



Efficacy of Nebulized Glycopyrrolate on Lung Hyperinflation in Patients with COPD

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ABSTRACT

Introduction: Lung hyperinflation in chronic obstructive pulmonary disease (COPD) is associated with activity limitation, impaired cardiac output, and mortality. Several studies have demonstrated that long-acting muscarinic antagonists (LAMAs) delivered by dry powder inhalers can promote lung deflation; however, the potential of nebulized LAMAs on improving hyperinflation in COPD is currently unknown.

Methods: This single-center, randomized, double-blind, two-way crossover study (NCT04155047) evaluated the efficacy of a single dose of nebulized LAMA [glycopyrrolate (GLY) 25 µg] versus placebo in patients with COPD and lung hyperinflation. Patients with moderate-to-severe COPD and a residual volume (RV) \geq 130% of predicted normal were included. The primary endpoint was changed from baseline in RV at 6 h post-treatment. Other endpoints included changes from

baseline in spirometric and plethysmographic measures up to 6 h post-treatment.

Results: A total of 22 patients (mean pre-bronchodilator RV, 153.7% of predicted normal) were included. The primary objective of the study was not met; the placebo-adjusted least squares (LS) mean [95% confidence interval (CI) change from baseline in RV with GLY at 6 h post-treatment was -0.323 l (-0.711 to 0.066); $p = 0.0987$]. A post hoc evaluation of the primary analysis was conducted after excluding a single statistical outlier; substantial improvements in RV with GLY compared with placebo was observed after exclusion of this outlier [placebo-adjusted LS mean change from baseline (95% CI) in RV was -0.446 l (-0.741 to -0.150)]. Improvements from baseline were also observed with GLY compared with placebo in spirometric and plethysmographic measures up to 6 h post-treatment. GLY was generally safe, and no new safety signals were detected.

Conclusions: This is the first study to evaluate the effect of nebulized GLY on lung deflation. Nebulized GLY resulted in marked improvements in RV up to 6 h post-treatment, compared with placebo. Improvements were also observed with GLY in spirometric and plethysmographic parameters of lung function.

Trial Registration: ClinicalTrials.gov identifier, NCT04155047.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s41030-021-00166-5>.

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Infographic:

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INTRODUCTION

- Patients with COPD exhibit air trapping in the lungs, which leads to hyperinflation, even in early stages of the disease¹
- Lung hyperinflation is associated with increased mortality in COPD and can affect cardiac functions²
- LAMAs delivered via DPIs have been shown to reduce lung hyperinflation in COPD; however, the impact of nebulized LAMAs on hyperinflation is currently unknown

OBJECTIVE

Evaluate the efficacy of a single dose of nebulized GLY (25 µg) versus placebo in reducing lung hyperinflation in patients with moderate-to-severe COPD (NCT04155047)

PATIENTS AND STUDY DESIGN

Key inclusion criteria:

- Age ≥40 years, current or ex-smokers with ≥10 pack-year history, and a diagnosis of moderate-to-severe COPD per GOLD guidelines³
- FEV₁/FVC ratio of <0.70; mMRC score ≥2
- Screening pre-bronchodilator RV ≥130% of predicted normal

Key exclusion criteria:

- Recent history of COPD exacerbation requiring hospitalization 12 weeks prior to screening

Single center, randomized, double-blind, placebo-controlled, single-dose, two-way crossover study

Primary endpoint:

- Change from baseline in RV following a single dose of GLY 25 µg or placebo at 6 hours post-treatment

Key secondary endpoints:

- Change from baseline in spirometric and plethysmographic measures at 6 hours post-treatment

Safety assessments:

- AEs, SAEs, AEs leading to discontinuation

RESULTS

A total of 22 patients (mean age of 65.9 years) were enrolled in this study

82% At baseline, ~82% had an mMRC score ≥3

154% Mean pre-bronchodilator RV was 154% of predicted normal

Improvements in hyperinflation were observed with GLY up to 6 hours post-treatment

Time (hours post-treatment)	Placebo-adjusted LS mean difference in RV (L)
Baseline	0.000
1	-0.216
2	-0.297
3	-0.378
6	-0.323

Improvements in lung function/volume measures were observed with GLY at 6 hours post-treatment

Measure	Placebo-adjusted change from baseline (L)
FEV ₁	0.150*
FVC	0.223*
IC	0.203*

Measure	Placebo-adjusted change from baseline
sRaw	-5.841*
Raw	-0.847*

KEY TAKEAWAYS

- A single dose of nebulized GLY 25 µg was associated with improvements in lung hyperinflation up to 6 hours post-treatment
- Increases in lung function/volume measures and decreases in airway resistance were noted up to 6 hours post-treatment, with no new safety signals
- This Phase IV study highlights the potential of nebulized GLY in reducing lung hyperinflation and improving lung function in patients with COPD

PEER-REVIEWED INFOGRAPHIC

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Key Summary Points

Why carry out this study?

Patients with chronic obstructive pulmonary disease (COPD) suffer from dyspnea (or shortness of breath); dyspnea is often due to an increase in the amount of gas in the lungs at the end of expiration (known as hyperinflation).

This phase IV study evaluated the efficacy of a single dose of nebulized glycopyrrolate (GLY 25 µg; a bronchodilator) versus placebo in reducing lung hyperinflation in patients with moderate-to-severe COPD.

What was learned from the study?

Nebulized GLY showed substantial improvements in hyperinflation as measured by residual volume after 6 h of treatment, compared with placebo. This was accompanied by increases in forced expiratory volume in 1 s (FEV₁) and inspiratory capacity, and reduced airway resistance (Raw and sRaw).

This study highlights the potential of nebulized GLY in reducing lung hyperinflation and improving lung function in patients with COPD.

