT01387230 [30]	12 weeks	• Placebo-adjusted LSM change from baseline in trough FEV_1 of 0.127 L ($p < 0.001$ compared to placebo) • Placebo-adjusted mean change from baseline in SGRQ total score of 7.9 units ($p < 0.001$ compared to placebo)
			NCT01313650 [31]	24 weeks	• Statistically significant placebo-adjusted mean change from baseline in trough FEV_1 of 0.115 L ($p < 0.001$) • Mean change from baseline in SGRQ total score of –7.25 units • ($p \leq 0.001$ compared to placebo)
	125 mcg q.d.	ELLIPTA™ dry powder inhaler	NCT01313637 [32]	24 weeks	• Statistically significant placebo-adjusted mean change from baseline in trough FEV_1 of 0.160 L ($p < 0.001$) • Mean SGRQ total score at week 24 was not statistically different from placebo
			NCT01316887 [33]	52 weeks	• Placebo-adjusted mean change from baseline in trough FEV_1 • of 0.178 L

AUC, area under the curve; b.i.d., twice daily; FEV_1, forced expiratory volume in 1 s; LSM, least squares mean; q.d., once daily; SGRQ, St George's Respiratory Questionnaire; TIO, tiotropium.

Table 2. Summary of phase II clinical studies.

Trial name	Study design	Patient population and functional criteria for study inclusion	Treatments	Primary outcomes
Leaker et al. [43]	• Two-center • Randomized • Placebo-controlled • Double-blind • Dose finding • Single dose • Six-way cross-over	• N = 42 • Moderate-to-severe COPD • FEV_1 30–70% of predicted normal • At least 12% and 0.150 L reversibility to inhaled ipratropium bromide	• GLY/eFlow (12.5, 25, 50, 100, and 200 mcg single dose)	• Significant improvements in mean change from baseline in FEV_1 at 24 h with doses ≥50 mcg • Dose-response relationship for improvements in FEV_1
GOLDEN 1 [41,45]	• Multicenter • Randomized • Double-blind • Placebo-controlled • Seven arm • Four-period crossover • Incomplete block design • 1 week	• N = 140 • Moderate-to-severe COPD • FEV_1 between 30–70% of predicted normal • FEV_1/FVC <0.70 • Post-bronchodilator improvement in FEV_1 ≥ 12% and ≤30%, and a minimum of 0.100 L	• GLY/eFlow (25, 50, 100, and 200 mcg q.d.) • Tiotropium bromide via HandiHaler® (18 mcg q.d.) • Ipratropium bromide via general purpose nebulizer (500 mcg three times daily)	• Dose-dependent and significant improvements in lung function, as measured by FEV_1 $AUC_{(0\text{-}24h)}$ on day 7
GOLDEN 2 [39]	• Randomized • Double-blind • Placebo-controlled • Parallel arm • 4 weeks	• N = 282 • Moderate-to-severe COPD • FEV_1 between 30–70% of predicted normal • FEV_1/FVC <0.70 • At least 12% and 0.100 L reversibility to inhaled ipratropium bromide	• GLY/eFlow CS (12.5, 25, 50, and 100 mcg b.i.d.)	• Pooled analysis of GOLDEN 2 and GOLDEN 6 showed that GLY treatment resulted in clinically important and statistically significant improvements in lung function, at days 7 and 28 • On day 7, placebo-adjusted changes from baseline in trough FEV_1 of >0.100 L were observed with GLY 12.5, 25, and 50 mcg b.i.d. doses • GLY 25 and 50 mcg b.i.d. doses were comparable to aclidinium bromide 400 mcg
GOLDEN 6 [39]	• Randomized • Double-blind • Placebo- and active-controlled • Crossover • 1 week	• N = 96 • Moderate-to-severe COPD • FEV_1 between 40–70% of predicted normal • FEV_1/FVC <0.70 • At least 12% and 0.100 L reversibility to inhaled ipratropium bromide	• GLY/eFlow CS (3, 6.25, 12.5, 25, and 50 mcg b.i.d.) • Aclidinium bromide 400 mcg b.i.d. via Pressair®	

AUC, area under the curve; b.i.d., twice daily; FEV_1, forced expiratory volume in 1 s; GLY, glycopyrrolate; q.d., once daily.

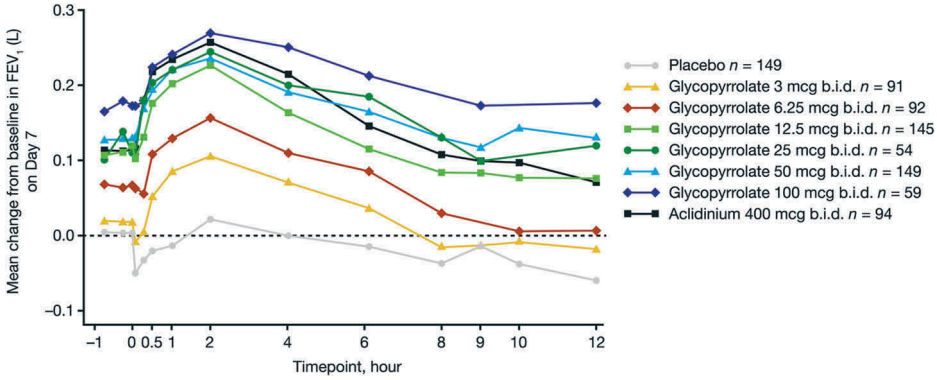

Figure 1. Mean change from baseline in FEV_1 over time on Day 7 (pooled population) in the GOLDEN 2 and GOLDEN 6 studies [39]. **Redrawn with author's permission.**

b.i.d., twice daily; FEV_1, forced expiratory volume in 1 s.

