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 Science
Office of Biostatistics

Statistical Review

CLINICAL STUDIES

NDA / Sequence Number:	NDA 208294 / Seq 0000
Drug Name:	Bevespi Aerosphere (glycopyrrolate/formoterol fumarate)
Proposed Indication:	COPD
Applicant:	(b) (4)
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Keywords: NDA review, Clinical Studies

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1 EXECUTIVE SUMMARY

Two randomized, placebo-controlled, double-blinded, parallel arm studies demonstrate that, compared to placebo, Bevespi Aerosphere, a combination of 9 mcg glycopyrrolate and 4.8 mcg of formoterol fumarate administered in two inhalations twice daily, reduces airway obstruction in patients with moderate to severe COPD, as measured by an increase in trough FEV_1 from baseline at week 24, and by peak FEV_1 within two hours of treatment administration. The trials further demonstrate that each component of Bevespi Aerosphere contributes to the reduction in airway obstruction, with the combination product providing greater improvements than placebo or either of its mono-components for increase in trough FEV_1 from baseline and peak improvement in FEV_1.

In one of the studies, compared to placebo, Bevespi Aerosphere significantly improved percent of patients who showed positive responses measured by St George's Respiratory Questionnaire (SGRQ) at week 24. In the other study, numerical improvements compared to placebo were observed but were not statistically significant.

2 INTRODUCTION

2.1 Overview

2.1.1 Drug Class and Indication

Bevespi Aerosphere, a combination of glycopyrrolate, an anticholinergic, and formoterol fumarate, a long-acting β_2 agonist (LABA), is proposed for the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD).

2.1.2 History of Drug Development

Submissions regarding this inhaled combination of glycopyrrolate and formoterol for treatment of COPD were initiated on January 1, 2010. In the pre-IND meeting minutes dated April 12, 2010, the Division noted that further dose response characterizations were needed for both glycopyrrolate and formoterol fumarate before they could be combined into a single combination drug.

In a type-B meeting minutes dated May 27, 2011, the Division concurred with the sponsor's finding that the bioavailability of both glycopyrrolate and formoterol fumarate were reduced when administered in a fixed combination. The sponsor responded that such reductions would not obscure interpretations of the combination rule. The Division also noted that, in fixed combination products, each of the corresponding single-ingredient products should be completely characterized and show substantial evidence of efficacy. Adequacy of planned dose ranging studies continued to be an issue.

In a written response to the sponsor dated April 19, 2012, the Division agreed that it would be appropriate to carry a formoterol dose of 9.6 mcg two times daily (F) into upcoming phase 3 trials, both as a monotherapy and as a component of the planned glycopyrrolate/formoterol combination product. The Division also agreed that 18 mcg of glycopyrrolate or less would be appropriate for further dose ranging, and underscored the need to use the same administration device for administering monotherapy and combination products during safety and confirmatory efficacy trials.

(b) (4)

On January 17, 2013, the Division communicated to the sponsor that 18 mcg glycopyrrolate BID (G) was an acceptable dose for planned phase 3 studies, and that while the designs of planned phase 3 studies PT003006 and Study PT003007 (studies 6 and 7) were generally acceptable, advantages of the combination product over the component monotherapies should be evaluated using the same primary endpoint. Further, the Division recommended that the sponsor: (i) develop clear plans regarding missing data in the context of proposed mixed model repeated measures analyses, (ii) evaluate the primary endpoint at the 24-week landmark (b) (4) and (iii) avoid re-enrolling patients from phase 2 trials into the phase 3 trials.

In pre-NDA meeting minutes dated July 1, 2014, the Division reiterated the need for a primary landmark analysis of trough FEV_1 at 24 weeks. The Division further stated that cumulative responder analyses would be needed to evaluate the impact of missing data on treatment efficacy.

2.2 Data Sources

Data Sources for the current review are located at

\\cdsesub1\evsprod\NDA208294\0000\m5\datasets.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Datasets, programs, and documentation provided by the applicant were adequate to evaluate the proposed claims. Results from review analyses generally matched those in the submission.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The present submission provides results from replicate randomized, placebo-controlled, double-blind, parallel-arm trials PT003006 and PT003007 (studies 6 and 7), which were designed to evaluate the effects on COPD of the combination drug 18 mcg glycopyrrolate plus formoterol 9.6 mcg two times daily (GF) compared to placebo (Pbo) and to its component monotherapies. Subjects with COPD were randomized in a 7:6:6:6:3 ratio to GF, F, G, open-label Spiriva (OLS), or Pbo, stratified by ventolin reversibility (≥12% and ≥200 mL vs. otherwise), disease severity (moderate vs. severe or very severe), and participation in a 12-hour pulmonary function test substudy (yes, no). The primary endpoint was change of trough FEV_1 from baseline (Δ trough FEV_1) after 24 weeks of treatment administration (W24), with secondary endpoints Δ trough FEV_1 over 24 weeks (24W), peak Δ FEV_1 within 2 hours of treatment administration at W24, change from baseline St George's Respiratory Questionnaire (Δ SGRQ) at W24, change from baseline rescue medication (Δ rescue medication) over 24W, and time to onset of action on day 1 (D1).

Table 1. Trial Designs

Study[1]	**Design**	**Population**	**Endpoints**
PT003006	GF	COPD	*Primary:*
(Study 6)	F	Age ≥ 40 yr and ≤ 80 yr	Δ Trough FEV_1 at W24
(Trial 1)	G	Smoking ≥ 10 pack yr	
	Pbo	Post bronc FEV_1 < 80% pred	*Secondary:*
PT003007	OLS (study 6)	FEV_1/FVC ≤ 70%	Δ Trough FEV_1 over 24W
(Study 7)			Peak Δ FEV_1 at W24
(Trial 2)	PA	N 1650 7:6:6:3:6 (study 6)	Δ SGRQ at W24
	DB	1614 7:6:6:3 (study 7)	Δ rescue medication over 24W
			Time to onset of action D1
	Pbo to W24	strat: ventolin reversibility	
		disease severity	
		12hr PFT sub-study	

Source: Reviewer

[1]Trial numbers in parentheses cross references to label.

G two 9 mcg doses of glycopyrrolate BID, F two 4.8 mcg doses of formoterol fumarate BID, GF combination product consisting of G and F above, OLS open label Spiriva, Pbo placebo, PA parallel arm, DB double blind, W24 week 24, FEV_1 one second forced expiratory volume, FVC forced vital capacity, PFT pulmonary function tests, SGRQ St. George's Respiratory Questionnaire, D1 Day 1, TDI transition dyspnea index

3.2.2 Statistical Methodologies

Differences between treatments for mean ΔFEV_1, ΔSGRQ, and Δ number of puffs of rescue medication per day were evaluated using a mixed effect model repeated measures analysis with independent factors treatment, baseline, percent reversibility using Ventolin HFA, baseline smoking status (former smoker/current smoker), baseline inhaled corticosteroid (ICS) use (yes/no), treatment, visit, and treatment by visit interaction. Degrees of freedom were calculated using the Kenward-Rogers approximation. The covariance matrix was unstructured.

For Δ number of puffs of rescue medication per day, individual visits were replaced in the analysis model by the number of the relevant four-week interval (1 to 6) during the 24-week treatment period.

Time to onset of action for each treatment was evaluated using post-dosing assessments on day 1. Because fewer than half of the five-minute assessments were conducted within the planned window of seven minutes, the window was extended to include measurements at eight and nine minutes post-dose. Measurements obtained at ten minutes were then included in the 15-minute time window.

Missing data of the above variables were maintained as missing in the analysis datasets, unless specified otherwise. When missing data were imputed, the analysis dataset contained a new variable with the imputed value and the original variable value was maintained as missing.

The SGRQ responders were subjects improving at least 4 units from baseline at W24. Responder analyses were performed using logistic regression with independent factors treatment, baseline, percent reversibility to Ventolin HFA, baseline smoking status, and baseline ICS use. Calculated odds ratios assumed a balanced smoking status and ICS use in the population (50-50 split for each categorical variable) and arithmetic mean levels of the baseline SGRQ and reversibility to Ventolin HFA. P-values were calculated using the Wald chi-square test. For the SGRQ responder analyses, patients with missing data were classified as non-responders.