DIGITAL FEATURES

This article is published with digital features, including an infographic, to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.14815074>.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by persistent respiratory symptoms and airflow limitation [1]. COPD is a result

of airway and/or alveolar abnormalities, which typically occur from exposure to noxious particles or gases, although genetic factors may also play a role [1]. The most common respiratory symptoms in COPD include dyspnea, cough, and/or sputum production [1]. Patients with COPD also exhibit air trapping in the lungs, which leads to an increase in residual volume (RV), even in early stages of the disease [2]; while there is no precise definition for air trapping, $RV \geq 20\%$ of the predicted normal levels is considered significant [3]. Further, as COPD worsens, airflow limitation increases, and lung hyperinflation occurs [2]. RV and functional residual capacity (FRC) progressively increase as COPD worsens [3]. Lung hyperinflation is associated with increased mortality in COPD, and can affect cardiovascular functions [4–7].

Long-acting β_2 -agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) are the mainstay for bronchodilator therapy. LAMAs are considered to be the cornerstones of monotherapy [1], and several studies have explored the effects of a LAMA (e.g., tiotropium, aclidinium bromide) delivered via dry-powder inhalers (DPIs) twice-daily (BID) on lung deflation [8, 9]. The ACTIVATE study assessed the effect of aclidinium bromide/formoterol 12 μg BID delivered via a DPI in 267 patients with moderate-to-severe COPD; following 4 weeks of treatment, improvements in lung hyperinflation and exercise tolerance were observed with aclidinium bromide/formoterol compared with placebo [9]. In addition, LAMA/DPIs have also been shown to improve hyperinflation in COPD when administered once-daily (QD) [10–16]. While LAMAs delivered via DPIs may improve hyperinflation in COPD, the impact of nebulized LAMAs on hyperinflation is currently unknown. Pulmonary drug delivery via nebulization has documented advantages over DPIs, as it allows for greater delivery of the drug to the lungs, and may be suitable for patients with COPD who have difficulty using DPIs because of coordination difficulties and low inspiratory flow rates (e.g., elderly patients) [17].

Glycopyrrolate inhalation solution (GLY; Lonhala[®], Sunovion Pharmaceuticals Inc., Marlborough, MA, USA) 25 μg BID delivered by the eFlow[®] Closed System nebulizer (Magnair[®],

PARI Pharma GmbH, Starnberg, Germany) [18] was the first nebulized LAMA to be approved by the US Food and Drug Administration for the long-term maintenance treatment of airflow obstruction in patients with moderate-to-very-severe COPD in December 2017 [19]. This approval was based on the efficacy and safety demonstrated by the 12-week, replicate, placebo-controlled Glycopyrrolate for Obstructive Lung Disease Via Electronic Nebulizer (GOLDEN) 3 and GOLDEN 4 (NCT02347761 and NCT02347774, respectively), and the 48-week GOLDEN 5 (NCT02276222) phase III randomized clinical trials [20, 21]. Magnair[®] generates GLY aerosols in the respirable range (1–5 μm) in vitro, allowing efficient pulmonary deposition [18, 22–24]. The objective of the current study was to characterize the effects of a single dose of nebulized LAMA (GLY 25 μg) on hyperinflation in patients with moderate-to-severe COPD.

METHODS

Study Design

This was a single-center (United States), randomized, double-blind, placebo-controlled, single-dose, two-way crossover, phase IV study (NCT04155047) conducted between November 7, 2019, and March 31, 2020. The study consisted of a screening period, a randomized two-way cross-over treatment period, and a follow-up 7 (± 2) days after the last dose (Fig. 1). Patients were randomized to the crossover treatment sequences (AB or BA) in a 1:1 ratio, to receive two single doses of GLY 25 μg and placebo, separated by a 7-day washout period. In sequence AB, patients received GLY 25 μg in treatment period 1 and placebo in treatment period 2; in sequence BA, patients received placebo in treatment period 1, followed by GLY 25 μg in treatment period 2.

During treatment period 1 (day 1), a single dose of GLY 25 μg /placebo was prepared by the clinical staff and self-administered by the patients in the morning according to the randomization schedule. To maintain blinding, clinical staff who were unblinded to the

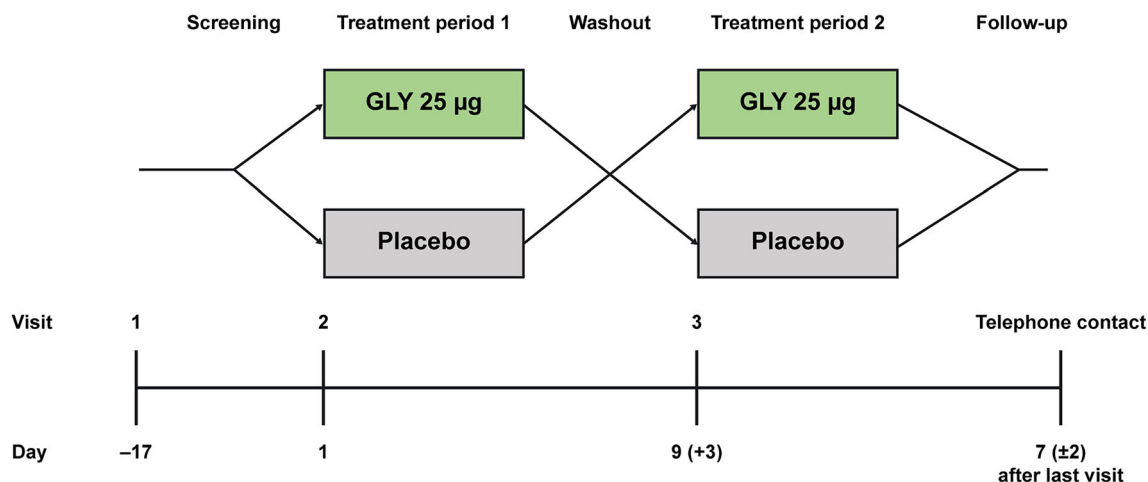


Fig. 1 SUN101-402 double-blind, two-way crossover study design. *GLY* glycopyrrolate

treatment performed the randomization and assisted with study drug administration but did not perform any other study procedures. Each patient was assigned a nebulizer, which was operated and sanitized according to the manufacturer's instructions by the site clinical staff. Patients returned to the clinical site on day 9 (+ 3) for treatment period 2, and a single dose of GLY 25 µg/placebo was prepared by the clinical staff and self-administered by the patients in the morning (within 1 h of treatment period 1 dosing time) according to the assigned treatment sequence.

