CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 208-437
Drug Name:	Lonhala Magnair (SUN-101; Glycopyrrolate Inhalation Solution administered through eFlow nebulizer) 25 mcg twice daily or 50 mcg twice daily
Indication(s):	Patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema
Applicant:	Sunovion Respiratory Development Inc.
Date(s):	Stamp Date: 7/29/2016 PDUFA date: 5/29/ 2017
Review Priority:	Standard
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Keywords: double-blind, longitudinal data analysis, mixed models, repeated measure ANCOVA, sensitivity analyses & subgroup analyses

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1 EXECUTIVE SUMMARY

This review considers the inhaled, nebulized long-acting muscarinic antagonist (LAMA) glycopyrrolate solution (SUN-101) administered using a portable PARI eFlow closed system (CS) device for maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. We focus in this review on two phase 3 studies and two phase 2 studies. The two phase 3 studies are multicenter, randomized, double-blind, parallel-group, placebo-controlled clinical trials designed to evaluate the efficacy of SUN-101 25 mcg and/or 50 mcg twice daily (BID) with respect to pulmonary function at week 12. These studies included patients with very severe disease, patients remaining on background long-acting beta2 agonists (LABA), and patients with a high-risk for cardiovascular (CV) disease. The two phase 2 studies are placebo-controlled dose finding studies with durations of 28 days and 7 days respectively.

There was statistical evidence of benefit for SUN-101 25 mcg and50 mcg BID with respect to the primary endpoint, change from baseline in trough FEV_1, in two independent phase 3 clinical trials. Treatment with SUN-101 25 mcg BID provided 0.10 L (95% confidence interval [CI]: 0.06, 0.13) and 0.08 L (95% CI: 0.04, 0.12) mean improvements over placebo in trough FEV_1 at week 12 in these two trials. Treatment with SUN-101 50 mcg BID provided 0.10 L (95% CI: 0.07, 0.14) and 0.07 L (95% CI: 0.04, 0.11) mean improvements over placebo in trough FEV_1 at week 12 in these trials, respectively. Estimated treatment effects for SUN-101 were largely consistent across subgroups of interest, including sex, age and race.

There was also statistical evidence of benefit for SUN-101 25 mcg BID or 50 mcg BID with respect to the secondary endpoint, change from baseline in trough FVC in both independent phase 3 clinical trials.

Evaluation of secondary endpoints of change from baseline of St. George's Respiratory Questionnaire (SGRQ) score compare to placebo and change from baseline in number of daily rescue medications used compared to placebo in phase 3 studies did not show consistent efficacy results for all dose levels in all studies.

Two independent phase 2 studies have also shown the benefit of SUN-101 25 mcg or 50 mcg BID with respect to the primary endpoint, change from baseline of FEV_1 at treatment day 28 and day 7 respectively.

Overall, the results of the Phase 2 and Phase 3 clinical development program provide evidence of the efficacy of SUN-101 25 mcg BID and 50 mcg BID in terms of primary endpoints. However, there is no statistically significant benefit for SUN-101 over placebo in terms of SGRQ.

2 INTRODUCTION

2.1 Overview

2.1.1 Background

Chronic obstructive pulmonary disease (COPD) is a common, progressive disease. It can cause coughing that produces large amounts of mucus, wheezing, shortness of breath, chest tightness, and other symptoms. It increases risks of disability and death. Most people who have COPD are smokers or used to be smokers. Patients with COPD may have chronic bronchitis and/or emphysema. Chronic bronchitis is the inflammation of the lining of bronchial tubes that leads to increased mucus formation and airflow obstruction. In emphysema, air is being trapped in the air sacs (alveoli) at the end of the smallest airways (bronchioles), causing air sacs to expand and rupture.

Medications used to treat patients with COPD include bronchodilators and steroids. Bronchodilators, usually administered through an inhaler, relax muscles around the airways in order to improve airflow and relieve symptoms. There are two major types of bronchodilators: β2 agonists, which act on β2 receptors, and muscarinic antagonists, which inhibit the action of cholinergic nerves. Bronchodilators may be either short-acting or long-acting, and many have been approved by FDA for treatment of airflow obstruction in COPD. Approved bronchodilators include but are not limited to the short-acting β2 agonist salbutamol, short-acting muscarinic antagonist ipratropium, long-acting β2 agonists (LABAs) salmeterol and formoterol, and long-acting muscarinic antagonists (LAMAs) tiotropium and aclidinium. FDA has also approved inhalers that combine a LABA and inhaled corticosteroid (ICS), such as Advair (salmeterol and fluticasone propionate), Symbicort (formoterol and budesonide), and Breo (vilanterol and fluticasone furoate).

This review considers the inhaled muscarinic antagonist Glycopyrrolate (SUN-101) for long-term, twice-daily, maintenance treatment of airflow obstruction in patients with COPD. Two doses of SUN-101, 25 mcg twice daily and 50 mcg twice daily were evaluated in the phase 3 clinical development programs; 25 mcg is proposed for approval. We often omit the mcg unit when referring to the dose of SUN-101 in this review.

2.1.2 History of Drug Development

During both IND 110663 development and the pre-NDA meeting, statistical advice regarding the design and analysis of the phase 3 trials was given to the applicant. Advice and comments from the Division were delivered through one end-of-phase 2 meeting, Protocol/SAP review written responses, and a pre-NDA meeting. Table 2 summarizes these interactions.

Table 1: List of Key Correspondences and Meeting Minutes

Document	Meeting Date/ Document Date	Topic	Reference Number
Type B EOP2 Meeting Minutes	17 Sept 2013/ 17 Oct 2013	Dose selection, inclusion criteria, study design	IND 110663
iPSP (Seq.0038) Accepted PSP (Seq.0043)	6 Feb 2014	Agreement of initial Pediatric Study Plan	IND 110663
Type C Teleconference Minutes	15 Sept 2014/ 8 Oct 2014	Discussion of estimand, missing data handling, retrieved drop outs, multiplicity adjustments, sensitivity analysis, etc.	IND 110663
Written Response	9 Jun 2015	ISE, ISS, SAP for SUN101-301 and SUN101-302, subgroup analyses by race and region	IND 110663
Conditional Acceptance Letter	May 27, 2016	Request for Proprietary Name Review: Lonhala Magnair	IND 110663
Type B pre-NDA Meeting Minutes	12 Apr 2016/ 11 May 2016	Discussion of studies completed to support the registration of NDA	IND 110663

Several topics have been discussed during the development of the program:

1. The agency emphasized its interest of the ITT estimand, requests the applicant to continue collecting data after the patients discontinue treatment and to include these data in the analyses.

2. Sensitivity analysis comments were given to the applicant regarding cumulative responder analysis and responder/non-responder analysis.

2.1.3 Specific Studies Reviewed

The Applicant has submitted the results of three phase 2 studies (EP-101-03, EP-101-04, and SUN101-201) and three phase 3 studies (SUN101-301, SUN101-302, and SUN101-303). SUN 101-303 was a long-term safety study whose safety findings were consistent with the safety findings of the two phase 3 trials per the clinical reviewer's (Dr. E. Torjusen) review.

This review focuses on two placebo-controlled phase 3 clinical trials (SUN101-301, and SUN101-302), two placebo-controlled phase 2 studies (EP-101-04, and SUN101-201).

Studies SUN101-301 and SUN101-302 are identical in designs (with the exception that SUN101-301 included a substudy to define the FEV_1 AUC over a 12-hour period). Both studies had the same entry criteria, and enrolled patients from the US only. Both studies included patients with severe disease, patients remaining on background LABA use, and patients with high-risk of CV disease.

Studies EP-101-04 and SUN101-201 are the primary studies in the phase 2 program, they informed the selection of SUN-101 25 mcg and 50 mcg BID as the doses to be evaluated in the

phase 3 clinical studies. In our review, we will focus on the efficacy results in terms of the primary endpoint in these studies.

In this review, we will omit suffix SUN101 and EP-101 whenever referring the studies, retaining instead only the numerical references 04, 201, 301, and 302 when referring to these studies.

Table 2: List of Key Phase 2 and Phase 3 Studies in the Clinical Development Program

Study	Treatment Period	# of Randomized Subjects per Arm	Study Objectives
EP-101-04	28 days	PBO/12.5/25/50/100 57/55/54/57/59	Dose-ranging and safety and efficacy
SUN101-201	7 days (6-way cross-over with 5-7 day washout)	PBO/3/6.25/12.5/50/Aclidinium 400 92/91/92/90/92/94	Dose-ranging and safety and efficacy, PK
SUN101-301	12 weeks	PBO/25/50 218/217/218	Safety and efficacy
SUN101-302	12 weeks	PBO/25/50 212/214/214	Safety and efficacy

2.1.4 Statistical Issues

There were no statistical issues found in this application.

2.2 Data Sources

Data were submitted by the applicant to the CDER electronic data room in SAS transport format. Protocols, correspondence, data listings, and study reports were accessed under the network path \\CDSESUB1\evsprod\NDA208437\208437.enx

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The submitted datasets were of acceptable quality and were adequately documented. We were able to reproduce the results of all key primary and secondary analyses.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

3.2.1.1 Studies SUN-101-301 and SUN-101-302

Two pivotal studies 301 and 302 were replicate phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter studies of 12-week treatment duration to compare the efficacy and safety of SUN-101 to placebo in patients with COPD, with the exception that some

of the patients in study 301 were randomized in a substudy. Figure 1 presents the design scheme for studies 301 and 302

Figure 1: Design Scheme for Studies 301 and 302

Screen	Treatment Period					Follow-up[a]
Visit 1 Up to 3 weeks[b]	Visit 2 Week 0 Baseline/ Randomization Serial Spirometry[c]	Visit 3 Week 2	Visit 4 Week 4	Visit 5 Week 8	Visit 6 Week 12 End of Study Serial Spirometry[c]	Telephone Contact

Note: Visit 6 (Week 12) is the end of treatment. All subjects should be followed for the full 12 weeks of the treatment period, regardless of discontinuation of study treatment. However, subjects who must discontinue the study prior to Visit 6 (Week 12) will undergo End of Study procedures and assessments at the time of study discontinuation.

[a] All subjects will be contacted by telephone 5-7 days after the last study visit (ie, Visit 6 or End of Study visit) for a safety assessment unless seen in the clinic in the same time frame.

[b] Visit 1 may occur over more than one clinic visit and may be up to 3 weeks, but must be a minimum of 1 week prior to randomization (Visit 2) to ensure that at least 1 week of rescue medication use and COPD symptoms are recorded prior to randomization.

[c] Serial spirometry will be performed in the Substudy Population at 5, 15, 30 and 60 minutes, and at 2, 3, 6, and 12 hours after the morning dose, and at 23 hours and 15 minutes and 23 hours and 45 minutes after the previous morning dose. Serial spirometry at Visit 6 (Week 12) is to be performed only in subjects who complete the 12 weeks of study treatment.

Source: Figure 1 in Applicant's Study 301 and 302 protocols.

Subjects who qualified for the studies were randomized in a double-blind manner in a 1:1:1 ratio to the three treatment arms:

- SUN-101 25 mcg BID
- SUN-101 50 mcg BID
- PBO BID

Randomization in these two studies was stratified by two characteristics:

- Baseline cardiovascular risk (high risk vs low risk)
- Background long-acting beta2 agonist (LABA) use (yes/no) during the study

The patients in the trials are male or female aged greater than or equal to 40 years, diagnosed with COPD according to the GOLD 2014 guidelines, and whose post-bronchodilator FEV_1 was less than 80% of predicted normal and greater than 0.7 L during screen, and whose post-bronchodilator FEV_1/FVC ratio was less than 0.70 during screening.

LABAs, inhaled corticosteroid (ICS), fixed dose combination of LABA and ICS use were permitted during the study. But the number of such patients was capped at 30% of randomized

patients. All the other patients were required to withhold their LABA or LABA/ICS treatment for 48 hours prior to spirometry assessments during the whole study.

The treatment duration was 12 weeks. Some of the patients in study 301 were randomized to participate in a substudy. These patients were required to take additional spirometry measurements at visit 2 and visit 6.

Patients were to receive a follow-up call 5-7 days after the last visit. The rescue medication used in the studies was Albuterol.

Table 3 lists the key endpoints used in these two studies.

Table 3: Primary and Secondary Endpoints of Studies 301 and 302

	Study 301	Study 302
Primary Endpoint	Change from baseline in trough FEV1 at week 12	Change from baseline in trough FEV1 at week 12
Key Secondary Endpoints	Standardized change from baseline at week 12 in FEV1 AUC0-12 in the substudy population	
	Change from baseline in trough FVC at week 12	Change from baseline in trough FVC at week 12
	Change from baseline in health status measured by SGRQ* at week 12	Change from baseline in health status measured by SGRQ* at week 12
	Change in number of rescue medication puffs per day over the 12-week period	Change in number of rescue medication puffs per day over the 12-week period

*: Saint George's Respiratory Questionnaires

3.2.1.2 Study 04

Study 04 is a phase 2b, randomized, double-blind, placebo-controlled, dose-ranging study of the efficacy and safety of SUN-101 in subjects with moderate-to-severe COPD.

Subjects who qualified for the studies were randomized in a double-blind manner in a 1:1:1:1:1 ratio to the five treatment arms:

- SUN-101 12.5 mcg BID
- SUN-101 25 mcg BID
- SUN-101 50 mcg BID
- SUN-101 100 mcg BID
- PBO BID

Randomization was stratified by two characteristics:

- Inhaled corticosteroid (ICS) use (current ICS users versus non-ICS users)
- Extended spirometry assessments (yes/no)

The treatment duration for this study is 28 days.

The primary efficacy endpoint for this study is change from baseline in trough FEV_1 on day 28.

3.2.1.3 Study 201

Study 201 is a phase 2, dose-ranging study of SUN-101 in subjects with moderate to severe COPD. It was a randomized, 6-way crossover study. The study was double-blind for SUN-101 and placebo and open-label for aclidinium bromide (hereafter also referred to as aclidinium).

Each subject was to receive each of the following 6 treatments in a random order, BID:

- SUN-101 placebo
- SUN-101 3 mcg
- SUN-101 6.25 mcg
- SUN-101 12.5 mcg
- SUN-101 50 mcg
- Aclidinium 400 mcg

SUN-101 and placebo were administered using eFlow CS nebulizer, Aclidinium was given using the PRESSAIR inhaler device.

For each subject, there is a 5-7 days wash out period between two treatment periods.

The primary efficacy endpoint for this study is change from baseline in trough FEV_1 on treatment visit day 7.

3.2.2 Statistical Methodologies

3.2.2.1 Studies 301 and 302

The efficacy analyses were conducted on the ITT population, using all collected data regardless of whether the subject remained on randomized treatment or not, and regardless of potential effects of other therapies.

The primary efficacy endpoint was change from baseline in trough FEV_1 at week 12. It was analyzed by means of mixed model repeated measures (MMRM). The response variable in the model is change from baseline in trough FEV_1, the model included factors of treatment group, CV risk (high/low), background LABA use (yes/no), visit week, and visit week by treatment group interaction, and baseline FEV_1 as covariates. For tests of fixed effects, an unstructured (UN) covariance matrix and the Kenward and Roger correction to the degrees of freedom was used.

The primary interest of these studies was the comparisons of the changes from baseline in trough FEV_1 at week 12 between each SUN-101 dose and placebo.

Statistical significance was evaluated using a two-sided hypothesis test at the 5% significance level.