The phase IIb, GOLDEN 1 study was a multicenter, randomized, double-blind, placebo-controlled study assessing the efficacy and safety of nebulized GLY after 7 days of dosing in patients with moderate-to-severe COPD. Four doses of nebulized GLY (25, 50, 100, and 200 mcg once daily [q.d.]) were compared to open-label TIO 18 mcg q.d., open-label ipratropium 500 mcg three times daily via jet nebulizer, and GLY-matched placebo. All nebulized GLY doses were well tolerated, with similar adverse event (AE) rates to placebo, and there was no dose-dependent relationship with incidence and severity of AEs. All doses of nebulized GLY resulted in dose-dependent improvements in lung function, as measured by FEV_1 area under the curve (AUC) between 0 and 24 h on day 7, compared with placebo (estimated differences from placebo ranged between 0.110–0.169 L) [41].

Dose selection for the phase III studies was based on the outcomes of the GOLDEN 2 and GOLDEN 6 dose-finding studies. GOLDEN 2 was a 28-day, parallel-group study, while GOLDEN 6 was a 7-day crossover study, both in patients with moderate-to-severe COPD [39]. Subjects were randomized to placebo, GLY ranging from 3, 6.25, 12.5, 25, 50, or 100 mcg twice daily (b.i.d.), or aclidinium bromide 400 mcg b.i.d. The primary endpoint of both studies was the change from baseline in trough FEV_1. The bronchodilator dose-response relationship was also characterized; in addition, safety assessments included the incidence of treatment-emergent adverse events (TEAEs), serious TEAEs, and discontinuations due to TEAEs. Pooled analysis of the two studies showed that treatment with nebulized GLY resulted in clinically important and statistically significant improvements in lung function at days 7 and 28 (Figure 1). The improvements observed with GLY 25 and 50 mcg b.i.d. were comparable to those with aclidinium bromide 400 mcg b.i.d. In addition, acceptable safety outcomes were observed across all dose groups in both studies [39]. The results of these two studies supported the selection of GLY 25 and 50 mcg b.i.d. doses for the phase III GOLDEN studies.

2.2. Phase III studies

2.2.1. Study design

The three phase III studies of GLY/eFlow CS in subjects with moderate-to-severe COPD evaluated the efficacy and safety of the 25 and 50 mcg b.i.d. doses of nebulized GLY, compared to placebo in the 12-week GOLDEN 3 and GOLDEN 4 studies [42], and compared to an active comparator, TIO 18 mcg q.d., in the 48-week GOLDEN 5 study [40].

The GOLDEN 3 and GOLDEN 4 studies were replicate randomized, double-blind, US-based, multicenter, placebo-controlled studies conducted over a 12-week period [42]. Subjects ≥40 years of age, who were current or ex-smokers with a ≥10 pack-year history of smoking, and with a clinical diagnosis of moderate-to-severe COPD, were included. Post-bronchodilator qualifying pulmonary function criteria required at screening included an FEV_1 ≤0% of predicted normal, FEV_1 >0.70 L, and FEV_1/forced vital capacity (FVC) ratio <0.70. Importantly, subjects with very severe COPD, with cardiovascular (CV) co-morbidities and risks, and/or using a LABA or ICS were not excluded from the studies. Subjects were prospectively stratified by background LABA use (yes/no, limited to approximately 30% of all subjects) and by CV risk (high or low). The primary efficacy endpoint of both studies was the change from baseline in trough FEV_1 at week 12; secondary efficacy endpoints included change from baseline in trough FVC, SGRQ total scores, both at week 12, and change in rescue medication use over the duration of the studies. Safety endpoints in both studies included the number and percentage of subjects with TEAEs, serious TEAEs, and discontinuation due to TEAEs, as well as the number, percentage, and incidence rate of major adverse cardiac events (MACE) over the duration of the studies [42].

The GOLDEN 5 study was a randomized, open-label, active-controlled study conducted in four countries (United States, Czech Republic, Hungary, and Russia). This long-term safety study over 48 weeks compared nebulized GLY 50 mcg b.i.d. to TIO 18 mcg q.d. administered using the HandiHaler® DPI device. Eligibility criteria were identical to those of the GOLDEN 3 and GOLDEN 4 studies, and subjects were also stratified by background LABA use (limited to 40% of all subjects) and CV risk. The primary safety endpoints were the incidence of TEAEs, serious TEAEs, and discontinuations due to TEAEs, while assessment of CV safety was included as a secondary safety endpoint. Efficacy endpoints included mean change from baseline in trough FEV_1 and assessment of SGRQ total scores at baseline and weeks 12, 24, and 48 [40].