Spirometry measurements were conducted at screening during both treatment periods (day 1 and day 9; 45 min pre-treatment and 6 h post-treatment) in accordance with the American Thoracic Society/European Respiratory Society (ATS/ERS) 2005 guidelines [25]. Plethysmography measurements were performed at screening during both treatment periods (day 1 and day 9; 45 min pre-treatment and 1, 2, 3, 4, and 6 h post-treatment), and were conducted in accordance with the current ATS/ERS 2005 guidelines [26]. Plethysmography was performed prior to spirometry when time-points coincided.

The study (SUN101-402: project approval number 39173) protocol was approved by Quorum Review institutional review board prior to enrollment, and was conducted in accordance with the protocols of the International Conference on Harmonization Good Clinical

Practice guidelines, and Declaration of Helsinki. All patients provided written informed consent before participating in this study.

Participants

Male or female patients, ≥ 40 years, current or ex-smokers with a ≥ 10 pack-year history, and a clinical diagnosis of COPD were eligible to participate in the study. Additional inclusion criteria at screening were a pre-bronchodilator RV of $\geq 130\%$ of predicted normal, moderate-to-severe COPD according to GOLD guidelines [post-bronchodilator (following inhalation of ipratropium bromide 68 µg) forced expiratory volume in 1 s (FEV_1) between $\geq 30\%$ and $< 80\%$ of predicted normal] [1], FEV_1 /forced vital capacity (FVC) ratio of < 0.70 , and a modified Medical Research Council Dyspnea Scale (mMRC) score of ≥ 2 . Key exclusion criteria included a recent history of COPD exacerbation requiring hospitalization 12 weeks prior to screening and inability to have plethysmography lung volume testing. Rescue medication (albuterol) was provided by the site during the study.

Endpoints

The primary endpoint was change from baseline in RV following a single dose of GLY 25 µg or

placebo at 6-h post-treatment. Other endpoints included change from baseline in spirometric (FEV₁ and FVC), and plethysmography measures up to 6 h post-treatment. Plethysmography measurements included inspiratory capacity (IC), expiratory reserve volume (ERV), functional residual capacity (FRC), total lung capacity (TLC), airway resistance (Raw; cmH₂O/l/s), and specific airway resistance (sRaw; cmH₂O/l/s/l); additional measures included standardized area under the curve (AUC) at 3, 4, and 6 h post-treatment for the aforementioned parameters. Pearson's correlations between plethysmography endpoints with FEV₁ and FVC by treatment group were estimated at 6-h post-treatment. Safety assessments included the monitoring of adverse events (AEs), serious adverse events (SAEs), vital signs, and electrocardiogram (ECG). AEs were coded using MedDRA v22.1, and summarized by treatment, system organ class, and preferred term.

Exploratory endpoints included evaluation of the feasibility of using a biosensor, VitalPatch[®], in combination with the accelerateIQ[®] platform. The results from the exploratory assessment will be discussed in a separate publication.

Statistical Analysis

Baseline was defined as the pre-dose measurement collected 45 min prior to dosing in each treatment period. The efficacy population consisted of patients who received ≥ 1 dose of study drug and had a baseline and ≥ 1 post-baseline RV measurement within the same period. The safety population consisted of all patients who received ≥ 1 dose of study drug. Patients were analyzed according to randomized treatment group. All *p* values and 95% confidence intervals were two-sided; no multiplicity adjustments were made for treatment comparisons. All statistical procedures were performed using SAS[®] version 9.4 (SAS Institute Inc., Cary, NC, USA).

The sample size for this study was determined by a two-sample *t* test (cross-over ANOVA) using nQuery version 4.0 (nQuery + nTerim version 4.0, Statistical Solutions, Cork,

Ireland). A sample size of ten evaluable patients per treatment sequence (20 patients in total), was required to achieve 88% power to detect a mean difference in the change from baseline in RV of -0.3 l (single dose of GLY compared with placebo), assuming a standard deviation (SD) of the differences of 0.4 l, with a one-sided significance level of 0.025.

For the analysis of the primary endpoint, data were analyzed using a two-way crossover analysis of covariance (ANCOVA) using the efficacy population. The ANCOVA model included terms for treatment, period and sequence as fixed effects, period baseline as a covariate, and patients nested within sequence as a random effect. The Kenward and Roger correction for the degrees of freedom was used. Least squares (LS) mean difference in the change from baseline in RV at 6-h post-treatment was calculated from the primary ANCOVA model. LS mean [and 95% confidence interval (CI)] for each treatment group, and LS mean difference (and 95% CI), and the associated *p* value for the difference between the single dose of GLY and placebo were estimated.

Changes from baseline in RV, ERV, IC, FRC, TLC, sRaw, Raw, FEV₁, and FVC up to 6-h post-treatment were analyzed similarly. Potential outliers among the 22 patients were evaluated using Tukey's 3 interquartile range (IQR) method after visual inspection of the unblinded data [27]. The primary analysis was then repeated post hoc after excluding any outliers.

