

# Inhaled glycopyrrolate for the treatment of chronic obstructive pulmonary disease

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**Abstract:** Long-acting muscarinic antagonists (LAMAs), along with long-acting  $\beta_2$ -agonists (LABAs), are the mainstay for treatment of patients with COPD. Glycopyrrolate, or glycopyrronium bromide, like other LAMAs, inhibits parasympathetic nerve impulses by selectively blocking the binding of acetylcholine to muscarinic receptors. Glycopyrrolate is unusual in that it preferentially binds to  $M_3$  over  $M_2$  muscarinic receptors, thereby specifically targeting the primary muscarinic receptor responsible for bronchoconstriction occurring in COPD. Inhaled glycopyrrolate is slowly absorbed from the lungs and rapidly eliminated from the bloodstream, most likely by renal excretion in its unmetabolized form, limiting the potential for systemic adverse events. Inhaled glycopyrrolate is a fast-acting, efficacious treatment option for patients with moderate–severe COPD. It improves lung function, reduces the risk of exacerbations, and alleviates the symptoms of breathlessness, which in turn may explain the improvement seen in patients' quality of life. Inhaled formulations containing glycopyrrolate are well tolerated, and despite being an anticholinergic, few cardiovascular-related events have been reported. Inhaled glycopyrrolate is thus of value as both monotherapy and in combination with other classes of medication for maintenance treatment of COPD. This review covers the mechanism of action of inhaled glycopyrrolate, including its pharmacokinetic, pharmacodynamic, and safety profiles, and effects on mucus secretion. It also discusses the use of inhaled glycopyrrolate in the treatment of COPD, as monotherapy and in fixed-dose combinations with LABAs and inhaled corticosteroid–LABAs, including a triple therapy recently approved in Europe.

**Keywords:** glycopyrronium bromide, long-acting muscarinic antagonist, anticholinergic, bronchodilator

## Plain language summary

Patients with COPD have narrowed airways and cannot fully empty their lungs, which together can make breathing uncomfortable. Doctors often prescribe an inhaler containing drugs that widen the airways or reduce inflammation in the lungs, making it easier for patients with COPD to breathe. Patients who do not show enough benefit from treatment with one drug alone may be given two or more drugs, which can be combined into one inhaler. One drug used to widen the airways in patients with COPD is glycopyrrolate (also referred to as glycopyrronium bromide). Glycopyrrolate can be used to treat COPD on its own, as well as in combination with other drugs. In this article, we discuss the evidence for how glycopyrrolate works in the body, how glycopyrrolate enters and leaves the body, and the effectiveness and side effects of glycopyrrolate when used to treat patients with COPD in clinical trials alone and combined in one inhaler with another airway-widening drug with or without a drug used to reduce inflammation in the lungs.

## Introduction

Long-acting muscarinic antagonists (LAMAs) or long-acting  $\beta_2$ -agonists (LABAs), alone or in combination, are the mainstay for the maintenance treatment of patients

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with COPD.<sup>1,2</sup> In the 1980s, inhaled glycopyrrolate, also known as glycopyrronium bromide, was found to be a long-acting bronchodilator<sup>3,4</sup> and improved pulmonary function after exercise in patients with asthma,<sup>5</sup> although inhaled glycopyrrolate is not currently licensed for use in asthma.<sup>6</sup> Inhaled glycopyrrolate, a rapid-onset LAMA, is now US Food and Drug Administration (FDA)- and European Medicines Agency (EMA)-approved for maintenance treatment of patients with COPD.<sup>1,6,7</sup> This review covers the mechanism of action of inhaled glycopyrrolate, its pharmacokinetic (PK) and pharmacodynamic (PD) profiles, safety profile, effects on mucus secretion, and use in the treatment of COPD as monotherapy and in fixed-dose combinations (FDCs) with LABAs and inhaled corticosteroid (ICS)-LABAs.

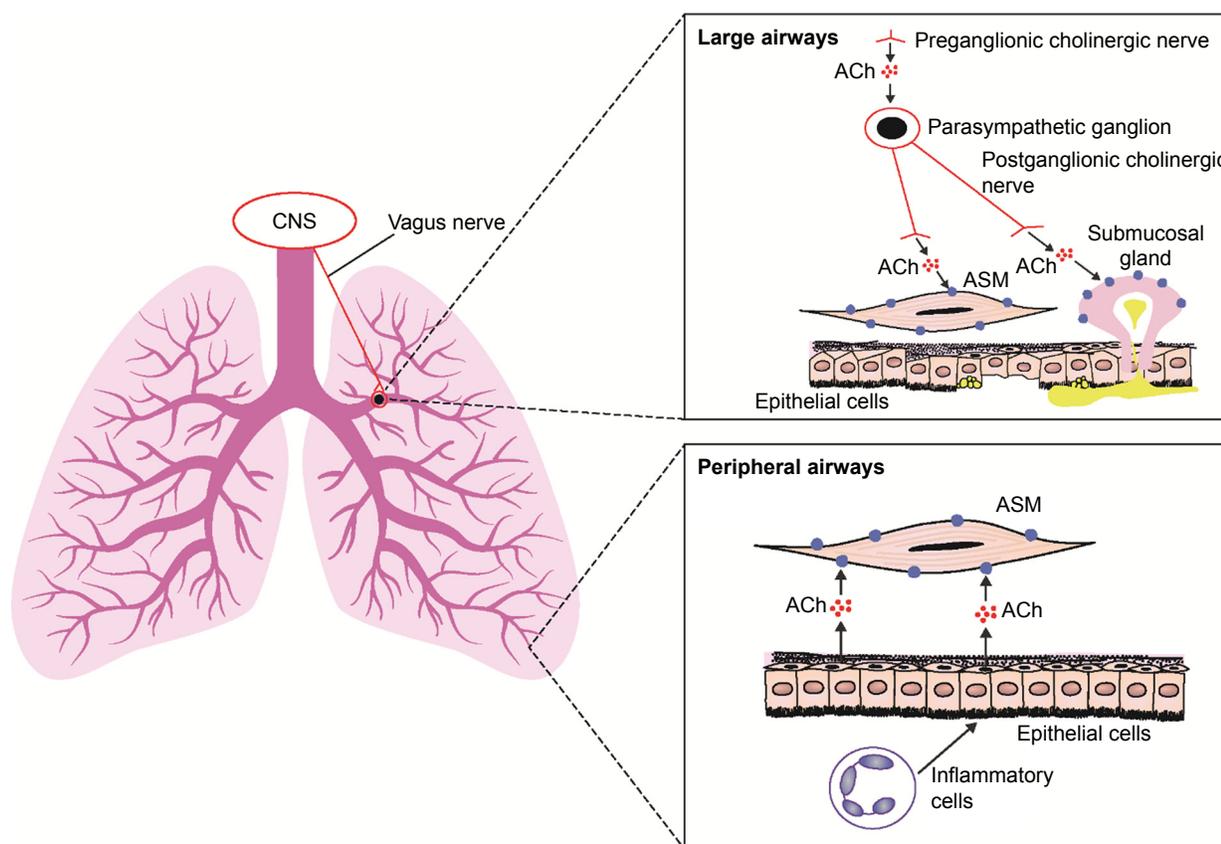
## Pharmacokinetics and pharmacodynamics of inhaled glycopyrrolate

Preganglionic parasympathetic nerves innervate the airways via the vagus nerve (Figure 1).<sup>8</sup> At parasympathetic

ganglia, preganglionic nerves synapse with postganglionic nerves.<sup>8</sup> Acetylcholine (ACh) is a neurotransmitter that is released during parasympathetic nerve impulses and acts by binding to and activating muscarinic receptors and nicotinic receptors.<sup>8,9</sup> There are five muscarinic receptor subtypes, referred to as  $M_1$ – $M_5$ .<sup>9</sup>

$M_1$  receptors are highly expressed in the peripheral airways, whereas  $M_2$  and  $M_3$  receptors predominate in the larger airways.<sup>8</sup>  $M_3$  receptors are the muscarinic receptors primarily responsible for ACh-induced bronchoconstriction,<sup>8</sup> as they activate phospholipase C, which produces inositol 1,4,5-triphosphate and diacylglycerol, leading to intracellular calcium release.<sup>9</sup> Anticholinergics block parasympathetic nerve impulses by selectively preventing ACh from binding to muscarinic receptors.<sup>8,10</sup> These drugs inhibit bronchoconstriction in peripheral airways by antagonizing the effects on airway smooth muscle cells of ACh released by epithelial cells; this release is stimulated by inflammatory cells.<sup>11</sup>

The anticholinergic effects of inhaled glycopyrrolate are primarily limited to the airways, thereby reducing the



**Figure 1** Role of ACh and muscarinic receptors in the lung.

**Notes:** Data from these studies.<sup>11,17</sup> In large airways, ACh released from cholinergic nerves activates  $M_3$  receptors on ASM, causing bronchoconstriction. In peripheral airways, where cholinergic nerves are absent, inflammatory cells stimulate epithelial cells to release ACh, activating  $M_3$  receptors on ASM and causing bronchoconstriction.  $M_3$  muscarinic receptors are shown as solid blue circles. For simplicity, other types of muscarinic receptor are not shown.