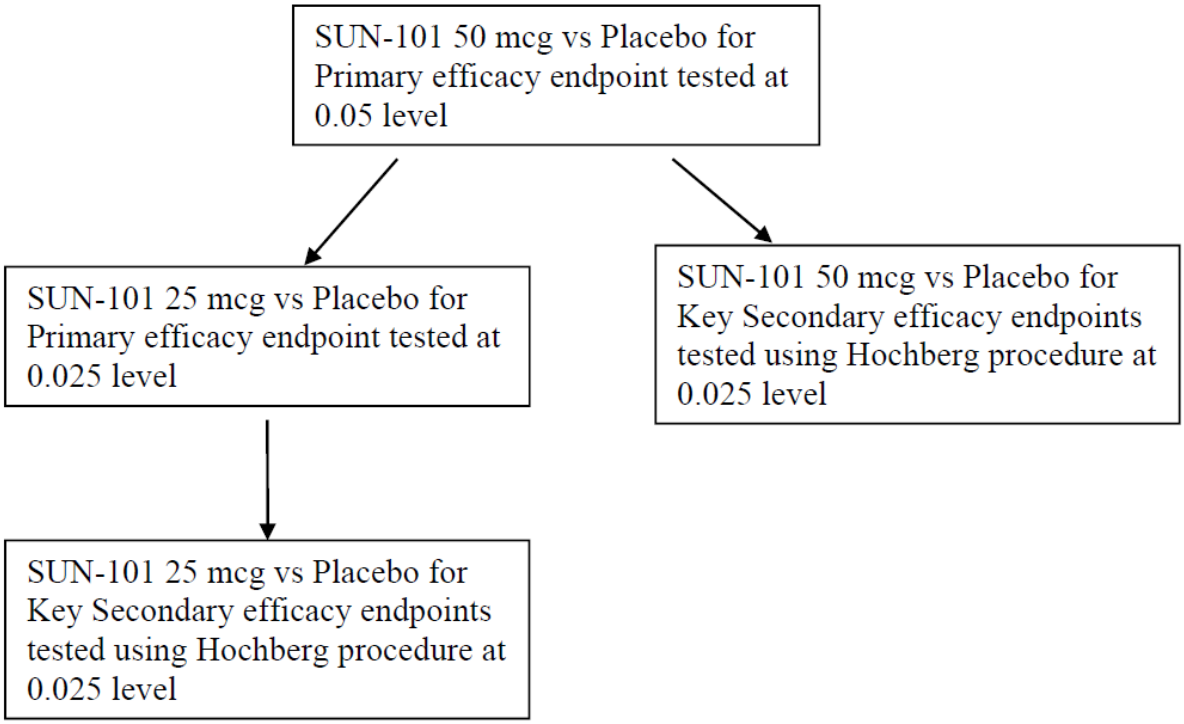
Analyses of secondary efficacy endpoint of standardized FEV_1 area under the change from baseline curves from 0-12 hours ($AUC_{(0-12)}$) and endpoint of change from baseline trough FVC use the same analysis methods as for the primary endpoint.

Analyses of secondary endpoint of change from baseline of SGRQ total score at Week 12/EOS, is based on the ITT population, is via an ANCOVA, with change from baseline in SGRQ total score as the response variable including factors for treatment group, cardiovascular risk (high/low), background LABA use (yes/no), and baseline SGRQ as model covariates.

Analyses of the secondary endpoint of change from baseline rescue medication puffs per day is based on the ITT population and is carried out by means of an ANCOVA, with change from baseline in the average number of rescue medication puffs per day as the response variable and with factors for treatment group, cardiovascular risk (high/low), background LABA use (yes/no), and baseline rescue medication puffs per day included as model covariates.

To control the family-wise Type I error rate, a tree-structured gatekeeping procedure was used for comparisons of the primary efficacy endpoint and the key secondary efficacy endpoints. Figure 2 illustrates this testing procedure.

Figure 2: Applicant's Testing Procedure to Adjust for Multiplicity



Source: Figure 1 of Applicant's Draft SAP.

3.2.2.2 Study 04

The primary efficacy endpoint was change from baseline in trough FEV_1 at day 28, it was analyzed using the ITT population by means of a mixed model repeated measures analysis (MMRM), with change from baseline in trough FEV_1 as the response variable and with factors for treatment group, ICS use, subject participation in extended spirometry assessments (yes/no), visit day, and visit day by treatment group interaction, and baseline FEV_1 included as covariates. An unstructured covariance model was used to model intra-subject correlation in conjunction with treating subject as a random effect

3.2.2.3 Study 201

The primary efficacy endpoint was change from baseline in trough FEV_1 at day 7; it was analyzed by means of an analysis of covariance (ANCOVA) model, with change from baseline in trough FEV_1 as the response variable and with factors for treatment group, period, treatment sequence, and first-order carry-over as fixed effects, and baseline FEV_1 as a covariate. Subject nested within sequence was included as a random effect. If the first-order carry-over was not significant at the 0.10 level, it was to be removed from the model.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Patient Disposition

In this application, among the two phase 3 studies, the main reasons for study discontinuation were withdrawal by subject and loss to follow-up. Among the three treatment arms, placebo arm had the largest study discontinuation rate. The patient dispositions for these studies are summarized in Table 4 and Table 5.

In study 301, there were about 11% to 19% patients discontinuing the treatment, with a higher rate of discontinuation in the placebo arm. However, patients discontinuing the treatment were followed and spirometry measurements continued to be taken, so at the end there are about 7% to 12% patients discontinue the study.

In study 302, there were about 11% to 17% patients discontinuing the treatment, with a higher rate in the placebo arm. However, patients discontinuing the treatment still being followed and spirometry measurements continue being taken, so at the end there are about 7% to 11% patients discontinue the study.

Table 4: Patient Disposition - Study 301

	PBO n (%)	**SUN-101 25 mcg BID n (%)**	**SUN-101 50 mcg BID n (%)**	**Total n (%)**
Screened				974
Randomized				653
ITT	218	217	218	653
Safety	218 (100)	217 (100)	218 (100)	653 (100)
Substudy	42 (19.3)	49 (22.6)	62 (28.4)	153 (23.4)
Completed On-Study Treatment Period	176 (80.7)	194 (89.4)	191 (87.6)	561 (85.9)
Completed Study Participation	191 (87.6)	203 (93.5)	201 (92.2)	595 (91.1)
Withdrawal by Subject	22 (10.1)	11 (5.1)	11 (5.0)	44 (6.7)
Lost to Follow-up	3 (1.4)	2 (0.9)	3 (1.4)	8 (1.2)
Death	0 (0)	0 (0)	1	1 (0.2)
Other	2 (0.9)	1 (0.5)	2 (0.9)	5 (0.8)

Table 5: Patient Disposition – Study 302

	PBO	SUN-101 25 mcg BID	SUN-101 50 mcg BID	Total
Screened				1082
Randomized	213	214	214	641
ITT	212	214	214	640
Safety	212	214	214	640
Completed On-Study Treatment Period	177 (83.5)	183 (85.5)	190 (88.8)	550 (85.9)
Completed Study Participation	188 (88.7)	193 (90.2)	199 (93.0)	580 (90.6)
Withdrawal by Subject	15 (7.1)	9 (4.2)	8 (3.7)	32 (5)
Lost to Follow-up	2 (0.9)	6 (2.8)	3 (1.4)	11 (1.7)
Other	7 (3.3)	6 (2.8)	4 (1.9)	17 (2.7)

3.2.3.2 Patient Demographic and Baseline Characteristics

Demographics and baseline characteristics data for the ITT population are summarized in Table 6 and Table 7. As expected, due to the random treatment assignment, the treatment arms are fairly balanced with respect to each factors considered.

Table 6: Patient Demographic and Baseline Characteristics – Study 301

		PBO	SUN-101 25 mcg BID	SUN-101 50 mcg BID	Total
Sex		**218**	**217**	**218**	**653**
	F	107 (49.1)	99 (45.6)	98 (45.0)	304 (46.6)
	M	111 (50.9)	118 (54.4)	120 (55)	349 (53.4)
Age (yrs)		**218**	**217**	**218**	**653**
	< 65 years	109 (50.0)	122 (56.2)	135 (61.9)	366 (56.0)
	65 – 74 years	93 (42.7)	73 (33.6)	66 (30.3)	232 (35.5)
	>= 75 years	16 (7.3)	22 (10.1)	17 (7.8)	55 (8.4)
Race		**218**	**217**	**218**	**653**
	White	196 (89.9)	200 (92.1)	198 (90.8)	594 (90.9)
	Black or African American	20 (9.1)	15 (6.9)	18 (8.2)	53 (8.1)
	Asian	1 (0.5)	1 (0.5)	0 (0)	2 (0.3)
	American Indian or Alaska Native	1 (0.5)	1 (0.5)	1 (0.5)	3 (0.4)
	Native Hawaiian or Other Pacific Islander	0 (0)	0 (0)	1 (0.5)	1 (0.2)
Ethnic Group		**218**	**217**	**218**	**653**
	Hispanic or Latino	6 (2.8)	7 (3.2)	6 (2.8)	19 (2.9)

CV Risk		**218**	**217**	**218**	**653**
	Low	76 (34.9)	78 (35.9)	77 (35.3)	231 (35.4)
	High	142 (65.1)	139 (64.1)	141 (64.7)	422 (64.6)
Background LABA Use		**218**	**217**	**218**	**653**
	Yes	63 (28.9)	66 (30.4)	68 (31.2)	197 (30.2)
	No	155 (71.1)	151 (69.6)	150 (68.8)	456 (69.8)
ICS Use		**218**	**217**	**218**	**653**
	Yes	60 (27.5)	62 (28.6)	63 (28.9)	185 (28.3)
	No	158 (72.5)	155 (71.4)	155 (71.1)	468 (71.7)

Table 7: Patient Demographic and Baseline Characteristics - Study 302

		PBO	**SUN-101 25 mcg BID**	**SUN-101 50 mcg BID**	**Total**
Sex		**212**	**214**	**214**	**640**
	F	88 (41.5)	90 (42.1)	87 (40.7)	265 (41.4)
	M	124 (58.5)	124 (57.9)	127 (59.3)	375 (58.6)
Age (years)		**212**	**214**	**214**	**640**
	< 65 years	111 (52.4)	109 (50.9)	119 (55.6)	339 (53.0)
	65 – 74 years	76 (35.8)	80 (37.4)	74 (34.6)	230 (35.9)
	>= 75 years	25 (11.8)	25 (11.7)	21 (9.8)	71 (11.1)
Race		**212**	**214**	**214**	**640**
	White	192 (90.6)	185 (86.4)	188 (87.9)	565 (88.3)
	Black or African American	19 (9.0)	27 (12.6)	26 (12.1)	72 (11.3)
	Asian	0 (0)	1 (0.5)	0 (0)	1 (0.2)
	American Indian or Alaska Native	1 (0.5)	0 (0)	0 (0)	1 (0.2)
	Native Hawaiian or Other Pacific Islander	0 (0)	1 (0.5)	0 (0)	1 (0.2)
Ethnic Group		**212**	**214**	**214**	**640**
	Hispanic or Latino	3 (1.4)	2 (0.9)	3 (1.4)	8 (1.3)
CV Risk		**212**	**214**	**214**	**640**
	Low	76 (35.8)	78 (36.4)	80 (37.4)	234 (36.6)
	High	136 (64.2)	136 (63.6)	134 (62.6)	406 (63.4)
Background LABA Use		**212**	**214**	**214**	**640**
	Yes	69 (32.5)	69 (32.2)	67 (31.3)	205 (32)
	No	143 (67.5)	145 (67.8)	147 (68.7)	435 (68)
ICS Use		**212**	**214**	**214**	**640**
	Yes	67 (31.6)	64 (29.9)	59 (27.6)	190 (29.7)
	No	145 (68.4)	150 (70.1)	155 (72.4)	450 (70.3)

3.2.4 Results and Conclusions

Primary and secondary endpoints and analysis methods were introduced in section 3.2.2.

For the two pivotal studies 301 and 302, both the SUN-101 25 mcg and 50 mcg BID doses produced statistically significant improvements in trough FEV_1 at Week 12. However, there was no separation of doses. For the key secondary endpoint of change from baseline of FVC at Week 12, both studies showed statistically significant improvement over the placebo. In terms of secondary endpoints of change from baseline of SGRQ total score and change from baseline of rescue medication puffs per day at Week 12, there was no statistically significant benefit of SUN-101 over the placebo. For the substudy of study 301, results of change from baseline of trough FEV_1 $AUC_{(0\text{-}12\ hrs)}$ at Week 12 were not significantly better than the placebo in both SUN-101 doses.

Table 8 summarizes the analysis results of the primary endpoint of studies 301 and 302. Table 9 to Table 12 summarizes the analysis results of the key secondary endpoints of studies 301 and 302. All the p-values reported here were adjusted p-values (unless otherwise stated) according to pre-specified testing procedures. Please refer to section 3.2.2 for these pre-specified testing procedures. The p-values should be compared to 0.05; if a p-value is less than 0.05, then the SUN-101 arm is significantly different from the placebo arm.

In the analyses using MMRM model, the missing data were imputed by SAS using missing at random assumption. This assumption may not hold, subjects who discontinue treatment tend to have worse outcome than subjects who stay on treatment. However, notice that in both studies 301 and 302, the placebo arms have higher rate of missingness, the overall missingness rate is not very high (7% to 13%). The percentage of missing data in study 301 is 12.4%, 6.5% and 7.8% in placebo arm, 25 mcg arm and 50 mcg arm respectively. The percentage of missing data in study 302 is 11.3%, 9.8% and 7.0% in placebo, 25 mcg arm and 50 mcg arm.

To assess the impact of missing data on efficacy results, tipping point analyses assuming missing not at random were conducted; these analyses are discussed in Section 5. These results showed that it is highly unlikely that the efficacy results will be changed from significantly effective to not significantly effective.

Table 13 and Table 14 summarize the primary efficacy results of the two phase 2 studies of change from baseline of trough FEV_1 at treatment day 28 and day 7 respectively. The results indicated that SUN-101 25 mcg arm or 50 mcg arm in both studies have improvements over placebo in trough FEV_1 at day 28 and day 7.

For Study 04, analyses of mean change from baseline in FEV_1 over 0-24 hours post dose were also conducted on treatment day1 and treatment day 28. These analyses demonstrated a dose-response effect on peak and trough FEV_1 over 24-hour dosing period. Please refer to Figures 3 and 4.

3.2.4.1 Studies 301 and 302

Table 8: Primary Efficacy Analysis (Study 301 and Study 302): Mean Change from Baseline of FEV_1 at Week 12 (ITT Population: All Collected Data)

	Study 301			Study 302		
	PBO	**SUN-101 25 mcg BID**	**SUN-101 50 mcg BID**	**PBO**	**SUN-101 25 mcg BID**	**SUN-101 50 mcg BID**
ITT Population	N = 218	N = 217	N = 218	N = 212	N = 214	N = 214
Mean change from baseline FEV_1 at week 12: L	-0.007	0.089	0.096	0.011	0.092	0.085
Difference from PBO: L (95% CI)		0.096 (0.059,0.133)	0.104 (0.066,0.141)		0.081 (0.042,0.12)	0.074 (0.035,0.113)
Adj. p-value compare to PBO		< 0.0001	< 0.0001		0.0001	0.0002

Table 9: Substudy of Study 301: Standardized Mean Change from Baseline in FEV_1 $AUC_{(0\text{-}12hrs)}$ at Week 12 (ITT Population: All Collected Data)

	Study 301		
	PBO	**SUN-101 25 mcg BID**	**SUN-101 50 mcg BID**
ITT Population Substudy	N = 42	N = 49	N = 62
Mean change from baseline FEV_1 $AUC_{0\text{-}12\ hrs}$	-0.047	0.058	0.075
Difference from PBO: L (95% CI)		0.105 (0.022, 0.189)	0.122 (0.043, 0.201)
Adj. p-value compare to PBO		0.055	0.016

Table 10: Secondary Efficacy Analysis (Study 301 and Study 302): Mean Change from Baseline of FVC at Week 12 (ITT Population: All Collected Data)

	Study 301			Study 302		
	PBO	**SUN-101 25 mcg BID**	**SUN-101 50 mcg BID**	**PBO**	**SUN-101 25 mcg BID**	**SUN-101 50 mcg BID**
ITT Population	N = 218	N = 217	N = 218	N = 212	N = 214	N = 214
FVC CFB: L	0.015	0.152	0.148	0.016	0.135	0.109
Difference from PBO: L (95% CI)		0.137 (0.076, 0.197)	0.133 (0.072, 0.194)		0.119 (0.058, 0.180)	0.093 (0.033, 0.154)
Adj. p-value compare to PBO		< 0.0001	0.0002		0.0008	0.0101

Table 11: Secondary Efficacy Analysis (Study 301 and Study 302): Mean Change from Baseline of SGRQ Total Score at Week 12 (ITT Population: All Collected Data)

	Study 301			Study 302		
	PBO	**SUN-101 25 mcg BID**	**SUN-101 50 mcg BID**	**PBO**	**SUN-101 25 mcg BID**	**SUN-101 50 mcg BID**
ITT Population	N = 218	N = 217	N = 218	N = 212	N = 214	N = 214
SGRQ CFB	-0.884	-4.250	-2.363	-0.138	-3.225	-3.825
Difference from PBO: L (95% CI)		-3.366 (-5.56, -1.171)	-1.479 (-3.700, 0.741)		-3.086 (-5.253, -0.920)	-3.687 (-5.836, -1.538)
Adj. p-value compare to PBO		0.016	0.553		0.0212	0.0048

Table 12: Secondary Efficacy Analysis (Study 301 and Study 302): Mean Change from Baseline of Rescue Medication Puffs per Day Over the Double-blind Period (ITT Population: All Collected Data)

