

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207930Orig1s000

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

SECONDARY REVIEW CLINICAL STUDIES

NDA/BLA #: NDA 207-930/0000

Drug Name: QVA149 (indacaterol/glycopyrrolate) Inhalation Powder Hard Capsules

Indication(s): Long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema

Applicant: Novartis

Date(s): Receipt date: December 29, 2014
PDUFA date: October 29, 2015

Review Priority: Standard

Biometrics Division: Division of Biometrics II

Statistical Reviewer: Kiya Hamilton, Ph.D.

Concurring Reviewers: David Petullo, M.S., Team Leader

Medical Division: Division of Pulmonary, Allergy and Rheumatology Products

Clinical Team: Erika Torjusen, M.D., Medical Reviewer
Anthony Durmowicz, M.D., Team Leader
Badrul A. Chowdhury, M.D. Ph.D., Medical Division Director

Project Manager: Christine Ford

Keywords: NDA, clinical studies

Table of Contents

LIST OF TABLES	3
LIST OF FIGURES	4
1 EXECUTIVESUMMARY	5
2 INTRODUCTION	5
2.1 OVERVIEW	5
2.1.1 <i>Class and Indication</i>	5
2.1.2 <i>History of Drug Development</i>	5
2.1.3 <i>Specific Studies Reviewed</i>	5
2.2 DATA SOURCES.....	5
3 STATISTICAL EVALUATION	5
3.1 DATA AND ANALYSIS QUALITY.....	5
3.2 EVALUATION OF EFFICACY	5
3.2.1 <i>Study Design and Endpoints</i>	5
3.2.1 <i>Statistical Methodologies</i>	6
3.2.2 <i>Patient Disposition</i>	6
3.2.4 <i>Results and Conclusions</i>	7
3.2.4.1 <i>Study 2210</i>	7
4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS.....	8
5 SUMMARY AND CONCLUSIONS	8
5.1 STATISTICAL ISSUES	8
5.2 CONCLUSIONS AND RECOMMENDATIONS	8
5.3 COMMENT ON THE PROPOSED LABEL	9

LIST OF TABLES

Table 1. Summary of Study Design and Primary Endpoints.....	6
Table 2. Summary of Patient Disposition in Study 2210.....	7
Table 3. Efficacy Results- Change from Period Baseline in FEV ₁ (L) AUC _{0-24h} - Study 2210 (FAS Population).....	7

LIST OF FIGURES

Figure 1. 24 Hour Profile of Change from Period Baseline in FEV ₁ (FAS).....	8
---	---

1 EXECUTIVE SUMMARY

Dose-ranging study QVA149A2210 (2210) examined five different doses of indacaterol (QAB149). My analyses of the data is consistent with the results reported by the applicant and support the evaluation of indacaterol 27.5 µg twice daily in the phase 3 program for COPD.

2 INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Refer to the original Statistical Review and Evaluation for the class and indication for this NDA, submitted in DARRTS dated September 25, 2015.

2.1.2 History of Drug Development

The Division of Pulmonary, Allergy, and Rheumatology Products requested the analysis of the dose ranging study, study 2210. The endpoint, trough FEV₁ was analyzed based on claims in the label.

2.1.3 Specific Studies Reviewed

This review will focus on the results from study QVA149A2210 (hereafter referred to as 2210).

2.2 Data Sources

The datasets from the phase 2 study are archived under the network path location \\cdsesub1\evsprod\nda207930\0000.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Datasets, programs, and documentation provided by the applicant were adequate to evaluate the additional information that was requested by the Division. Results from my analyses generally matched those submitted by the applicant.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

A summary of the study design is shown in Table 1. The study is discussed briefly below.

Table 1. Summary of Study Design and Primary Endpoints

Study ID	Length of the Study	Treatment Arms*	Number of Patients	Study Population	Primary Efficacy Endpoint(s)
QVA149A2210	Six period-72 days	QAB 27.5 bid QAB 37.5 od QAB 55 od QAB 75 od QAB 150 od Placebo	91 patients total	Patients with persistent asthma	FEV ₁ AUC _{0-24h}

* b.i.d: Twice a day, o.d.: Once a day

There were a total of 91 patients in the study. Each patient received each treatment.

Source: Reviewer

Study 2210 was a phase 2, randomized, double-blind, placebo-controlled, 6-period, 6-sequence crossover, multi-center study. All doses were delivered via the single dose dry powder inhaler in patients with persistent asthma. Each patient received all study treatments along with background asthma controller therapy with fluticasone propionate.

3.2.1 Statistical Methodologies

All efficacy analyses were performed using the full analysis set (FAS), which was defined as all randomized patients who received at least one dose of study drug.

The primary endpoint was the mean FEV₁ AUC_{0-24h}, baseline was defined as the average of two values measured at 45 and 15 minutes prior to the first dose of study drug in that period. The mean FEV₁ AUC_{0-24h} was analyzed using a linear mixed model (LMM) with treatment, and period as fixed effects, patient as a random effect, patient average baseline FEV₁ and period-adjusted baseline correction.

3.2.2 Patient Disposition

The summary of the patient disposition in study 2210 is given in Table 2. Approximately 7% of the patients discontinued due to adverse events (AE).

Table 2. Summary of Patient Disposition in Study 2210

	Total n (%)
Randomized	91 (100)
Completed	84 (92)
Protocol deviation	6 (7)
Adverse events	1 (1)

Since this was a crossover study, a patient could be counted in more than one of the treatment groups. Percentages of patients completed and discontinued are calculated using the number of randomized patients as the denominator. All other percentages in this table are based on the number of discontinued patients as the denominator.

Source: Full Clinical Study Report-Protocol Number QVA 149A2210 Table 10-1, page 58

3.2.4 Results and Conclusions

3.2.4.1 Study 2210

In study 2210, all doses of QAB149 demonstrated a statistically significant change from period baseline in FEV₁ AUC_{0-24h} compared to placebo (Table 3). The difference versus placebo for the 27.5 µg bid treatment dose was 0.12 L.

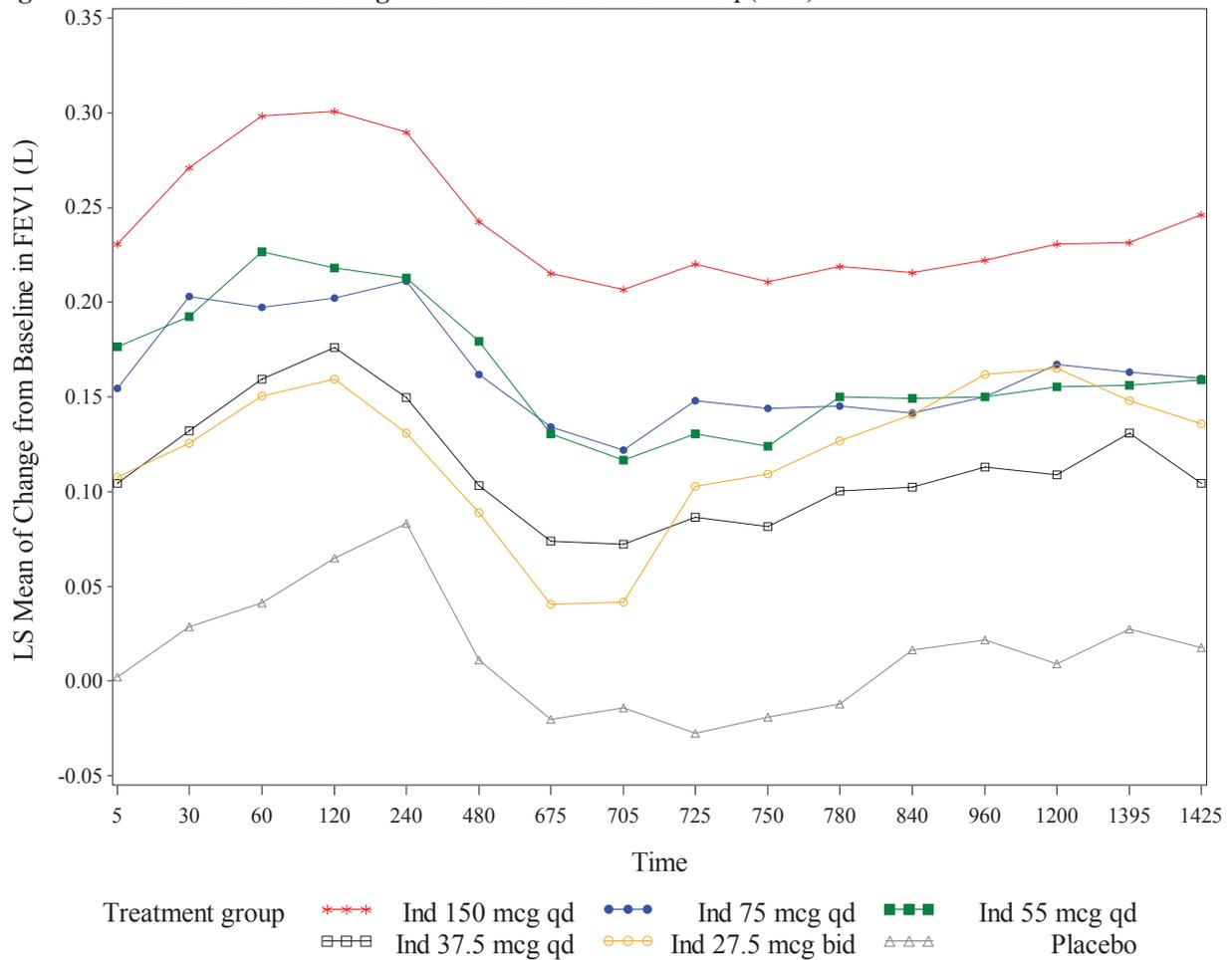
Table 3. Efficacy Results - Change from Period Baseline in FEV₁ (L) AUC_{0-24h} - Study 2210 (FAS Population)

Treatment	n	Baseline Mean	Mean Treatment Δ from placebo		
			Mean	95 % CI	p-value
QAB 150 µg od	84	2.24	0.19	0.16, 0.22	<0.0001
QAB 75 µg od	86	2.28	0.14	0.11, 0.17	<0.0001
QAB 55 µg od	85	2.27	0.13	0.10, 0.16	<0.0001
QAB 37.5 µg od	84	2.28	0.10	0.07, 0.13	<0.0001
QAB 27.5 µg bid	87	2.30	0.12	0.09, 0.15	<0.0001
Placebo	86	2.28	-	-	-

Source: Full Clinical Study Report-Protocol Number QVA 149A2210 Table 11-5, page 66

Figure 1 shows the 24 hour profile of the mean change from period baseline in FEV₁ for all five indacaterol doses. All five doses did better than placebo.