**Abbreviations:** ACh, acetylcholine; ASM, airway smooth muscle; CNS, central nervous system.

likelihood of systemic adverse events (AEs).<sup>12</sup> Inhaled glycopyrrolate has a bioavailability of 57%, with 53% absorbed via the lungs.<sup>12</sup> Based on its ability to inhibit methacholine-induced calcium release (half-life [ $t_{1/2}$ ] 6.1±2.1 minutes), inhaled glycopyrrolate has a rapid onset of action.<sup>13</sup> Inhaled glycopyrrolate is long lasting in the body, with a terminal elimination-phase  $t_{1/2}$  of 52.5 hours following inhalation (vs  $t_{1/2}$  of 6.2 hours following intravenous administration).<sup>12</sup> Population PK modeling has shown that inhaled glycopyrrolate is absorbed slowly, predominantly unchanged, from the lungs.<sup>12</sup> It has a slow-phase absorption  $t_{1/2}$  of 3.5 days, accounting for 79% of drug absorption.<sup>12</sup> Furthermore, inhaled glycopyrrolate is eliminated rapidly from the bloodstream.<sup>12</sup> Intravenous glycopyrrolate is excreted, mainly in its unmetabolized form, by the kidney.<sup>14,15</sup> Metabolism is less important for the elimination of this drug from the body.<sup>14,15</sup> Renal excretion is also likely to be important for the elimination of glycopyrrolate systemically absorbed from the lung.<sup>15</sup> However, no inhaled glycopyrrolate dose adjustments are required for patients with mild–moderate renal impairment, and those with severe renal impairment

may be given inhaled glycopyrrolate if the benefits are judged to outweigh the risks.<sup>6</sup>

## Pharmacokinetic and pharmacodynamic profiles of inhaled glycopyrrolate vs other LAMAs

Available anticholinergic drugs bind to all muscarinic ACh receptors present in the airways (ie,  $M_1$ – $M_3$ ).<sup>8,16</sup> Importantly,  $M_3$  receptors are the primary therapeutic target for bronchodilation, with antagonism at  $M_2$  autoreceptors tending to attenuate bronchodilator effects.<sup>17</sup> The PK and PD profiles of glycopyrrolate have been compared with other LAMAs in various preclinical studies, although not all of these studies tested the inhaled delivery of glycopyrrolate (Table 1).<sup>13,16,18,19</sup> Glycopyrrolate is the only anticholinergic to date to show higher relative affinity for  $M_3$  than  $M_2$  receptors, although its absolute binding affinity for these receptors is lower than that of acclidinium and tiotropium.<sup>13,16</sup> Glycopyrrolate, acclidinium, tiotropium, and ipratropium (a short-acting muscarinic antagonist) all dissociate more rapidly from  $M_2$  than  $M_3$  receptors, with all four drugs showing similar ratios of dissociation  $t_{1/2}$ .<sup>13,16</sup>

**Table 1** Preclinical studies comparing the pharmacological profile of glycopyrrolate with other LAMAs and ipratropium

Study	Characteristic	Glycopyrrolate	Acclidinium	Tiotropium	Ipratropium
In vitro calcium assay <sup>13</sup>	Equilibrium binding constant, mean ± SE:		–		–
	$M_2$	8.70±0.04		10.05±0.03	
	$M_3$	9.59±0.05		10.37±0.04	
	Drug binding $t_{1/2}$ (minutes) at $M_3$ vs $M_2$ receptors (kinetic selectivity ratio)	11.4 vs 1.07 (10.7)	–	46.2 vs 10.8 (4.3)	–
In vitro study of recombinant human receptors <sup>16</sup>	Muscarinic receptor-binding affinity ( $K_i$ , nM), mean ± SE:				
	$M_2$	1.77±0.06	0.14±0.04	0.13±0.04	1.12±0.13
	$M_3$	0.52±0.04	0.14±0.02	0.19±0.04	1.24±0.08
Ex vivo binding in rat lungs <sup>18</sup>	Binding to muscarinic receptors in lung	Binding lasted 24 hours	–	Binding lasted 24 hours	Binding observed at 2 hours, but not at 12 hours
In vitro study of recombinant human receptors <sup>16</sup>	$M_3$ vs $M_2$ receptors, dissociation $t_{1/2}$ in hours (kinetic selectivity ratio)	8.1 vs 1.1 (7.3)	29.2 vs 4.7 (6.2)	62.2 vs 15.1 (4.1)	0.5 vs 0.1 (5.9)
In vivo study in guinea pigs <sup>16</sup>	Onset of action (hours) postadministration	2	2	4	2
Ex vivo study in human airways <sup>19</sup>	Onset of action of 1 µM dose, minutes ± SEM	3.4±0.4	6.4±0.5	8.4±1.1	–
In vitro study in guinea pig trachea <sup>16</sup>	Duration of action ( $t_{1/2}$ offset of electrically stimulated contractions) at $M_3$ receptors	>8 hours	>8 hours	>8 hours	42 minutes
In vivo study in guinea pigs <sup>16</sup>	Duration of bronchodilator action, in hours ( $t_{1/2}$ offset of maximal inhibitory effect)	13	29	64	8
In vivo rat salivation study <sup>16</sup>	ED <sub>50</sub> (µg/kg) for inhibition of salivation	0.74	38	0.88	–
In vitro human plasma study <sup>16</sup>	Hydrolysis $t_{1/2}$ in plasma (hours)	6	0.04	1.6	33

**Notes:** \* $P$ <0.05 vs both acclidinium and tiotropium at equal concentrations. “–” indicates data not available.

**Abbreviations:** ED<sub>50</sub>, dose required to inhibit salivation in 50% of rats;  $K_i$ , antagonist dissociation constant; LAMAs, long-acting muscarinic antagonists; SE, standard error; SEM, standard error of the mean;  $t_{1/2}$ , half-life.

In addition, glycopyrrolate has a shorter absolute dissociation time at both  $M_2$  and  $M_3$  receptors than at acclidinium and tiotropium.<sup>16</sup> An *ex vivo* study examining muscarinic receptor binding in the rat lung showed receptor binding lasted 24 hours for glycopyrrolate and tiotropium, whereas ipratropium binding was observed at 2 hours, but not at 12 hours.<sup>18</sup>

In an *in vivo* study on guinea pigs, glycopyrrolate, ipratropium, and acclidinium had a similar onset of action, which was more rapid than tiotropium.<sup>16</sup> However, in isolated human airways, glycopyrrolate had significantly more rapid onset of action than both acclidinium and tiotropium.<sup>19</sup> Glycopyrrolate had a similar duration of action at  $M_3$  receptors to that of acclidinium and tiotropium *in vitro*, but had a shorter duration of action than tiotropium and acclidinium *in vivo* in guinea pig studies.<sup>16</sup> Sykes et al proposed that drug molecules, once dissociated from their target receptors, may not be able to diffuse away from the receptor environment and thus are likely to rebind to localized receptors.<sup>13</sup> The authors suggested that this may explain why some LAMAs have a long duration of action, despite rapid dissociation rates.<sup>13</sup> In an *in vitro* study, acclidinium was shown to have lower stability than tiotropium, which in turn had lower stability than glycopyrrolate in rat, guinea pig, and human plasma.<sup>16</sup> This indicates that glycopyrrolate undergoes a slower rate of hydrolysis, which may result in a propensity to cause anticholinergic AEs in patients with COPD.<sup>16</sup> These findings are in agreement with a previous study that compared the plasma stability of acclidinium with tiotropium and ipratropium, with acclidinium found to be the least stable of the three bronchodilators evaluated.<sup>20</sup> Furthermore, a lower dose of glycopyrrolate and tiotropium than acclidinium is required to inhibit salivation effectively in rats, possibly because of the slower rate of hydrolysis in the blood.<sup>16</sup>