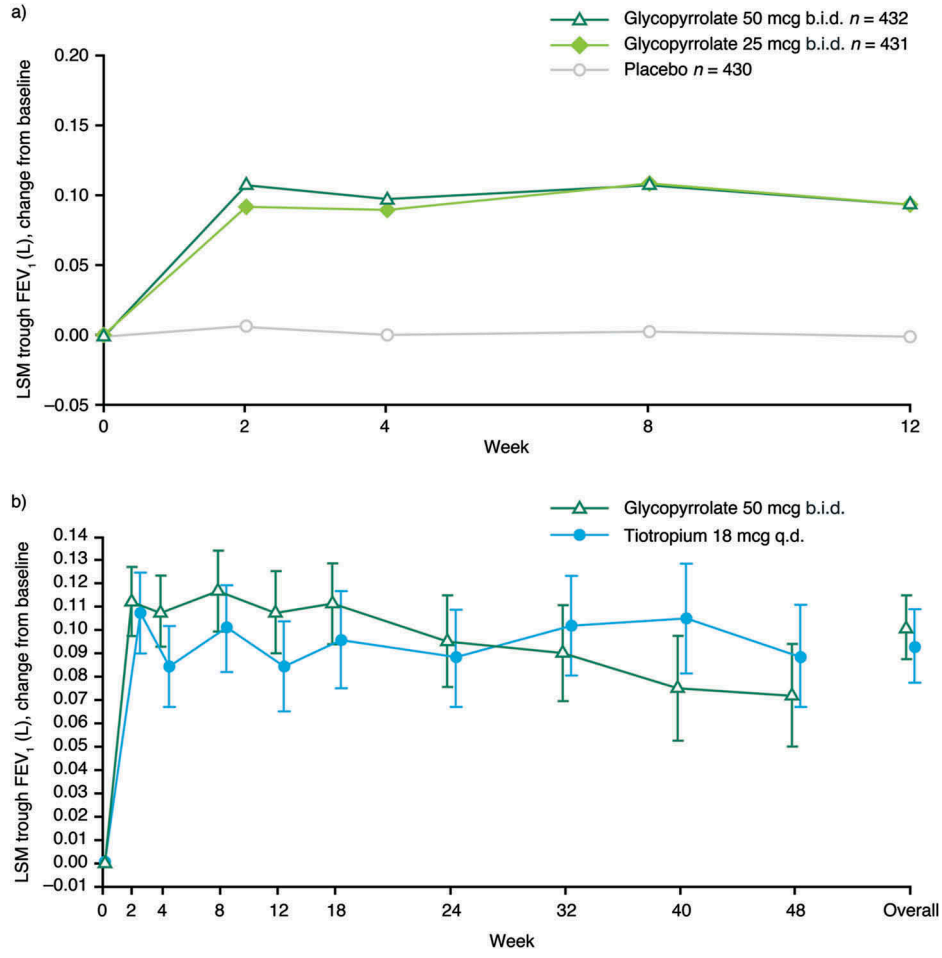

Figure 2. **Least squares mean change from baseline in trough FEV_1 in subjects receiving GLY 25 or 50 mcg b.i.d. or placebo in pooled analysis of the GOLDEN 3 and GOLDEN 4 studies (a) and in subjects receiving GLY 50 mcg b.i.d. (57% of total population) or TIO 18 mcg q.d. (43% of total population) in the GOLDEN 5 study (b)** [40,42]. **Redrawn with author's permission.**

b.i.d., twice daily; GLY, glycopyrrolate; LSM, least squares mean; FEV_1, forced expiratory volume in 1 s; q.d., once daily; TIO, tiotropium.