RESULTS

Patient Demographics and Baseline Characteristics

A total of 44 patients were screened, of which 22 (50.0%) were enrolled in the study (Fig. 2). Patient demographics and baseline characteristics are summarized in Table 1. Patients were all white, 54.5% female, with a mean age of 65.9 years. At baseline, 18/22 (81.8%) patients had an mMRC score ≥ 3 ; mean pre- and post-bronchodilator RV %predicted were 153.7 and 123.8%, respectively. Two patients terminated the study early, after completing the GLY

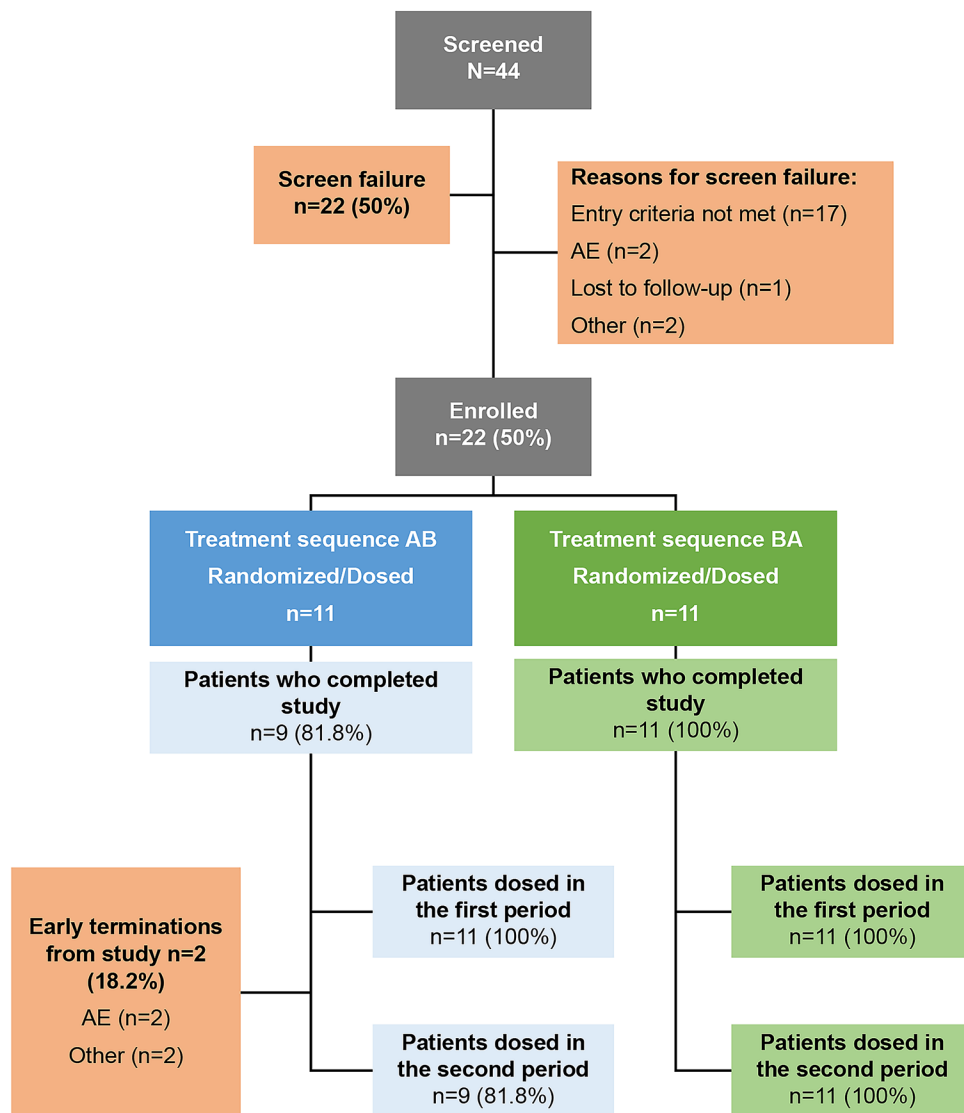


Fig. 2 Patient disposition in the SUN101-402 phase IV study. Treatment sequence AB involved administration of GLY 25 µg in treatment period 1, and placebo in treatment period 2. Treatment sequence BA involved administration of placebo in treatment period 1, and GLY

25 µg in treatment period 2. *AE* adverse event, *GLY* glycopyrrolate

treatment period, but before the placebo treatment period, one due to AE and one due to other reasons (COVID-19). As such, the placebo period data is missing for these two subjects.

Efficacy

Nebulized GLY was associated with improvements from baseline in RV at all time-points

analyzed in this study (Fig. 3a). Improvements in RV were observed with GLY relative to placebo at each hourly time-point post-treatment; however, statistical significance was not reached at the primary endpoint (6-h post-treatment). The placebo-adjusted LS mean (95% CI) change from baseline in RV at 6-h post-treatment was -0.323 l (-0.711 to 0.066 ; $p = 0.0987$; Fig. 3a). These results demonstrate

Table 1 Baseline demographics and clinical characteristics

Parameter, mean (SD)	Patients (<i>N</i> = 22)
Age, years	65.9 (7.9)
Female, <i>n</i> (%)	12 (54.5)
BMI, kg/m ²	32.4 (6.9)
Race, white, <i>n</i> (%)	22 (100.0)
Current smoker, <i>n</i> (%)	11 (50.0)
Number of pack-years	52.9 (24.0)
Pre-BD FEV ₁ %predicted	51.9 (12.2)
Post-BD FEV ₁ %predicted	59.7 (13.2)
Pre-BD FEV ₁ /FVC, %	51.1 (8.9)
Post-BD FEV ₁ /FVC, %	52.7 (9.2)
Pre-BD RV %predicted	153.7 (20.4)
Post-BD RV %predicted	123.8 (23.9)
COPD exacerbations within 12 months prior to screening	0.2 (0.5)
mMRC, <i>n</i> (%)	
2	4 (18.2)
3	15 (68.2)
4	3 (13.6)
SGRQ total scores	43.8 (13.9)
Symptoms	58.9 (22.2)
Activity	59.6 (18.8)
Impacts	30.1 (14.0)

BD bronchodilator, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *FEV₁* forced expiratory volume in one second, *FVC* forced vital capacity, *mMRC* modified Medical Research Council dyspnea scale, *RV* residual volume, *SGRQ* St George's Respiratory Questionnaire

clinically significant improvements in RV with nebulized GLY up to 6 h. The trend over time demonstrated meaningful improvements.