	Study 301			Study 302		
	PBO	**SUN-101 25 mcg BID**	**SUN-101 50 mcg BID**	**PBO**	**SUN-101 25 mcg BID**	**SUN-101 50 mcg BID**
ITT Population	N = 218	N = 217	N = 218	N = 212	N = 214	N = 214
Rescue Med CFB	-0.632	-0.609	-0.815	-0.678	-0.959	-0.845
Difference from PBO: L (95% CI)		0.024 (-0.310, 0.357)	-0.183 (-0.512, 0.147)		-0.281 (-0.634, 0.072)	-0.167 (-0.520, 0.186)
Adj. p-value compare to PBO		> 0.999	0.553		0.2371	0.7087

3.2.4.2 Studies 04 and 201

Table 13: Primary Efficacy Analysis of Study 04: Mean Change from Baseline of FEV_1 at Day 28

	Study 04				
	PBO	**SUN-101 12.5 mcg BID**	**SUN-101 25 mcg BID**	**SUN-101 50 mcg BID**	**SUN-101 100 mcg BID**
ITT Population	N = 57	N = 55	N = 54	N = 57	N = 59
Change from baseline to morning trough on day 28: L	0.001	0.106	0.133	0.134	0.179
Difference from PBO: L (95% CI)		0.117 (0.037, 0.197)	0.128 (0.048, 0.209)	0.146 (0.067, 0.226)	0.177 (0.099, 0.255)
Adj. p-value compare to PBO		0.0043	0.0019	0.0004	< 0.0001

Table 14: Primary Efficacy Analysis of Study 201: Mean Change from Baseline of FEV_1 at Day 7

	Study 201					
	PBO	**SUN-101 3 mcg BID**	**SUN-101 6.25 mcg BID**	**SUN-101 12.5 mcg BID**	**SUN-101 50 mcg BID**	**ACL 400 mcg BID**
ITT Population	N = 92	N = 91	N = 92	N = 90	N = 92	N = 94
Change from baseline to morning trough on day 7: L	-0.034	-0.012	0.063	0.097	0.101	0.120
Difference from PBO: L (95% CI)		0.013 (-0.032, 0.057)	0.082 (0.038, 0.126)	0.109 (0.064, 0.153)	0.138 (0.093, 0.182)	0.157 (0.112, 0.201)
Un-adj. p-value compare to PBO		0.5773	0.0003	< 0.0001	< 0.0001	< 0.0001

Figure 3: Mean Change from Baseline in FEV1 (L) Over Time on Day 1 (Study 04)

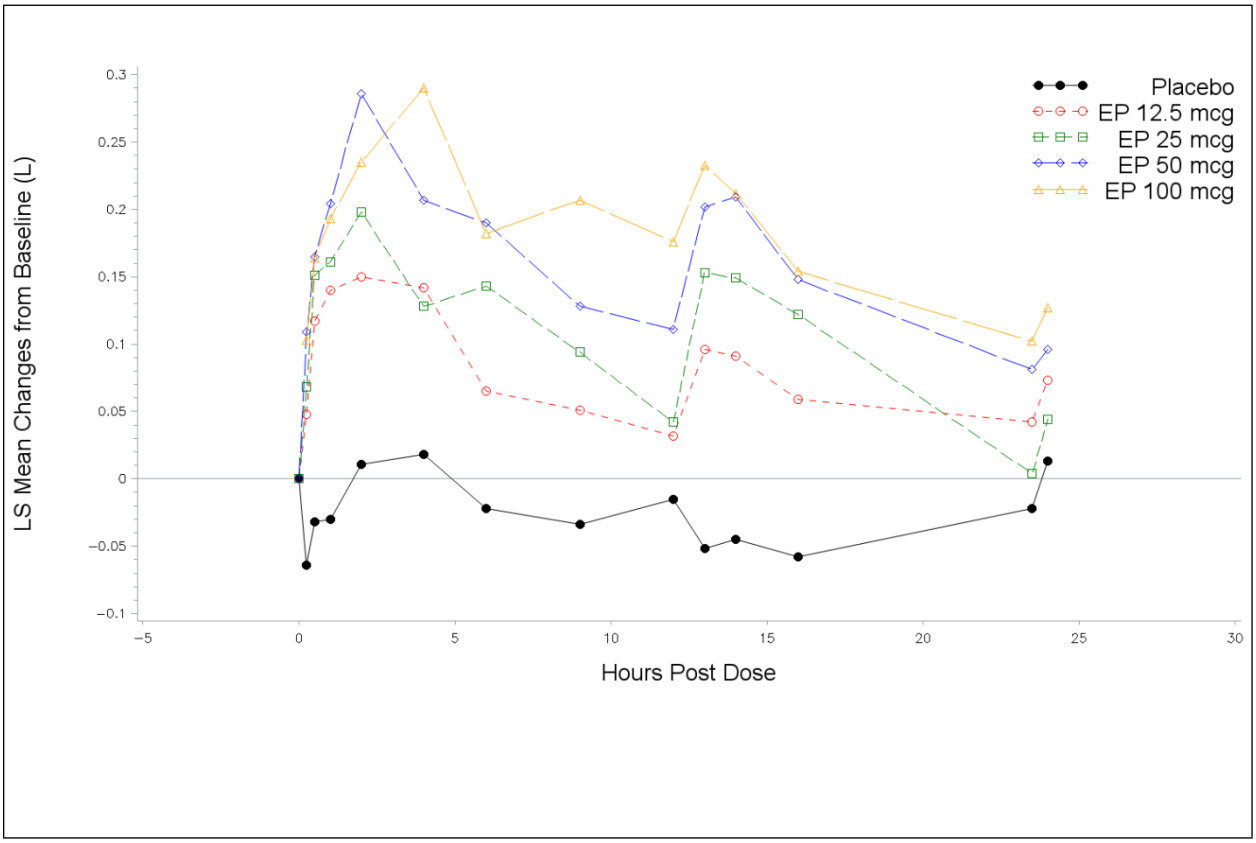
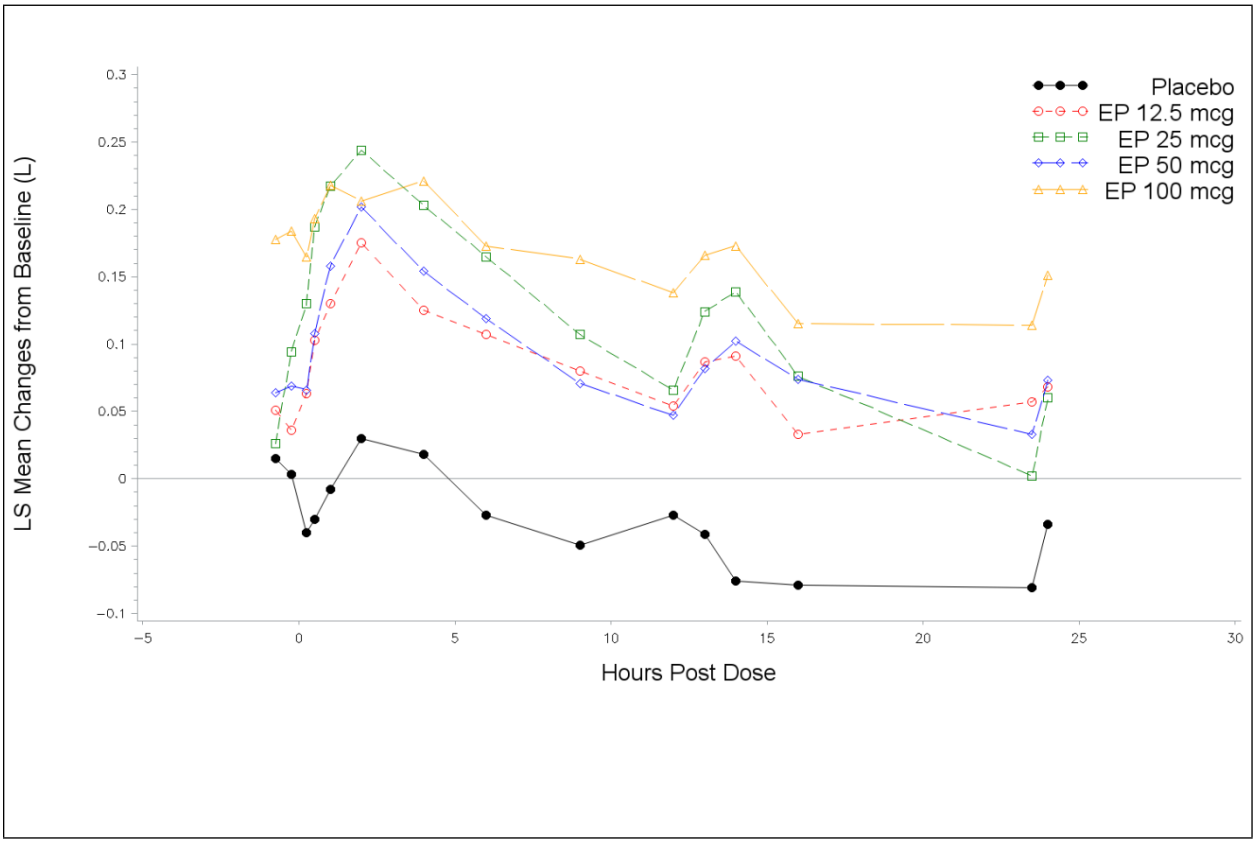


Figure 4: Mean Change from Baseline in FEV1 (L) Over Time on Day 28 (Study 04)



3.3 Evaluation of Safety

Please refer to the evaluation of safety in the clinical review by Dr. E. Torjusen.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

In this review, subgroup analyses were conducted for all primary and secondary endpoints for both Study 301 and Study 302.

For the primary endpoint, subgroup analyses were performed for the following factors:

1. Three demographic factors: age (< 65, 65-74, >=75), sex (F, M), and race (White, Non-White).
2. Four baseline disease characteristics: baseline in-check PIFR (< 30, 30-60, 60-90, > 90), spirometry PIFR (<= 60, > 60-90, > 90-120, > 120-150, > 150-180, > 180-210, > 210), background LABA use (yes, no), and baseline COPD severity (< 30% Predicted, >= 30% to 50 % Predicted, >= 50% Predicted)

For the secondary endpoints, subgroup analyses were performed for the following factors:

1. Three demographic factors: age (< 65, 65-74, >=75), sex (F, M), and race (White, Non-White).

2. One baseline disease characteristic: baseline COPD severity (< 30% Predicted, >= 30% to 50 % Predicted, >= 50% Predicted).

For the substudy of study 301, subgroup analyses on the primary endpoint and secondary endpoints were conducted similarly as above.

Table 15 to Table 23 list the complete subgroup analysis results for the primary endpoint and secondary endpoints for studies 301 and 302 for both 25 mcg arm and 50 mcg arm.

Figure 3 to Figure 20 illustrate the complete subgroup analysis results for the primary endpoint and secondary endpoints for studies 301 and 302 for both 25 mcg arm and 50 mcg arm.

Interpretation of the key results will be given in section 4.1 and 4.2.

Table 15: Study 301: Subgroup Analyses on Primary Endpoint of Change from Baseline of FEV_1 at Week 12

	Mean Difference of FEV1 25 mcg					Mean Difference of FEV1 50 mcg					Interaction
	N	Est.	LL	UL	p-value	N	Est.	LL	UL	p-value	Test p-value
----Age Group----	.	.	.	.	.	.	.	.	.	.	0.5122
< 65	122	0.076	0.025	0.127	0.0037	135	0.109	0.058	0.159	<0.0001	.
65 - 74	73	0.114	0.054	0.175	0.0002	66	0.078	0.016	0.140	0.014	.
>= 75	22	0.184	0.060	0.308	0.0037	17	0.197	0.067	0.328	0.0031	.
----Sex----	.	.	.	.		.	.	.	.		0.0795
F	99	0.106	0.052	0.159	0.0001	98	0.072	0.018	0.125	0.0090	.
M	118	0.086	0.035	0.137	0.0010	120	0.128	0.077	0.179	<0.0001	.
----Race----	.	.	.	.		.	.	.	.		0.1235
White	200	0.105	0.066	0.144	<0.0001	198	0.107	0.067	0.146	<0.0001	.
Non-white	17	-0.0005	-0.125	0.124	0.9932	20	0.077	-0.041	0.194	0.1994	.
----In-Check PIFR----	.		.	.	.	.		.	.	.	0.6007
< 30	9	0.108	-0.094	0.310	0.2937	7	0.226	0.012	0.441	0.0389	.
30 – 60	50	0.035	-0.042	0.112	0.3732	51	0.068	-0.010	0.146	0.0858	.
60 – 90	46	0.104	0.016	0.191	0.0204	49	0.137	0.051	0.222	0.0018	.
> 90	111	0.123	0.072	0.174	<0.0001	111	0.098	0.047	0.150	0.0002	.
----Spirometry PIFR----	.	.	.	.			.	.	.	.	0.0422
<= 60	16	0.129	-0.020	0.277	0.0889	10	0.122	-0.047	0.291	0.1544	
> 60 - 90	30	0.110	0.012	0.208	0.0284	29	0.083	-0.015	0.180	0.0984	.
> 90 - 120	40	0.123	0.040	0.206	0.0038	39	0.127	0.042	0.211	0.0036	.
> 120 - 150	45	0.144	0.050	0.237	0.0026	33	0.077	-0.023	0.176	0.1306	.
> 150 -180	26	-0.046	-0.163	0.071	0.4368	28	0.123	0.009	0.237	0.0341	.
> 180 -210	20	0.053	-0.082	0.189	0.4418	17	0.200	0.056	0.339	0.0063	.
> 210	15	0.104	-0.032	0.240	0.1340	19	0.084	-0.045	0.213	0.2004	.
---- Background LABA Use----	.	.	.	.		.	.	.	.	.	0.8372
Y	66	0.071	0.002	0.140	0.0433	68	0.081	0.012	0.149	0.0212	.
N	151	0.106	0.061	0.150	<0.0001	150	0.112	0.067	0.157	<0.0001	.
----COPD Severity----	.	.	.	.		.	.	.	.	.	0.3378
<30% Predicated	12	0.070	-0.090	0.230	0.3898	16	0.094	-0.058	0.246	0.2231	
>= 30% to 50% Predicated	83	0.067	0.005	0.128	0.0338	82	0.072	0.010	0.133	0.0223	
>= 50% Predicted	121	0.121	0.073	0.170	<0.0001	120	0.134	0.085	0.183	<0.0001	

Figure 5: Study 301 25 mcg Arm: Subgroup Analyses on Primary Endpoint of Change from Baseline of FEV_1 at Week 12

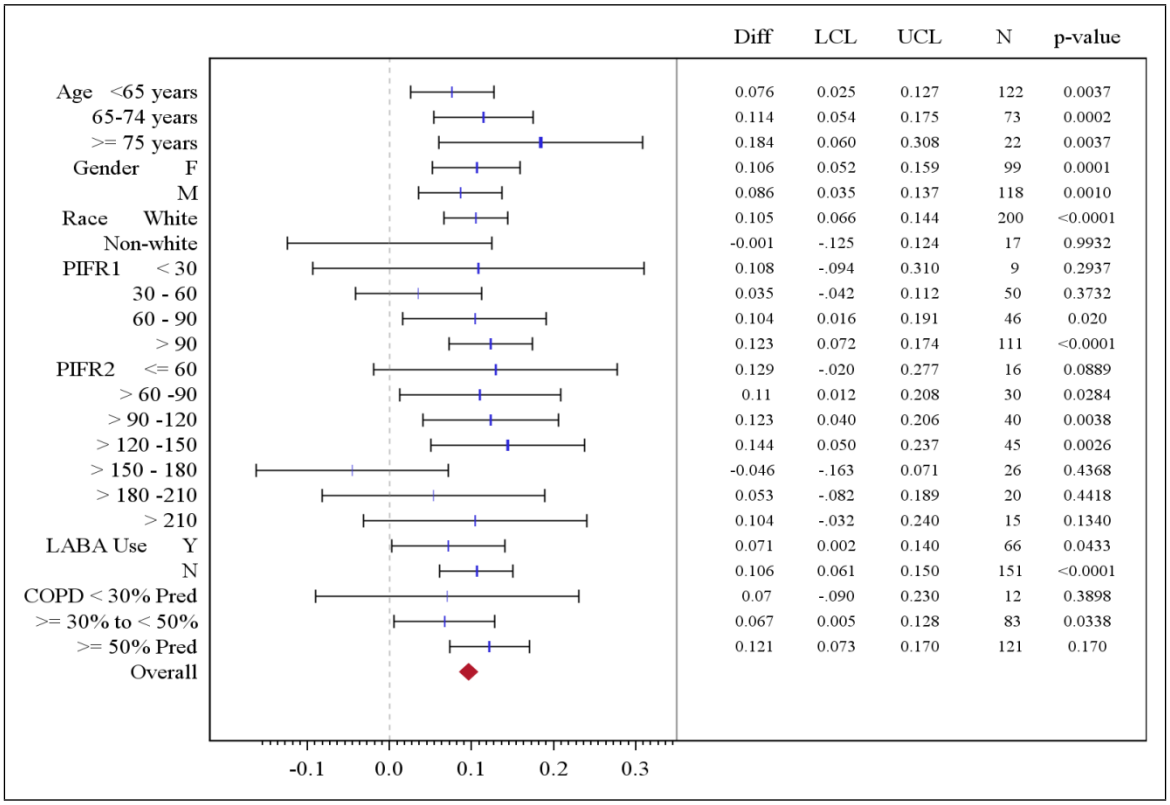


Figure 6: Study 301 50 mcg Arm: Subgroup Analyses on Primary Endpoint of Change from Baseline of FEV_1 at Week 12