## Inhaled glycopyrrolate: effects on mucus secretion and mucociliary clearance in COPD

Mucus is secreted by submucosal mucus glands and goblet cells in the bronchi, and excessive mucus secretion is a feature of chronic bronchitis and COPD.<sup>21</sup>  $M_1$  and  $M_3$  receptors are expressed at a 1:2 ratio in submucosal glands.<sup>22</sup> The  $M_3$  receptor is involved primarily in mediating mucus secretion, whereas water and electrolyte secretion are likely to be regulated by  $M_3$  and  $M_1$  receptors in combination.<sup>22</sup> LABAs are known to enhance mucociliary clearance in patients with COPD,<sup>23</sup> probably via an effect on ciliary beat frequency,<sup>24</sup> and there are numerous theories regarding the alteration of mucus production by LAMAs.<sup>25</sup> However, the results from clinical trials testing these theories are conflicting.<sup>25</sup>

In an open-label, non-placebo-controlled trial in 22 patients with COPD, tiotropium reduced cough symptoms and nasal clearance times.<sup>26</sup> The authors concluded that this effect may result from inhibition of mucus hypersecretion and an increase in mucociliary clearance in the airways.<sup>26</sup> However, this supposition is not supported by other studies: in a randomized, double-blind trial, Hasani et al failed to find an effect of tiotropium on mucociliary clearance in 34 patients with COPD,<sup>27</sup> whereas Meyer et al reported that tiotropium treatment slowed mucociliary clearance in their randomized, open-label, crossover study in 24 patients.<sup>28</sup> Furthermore, in a double-blind, crossover study, ipratropium was actually found to decrease cough clearance of secretions in patients with COPD.<sup>29</sup>

Oral glycopyrrolate is known to reduce drooling in children, and glycopyrrolate injections can reduce preoperative salivation, as well as respiratory secretions during end-of-life care.<sup>30,31</sup> However, on review of published literature cited in PubMed, no studies could be found that examined the role of inhaled glycopyrrolate in mucus secretion. There also appear to be limited published data examining the effect of glycopyrrolate on mucociliary clearance,<sup>25</sup> and hence, there is a need for further study in this area.

## The effect of inhaled glycopyrrolate on cognition

Glycopyrrolate is a water-soluble, highly polar quaternary ammonium compound, which limits its passage across lipid membranes such as the blood–brain barrier; therefore, glycopyrrolate does not exhibit any central nervous system activity.<sup>32</sup> Inhaled glycopyrrolate is thus unlikely to have a significant effect on cognition in patients with COPD, although there is a lack of evidence to support this.

## Clinical evidence for the use of inhaled glycopyrrolate in patients with COPD

In its inhaled form, glycopyrrolate and other approved LAMAs are used for the management of COPD.<sup>1,6,33–37</sup> Glycopyrrolate is available as a monotherapy via a dry-powder inhaler (DPI)<sup>6</sup> and was approved by the FDA in 2017 as a nebulized monotherapy (Table 2).<sup>38</sup> Inhaled glycopyrrolate is also available in an FDC with formoterol, delivered using co-suspension delivery technology in a pressurized metered dose inhaler (pMDI),<sup>34</sup> and in a DPI FDC with indacaterol.<sup>35,36</sup> Inhaled glycopyrrolate has been approved in Europe as a triple FDC with formoterol and beclomethasone, delivered via a pMDI.<sup>39</sup>

**Table 2** Available glycopyrrolate and other LAMA formulations

Formulation	Brand name	Delivery method	Regions approved	Approved dosage
<b>Glycopyrrolate formulations</b>				
Monotherapy <sup>6,33</sup>	Seebri Neohaler	DPI	US	15.6 µg BID
	Seebri Breezhaler	DPI	Europe	50 µg QD (glycopyrronium moiety in capsule)
Monotherapy <sup>78</sup>	Lonhala Magnair	Nebulized	US	25 µg BID
Glycopyrrolate–formoterol <sup>34</sup>	Bevespi Aerosphere	pMDI	US	18/9.6 µg BID (as glycopyrrolate–formoterol fumarate)
Glycopyrrolate–indacaterol <sup>35,36</sup>	Utibron Neohaler	DPI	US	15.6/27.5 µg BID
	Ultibro Breezhaler	DPI	Europe	50/110 µg QD (in capsule, as glycopyrronium/indacaterol)
Glycopyrrolate–beclomethasone–formoterol <sup>37</sup>	Trimbow	pMDI	Europe	12.5/100/6 µg BID (metered dose, as glycopyrronium bromide–beclomethasone dipropionate–formoterol fumarate dihydrate)
<b>Tiotropium formulations</b>				
Monotherapy <sup>79,80</sup>	Spiriva HandiHaler	DPI	US	18 µg QD (as tiotropium bromide)
	Spiriva Respimat	SMI	US	5 µg QD (as tiotropium bromide)
Tiotropium–olodaterol <sup>81,82</sup>	Stiolto Respimat	SMI	US	5/5 µg QD
	Spolto Respimat	SMI	Europe	5/5 µg QD (delivered dose, as tiotropium bromide monohydrate–olodaterol hydrochloride)
<b>Umeclidinium formulations</b>				
Monotherapy <sup>83,84</sup>	Incruse Ellipta	DPI	US	62.5 µg QD
	Incruse Ellipta	DPI	Europe	62.5 µg QD (predispensed dose, as umeclidinium)
Umeclidinium–vilanterol <sup>85,86</sup>	Anoro Ellipta	DPI	US	62.5/25 µg QD
	Anoro Ellipta	DPI	Europe	62.5/25 µg QD (predispensed dose, as umeclidinium–vilanterol trifenate)
Umeclidinium–fluticasone furoate–vilanterol <sup>87</sup>	Trelegy Ellipta	DPI	US	62.5/100/25 µg QD (as umeclidinium–fluticasone furoate–vilanterol)
<b>Acclidinium formulations</b>				
Monotherapy <sup>88–90</sup>	Eklira Genuair	DPI	Europe	400 µg BID (as acclidinium bromide)
	Bretaris Genuair	DPI	Europe	400 µg BID (as acclidinium bromide)
	Tudorza Pressair	DPI	US	400 µg BID (as acclidinium bromide)
Acclidinium–formoterol <sup>91</sup>	Duaklir Genuair	DPI	Europe	400/12 µg BID (as acclidinium bromide–formoterol fumarate dihydrate)
<b>Revefenacin formulation</b>				
Monotherapy <sup>92</sup>	TBC <sup>a</sup>	Nebulized	Completed Phase III trials	NA

**Note:** <sup>a</sup>Theravance Biopharma and Mylan submitted a new drug application for revefenacin use in patients with COPD in November 2017 and were waiting for a response at the time of submission of this review article.<sup>93</sup>

**Abbreviations:** BID, bis in die (twice daily); DPI, dry-powder inhaler; LAMA, long-acting muscarinic antagonist; NA, not applicable; pMDI, pressurized metered dose inhaler; QD, quaque die (once daily); SMI, soft-mist inhaler; TBC, to be confirmed.