Figure 1. 24 Hour Profile of Change from Period Baseline in FEV₁ (FAS)



4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

No subgroup analyses were conducted.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

No outstanding statistical issues were identified in this review.

5.2 Conclusions and Recommendations

Analysis from the phase 2, dose-ranging study was conducted to examine the acute (24-hour) bronchodilator effects of five different doses of QAB149 compared to placebo in asthma patients. Significant differences were seen for all QAB149 doses for FEV₁ AUC_{0-24h} compared to placebo. There was an improvement of 0.12 L for 27.5 µg bid compared to placebo. The results

from this study support the evaluation of indacaterol 27.5 mcg twice daily in the phase 3 program for COPD.

5.3 Comment on the Proposed Label

The following are suggestions for the applicant's proposed label.

- Insert 24 hour profile of FEV₁ from study A2210 to section 14.

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

/s/

KIYA HAMILTON
10/15/2015

DAVID M PETULLO
10/15/2015



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 207-930/0000

Drug Name: QVA149 (indacaterol/glycopyrrolate) Inhalation Powder Hard Capsules

Indication(s): Long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema

Applicant: Novartis

Date(s): Receipt date: December 29, 2014
PDUFA date: October 29, 2015

Review Priority: Standard

Biometrics Division: Division of Biometrics II

Statistical Reviewer: Kiya Hamilton, Ph.D.

Concurring Reviewers: David Petullo, M.S., Team Leader

Medical Division: Division of Pulmonary, Allergy and Rheumatology Products

Clinical Team: Erika Torjusen, M.D., Medical Reviewer
Anthony Durmowicz, M.D., Team Leader
Badrul A. Chowdhury, M.D. Ph.D., Medical Division Director

Project Manager: Christine Ford

Keywords: NDA, clinical studies

Table of Contents

LIST OF TABLES	3
LIST OF FIGURES	4
SUMMARY OF REVISIONS.....	5
1 EXECUTIVESUMMARY	5
2 INTRODUCTION	5
2.1 OVERVIEW.....	5
2.1.1 <i>Class and Indication</i>	5
2.1.2 <i>History of Drug Development</i>	6
2.1.3 <i>Specific Studies Reviewed</i>	6
2.2 DATA SOURCES.....	6
3 STATISTICAL EVALUATION	6
3.1 DATA AND ANALYSIS QUALITY.....	6
3.2 EVALUATION OF EFFICACY.....	6
3.2.1 <i>Study Design and Endpoints</i>	6
3.2.2 <i>Statistical Methodologies</i>	8
3.2.3 <i>Patient Disposition, Demographic and Baseline Characteristics</i>	9
3.2.4 <i>Results and Conclusions</i>	12
3.3 EVALUATION OF SAFETY.....	22
4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS.....	22
4.1 GENDER, RACE, AND AGE.....	22
4.2 OTHER SPECIAL/SUBGROUP POPULATIONS.....	24
5 SUMMARY AND CONCLUSIONS	26
5.3 COMMENT ON THE PROPOSED LABEL.....	27

LIST OF TABLES

Table 1. Summary of Study Design and Primary Endpoints.....	7
Table 2. Summary of Patient Disposition in Study 2336.....	10
Table 3. Summary of Patient Disposition in Study 2337.....	10
Table 4. Demographics in Study 2336 - Randomized Set.....	11
Table 5. Demographics in Study 2337 - Randomized Set.....	11
Table 6. Summary of Patient Disposition Study 2340.....	12
Table 7. Demographics in Study 2340- Randomized Set.....	12
Table 8. Primary Efficacy Results-Change from Baseline in FEV ₁ (L) AUC _(0-12h) at Week 12- Study 2336 (FAS Population).....	13
Table 9. Primary Efficacy Results-Change from Baseline in FEV ₁ (L) AUC _(0-12h) at Week 12- Study 2337 (FAS Population).....	14
Table 10. Tipping Point Analysis at Day 85 Change from Baseline FEV ₁ AUC _{0-12h}	14
Table 11. SGRQ Total at Week 12- Study 2336 (FAS).....	15
Table 12. SGRQ Total at Week 12- Study 2337 (FAS).....	15
Table 13. Proportion of patients with a clinically important improvement of at least 4 units in the SGRQ Total Score at Week 12- Study 2336 (FAS).....	16
Table 14. Proportion of Patients with a Clinically Important Improvement of at Least 4 Units in the SGRQ Total Score at Week 12- Study 2337 (FAS).....	17
Table 15. Change from Baseline Pre-dose Trough FEV ₁ (L), by visit- study 2340 (FAS).....	18
Table 16. Results Time to First Moderate or Severe COPD Exacerbation- Study 2340 (FAS).....	21
Table 17. Rate of Moderate or Severe COPD Exacerbations During Treatment-Study 2340 (FAS).....	21

LIST OF FIGURES

Figure 1. Change from Baseline in Pre-dose Trough FEV ₁ (L) over Post-baseline Visits-Study 2340 (FAS).....	20
Figure 2. Forest Plot Subgroup Analysis of FEV ₁ (L) AUC _{0-12h} at Week 12 QVA 149 vs. QAB149- Study 2336.....	22
Figure 3. Forest Plot Subgroup Analysis of FEV ₁ (L) AUC _{0-12h} at Week 12, QVA 149 vs. NVA237- Study 2336.....	23
Figure 4. Forest Plot Subgroup Analysis of FEV ₁ (L) AUC _{0-12h} at Week 12, QVA 149 vs. QAB149- Study 2337.....	23
Figure 5. Forest Plot Subgroup Analysis of FEV ₁ (L) AUC _{0-12h} at Week 12, QVA 149 vs. NVA237- Study 2337.....	24
Figure 6. Forest Plot Other Subgroup Analysis of FEV ₁ (L) AUC _{0-12h} at Week 12 QVA 149 vs. QAB149- Study 2336	25
Figure 7. Forest Plot Other Subgroup Analysis of FEV ₁ (L) AUC _{0-12h} at Week 12 QVA 149 vs. NVA237- Study 2336	25
Figure 8 Forest Plot Other Subgroup Analysis of FEV ₁ (L) AUC _{0-12h} at Week 12 QVA 149 vs. QAB149- Study 2337	26
Figure 9 Forest Plot Other Subgroup Analysis of FEV ₁ (L) AUC _{0-12h} at Week 12 QVA 149 vs. NVA237- Study 2337	26

SUMMARY OF REVISIONS

- Page 16. The following statement was incorrect: “in neither study, was the combination product significantly different from the monotherapies.” The correct statement should be: “in study 2336 the combination product was significantly different from both monotherapies but in study 2337 the combination product was not different from either monotherapy.”

1 EXECUTIVE SUMMARY

Novartis proposes QVA149, a combination product of indacaterol (QAB149) and glycopyrrolate (NVA237) for the long term maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

To support efficacy, the applicant submitted the results from two 12 week, phase 3, multi-center, double-blind, placebo- and active-controlled, parallel-group, randomized efficacy and safety studies, QVA149A2336 (2336) and QVA149A2337 (2337). In these studies, compared to each monotherapy component, QVA149 27.5/12.5 µg b.i.d. demonstrated a statistically significant improvement in the primary endpoint, FEV₁ AUC_{0-12h} at week 12 and placebo. In the analysis of St George’s Respiratory Questionnaire (SGRQ), a secondary endpoint of interest, the combination product and each monotherapy demonstrated a significant improvement over placebo in both studies. In study 2337, the combination product also demonstrated a significant improvement when compared to the monotherapy components. This effect was not noted in study 2336.

Efficacy was also demonstrated in a long term safety study, QVA149A2340 (2340). This 52-week study was a multi-center, double-blind, active-controlled, parallel-group, randomized, efficacy and safety study of QVA149 27.5/12.5 µg b.i.d. and QVA149 27.5/25 µg b.i.d. versus indacaterol (QAB149) 75 µg once daily in patients with COPD with moderate to severe airflow limitations. There were significant differences between both doses of QVA149 and QAB149 in the change from baseline in pre-dose trough FEV₁ at each visit over the 52 weeks. However, regardless of dose, there were no differences in time to first moderate or severe COPD exacerbation and annual rate of moderate or severe COPD exacerbation between QVA149 and QAB149.

2 INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Novartis developed a fixed dose combination of two long acting bronchodilators, indacaterol maleate (QAB149) which is a long-acting β₂-adrenergic agonist, and glycopyrronium bromide

(NVA237) which is a long acting muscarinic antagonist. NVA237 is currently being reviewed as a monotherapy under NDA 207923. The applicant proposes the combination product, indacaterol/glycopyrrolate inhalation powder, hereafter referred to as QVA149 27.5/12.5 µg twice daily for the long term treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

2.1.2 History of Drug Development

There were several interactions between Novartis and the Division of Pulmonary, Allergy, and Rheumatology Products (DPAAP) regarding the development program of QVA149 under IND 76,377. However, these interactions were not relevant to this statistical review.

2.1.3 Specific Studies Reviewed

This review will focus on the results from studies QVA149A2336, QVA149A2337, and QVA149A2340 (hereafter referred to as 2336, 2337, and 2340 respectively).

2.2 Data Sources

The submission of NDA 207-930 was received on December 29, 2014. The study reports including protocols, statistical analysis plan, and all referenced literature were submitted by the applicant to the Agency. The data and final study report for the electronic submission were archived under the network path location \\cdsesub1\evsprod\nda207930\0000.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

In general, the electronic data submitted by the applicant were of sufficient quality to allow a thorough review of the data. I was able to reproduce the analyses of the primary and secondary efficacy endpoints for each clinical study submitted and were able to verify the randomization of the treatment assignments.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

A summary of the study design and endpoints for the efficacy studies are shown in Table 1. Each study is discussed below.