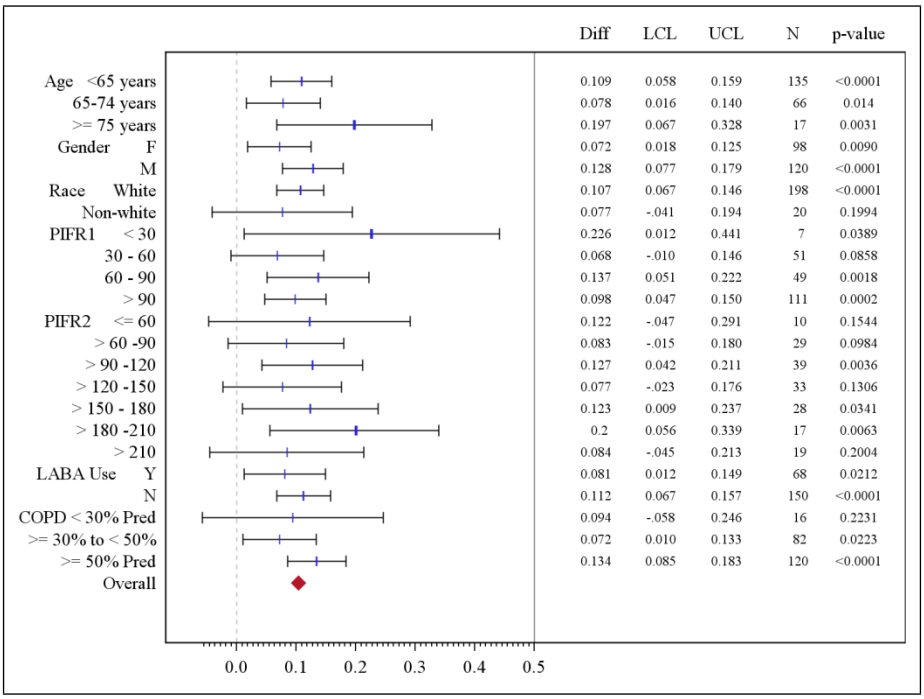


Table 16: Substudy of Study 301: Subgroup Analyses on Secondary Endpoint of Change from Baseline of FEV_1 $AUC_{(0\text{-}12)}$ at Week 12

	Mean Difference of FEV1 AUC 25 mcg					Mean Difference of FEV1 AUC 50 mcg					Interaction Test p-value
	N	Est.	LL	UL	p-value	N	Est.	LL	UL	p-value	
----Age Group----	.	.	.	.	.	.	.	.	.	.	0.1160
< 65	28	0.040	-0.063	0.143	0.4453	39	0.118	0.022	0.213	0.0164	.
65 - 74	18	0.181	0.021	0.340	0.0266	15	0.124	-0.039	0.287	0.1354	.
>= 75	3	0.236	-0.193	0.665	0.2776	8	0.109	-0.287	0.505	0.5857	.
----Sex----	.	.	.	.		.	.	.	.	.	0.9923
F	22	0.109	-0.007	0.226	0.0655	27	0.121	0.012	0.230	0.0297	.
M	27	0.086	-0.036	0.208	0.1653	35	0.109	-0.008	0.225	0.0680	.
----Race----	.	.	.	.		.	.	.	.	.	0.3279
White	47	0.101	0.013	0.189	0.0245	54	0.132	0.047	0.217	0.0026	.
Non-white	2	0.236	-0.088	0.560	0.1519	8	0.049	-0.182	0.279	0.676	.
----In-Check PIFR----	.		.	.	.	.		.	.	.	0.1238
< 30	3	0.211	-0.211	0.633	0.3244	2	0.498	0.052	0.945	0.0291	.
30 – 60	15	0.161	0.011	0.310	0.0354	20	0.224	0.081	0.366	0.0024	.
60 – 90	8	0.049	-0.159	0.256	0.6416	16	-0.012	-0.189	0.165	0.8914	.
> 90	23	0.089	-0.027	0.205	0.1320	24	0.087	-0.029	0.202	0.1388	.
----Spirometry PIFR----	.	.	.	.	.		.	.	.	.	0.1011
<= 60	2	-0.039	-0.355	0.277	0.8055	3	0.363	0.078	0.649	0.0133	
> 60 - 90	10	0.114	-0.084	0.313	0.2553	7	0.170	-0.048	0.388	0.1249	.
> 90 - 120	6	0.156	-0.049	0.360	0.1350	12	0.028	-0.140	0.195	0.7433	.
> 120 - 150	10	0.261	-0.095	0.617	0.1485	9	0.271	-0.086	0.628	0.1350	.
> 150 -180	9	0.061	-0.228	0.349	0.6771	6	0.156	-0.147	0.459	0.3074	.
> 180 -210	3	0.088	-0.332	0.509	0.6770	2	0.526	0.031	1.021	0.0376	.

> 210	1	-0.112	-0.521	0.296	0.5859	1	N/A	N/A	N/A	N/A	.
----COPD Severity----	.	.	.	.		.	.	.	.	.	0.3689
<30% Predicated	2	0.113	-0.254	0.481	0.5431	5	0.019	-0.289	0.326	0.9034	
>= 30% to 50% Predicated	16	0.095	-0.055	0.245	0.2137	22	0.200	0.056	0.343	0.0067	
>= 50% Predicted	31	0.120	0.017	0.222	0.0223	35	0.112	0.012	0.211	0.0278	

Figure 7: Substudy of Study 301 25 mcg Arm: Subgroup Analyses on Secondary Endpoint of Change from Baseline of FEV_1 $AUC_{(0-12)}$ at Week 12

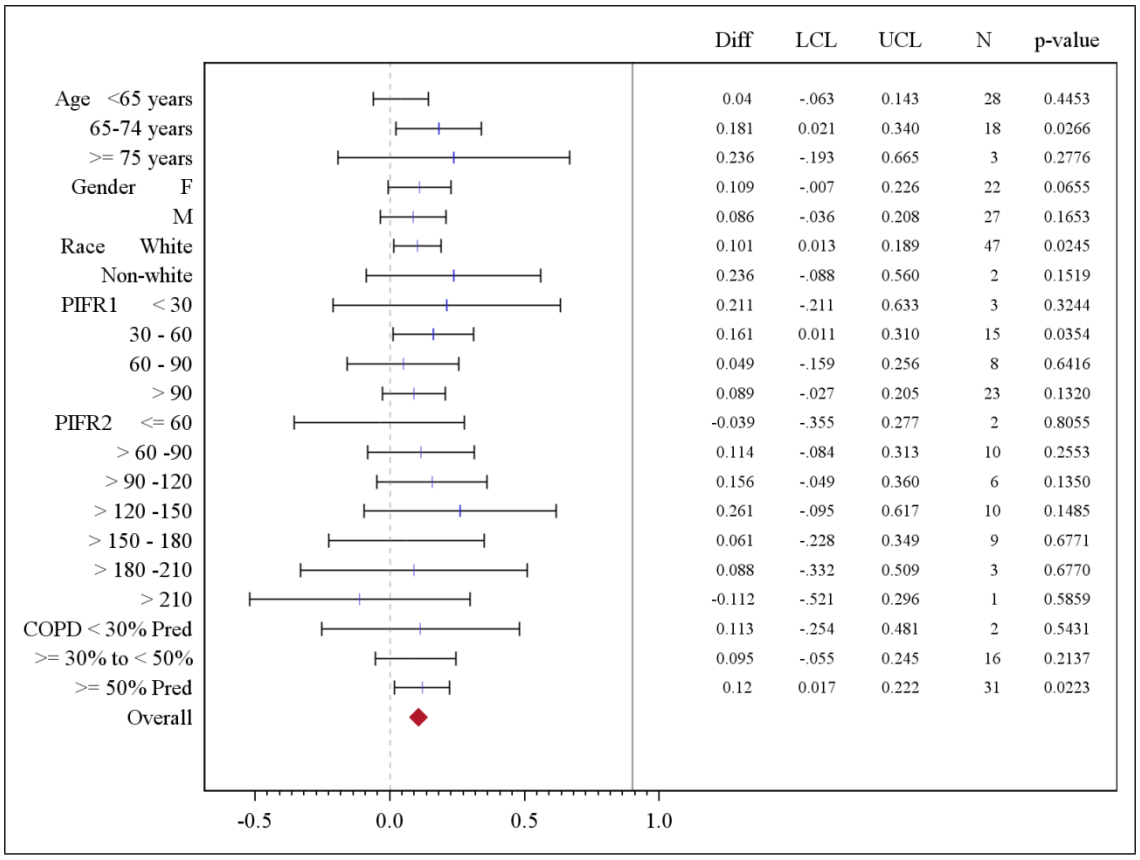


Figure 8: Study 301 Substudy 50 mcg Arm: Subgroup Analyses on Secondary Endpoint of Change from Baseline of FEV1 AUC (0-12) at Week 12

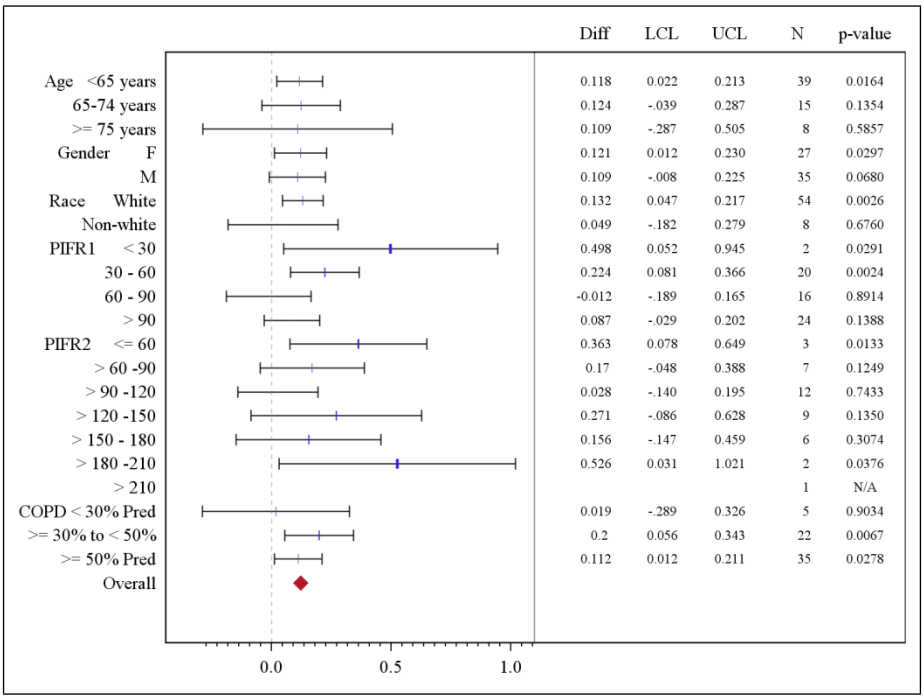


Table 17: Study 301: Subgroup Analyses on Secondary Endpoint of Change from Baseline of Trough FVC at Week 12

	Mean Difference of FVC 25 mcg					Mean Difference of FVC 50 mcg					Interaction Test p-value
	N	Est.	LL	UL	p-value	N	Est.	LL	UL	p-value	
----Age Group----	.	.	.	.	.	.	.	.	.	.	0.4477
< 65	122	0.087	0.004	0.170	0.0410	135	0.128	0.047	0.210	0.0022	.
65 - 74	73	0.199	0.100	0.298	<0.0001	66	0.106	0.004	0.207	0.0408	.
>= 75	22	0.227	0.025	0.428	0.0277	17	0.290	0.078	0.503	0.0075	.
----Sex----	.	.	.	.		.	.	.	.	.	0.0984
F	99	0.154	0.068	0.241	0.0005	98	0.096	0.009	0.182	0.0299	.
M	118	0.114	0.032	0.197	0.0065	120	0.163	0.080	0.245	0.0001	.
----Race----	.	.	.	.		.	.	.	.	.	0.0851
White	200	0.150	0.086	0.213	<0.0001	198	0.135	0.071	0.199	<0.0001	.
Non-white	17	-0.001	-0.204	0.202	0.9917	20	0.117	-0.074	0.308	0.2281	.
----COPD Severity----	.	.	.	.	.	.	.	.	.	.	0.7205
<30% Predicated	12	0.149	-0.112	0.411	0.2634	16	0.215	-0.033	0.464	0.0896	.
>= 30% to 50% Predicated	83	0.114	0.013	0.214	0.0277	82	0.077	-0.024	0.178	0.1343	.
>= 50% Predicted	121	0.148	0.068	0.228	0.0003	120	0.154	0.073	0.234	0.0002	.

Figure 9: Study 301 25 mcg Arm: Subgroup Analyses on Secondary Endpoint of Change from Baseline of Trough FVC at Week 12

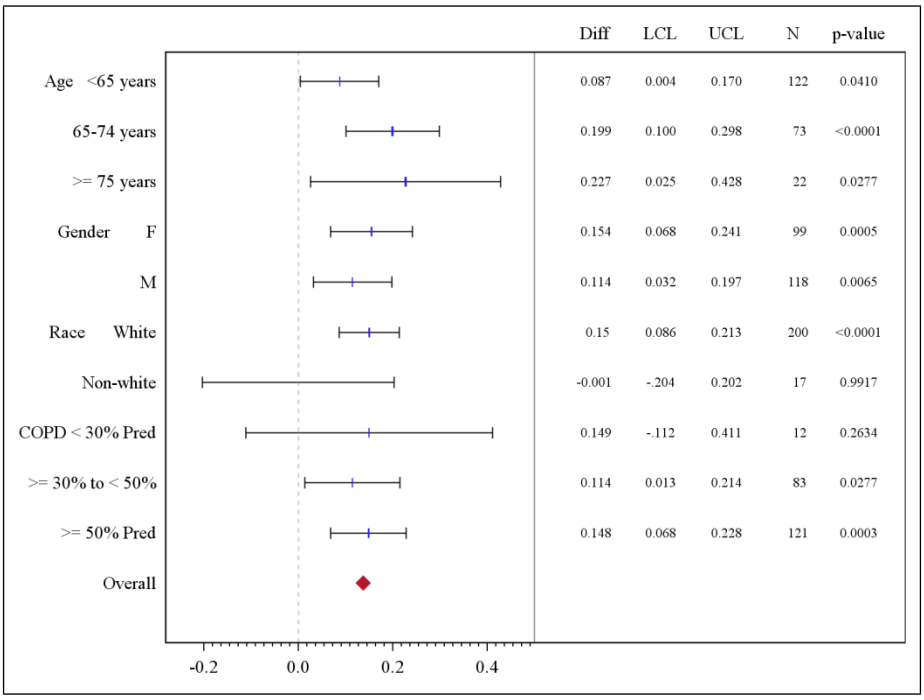


Figure 10: Study 301 50 mcg Arm: Subgroup Analyses on Secondary Endpoint of Change from Baseline of Trough FVC at Week 12

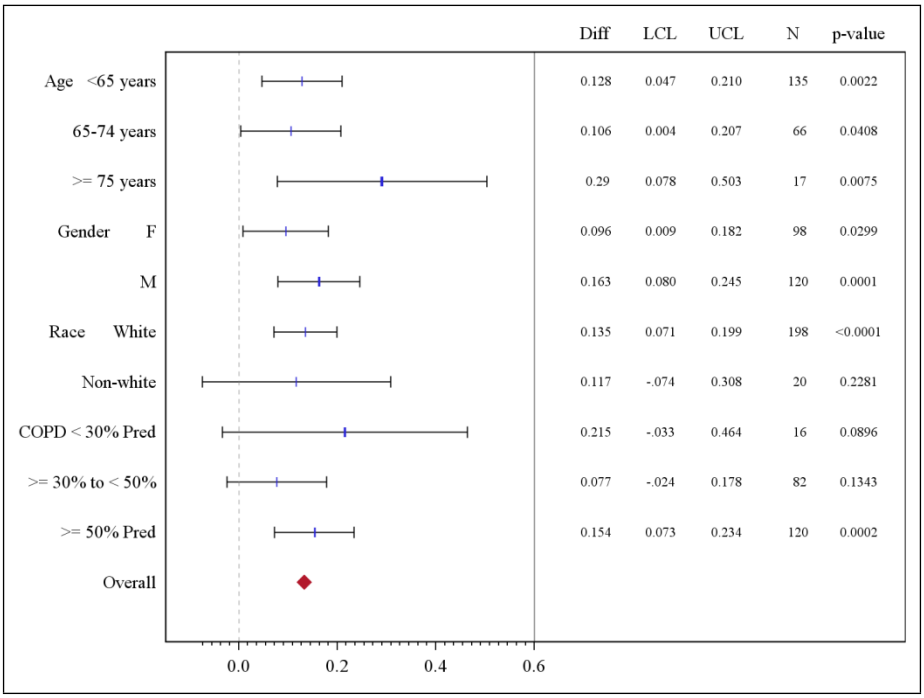


Table 18: Study 302: Subgroup Analyses on Primary Endpoint of Change from Baseline of FEV_1 at Week 12

