

Efficacy and Safety of Nebulized Glycopyrrolate (EP-101) for Administration Using High Efficiency Nebulizer in Patients with COPD – Phase 2a Study

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Abstract

Introduction: EP-101 is a long-acting muscarinic antagonist formulation of glycopyrrolate optimized for nebulization in development for the treatment of COPD. This dose-ranging study assessed the efficacy and safety of single doses of nebulized EP-101 in patients with COPD.

Methods: This was a randomized, double-blind, placebo-controlled, 6-period cross-over study in 42 patients with moderate-to-severe COPD. Patients were randomized to receive single doses of EP-101 (12.5, 50, 100, 200 and 400 µg) and placebo via a high efficiency nebulizer, with a 5-12 days of washout between treatments. Plasma PK was assessed in a subset of patients.

Results: The study patients had a mean age of 62 years, COPD duration of 7.5 years, post-bronchodilator FEV₁ of 54% predicted normal, FEV₁/FVC of 44.9%, FEV₁ reversibility of 27.3%.

All treatments were well tolerated with similar AE rates between all treatments and no clinically relevant changes in vital signs (heart rate, systolic and diastolic blood pressure) and ECG parameters including QTc interval.

Following treatment with EP-101 at all doses there was a rapid bronchodilatory response at 5 minutes. Statistically significant improvements in mean change in trough FEV₁ at 24 hours were reported at doses ≥50 µg compared with placebo (37mL, 72mL, 104mL, 118mL and 95mL at doses 12.5, 50, 100, 200 and 400 µg, respectively).

Conclusion: Single doses of EP-101 ranging from 12.5 µg to 400 µg were well tolerated. EP-101 demonstrated rapid onset of bronchodilation with clinically meaningful improvements in lung function over 24 hours following nebulization in patients with COPD.

Introduction

➤ Regular treatment with a LAMA bronchodilator is more effective and convenient than treatment with short-acting bronchodilators in COPD^{1,2}.

➤ While MDIs and DPIs are the most widely prescribed medications for COPD patients, up to 75% of COPD patients do not receive an optimal dose from inhalers due to poor coordination, inability to inhale rapidly and forcefully, or inability to hold their breath after the dose³.

➤ Currently available bronchodilator medications for nebulization are shorter-acting requiring two to four treatments a day when administered via a general purpose jet nebulizer.

➤ In addition to frequent treatments required with currently available nebulized medications, patients are burdened with non-portable compressor nebulizer systems that can take up to 10-15 minutes to deliver each dose.

➤ Elevation Pharmaceuticals is developing a solution formulation of glycopyrrolate (EP-101) for delivery using a high efficiency nebulizer (investigational eFlow® nebulizer, PARI) for the long-term, once-daily, maintenance treatment of bronchoconstriction in patients with COPD who prefer nebulizer treatments or require nebulizer treatments due to their inability to achieve an optimal dose with an MDI or DPI.

➤ This Phase 2a study was a randomized, placebo-controlled, double-blind, dose ranging, single dose, 6-way crossover study in patients with moderate to severe COPD.

Objectives

➤ To establish the dose response characteristics of EP-101 as demonstrated by changes in FEV₁ (including trough FEV₁ at 24 hours and FEV₁ AUC).

➤ To assess the pharmacokinetics, safety and tolerability of EP-101.

Methods

Patients:

➤ 40-75 years of age.

➤ Moderate to severe COPD (GOLD guidelines).

➤ Post-bronchodilator FEV₁ 30-70% of predicted normal at the Screening Visit.

➤ Post-bronchodilator FEV₁/FVC ratio < 0.70 at the Screening Visit.

➤ Improvement in FEV₁ >12% and 150 mL following inhalation of ipratropium bromide at the Screening Visit.

➤ No recent history of hospitalization due to an exacerbation of airway disease within 3 months or need for increased treatments for COPD within 6 weeks prior to the Screening Visit.

Study Design and Assessments:

➤ Randomized, placebo-controlled, double-blind, single dose, 6-way crossover study at two centers.

➤ Subjects were randomly allocated to one of 6 treatment sequences to receive all 6 treatments with 5-12 days of washout period between each treatment.

➤ Serial spirometry (FEV₁) was measured at 30 minutes pre-dose, and 5, 15 and 30 minutes and 1, 2, 4, 6, 8, 10, 12, 14, 20, 23 hours 30 minutes, 24, 27, and 30 hours post-dose.