Table 1. Summary of Study Design and Primary Endpoints

Study ID	Length of the Study	Treatment Arms*	Number of Patients	Study Population	Primary Efficacy Endpoint(s)
2336	12 weeks DB period	QVA149 27.5/12.5 bid	258	Moderate to severe airflow limitation	FEV ₁ AUC ₀₋₁₂ hours at week 12
		QAB149 27.5 bid	260		
		NVA 12.5 bid	261		
		Placebo	261		
2337	12 weeks DB period	QVA149 27.5/12.5 bid	250	Moderate to severe airflow limitation	FEV ₁ AUC ₀₋₁₂ hours at week 12
		QAB149 27.5 bid	251		
		NVA 12.5 bid	250		
		Placebo	247		
2340	52 weeks DB period	QVA149 27.5/12.5 bid	204	Moderate to severe airflow limitation	Safety: Overall AE rate
		QVA149 27.5/25 bid	204		
		QAB149 75 od	206		

Source: Reviewer

* bid: Twice a day, od: Once a day

3.2.1.1 Studies 2336 and 2337

Studies 2336 and 2337 were phase 3, randomized, double-blind, parallel-group, placebo- and active-controlled, multi-center, 12 week studies. These studies were designed to evaluate the efficacy and safety of QVA149 27.5/12.5 µg administered twice daily (b.i.d.) versus the monotherapy components QAB149 27.5 µg b.i.d and NVA237 12.5 µg b.i.d. as well as placebo in COPD patients with moderate to severe airflow limitation. Patients were randomized in a 1:1:1:1 ratio and stratified by smoking (current / ex-smoker) status.

The primary endpoint for both studies was change from baseline in FEV₁ AUC_{0-12h} post morning dose at week 12. Baseline FEV₁ was defined as the mean of the pre-dose FEV₁ measured at -45 minutes and -15 minutes at day 1. The key secondary endpoints are St. George's Respiratory Questionnaire (SGRQ) total score at week 12 and percentage of patients with clinically significant improvement in SGRQ total score at week 12.

3.2.1.2 Study 2340

Study 2340 was a multi-center, double-blind, active controlled, parallel-group, randomized 52-week treatment efficacy and safety study of QVA149 27.5/12.5 µg b.i.d. in patients with COPD with moderate to severe airflow limitations. Patients were permitted COPD background therapy in this long-term safety study. Patients were randomized in a 1:1:1 ratio to either QVA149 27.5/12.5 µg b.i.d., QVA149 27.5/25 µg b.i.d, or QAB149 75 µg o.d. Note, QAB149 is an approved bronchodilator. Treatment randomization was stratified by smoking (current or ex-smoker), ICS use (yes or no), and severity of airflow limitation (moderate or severe).

The secondary efficacy endpoints, change from baseline in pre-dose trough FEV₁ (average of the two FEV₁ measurements 45 and 15 minutes pre-dose) at days 29, 57, 85, 141, 197, 253, 309, and 365, time to first moderate or severe COPD exacerbation, and annual rate of moderate or severe COPD exacerbation, will be discussed in this review. A COPD exacerbation was defined as a worsening of the following two or more major symptoms for at least two consecutive days: dyspnea, sputum volume and sputum purulence, or a worsening of any one major symptom together with an increase in any one of the following minor symptoms for at least two consecutive days: sore throat, colds (nasal discharge and/or nasal congestion), fever without other cause, cough and wheeze. A COPD exacerbation was considered of moderate severity if treatment with systemic corticosteroids or antibiotics or both was required and severe, if hospitalization was required. An emergency room visit of longer than twenty-four hours was considered a hospitalization. The primary endpoint was overall adverse event (AE) rate, a safety endpoint and is not discussed further in this review.

3.2.2 Statistical Methodologies

All efficacy analyses were performed using the full analysis set (FAS), which was defined as all randomized patients who received at least one dose of study drug.

3.2.2.1 Studies 2336 and 2337

Missing FEV₁ measurements were not imputed when deriving AUC_{0-12h}. FEV₁ measurements within 6 hours of rescue medication use or within 7 days of systemic corticosteroid use were considered missing.

In both studies the pre-specified analysis of the primary efficacy endpoint, change from baseline in FEV₁ AUC_{0-12h} post morning dose at week 12, was a mixed model for repeated measures (MMRM) with treatment, baseline FEV₁, smoking status at baseline, baseline ICS use, region, visit, treatment-by-visit interaction, and baseline FEV₁-by-visit interaction. The null hypothesis of no difference in FEV₁ AUC_{0-12h} in patients treated with the combination product and each monotherapy was tested at a significance level of 0.05. The key secondary endpoint, change from baseline in SGRQ total score was analyzed using a linear mixed model with treatment, baseline SGRQ score, smoking status at baseline, and history of ICS use as fixed effects. Center nested within region was included as a random effect. The proportion of patients who achieved a clinically important improvement of at least 4 units in the SGRQ total score was compared using logistic regression with treatment, baseline SGRQ score, smoking status at baseline, and history of ICS use as fixed effects. Center nested within region was included as a random effect in the model.

A gate keeping procedure was used to protect the overall type I error for the primary and key secondary endpoints.

- If superiority of QVA149 27.5/12.5 µg b.i.d. over each of its monotherapy components: QAB149 27.5 and NVA237 12.5 µg b.i.d. was established for FEV₁ AUC_{0-12h} at week 12 at the 0.05 level (for each component)
- Then the test for SGRQ total score was performed. If superiority of QVA149 27.5/12.5 µg b.i.d. over placebo in SGRQ total score was statistically significant at the 0.05 level

- Then QVA149 27.5/12.5 µg b.i.d. was compared to placebo for percentage of patient with clinically significant improvement of at least 4 units in SGRQ total score at the 0.05 level.

The trapezoidal rule was used to calculate FEV₁ AUC_{0-12h} similar to a time weighted average. For each patient, an AUC was calculated based on the existing FEV₁ measurements (i.e., the missing FEV₁ measurements were not to be interpolated). The following is an excerpt from the clinical study report.

Specifically, for those patients who had a FEV₁ assessment at only one time point, their AUC was approximated by the observed FEV₁. For those patients who had more than one FEV₁ assessment, their AUC was approximated by $\sum_{k=2}^m w_k \tilde{y}_k$, where $\tilde{y}_k = 0.5(y_k + y_{k-1})$, $w_k = (t_k - t_{k-1}) / (t_m - t_1)$, and y_j is the FEV₁ value at time t_j , for $j = 1, \dots, m$, in which $t_1 < \dots < t_m$ are the time points when FEV₁ are measured. Scheduled measurement times t_j rather than actual times were used. If FEV₁ AUC_{0-12h} was missing at week 12, then the FEV₁ AUC_{0-12h} measured at day 1 was not carried forward.

To evaluate the impact of missing data at day 85 for the primary endpoint, change from baseline in FEV₁ AUC_{0-12h}, tipping point analyses were provided by the applicant. This included the possibility that patients with missing data in the active arms had worse outcomes than patients with missing data in the placebo arm. Using a multiple imputation approach, values for the active arm were decreased by a specific delta and primary analysis was repeated. If the conclusions did not change, i.e. there was still a significant treatment effect, the delta was increased and the analysis was repeated. This process continued until significance was no longer noted, i.e. the analysis tipped.

3.2.2.2 Study 2340

The change from baseline in pre-dose trough FEV₁ at weeks 4 and 52 was analyzed using a repeated measures analysis of covariance (ANCOVA) model with treatment, baseline FEV₁, visit, treatment by visit interaction, visit by baseline FEV₁ interaction, smoking status at baseline, baseline ICS use, airflow limitation severity, and region as fixed effects. Time to first moderate or severe COPD exacerbation was analyzed using Cox regression model with treatment, baseline total symptom score, baseline COPD exacerbation history (i.e. number of COPD exacerbations during 12 months prior to study), smoking status at baseline, baseline ICS use, airflow limitation severity, and region as fixed effects. The rate of moderate or severe COPD exacerbations was analyzed using a generalized linear model assuming a negative binomial distribution. The model included with treatment, baseline FEV₁, visit, treatment by visit interaction, visit by baseline FEV₁ interaction, smoking status at baseline, baseline ICS use, airflow limitation severity, and region as fixed effects.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Study 2336 and 2337

The summary of the patient disposition in studies 2336 and 2337 are given in Tables 2 and 3. Approximately 1%-6% of the patients discontinued study medication in both studies over 12 weeks. The primary reason for discontinuation in both groups was patient/guardian decision.

Table 2. Summary of Patient Disposition in Study 2336

	QVA 149 27.5/12.5 bid	QAB149 27.5 bid	NVA237 12.5 bid	Placebo
Randomized	260	260	261	261
FAS	258 (99)	260 (100)	261 (100)	261 (100)
Completed	255 (98)	251 (97)	258 (98)	246 (94)
Discontinued	5 (2)	9 (4)	3 (1)	15 (6)
Patient/guardian decision	4 (2)	4 (2)	2 (1)	11 (4)
Protocol deviation	1 (<1)	1 (<1)	0	1 (<1)
Death	0	1 (<1)	1 (<1)	1 (<1)
Physician decision	0	1 (<1)	0	2 (1)
Lost to follow-up	0	2 (1)	0	0

Source: Full Clinical Study Report-Protocol Number QVA 149A2336 Table 10-1, page 92

Table 3. Summary of Patient Disposition in Study 2337

	QVA 149 27.5/12.5 bid	QAB149 27.5 bid	NVA237 12.5 bid	Placebo
Randomized	250	251	251	249
FAS	250 (100)	251 (100)	250 (99)	247 (99)
Completed	244 (98)	241 (96)	245 (98)	236 (95)
Discontinued	6 (2)	10 (4)	6 (2)	13 (5)
Patient/guardian decision	3 (1)	9 (4)	3 (1)	9 (4)
Protocol deviation	1 (<1)	0	1 (<1)	0
Death	0	1 (<1)	0	0
Technical problems	0	0	2 (1)	1 (<1)
Lost to follow-up	0	0	2 (1)	1 (<1)

Source: Full Clinical Study Report-Protocol Number QVA 149A2337 Table 10-1, page 88

Demographics and baseline characteristics for all randomized patients in studies 2336 and 2337 are given in Tables 4 and 5. The patients' mean age was approximately 64 years and most of the patients were White (88%-94%). These factors were generally well-balanced across the treatment groups.