For comparisons to placebo, control of type 1 error rate in studies 6 and 7 was planned by testing the primary and first two endpoints sequentially, in the order provided in Table 1 above. The last two endpoints were tested simultaneously using the Hochberg procedure. Endpoints for glycopyrrolate were tested first, then for formoterol, and then for the combination product. After comparison to placebo, the combination product was evaluated for superiority to formoterol monotherapy and then to glycopyrrolate monotherapy.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

There were no obvious differences between treatment groups for baseline characteristics in the submitted studies (Table 2 and Table 3).

Table 2. Baseline Demographics, Study 6

Category	GF	F	G	Pbo	S
Randomized	526	449	451	219	451
Age (mean)	63	63	63	63	63
Age (< 65 years)	56%	53%	55%	58%	55%
Male (%)	55%	55%	57%	56%	60%
Race (%)					
White	483 (92%)	413 (92%)	414 (92%)	203 (93%)	402 (89%)
Black	39 (7%)	33 (7%)	31 (7%)	14 (6%)	27 (8%)
Asian	1 (0.2%)	1 (0.2%)	1 (0.2%)	0 (0%)	1 (0.2%)
Other	1 (0.2%)	2 (0.4%)	4 (0.8%)	0 (0%)	8 (1.5%)
Current Smoker	53%	54%	54%	58%	53%

Source: CSR Table 6-6

Table 3. Baseline Demographics, Study 7

Category	GF	F	G	Pbo
Randomized	510	437	439	223
Age (mean)	63	63	63	64
Age (< 65 years)	56%	57%	54%	48%
Male (%)	53%	57%	55%	56%
Race (%)				
White	458 (90%)	398 (91%)	399 (91%)	198 (88%)
Black	43 (8%)	34 (8%)	34 (8%)	24 (11%)
Asian	6 (1.2%)	1 (0.2%)	1 (0.2%)	0 (0%)
Other	3 (0.6%)	4 (0.9%)	3 (0.7%)	0 (0%)
Current Smoker	53%	58%	52%	49%

Source: CSR Table 6-6

Patterns of patient disposition did not contradict efficacy of GF, F, or G, with discontinuations of treatment due to lack of efficacy numerically higher among patients randomized to placebo than among patients randomized to GF or either of its mono-components (Table 4 and Table 5).

Table 4. Patient Disposition, Study 6

	GF N (%)	**F N (%)**	**G N (%)**	**Pbo N (%)**	**S N(%)**
Randomized	527	452	451	220	453
Completed W24	429 (81%)	370 (82%)	345 (77%)	160 (73%)	39 (86%)
Early discontinuation	98 (19%)	82 (18%)	106 (24%)	60 (27%)	62 (14%)
Adverse event	33 (6.3%)	19 (4%)	31 (6.9%)	11 (5.0%)	20 (4.4%)
Lack of efficacy	7 (1.3%)	9 (2.0%)	12 (2.7%)	9 (4.1%)	3 (0.7%)
Investigator discretion	1 (0.2%)	3 (0.7%)	5 (1.1%)	7 (3.2%)	3 (0.7%)
Protocol specified criteria	13 (2.5%)	8 (1.8%)	10 (2.2%)	7 (3.2%)	5 (1.1%)
Withdrawal of consent	19 (4%)	16 (4%)	27 (6%)	11 (5%)	13 (3%)

Source: CSR Tables 6-1 and 1.2.2

Table 5. Patient Disposition, Study 7

	GF N (%)	**F N (%)**	**G N (%)**	**Pbo N (%)**
Randomized	512	439	440	224
Completed W24	432 (84%)	346 (79%)	365 (83%)	165 (74%)
Early discontinuation	80 (16%)	93 (21%)	75 (17%)	59 (26%)
Adverse event	23 (5%)	21 (5%)	14 (3%)	19 (9%)
Lack of efficacy	4 (0.8%)	3 (0.7%)	8 (1.8%)	7 (3.1%)
Investigator discretion	2 (0.4%)	7 (1.6%)	5 (1.1%)	4 (1.8%)
Protocol specified criteria	10 (2%)	15 (3%)	15 (3%)	7 (3%)
Withdrawal of consent	20 (4%)	11 (3%)	17 (4%)	10 (5%)

Source: CSR Tables 6-1 and 1.2.2

3.2.4 Results and Conclusions

3.2.4.1 *Δ FEV_1*

The combination product, GF, and each of its component monotherapies, were superior to placebo for change from baseline trough FEV_1 (Table 6). Further, GF was superior to its component monotherapies (Table 7). Tipping point analyses support the robustness of efficacy for the primary endpoint (see Appendix 6.2).

Table 6. Δ Trough FEV_1. Comparison to Placebo, Week 24

Study	Δ FEV_1 (N)				Difference from Pbo (P-Value) (95% CI)		
	GF	G	F	Pbo	GF - Pbo	G - Pbo	F - Pbo
6	126	66	62	-24	150	91	86
	(429)	(344)	(367)	(161)	(<.0001)	(<.0001)	(<.0001)
					(114, 186)	(53, 128)	(49, 123)
7	116	63	61	13	103	49	47
	(433)	(367)	(350)	(170)	(<.0001)	(.01)	(.01)
					(67, 140)	(12, 87)	(10, 85)

Source: Table 7-7 CSR Study 6, Table 7-4 CSR Study 7, reviewer program FEV1SGRQ 2015 07 24.sas

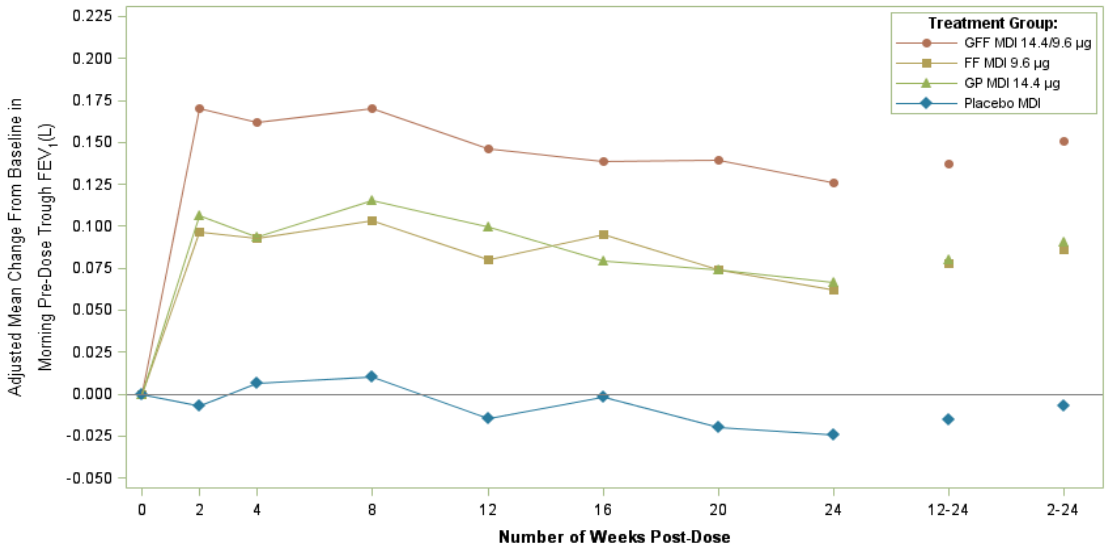
Table 7. Δ Trough FEV_1, Combination versus Monotherapies, Week 24

Study	Δ FEV_1 (N)			Difference from Mono (P-Value) (95% CI)	
	GF	G	F	GF - G	GF - F
6	126	66	62	59	64
	(429)	(344)	(367)	(<.0001)	(<.0001)
				(31, 88)	(36, 92)
7	116	63	61	54	56
	(433)	(367)	(350)	(.0003)	(.0002)
				(25, 83)	(27, 85)