	Mean Difference of FEV1 25 mcg					Mean Difference of FEV1 50 mcg					Interaction Test p-value
	N	Est.	LL	UL	p-value	N	Est.	LL	UL	p-value	
----Age Group----	.	.	.	.	.	.	.	.	.	.	0.7617
< 65	109	0.051	-0.004	0.105	0.0708	119	0.040	-0.013	0.094	0.1378	.
65 - 74	79	0.120	0.055	0.186	0.0004	74	0.136	0.070	0.202	<0.0001	.
>= 75	25	0.096	-0.018	0.210	0.0974	21	0.035	-0.083	0.152	0.5620	.
----Sex----	.	.	.	.		.	.	.	.	.	0.7329
F	89	0.075	0.015	0.136	0.0149	87	0.056	-0.006	0.117	0.0742	.
M	124	0.086	0.034	0.137	0.0012	127	0.086	0.035	0.136	0.0009	.
----Race----	.	.	.	.		.	.	.	.	.	0.2279
White	184	0.085	0.043	0.126	<0.0001	188	0.086	0.044	0.127	<0.0001	.
Non-white	29	0.046	-0.073	0.165	0.4479	26	-0.023	-0.146	0.099	0.7083	.
----In-Check PIFR----	.		.	.	.	.		.	.	.	0.3375
< 30	3	0.174	-0.150	0.497	0.2927	3	0.052	-0.246	0.351	0.7301	.
30 – 60	65	0.073	0.001	0.146	0.0465	70	0.104	0.033	0.175	0.0040	.
60 – 90	45	0.117	0.033	0.200	0.0062	51	0.032	-0.048	0.112	0.4373	.
> 90	100	0.066	0.008	0.125	0.0258	89	0.076	0.017	0.136	0.0120	.
----Spirometry PIFR----	.	.	.	.			.	.	.	.	0.5885
<= 60	8	0.152	-0.040	0.345	0.1201	17	0.120	-0.036	0.275	0.1313	.
> 60 - 90	29	0.030	-0.075	0.135	0.5721	26	0.022	-0.083	0.128	0.6798	.
> 90 - 120	38	0.145	0.054	0.236	0.0018	30	0.082	-0.014	0.178	0.0942	.
> 120 - 150	39	0.086	-0.008	0.180	0.0727	42	0.127	0.036	0.217	0.0062	.
> 150 -180	28	0.002	-0.107	0.111	0.9688	25	0.068	-0.045	0.181	0.2350	.
> 180 -210	16	0.154	0.003	0.304	0.0451	20	0.129	-0.014	0.272	0.0762	.
> 210	28	0.153	0.049	0.256	0.0041	27	0.038	-0.067	0.144	0.4774	.
---- Background LABA Use----	.	.	.	.		.	.	.	.	.	0.7733
Y	69	0.123	0.054	0.192	0.0005	67	0.085	0.015	0.155	0.0173	.
N	144	0.060	0.012	0.108	0.0151	147	0.069	0.021	0.116	0.0044	.
----COPD Severity----	.	.	.	.		.	.	.	.	.	0.1440
<30% Predicated	17	-0.085	-0.238	0.068	0.2752	19	-0.030	-0.178	0.119	0.6969	
>= 30% to 50% Predicated	72	0.054	-0.012	0.119	0.1096	76	0.063	-0.002	0.128	0.0557	
>= 50% Predicted	124	0.118	0.066	0.169	<0.0001	119	0.095	0.043	0.146	0.0003	

Figure 11: Study 302 25 mcg Arm: Subgroup Analyses on Primary Endpoint of Change from Baseline of FEV_1 at Week 12

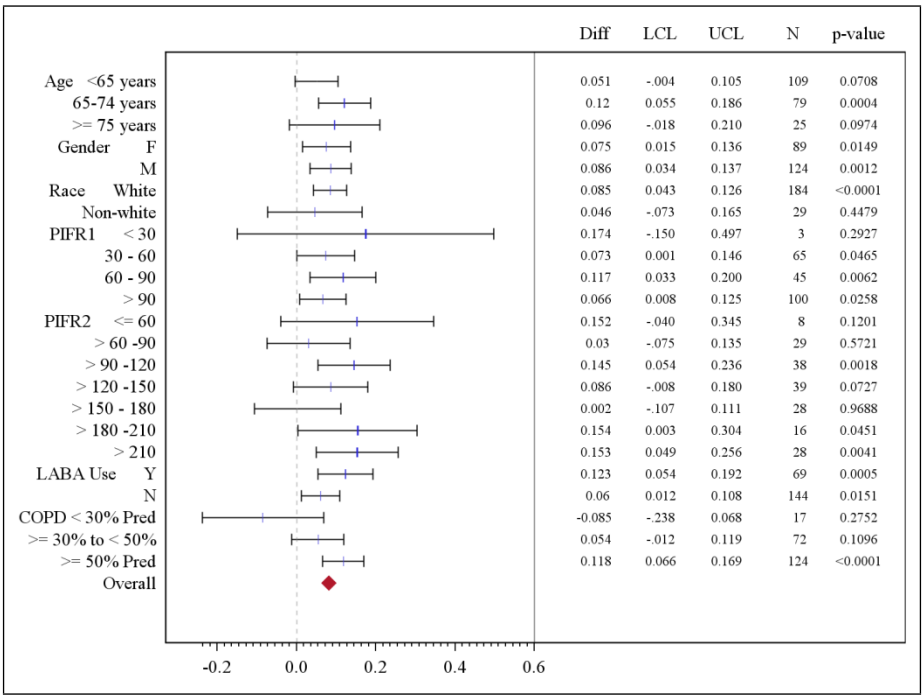


Figure 12: Study 302 50 mcg Arm: Subgroup Analyses on Primary Endpoint of Change from Baseline of FEV_1 at Week 12

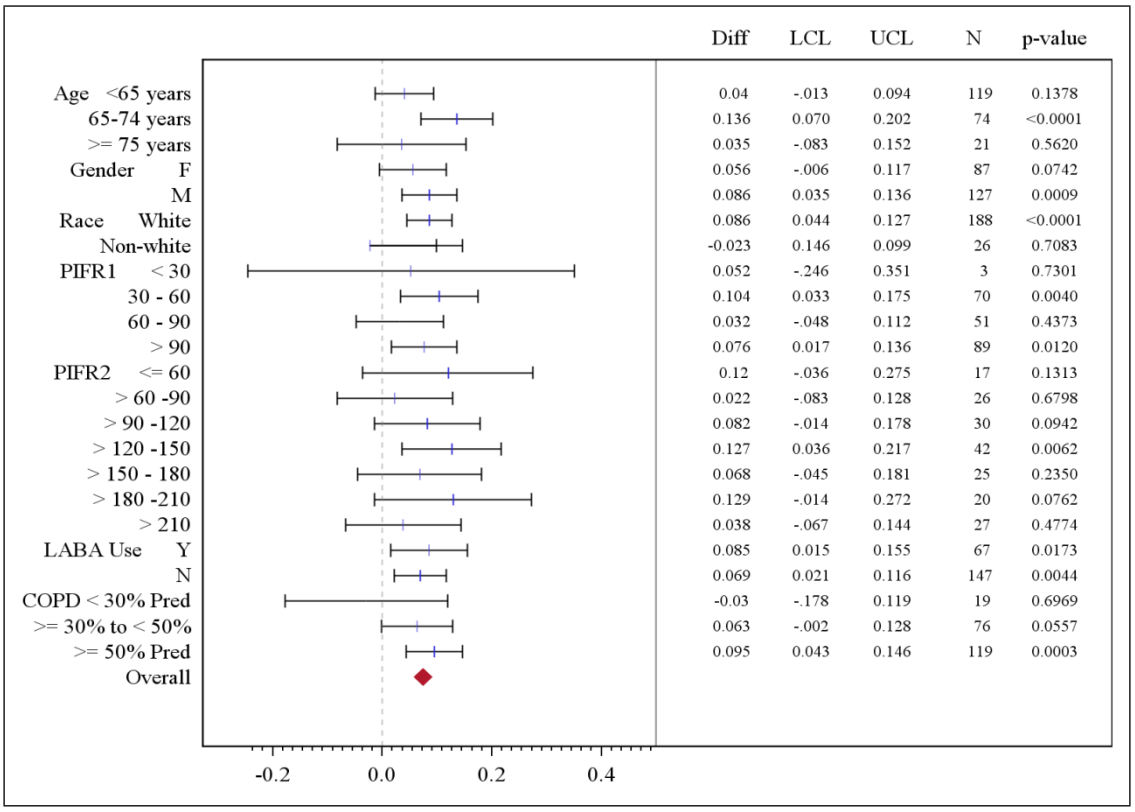


Table 19: Study 302: Subgroup Analyses on Secondary Endpoint of Change from Baseline of Trough FVC at Week 12

	Mean Difference of RESC 25 mcg					Mean Difference of RESC 50 mcg					Interaction Test p-value
	N	Est.	LL	UL	p-value	N	Est.	LL	UL	p-value	
----Age Group----	.	.	.	.	.	.	.	.	.	.	0.3291
< 65	109	0.057	-0.028	0.142	0.1866	119	0.031	-0.051	0.114	0.4580	.
65 - 74	79	0.206	0.105	0.308	<0.0001	74	0.198	0.096	0.301	0.0001	.
>= 75	25	0.124	-0.053	0.300	0.1689	21	0.057	-0.125	0.238	0.541	.
----Sex----	.	.	.	.		.	.	.	.	.	0.4199
F	89	0.087	-0.005	0.180	0.0650	87	0.062	-0.031	0.156	0.1904	.
M	124	0.140	0.062	0.219	0.0005	127	0.113	0.036	0.191	0.0041	.
----Race----	.	.	.	.		.	.	.	.	.	0.1174
White	184	0.124	0.059	0.189	0.0002	188	0.113	0.050	0.177	0.0005	.
Non-white	29	0.081	-0.103	0.265	0.3861	26	-0.052	-0.241	0.137	0.5894	.
----COPD Severity----	.	.	.	.	.	.	.	.	.	.	0.2573
<30% Predicated	17	-0.116	-0.353	0.121	0.3378	19	-0.001	-0.232	0.229	0.9918	.
>= 30% to 50% Predicated	72	0.090	-0.013	0.192	0.0857	76	0.064	-0.037	0.165	0.212	.
>= 50% Predicted	124	0.166	0.086	0.246	<0.0001	119	0.120	0.040	0.200	0.0034	.

Figure 13: Study 302 25 mcg Arm: Subgroup Analyses on Secondary Endpoint of Change from Baseline of Trough FVC at Week 12

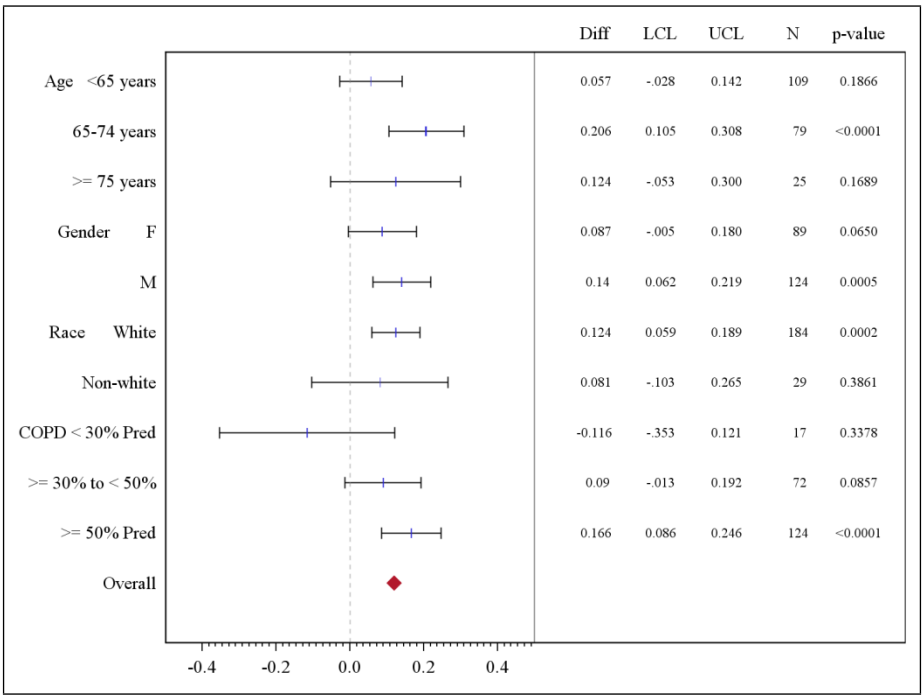
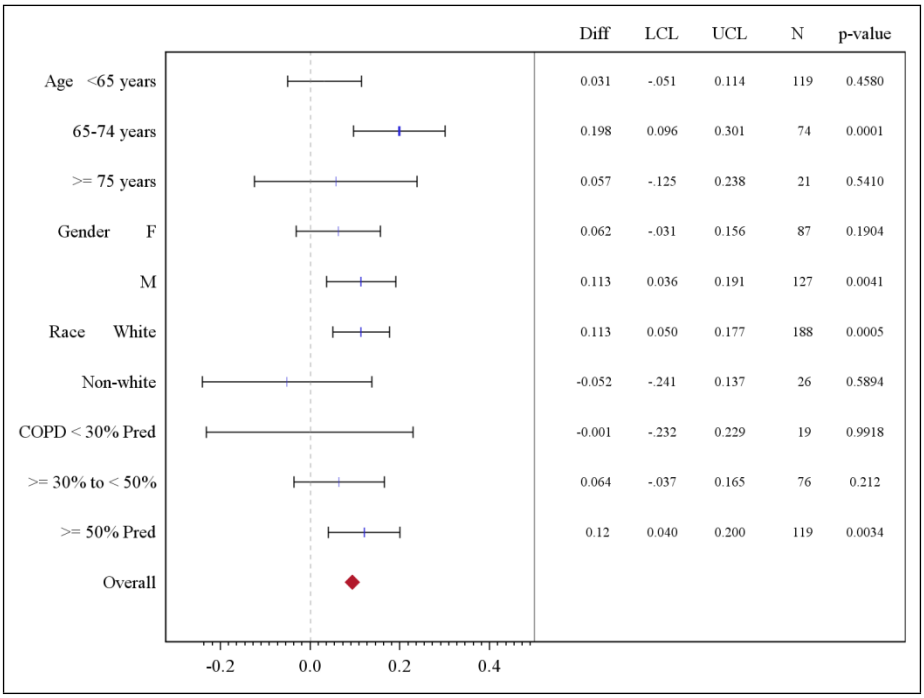


Figure 14: Study 302 50 mcg Arm: Subgroup Analyses on Secondary Endpoint of Change from Baseline of Trough FVC at Week 12



4.1 Sex, Race, Age, and Geographic Region

Subgroup analyses were performed on sex, race and age. Since all the clinical trials were conducted in the USA, there were no subgroup analyses on geographic region.

The treatment-by-subgroup interaction is evaluated at significance level of 0.10.

Table 15 summarizes the results of study 301 on the primary endpoint change from baseline of trough FEV_1 at Week 12. The analyses are based on all data collected on the ITT population:

1. There was a statistically significant treatment-by-gender interaction effect (p-value of 0.0795). Treatment with both doses of SUN-101 demonstrated improvements in trough FEV_1 in both male and female subgroups at Week 12. The mean, placebo-adjusted trough FEV_1 increased by 0.086 L and 0.128 L in subjects in the SUN-101 25 mcg and 50 mcg male subgroups respectively. The mean, placebo-adjusted trough FEV_1 increased by 0.106 L and 0.072 L in the SUN-101 25 mcg and 50 mcg female subgroup. Due to clinically insignificant responses within and between the male and female subgroups, the gender subgroup results do not support an alternative dosing recommendation to either the SUN-101 25 mcg or 50 mcg doses.
2. There was no statistically significant treatment-by-age group interaction effect (p-value of 0.5122).
3. There was no statistically significant treatment-by-race interaction effect (p-value of 0.1235).