Statistical Analysis:

➤ Analysis was performed on Intent-to-Treat (ITT) population.

➤ An analysis of covariance (ANCOVA) with fixed effects for center, treatment, period, sequence, and a random effect for subject within sequence was used to calculate LS means using pre-dose FEV₁ as a covariate.

➤ For comparisons, point estimates, 95% confidence intervals and p-values for the difference between each EP-101 treatment vs. placebo were constructed using the residual mean square error obtained from the ANCOVA.

➤ Standardized FEV₁ AUCs were calculated using the linear trapezoidal rule using WinNonlin.

Results

Patient characteristics:

➤ Of the 42 enrolled subjects, 35 completed the study.

➤ 7 subjects discontinued prematurely from the study: 4 withdrawn due to AEs (3 COPD exacerbations, 1 hip/groin pain); 1 subject withdrew consent, and 2 subjects withdrawn due to protocol non-compliance.

➤ Patient demographics and baseline characteristics are summarized in Table 1.

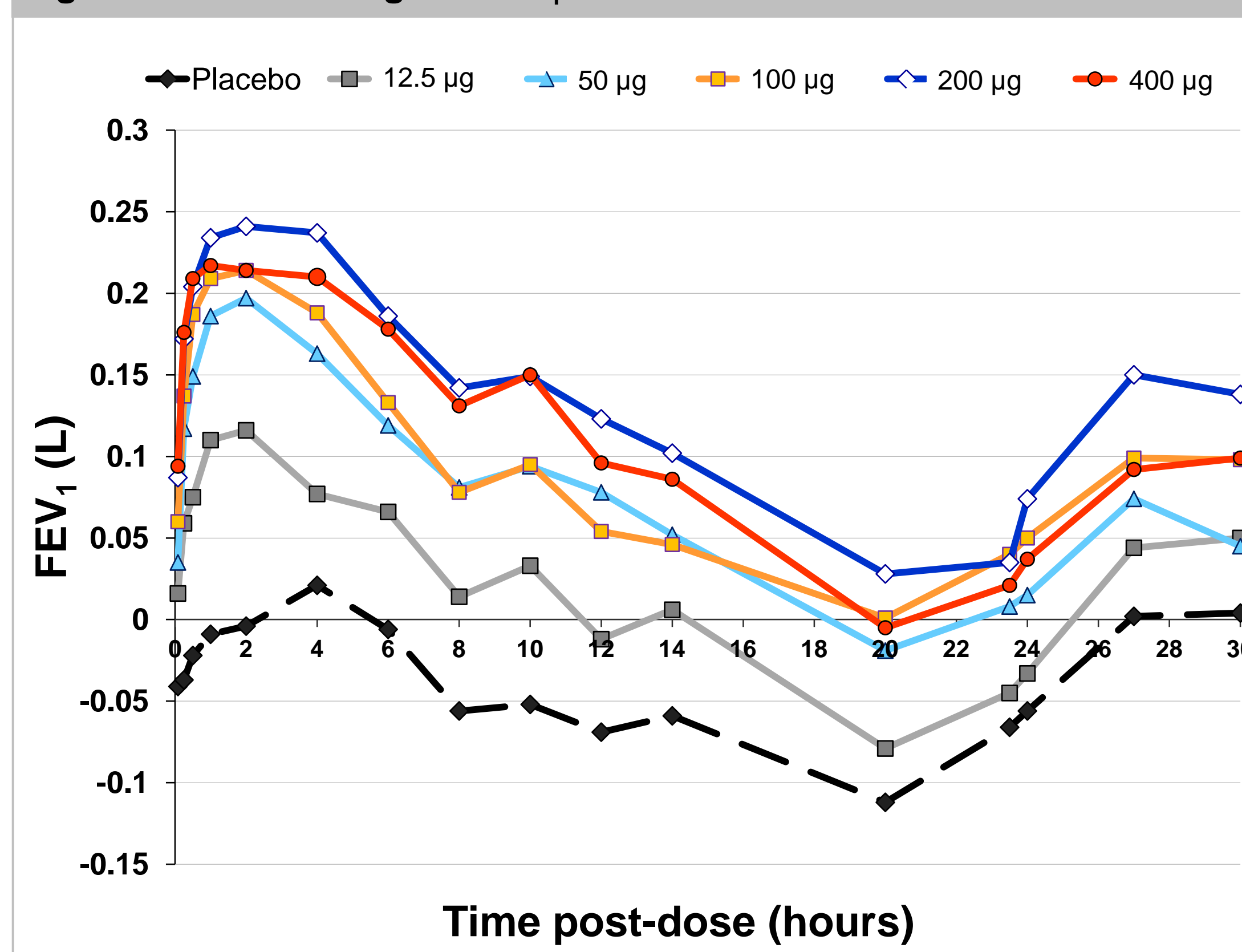
Table 1. Demographics and baseline data (mean±SD)