2.2.2. Summary of efficacy outcomes

Six hundred and fifty-three subjects were randomized to receive treatment in GOLDEN 3 (218, 217, and 218 received placebo, GLY 25 mcg b.i.d., and GLY 50 mcg b.i.d.) and 641 in GOLDEN 4 (212, 214, and 214 received placebo, GLY 25 mcg b.i.d., and GLY 50 mcg b.i.d.). In both studies, administration of either GLY 25 or 50 mcg b.i.d. resulted in statistically significant and clinically important improvements in lung function parameters compared to placebo. Placebo-adjusted change from baseline in trough FEV_1 at week 12 was 0.105 L and 0.126 L with GLY 25 and 50 mcg b.i.d., respectively, in GOLDEN 3, and 0.084 L and 0.082 L, respectively, in GOLDEN 4. Pooled analysis of GOLDEN 3 and GOLDEN 4 showed improved change from baseline in FEV_1 with both doses of nebulized GLY compared to placebo at all time-points tested in both studies (Figure 2a). Treatment with nebulized GLY also resulted in statistically significant improvements in trough FVC versus placebo. In GOLDEN 3, placebo-adjusted change from baseline in SGRQ total scores was significantly improved with nebulized GLY 25 mcg b.i.d., while the changes with 50 mcg b.i.d. dose were not significant (least squares mean difference from placebo ± standard error: GLY 25 mcg b.i.d.: – 3.072 ± 1.125 units; $p < 0.05$; GLY 50 mcg b.i.d.: – 1.848 ± 1.140 units; Figure 3a); the median change from baseline in SGRQ scores was greater than the minimal clinically important difference (–4.0 units) in subjects receiving GLY 25 mcg b.i.d. In the GOLDEN 4 study, both GLY 25 and 50 mcg b.i.d. resulted in statistically significant placebo-adjusted changes from baseline in SGRQ scores (least squares mean difference from placebo ± standard error: – 3.585 ± 1.123 and – 3.557 ± 1.116 units, respectively; $p < 0.01$; Figure 3b). The SGRQ responder rates, defined as the proportion of subjects achieving a –4.0 unit reduction in total score at week 12, were 39.7%, 49.7%, and 44.1% in GOLDEN 3 and 29.6%, 43.7%, and 39.4% in GOLDEN 4, with placebo, GLY 25 mcg b.i.d., and GLY 50 mcg b.i.d., respectively. In both studies, subjects receiving GLY 25 or 50 mcg b.i.d. achieved greater improvements in EXACT-RS scores at week 12, with GLY 25 mcg in GOLDEN 3 and both GLY doses in GOLDEN 4 showing statistically significant differences compared to placebo [42].

In the GOLDEN 5 study, efficacy outcomes of trough FEV_1 and SGRQ scores were secondary endpoints. Open-label treatment with GLY 50 mcg b.i.d. or TIO 18 mcg q.d. resulted in sustained improvements from baseline in trough FEV_1 (Figure 2b), with a least squares mean change from baseline of 0.102 L and 0.093 L with GLY and TIO, respectively, over 48 weeks. Differences between the two treatments in trough FEV_1 over 48 weeks were