## Efficacy of inhaled glycopyrrolate monotherapy

### Onset of action

In a randomized, double-blind study to determine the most appropriate dose of inhaled glycopyrrolate monotherapy (delivered via a DPI) for patients with moderate–severe COPD, glycopyrrolate 50 µg once daily (QD) provided significant bronchodilation over 24 hours.<sup>40</sup> However, the efficacy of glycopyrrolate 50 µg QD was not significantly different from the same total daily dose administered twice daily (BID).<sup>40</sup> The randomized GLOW trials were conducted to evaluate the use of 50 µg QD of inhaled glycopyrrolate

for treating patients with moderate–severe COPD.<sup>41–46</sup> The GLOW1 study showed that glycopyrrolate 50 µg QD had a rapid onset of bronchodilation in patients with COPD, with a significant improvement from baseline in lung function vs placebo as early as 5 minutes after treatment ( $P < 0.001$ ).<sup>41</sup> Supporting the preclinical data, inhaled glycopyrrolate has been shown to have faster onset of action than tiotropium in several clinical trials. In the randomized GLOW2 study, glycopyrrolate 50 µg QD resulted in significantly more rapid bronchodilation than tiotropium 18 µg QD treatment at all time points from 5 minutes to 4 hours after the first dose on day 1 ( $P < 0.01$ ).<sup>42</sup> Similarly, in the randomized

GLOW5 study, glycopyrrolate 50 µg QD resulted in significantly more rapid improvement in lung function than tiotropium 18 µg QD treatment at 5 and 15 minutes after first dose.<sup>45</sup> Additionally, in a post hoc analysis of the randomized SPRING study in patients with moderate–severe COPD, glycopyrrolate 50 µg QD resulted in a significantly greater improvement in lung function than tiotropium 18 µg QD at 5 minutes, 15 minutes, and 1 hour after the first dose on day 1 ( $P=0.015$ ,  $P=0.026$ , and  $P=0.014$ , respectively).<sup>47</sup> In a further study in patients with moderate–severe COPD, single doses of both glycopyrrolate (50 µg) and aclidinium (400 µg) had more rapid onset of action than tiotropium (18 µg), resulting in greater levels of bronchodilation 90 minutes after treatment, although the authors concluded that faster onset of action seen in the clinic may not be relevant for patients who are undergoing long-term treatment for chronic disease.<sup>19</sup>

### Lung function and other efficacy end points

The efficacy of inhaled glycopyrrolate monotherapy (via a DPI) has been investigated in patients with COPD in

numerous clinical studies, including the GLOW study series and the GEM studies (Table 3).<sup>38,41–52</sup> Two network meta-analyses have also been conducted to compare the efficacy of glycopyrrolate with other LAMAs.<sup>53,54</sup> The first (including 21 trials) compared glycopyrrolate 50 µg QD with aclidinium 400 µg BID, tiotropium 18 µg QD (HandiHaler), and tiotropium 5 µg QD (Respimat) in patients with moderate–severe COPD.<sup>53</sup> After 24 weeks, glycopyrrolate 50 µg treatment resulted in a similar improvement in lung function compared with aclidinium 400 µg, tiotropium 18 µg, and tiotropium 5 µg.<sup>53</sup> At the same time point, glycopyrrolate 50 µg treatment resulted in similar improvements in St George's Respiratory Questionnaire (SGRQ) scores from baseline compared with aclidinium 400 µg and tiotropium 18 µg, and a greater improvement compared with tiotropium 5 µg.<sup>53</sup> Improvements in breathlessness symptoms were similar for all treatments.<sup>53</sup>

The second network meta-analysis (including 24 trials) compared the efficacy of glycopyrrolate 50 µg QD, tiotropium 18 µg QD, aclidinium 400 µg BID, and umeclidinium 62.5 µg QD in patients with COPD.<sup>54</sup> At weeks 12 and 24,

**Table 3** Clinical evidence of the efficacy of glycopyrrolate monotherapy in patients with COPD

Clinical trial	Treatment duration	Treatments	Key findings
<b>GLOW trials: double-blind, randomized, placebo-controlled studies in patients with moderate–severe COPD</b>			
Phase III GLOW1 <sup>41</sup>	26 weeks	Glycopyrrolate 50 µg QD (n=552), placebo (n=270)	Glycopyrrolate significantly increased trough FEV <sub>1</sub> vs placebo at week 12 (LSM treatment difference 0.108 L, $P<0.001$ ), increase maintained at week 26 (LSM treatment difference 0.113 L, $P<0.001$ ) Significant improvements in dyspnea (TDI focal score 1.84 vs 0.80 points, $P<0.001$ ) and time to first moderate/severe exacerbation ( $P=0.023$ ) vs placebo at week 26
Phase III GLOW2 <sup>42</sup>	52 weeks	Glycopyrrolate 50 µg QD (n=529), placebo (n=269), open-label tiotropium 18 µg QD (n=268)	Glycopyrrolate significantly increased trough FEV <sub>1</sub> vs placebo at week 12 (LSM treatment difference 97 mL, $P<0.001$ ) Glycopyrrolate significantly increased trough FEV <sub>1</sub> vs tiotropium at week 26 (LSM treatment difference 50 mL, $P<0.01$ ), while trough FEV <sub>1</sub> was similar at weeks 12 and 52 (LSM treatment difference 14 and 19 mL, respectively) Significant improvements in dyspnea at week 26 (TDI focal score 2.13 vs 1.32, $P=0.002$ ) and risk of exacerbations at week 52 ( $P=0.001$ ) vs placebo
Phase III GLOW3 crossover <sup>43</sup>	3 weeks	Glycopyrrolate 50 µg QD, then placebo (n=55); placebo, then glycopyrrolate 50 µg QD (n=53)	Glycopyrrolate significantly improved submaximal exercise endurance time vs placebo on day 1 ( $P<0.001$ ), and this improvement increased at day 21 ( $P<0.001$ )
Phase III GLOW5 <sup>45</sup>	12 weeks	Glycopyrrolate 50 µg QD (n=327), tiotropium 18 µg QD (n=330)	Glycopyrrolate was noninferior to tiotropium for trough FEV <sub>1</sub> at week 12 (LSM treatment difference 0 L, $P<0.001$ ) Glycopyrrolate had a significantly faster onset of action on day 1 than tiotropium (postdose FEV <sub>1</sub> at 0- to 4-hour time points, all $P<0.001$ )
GLOW7 <sup>46</sup>	26 weeks	Glycopyrrolate 50 µg QD (n=306), placebo (n=154)	Glycopyrrolate significantly improved trough FEV <sub>1</sub> vs placebo at week 12 (LSM treatment difference 141 mL, $P<0.001$ ) Glycopyrrolate significantly improved SGRQ scores (LSM treatment difference -4.92 points, $P<0.001$ ) and dyspnea severity (LSM treatment difference 1 point, $P<0.001$ ) at week 26 vs placebo

(Continued)

Table 3 (Continued)