An evaluation of change from baseline in RV at 6-h post-treatment in individual patients (Fig. 3c, d) identified a statistical outlier value

from one patient (65-year-old female) treated with GLY during treatment period 2. The outlier value of 2.41 l was identified based on Tukey's 3 IQR method. When the primary analysis was repeated post hoc after excluding this outlier, placebo-adjusted LS mean (95% CI) change from baseline in RV was -0.446 l (-0.741 to -0.150 ; Fig. 3b).

Other Efficacy Endpoints

At 6-h post-treatment, improvements with GLY compared with placebo were observed in both spirometric (FEV₁ and FVC; Fig. 4a) and plethysmographic (IC, sRaw, and Raw) parameters (Fig. 4b–d). Change from baseline in plethysmography endpoints were also assessed at 1, 2, 3, and 4 h post-treatment; RV and IC were the only endpoints to achieve notable improvements at all time-points tested (Tables S1, S2). For RV, IC, FRC, and sRaw, improvements from baseline with GLY compared with placebo were also observed in AUC from time zero to 3, 4, and 6 h post-treatment (Tables 2, 3).

Pearson's correlations (*r*) between changes in spirometric measures (FEV₁ or FVC) with those in plethysmographic measures at 6-h post-treatment were estimated. Moderate correlations (95% CI) between changes from baseline in FEV₁ in the GLY treatment arm were observed with several plethysmographic measures, including RV [$r = -0.535$ (-0.78 to -0.15)], and IC [$r = 0.726$ (0.44 – 0.88)]; similar correlations were also observed with FVC (Table S3).

Safety

GLY was generally well tolerated, with a low incidence of AEs and AEs leading to study discontinuation (Table 4). One AE of COPD worsening (moderate intensity and unrelated to the study medication) was reported in a patient treated with a single dose of GLY, which led to study discontinuation. There was 1 SAE (COPD worsening) reported during the screening period, and the patient withdrew from the study before drug administration. There were no