Source: Table 7-7 CSR Study 6, Table 7-4 CSR Study 7, reviewer program FEV1SGRQ 2015 07 24.sas

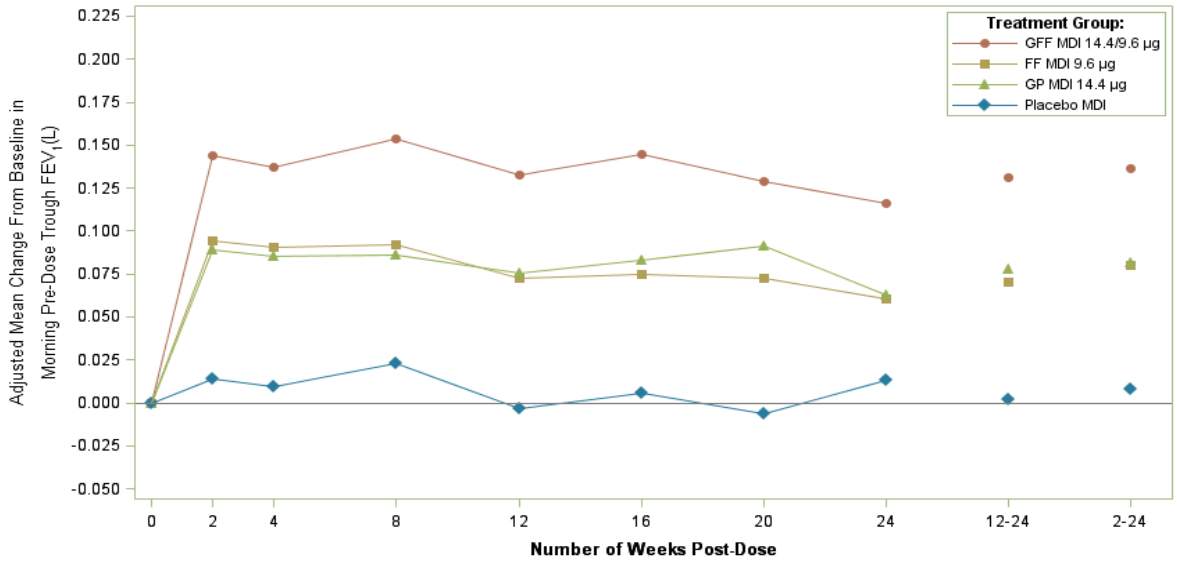
Differences between treatments in Δ trough FEV_1 appeared as early as week 2 and were maintained through week 24 in both studies (Figure 1 and Figure 2).

Figure 1. Δ Trough FEV_1 From Baseline to Week 24, Study 6



Source: Table 7-7 Figure 7-1 CSR Study 6, Figure CSR Study 7, reviewer program Trough Graph Label.sas

Figure 2. Δ Trough FEV_1 From Baseline to Week 24, Study 7



Source: Table 7-7 Figure 7-1 CSR Study 7, reviewer program Trough Graph Label.sas

3.2.4.2 Peak Δ FEV_1

The combination product GF as well as each of its component monotherapies were superior to placebo for peak change from baseline trough FEV_1(Table 8). Further, GF was superior to its component monotherapies (Table 9).

Table 8. Peak Δ FEV_1 Within Two Hours Post Dose. Comparison to Placebo, Week 24

Study	Peak Δ FEV_1 (N)				Difference from Pbo (P-Value) (95% CI)		
	GF	G	F	Pbo	GF - Pbo	G - Pbo	F - Pbo
6	356 (428)	223 (343)	263 (367)	65 (160)	291 (<.0001) (252, 331)	158 (<.0001) (117, 199)	198 (<.0001) (158, 238)
7	350 (431)	223 (365)	268 (346)	83 (165)	267 (<.0001) (226, 308)	140 (<.0001) (99, 182)	185 (<.0001) (143, 227)

Source: Table 7-16 CSR Study 6, Table 7-12 CSR Study 7, reviewer program FEV1SGRQ 2015 07 24.sas

Table 9. Peak Δ FEV_1, Combination versus Monotherapies, Week 24

Study	Peak Δ FEV_1 (N)			Difference from Mono (P-Value) (95% CI)	
	GF	G	F	GF -G	GF - F
6	356 (428)	223 (343)	263 (367)	133 (<.0001) (102, 164)	93 (<.0001) (63, 124)
7	350 (431)	223 (365)	268 (346)	126 (<.0001) (94, 159)	81 (<.0001) (49, 114)

Source: Table 7-16 CSR Study 6, Table 7-12 CSR Study 7, reviewer program FEV1SGRQ 2015 07 24.sas

3.2.4.3 Δ SGRQ

For Δ SGRQ, the combination product GF was statistically significantly superior to placebo in study 6 but not in study 7 (Table 10). For study 7, although not generally statistically significant, numerical trends were in the direction expected if the combination product is superior to placebo and its mono-components (Table 10 and Table 11).

Table 10. Δ SGRQ, Comparison to Placebo, Week 24

Study	Δ SGRQ (N)				Difference from Pbo (P-Value) (95% CI)		
	GF	G	F	Pbo	GF - Pbo	G - Pbo	F - Pbo
6	-3.3	-0.97	-2.65	-0.78	-2.52	-0.19	-1.87
	(433)	(350)	(372)	(162)	(.02)	(.9)	(.09)
					(-4.64, -0.39)	(-2.37, 2)	(-4.05, 0.3)
7	-2.97	-2.18	-2.3	-1.25	-1.72	-0.94	-1.06
	(434)	(366)	(354)	(170)	(.1)	(.4)	(.3)
					(-3.80, 0.37)	(-3.07, 1.2)	(-3.20, 1.09)

Source: Table 7-19 CSR Study 6, Table 7-15 CSR Study 7, reviewer program FEV1SGRQ 2015 07 24.sas

Table 11. Δ SGRQ, Combination versus Monotherapies, Week 24

Study	Δ SGRQ (N)			Difference from Mono (P-Value) (95% CI)	
	GF	G	F	GF -G	GF - F
6	-3.3	-0.97	-2.65	-2.33	-0.64
	(433)	(350)	(372)	(.006)	(.4)
				(-4, -0.66)	(-2.3, 1.01)
7	-2.97	-2.18	-2.3	-0.78	-0.66
	(434)	(366)	(354)	(.4)	(.4)
				(-2.43, 0.86)	(-2.32, 0.99)

Source: Table 7-19 CSR Study 6, Table 7-15 CSR Study 7, reviewer program FEV1SGRQ 2015 07 24.sas

Compared to placebo, GF provided statistically significant improvements in SGRQ response (improvement from baseline SGRQ ≥ 4) rates in study 6 but not in study 7 (Table 12). Statistically significant differences were not seen in either study between G and Pbo (Table 12), F and Pbo (Table 12), or GF and F (Table 13). In study 6, but not in study 7, patients treated with GF were significantly improved compared to patients treated with G (Table 13).