Table 4. Demographics in Study 2336 - Randomized Set

	QVA 149 27.5/12.5 bid N=260	QAB149 27.5 bid N=260	NVA237 12.5 bid N=261	Placebo N=261
Age (years)				
Mean (SD)	64 (9)	64 (8)	64 (9)	64 (8)
Sexn (%)				
Female	90 (35)	74 (29)	78 (30)	92 (35)
Male	170 (65)	186 (72)	183 (70)	169 (65)
Race n (%)				
White	241 (93)	239 (92)	230 (88)	244 (94)
Black	10 (4)	8 (3)	15 (6)	8 (3)
Asian	8 (3)	10 (4)	13 (5)	8 (3)
Native American	0	0	1 (<1)	1 (<1)
Pacific Islander	0	0	0	0
Unknown	0	1 (<1)	0	0
Other	1 (1)	2 (1)	2 (1)	0
Height				
Mean (SD)	169 (9)	170 (9)	170 (8)	168 (10)
Weight (kg)				
Mean (SD)	77 (17)	80 (17)	80 (18)	78 (17)

Source: Reviewer Analysis

Table 5. Demographics in Study 2337 - Randomized Set

	QVA 149 27.5/12.5 bid N=250	QAB149 27.5 bid N=251	NVA237 12.5 bid N=251	Placebo N=249
Age (years)				
Mean (SD)	63 (9)	64 (9)	63 (9)	63 (8)
Sexn (%)				
Female	96 (38)	101 (40)	107 (43)	111 (45)
Male	154 (62)	150 (60)	144 (57)	138 (55)
Race n (%)				
White	230 (92)	224 (89)	222 (88)	227 (91)
Black	7 (3)	11 (4)	9 (4)	11 (4)
Asian	0	1 (<1)	0	0
Native American	12 (5)	15 (6)	19 (8)	10 (4)
Pacific Islander	0	0	0	0
Unknown	0	0	0	0
Other	1 (<1)	0	1 (<1)	1 (<1)
Height				
Mean (SD)	170 (9)	169 (10)	169 (10)	169 (9)
Weight (kg)				
Mean (SD)	79 (18)	80 (18)	79 (20)	76 (18)

Source: Reviewer Analysis

3.2.3.2 Study 2340

The summary of the patient disposition in study 2340 is given in Table 6. Approximately 11% of the patients discontinued study medication over 52 weeks. The primary reason for discontinuation in each group was patient/guardian decision.

Table 6. Summary of Patient Disposition Study 2340

	QVA 149 27.5/12.5 bid n (%)	QVA 149 27.5/25 bid n (%)	QAB149 75 od n (%)
Randomized	204	204	207
FAS			
Completed	177 (87)	187 (92)	183 (88)
Discontinued	27 (13)	17 (8)	24 (12)
Patient/guardian Decision	19 (9)	12 (6)	10 (5)
Lost to follow-up	5 (3)	1 (1)	6 (3)
Protocol deviation	1 (1)	0	1 (1)
Death	1 (1)	3 (2)	4 (2)
Physician decision	0	0	1 (1)
Adverse event	0	1 (1)	2 (1)
Technical problems	1 (1)	0	0

Source: Full Clinical Study Report-Protocol Number QVA 149A2340 Table 10-1, page 98

Demographics and baseline characteristics for all randomized patients in study 2340 are given in Table 7. The patients' mean age was approximately 64 years and most of the patients were White (98%) in this study. These factors were generally well-balanced across the treatment groups.

Table 7. Demographics in Study 2340- Randomized Set

	QVA 149 27.5/12.5 bid N=204	QVA 149 27.5/25 bid N=204	QAB149 75 od N=207
Age (years)			
Mean (SD)	64 (8)	64 (9)	63 (9)
Sex n (%)			
Female	73 (36)	81 (40)	58 (28)
Male	131 (64)	123 (60)	149 (72)
Race n (%)			
White	199 (98)	202 (99)	200 (97)
Black	3 (2)	2 (1)	4 (2)
Asian	0	0	0
Native American	1 (1)	0	1 (1)
Other	1 (1)	0	2 (1)
Height			
Mean (SD)	168 (9)	168 (9)	170 (9)
Weight (kg)			
Mean (SD)	78 (17)	78 (18)	80 (18)
At United States site, n (%)			
No	110 (54)	112 (55)	127 (61)
Yes	94 (46)	92 (45)	80 (39)

Source: Full Clinical Study Report-Protocol Number QVA 149A2340 Table 11-2, page 103

3.2.4 Results and Conclusions

3.2.4.1 Studies 2336 and 2337

In both studies, QVA149 27.5/12.5 µg demonstrated a statistically significant improvement in the FEV₁ AUC_{0-12h} at week 12 compared to each monotherapy, QAB149 27.5 µg and NVA237 12.5 µg. Results are shown in Tables 8 and 9. This statistically significant improvement in both studies supports the demonstration of the benefit of QVA149 27.5/12.5 µg over each its monotherapy components with respect to lung function. In both studies compared to placebo, QVA149 27.5/12.5 µg and each of its monotherapy components demonstrated a statistically significant improvement in the primary endpoint in both studies.

Table 8. Primary Efficacy Results-Change from Baseline in FEV₁ (L) AUC_(0-12h) at Week 12- Study 2336 (FAS Population)

	QVA 149 27.5/12.5 bid N=258	QAB149 27.5 mcg bid N=260	NVA237 12.5 bid N=261	Placebo N=261
Mean at week 12	0.21	0.12	0.11	-0.02
Mean treatment Δ QVA 149 27.5/12.5 vs QAB 27.5	0.094			
95% CI	0.06, 0.13			
p-value	<0.001			
Mean treatment Δ QVA 149 27.5/12.5 vs NVA 12.5	0.10			
95% CI	0.06, 0.14			
p-value	<0.001			
Mean treatment Δ Drug vs Placebo	0.23	0.14	0.13	
95% CI	0.19, 0.27	0.10, 0.18	0.09, 0.17	
p-value	<0.001	<0.001	<0.001	

N: Number of observations used in the analysis

Source: Full Clinical Study Report-Protocol Number QVA 1492336 Table 11-7, page 104

Table 9. Primary Efficacy Results-Change from Baseline in FEV₁ (L) AUC_(0-12h) at Week 12- Study 2337 (FAS Population)

	QVA 149 27.5/12.5 bid N=249	QAB149 27.5 mcg bid N=251	NVA237 12.5 bid N=250	Placebo N=246
Mean at week 12	0.23	0.12	0.16	-0.03
Mean treatment Δ QVA 149 27.5/12.5 vs QAB 27.5	0.11			
95% CI	0.07, 0.15			
p-value	<0.001			
Mean treatment Δ QVA 149 27.5/12.5 vs NVA 12.5	0.08			
95% CI	0.04, 0.12			
p-value	<0.001			
Mean treatment Δ Drug vs Placebo	0.26	0.15	0.18	
95% CI	0.22, 0.30	0.11, 0.19	0.15, 0.22	
p-value	<0.001	<0.001	<0.001	

N: Number of observations used in the analysis

Source: Full Clinical Study Report-Protocol Number QVA 1492337 Table 11-7, page 101

Tipping point analyses conducted for both studies (Table 10) support the primary analyses. Values of delta at which the analyses tipped, i.e. treatment effect was no longer significant, were considered large and not likely to occur. Hence, the primary analysis was considered robust with respect to missing data at Day 85.

Table 10. Tipping Point Analysis at Day 85 Change from Baseline FEV₁ AUC_{0-12h}

Study	Comparison	Tipping Point (L)
QVA 149A2336	QVA vs. QAB	1.00
	QVA vs. NVA	1.09
	QVA vs. Placebo	3.16
QVA 149A2337	QVA vs. QAB	1.46
	QVA vs. NVA	0.86
	QVA vs. Placebo	4.03

Source: Response to Information Request – Statistics Table 2-1, page 4

In both studies the by-treatment group comparison for the first primary efficacy endpoint, FEV₁ AUC_{0-12h} at week 12 was statistically significant for the QVA149 27.5/12.5 µg group, therefore; according to the pre-specified multiplicity plan, inferential statistical analysis proceeded to the first key secondary efficacy endpoint, SGRQ total score at week 12 for QVA149 27.5/12.5 µg versus placebo.

SGRQ total is shown in Table 11 for study 2336 and Table 12 for study 2337. QVA149 27.5/12.5 µg demonstrated a statistically significant improvement in the SGRQ total at week 12 compared to placebo for both studies.

Table 11. SGRQ Total at Week 12- Study 2336 (FAS)

	QVA 149 27.5/12.5 bid N=246	QAB149 27.5 mcg bid N=244	NVA237 12.5 bid N=243	Placebo N=223
Mean at week 12	-6.4	-4.6	-4.8	-2.7
Mean treatment Δ QVA 149 27.5/12.5 vs QAB 27.5	-1.9			
95% CI	-3.8, 0.0			
p-value	0.052			
Mean treatment Δ QVA 149 27.5/12.5 vs NVA 12.5	-1.7			
95% CI	-3.6, 0.2			
p-value	0.083			
Mean treatment Δ Drug vs Placebo	-3.8	-1.9	-2.1	
95% CI	-5.7, -1.8	-3.8, 0.1	-4.0, -0.1	
p-value	<0.001	0.058	0.036	

N: Number of observations used in the analysis

Source: Full Clinical Study Report-Protocol Number QVA 1492336 Table 11-9, page 112

Table 12. SGRQ Total at Week 12- Study 2337 (FAS)

	QVA 149 27.5/12.5 bid N=238	QAB149 27.5 mcg bid N=234	NVA237 12.5 bid N=237	Placebo N=226
Mean at week 12	-7.5	-5.9	-6.0	-1.1
Mean treatment Δ QVA 149 27.5/12.5 vs QAB 27.5	-1.5			
95% CI	-3.6, 0.6			
p-value	0.158			
Mean treatment Δ QVA 149 27.5/12.5 vs NVA 12.5	-1.4			
95% CI	-3.5, 0.7			
p-value	0.190			
Mean treatment Δ Drug vs Placebo	-6.4	-4.8	-4.9	
95% CI	-8.5, -4.2	-7.0, -2.7	-7.1, -2.8	
p-value	<0.001	<0.001	<0.001	

N: Number of observations used in the analysis

Source: Full Clinical Study Report-Protocol Number QVA 1492337 Table 11-9, page 108

Again, for both studies, the comparison for change in baseline in SGRQ total score was statistically significant so the inferential statistical analysis proceeded to the next key secondary endpoint, proportion of patients who achieved a clinically important improvement of at least 4 in the SGRQ total score at week 12, shown in Tables 13 and 14. Compared to placebo, QVA149 27.5/12.5 µg demonstrated a statistically significant improvement over placebo in the analysis of the proportion of patients with a clinically meaningful improvement of at least 4 units in the SGRQ total score in both studies 2336 and 2337. In study 2336, QAB149 27.5 µg and NVA237

12.5 µg did not demonstrate significance difference compared to placebo. However, in study 2337, each monotherapy was significantly different from placebo. In study 2336 the combination product was significantly different from both monotherapies but in study 2337 the combination product was not different from either monotherapy. Note these comparisons were not pre-specified in the multiplicity plan. Therefore, the results of the key secondary analyses are only considered supportive of the primary analysis.