	Total (n=42)
Age (years)	62.0 (7.0)
Gender, n(%)	27 / 15 (64 / 36)
Male/Female	
Duration of COPD (years)	7.5 (6.1)
Tobacco pack-years (years)	42.9 (17.9)
Smoking History, n (%)	
Current smoker	24 (57)
Ex-smoker	18 (43)
ICS use, n (%)	
Current	29 (69)
None	13 (31)
FEV1 pre-bronchodilator (L)	1.21 (0.40)
FEV1 pre-bronchodilator (% predicted)	42.7 (11.5)
FEV1 post-bronchodilator (L)	1.52 (0.46)
FEV1 post-bronchodilator (% predicted)	54.0 (12.7)
FEV1/FVC post-bronchodilator (%)	44.9 (11.0)
FEV1 reversibility (mL)	306 (119)
FEV1 reversibility (%)	27.3 (11.8)

Efficacy:

➤ At all tested doses there was rapid onset of response (at 5 minutes, the first assessment) in FEV₁ and the response followed the normal circadian rhythm over the 24 hour period post-dose (Figure 1).

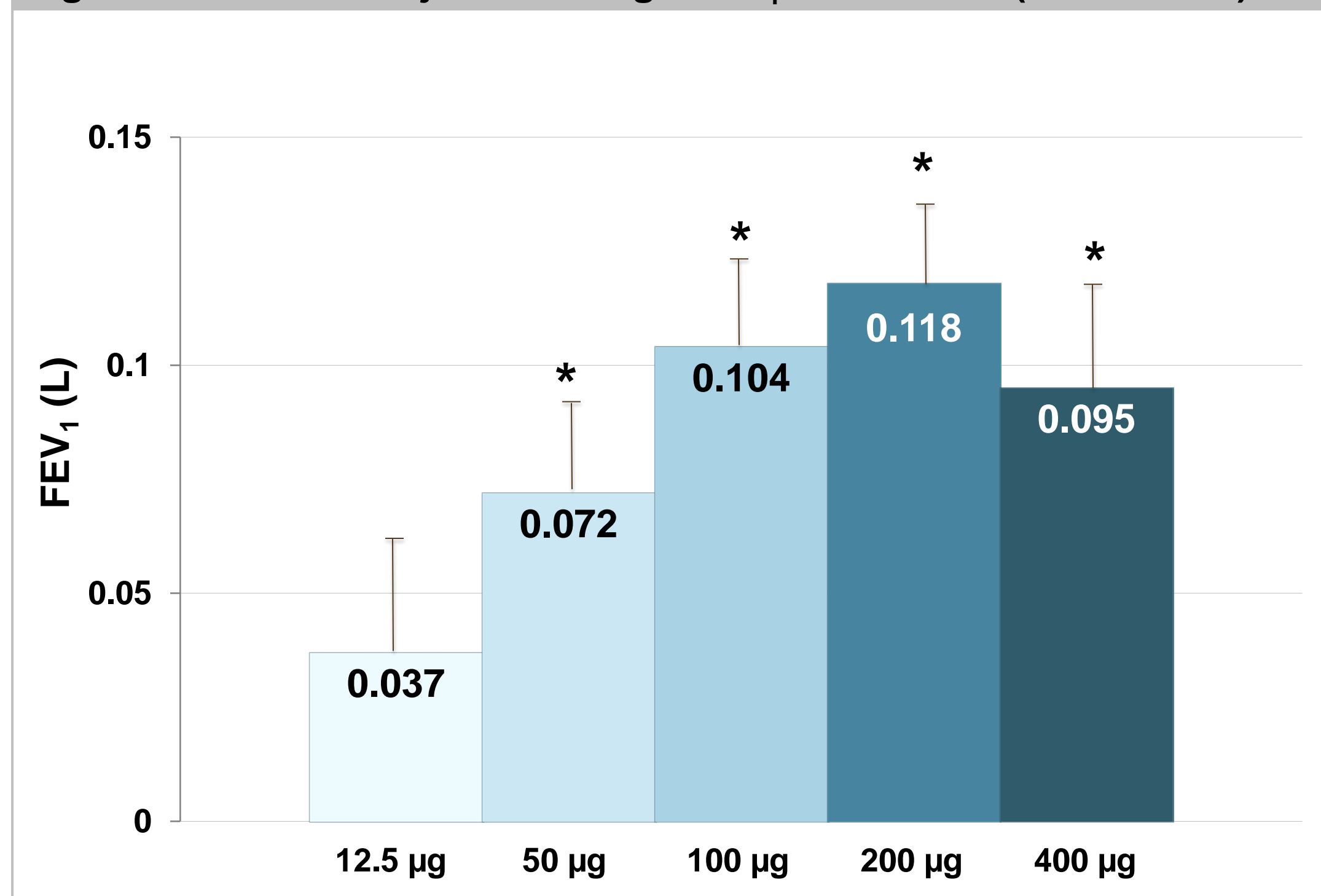
Figure 1. Mean change in FEV₁



➤ The improvement in mean change from baseline in 24-hour trough FEV₁ was statistically significant when compared with placebo (p<0.001) at doses ≥50 µg. A dose-response relationship in mean trough FEV₁ was observed at 24 hours for the 12.5 to 200 µg doses; no further improvement was observed at 400 µg dose (Figure 2).

➤ Both the 100 and 200 µg doses of EP-101 showed clinically significant improvements (i.e., >100 mL) in placebo-adjusted trough FEV₁ at 24 hours.

Figure 2. Placebo-adjusted Trough FEV₁ at 24 hours (mean±SEM)



➤ All EP-101 dose levels showed statistically significant (p<0.005) improvements in the first (FEV₁ AUC_{0-12h}) and second (FEV₁ AUC_{12-24h}) half of the FEV₁-time profile compared to placebo.

➤ The improvements in FEV₁ in the first 12 hours were sustained at clinically meaningful levels in the second 12 hours for EP-101 doses ≥ 50 µg (Figure 3).

➤ A dose related increase in percent change in peak FEV₁ (0-4 hours) was observed up to 200 µg, with no further increases at 400 µg (Figure 4).

Figure 3. Mean placebo-adjusted standardized FEV₁ AUC (mean±SEM)