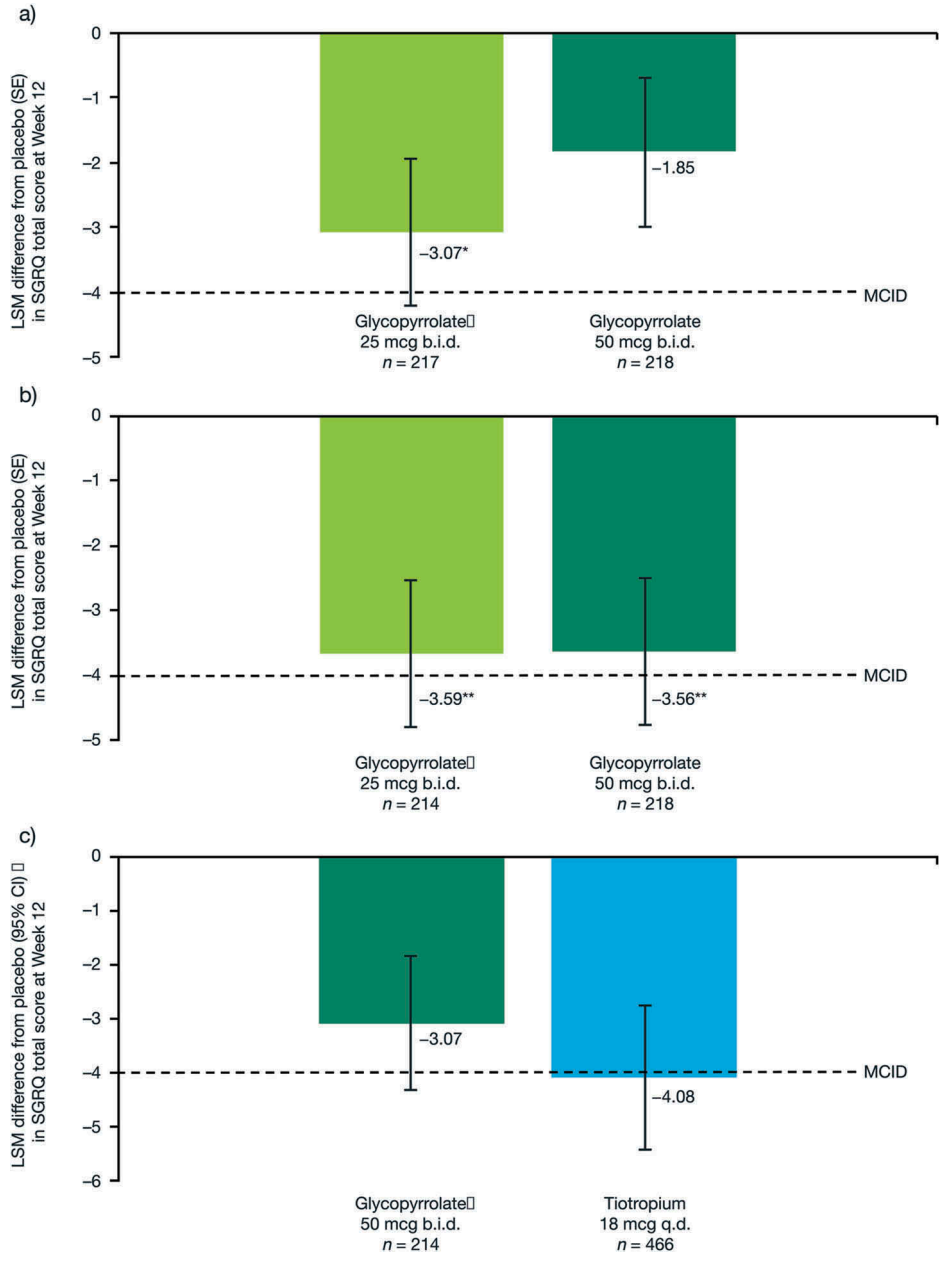

Figure 3. Placebo-adjusted, least squares mean change from baseline in SGRQ total scores in subjects receiving GLY 25 or 50 mcg b.i.d. in the GOLDEN 3 (a) and GOLDEN 4 (b) studies, and in subjects receiving GLY 50 mcg b.i.d. (57% of total population) or TIO 18 mcg q.d. (43% of total population) in the GOLDEN 5 study (c) [40,42].

*$p < 0.05$; **$p < 0.01$ versus placebo.b.i.d., twice daily; CI, confidence interval; GLY, glycopyrrolate; LSM, least squares mean; MCID, minimal clinically important difference; q.d., once daily; SE, standard error; SGRQ, St George's respiratory questionnaire; TIO, tiotropium.

Table 3. Summary of the safety profile of nebulized GLY from the GOLDEN phase III studies [40,42].

	GOLDEN 3			GOLDEN 4			GOLDEN 5	
	Placebo (*n* = 218)	GLY 25 mcg b.i.d. (*n* = 217)	GLY 50 mcg b.i.d. (*n* = 218)	Placebo (*n* = 212)	GLY 25 mcg b.i.d. (*n* = 214)	GLY 50 mcg b.i.d. (*n* = 214)	GLY 50 mcg b.i.d. (*n* = 620)	TIO 18 mcg q.d. (*n* = 466)
Overall incidence of any TEAE, %	52.3	39.6	48.2	52.4	47.2	53.3	69.4	67.0
Discontinuations due to TEAEs, %	9.6	3.2	3.7	9.0	7.0	4.2	10.0	2.8

b.i.d., twice daily; GLY, glycopyrrolate; q.d., once daily; TEAE, treatment-emergent adverse event; TIO, tiotropium.

not significant. Changes from baseline in SGRQ total scores at 48 weeks were similar in both treatments (Figure 3c), with least squares mean difference from placebo (± standard error) of −3.07 ± 1.125 and − 4.08 ± 1.140 units with GLY and TIO,

Table 4. **Most common TEAEs (≥5% in any treatment group) observed in the GOLDEN phase III studies** [40,42].

	GOLDEN 3			GOLDEN 4			GOLDEN 5	
Preferred term, %	Placebo (n = 218)	GLY 25 mcg b.i.d. (n = 217)	GLY 50 mcg b.i.d. (n = 218)	Placebo (n = 212)	GLY 25 mcg b.i.d. (n = 214)	GLY 50 mcg b.i.d. (n = 214)	GLY 50 mcg b.i.d. (n = 620)	TIO 18 mcg q.d. (n = 466)
Cough	10.1	7.4	9.6	6.6	6.5	8.4	11.8	5.6
COPD	8.3	5.1	10.6	9.0	7.9	6.5	16.6	20.2
Bronchitis	1.4	0.9	0.9	1.4	1.4	2.3	4.5	5.2
Dyspnea	2.3	2.3	1.4	3.8	7.5	5.1	4.5	3.2
Nasopharyngitis	1.4	1.4	2.8	0.5	1.9	0.9	4.0	6.0
Upper respiratory tract infection	0.9	0.5	2.8	0.9	2.3	4.2	6.1	5.4

b.i.d., twice daily; COPD, chronic obstructive pulmonary disease; GLY, glycopyrrolate; q.d., once daily; TEAE, treatment-emergent adverse event; TIO, tiotropium.

respectively, at week 48. The SGRQ responder rates were also similar across both treatments, with 43.7% and 44.5% achieving a ≥ 4.0 unit decrease from baseline in total SGRQ score [40].