Table 13. Proportion of patients with a clinically important improvement of at least 4 units in the SGRQ Total Score at Week 12- Study 2336 (FAS)

	QVA 149 27.5/12.5 bid N=258	QAB149 27.5 mcg bid N=260	NVA237 12.5 bid N=261	Placebo N=261
n/M (%)	141/246 (57)	117/244 (48)	112/243 (46)	87/223 (39)
Odds Ratio QVA 149 27.5/12.5 / QAB 27.5	1.53			
95% CI	1.06, 2.22			
p-value	0.024			
Odds Ratio QVA 149 27.5/12.5 / NVA 12.5	1.60			
95% CI	1.10, 2.32			
p-value	0.014			
Odds Ratio Drug/ Placebo	2.20	1.44	1.38	
95% CI	1.50, 3.24	0.98, 2.10	0.94, 2.02	
p-value	<0.001	0.062	0.101	

n: Number of patients who achieved an improvement of at least 4 units, i.e. a decrease ≥ 4

M: Number of patients with a SGRQ total score (included in the analysis)

N: Number of patients in the analysis set

Source: Full Clinical Study Report-Protocol Number QVA 1492336 Table 11-10, page 114

Table 14. Proportion of Patients with a Clinically Important Improvement of at Least 4 Units in the SGRQ Total Score at Week 12- Study 2337 (FAS)

	QVA 149 27.5/12.5 bid N=250	QAB149 27.5 mcg bid N=251	NVA237 12.5 bid N=250	Placebo N=247
n/M (%)	141/238 (59)	133/234 (57)	122/237 (52)	78/226 (35)
Odds Ratio QVA 149 27.5/12.5 / QAB 27.5	1.13			
95% CI	0.78, 1.65			
p-value	0.520			
Odds Ratio QVA 149 27.5/12.5 / NVA 12.5	1.40			
95% CI	0.96, 2.04			
p-value	0.081			
Odds Ratio Drug/ Placebo	2.85	2.52	2.04	
95% CI	1.93, 4.21	1.70, 3.73	1.38 3.01	
p-value	<0.001	<0.001	<0.001	

n: Number of patients who achieved an improvement of at least 4 units, i.e. a decrease ≥ 4

M: Number of patients with a SGRQ total score (included in the analysis)

N: Number of patients in the analysis set

Source: Full Clinical Study Report-Protocol Number QVA 1492337 Table 11-10, page 110

3.2.4.2 Study 2340

There were no multiplicity adjustments made for any of the secondary endpoints evaluated in this study. The results are described for descriptive purposes only. The primary endpoint for study 2340 was AE rate, a safety endpoint and was not included in this efficacy review. However, the results for the secondary efficacy endpoint, pre-dose trough FEV₁ are shown in Table 15 by visit was included. A difference was demonstrated in the pre-dose trough FEV₁ at each visit over the 52 weeks for both doses of QVA149, 27.5/12.5 µg b.i.d. and 27.5/25 µg b.i.d compared to one of its monotherapy components, QAB149 75 µg o.d. This improvement supports the demonstration of the benefit of QVA149 over one of its monotherapy components, QAB149 75 µg o.d.

Table 15. Change from Baseline Pre-dose Trough FEV1 (L), by visit- study 2340 (FAS)

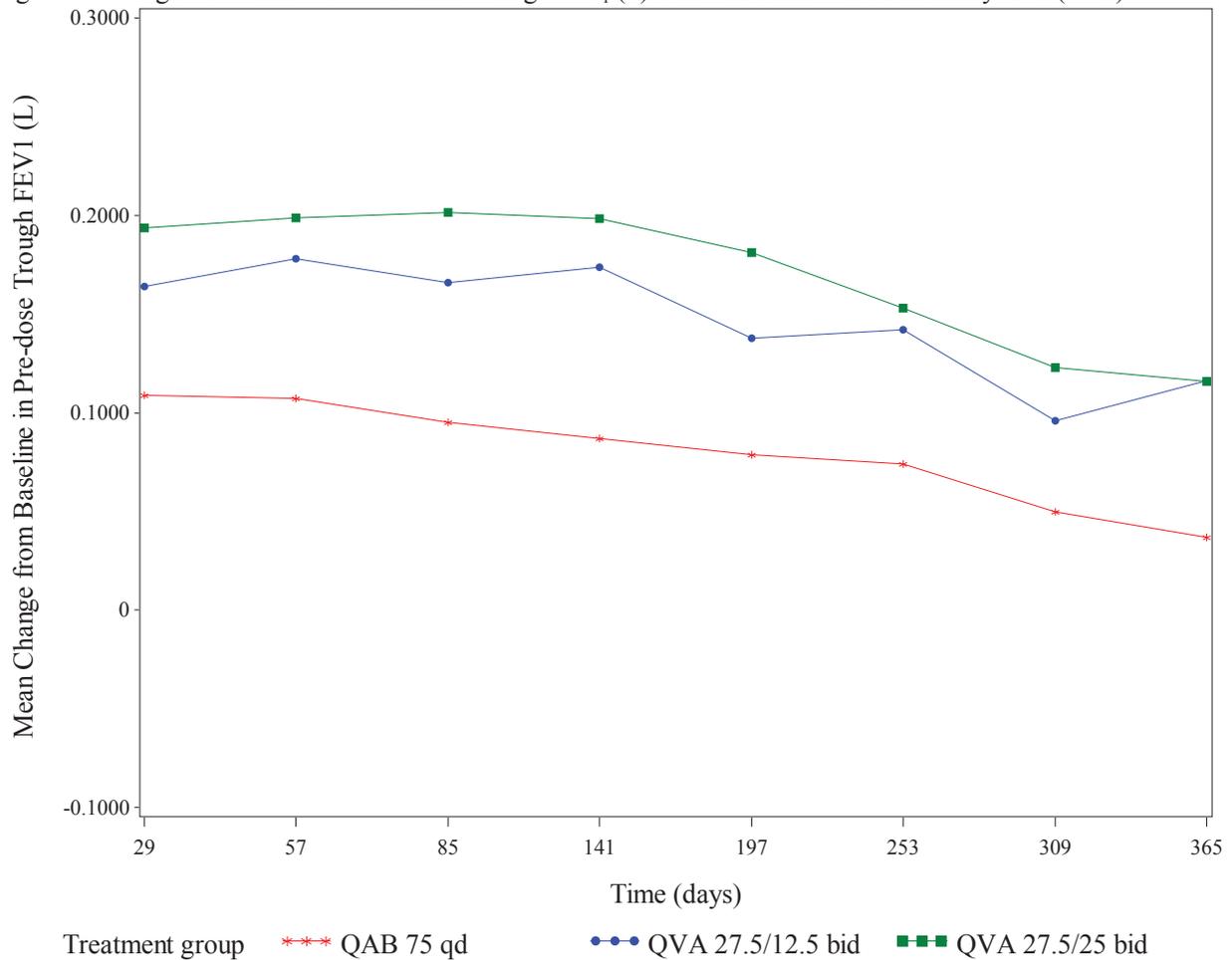
Day		QVA 149 27.5/12.5 bid N=192	QVA 149 27.5/25 mcg bid N=196	QAB149 75 mcg od N=199
Day 29	Mean	0.164	0.19	0.11
	Mean treatment Δ QVA 149 27.5/12.5 vs QAB149 75	0.06		
	95% CI	0.02, 0.09		
	p-value	0.006		
	Mean treatment Δ QVA 149 27.5/25 vs QAB149 75		0.09	
Day 57	95% CI		0.05, 0.12	
	p-value		<0.001	
	Mean	0.18	0.20	0.11
	Mean treatment Δ QVA 149 27.5/12.5 vs QAB149 75	0.07		
	95% CI	0.03, 0.11		
Day 85	p-value	<0.001		
	Mean treatment Δ QVA 149 27.5/25 vs QAB149 75		0.09	
	95% CI		0.05, 0.13	
	p-value		<0.001	
	Mean	0.17	0.20	0.10
Day 141	Mean treatment Δ QVA 149 27.5/12.5 vs QAB149 75	0.07		
	95% CI	0.03, 0.11		
	p-value	0.001		
	Mean treatment Δ QVA 149 27.5/25 vs QAB149 75		0.11	
	95% CI		0.06, 0.15	
Day 197	p-value		<0.001	
	Mean	0.14	0.20	0.09
	Mean treatment Δ QVA 149 27.5/12.5 vs QAB149 75	0.09		
	95% CI	0.04, 0.13		
	p-value	<0.001		
Day 197	Mean treatment Δ QVA 149 27.5/25 vs QAB149 75		0.11	
	95% CI		0.06, 0.16	
	p-value		<0.001	
	Mean	0.14	0.18	0.08
	Mean treatment Δ QVA 149 27.5/12.5 vs QAB149 75	0.06		
95% CI	0.01, 0.10			
p-value	0.012			

Day 253	Mean treatment Δ			
	QVA 149 27.5/25 vs			
	QAB149 75		0.10	
	95% CI		0.06, 0.15	
	p-value		<0.001	
Day 309	Mean	0.14	0.15	0.10
	Mean treatment Δ			
	QVA 149 27.5/12.5			
	vs QAB149 75	0.070		
	95% CI	0.02, 0.11		
Day 365	p-value	0.004		
	Mean treatment Δ			
	QVA 149 27.5/25 vs			
	QAB149 75		0.08	
	95% CI		0.03, 0.13	
Day 309	p-value	0.10	<0.001	0.05
	Mean	0.10	0.12	0.05
	Mean treatment Δ			
	QVA 149 27.5/12.5			
	vs QAB149 75	0.05		
Day 365	95% CI	0.002, 0.09		
	p-value	0.041		
	Mean treatment Δ			
	QVA 149 27.5/25 vs			
	QAB149 75		0.07	
Day 365	95% CI		0.03, 0.12	
	p-value		0.001	
	Mean	0.12	0.12	0.04
	Mean treatment Δ			
	QVA 149 27.5/12.5			
Day 365	vs QAB149 75	0.08		
	95% CI	0.03, 0.13		
	p-value	<0.001		
	Mean treatment Δ			
	QVA 149 27.5/25 vs			
Day 365	QAB149 75		0.08	
	95% CI		0.03, 0.13	
	p-value		<0.001	

Source: Full Clinical Study Report-Protocol Number QVA 149A2340 Table 11-7, pages 112-113

A graph of the change from baseline pre-dose trough FEV₁ over the post-baseline visits is shown below, see Figure 1. A separation in the curves is seen between both doses of QVA149 and QAB149 75 µg.