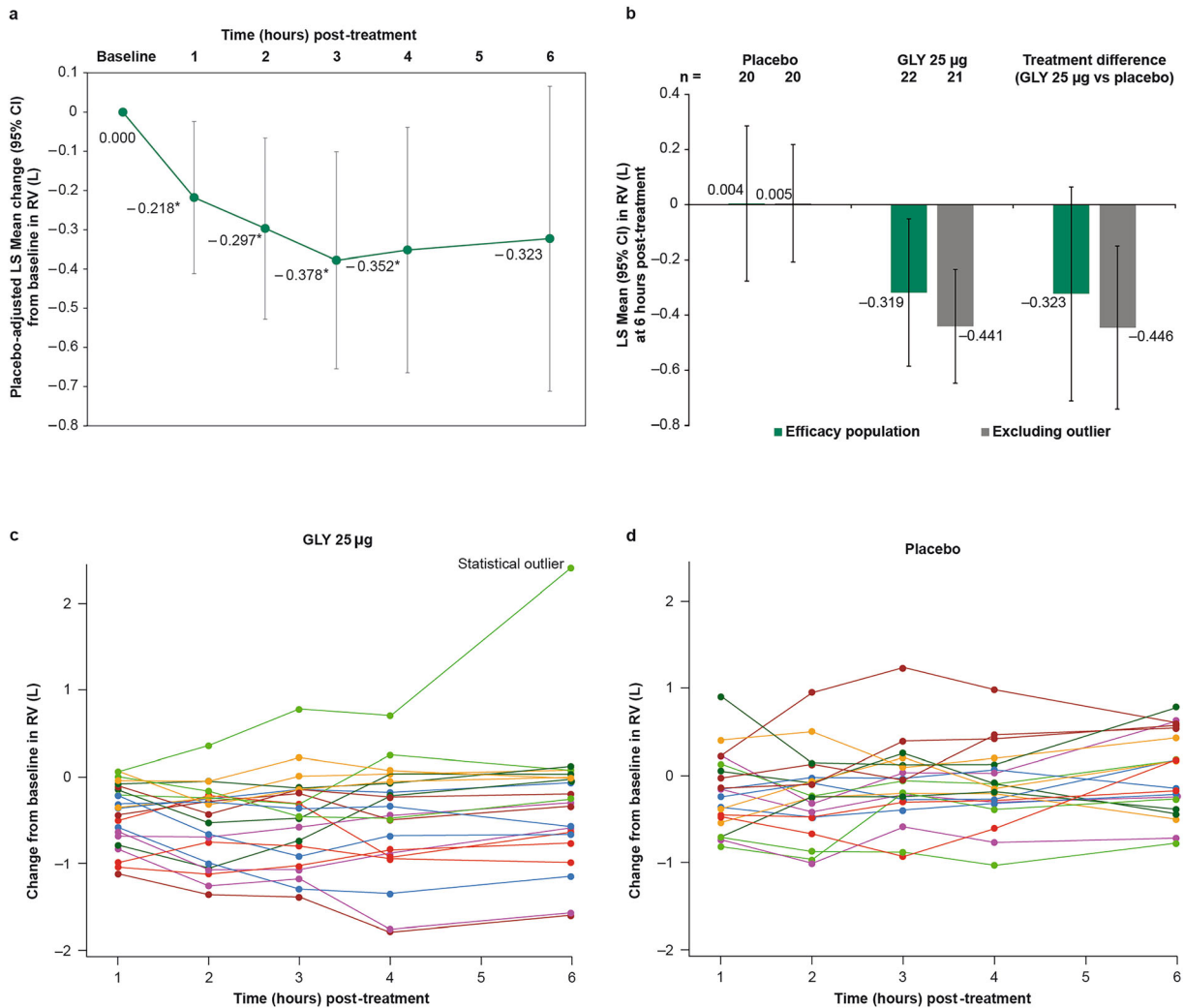


Fig. 3 Change from baseline in residual volume **a** with treatment time in the efficacy population, **b** at the primary endpoint in either the efficacy population or after exclusion of the outlier, and for individual patients treated with **c** GLY or **d** placebo. * $p < 0.05$; ** $p < 0.01$ vs.

placebo. *CI* confidence interval, *GLY* nebulized glycopyrrolate, *LS* least squares, *RV* residual volume

deaths or SAEs reported during the randomized treatment period.

DISCUSSION

This is the first study to evaluate the effect of a single dose of nebulized LAMA (GLY 25 µg) on hyperinflation in patients with COPD. The primary endpoint of this study, RV improvement at 6 h post-GLY nebulization, was not met; however, at all time-points assessed in this

study, a single dose of GLY showed marked improvements in RV compared with placebo. The placebo-adjusted LS mean change from baseline in RV with GLY were -0.218 , -0.297 , -0.378 , and -0.352 l, at 1, 2, 3, and 4 h post-treatment, respectively ($p < 0.05$ at all time-points). At 6-h post-treatment (primary endpoint), the placebo-adjusted LS mean change from baseline was -0.323 l; however, it did not reach statistical significance at the 5% level. After excluding a single statistical outlier value

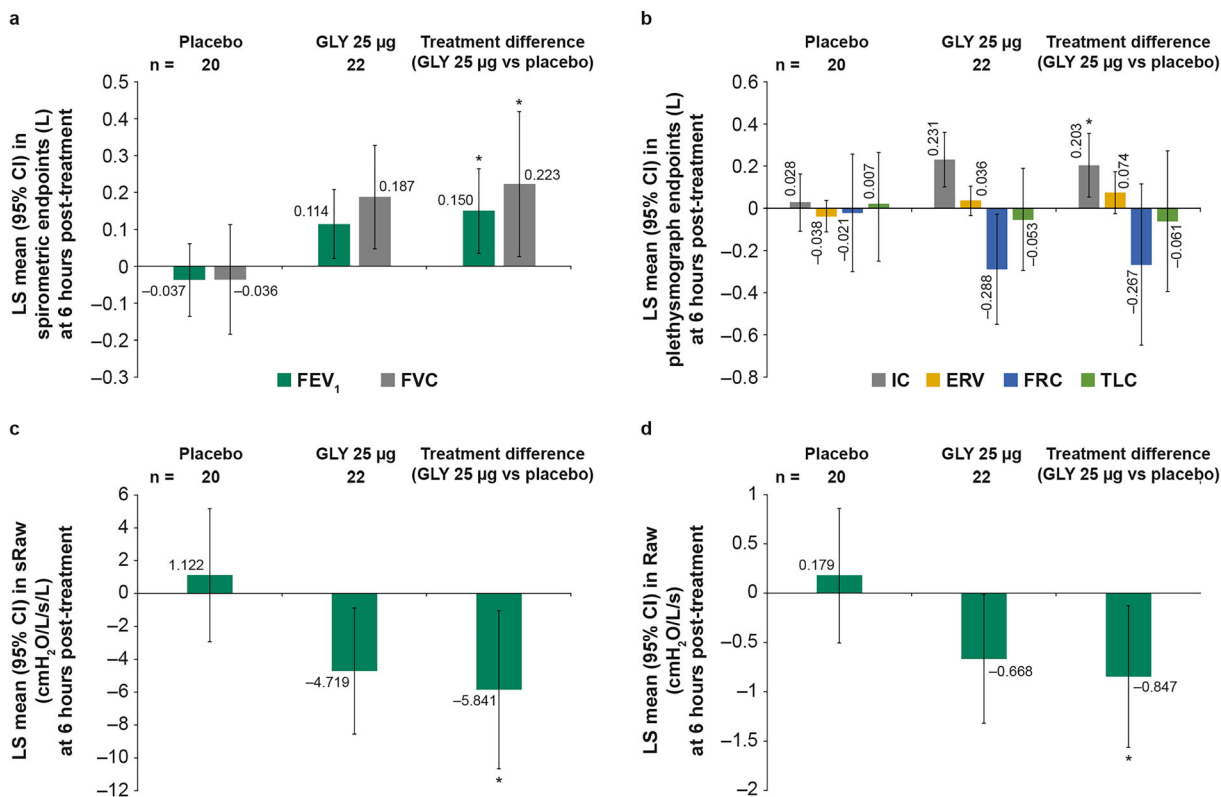


Fig. 4 Change from baseline in spirometric (a), plethysmographic (b) endpoints, specific airway resistance (c), and airways resistance (d) at 6-h post-treatment, in the efficacy population. **p* < 0.05 vs. placebo. *CI* confidence interval, *ERV* expiratory reserve volume, *FEV₁* forced expiratory volume in 1 s, *FRC* functional residual capacity, *FVC*

forced vital capacity, *GLY* glycopyrrolate, *IC* inspiratory capacity, *l* liter(s), *LS* least squares, *Raw* airway resistance, *RV* residual volume, *sRaw* specific airway resistance, *TLC* total lung capacity

(change from baseline in *RV* of 2.41 l) based on Tukey’s 3 IQR method, a post hoc analysis of the primary endpoint showed greater improvements in *RV* (placebo-adjusted *LS* mean change from baseline of - 0.446 l). *AUC* analysis for *RV* performed at 0–3, 0–4, and 0–6 h post-treatment showed improvements in placebo-adjusted change from baseline with *GLY* 25 µg, which suggests a rapid reduction in hyperinflation after the first dose. Further, standardized changes from baseline in *AUC*_{0–3 h}, *AUC*_{0–4 h}, and *AUC*_{0–6 h} for *IC*, *FRC*, and *sRaw* demonstrated improvements at all three time-points (*p* < 0.05). These results suggest that *AUC* measures may be more valuable than single time-points, when assessing improvements after a single dose.