2.2.3. Overall safety profile

The safety of nebulized GLY in subjects with moderate-to-severe COPD was evaluated across the three phase III studies. In GOLDEN 3, the frequency of TEAEs was highest among subjects receiving placebo (52.3%) compared to those receiving GLY 25 and 50 mcg b.i.d. (39.6% and 48.2%, respectively); in GOLDEN 4, the frequency of TEAEs was similar between subjects receiving placebo or GLY 50 mcg b.i.d. (52.4% and 53.3%, respectively) and was lowest among subjects receiving GLY 25 mcg b.i.d. (47.2%; Table 3). The most frequent TEAEs reported in both studies were worsening/exacerbation of COPD and cough, occurring to a similar extent in subjects receiving placebo or nebulized GLY (Table 4). Discontinuations due to TEAEs were observed in a greater proportion of subjects receiving placebo compared to those receiving GLY 25 or 50 mcg b.i.d. (9.6%, 3.2%, and 3.7%, respectively) in the GOLDEN 3 study. Similar results in terms of discontinuations due to TEAEs were observed in the GOLDEN 4 study, with more subjects receiving placebo discontinuing due to TEAEs compared to either dose of nebulized GLY (9.0%, 7.0%, and 4.2% with placebo, GLY 25 mcg b.i.d., and GLY 50 mcg b.i.d., respectively; Table 3). The incidence of CV events and cerebrovascular TEAEs were low and similar with GLY or placebo in both studies [42].

The overall TEAE incidence was similar across treatments throughout the GOLDEN 5 study (Table 3), with the most frequent TEAEs being COPD worsening and cough (Table 4). Discontinuations due to TEAEs were higher with GLY compared to TIO (10.0% vs. 2.8%; Table 3), with the most common cause being cough, COPD exacerbation/worsening, and dyspnea. The incidence of serious TEAEs was similar across the two treatment groups (12.3% and 10.5% with GLY and TIO, respectively). The number of MACE (8 vs. 3) and incidence rate (20.3 per thousand person-years vs 6.4 per thousand person-years) were higher with TIO compared with GLY, respectively [40].

The higher incidence of cough, and discontinuations due to cough, among subjects receiving nebulized GLY compared to TIO in the GOLDEN 5 study (11.8% vs. 5.6%, respectively) may be due to incorrect nebulizer use as less than 10% of subjects in the study had prior nebulizer experience [40]. Irritation from the inhaled solution may also have contributed to these observations. It is unlikely that nebulized GLY was the underlying reason for the increased incidence of cough, given that the incidence of cough in placebo subjects in the GOLDEN 3 and GOLDEN 4 studies was 10.1% and 6.6%, with similar or lower rates in subjects receiving nebulized GLY [42]. This supports the need for patient education in proper device usage as well as highlighting the importance of tailoring both drug and device to the patients' needs.

Interestingly, incidence of some of the expected LAMA-associated, anticholinergic TEAEs were low among subjects receiving nebulized GLY, such as dry mouth which occurred in ~1% of subjects (compared to 0.2% of subjects receiving placebo in GOLDEN 3 and GOLDEN 4, and 2.8% in subjects receiving TIO) [40,42]. Similarly, incidence of other TEAEs associated with anticholinergic drugs, including dry eyes, glaucoma-related AEs, pneumonia, pyrexia, tachycardia, urinary retention and dizziness, were also low in all three trials. These results support the tolerable safety profile of nebulized GLY.

2.2.4. Subgroup analyses

Secondary analyses of data from the phase III GOLDEN studies have investigated the safety and efficacy of nebulized GLY according to peak inspiratory flow rate (PIFR), FEV_1% predicted at baseline, age, use of background LABA, and CV risk status.

Subjects with a suboptimal PIFR (<60 L/min) may be unable to use their handheld inhalers correctly, and are generally underrepresented in clinical trials [34,46,47]. A pooled subanalysis of the GOLDEN 3 and GOLDEN 4 studies showed that both doses of nebulized GLY (25 and 50 mcg b.i.d.) produced statistically significant improvements from baseline in trough FEV_1 and SGRQ total scores at week 12 compared with placebo regardless of PIFR subgroup (<60 L/min or ≥60 L/min). The safety profile of nebulized GLY was also similar in both PIFR subgroups [48].

The effects of baseline lung function, as measured by baseline post-bronchodilator % predicted FEV_1, and patient age on the efficacy and safety of nebulized GLY were also assessed in a secondary analysis of the GOLDEN 3 and GOLDEN 4 studies [49]. This is relevant given the real-world situation in which approximately 30% of COPD patients present with severe or very severe airflow limitation at diagnosis [50]. Subjects were categorized according to baseline FEV_1 < 50% or ≥50% predicted, and by age <65 and ≥65 years. At week 12, nebulized GLY resulted in significant improvements in mean trough FEV_1

and SGRQ total score versus placebo in both FEV_1 <50% and ≥50% predicted subgroups. Incidence of AEs leading to discontinuation was similar between FEV_1 subgroups. Nebulized GLY was also associated with improvements in mean trough FEV_1 and SGRQ total scores versus placebo at week 12 in both age groups, with greater improvements in FEV_1 in subjects ≥65 years. Incidence of AEs leading to discontinuation was similar between age groups [49].