Figure 1. Change from Baseline in Pre-dose Trough FEV₁ (L) over Post-baseline Visits - Study 2340 (FAS)



Time to first moderate or severe COPD exacerbation and annual rate of moderate and severe COPD exacerbations, are included in this review.

Time to first moderate or severe COPD exacerbation is shown in Table 16. There were about the same number of patients in both QVA149 27.5/12.5 µg b.i.d. and QVA149 27.5/25 µg b.i.d groups that had experienced a moderate or severe COPD exacerbation. There were no differences noted between the treatment groups with respect to COPD exacerbations.

Table 16. Results Time to First Moderate or Severe COPD Exacerbation- Study 2340 (FAS)

	QVA 149 27.5/12.5 bid N=204	QVA 149 27.5/25 mcg bid N=204	QAB149 75 mcg od N=206
n/M (%)	47/200 (24)	50/201 (25)	54/200 (27)
Hazard Ratio QVA 149 27.5/12.5 QAB149 75	0.88		
95% CI	0.59, 1.30		
p-value	0.516		
Hazard Ratio QVA 149 27.5/12.5 QVA 149 27.5/25	1.00		
95% CI	0.67, 1.49		
p-value	0.0.993		
Hazard Ratio QVA 149 27.5/25 QAB149 75		0.88	
95% CI		0.60, 1.29	
p-value		0.502	

n: Number of patients with a moderate or severe COPD exacerbation

M: Number of patients included in the analysis

N: Number of patients in the analysis set

Source: Full Clinical Study Report-Protocol Number QVA 149A2340 Table 11-8, pages 116

The results for the annual rate of moderate or severe COPD exacerbations are shown in Table 17. There were no significant differences demonstrated between the two treatment groups.

Table 17. Rate of Moderate or Severe COPD Exacerbations During Treatment-Study 2340 (FAS)

	QVA 149 27.5/12.5 bid N=204	QVA 149 27.5/25 mcg bid N=204	QAB149 75 mcg od N=206
N	200	201	200
Rate Ratio QVA 149 27.5/12.5 QAB149 75	0.75		
95% CI	0.51, 1.12		
p-value	0.163		
Rate Ratio QVA 149 27.5/12.5 QVA 149 27.5/25	0.87		
95% CI	0.58, 1.30		
p-value	0.497		
Rate Ratio QVA 149 27.5/25 QAB149 75		0.87	
95% CI		0.69, 1.27	
p-value		0.464	

n: Number of patients included in the analysis

N: Number of patients in the analysis set

Source: Full Clinical Study Report-Protocol Number QVA 149A2340 Table 11-9, pages 117

3.3 Evaluation of Safety

Safety evaluations for this submission will be evaluated by the Medical Reviewer, Erika Torjusen, M.D. Refer to her review for more details regarding the safety findings of QVA149.

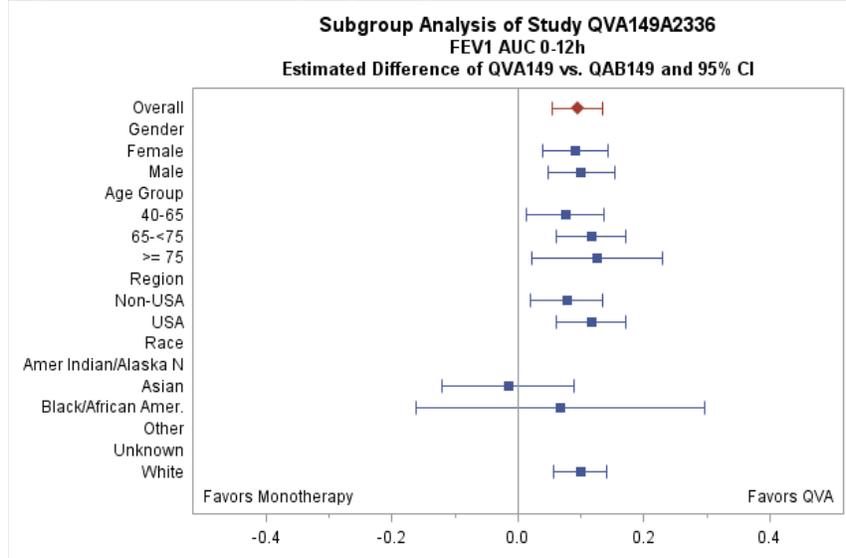
4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analysis on the primary and key secondary efficacy endpoints are shown by gender, age, race (Black or African American, American Indian or Alaskan Native, Asian, White, and Other), airflow limitation, smoking status, and ICS use in studies 2336 and 2337 only. The subgroups were examined by adding the relevant subgroup and treatment by subgroup interaction to the primary analysis model, with results evaluated at the nominal 0.05 level of significance. The subgroup analyses were performed using the FAS population.

4.1 Gender, Race, and Age

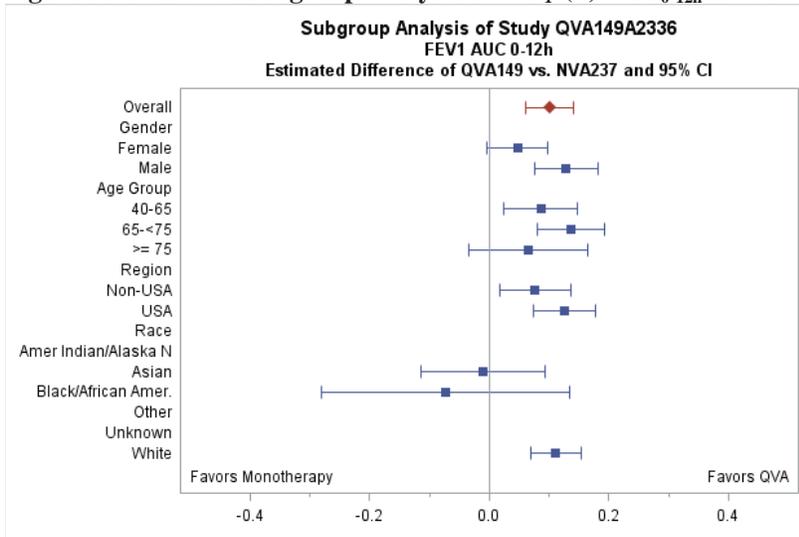
Figures 2-5 below summarize the efficacy results by subgroups for studies 2336 and 2337 for gender, race, and age. The figures are separated by the comparison of QVA149 versus each of its monotherapy components, QAB149 and NVA237. In general, the subgroup analyses were consistent with the primary and key secondary results from the overall population. However, these studies were not designed or powered to detect differences in these specific groups.

Figure 2. Forest Plot Subgroup Analysis of FEV₁ (L) AUC_{0-12h} at Week 12 QVA149 vs. QAB149- Study 2336



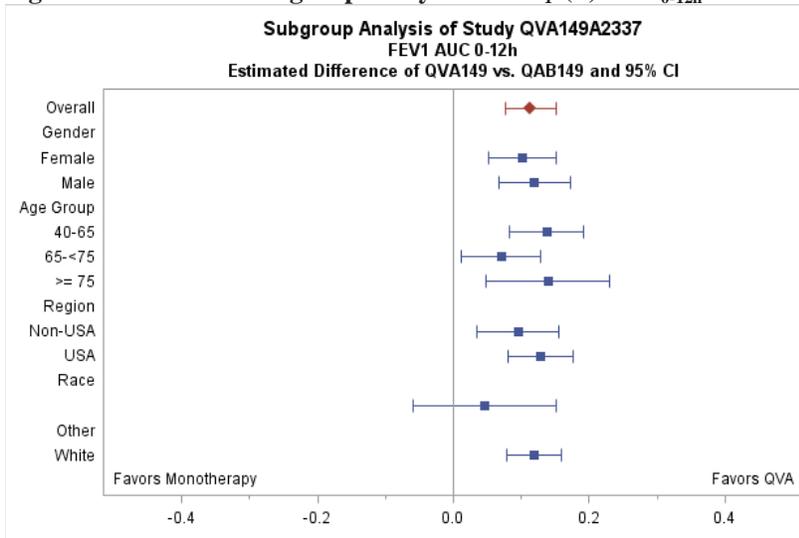
Source: Reviewer

Figure 3. Forest Plot Subgroup Analysis of FEV₁ (L) AUC_{0-12h} at Week 12, QVA149 vs. NVA237- Study 2336



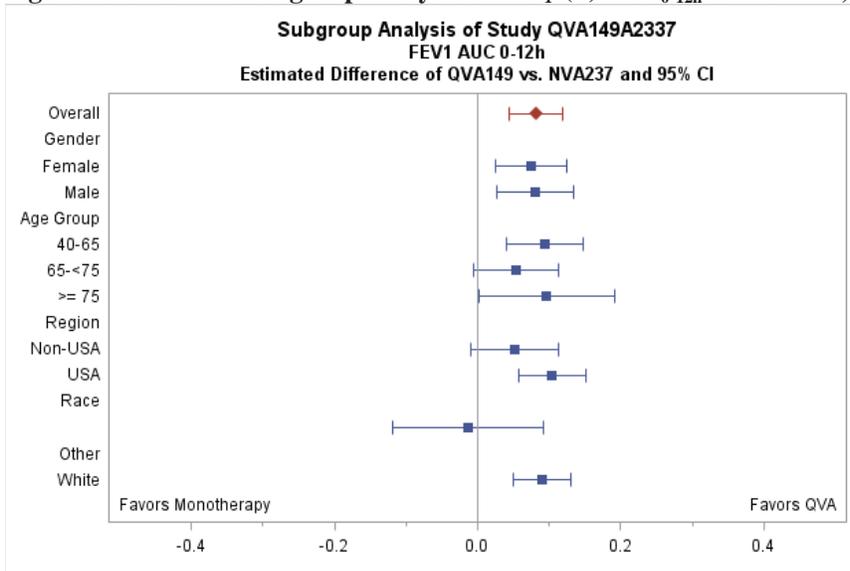
Source: Reviewer

Figure 4. Forest Plot Subgroup Analysis of FEV₁ (L) AUC_{0-12h} at Week 12, QVA149 vs. QAB149- Study 2337