Table 12. Δ SGRQ Response, Comparison to Placebo, Week 24

Study	**% SGRQ Response (N)**				**Odds Ratio (P-Value) (95% CI)**		
	GF	**G**	**F**	**Pbo**	**GF:Pbo**	**G:Pbo**	**F:Pbo**
6	37.0 (526)	30.3 (451)	34.8 (449)	28.9 (219)	1.49 (.02) (1.05, 2.11)	1.07 (.7) (0.75, 1.54)	1.34 (.11) (0.94, 1.91)
7	39.6 (510)	34.6 (439)	33.9 (437)	33.7 (223)	1.31 (.11) (0.94, 1.84)	1.07 (.7) (0.76, 1.51)	1.02 (.9) (0.72, 1.44)

Source of odds ratio analyses: reviewer program SGRQ Resp 2016 02 11a.sas, Table 7-19 CSR Study 6, Table 7-15 CSR Study 7
Source of % response estimates reviewer program SGRQ Resp 2016 02 11a.sas, *after* Spiegelman D, and E Hertzmark. 2005. Am J Epidemiol 162:199-200

Table 13. Δ SGRQ Response, Combination versus Monotherapies, Week 24

Study	**% SGRQ Response[a.] (N)**			**Odds Ratio (P-Value) (95% CI)**	
	GF	**G**	**F**	**GF:G**	**GF:F**
6	37 (526)	30.3 (451)	34.8 (449)	1.39 (.02) (1.06, 1.82)	1.11 (.4) (0.85, 1.45)
7	39.6 (510)	34.6 (439)	33.9 (437)	1.23 (.14) (0.94, 1.61)	1.29 (.06) (0.99, 1.7)

Source of odds ratio analyses: reviewer program SGRQ Resp 2016 02 11a.sas, Table 7-19 CSR Study 6, Table 7-15 CSR Study 7
Source of % response estimates reviewer program SGRQ Resp 2016 02 11a.sas, *after* Spiegelman D, and E Hertzmark. 2005. Am J Epidemiol 162:199-200

3.2.4.4 *Δ Daily Rescue Medication*

The combination product GF as well as each of its component monotherapies were superior to placebo for peak change from mean baseline daily rescue medication (Table 14). Although numerical trends were consistent with efficacy, GF was significantly superior to its component monotherapies in study 7 but not in study 6 (Table 15).

Table 14. Δ Mean Daily Rescue Medication, Comparisons to Placebo, Over 24 Weeks

Study	Δ Number Puffs Albuterol (N)				Difference from Pbo (P-Value) (95% CI)		
	GF	G	F	Pbo	GF - Pbo	G - Pbo	F - Pbo
6	-0.77 (526)	-0.52 (451)	-0.77 (449)	0.31 (219)	-1.08 (<.0001) (-1.43, -0.74)	-0.83 (<.0001) (-1.18, -0.48)	-1.08 (<.0001) (-1.43, -0.73)
7	-1.02 (510)	-0.44 (438)	-0.73 (437)	0.03 (223)	-1.04 (<.0001) (-1.37, -0.72)	-0.47 (.005) (-0.8, -0.14)	-0.75 (<.0001) (-1.08, -0.42)

Source: Table 2.5.1 Study 6, Table 2.5.1 Study 7 reviewer program Rescue 2015 07 24.sas

Table 15. Δ Mean Daily Rescue Medication, Combination versus Monotherapies, Week 24

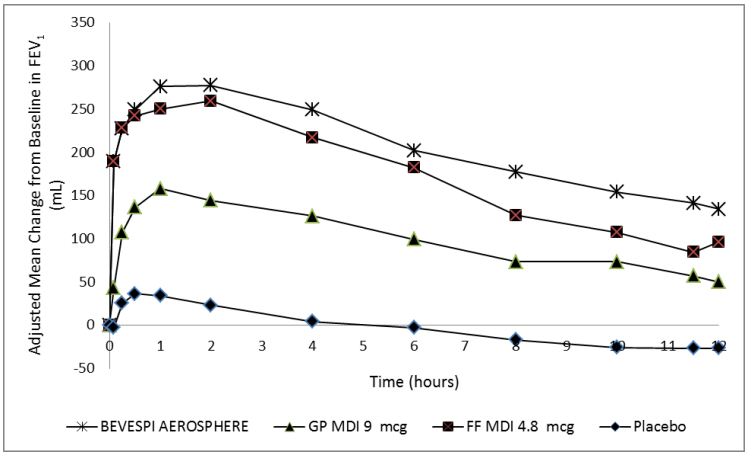
Study	Δ Number Puffs Albuterol (N)			Difference from Mono (P-Value) (95% CI)	
	GF	G	F	GF -G	GF - F
6	-0.77 (526)	-0.52 (451)	-0.77 (449)	-0.26 (.06) (-0.53, 0.01)	-0.01 (.97) (-0.27, 0.26)
7	-1.02 (510)	-0.44 (438)	-0.73 (437)	-0.57 (<.0001) (-0.83, -0.31)	-0.29 (.03) (-0.55, -0.03)

Source: Table 2.5.1 Study 6, Table 2.5.1 Study 7 reviewer program Rescue 2015 07 24.sas

Serial Spirometric Evaluations

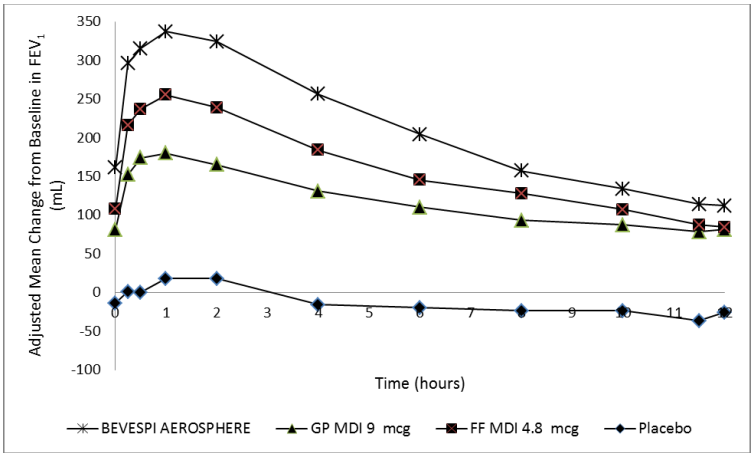
The sponsor proposed inclusion in the label of study 6 serial spirometric evaluations conducted on Day 1 and Week 12 (Figure 3 and Figure 4). As evidenced in the figures by the larger difference between GF and F during the first two hours after administration, the onset of contribution by G to the combination product seems to be more rapid at week 12 than on day 1.

Figure 3. Δ FEV_1, 12-Hour Serial Measurements, Day 1, Study 6



Source: proposed label Figure 5, Study 6 CSR, Figure 2.18.1B, reviewer program onset 2015 09 11.sas

Figure 4. Δ FEV_1, 12-Hour Serial Measurements, Week 12, Study 6



Source: proposed label Figure 5, Study 6 CSR, Figure 2.19.1B, reviewer program onset 2015 09 11.sas

Similar to study 6, a more rapid onset of contributions by G to effectiveness of the combination product was seen at week 12 than on day 1 in study 7 (Figure 5 and Figure 6). Whether more rapid onset of contributions by G later in the study is real or just due to incidental factors such as differential dropout or sheer coincidence, is further examined in Section 3.2.4.5.

Figure 5. Δ FEV_1, 12-Hour Serial Measurements, Day 1, Study 7

Source: Study 7 CSR, Figure 2.18.1B, reviewer program onset 2015 09 11.sas

Figure 6. Δ FEV_1, 12-Hour Serial Measurements, Week 12, Study 7

Source: Study 7 CSR, Figure 2.19.1B, reviewer program onset 2015 09 11.sas

3.2.4.5 Time of Onset

Compared to placebo, time to statistically significant effects was less than five minutes (0.08 hours) for the combination product GF as well as each of its component monotherapies
(

Table 16 and Table 17), with increases from trough FEV_1 within five minutes of GF administration roughly equal to 185 mL in both studies 6 and 7. Although the added benefit of G for Δ trough FEV_1 was nearly equal to that of F (Table 7), it provided only minimal increases in FEV_1 during the first two hours after treatment (Figure 3, Figure 5, Table 18, and Table 19), presumably due to slower onset of action of G compared to F in the GF combination product.