Clinical trial	Treatment duration	Treatments	Key findings
<b>SPRING trial: randomized, blinded study in patients with moderate-severe COPD</b>			
SPRING crossover <sup>47</sup>	4 weeks	Glycopyrrolate 50 µg QD, then tiotropium 18 µg QD; tiotropium 18 µg QD, then glycopyrrolate 50 µg QD (n=126)	On day 1, glycopyrrolate 50 µg treatment significantly improved FEV <sub>1</sub> AUC <sub>0-4</sub> after the first dose compared with tiotropium 18 µg (LSM treatment difference 0.030 L, P=0.025) Improvements in morning symptoms of COPD were similar between treatments
<b>GEM trials: Phase III, double-blind, randomized, placebo-controlled studies in patients with COPD and moderate-severe airflow limitation</b>			
GEM1 <sup>48</sup>	12 weeks	Glycopyrrolate 15.6 µg BID (n=222), placebo (n=219)	Glycopyrrolate significantly improved FEV <sub>1</sub> AUC <sub>0-12</sub> vs placebo at week 12 (LSM treatment difference 0.139 L, P<0.001) Glycopyrrolate significantly improved TDI (LSM treatment difference 0.92 points, P=0.003) and SGRQ scores (LSM treatment difference -2.8 points, P=0.016) vs placebo at week 12
GEM2 <sup>49</sup>	12 weeks	Glycopyrrolate 15.6 µg BID (n=216), placebo (n=216)	Glycopyrrolate significantly improved FEV <sub>1</sub> AUC <sub>0-12</sub> vs placebo at day 1 (LSM treatment difference 0.119 L, P<0.001), improvement maintained at week 12 (LSM treatment difference 0.123 L, P<0.001) Glycopyrrolate significantly improved SGRQ scores (LSM treatment difference -5.2 points, P<0.001) vs placebo at week 12
<b>GOLDEN trials: Phase III, randomized studies of nebulized glycopyrrolate in patients with moderate-very severe COPD</b>			
Double-blind, placebo-controlled GOLDEN 3 and GOLDEN 4 <sup>38</sup>	12 weeks	Glycopyrrolate 25 µg BID (n=431), glycopyrrolate 50 µg BID (n=432), placebo (n=430)	At week 12, treatment with glycopyrrolate 25 and 50 µg BID resulted in significant and clinically important improvements in trough FEV <sub>1</sub> vs placebo (GOLDEN 3 [LSM difference 0.105 and 0.126 L, respectively] and GOLDEN 4 [LSM difference 0.084 and 0.082 L, respectively], all P≤0.0001) At week 12, glycopyrrolate 25 and 50 µg BID significantly improved trough FVC vs placebo (GOLDEN 3 [LSM difference 0.149 and 0.167 L, respectively; both P<0.001], GOLDEN 4 [LSM difference 0.130 and 0.113 L, respectively; P<0.01]) At week 12/end of study, glycopyrrolate 25 and 50 µg BID significantly increased SGRQ scores vs placebo (GOLDEN 3 [LSM difference -3.072, P<0.05 and -1.848 points, P=NS, respectively]; GOLDEN 4 [LSM difference -3.585 and -3.557 points, respectively; P<0.01])
Open-label, active-controlled GOLDEN 5 <sup>51</sup>	48 weeks	Glycopyrrolate 50 µg BID (n=621), tiotropium 18 µg QD (n=466)	Glycopyrrolate treatment improved trough FEV <sub>1</sub> from baseline, which was maintained until week 48 (LSM change from baseline at week 48 0.069 L) Change from baseline in FEV <sub>1</sub> at 48 weeks did not differ significantly between glycopyrrolate and tiotropium
<b>Randomized, double-blind studies of glycopyrrolate delivered using co-suspension delivery technology in patients with moderate-severe COPD<sup>a</sup></b>			
Chronic-dosing, Phase II, crossover trial <sup>52</sup>	2 weeks	Glycopyrrolate 18, 9, 4.6, 2.4, 1.2, 0.6 µg BID (n=64, 64, 62, 64, 57, 59, respectively), open-label tiotropium 18 µg QD (n=62), placebo BID (n=62)	After 14 days' treatment, glycopyrrolate at doses 18, 9, 4.6, and 2.4 µg BID resulted in significant and clinically relevant improvements in FEV <sub>1</sub> AUC <sub>0-12</sub> compared with placebo (LSM difference from baseline 126-158 mL, P<0.0001) Glycopyrrolate 18 µg BID was noninferior to open-label tiotropium 18 µg QD for peak change in FEV <sub>1</sub> on day 1 (LSM change from baseline 0.231 vs 0.270 L) and morning predose trough FEV <sub>1</sub> on day 14 (LSM change from baseline 0.089 vs 0.126 L) and was the most appropriate dose for further evaluation
Chronic-dosing, Phase IIB, incomplete block, crossover trial <sup>57</sup>	7 days	Glycopyrrolate (as glycopyrronium) 28.8, 14.4, 7.2, 3.6 µg BID (n=192), placebo BID (n=48), open-label ipratropium 34 µg QID (n=48) <sup>b</sup>	At day 7, all glycopyrrolate doses were superior to placebo for improvement from baseline in FEV <sub>1</sub> AUC <sub>0-12</sub> (LSM treatment differences vs placebo 0.121-0.191 L, all P<0.0001) All glycopyrrolate doses were noninferior to ipratropium (data not shown) Glycopyrrolate 28.8 and 14.4 µg were the most effective doses for improving all secondary efficacy end points

**Notes:** <sup>a</sup>Phase II studies included, as Phase III trial data have not yet been published for this product; <sup>b</sup>each patient received three treatments of two doses of glycopyrrolate and either placebo or ipratropium.

**Abbreviations:** AUC, area under curve; BID, bis in die (twice daily); FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; LSM, least squares mean; NS, not significant; QD, quaque die (once daily); QID, quater in die (four times daily); SGRQ, St George's Respiratory Questionnaire; TDI, Transition Dyspnea Index.

all LAMA treatments evaluated resulted in clinically relevant (>100 mL) improvements in trough forced expiratory volume in 1 second (FEV<sub>1</sub>) compared with placebo.<sup>54</sup> Glycopyrrolate 50 µg treatment resulted in the greatest improvement over placebo in lung function at week 24 (FEV<sub>1</sub> difference 135.8 mL).<sup>54</sup> For all LAMAs vs placebo, improvements were seen from baseline in 24-week SGRQ and Transition Dyspnea Index (TDI) scores.<sup>54</sup> Glycopyrrolate 50 µg QD treatment did not reach the minimal clinically important difference (MCID) in SGRQ score of 4 units compared with placebo, but did reach the MCID of ≥1 for TDI focal score.<sup>54</sup> However, aclidinium 400 µg and umeclidinium 62.5 µg treatments reached MCID for both SGRQ and TDI focal scores compared with placebo, whereas tiotropium did not reach MCID for either of the two measures.<sup>54</sup>

For patients with moderate–severe COPD, clinical trial data for treatment with inhaled glycopyrrolate as a monotherapy indicate that glycopyrrolate 50 µg QD (the EMA-approved dose) improves lung function and health-related quality of life (HRQoL), decreases the severity of breathlessness and the risk of exacerbations, and improves morning symptoms.<sup>41,42,45,47,51</sup> Furthermore, glycopyrrolate 50 µg QD was found to be noninferior to tiotropium in its ability to increase airflow to the lungs.<sup>45</sup> In a short-term, cross-over trial (3-week treatment periods), glycopyrrolate also significantly improved patients' abilities to exercise vs placebo.<sup>43</sup> In Phase III trials of glycopyrrolate 15.6 µg BID (the FDA-approved dose) in patients with moderate–severe COPD, there were also significant improvements in FEV<sub>1</sub> scores from baseline, TDI focal scores, and SGRQ scores vs placebo.<sup>48,49</sup> In two Phase III trials of the nebulized form of glycopyrrolate, 50 µg BID treatment resulted in significant and clinically important increases from baseline in lung function and SGRQ scores vs placebo.<sup>38</sup> Finally, in two studies in patients with moderate–severe COPD, glycopyrrolate was delivered by pMDI using innovative co-suspension delivery technology, which allows aerosol delivery of micronized drug suspended with microsized, phospholipid-based porous particles.<sup>52,55–57</sup> In these studies, patients treated with glycopyrrolate (doses ≥2.4 µg BID) showed clinically relevant, significant improvements in lung function from baseline vs placebo.<sup>52,57</sup> Furthermore, the highest glycopyrrolate dose tested in the first study (18 µg BID) was found to be noninferior to tiotropium 18 µg QD for improving lung function.<sup>52</sup> In the second study, all glycopyrrolate doses (delivered as glycopyrronium 28.8, 14.4, 7.2, and 3.6 µg BID) were found to be noninferior to ipratropium 34 µg 4 times daily.<sup>57</sup> Based on these studies, 18 µg (equivalent to 14.4 µg glycopyrronium) was selected

as the optimal glycopyrrolate dose for the glycopyrrolate–formoterol combination studies.<sup>52,57</sup>

## Efficacy of inhaled glycopyrrolate combinations

Combining a LAMA with a LABA can increase efficacy, as they have distinctly different mechanisms of action (ie, target different receptors). In addition, LABAs modify the release of ACh, leading to amplification of bronchial smooth muscle relaxation induced by the LAMA.<sup>58</sup> Moreover, LABAs act on presynaptic β<sub>2</sub>-receptors in the efferent cholinergic pathway, resulting in the inhibition of cholinergic transmission.<sup>59</sup>