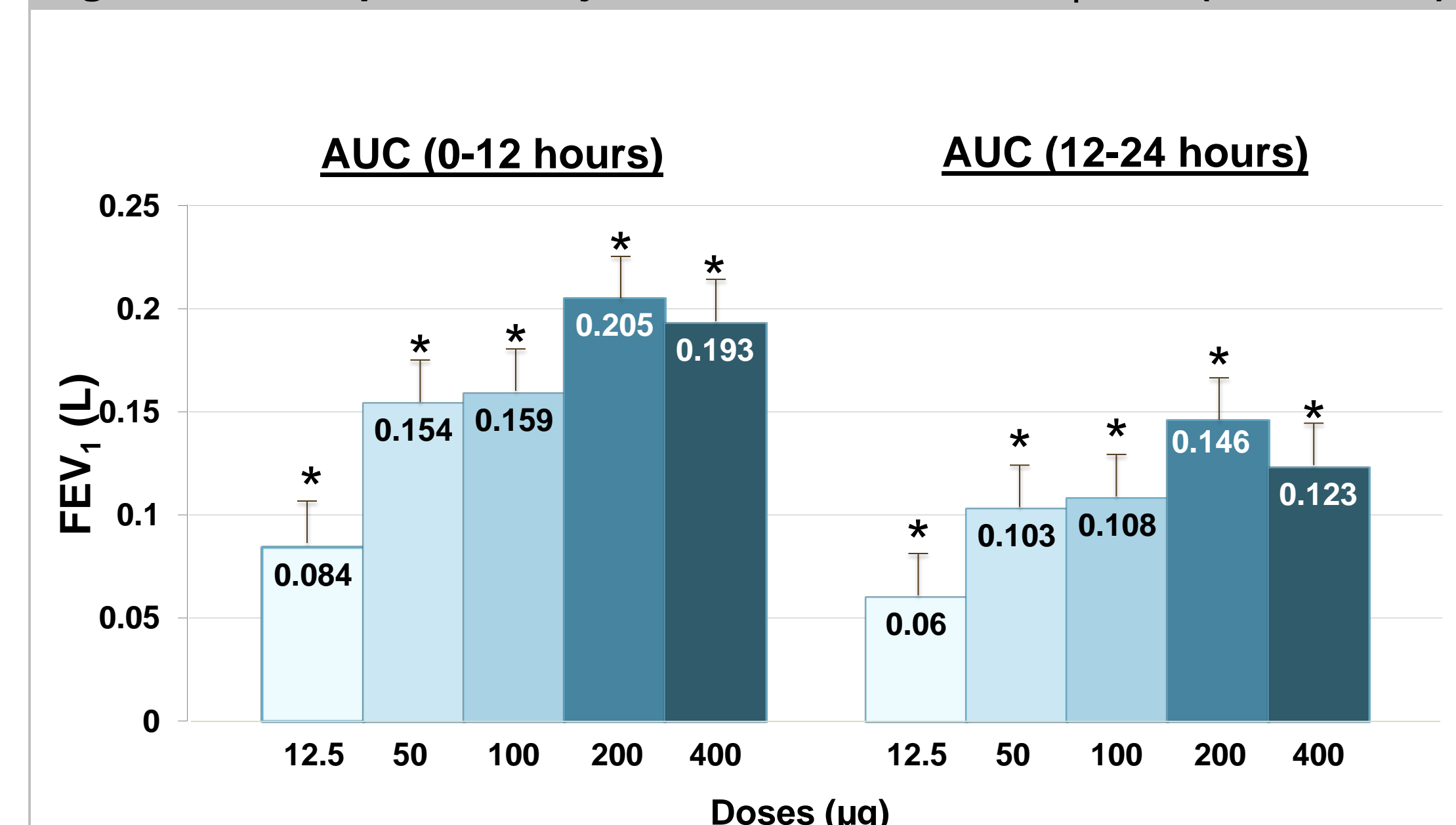