Table 16. Time of Onset Compared to Placebo, Day 1, Study 6

Hours	**Δ FEV_1**				**Difference from Pbo (P-Value) (95% CI)**		
N=	**GF (526)**	**G (450)**	**F (448)**	**Pbo (219)**	**GF - Pbo**	**G - Pbo**	**F - Pbo**
0.08	185	42	182	-2	187 (<.0001) (168, 205)	44 (<.0001) (25, 63)	184 (<.0001) (165, 203)
0.25	226	101	212	22	205 (<.0001) (185, 224)	80 (<.0001) (60, 100)	191 (<.0001) (171, 211)
0.5	249	136	224	29	219 (<.0001) (197, 241)	106 (<.0001) (84, 129)	194 (<.0001) (172, 217)
1	279	161	243	31	248 (<.0001) (224, 272)	130 (<.0001) (106, 155)	212 (<.0001) (187, 237)
2	287	164	257	28	260 (<.0001) (234, 285)	136 (<.0001) (109, 162)	229 (<.0001) (203, 255)

Source: Table 7-25 CSR Study 6, reviewer program Onset 2015 07 24.sas

Table 17. Time of Onset Compared to Placebo, Day 1, Study 7

Hours	**Δ FEV_1**				**Difference from Pbo (P-Value) (95% CI)**		
N=	**GF (510)**	**G (439)**	**F (436)**	**Pbo (223)**	**GF - Pbo**	**G - Pbo**	**F - Pbo**
0.08	192	52	175	6	186 (<.0001) (164, 207)	46 (<.0001) (24, 68)	169 (<.0001) (147, 191)
0.25	237	109	212	22	215 (<.0001) (193, 237)	88 (<.0001) (65, 110)	190 (<.0001) (168, 213)
0.5	261	140	232	31	230 (<.0001) (207, 254)	109 (<.0001) (85, 133)	201 (<.0001) (177, 225)
1	284	165	256	36	248 (<.0001) (224, 273)	130 (<.0001) (104, 155)	220 (<.0001) (195, 246)
2	302	163	263	36	267 (<.0001) (240, 294)	127 (<.0001) (100, 155)	227 (<.0001) (200, 255)

Source: reviewer program Onset 2015 07 24.sas

Table 18. Time of Onset, Combination versus Monotherapies, Day 1, Study 6

Hours	**Δ FEV_1 (N)**			**Difference from Mono (P-Value) (95% CI)**	
	GF (526)	**G (450)**	**F (448)**	**GF -G**	**GF - F**
0.08	185	42	182	143 (<.0001) (128, 158)	3 (.7) (-12, 18)
0.25	226	101	212	125 (<.0001) (109, 140)	14 (.080) (-2, 30)
0.5	249	136	224	113 (<.0001) (96, 131)	25 (.005) (7, 42)
1	279	161	243	117 (<.0001) (98, 137)	36 (.0003) (16, 55)
2	287	164	257	124 (<.0001) (104, 144)	31 (.003) (10, 51)

Source: reviewer program Onset 2015 07 24.sas

Table 19. Time of Onset, Combination versus Monotherapies, Day 1, Study 7

Hours	Δ FEV_1 (N)			Difference from Mono (P-Value) (95% CI)	
	GF (510)	G (439)	F (436)	GF -G	GF - F
0.08	192	52	175	140 (<.0001) (122, 157)	17 (.053) (0, 34)
0.25	237	109	212	128 (<.0001) (110, 146)	25 (.006) (7, 43)
0.5	261	140	232	121 (<.0001) (102, 140)	30 (.002) (10, 49)
1	284	165	256	119 (<.0001) (99, 139)	28 (.006) (8, 48)
2	302	163	263	140 (<.0001) (118, 161)	40 (.0004) (18, 62)

Source: reviewer program Onset 2015 07 24.sas

Perhaps to counter the perception that the contribution of G to the GF combination is minimal during the first two hours after administration, the applicant additionally proposed inclusion in the label of analyses conducted at week 12, which appeared to demonstrate greater contributions of G to the combination product within 2 hours of administration (Figure 4, Figure 6, Table 20, and Table 21). While it seems possible that the magnitude of the contribution by G to the combination product truly did improve after weeks of initial use, because the week 12 analyses were conducted after dropout, between day 1 and week 12, it is also possible that the apparent faster onset of action of G in the GF combination at week 12 compared to week 6 was driven by dropouts in the GF arm among patients who did not experience a benefit of GF compared to F alone.

Examination of data at week 2, in which dropout and missing data were minimal, supports the hypothesis that, during the minutes after treatment administration, the contribution of G to the GF combination increased after day 1 of the trial. With minimal dropout or missing data, the magnitude of contribution during the minutes after treatment administration by G to the GF combination at week 2 (Table 22 and Table 23) was greater than on day 1 (Table 18 and Table 19) but similar to weeks 12 (Table 20 and Table 21) and 24 (Table 24 and Table 25).

Table 20. Time of Onset, Combination versus Monotherapies, Week 12, Study 6

Hours	**Δ FEV_1 (N)**			**Difference from Mono (P-Value) (95% CI)**	
	GF (470)	**G (380)**	**F (388)**	**GF -G**	**GF - F**
0.08	255	199	121	56 (.7) (-263, 374)	134 (.2) (-105, 373)
0.25	278	166	201	112 (<.0001) (83, 142)	78 (<.0001) (48, 107)
0.5	303	188	217	116 (<.0001) (86, 145)	86 (<.0001) (56, 116)
1	326	204	236	122 (<.0001) (92, 152)	91 (<.0001) (61, 121)
2	320	191	231	129 (<.0001) (98, 161)	89 (<.0001) (58, 120)

Source: reviewer program Onset 2015 09 11.sas

Table 21. Time of Onset, Combination versus Monotherapies, Week 12, Study 7

Hours	**Δ FEV_1 (N)**			**Difference from Mono (P-Value) (95% CI)**	
	GF (461)	**G (388)**	**F (377)**	**GF -G**	**GF - F**
0.08	338	100	267	238 (.4) (-503, 979)	72 (.9) (-1036, 1179)
0.25	282	148	200	134 (<.0001) (105, 163)	82 (<.0001) (53, 112)
0.5	299	175	210	124 (<.0001) (94, 153)	89 (<.0001) (60, 119)
1	319	192	232	127 (<.0001) (97, 157)	87 (<.0001) (57, 118)
2	322	189	229	133 (<.0001) (102, 163)	93 (<.0001) (63, 124)

Source: reviewer program Onset 2015 09 11.sas

Table 22. Time of Onset, Combination versus Monotherapies, Week 2, Study 6

Hours	**Δ FEV_1 (N)**			**Difference from Mono (P-Value) (95% CI)**	
	GF (514)	**G (436)**	**F (435)**	**GF -G**	**GF - F**
0.08	308	182	231	127 (<.0001) (102, 152)	77 (<.0001) (52, 102)
0.25	325	206	243	119 (<.0001) (94, 144)	82 (<.0001) (58, 107)
0.5	355	229	265	125 (<.0001) (99, 151)	90 (<.0001) (64, 115)
1	362	219	264	143 (<.0001) (116, 170)	99 (<.0001) (72, 125)
2	308	182	231	127 (<.0001) (102, 152)	77 (<.0001) (52, 102)

Source: reviewer program Onset 2015 09 11.sas

Table 23. Time of Onset, Combination versus Monotherapies, Week 2, Study 7

Hours	**Δ FEV_1 (N)**			**Difference from Mono (P-Value) (95% CI)**	
	GF (494)	**G (425)**	**F (422)**	**GF -G**	**GF - F**
0.25	292	168	222	124 (<.0001) (99, 150)	70 (<.0001) (45, 96)
0.5	314	192	241	122 (<.0001) (96, 147)	73 (<.0001) (47, 99)
1	348	211	266	136 (<.0001) (109, 163)	81 (<.0001) (54, 108)
2	351	208	265	143 (<.0001) (115, 172)	87 (<.0001) (58, 115)

Source: reviewer program Onset 2015 09 11.sas

Table 24. Time of Onset, Combination versus Monotherapies, Week 24, Study 6

Hours	Δ FEV_1 (N)			Difference from Mono (P-Value) (95% CI)	
	GF (428)	G (343)	F (367)	GF -G	GF - F
0.25	275	133	193	142 (<.0001) (110, 174)	82 (<.0001) (51, 113)
0.5	295	159	202	137 (<.0001) (105, 168)	93 (<.0001) (62, 124)
1	314	173	226	141 (<.0001) (108, 173)	88 (<.0001) (56, 121)
2	275	133	193	142 (<.0001) (109, 175)	95 (<.0001) (62, 127)

Source: reviewer program Onset 2015 09 11.sas

Table 25. Time of Onset, Combination versus Monotherapies, Week 24, Study 7

Hours	Δ FEV_1 (N)			Difference from Mono (P-Value) (95% CI)	
	GF (431)	G (365)	F (346)	GF -G	GF - F
0.25	254	135	178	119 (<.0001) (86, 152)	75 (<.0001) (42, 109)
0.5	275	167	199	109 (<.0001) (76, 141)	76 (<.0001) (43, 109)
1	307	178	224	129 (<.0001) (96, 162)	83 (<.0001) (49, 117)
2	305	170	215	135 (<.0001) (102, 169)	90 (<.0001) (56, 125)

Source: reviewer program Onset 2015 09 11.sas

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Impacts of sex, age class, race, and country on treatment effect were evaluated by adding the subgroup to be evaluated and its interaction with treatment to the primary analysis model for Δ trough FEV_1. The interaction term was then evaluated at the unadjusted .05 level of significance.