In 2016, glycopyrrolate–formoterol pMDI 18/9.6 µg BID was licensed by the FDA “for the long-term maintenance treatment of airflow obstruction in patients with COPD”.<sup>34</sup> Several randomized controlled trials have examined the efficacy of glycopyrrolate–formoterol 18/9.6 µg BID (Table 4).<sup>60,61</sup> Five studies (PINNACLE-1, PINNACLE-2, PT003011, PT003012, and PINNACLE-3) showed that (as expected) glycopyrrolate–formoterol 18/9.6 µg BID significantly improved lung function compared with individual components and placebo.<sup>60–62</sup> In addition, glycopyrrolate–formoterol 18/9.6 µg BID was at least as efficacious as open-label tiotropium 18 µg QD.<sup>61,62</sup> Furthermore, the efficacy of glycopyrrolate–formoterol 18/9.6 µg BID was maintained over the 1-year treatment period.<sup>60,61</sup> A post hoc analysis of PINNACLE-1 and -2 indicated that glycopyrrolate–formoterol improved FEV<sub>1</sub> independently of baseline symptom severity, although high baseline symptom severity was significantly correlated with greater improvement in health outcomes after treatment.<sup>63</sup>

Inhaled glycopyrrolate has also been combined with indacaterol for maintenance therapy in patients with COPD. Glycopyrrolate–indacaterol DPI was approved for use by the FDA in 2015 (at 15.6/27.5 µg BID)<sup>36</sup> and by the EMA in 2013 (at 50/110 µg QD).<sup>35</sup> Glycopyrrolate–indacaterol 50/110 µg QD significantly improved lung function compared with individual components ( $P<0.001$ )<sup>64</sup> and tiotropium 18 µg QD ( $P=0.0017$ ).<sup>65</sup> The glycopyrrolate–indacaterol combination was also preferred to tiotropium by both patients ( $P=0.00004$ ) and physicians ( $P<0.0001$ ).<sup>65</sup> Furthermore, glycopyrrolate–indacaterol 50/110 µg QD significantly increased lung function, and a significantly greater proportion of patients achieved a clinically relevant improvement in dyspnea compared with tiotropium 18 µg QD plus formoterol 12 µg BID.<sup>66</sup> In two clinical trials, glycopyrrolate–indacaterol 50/110 µg QD was more effective at reducing COPD exacerbations than the ICS–LABA combination fluticasone propionate–salmeterol 500/50 µg BID.<sup>67,68</sup> Additionally,

**Table 4** Recent clinical evidence (2015 to present) of efficacy of glycopyrrolate combinations in patients with COPD

Clinical trial	Treatment duration	Treatments	Key findings
<b>Glycopyrrolate–formoterol FDC delivered using co-suspension delivery technology via a pMDI</b>			
Phase III, randomized, double-blind, PINNACLE-1 and -2 studies in moderate–very severe COPD <sup>60</sup>	24 weeks	Glycopyrrolate–formoterol 18/9.6 µg BID (n=1,039), glycopyrrolate 18 µg BID (n=891), formoterol 9.6 µg BID (n=891), placebo BID (n=444), open-label tiotropium 18 µg (PINNACLE-1 only, QD; n=453)	At week 24, the change in predose trough FEV <sub>1</sub> for glycopyrrolate–formoterol was significantly greater than for glycopyrrolate, formoterol, and placebo (LSM difference in change from baseline vs comparators, PINNACLE-1, 0.059–0.150 L, $P<0.0001$ ; PINNACLE-2, 0.054–0.103 L, $P<0.001$ ) Change in predose trough FEV <sub>1</sub> for glycopyrrolate–formoterol did not differ significantly from tiotropium in PINNACLE-1, but did in PINNACLE-2 (LSM difference in change from baseline 0.021, $P=NS$ and 0.103, $P<0.001$ , respectively)
Phase III, randomized, double-blind trial (PINNACLE-3 [a PINNACLE-1 and -2 extension study]) <sup>61</sup>	28 weeks	Glycopyrrolate–formoterol 18/9.6 µg BID (n=290), glycopyrrolate 18 µg BID (n=218), formoterol 9.6 µg BID (n=213), open-label tiotropium 18 µg QD (n=171)	At week 52, the change in predose trough FEV <sub>1</sub> for glycopyrrolate–formoterol was significantly greater than that for all other treatments (LSM difference in change from baseline 0.025–0.065 L, $P\leq 0.0117$ )
Two Phase IIIB, double-blind, crossover studies (PT003011 and PT003012) in moderate–very severe COPD <sup>62</sup>	4 weeks	Glycopyrrolate–formoterol 18/9.6 µg BID (n=115), placebo (n=112), open-label tiotropium 5 µg QD (PT003011 only, n=73)	By day 29, glycopyrrolate–formoterol had significantly improved FEV <sub>1</sub> AUC <sub>0–24</sub> vs placebo (LSM treatment difference, PT003011, 0.265 L; PT003012, 0.249 L; both $P<0.0001$ ) In PT003011, glycopyrrolate–formoterol treatment resulted in significantly improved FEV <sub>1</sub> AUC <sub>0–12</sub> vs tiotropium (LSM treatment difference 0.080 L, $P=0.0001$ ) FEV <sub>1</sub> AUC <sub>12–14</sub> improvements with glycopyrrolate–formoterol were also greater than for placebo (LSM treatment difference for FEV <sub>1</sub> AUC <sub>0–12</sub> , PT003011 0.251 and PT003012 0.255; for AUC <sub>0–24</sub> , PT003011 0.277 and PT003012 0.242)
<b>Glycopyrrolate–indacaterol FDC via a DPI</b>			
Randomized, double-blind, noninferiority FLAME trial in patients with high-exacerbation risk <sup>67</sup>	52 weeks	Glycopyrrolate–indacaterol 50/110 µg QD (n=1,680), fluticasone propionate–salmeterol 500/50 µg BID (n=1,682)	The glycopyrrolate–indacaterol combination was found to be superior to fluticasone propionate–salmeterol in reducing annual COPD exacerbations ( $P=0.003$ ) and increasing time to first exacerbation ( $P<0.001$ )
Randomized, double-blind, LANTERN study in moderate–severe COPD with a history of exacerbations <sup>68</sup>	26 weeks	Glycopyrrolate–indacaterol 50/110 µg QD (n=372), fluticasone propionate–salmeterol 500/50 µg BID (n=372)	At week 26, glycopyrrolate–indacaterol was significantly superior at improving trough FEV <sub>1</sub> to fluticasone propionate–salmeterol (LSM treatment difference 0.075, $P<0.001$ ) At week 26, the glycopyrrolate–indacaterol group showed a significantly greater improvement in FEV <sub>1</sub> AUC <sub>0–4</sub> than the fluticasone propionate–salmeterol group (LSM treatment difference 0.122 L, $P<0.001$ ) Glycopyrrolate–indacaterol treatment reduced moderate/severe exacerbations to a significantly greater extent than fluticasone propionate–salmeterol ( $P=0.048$ )
Post hoc analysis of pooled ILLUMINATE and LANTERN trials examining symptomatic (GOLD B and D) <sup>3</sup> patients with moderate–severe COPD <sup>72</sup>	26 weeks	Glycopyrrolate–indacaterol 50/110 µg QD (n=630), fluticasone propionate–salmeterol 500/50 µg BID (n=633)	At week 26, glycopyrrolate–indacaterol significantly improved lung function from baseline vs fluticasone propionate–salmeterol in symptomatic patients (LSM treatment difference in predose trough FEV <sub>1</sub> in GOLD B and D patients 0.10 and 0.08 L, respectively [both $P<0.0001$ ]; LSM treatment difference in FEV <sub>1</sub> AUC <sub>0–12</sub> 0.14 L [ $P<0.0001$ ] in GOLD B and 0.11 L [ $P<0.005$ ] in GOLD D)

(Continued)