Table 17 summarizes the results of Study 301 on the secondary endpoint change from baseline of trough FVC at Week 12. The analysis population is based on all data collected on the ITT population:

1. There was a treatment-by-gender interaction effect (p-value of 0.0984). Treatment with both doses of SUN-101 demonstrated improvements in trough FVC in the male and female subgroups at Week 12. The mean, placebo-adjusted trough FVC increased by 0.114 L and 0.163 L in the SUN-101 25 mcg and 50 mcg male subgroups. The mean, placebo adjusted trough FVC increased by 0.154 L and 0.096 L in the SUN-101 25 mcg and 50 mcg female subgroups. Due to clinically insignificant responses within and between the male and female subgroups, gender subgroup results do not support an alternative dosing recommendation to either the SUN-101 25 mcg or 50 mcg doses.
2. There was no treatment-by-age group interaction effect (p-value of 0.4477).
3. There was a treatment-by-race interaction effect (p-value of 0.0851). White subjects in the SUN-101 25 mcg group had a greater treatment effect relative to placebo than white subjects in the SUN-101 50 mcg group (0.149 L and 0.135 L). Conversely, nonwhite subjects in the SUN-101 25 mcg group had a lesser treatment effect relative to placebo than nonwhite subjects in the SUN-101 50 mcg group (-0.0011 L and 0.1173 L).

Table 20 summarizes the results of study 302 on the primary endpoint change from baseline of trough FEV_1 at Week 12. The analyses are based on all collected data for the ITT population:

1. There was no treatment-by-gender interaction effect (p-value of 0.7329).
2. There was no treatment-by-age group interaction effect (p-value of 0.7617).

3. There was no treatment-by-race interaction effect (p-value of 0.2279).

Table 21 summarizes the results of study 302 on the secondary endpoint change from baseline of trough FVC at Week 12. The analyses are based on is all collected data for the ITT population:

1. There were no treatment-by-gender interaction effects with interaction p-value of 0.4199.
2. There were no treatment-by-age group interaction effects with interaction p-value of 0.3291.
3. There were no treatment-by-race interaction effects with interaction p-value of 0.1174.

4.2 Baseline Disease Characteristics

Subgroup analyses were performed on in-check PIFR, spirometry peak inspiratory flow rate (PIFR), background LABA use, and baseline COPD severity on the primary endpoint. Subgroup analyses were performed on baseline COPD severity on the key secondary endpoints.

Table 15 summarizes the results of study 301 on the primary endpoint change from baseline of trough FEV_1 at Week 12. The analyses are based on all collected data for the ITT population:

1. There was no treatment-by-in-Check PIFR interaction effect (p-value of 0.6007).
2. There was a treatment-by-spirometry PIFR interaction effect (p-value of 0.0422). Generally, the mean effects are consistent within each treatment group across the various categories, with the exception that the SUN-101 25 mcg group had an apparently spurious low mean of -0.048 L in the > 150 to 180 L/min category compared to a range of 0.063 to 0.1327 for the other categories, and that the SUN-101 50 mcg group had an apparently spurious high mean of 0.260 L in the > 180 to 210 L/min category compared to a range of 0.057 to 0.121 for the other categories.
3. There was no treatment-by-background LABA interaction (p-value of 0.8372).
4. There was no treatment-by-COPD severity interaction effect (p-value of 0.3378). Treatment with both doses of SUN-101 showed improvements across different COPD severity categories.

Table 17 summarizes the results of study 301 on the secondary endpoint change from baseline of trough FVC at Week 12. The analyses are based on all collected data for the ITT population. There was no treatment-by-COPD severity interaction effect with interaction p-value of 0.7205.

Table 20 summarizes the results of study 302 on the primary endpoint change from baseline of trough FEV1 at Week 12. The analyses are based on all collected data for the ITT population:

1. There was no treatment-by-In-Check PIFR interaction effect (p-value of 0.3375).
2. There was no treatment-by-spirometry PIFR interaction effect (p-value of 0.5885).
3. There was no treatment-by-background LABA interaction (p-value of 0.7733).
4. There was no treatment-by-COPD severity interaction effect (p-value of 0.1440).

Table 21 summarizes the results of study 302 on the secondary endpoint change from baseline of trough FVC at Week 12. The analyses are based on all collected data for the ITT population. There was no treatment-by-COPD severity interaction effect (p-value of 0.2573).

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There were no statistical issues with this submission.

5.1.1 Missing Data and Sensitivity Analysis

5.1.1.1 Tipping Point Analysis for the Primary Endpoint

The primary endpoint in studies SUN101-301 and SUN101-302 is the change from baseline in trough FEV_1 at Week 12 for the ITT population. The primary analysis used all collected data, including data for patients who discontinued randomized treatment and were followed for 12 weeks. The tipping point analysis seeks to impute the remaining missing data under various scenarios.

Tipping point analysis is a means of exploring the influence of missingness on the overall conclusion by positing a wide spectrum of assumptions regarding the missingness mechanism. The analysis finds a "tipping" point in this spectrum of assumptions, at which conclusions change from being favorable to the experimental treatment to being unfavorable. After such a tipping point is determined, clinical judgement is applied as to the plausibility of the assumptions underlying this tipping point. In this submission, the sponsor submitted tipping point analysis results using delta-adjusted pattern imputation assuming missing-not-at-random (MNAR).

Under this method, subjects from the experimental or control treatment arm who discontinue at a given time-point would have, on average, their unobserved efficacy values worsen by some amount δ compared to the observed efficacy value. This method allows the assumptions about missingness on the experimental SUN-101 treatment and placebo arms to vary independently.

The amount of missing data in the two pivotal studies is relatively small. The number of subjects who were not followed for the full 12 weeks is shown in Table 20.

Table 20: Missing Data in Studies SUN101-301 and SUN101-302

	Placebo	SUN-101 25 mcg	SUN-101 50 mcg
Study SUN101-301	27 (12.4%)	14 (6.5%)	17 (7.8%)
Study SUN101-302	24 (11.3%)	21 (9.8%)	15 (7.0%)

The process for implementing the tipping point analysis in this submission includes:

1. Impute the missing values due to non-monotone reasons first. Missing baseline data is imputed using a monotone regression on 100 imputations with a model that includes gender, stratification of LABA use, stratification of cardiovascular risk, and age. Intermittent missing FEV_1 values are imputed for each treatment using non-missing data from all subjects within the treatment group by a Markov Chain Monte Carlo (MCMC)

imputation model. As a result, each dataset only has a monotone missing data pattern.

2. The missing values in a monotonic pattern are then imputed using PROC MI to impute the monotonic missing FEV_1 values within each treatment arm at Week 2, Week 4, Week 8, and Week 12 using a monotone regression. Imputation is performed on the first missing value from left to right (i.e. Week 2, Week 4, etc.), with each subsequent imputation using the non-missing data and the previously imputed data in the calculation. One-hundred imputations are generated.

3. For a range of penalty values the δ_1 values are added to the placebo subjects' change from baseline in monotonic imputed values, and the δ_2 values are added to the SUN-101 subjects' change from baseline in monotonic imputed values. Similarly, the post-baseline monotonic imputed FEV_1 values are also delta-adjusted for data summarization. The same δ_2 value is used for both SUN-101 25 mcg and SUN-101 50 mcg. For SUN101-301, δ_1 and δ_2 are equal to 0, -0.200, -0.400, -0.600, -0.700, -0.800 L and for SUN101-302, δ_1 and δ_2 are equal to 0, -0.100, -0.200, -0.300, -0.400, -0.500 L.

4. At each level of δ_1 and δ_2, re-run the MMRM model for the primary efficacy analysis for each of the 100 imputations. The MMRM model is also run at $\delta_1 = 0$ and $\delta_2 = 0$ as the base case.

5. Use PROC MIANALYZE to combine information from each imputation.

Table 21 to Table 24 list the tipping point analyses results for the primary endpoint of study 301 and study 302 in 25 mcg arm compared to the placebo arm and 50 mcg arm compared to the placebo arm.

Table 21: Tipping Point Analysis Results – Study 301 25 mcg arm

	δ_2 = 0 L	δ_2 = -0.2 L	δ_2 = -0.4 L	δ_2 = -0.6 L	δ_2 = -0.7 L	δ_2 = -0.8 L
δ_1 = 0 L	0.0949 (0.0580, 0.1319)	0.0811 (0.0430, 0.1192)	0.0672 (0.0264, 0.1080)	0.0533 (0.0085, 0.0982)	0.0464 (-0.0009, 0.0936)	0.0394 (-0.0104, 0.0893)
δ_1 = -0.2 L	0.1169 (0.0796, 0.1543)	0.1031 (0.0646, 0.1416)	0.0892 (0.0480, 0.1304)	0.0753 (0.0302, 0.1205)	0.0684 (0.0209, 0.1160)	0.0615 (0.0113, 0.1116)
δ_1 = -0.4 L	0.1390 (0.1000, 0.1779)	0.1251 (0.0851, 0.1652)	0.1112 (0.0686, 0.1539)	0.0974 (0.0509, 0.1439)	0.0904 (0.0416, 0.1393)	0.0835 (0.0322, 0.1349)
δ_1 = -0.6 L	0.1610 (0.1193, 0.2027)	0.1471 (0.1045, 0.1898)	0.1333 (0.0882, 0.1784)	0.1194 (0.0706, 0.1682)	0.1125 (0.0615, 0.1635)	0.1055 (0.0521, 0.1589)
δ_1 = -0.7 L	0.1720 (0.1287, 0.2154)	0.1582 (0.1138, 0.2025)	0.1443 (0.0976, 0.1910)	0.1304 (0.0802, 0.1806)	0.1235 (0.0711, 0.1759)	0.1165 (0.0618, 0.1713)
δ_1 = -0.8 L	0.1830 (0.1378, 0.2282)	0.1692 (0.1230, 0.2153)	0.1553 (0.1069, 0.2037)	0.1414 (0.0896, 0.1933)	0.1345 (0.0806, 0.1884)	0.1276 (0.0713, 0.1838)

Source: Sponsor's Tipping Point Analysis Tables_301

Table 22: Tipping Point Analysis Results – Study 301 50 mcg arm

	δ_2 = 0 L	δ_2 = -0.2 L	δ_2 = -0.4 L	δ_2 = -0.6 L	δ_2 = -0.7 L	δ_2 = -0.8 L
δ_1 = 0 L	0.1022 (0.0652, 0.1392)	0.0866 (0.0485, 0.1248)	0.0710 (0.0301, 0.1119)	0.0553 (0.0104, 0.1002)	0.0475 (0.0002, 0.0947)	0.0396 (-0.0102, 0.0895)
δ_1 = -0.2 L	0.1243 (0.0869, 0.1617)	0.1088 (0.0702, 0.1473)	0.0931 (0.0519, 0.1344)	0.0774 (0.0322, 0.1227)	0.0696 (0.0220, 0.1172)	0.0618 (0.0116, 0.1120)
δ_1 = -0.4 L	0.1464 (0.1074, 0.1854)	0.1308 (0.0907, 0.1709)	0.1152 (0.0725, 0.1579)	0.0996 (0.0530, 0.1461)	0.0917 (0.0429, 0.1406)	0.0839 (0.0325, 0.1353)
δ_1 = -0.6 L	0.1684 (0.1267, 0.2101)	0.1529 (0.1102, 0.1956)	0.1373 (0.0921, 0.1824)	0.1216 (0.0728, 0.1704)	0.1138 (0.0628, 0.1648)	0.1060 (0.0526, 0.1594)
δ_1 = -0.7 L	0.1794 (0.1360, 0.2228)	0.1639 (0.1195, 0.2082)	0.1483 (0.1016, 0.1950)	0.1327 (0.0824, 0.1829)	0.1249 (0.0725, 0.1773)	0.1171 (0.0623, 0.1718)
δ_1 = -0.8 L	0.1904 (0.1452, 0.2357)	0.1749 (0.1287, 0.2211)	0.1593 (0.1109, 0.2078)	0.1437 (0.0918, 0.1956)	0.1359 (0.0820, 0.1899)	0.1281 (0.0719, 0.1843)

Source: Sponsor's Tipping Point Analysis Tables_301

Table 23: Tipping Point Analysis Results – Study 302 25 mcg arm

	δ_2 = 0 L	δ_2 = -0.1 L	δ_2 = -0.2 L	δ_2 = -0.3 L	δ_2 = -0.4 L	δ_2 = -0.5 L
δ_1 = 0 L	0.0775 (0.0378, 0.1172)	0.0672 (0.0272, 0.1072)	0.0568 (0.0161, 0.0976)	0.0465 (0.0045, 0.0885)	0.0362 (-0.0074, 0.0798)	0.0258 (-0.0197, 0.0714)
δ_1 = -0.1 L	0.0898 (0.0500, 0.1296)	0.0795 (0.0393, 0.1196)	0.0691 (0.0282, 0.1100)	0.0588 (0.0167, 0.1009)	0.0484 (0.0047, 0.0921)	0.0381 (-0.0076, 0.0838)
δ_1 = -0.2 L	0.1021 (0.0618, 0.1423)	0.0917 (0.0512, 0.1323)	0.0814 (0.0401, 0.1227)	0.0710 (0.0285, 0.1135)	0.0607 (0.0166, 0.1048)	0.0504 (0.0043, 0.0964)
δ_1 = -0.3 L	0.1143 (0.0733, 0.1553)	0.1040 (0.0627, 0.1453)	0.0936 (0.0516, 0.1357)	0.0833 (0.0401, 0.1265)	0.0730 (0.0282, 0.1178)	0.0626 (0.0159, 0.1094)
δ_1 = -0.4 L	0.1266 (0.0845, 0.1687)	0.1162 (0.0739, 0.1586)	0.1059 (0.0628, 0.1490)	0.0956 (0.0514, 0.1398)	0.0852 (0.0395, 0.1310)	0.0749 (0.0272, 0.1226)
δ_1 = -0.5L	0.1389 (0.0955, 0.1822)	0.1285 (0.0849, 0.1722)	0.1182 (0.0738, 0.1625)	0.1078 (0.0624, 0.1533)	0.0975 (0.0505, 0.1445)	0.0872 (0.0383, 0.1360)

Source: Sponsor's Tipping Point Analysis Tables_302

Table 24: Tipping Point Analysis Results – Study 302 50 mcg arm

	δ_2 = 0 L	δ_2 = -0.1 L	δ_2 = -0.2 L	δ_2 = -0.3 L	δ_2 = -0.4 L	δ_2 = -0.5 L
δ_1 = 0 L	0.0730 (0.0336, 0.1123)	0.0656 (0.0260, 0.1053)	0.0582 (0.0178, 0.0987)	0.0509 (0.0092, 0.0925)	0.0435 (0.0002, 0.0868)	0.0362 (-0.0091, 0.0814)
δ_1 = -0.1 L	0.0852 (0.0458, 0.1247)	0.0779 (0.0381, 0.1176)	0.0705 (0.0300, 0.1110)	0.0631 (0.0214, 0.1049)	0.0558 (0.0124, 0.0992)	0.0484 (0.0030, 0.0938)
δ_1 = -0.2 L	0.0975 (0.0576, 0.1374)	0.0901 (0.0499, 0.1303)	0.0828 (0.0418, 0.1237)	0.0754 (0.0332, 0.1176)	0.0680 (0.0242, 0.1118)	0.0607 (0.0149, 0.1064)
δ_1 = -0.3 L	0.1097 (0.0691, 0.1504)	0.1024 (0.0614, 0.1433)	0.0950 (0.0533, 0.1367)	0.0876 (0.0448, 0.1305)	0.0803 (0.0358, 0.1248)	0.0729 (0.0265, 0.1194)
δ_1 = -0.4 L	0.1220 (0.0803, 0.1637)	0.1146 (0.0726, 0.1566)	0.1073 (0.0645, 0.1500)	0.0999 (0.0560, 0.1438)	0.0925 (0.0471, 0.1380)	0.0852 (0.0378, 0.1326)
δ_1 = -0.5L	0.1343 (0.0912, 0.1773)	0.1269 (0.0836, 0.1702)	0.1195 (0.0755, 0.1636)	0.1122 (0.0670, 0.1573)	0.1048 (0.0581, 0.1515)	0.0974 (0.0489, 0.1460)

Source: Sponsor's Tipping Point Analysis Tables_302

The tipping point analyses evaluated the sensitivity of the results to possible violations of MAR assumptions of the primary analyses. It tests the scenarios where the outcomes for early dropouts are worse than outcomes for patients who complete 12 weeks of follow-up; it allows the δ_2 and δ_1 to vary independently.