Point estimates for the effect of GF compared to placebo for FEV_1 favored GF in all subgroups evaluated (Figure 7 and Figure 8).

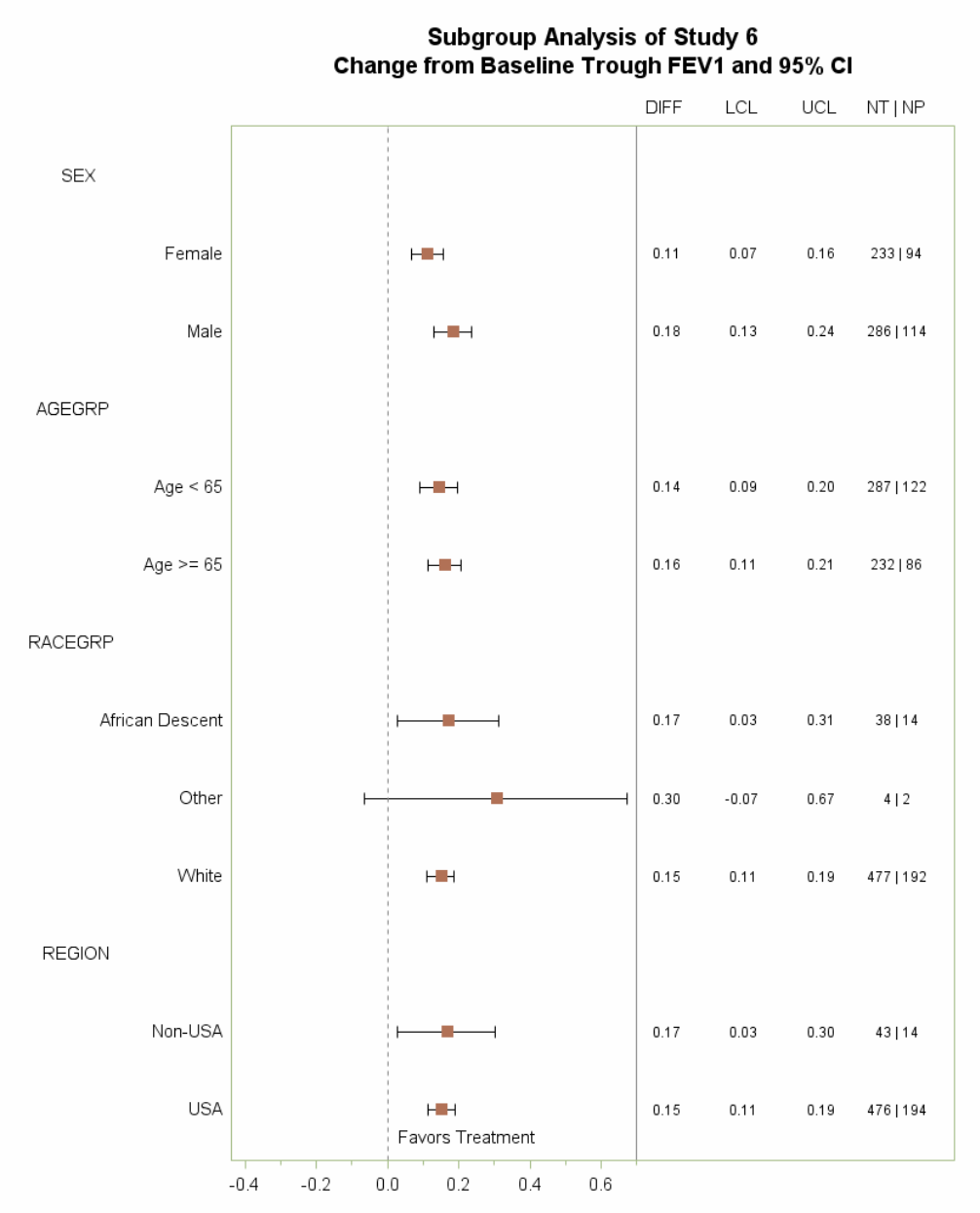
The interaction of sex and treatment was statistically significant in both studies (study 6 p=.0002, study 7 p=.04). However, the impact of sex on efficacy is of minimal concern because, in both sexes, GF, G, and F had positive effects compared to placebo, with numerical superiority of GF to mono-components G and F in both sexes (Table 26).

Table 26. Δ Trough FEV_1 by Sex. Comparison to Placebo, Week 24

Study	Sex	Δ FEV_1 (N)				Difference from Pbo (P-Value) (95% CI)		
		GF	G	F	Pbo	GF - Pbo	G - Pbo	F - Pbo
6	F	103 (188)	67 (155)	51 (165)	-8 (69)	111 (<.0001) (66, 156)	75 (.002) (28, 122)	59 (.01) (13, 106)
	M	145 (241)	65 (189)	71 (202)	-39 (92)	184 (<.0001) (130, 237)	103 (.0003) (48, 159)	109 (.0001) (54, 165)
7	F	111 (207)	45 (162)	70 (150)	20 (80)	90 (<.0001) (49, 131)	25 (.2505) (-18, 68)	50 (.02) (7, 93)
	M	122 (226)	76 (205)	53 (200)	6 (90)	116 (<.0001) (58, 174)	70 (.02) (11, 128)	47 (.12) (-12, 106)

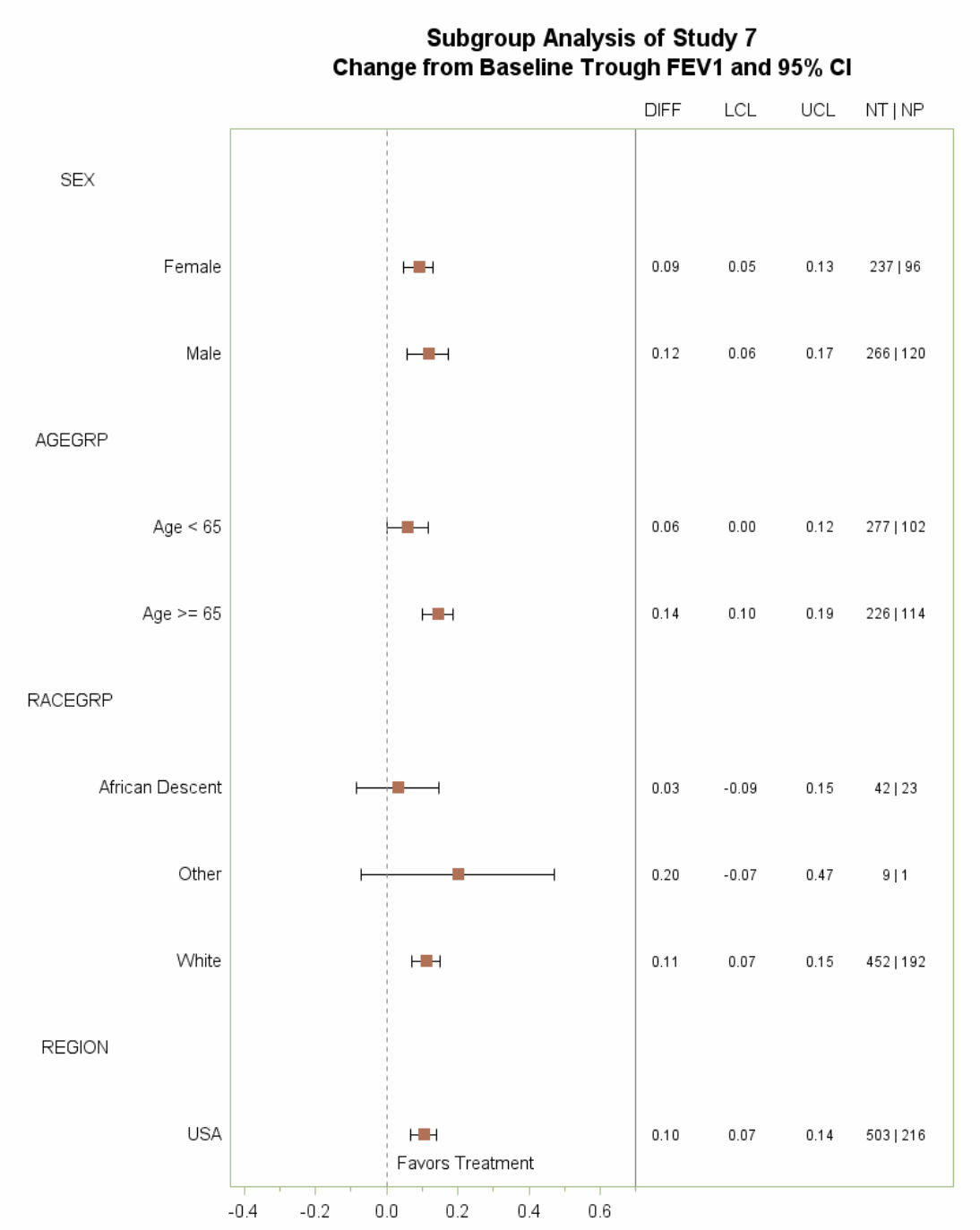
Source: reviewer program FEV1SGRQsubgr 2015 09 04.sas