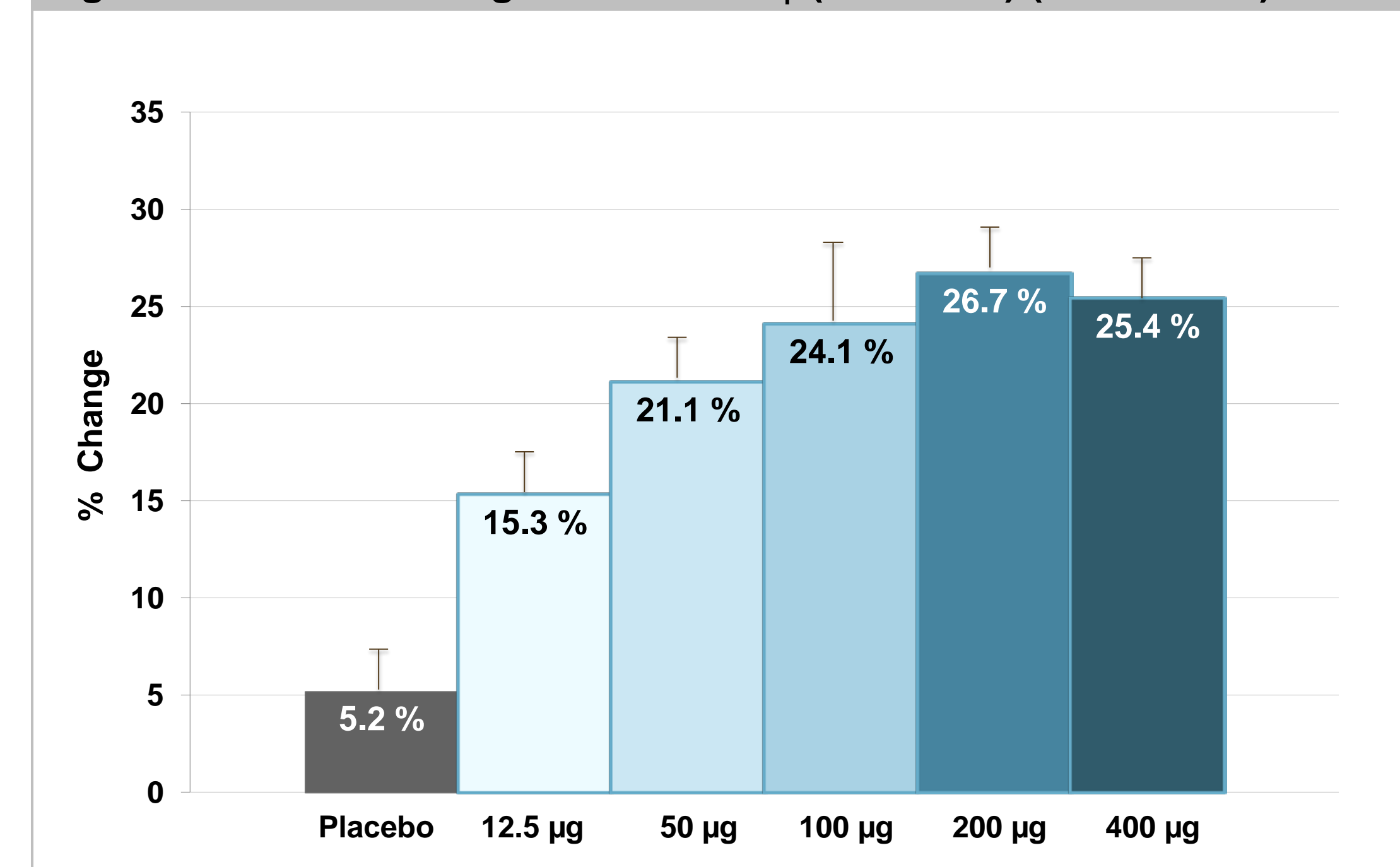