Source: Reviewer

Figure 5. Forest Plot Subgroup Analysis of FEV₁ (L) AUC_{0-12h} at Week 12, QVA149 vs. NVA237- Study 2337

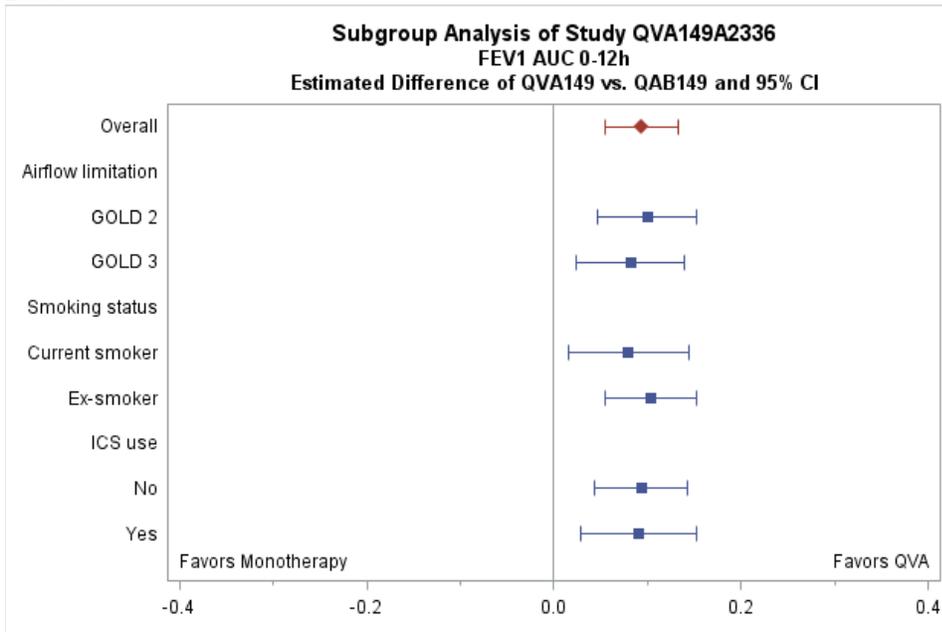


Source: Reviewer

4.2 Other Special/Subgroup Populations

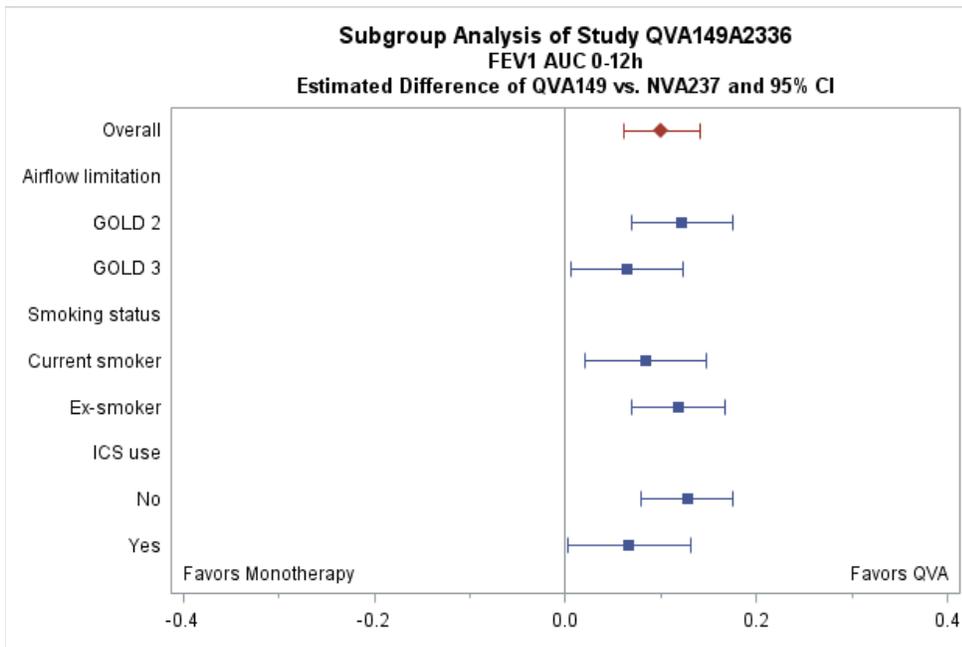
Figures 6-9 below summarize the efficacy results by subgroups for studies 2336 and 2337 for airflow limitation, smoking, and ICS use. The figures are separated by the comparison of QVA149 versus each of its mono-components, QAB149 and NVA237. In general, the subgroup analyses were consistent with the primary and key secondary results from the overall population. However, these studies were not designed or powered to detect differences in these specific groups.

Figure 6. Forest Plot Other Subgroup Analysis of FEV₁ (L) AUC_{0-12h} at Week 12 QVA149 vs. QAB149- Study 2336



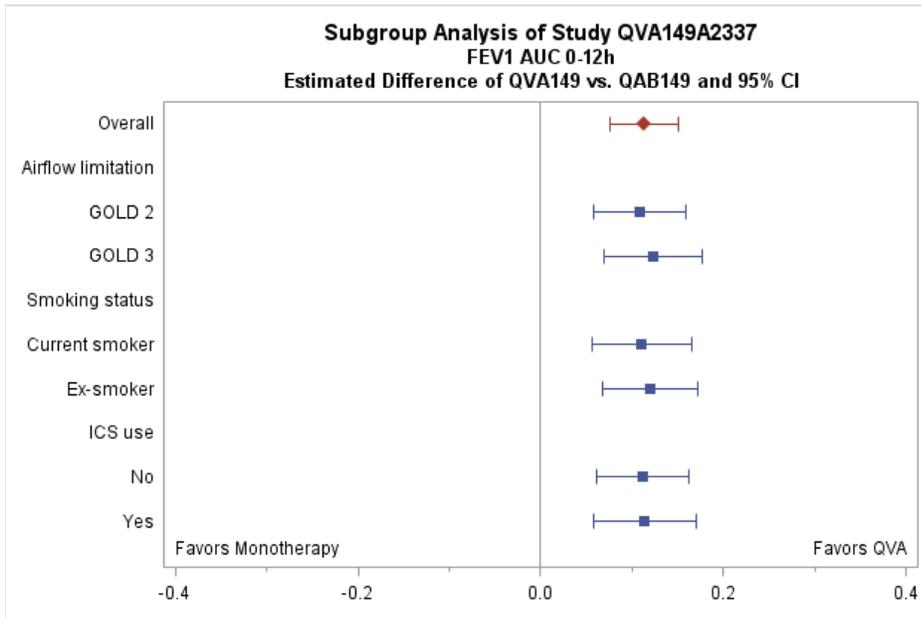
Source: Reviewer

Figure 7. Forest Plot Other Subgroup Analysis of FEV₁ (L) AUC_{0-12h} at Week 12 QVA149 vs. NVA237- Study 2336



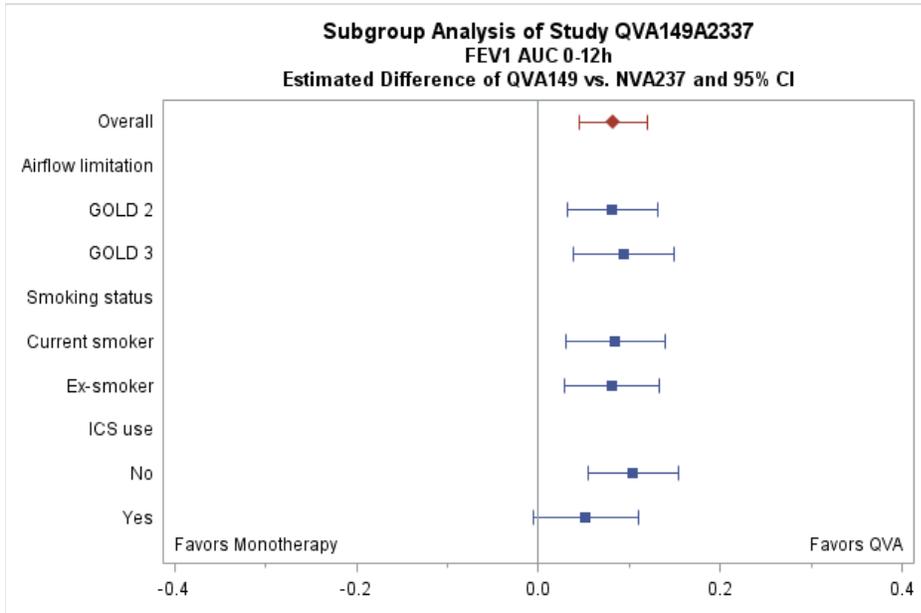
Source: Reviewer

Figure 8 Forest Plot Other Subgroup Analysis of FEV₁ (L) AUC_{0-12h} at Week 12 QVA149 vs. QAB149- Study 2337



Source: Reviewer

Figure 9 Forest Plot Other Subgroup Analysis of FEV₁ (L) AUC_{0-12h} at Week 12 QVA149 vs. NVA237- Study 2337



Source: Reviewer

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

During the course of this review, an information request (IR) was sent to the applicant. The IR requested tipping point sensitivity analyses in the two efficacy studies 2336 and 2337 to examine the impact of missing data on primary analyses. The applicant submitted a detailed description of the tipping point analyses for the primary endpoint, FEV₁ AUC_{0-12h} to address this concern. No other statistical concerns were noted.