The impact of background LABA use on the efficacy and safety of nebulized GLY was also evaluated [51]. The design of the three phase III studies allowed for ~30–40% of subjects to continue background LABA, and the majority of those were also receiving background ICS, making them more representative of the general COPD population, and indicative of more severe disease [40,42]. In the 12-week studies, nebulized GLY led to significant improvements versus placebo in mean trough FEV_1 and change from baseline in SGRQ total score across LABA subgroups. In the 48-week GOLDEN 5 study, overall improvements in mean trough FEV_1 and change from baseline in SGRQ total score were similar with nebulized GLY and TIO in both subjects receiving and not receiving background LABA. Exacerbation rates were comparable between GLY and placebo and between GLY and TIO, respectively, albeit exacerbation rates were lower among subjects not receiving background LABA, consistent with that group having less severe disease. Incidence of AEs leading to discontinuation was similar regardless of background LABA use [51].

A further sub-analysis of the phase III studies assessed the safety and efficacy of nebulized GLY in subjects with high or low CV risk [52]. CV disease is highly prevalent among COPD patients, and some evidence suggests that LAMAs may increase the risk of CV events [12,53,54]. The phase III GOLDEN studies were prospectively designed to include subjects at high CV risk [40,42]. High CV risk was determined based on a history of one or more of the following prespecified disorders: ischemic heart disease, cerebrovascular disease, peripheral arterial disease, clinically significant arrhythmia, heart failure, and/or hypertension [40,42]. At 12 weeks, rates of AEs leading to discontinuation were similar in high and low CV risk subgroups in the GOLDEN 3 and GOLDEN 4 studies, whereas at 48 weeks, discontinuations were numerically higher in the high CV risk subgroup in the GOLDEN 5 study [52]. CV risk status did not impact the incidence of CV events of special interest or MACE. Improvements from baseline in placebo-adjusted trough FEV_1 were similar for GLY 25 and 50 mcg b.i.d. at 12 weeks and for GLY and TIO at 48 weeks in both CV risk subgroups. At 12 weeks, both GLY 25 and 50 mcg b.i.d. produced statistically significant improvements in placebo-adjusted SGRQ total scores in the high CV risk subgroup, while only GLY 25 mcg b.i.d. produced significant improvement compared to placebo in the low CV risk subgroup. Over 48 weeks, changes from baseline in SGRQ total scores were numerically higher for GLY versus TIO in the high CV risk subgroup but lower in the low CV risk subgroup [52].

Taken together, the findings of the subgroup analyses from the phase III GOLDEN studies indicate that nebulized GLY is effective and well tolerated across a broad range of patients, irrespective of age, disease severity, PIFR status, and CV risk.

3. Summary and conclusions

GLY/eFlow CS is the first nebulized LAMA to be approved by the FDA; the efficacy and safety of nebulized GLY have been well characterized in the GOLDEN phase III studies, which together with the innovative drug delivery characteristics of the eFlow CS nebulizer, make it an important new treatment option for patients with moderate-to-severe COPD. In particular, nebulized GLY provides an alternative for patients unable to use handheld inhalers, with subgroup analyses showing similar efficacy and safety in older patients, as well as patients with poor lung function, more severe disease, and high CV risk. In addition to improvements in lung function, health status was also significantly improved with nebulized GLY.

4. Regulatory affairs

GLY/eFlow CS is approved by the FDA for use in the US for the long-term maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema.

5. Expert commentary: gaps and future studies

Additional studies would help to further characterize the efficacy and safety of nebulized GLY. One major gap relates to the effect of nebulized GLY on the incidence of COPD exacerbations, which remain a major cause of COPD-associated hospitalizations and COPD-related healthcare costs [55]. While all three phase III studies assessed the incidence of COPD exacerbations, these studies excluded subjects with a history of COPD exacerbations requiring hospitalization [40,42]. As such, these studies were not powered to assess the impact of nebulized GLY in patients with a history, and subsequently higher risk, of exacerbations; additional, long-term studies are needed in patients at increased risk of exacerbations. It is important to note that if a patient using nebulized GLY required addition of a LABA due to emergence of exacerbations, a different delivery system would be required as there are currently no LABAs that can be administered via the eFlow CS nebulizer; the requirement to use two inhalation devices may be less convenient for patients compared with existing fixed-dose LABA/LAMA combinations.

One feature of nebulized GLY is the b.i.d. dosing schedule, which might be advantageous over q.d. dosing schedules, especially in patients with nocturnal and early morning symptoms. An evening dose may improve nighttime symptoms such as cough, reduce mucus, and increase the ability to exercise in the morning, albeit adherence to a b.i.d. rather than a q.d. dosing schedule needs to be considered [56–58]. While the impact of nebulized GLY on nighttime symptoms has not been studied, a study of aclidinium bromide 400 mcg b.i.d. compared to TIO 18 mcg q.d. showed significant reductions in the severity of early morning cough, wheeze, shortness of breath, and phlegm, and of nighttime symptoms versus placebo only with aclidinium bromide [59]. This

indicates the potential beneficial effect of a second, nighttime dose of a LAMA on nighttime symptoms in patients with COPD. However, a study comparing formoterol 24 mcg q.d. to 12 mcg b.i.d. showed comparable efficacy and tolerability between the two treatment regimens, although statistically the q.d. dosing was not noninferior to the b.i.d. dosing [60]. Alleviating nighttime symptoms represents an unmet need in COPD [61], and studies utilizing measures such as the Nighttime Symptoms of COPD instrument [62], are needed to assess the impact of b.i.d. nebulized GLY on nighttime symptoms.