The results showed that:

1. For study 301, 25 mcg arm compared to placebo arm, when early dropouts in SUN-101 treated arm on average are at least 0.7 L worse than the observed follow-ups in trough FEV_1 at Week 12, while in the placebo arm the early dropouts on average have the same effects as the completers then the efficacy results will change to insignificant. The tipping point is where at least 0.7 L average worse in missing data on the treated arm than observed data.

2. For study 301, 50 mcg arm compared to placebo arm, when early dropouts in SUN-101 treated arm on average are at least 0.8 L worse than the observed follow-ups in trough FEV_1 at Week 12, while in the placebo arm the early dropouts on average have the same effects as the completers then the significant efficacy results will change to insignificant. The tipping point is where at least 0.8 L average worse in missing data on the treated arm than observed data.

3. For study 302, 25 mcg arm compare to placebo arm, when early dropouts in SUN-101 treated arm on average are at least 0.4 L worse than the observed follow-ups in trough FEV_1 at Week 12, while in the placebo arm the early dropouts on average have the same effects as the completers then the significant efficacy results will change to insignificant. The tipping point is where at least 0.4 L average worse in missing data than observed data.

4. For study 302, 50 mcg arm compare to placebo arm, when early dropouts in SUN-101 treated arm on average are at least 0.5 L worse than the observed follow-ups in trough FEV_1 at Week 12, while in the placebo arm the early dropouts on average have the same effects as the completers then the significant efficacy results will change to insignificant. The tipping point is where at least 0.5 L average worse in missing data than observed data.

In the individual pivotal studies, the LS mean FEV_1 increases from baseline compared to placebo for both the 25 and 50 mcg BID SUN-101 doses ranged from 0.074 L to 0.104 L (please refer to Table 8), therefore the tipping point scenarios to decrease 0.4 L to 0.8 L are clinically implausible. Decrease of 0.4 - 0.7 L for an individual patient was inconsistent with the efficacy results of studies 301 and 302.

5.1.1.2 SGRQ Responder Analysis at Week 12/EOT

The St. George's Respiratory Questionnaire (SGRQ) is an index to measure and quantify health-

related status in patients with chronic airflow limitation. Studies showed that SGRQ correlate well with established measures of symptom level, disease activity and disability.

The first part of SGRQ is Symptoms which evaluates symptomatology, including frequency of cough, sputum production, wheezing, breathlessness and duration and frequency of attacks of breathlessness or wheezing. The second part of SGRQ has two components: Activity and Impacts. The Activity section addresses activities that cause breathlessness or are limited because of breathlessness. The Impacts section covers a range of factors including influence on employment being in control of health, panic, stigmatization, the need for medication, side effects of prescribed therapies, expectations for health and disturbances of daily life.

Change from baseline of SGRQ score is one of the key secondary endpoints in both studies 301 and 302. Analyses of SGRQ compare to placebo showed that 25 mcg arm of study 301and both 25 mcg and 50 mcg arms of study 302 have significant improvements at the end of Week 12/EOT, however 50 mcg arm of study 301 has no significant improvement.

During the NDA review, FDA requested the applicant to conduct additional SGRQ responder analyses on both studies. The purpose of these analyses is to further examine this important endpoint from the perspective of improvement of SGRQ Responder rate.

A “responder” was defined as a patient having a change from baseline in SGRQ total score of at least 4 points in the direction of improvement (decrease), the patient is a non-responder otherwise; responder rate was computed based on total evaluable data for each arm.

A logistic regression model was used to analyze the SGRQ Responder at Week 12/EOT. The model includes factors of treatment group, cardiovascular risk, and background LABA use and with baseline SGRQ as a covariate. Odds ratio (OR) were reported.

Odds ratio of SGRQ Responder analysis is a relative measure of number of patients being a responder in SUN-101 treated group compare to the placebo group. Odds ratio is a ratio of a numerator being the odds of responder in SUN-101 treated group and denominator being the odds of responder in the placebo group. If OR >1, the SUN-101 treated group is better than the control group in terms of SGRQ responder; if OR <1, then the placebo group is better than the SUN-101 treated group in terms of SGRQ responder.

The results of SGRQ Responder analyses of study 301 are summarized in Table 25, results of study 302 are summarized in Table 26.

Table 25: Results of SGRQ Responder Analysis of Study 301

	Placebo (n = 218) n (%)	**SUN-101 25 mcg BID (n = 217) n (%)**	**SUN-101 50 mcg BID (n = 217) n (%)**
# of subjects with evaluable data	179	189	179
Responder	71 (39.7)	94 (49.7)	79 (44.1)
Non-responder	108 (60.3)	95 (50.3)	100 (55.9)
Odds Ratio (95% CI)		1.486 (0.974, 2.267)	1.215 (0.791, 1.866)

Table 26: Results of SGRQ Responder Analysis of Study 302

	Placebo (n = 212) n (%)	**SUN-101 25 mcg BID (n = 217) n (%)**	**SUN-101 50 mcg BID (n = 217) n (%)**
# of subjects with evaluable data	186	183	188
Responder	55 (29.6)	80 (43.7)	74 (39.4)
Non-responder	131 (70.4)	103 (56.3)	114 (60.6)
Odds Ratio (95% CI)		1.906 (1.220, 2.976)	1.538 (0.985, 2.401)

The SGRQ Responder analysis results showed that all the results are in the direction to favor the SUN-101 treated groups in both studies and both dose levels. However, a logistic regression model analyses showed that they are not statistically significant in terms of odds ratio except for 25 mcg group pf study 302.

5.1.2 Subgroup Analysis

Studies 301 and 302 were not powered for subgroup analyses. Some of the subgroups have small sample sizes and result in wide confidence interval. Such subgroups are non-white, age >= 75, and some baseline disease subgroups.

5.2 Collective Evidence

As summarized in Table 27, effectiveness of two different dosages was examined: SUN-101 25 mcg BID and SUN-101 50 mcg BID. The review focused on two phase 3 studies. Statistically significant and reliable (despite small number of missing data) demonstration of efficacy of SUN-101 over placebo was achieved in change from baseline of FEV_1 at Week 12. Statistically significant demonstration of efficacy of SUN-101 over placebo was achieved in change from baseline of FVC at Week 12. However, no statistically significant benefits of SUN-101 over

placebo were identified for other key secondary efficacy endpoints, change from baseline of SGRQ total score at Week 12 and change from baseline of rescue medication puffs per day over the double-blind period.

Table 27: Summary of the Key Efficacy Test Results

	Study 301		Study 302	
Endpoints	**25 mcg vs. Placebo**	**50 mcg vs. Placebo**	**25 mcg vs. Placebo**	**50 mcg vs. Placebo**
FEV_1	✓	✓	✓	✓
FEV_1 $AUC_{(0-12)}$	×	✓		
FVC	✓	✓	✓	✓
SGRQ	✓	×	✓	✓
RES	×	×	×	×

5.3 Conclusions and Recommendations

Sunovion Respiratory Development Inc. has proposed SUN-101 25 mcg twice daily (BID) for treating patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema.

Effectiveness and safety of two different dosages of SUN-101 were examined with this submission: SUN-101 25 mcg BID and SUN-101 50 mcg BID. The review focused on two phase 3 studies to investigate the efficacy of SUN-101 in terms of change from baseline of FEV_1 at Week 12.

The contribution of SUN-101 over placebo for all major endpoints was directly examined. In support of the efficacy of SUN-101, patients with or without background LABA and ICS therapies or patients with severe disease showed statistically greater improvement in pre-defined change from baseline of FEV_1 at Week 12 and change from baseline of FVC at Week 12. However, statistical significance was not reached in the clinical endpoint of change from baseline of SGRQ total score and change from baseline of rescue medication puffs per Day.

Impact of missing data on the primary efficacy results were assessed using tipping point analyses assuming missing not at random. The tipping point analyses results support the primary efficacy results.

Subgroup analyses were conducted to investigate the level of consistency or heterogeneity of the treatment effect across subgroups of interest, including demographic factors age, sex, race, and baseline disease characteristics including in-check PIFR, spirometry PIFR, background LABA use, and baseline COPD severity. Almost all the subgroups have results consistent results with the overall data results except that the subgroup effects have wider confidence interval in general due to smaller sample sizes.

This submission supports effectiveness of SUN-101 25 mcg BID for the treatment of patients with COPD in terms of change from baseline of FEV_1 at Week 12 and change from baseline of FVC at Week 12. However, there were no statistically significant benefits of change from baseline of SGRQ total score at Week 12 or change from baseline of rescue medication puffs per day during the double-blind treatment period.

APPENDICES

Table 28: Study 301: Subgroup Analyses on Secondary Endpoint of Change from Baseline of SGRQ Total Score at week 12

	Mean Difference of SGRQ 25 mcg					Mean Difference of SGRQ 50 mcg					Interaction
	N	Est.	LL	UL	p-value	N	Est.	LL	UL	p-value	Test p-value
----Age Group----	.	.	.	.	.	.	.	.	.	.	0.8124
< 65	116	-3.552	-6.567	-0.537	0.0210	125	-1.416	-4.406	1.574	0.3526	.
65 - 74	70	-2.593	-6.167	0.981	0.1547	61	-2.074	-5.803	1.656	0.2752	.
>= 75	20	-5.178	-12.795	2.438	0.1823	15	0.749	-7.344	8.841	0.8559	.
----Sex----	.	.	.	.		.	.	.	.	.	0.5025
F	94	-2.543	-5.740	0.654	0.1188	90	-0.166	-3.391	3.059	0.9195	.
M	112	-4.278	-7.307	-1.248	0.0057	111	-2.777	-5.842	0.288	0.0757	.
----Race----	.	.	.	.		.	.	.	.	.	0.6799
White	189	-3.708	-6.018	-1.398	0.0017	183	-1.753	-4.095	0.589	0.1421	.
Non-white	17	-0.497	-7.826	6.833	0.8941	18	1.686	-6.400	7.722	0.8493	.
----COPD Severity----	.	.	.	.	.	.	.	.	.	.	0.0662
<30% Predicated	11	-12.205	-21.636	-2.774	0.0113	15	1.972	-6.979	10.923	0.6654	.
>= 30% to 50% Predicated	80	-2.623	-6.256	1.010	0.1567	77	-2.346	-6.006	1.314	0.2086	.
>= 50% Predicted	114	-2.906	-5.773	-0.040	0.0469	109	-1.227	-4.160	1.707	0.4118	.

Table 29: Study 301: Subgroup Analyses on Secondary Endpoint of Change from Baseline of Rescue Medication Puffs per Day Over the Double-blind Period

	Mean Difference of RESC 25 mcg					Mean Difference of RESC 50 mcg					Interaction
	N	Est.	LL	UL	p-value	N	Est.	LL	UL	p-value	Test p-value
----Age Group----	.	.	.	.	.	.	.	.	.	.	0.3710
< 65	110	-0.010	-0.467	0.446	0.9640	126	-0.425	-0.868	0.017	0.0596	.
65 - 74	66	0.055	-0.497	0.607	0.8451	63	0.055	-0.499	0.609	0.8450	.
>= 75	21	0.157	-0.961	1.275	0.7834	17	0.600	-0.572	1.771	0.3150	.
----Sex----	.	.	.	.		.	.	.	.	.	0.3342
F	91	-0.233	-0.717	0.251	0.3455	94	-0.379	-0.854	0.096	0.1179	.
M	106	0.247	-0.216	0.709	0.2952	112	-0.007	-0.464	0.450	0.9761	.
----Race----	.	.	.	.		.	.	.	.	.	0.5436
White	182	-0.011	-0.360	0.338	0.9507	189	-0.238	-0.583	0.106	0.1751	.
Non-white	15	0.396	-0.759	1.552	0.5008	17	0.414	-0.709	1.538	0.4690	.
----COPD Severity----	.	.	.	.	.	.	.	.	.	.	0.6836
<30% Predicated	11	-0.588	-2.024	0.848	0.4215	15	0.134	-1.208	1.476	0.8445	.
>= 30% to 50% Predicated	77	0.106	-0.438	0.650	0.7029	77	-0.250	-0.793	0.293	0.367	.
>= 50% Predicted	108	0.016	-0.424	0.456	0.9442	114	-0.217	-0.650	0.216	0.3247	.

Table 30: Study 302: Subgroup Analyses on Secondary Endpoint of Change from Baseline of SGRQ Total Score at Week 12

	Mean Difference of RESC 25 mcg					Mean Difference of RESC 50 mcg					Interaction Test p-value
	N	Est.	LL	UL	p-value	N	Est.	LL	UL	p-value	
----Age Group----	.	.	.	.	.	.	.	.	.	.	0.7430
< 65	103	-2.973	-5.981	0.035	0.0527	117	-3.043	-5.967	-0.120	0.0414	.
65 - 74	75	-3.105	-6.700	0.489	0.0903	70	-5.396	-9.034	-1.758	0.0037	.
>= 75	23	-3.279	-9.632	3.074	0.3112	21	-1.531	-8.003	4.942	0.6424	.
----Sex----	.	.	.	.		.	.	.	.	.	0.4171
F	85	-4.201	-7.569	-0.834	0.0146	85	-5.401	-8.785	-2.017	0.0018	.
M	116	-2.250	-5.072	0.572	0.1179	123	-2.502	-5.283	0.279	0.0777	.
----Race----	.	.	.	.		.	.	.	.	.	0.1382
White	176	-3.478	-5.779	-1.176	0.0031	182	-4.456	-6.733	-2.180	0.0001	.
Non-white	25	0.254	-6.157	6.666	0.9379	26	2.505	-3.968	8.978	0.4475	.
----COPD Severity----	.	.	.	.	.	.	.	.	.	.	0.9644
<30% Predicated	14	-2.557	-11.211	6.098	0.5620	19	-3.257	-11.261	4.747	0.4245	.
>= 30% to 50% Predicated	67	-2.377	-6.069	1.315	0.2065	74	-4.161	-7.763	-0.559	0.0236	.
>= 50% Predicted	120	-3.549	-6.361	-0.736	0.0135	115	-3.581	-6.437	-0.724	0.0141	.

Table 31: Study 302: Subgroup Analyses on Secondary Endpoint of Change from Baseline of Rescue Medication Puffs per Day Over the Double-blind Period

Subgroup RESC	Mean Difference of RESC 25 mcg					Mean Difference of RESC 50 mcg					Interaction Test p-value
	N	Est.	LL	UL	p-value	N	Est.	LL	UL	p-value	
----Age Group----	.	.	.	.	.	.	.	.	.	.	0.2243
< 65	97	-0.484	-0.968	0.000	0.0501	108	-0.350	-0.820	0.119	0.1432	.
65 - 74	75	-0.045	-0.631	0.541	0.8801	67	-0.213	-0.814	0.388	0.4867	.
>= 75	23	0.160	-0.868	1.188	0.7605	19	0.895	-0.178	1.968	0.1019	.
----Sex----	.	.	.	.		.	.	.	.	.	0.8651
F	83	-0.330	-0.871	0.210	0.2300	79	-0.109	-0.655	0.438	0.6968	.
M	112	-0.246	-0.712	0.220	0.3004	115	-0.218	-0.680	0.244	0.3546	.
----Race----	.	.	.	.		.	.	.	.	.	0.3718
White	167	-0.242	-0.617	0.132	0.2044	169	-0.217	-0.590	0.156	0.2533	.
Non-white	28	-0.762	-1.832	0.307	0.1622	25	-0.036	-1.127	1.055	0.9486	.
----COPD Severity----	.	.	.	.	.	.	.	.	.	.	0.8646
<30% Predicated	16	0.316	-0.952	1.583	0.6249	15	-0.009	-1.280	1.263	0.9895	.
>= 30% to 50% Predicated	69	-0.328	-0.911	0.254	0.2691	66	-0.083	-0.670	0.505	0.7822	.
>= 50% Predicted	110	-0.355	-0.812	0.102	0.1280	113	-0.244	-0.698	0.211	0.2931	.