It is important to note that the reduction in *RV* was also accompanied by an increase in *IC*, and a reduction in airway resistance (*Raw* and *sRaw*), whereas the *TLC* remained generally unchanged following treatment. Spirometric measures (*FEV₁* and *FVC*) also showed improvements from baseline with *GLY* compared with placebo at 6-h post-treatment; these improvements correlated negatively (with changes in *RV*, *FRC*, *Raw*, *sRaw*), and positively (with changes in *IC*). Together, these results demonstrate that a single dose of nebulized *GLY* 25 µg may improve functional lung capacity as early as 6-h post-treatment in patients with *COPD* and hyperinflation.

Previous studies with *LAMAs* delivered via *DPIs* have demonstrated lung deflation in

Table 2 LS mean (SE) standardized change from baseline in AUC of plethysmography endpoints by treatment (efficacy population)

Parameter (L)	Time-points	Placebo N = 20 LS mean (SE)	GLY 25 µg N = 22 LS mean (SE)	Treatment difference from placebo		
				LS mean (SE)	95% CI	p value
RV	AUC _{0-3 h}	- 0.1625 (0.0709)	- 0.3987 (0.0675)	- 0.2362 (0.0765)	- 0.3984, - 0.0740	0.0071
	AUC _{0-4 h}	- 0.1508 (0.0779)	- 0.4189 (0.0739)	- 0.2681 (0.0893)	- 0.4566, - 0.0796	0.0081
	AUC _{0-6 h}	- 0.1220 (0.0892)	- 0.4132 (0.0843)	- 0.2911 (0.1097)	- 0.5215, - 0.0607	0.0161
IC	AUC _{0-3 h}	- 0.0031 (0.0453)	0.2123 (0.0431)	0.2155 (0.0521)	0.1064, 0.3245	0.0006
	AUC _{0-4 h}	- 0.0037 (0.0517)	0.2250 (0.0493)	0.2288 (0.0563)	0.1106, 0.3470	0.0007
	AUC _{0-6 h}	0.0013 (0.0560)	0.2292 (0.0536)	0.2279 (0.0585)	0.1050, 0.3508	0.0011
ERV	AUC _{0-3 h}	- 0.0111 (0.0238)	0.0337 (0.0226)	0.0448 (0.0330)	- 0.0218, 0.1113	0.1812
	AUC _{0-4 h}	- 0.0224 (0.0246)	0.0267 (0.0234)	0.0491 (0.0339)	- 0.0197, 0.1179	0.1565
	AUC _{0-6 h}	- 0.0303 (0.0262)	0.0269 (0.0247)	0.0572 (0.0358)	- 0.0179, 0.1322	0.1272
FRC	AUC _{0-3 h}	- 0.1461 (0.0692)	- 0.3920 (0.0656)	- 0.2459 (0.0781)	- 0.4106, - 0.0811	0.0059
	AUC _{0-4 h}	- 0.1446 (0.0758)	- 0.4174 (0.0717)	- 0.2728 (0.0892)	- 0.4605, - 0.0852	0.0069
	AUC _{0-6 h}	- 0.1241 (0.0863)	- 0.4071 (0.0815)	- 0.2830 (0.1084)	- 0.5101, - 0.0559	0.0173
TLC	AUC _{0-3 h}	- 0.1466 (0.0566)	- 0.1796 (0.0537)	- 0.0330 (0.0667)	- 0.1727, 0.1068	0.6265
	AUC _{0-4 h}	- 0.1449 (0.0619)	- 0.1920 (0.0586)	- 0.0472 (0.0747)	- 0.2038, 0.1095	0.5357
	AUC _{0-6 h}	- 0.1200 (0.0708)	- 0.1766 (0.0670)	- 0.0565 (0.0884)	- 0.2414, 0.1284	0.5303

AUC area under the curve, CI confidence interval, ERV expiratory reserve volume, FRC functional residual capacity, GLY glycopyrrolate, IC inspiratory capacity, l liter(s), LS least squares, RV residual volume, SE standard error, TLC total lung capacity

COPD. In a study of 20 patients with stable COPD and hyperinflation, DPI-mediated administration of tiotropium (a LAMA) or budesonide/formoterol (inhaled corticosteroid [ICS]/LABA) showed improvements in spirometry and hyperinflation in both treatment groups [28]. In a study of 37 patients with severe-to-very-severe COPD with hyperinflation (RV > 125% of predicted normal), two LAMAs—acclidinium bromide 400 µg or glycopyrronium 50 µg QD (both delivered via DPis) – reduced hyperinflation and dyspnea; reduction in RV with acclidinium bromide 400 µg occurred earlier (5–180 min post-treatment), compared with glycopyrronium 50 µg (60 and 180 min) [14]. The improvements in lung hyperinflation observed in the current study are comparable to those reported with single doses of LAMA delivered via DPis [14].