Figure 7. Δ Trough FEV_1 Subgroup Analyses for GF vs Placebo, Study 6



Source: reviewer program forest plot 2015 09 23.sas

Figure 8. Δ Trough FEV_1 Subgroup Analyses for GF vs Placebo, Study 7



Source: reviewer program forest plot 2015 09 22.sas

The interaction of age class (< 65, ≥ 65 years) and treatment was statistically significant in study 6 (p = .044) but not in study 7 (p = .051). However, the impact of age class on efficacy is of minimal concern because, in both age classes, GF, G, and F had positive effects compared to placebo, with numerical superiority of GF to mono-components G and F in both age classes (Table 27).

Table 27. Δ Trough FEV_1 by Age Class. Comparison to Placebo, Week 24

Study	Age	Δ FEV_1 (N)				Difference from Pbo (P-Value) (95% CI)		
		GF	G	F	Pbo	GF - Pbo	G - Pbo	F - Pbo
6	<65	125 (230)	78 (191)	70 (188)	-18 (95)	143 (<.0001) (90, 197)	97 (.0006) (42, 152)	88 (.002) (33, 143)
	≥ 65	130 (199)	56 (153)	55 (179)	-30 (66)	160 (<.0001) (113, 207)	86 (.0005) (38, 134)	85 (.0005) (38, 133)
7	<65	113 (235)	56 (200)	76 (204)	55 (82)	59 (.0484) (0, 117)	2 (.96) (-58, 61)	21 (.5) (-38, 80)
	≥ 65	119 (198)	70 (167)	43 (146)	-24 (88)	143 (<.0001) (100, 186)	94 (<.0001) (50, 139)	66 (.004) (21, 111)

Source: reviewer program FEV1SGRQsubgr 2015 09 04.sas

The interaction of country (USA, not USA) and treatment effect was not statistically significant in study 6 (p=.5). It could not be evaluated in study 7 because all patients in that study were located in the United States.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical issues

There are no unresolved statistical issues in this submission. Several patients were found to have enrolled in both trials or multiple times in a single trial (Appendix 6.1). Results for Δ trough FEV_1, peak Δ FEV_1 within two hours post-dose, and Δ SGRQ were re-calcuated excluding all such patients, regardless of whether they were included in the sponsor's ITT population. Exclusion of all such patients did not materially affect any of the results for these variables provided in this review.

5.2 Collective Evidence

This submission clearly demonstrates that glycopyrrolate in combination with formoterol is an effective bronchodilator in patients with moderate to severe COPD.

5.3 Conclusions and Recommendations

Two randomized, placebo-controlled, double-blinded, parallel arm studies demonstrate that, compared to placebo, Bevespi Aerosphere, a combination of 9 mcg glycopyrrolate and 4.8 mcg of formoterol fumarate administered in two inhalations twice daily, reduces airway obstruction in patients with moderate to severe COPD, as measured by an increase in trough FEV_1 from baseline at week 24, and by peak FEV_1 within two hours of treatment administration. The trials further demonstrate that each component of Bevespi Aerosphere contributes to the reduction in airway obstruction, with the combination product providing greater improvements than placebo or either of its monocomponents for increase in trough FEV_1 from baseline and peak improvement in FEV_1.

In one of the studies, compared to placebo, Bevespi Aerosphere significantly improved percent of patients who showed positive responses measureed by St George's Respiratory Questionnaire (SGRQ) at week 24. In the other study, numerical improvements compared to placebo were observed but were not statistically significant..

5.4 Labeling Recommendations

Proposed product labeling should be reevaluated for potential: (b) (4) since it is not the basis for any regulatory decisions and does not provide additional regulatory information.

6 Appendices

6.1 Patient exclusions associated with enrollment in multiple trials

Subject	Subject ID	Trial	Treatment group	ITT population	PP population
1	145039	3006	SHH	N	N
	152030	3006	GFF	N	N
	426004	3007	GFF	N	N
2	49029	3006	SHH	N	N
	355030	3007	PBO	N	N
3	6030	3006	GFF	Y	Y
	344015	3007	FF	Y	N
4	23004	3006	FF	Y	Y
	329011	3007	GFF	Y	N
5	4027	3006	FF	Y	Y
	426028	3007	FF	Y	N
6	70010	3006	GP	Y	Y
	316008	3007	PBO	Y	N
7	66001	3006	GP	Y	Y
	407051	3007	GP	Y	Y
8	25018	3006	SHH	Y	N
	360002	3007	PBO	Y	Y
9	79005	3006	GP	Y	Y
	369012	3007	GFF	N	N
	79005	3008	GP	N	N
10	32005	3006	GP	Y	Y
	434003	3007	GP	N	N
	435011	3007	FF	N	N
11	23021	3006	GP	Y	Y
	28031	3006	FF	N	N
12	23019	3006	FF	Y	Y
	28030	3006	FF	N	N
13	56004	3006	FF	Y	Y
	112050	3006	PBO	N	N
14	127002	3006	FF	Y	Y
	132014	3006	FF	N	N
15	328024	3007	FF	Y	Y
	305070	3007	FF	N	N

Source: CSR PT003006 and PT003007, Tables 6-4

6.2 **Tipping Point Analyses**

Tipping point analyses conducted on missing data confirmed the robustness of efficacy results for the primary endpoint, Δ trough FEV_1 at week 24 (Table 28, Table 29, Table 30, Table 31, Table 32, and Table 33). For example, statistical significance of the difference between GF and Pbo in study 6 was retained when imputed results were decreased by 300 mL from the primary endpoint mean of 126 mL for GF and increased by 300 mL from the primary endpoint mean of -24 mL for Pbo (Table 28). At that δ = (-300, +300) shift, respective imputed treatment means for GF and Pbo were 126 - 300 = -174 mL for GF and -24 + 300 = 276 mL for Pbo, representing an unlikely scenario for missing data in which patients on GF would have experienced a 174 mL decrease from baseline at week 24 while patients on Pbo would have experienced a 276 mL increase from baseline at week 24. Similarly, for GF vs Pbo in study 7, respective imputed treatment means for GF and Pbo for the δ = (-300, +300) shift were -184 mL and 287 mL, again representing an unlikely scenario among patients with missing data. Statistical significance was also robust for GF vs F (Table 30 and Table 31) and for GF vs P (Table 32 and Table 33), with significance retained for scenarios in which treatment means among patients with missing data were negative for GFF and greater than 150 mL for the G and F monotherapies.