Figure 4. Mean % change in Peak FEV₁ (0-4 hours) (mean±SEM)



Pharmacokinetics:

➤ PK subset included 14 subjects.

➤ EP-101 was rapidly absorbed via the lung, with a peak plasma concentration within 5 – 15 minutes (medians) in all doses.

➤ Systemic exposure (AUC) increased over the dose range of 50 µg to 400 µg with dose proportional increases in C_{max}.

Delivery Time:

➤ The mean delivery time for all doses of EP-101 was less than 2 minutes (range 1.6 - 1.9 minutes), a rapid delivery time that compares favorably to standard general purpose nebulizers.

Safety:

➤ Overall the single dose administration of EP-101 (12.5 µg to 400 µg dose) was well tolerated.

➤ The percentage of subjects who reported at least one AE was similar when comparing EP-101 and placebo groups (Table 2).

➤ There were no clinically meaningful differences between EP-101 doses and placebo in vital signs and ECG (including QTc).

Table 2. Treatment-emergent AEs reported in at least 2 patients

Patients, n (%)	Placebo (n=37)	EP-101				
		12.5 µg (n=39)	50 µg (n=38)	100 µg (n=37)	200 µg (n=37)	400 µg (n=37)
TOTAL	14 (37.8%)	16 (41.0%)	14 (36.8%)	17 (45.9%)	15 (40.5%)	13 (35.1%)
Skin injury	2 (5.4%)	0	0	0	0	0
Headache	4 (10.8%)	6 (2.6%)	0	0	0	0
COPD	0	2 (5.1%)	1 (2.6%)	0	0	0
Cough	5 (13.5%)	3 (7.7%)	2 (5.3%)	5 (13.5%)	3 (8.1%)	3 (8.1%)
Dyspnoea	2 (5.4%)	3 (7.7%)	2 (5.3%)	1 (2.7%)	1 (2.7%)	1 (2.7%)

Conclusions

➤ EP-101 provided rapid onset and sustained bronchodilation over 24 hours.

➤ A dose-response relationship for trough FEV₁ and FEV₁ AUC was established at EP-101 doses ranging from 12.5 µg to 400 µg.

➤ The improvements observed in the first 12 hours (AUC_{0-12h}) were maintained during the second 12 hours (AUC_{12-24h}), with clinically meaningful improvements at all doses ≥50 µg, making EP-101 potentially suitable for once-daily dosing.

➤ Single doses of EP-101 delivered via the investigational eFlow nebulizer were safe and well tolerated.

➤ No clinically significant abnormal changes in vital signs, ECG (including QTc) and clinical laboratory results were recorded.

➤ A Phase 2b multiple-dose dose-ranging study with EP-101 is ongoing.

References

1. Van Noord JA et al. *Thorax* 2000; 55:289-294
2. Vincken W et al. *Eur Respir J* 2002; 19:209-216
3. Sestini P et al. *J Aerosol Med* 2006; 19:127-136