Recent studies with long-acting bronchodilators have demonstrated the positive impact of lung deflation on cardiac function in COPD patients with static hyperinflation [15, 29–32]. Treatment with indacaterol (a LABA; 150 µg) in 40 patients with stable COPD and RV ≥ 135% of predicted normal, showed reductions in hyperinflation in acute conditions, compared with placebo; further, this was associated with improvements in cardiac function [15]. The CLAIM study analyzed the effect of dual bronchodilation (LABA + LAMA combination: indacaterol 110 µg/glycopyrronium 50 µg) vs. placebo on cardiac function, in 62 patients with COPD and hyperinflation [29]. Following 14 days of treatment, indacaterol/glycopyrronium significantly improved cardiac function (left-ventricular end-diastolic volume) and FEV₁, and reduced hyperinflation, when compared with placebo [29]. While cardiac

Table 3 LS mean (SE) standardized change from baseline in AUC of plethysmography airway resistance by treatment (efficacy population)

Parameter	Time-points	Placebo N = 20 LS mean (SE)	GLY 25 µg N = 22 LS mean (SE)	Treatment difference from placebo		
				LS mean (SE)	95% CI	p value
sRaw	AUC _{0–3 h}	0.0537 (1.3522)	– 4.9773 (1.2759)	5.031 (1.7975)	– 8.8019, – 1.2601	0.0117
	AUC _{0–4 h}	0.1384 (1.4499)	– 5.0493 (1.3690)	– 5.1877 (1.8757)	– 9.1250, – 1.2503	0.0126
	AUC _{0–6 h}	0.3096 (1.5985)	– 4.9259 (1.5115)	– 5.2354 (1.9951)	– 9.4246, – 1.0463	0.0171
Raw	AUC _{0–3 h}	0.1261 (0.2636)	– 0.6077 (0.2501)	– 0.7338 (0.3638)	– 1.4708, 0.0033	0.0510
	AUC _{0–4 h}	0.1326 (0.2727)	– 0.6033 (0.2571)	– 0.7360 (0.3700)	– 1.5109, 0.0390	0.0614
	AUC _{0–6 h}	0.1369 (0.2879)	– 0.5955 (0.2719)	– 0.7324 (0.3671)	– 1.5016, 0.0368	0.0608

AUC area under the curve, CI confidence interval, GLY glycopyrrolate, LS least squares, Raw airway resistance (cmH₂O/l/s), SE standard error, sRaw specific airway resistance (cmH₂O/l/s/l)

Table 4 Summary of AEs, SAEs, and AEs leading to study discontinuation by treatment group (safety population)

	Placebo N = 20	GLY 25 µg N = 22
Any AE	0	1 (4.5)
Worsening of COPD	0	1 (4.5)
Any SAE	0	0
AE leading to study discontinuation	0	1 (4.5)

AE adverse event, COPD chronic obstructive pulmonary disease, SAE serious adverse event

functions were not assessed in this study, it is possible that the improvements in RV and other lung function parameters noted with nebulized GLY may be associated with improvements in cardiac function, similar to other trials.

A retrospective analysis conducted in 2265 patients with COPD showed that in patients with mild COPD (GOLD stage I), RV was ~ 135% of predicted normal, and sRaw was ~ 250% of predicted normal [3]. This is an important observation because it demonstrates that significant air trapping and hyperinflation can occur even with mild COPD. Patients with mild COPD are typically excluded from clinical

studies of COPD; however, for characterization of the impact of bronchodilators on hyperinflation, inclusion of GOLD I patients may be highly informative. This study also highlights the importance of serial lung volume measurements with body plethysmography in the diagnosis/treatment of hyperinflation in COPD. While plethysmography is not typically done in clinical practice, it can provide valuable insight for treating hyperinflation in patients with COPD. Many patients with COPD experience nocturnal symptoms [33]; though not the objective of this study, it would be interesting to evaluate if an additional evening dose of GLY has any benefits on static lung hyperinflation and nocturnal symptoms.

This study had a few limitations. The primary endpoint of this study (6-h post-treatment) may have been too early to detect maximal impacts on lung deflation. Further, a single-dose of GLY 25 µg was used in this study, and not the FDA-approved dose (25 µg BID). This study was conducted to understand the impact of a single dose of GLY 25 µg on lung hyperinflation. Assessments beyond 6 h of treatment, combined with the complete dose of GLY for longer periods of time, may provide insights into the long-term impact of nebulized GLY on lung hyperinflation in COPD. In addition, the relatively small sample size in this study may have limited the detection of safety signals and led to the undue influence of the

single statistical outlier value in the primary analysis. Regarding the statistical outlier, this patient did not have any known measurement or data entry errors nor did the patient have any characteristics that would result in their exclusion from the analysis. As such, we did not exclude this data point from the primary analysis; but we did perform an additional post hoc analysis excluding this data point to show its impact on the results. Despite not reaching statistical significance in the primary analysis ($p = 0.0987$), the placebo-adjusted improvement in RV of -0.323 l did exceed the 0.3 l minimal clinically important difference [34], underscoring that a clinically meaningful outcome for this patient population was observed.

CONCLUSIONS

This was the first randomized study to evaluate the impact of a single dose of a nebulized LAMA (GLY) on lung hyperinflation. A single dose of nebulized GLY $25 \mu\text{g}$ showed clinically important improvements in measures of lung hyperinflation up to 6-h post-treatment, compared with placebo. Further, notable improvements in both spirometric (FEV_1) and plethysmographic measures were observed up to 6-h post-treatment. This study highlights the potential of nebulized LAMAs in reducing lung hyperinflation in patients with COPD.

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Data availability. Sunovion Pharmaceuticals Inc. is part of a clinical trial data sharing consortium that facilitates access for qualified researchers to selected anonymized clinical trial data. For up-to-date information on data availability, please visit: <https://www.clinicalstudydatarequest.com/Study-Sponsors.aspx> and click on Sunovion.

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