**Table 4** (Continued)

Clinical trial	Treatment duration	Treatments	Key findings
Two randomized, double-blind, crossover studies (A2349 and A2350) in patients with moderate-severe COPD <sup>71</sup>	12 weeks	Glycopyrrolate-indacaterol 15.6/27.5 µg BID, umeclidinium-vilanterol 62.5/25 µg QD (A2349, n=357; A2350, n=355)	Noninferiority of glycopyrrolate-indacaterol vs umeclidinium-vilanterol for change from baseline in FEV <sub>1</sub> AUC <sub>0-24</sub> at week 12 was not met (lower boundary of 97.5% one-sided CI for glycopyrrolate-indacaterol below prespecified margin of -20 mL in both studies; LSM between-treatment differences -11.5 mL, 95% CI -26.9 to 3.8 [A2349] and -18.2 mL, 95% CI -34.2 to 2.3 [A2350]) Both glycopyrrolate-indacaterol and umeclidinium-vilanterol improved FEV <sub>1</sub> AUC <sub>12-24</sub> (208 and 203 mL [A2349], 163 and 154 mL [A2350]) and trough FEV <sub>1</sub> levels from baseline at week 12 (189 and 201 mL [A2349], 168 and 177 mL [A2350])
Randomized, double-blind, crossover, MOVE study in patients with moderate-severe COPD <sup>73</sup>	21 days	Glycopyrrolate-indacaterol 50/110 µg QD, then placebo; placebo, then glycopyrrolate-indacaterol 50/110 µg QD (n=194)	Glycopyrrolate-indacaterol significantly improved peak IC levels (LSM treatment difference 0.202 L, P<0.0001) and activity-related energy used (P=0.040) vs placebo after 21 days' treatment
Randomized, multicenter, blinded, QUANTIFY study in moderate-severe COPD <sup>66</sup>	26 weeks	Glycopyrrolate-indacaterol 50/110 µg QD (n=476), tiotropium 18 µg QD + formoterol 12 µg BID (n=458)	At week 26, glycopyrrolate-indacaterol was found to be noninferior to tiotropium + formoterol in improving SGRQ scores (LSM treatment difference -0.69) At week 26, significantly more patients using glycopyrrolate-indacaterol vs tiotropium + formoterol achieved a clinically relevant improvement in TDI score (49.6% vs 42.4%, P=0.033) and significantly improved predose FEV <sub>1</sub> (LSM treatment difference 0.068 L, P<0.001) and FVC (LSM treatment difference 0.074 L, P<0.01)
Randomized, open-label, crossover, FAVOR study in symptomatic (GOLD B or D) <sup>a</sup> patients who had previously received tiotropium therapy <sup>65</sup>	4 weeks	Open-label glycopyrrolate-indacaterol 50/110 µg QD, then tiotropium 18 µg QD (n=43); tiotropium 18 µg QD, then open-label glycopyrrolate-indacaterol 50/110 µg QD (n=45)	Glycopyrrolate-indacaterol significantly increased FEV <sub>1</sub> 1 hour postdose vs tiotropium after 4 weeks' treatment (treatment difference 0.081 L, P=0.0017)
Pooled analysis of randomized, double-blind, parallel-group, FLIGHT1 and FLIGHT2 studies in moderate-severe COPD <sup>69</sup>	12 weeks	Glycopyrrolate-indacaterol 15.6/27.5 µg BID (n=260), indacaterol 27.5 µg BID (n=260), glycopyrrolate 15.6 µg BID (n=261), placebo (n=261)	Glycopyrrolate-indacaterol improved FEV <sub>1</sub> AUC <sub>0-12</sub> significantly more than individual components (LSM treatment difference 0.103 L vs indacaterol and 0.088 L vs glycopyrrolate, respectively; both P<0.001) and placebo (LSM treatment difference 0.246 L, P<0.001) Compared with individual components and placebo, glycopyrrolate-indacaterol produced significantly greater and more clinically meaningful improvements in TDI total score (LSM treatment difference 0.78 points vs indacaterol, 0.73 points vs glycopyrrolate, and 1.64 points vs placebo; all P<0.001) and SGRQ score (LSM treatment difference -1.7 points vs indacaterol [P<0.05], -1.5 points vs glycopyrrolate [P<0.05], -5.0 points vs placebo [P<0.001])

(Continued)

Table 4 (Continued)

Clinical trial	Treatment duration	Treatments	Key findings
Randomized, multicenter, double-blind, parallel-group, FLIGHT3 study in moderate–severe COPD <sup>70</sup>	52 weeks	Glycopyrrolate–indacaterol 15.6/27.5 µg BID (n=204), glycopyrrolate–indacaterol 31.2/27.5 µg BID (n=204), indacaterol 75 µg QD (n=207)	Improvements in predose trough FEV <sub>1</sub> were greater with glycopyrrolate–indacaterol 15.6/27.5 µg and 31.2/27.5 µg (LSM treatment difference 0.080 L and 0.079 L, respectively), and improvements in 1-hour postdose FEV <sub>1</sub> were greater with glycopyrrolate–indacaterol 15.6/27.5 µg (LSM treatment difference 0.108 L) than indacaterol alone at week 52
<b>Glycopyrrolate via DPI plus FDC fluticasone propionate–salmeterol via DPI</b>			
Randomized, blinded, GLISTEN study in moderate–severe COPD <sup>74</sup>	12 weeks	Glycopyrrolate 50 µg QD + fluticasone propionate–salmeterol 500/50 µg BID (n=258), tiotropium 18 µg QD + fluticasone propionate–salmeterol 500/50 µg BID (n=258), placebo + fluticasone propionate–salmeterol 500/50 µg BID (n=257)	At week 12, glycopyrrolate + fluticasone propionate–salmeterol significantly improved trough FEV <sub>1</sub> from baseline vs placebo + fluticasone propionate–salmeterol (LSM treatment difference 0.101 L, P<0.001) At week 12, glycopyrrolate + fluticasone propionate–salmeterol was noninferior to tiotropium + fluticasone propionate–salmeterol (LSM treatment difference –0.007 L) At week 12, glycopyrrolate + fluticasone propionate–salmeterol significantly improved SGRQ total scores from baseline vs placebo + fluticasone propionate–salmeterol (LSM treatment difference –2.15, P=0.02)
<b>Extrafine glycopyrrolate–beclomethasone–formoterol FDC via pMDI</b>			
Randomized, double-blind, active-comparator, TRILOGY study in patients with symptomatic COPD <sup>75</sup>	52 weeks	2-week open-label run-in period, beclomethasone–formoterol 100/6 µg; patients then randomly assigned to beclomethasone–formoterol 100/6 µg (n=681) or stepped up to glycopyrrolate–beclomethasone–formoterol 12.5/100/6 µg (n=687)	At week 26, triple FDC significantly improved predose (treatment difference 0.081 L) and 2-hour postdose FEV <sub>1</sub> (treatment difference 0.117 L) from baseline vs the dual ICS–LABA (both P<0.001) At week 52, patients in the triple FDC group experienced 23% fewer moderate/severe exacerbations than those in the dual ICS–LABA FDC group
Randomized, double-blind, TRINITY study in patients with symptomatic COPD <sup>76</sup>	52 weeks	2-week open-label tiotropium 18 µg QD, then open-label tiotropium µg QD (n=1,075), glycopyrrolate–beclomethasone–formoterol 12.5/100/6 µg BID (n=1,078), beclomethasone–formoterol 100/6 µg BID + tiotropium 18 µg QD (n=538)	Glycopyrrolate–beclomethasone–formoterol was superior to tiotropium in reducing the rate of exacerbations (P=0.0025) and week 52 predose FEV <sub>1</sub> (treatment difference 0.061 L, P<0.0001) Glycopyrrolate–beclomethasone–formoterol had a similar efficacy to beclomethasone–formoterol + tiotropium in terms of risk of exacerbations (P=0.890) and was noninferior for improvement in predose FEV <sub>1</sub> at week 52 (treatment difference –0.003 L, P=0.85)

**Note:** \*GOLD B and D defined according to the 2013 GOLD guidelines (FAVOR), the 2010 GOLD guidelines (ILLUMINATE), or the 2009 GOLD guidelines (LANTERN).

**Abbreviations:** AUC, area under curve; BID, bis in die (twice daily); DPI, dry-powder inhaler; FDC, fixed-dose combination; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Pulmonary Disease; LSM, least squares mean; IC, inspiratory capacity; ICS–LABA, inhaled corticosteroid–long-acting β<sub>2</sub>-agonist; NS, not significant; pMDI, pressurized metered-dose inhaler; QD, quaque die (once daily); SGRQ, St George's Respiratory Questionnaire; TDI, Transition Dyspnea Index.

glycopyrrolate–indacaterol 50/110 µg QD was found to be noninferior to tiotropium 18 µg QD plus formoterol 12 µg BID in improving HRQoL.<sup>66</sup>

The 15.6/27.5 µg BID formulation of glycopyrrolate–indacaterol DPI has been shown to perform favorably in improving lung function when compared with its individual

components<sup>69,70</sup> and provide clinically meaningful improvements in breathlessness and HRQoL.<sup>69</sup> Two crossover studies of glycopyrrolate–indacaterol 15.6/27.5 µg BID vs umeclidinium–vilanterol 62.5/25 µg QD did not meet their primary efficacy end point of noninferiority of change from baseline in FEV<sub>1</sub> area under the curve from 0 to 24 hours at week 12.