Head-to-head comparisons of the efficacy of nebulized GLY relative to established treatments would also be beneficial. TIO was the active comparator in the GOLDEN 5 long-term safety study [40]; however, further studies focused on long-term efficacy would be valuable. Another head-to-head study that could provide insight into treatment strategies is nebulized GLY compared to the LABA/ICS combination, fluticasone propionate and salmeterol, which has been shown to provide improved lung function and decrease the incidence of COPD exacerbations compared to placebo [63,64]. Finally, studies to better identify patients failing proper use of handheld devices and those patients who would benefit from nebulized therapies would be of value.

6. Five-year view

Rapid nebulized therapies have major advantages for COPD patients in general, and hold a lot of promise, particularly for those patients with difficulties using handheld inhalers. The secondary analyses of the patient populations of the phase III GOLDEN studies have shed some insight into defining patient populations that may achieve efficacy and safety benefits from using nebulized GLY. The identification of the optimal drug-device combination for patients with COPD is essential [34], and further subgroup analyses are required to shed further light and delineate populations with enhanced response to treatment. Furthermore, head-to-head studies comparing the efficacy of GLY delivered by nebulizer or handheld inhaler, as well as studies comparing nebulized GLY to other LAMAs, are needed.

Another major advance in the COPD treatment landscape will be the development of additional drug formulations that could be administered using the eFlow CS nebulizer, in particular LABAs. This would allow combinations consistent with GOLD recommendations for patients with exacerbations or more advanced symptoms to be administered using a single nebulizer. The eFlow CS nebulizer has already shown efficacy and ease of use among patients with more severe disease and/or who may be prone to exacerbations [49,51,52].

Recently, triple fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) therapy was approved by the FDA [65]. Data from the IMPACT study, a 52-week trial conducted in more than 10,000 patients that compared FF/UMEC/VI to LABA/ICS (FF/VI) and LABA/LAMA (UMEC/VI) [66], showed lower rates of moderate or severe COPD exacerbations and hospitalizations with triple therapy compared to LABA/ICS or LABA/LAMA [67]. However, there was a higher incidence of pneumonia among patients receiving ICS, with a significantly higher risk of physician-diagnosed pneumonia with triple therapy compared to LAMA/LABA, in a time-to-first-event analysis [67]. Results from the TRILOGY and TRINITY studies comparing triple therapy (beclometasone dipropionate, formoterol fumarate, and glycopyrronium bromide; only approved in the EU) to beclometasone dipropionate, formoterol fumarate in the TRILOGY study and to TIO in the TRINITY study, showed improved lung function and had a tolerable safety profile [68,69]. These results highlight the benefits from triple therapy and the important role this treatment regimen may play in patients with severe COPD. It is interesting to note that the GOLDEN phase III studies of nebulized GLY included patients receiving background LABA/ICS, making it an open triple therapy in a subset of the population [40,42,51]. Improvements in trough FEV_1 and SGRQ total scores in patients receiving this open triple therapy were similar to those in patients not receiving background LABA/ICS [51]. Thus, these data support the potential benefit of nebulized GLY across the COPD continuum and in combination with LABA, with or without ICS.

Key issues

- GLY/eFlow CS is the first nebulized LAMA approved by the FDA for the maintenance treatment of patients with COPD, including chronic bronchitis and/or emphysema.
- The novel eFlow CS nebulizer is portable and provides short nebulization times (around 3 min), delivering ~88% of the nominal dose through tidal breathing.
- In the GOLDEN phase III clinical trials, nebulized GLY demonstrated statistically significant and clinically important improvements in lung function and health status over placebo in the 12-week studies, and similar efficacy to the established LAMA, TIO, in a 48-week study.
- Nebulized GLY has an acceptable safety profile, with the most common TEAEs being worsening of COPD and cough.
- Secondary analyses of the GOLDEN phase III studies showed nebulized GLY is effective and well tolerated in a broad range of patients, irrespective of baseline lung function, age, background LABA use, and CV risk status.
- Additional studies are required to assess the impact of the nebulized GLY on COPD exacerbations, night-time symptoms, and compare its efficacy and safety in head-to-head trials.

Information resources

In order to learn more about the newly FDA-approved nebulized GLY, the publications describing the eFlow CS nebulizer [44], the phase II dose-finding GOLDEN 2 and GOLDEN 6 studies [39], and the phase III 12-week GOLDEN 3 and GOLDEN 4 [42] and 48-week GOLDEN 5 studies [40] are recommended for further reading. Additionally, a review describing nebulized GLY and its place in therapy is available [11]. Further information is available in the LONHALA MAGNAIR prescribing information [38].

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