Table 28. Tipping Point Analysis for Δ Trough FEV_1 at Week 24, GF versus Pbo, Study 6. Deltas are change from 126 mL for GF (treatment) and -24 mL for Pbo (control)

	δ for Treatment, mLs worse				
		0	**100**	**200**	**300**
-δ for Control, mLs better	**0**	<0.0001	<0.0001	<0.0001	
	100	<0.0001	<0.0001	<0.0001	<0.0001
	200	<0.0001	<0.0001	<0.0001	<0.0001
	300		<0.0001	<0.0001	<0.0001

Source: Table 1, sequence 13, sponsor sensitivity analysis report

Table 29. Tipping Point Analysis for Δ Trough FEV_1 at Week 24, GF versus Pbo, Study 7. Deltas are change from 116 mL for GF (treatment) and 13 mL for Pbo (control)

	δ for Treatment, mLs worse				
		0	**100**	**200**	**300**
-δ for Control, mLs better	**0**	<0.0001	<0.0001	<0.0001	
	100	<0.0001	<0.0001	<0.0001	0.0002
	200	<0.0001	0.0001	0.0005	0.0019
	300		0.0011	0.0038	0.0119

Source: Table 3, sequence 13, sponsor sensitivity analysis report

Table 30. Tipping Point Analysis for Δ Trough FEV_1 at Week 24, GF versus F, Study 6. Deltas are change from 126 mL for GF (treatment) and 62 mL for F (control)

		δ for Treatment, mLs worse									
		0	**100**	**125**	**150**	**175**	**200**	**225**	**250**	**275**	**300**
-δ for Control, mLs better	**0**	<0.0001	0.0001				0.0020		0.0063		
	50						0.0052		0.0137	0.0225	0.0448
	75								0.0176	0.0266	0.0540
	100	0.0001	0.0011		0.0047		0.0154	0.0172	0.0301	0.0478	0.0749
	125						0.0190	0.0286	0.0409	0.0659	0.0914
	150		0.0045		0.0096	0.0187	0.0300	0.0431	0.0539	0.0852	0.1275
	175				0.0178	0.0259	0.0423	0.0613	0.0849		
	200	0.0010	0.0141		0.0241	0.0403	0.0646	0.0885	0.1228		0.2149
	225				0.0329	0.0586	0.0798				
	250		0.0216	0.0382	0.0484	0.0892	0.0952				
	275		0.0359	0.0506	0.0747	0.1035	0.1356				
	300		0.0490	0.0657	0.1165	0.1524	0.1930				0.4997

Source: Table 13, sequence 13, sponsor sensitivity analysis report

Table 31. Tipping Point Analysis for Δ Trough FEV_1 at Week 24, GF versus F, Study 7. Deltas are change from 126 mL for GF (treatment) and 62 mL for F (control)

		δ for Treatment, mLs worse												
		0	**25**	**50**	**75**	**100**	**125**	**150**	**175**	**200**	**225**	**250**	**275**	**300**
-δ for Control, mLs better	**0**	0.0002				0.0013				0.0072		0.0150	0.0204	
	25											0.0237	0.0273	0.0459
	50									0.0173	0.0216	0.0318	0.0430	0.0589
	75									0.0296	0.0431	0.0520	0.0764	0.0906
	100	0.0029		0.0054		0.0117		0.0232	0.0336	0.0342	0.0630	0.0715	0.0897	0.1158
	125							0.0334	0.0435	0.0632	0.0717	0.0941		
	150	0.0057		0.0128	0.0191	0.0284	0.0294	0.0436	0.0643	0.0768	0.0990	0.1397		0.2191
	175			0.0224	0.0241	0.0425	0.0510	0.0703	0.0947	0.0939				
	200	0.0154	0.0212	0.0288	0.0380	0.0574	0.0717	0.0995	0.1333	0.1440		0.2404		0.3765
	225	0.0237	0.0399	0.0470	0.0549	0.0823								
	250	0.0373	0.0489	0.0773	0.0871	0.1154								
	275	0.0537	0.0845	0.0955										
	300		0.1086	0.1250		0.2070				0.4057				0.7733

Source: Table 15, sequence 13, sponsor sensitivity analysis report

Table 32. Tipping Point Analysis for Δ Trough FEV_1 at Week 24, GF versus G, Study 6. Deltas are change from 126 mL for GF (treatment) and 66 mL for G (control)

		δ for Treatment, mLs worse												
		0	**25**	**50**	**75**	**100**	**125**	**150**	**175**	**200**	**225**	**250**	**275**	**300**
-δ for Control, mLs better	**0**	<0.0001				0.0007		0.0023		0.0073	0.0123	0.0188	0.0296	
	25									0.0115	0.0202	0.0353	0.0478	0.0723
	50					0.0033		0.0094	0.0150	0.0175	0.0310	0.0578	0.0862	0.1008
	75							0.0140	0.0214	0.0300	0.0561	0.0837		
	100	0.0014		0.0040		0.0102	0.0206	0.0293	0.0450	0.0669	0.0862	0.1250		0.2226
	125					0.0168	0.0273	0.0518	0.0683	0.0942				
	150	0.0054		0.0145	0.0191	0.0279	0.0607	0.0677	0.0934	0.1341				
	175			0.0245	0.0411	0.0530	0.0709	0.1130						
	200	0.0167	0.0242	0.0452	0.0559	0.0854	0.1320	0.1697		0.2864				0.6513
	225	0.0278	0.0380	0.0734	0.0825	0.1205								
	250	0.0427	0.0608	0.1111	0.1263	0.1977								
	275	0.0706	0.0941	0.1471										
	300		0.1402	0.2120		0.3636				0.7380				0.7378

Source: Table 17, sequence 13, sponsor sensitivity analysis report

Table 33. Tipping Point Analysis for Δ Trough FEV_1 at Week 24, GF versus G, Study 7. Deltas are change from 126 mL for GF (treatment) and 63 mL for G (control)

		δ for Treatment, mLs worse												
		0	**25**	**50**	**75**	**100**	**125**	**150**	**175**	**200**	**225**	**250**	**275**	**300**
-δ for Control, mLs better	**0**	0.0004				0.0021				0.0112		0.0214	0.0304	
	25											0.0242	0.0420	0.0562
	50									0.0211	0.0273	0.0406	0.0544	0.0707
	75									0.0272	0.0398	0.0528	0.0622	0.0749
	100	0.0023				0.0101		0.0197	0.0268	0.0375	0.0517	0.0675	0.0888	0.1203
	125							0.0279	0.0459	0.0535	0.0708	0.0944		
	150					0.0223	0.0283	0.0485	0.0502	0.0620	0.0842	0.1305		0.1927
	175					0.0299	0.0376	0.0519	0.0613	0.0812				
	200	0.0112		0.0168	0.0339	0.0423	0.0486	0.0751	0.0904	0.1206		0.1883		0.2855
	225			0.0286	0.0375	0.0539	0.0625	0.0865						
	250	0.0207	0.0276	0.0472	0.0538	0.0714	0.0995	0.1291		0.1699				
	275	0.0332	0.0405	0.0555	0.0762	0.1016								
	300		0.0566	0.0642	0.0834	0.1249		0.1956		0.2993				0.5698

Source: Table 19, sequence 13, sponsor sensitivity analysis report

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STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

BLA Number: 208294 **Applicant: Pearl** **Stamp Date: 6/25/2015**

Drug Name: Glycopyrrolate/Formoterol **NDA/BLA Type: Standard**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	x			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	x			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	x			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	x			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	x			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	x			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			x	
Appropriate references for novel statistical methodology (if present) are included.			x	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	x			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.		x		IR submitted prior to 74 day letter

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT ABUGOV
08/25/2015

DAVID M PETULLO
08/25/2015
I concur.