Figure 15: Study 301 25 mcg Arm: Subgroup Analyses on Secondary Endpoint of Change from Baseline of SGRQ Total Score at week 12

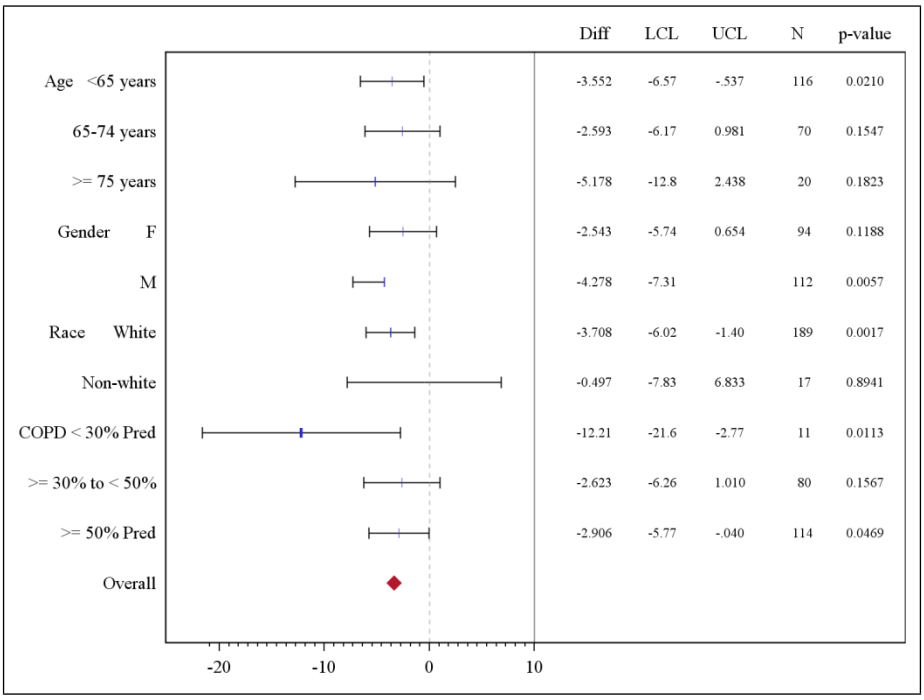


Figure 16: Study 301 50 mcg Arm: Subgroup Analyses on Secondary Endpoint of Change from Baseline of SGRQ Total Score at week 12

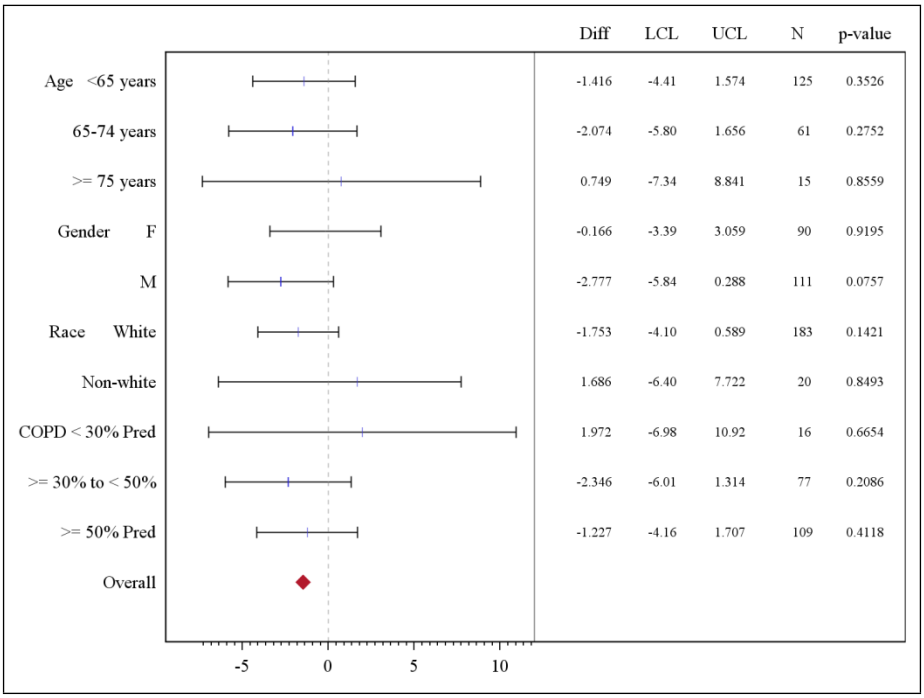


Figure 17: Study 301 25 mcg Arm: Subgroup Analyses on Secondary Endpoint of Change from Baseline of Rescue Medication Puffs per Day Over the Double-blind Period

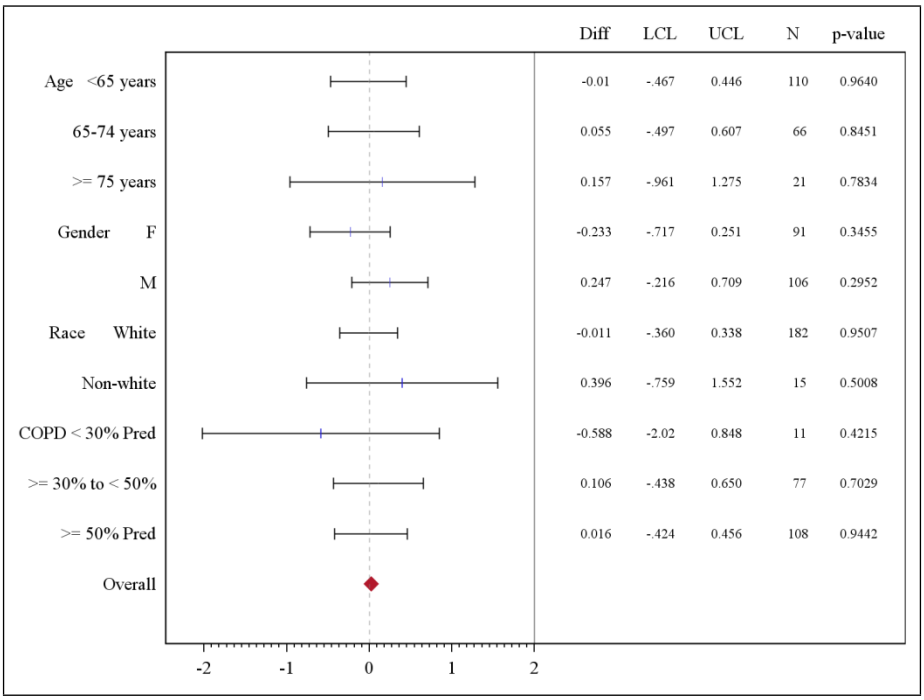


Figure 18: Study 301 50 mcg Arm: Subgroup Analyses on Secondary Endpoint of Change from Baseline of Rescue Medication Puffs per Day Over the Double-blind Period

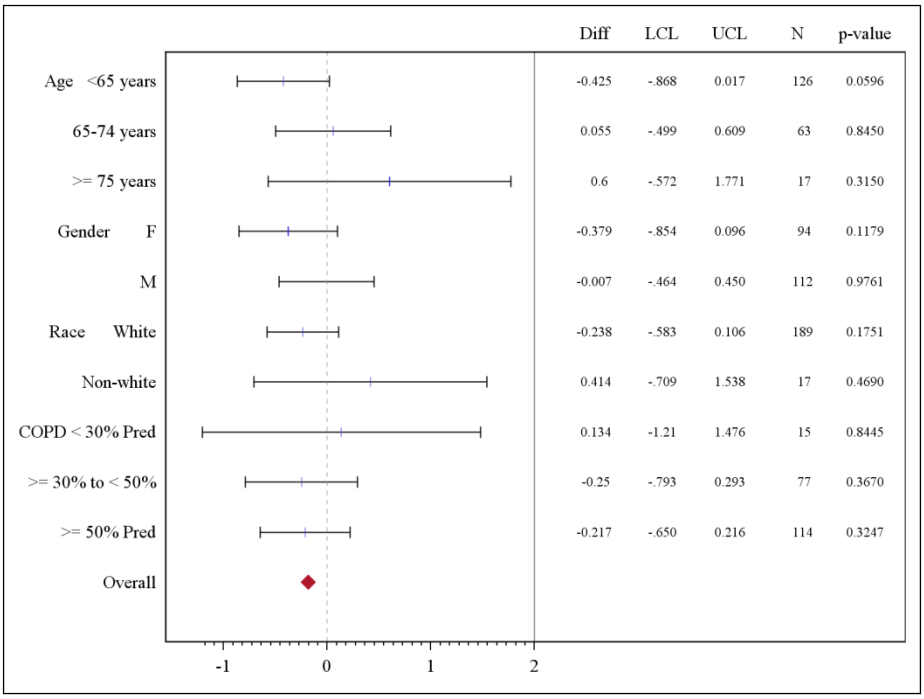


Figure 19: Study 302 25 mcg Arm: Subgroup Analyses on Secondary Endpoint of Change from Baseline of SGRQ Total Score at Week 12

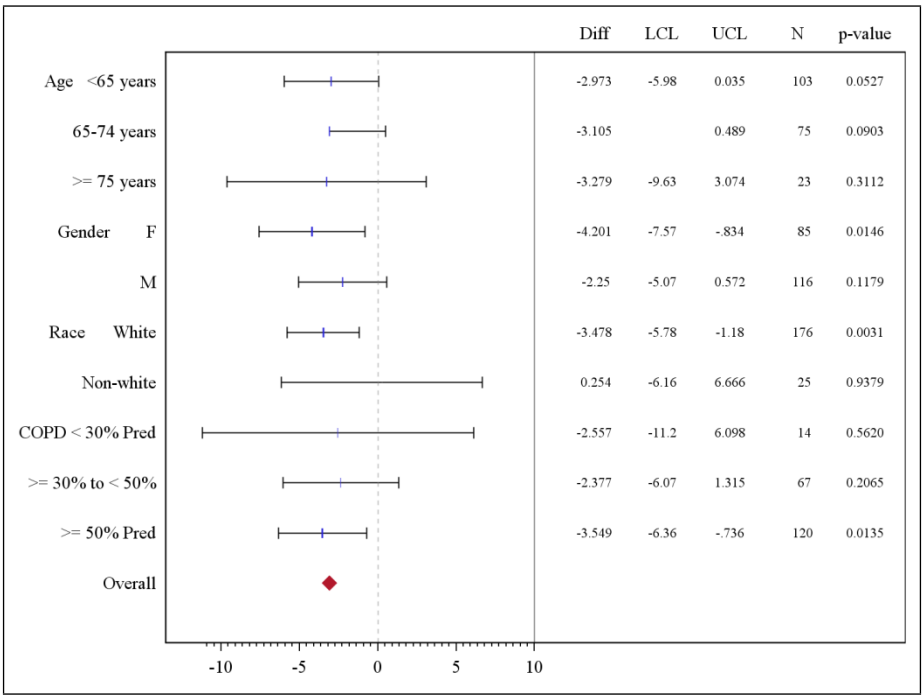


Figure 20: Study 302 50 mcg Arm: Subgroup Analyses on Secondary Endpoint of Change from Baseline of SGRQ Total Score at Week 12

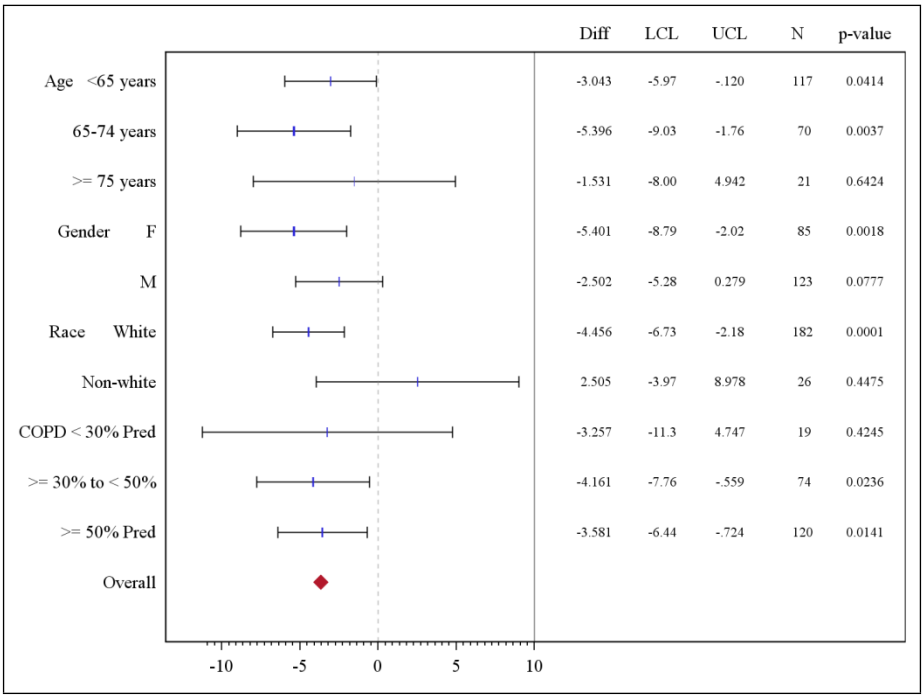


Figure 21: Study 302 25 mcg Arm: Subgroup Analyses on Secondary Endpoint of Change from Baseline of Rescue Medication Puffs per Day Over the Double-blind Period

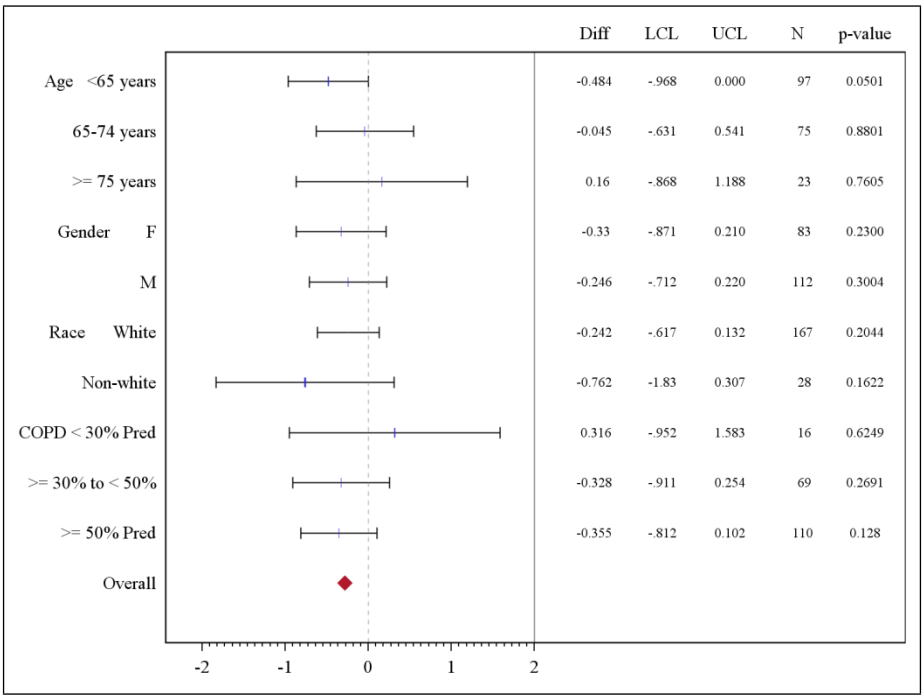
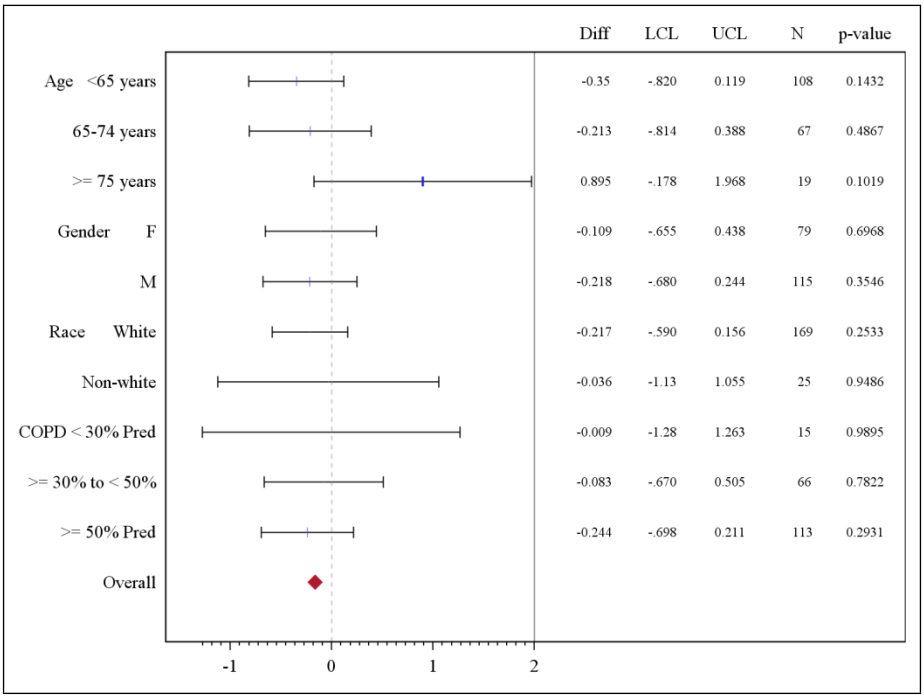


Figure 22: Study 302 50 mcg Arm: Subgroup Analyses on Secondary Endpoint of Change from Baseline of Rescue Medication Puffs per Day Over the Double-blind Period



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