The authors concluded that although glycopyrrolate–indacaterol was not non-inferior to umeclidinium–vilanterol, the differences in improvement in lung function between the combinations were not clinically relevant.<sup>71</sup> Several clinical trials have indicated that glycopyrrolate–indacaterol is effective at improving lung function in patients with moderate–severe COPD,<sup>68,69,71–73</sup> and patients with COPD and a high risk of exacerbations.<sup>67</sup> One of these trials also demonstrated that glycopyrrolate–indacaterol decreases hyperinflation and improves patients' ability to undertake daily physical activity.<sup>73</sup>

Glycopyrrolate also showed potential as a COPD treatment when added to the ICS–LABA combination fluticasone propionate–salmeterol.<sup>74</sup> After 12 weeks' treatment, glycopyrrolate 50 µg QD plus fluticasone propionate–salmeterol 500/50 µg BID significantly improved lung function when compared with placebo plus fluticasone propionate–salmeterol, and was noninferior to tiotropium (18 µg QD) plus fluticasone propionate–salmeterol.<sup>74</sup>

An inhaled triple FDC, glycopyrrolate–beclomethasone–formoterol (12.5/100/6 µg BID pMDI) was approved for use by the EMA in 2017 for the maintenance treatment of patients with COPD.<sup>39</sup> Two long-term trials have demonstrated that this triple FDC is efficacious in this patient group.<sup>75,76</sup> In the first trial, the triple FDC was significantly more effective at improving lung function vs beclomethasone–formoterol at week 26.<sup>75</sup> The triple FDC also decreased the risk of exacerbations from baseline to a greater extent than beclomethasone–formoterol by week 52.<sup>75</sup> The second trial provided evidence that this triple FDC was significantly superior to tiotropium in reducing the exacerbation rate and improving lung function from baseline.<sup>76</sup>

## Safety of inhaled glycopyrrolate monotherapy

Several trials have shown that glycopyrrolate 50 µg QD DPI is well tolerated,<sup>41–47</sup> with a similar overall incidence of AEs to tiotropium 18 µg QD.<sup>42,44,45,47</sup> In a study comparing glycopyrrolate 50 µg QD with open-label tiotropium 18 µg QD, the incidences of AEs and serious AEs were similar between groups; AEs with incidence >10% were worsening COPD (24% [glycopyrrolate] vs 33% [tiotropium]) and nasopharyngitis (31% vs 33%, respectively).<sup>44</sup> Glycopyrrolate also had an acceptable safety profile at 15.6 µg BID,<sup>48–50</sup> with AE incidence after 52 weeks' treatment similar to that seen after treatment with indacaterol 75 µg QD.<sup>50</sup> Furthermore, nebulized glycopyrrolate (50 µg BID) was also shown to have an acceptable safety profile over 48 weeks' treatment

compared with tiotropium 18 µg QD.<sup>51</sup> Treatment discontinuation due to treatment-emergent AEs was higher for nebulized glycopyrrolate than for tiotropium (10% vs 3%, respectively); the authors suggested several reasons for this, including the open-label nature of the trial.<sup>51</sup> In another study, nebulized glycopyrrolate was well tolerated at 25 and 50 µg BID, as measured by the incidences of AEs and cardiovascular (CV) events.<sup>38</sup> Finally, in two chronic-dosing trials of glycopyrrolate pMDI delivered using co-suspension delivery technology, glycopyrrolate had an acceptable safety profile at all doses evaluated, with no unexpected safety findings reported.<sup>52,57</sup>

Newly prescribed LAMAs and LABAs have been associated with a greater risk of CV events compared with nonuse in patients with COPD (adjusted OR 1.14 [95% CI 1.01–1.28,  $P=0.03$ ] and 1.31 [95% CI 1.12–1.52,  $P<0.001$ ] for LAMAs and LABAs, respectively).<sup>77</sup> However, the studies discussed in this review provide no evidence for an increased risk of CV events with glycopyrrolate monotherapy vs tiotropium or indacaterol monotherapy.<sup>45,50</sup> Furthermore, in one of the trials investigating nebulized glycopyrrolate, fewer patients treated with glycopyrrolate experienced major CV AEs than those treated with tiotropium (0.5% vs 1.7%).<sup>51</sup>

## Safety of inhaled glycopyrrolate combinations

The FDC glycopyrrolate–formoterol is designed to minimize the risk of AEs associated with high doses of LAMA or LABA monotherapies. In its Phase III clinical development program, glycopyrrolate–formoterol pMDI 18/9.6 µg BID showed a safety profile consistent with that of the individual components (PINNACLE-1 and -2), placebo (PINNACLE-1 and -2, PT003011, and PT003012), and open-label tiotropium 18 µg QD (PINNACLE-1 and PT003011).<sup>60–62</sup>

Furthermore, several clinical trials have indicated that the glycopyrrolate–indacaterol DPI combination at both EMA- and FDA-approved doses (50/110 µg QD and 15.6/27.5 µg QD, respectively) has good tolerability and an acceptable safety profile in patients with moderate–severe COPD.<sup>65,67–69,71–73</sup> A trial by Ferguson et al showed that the risk of CV events was similar with the glycopyrrolate–indacaterol FDC to with indacaterol alone.<sup>70</sup>

Safety end points have also been assessed in triple FDC therapy regimens that incorporate glycopyrrolate. For example, in a study comparing glycopyrrolate plus fluticasone propionate–salmeterol with the ICS–LABA combination administered with either tiotropium 18 µg QD or placebo, the authors reported no significant differences

between the number of AEs or severe AEs in any of the treatment groups evaluated.<sup>74</sup> In a study comparing the glycopyrrolate–beclomethasone–formoterol FDC with both tiotropium and beclomethasone–formoterol plus tiotropium, AE incidence was similar among treatment groups.<sup>76</sup> A further study comparing glycopyrrolate–beclomethasone–formoterol with beclomethasone–formoterol also reported similar rates of AEs between treatment groups, although one serious treatment-emergent AE (atrial fibrillation) occurred in a patient from the triple-FDC group.<sup>75</sup>

## Conclusion

Inhaled glycopyrrolate is a fast-acting, efficacious treatment option for patients with moderate–severe COPD and is available in a variety of doses. It improves lung function, reduces the risk of exacerbations, and alleviates the symptoms of breathlessness, which in turn may explain the improvement seen in patients' QoL. Glycopyrrolate has comparable effects on lung function to tiotropium, and glycopyrrolate and aclidinium showed more rapid onset of action than tiotropium. Formulations containing inhaled glycopyrrolate are well tolerated and, despite being an anticholinergic, few CV-related events have been reported, with glycopyrrolate showing a similar safety profile to tiotropium. Inhaled glycopyrrolate is thus of value both as monotherapy and for optimizing bronchodilation when used in FDCs with LABAs and ICS–LABAs for maintenance treatment of COPD.

## Acknowledgments

We thank Johan Karlberg, MD, PhD, of the Clinical Trial Magnifier Newsletter for some of the information in this manuscript. Medical writing support was provided by Carly Hayes, PhD, of Core (London, UK) and editorial support was provided by Maryam Vahdat, PGDip of Core (London, UK), which was in accordance with Good Publication Practice (GPP3) guidelines and funded by AstraZeneca LP (Wilmington, DE, USA). AstraZeneca LP reviewed the manuscript for medical accuracy prior to submission.

## Author contributions

DPT and NJG made substantial contributions to the conception of this article, drafted, and critically revised it for important intellectual content; provided final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of the work are appropriately investigated and resolved.

## Disclosure

DPT serves on advisory boards for AstraZeneca, Sunovion, Mylan, and Theravance/Innoviva, and as a speaker for AstraZeneca, Boehringer-Ingelheim, and Sunovion. NJG has no conflicts of interest.

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