5.2 Conclusions and Recommendations

In studies 2336 and 2337, QVA149 27.5/12.5 µg b.i.d. demonstrated a statistically significant improvement in the primary endpoint, FEV₁ AUC_{0-12h} at week 12 compared to each of its monotherapy components, QAB149 37.5 µg b.i.d. and NVA237 12.5 µg b.i.d. In addition, the combination product and each monotherapy were significantly better than placebo with respect to improvement in lung function at week 12. For SGRQ, a secondary endpoint that was not adjusted for multiplicity, when compared to placebo, the combination product, as well as, each monotherapy was better than placebo in study 2337. The benefit of the combination product over the monotherapies was not consistent. In study 2336, treatment with QVA149 27.5/12.5 µg b.i.d. demonstrated a significant improvement in SGRQ scores when compared to each monotherapy. In general, the analyses of SGRQ related endpoints were considered supportive of the primary endpoint.

Study 2340 demonstrated a significant difference in the treatment differences between both doses of QVA149 over one of its monotherapy components, QAB149 75 µg o.d. in the change from baseline in pre-dose trough FEV₁ at each visit over the 52 weeks. This statistically significant improvement supports the demonstration of the benefit of QVA149 over one of its monotherapy components, QAB149 75 µg o.d. in support of lung function. However, time to first moderate or severe COPD exacerbation and annual rate of moderate or severe COPD exacerbation did not demonstrate any significant differences QVA149 at any dose compared to QAB149 75 µg o.d.

Based on the results from the two efficacy studies and the one long term study comparing the study drug to its monotherapies, the efficacy of QVA149 27.5/12.5 µg b.i.d for the long-term, twice daily maintenance treatment of airflow obstruction in patients with COPD including chronic bronchitis and/or emphysema was demonstrated. For studies 2336 and 2337, the results of the tipping point analyses to evaluate the impact of missing data on primary analysis were considered robust and support the efficacy of the combination product.

5.3 Comment on the Proposed Label

The following suggestions have been made for Section 14 of the label.

- Removal of Figure 1
- Removal of (b) (4)
- Suggest that (b) (4). Show the individual study reports.

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

/s/

KIYA HAMILTON
10/15/2015

DAVID M PETULLO
10/15/2015
I concur.



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 207-930/0000

Drug Name: QVA149 (indacaterol/glycopyrrolate) Inhalation Powder Hard Capsules

Indication(s): Long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema

Applicant: Novartis

Date(s): Receipt date: December 29, 2014
PDUFA date: October 29, 2015

Review Priority: Standard

Biometrics Division: Division of Biometrics II

Statistical Reviewer: Kiya Hamilton, Ph.D.

Concurring Reviewers: David Petullo, M.S., Team Leader

Medical Division: Division of Pulmonary, Allergy and Rheumatology Products

Clinical Team: Erika Torjusen, M.D., Medical Reviewer
Anthony Durmowicz, M.D., Team Leader
Badrul A. Chowdhury, M.D. Ph.D., Medical Division Director

Project Manager: Christine Ford

Keywords: NDA, clinical studies

Table of Contents

LIST OF FIGURES	4
1 EXECUTIVE SUMMARY	5
2 INTRODUCTION	5
2.1 OVERVIEW	5
2.1.1 <i>Class and Indication</i>	5
2.1.2 <i>History of Drug Development</i>	5
2.1.3 <i>Specific Studies Reviewed</i>	6
2.2 DATA SOURCES	6
3 STATISTICAL EVALUATION	6
3.1 DATA AND ANALYSIS QUALITY	6
3.2 EVALUATION OF EFFICACY	6
3.2.1 <i>Study Design and Endpoints</i>	6
3.2.2 <i>Statistical Methodologies</i>	8
3.2.3 <i>Patient Disposition, Demographic and Baseline Characteristics</i>	9
3.2.4 <i>Results and Conclusions</i>	12
3.3 EVALUATION OF SAFETY	22
4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS	22
4.1 GENDER, RACE, AND AGE	22
4.2 OTHER SPECIAL/SUBGROUP POPULATIONS	24
5 SUMMARY AND CONCLUSIONS	26
5.3 COMMENT ON THE PROPOSED LABEL	27

LIST OF TABLES

Table 1. Summary of Study Design and Primary Endpoints	7
Table 2. Summary of Patient Disposition in Study 2336.....	10
Table 3. Summary of Patient Disposition in Study 2337.....	10
Table 4. Demographics in Study 2336 - Randomized Set.....	11
Table 5. Demographics in Study 2337 - Randomized Set.....	11
Table 6. Summary of Patient Disposition Study 2340.....	12
Table 7. Demographics in Study 2340- Randomized Set.....	12
Table 8. Primary Efficacy Results-Change from Baseline in FEV ₁ (L) AUC _(0-12h) at Week 12- Study 2336 (FAS Population).....	13
Table 9. Primary Efficacy Results-Change from Baseline in FEV ₁ (L) AUC _(0-12h) at Week 12- Study 2337 (FAS Population).....	14
Table 10. Tipping Point Analysis at Day 85 Change from Baseline FEV ₁ AUC0-12h	14
Table 11. SGRQ Total at Week 12- Study 2336 (FAS)	15
Table 12. SGRQ Total at Week 12- Study 2337 (FAS)	15
Table 13. Proportion of patients with a clinically important improvement of at least 4 units in the SGRQ Total Score at Week 12- Study 2336 (FAS).....	16
Table 14. Proportion of Patients with a Clinically Important Improvement of at Least 4 Units in the SGRQ Total Score at Week 12- Study 2337 (FAS).....	17
Table 15. Change from Baseline Pre-dose Trough FEV ₁ (L), by visit- study 2340 (FAS)	18
Table 16. Results Time to First Moderate or Severe COPD Exacerbation- Study 2340 (FAS).....	21
Table 17. Rate of Moderate or Severe COPD Exacerbations During Treatment-Study 2340 (FAS)	21

LIST OF FIGURES

Figure 1. Change from Baseline in Pre-dose Trough FEV ₁ (L) over Post-baseline Visits-Study 2340 (FAS).....	20
Figure 2. Forest Plot Subgroup Analysis of FEV ₁ (L) AUC _{0-12h} at Week 12 QVA149 vs. QAB149- Study 2336.....	22
Figure 3. Forest Plot Subgroup Analysis of FEV ₁ (L) AUC _{0-12h} at Week 12, QVA149 vs. NVA237- Study 2336.....	23
Figure 4. Forest Plot Subgroup Analysis of FEV ₁ (L) AUC _{0-12h} at Week 12, QVA149 vs. QAB149- Study 2337.....	23
Figure 5. Forest Plot Subgroup Analysis of FEV ₁ (L) AUC _{0-12h} at Week 12, QVA149 vs. NVA237- Study 2337.....	24
Figure 6. Forest Plot Other Subgroup Analysis of FEV ₁ (L) AUC _{0-12h} at Week 12 QVA149 vs. QAB149- Study 2336	25
Figure 7. Forest Plot Other Subgroup Analysis of FEV ₁ (L) AUC _{0-12h} at Week 12 QVA149 vs. NVA237- Study 2336	25
Figure 8 Forest Plot Other Subgroup Analysis of FEV ₁ (L) AUC _{0-12h} at Week 12 QVA149 vs. QAB149- Study 2337	26
Figure 9 Forest Plot Other Subgroup Analysis of FEV ₁ (L) AUC _{0-12h} at Week 12 QVA149 vs. NVA237- Study 2337	26

1 EXECUTIVE SUMMARY

Novartis proposes QVA149, a combination product of indacaterol (QAB149) and glycopyrrolate (NVA237) for the long term maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

To support efficacy, the applicant submitted the results from two 12 week, phase 3, multi-center, double-blind, placebo- and active-controlled, parallel-group, randomized efficacy and safety studies, QVA149A2336 (2336) and QVA149A2337 (2337). In these studies, compared to each monotherapy component, QVA149 27.5/12.5 µg b.i.d. demonstrated a statistically significant improvement in the primary endpoint, FEV₁ AUC_{0-12h} at week 12 and placebo. In the analysis of St George's Respiratory Questionnaire (SGRQ), a secondary endpoint of interest, the combination product and each monotherapy demonstrated a significant improvement over placebo in both studies. In study 2337, the combination product also demonstrated a significant improvement when compared to the monotherapy components. This effect was not noted in study 2336.

Efficacy was also demonstrated in a long term safety study, QVA149A2340 (2340). This 52-week study was a multi-center, double-blind, active-controlled, parallel-group, randomized, efficacy and safety study of QVA149 27.5/12.5 µg b.i.d. and QVA149 27.5/25 µg b.i.d. versus indacaterol (QAB149) 75 µg once daily in patients with COPD with moderate to severe airflow limitations. There were significant differences between both doses of QVA149 and QAB149 in the change from baseline in pre-dose trough FEV₁ at each visit over the 52 weeks. However, regardless of dose, there were no differences in time to first moderate or severe COPD exacerbation and annual rate of moderate or severe COPD exacerbation between QVA149 and QAB149.

2 INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Novartis developed a fixed dose combination of two long acting bronchodilators, indacaterol maleate (QAB149) which is a long-acting β₂-adrenergic agonist, and glycopyrronium bromide (NVA237) which is a long acting muscarinic antagonist. NVA237 is currently being reviewed as a monotherapy under NDA 207923. The applicant proposes the combination product, indacaterol/glycopyrrolate inhalation powder, hereafter referred to as QVA149 27.5/12.5 µg twice daily for the long term treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

2.1.2 History of Drug Development

There were several interactions between Novartis and the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) regarding the development program of QVA149 under IND 76,377. However, these interactions were not relevant to this statistical review.

2.1.3 Specific Studies Reviewed

This review will focus on the results from studies QVA149A2336, QVA149A2337, and QVA149A2340 (hereafter referred to as 2336, 2337, and 2340 respectively).

2.2 Data Sources

The submission of NDA 207-930 was received on December 29, 2014. The study reports including protocols, statistical analysis plan, and all referenced literature were submitted by the applicant to the Agency. The data and final study report for the electronic submission were archived under the network path location \\cdsesub1\evsprod\nda207930\0000.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

In general, the electronic data submitted by the applicant were of sufficient quality to allow a thorough review of the data. I was able to reproduce the analyses of the primary and secondary efficacy endpoints for each clinical study submitted and were able to verify the randomization of the treatment assignments.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

A summary of the study design and endpoints for the efficacy studies are shown in Table 1. Each study is discussed below.

Table 1. Summary of Study Design and Primary Endpoints

Study ID	Length of the Study	Treatment Arms*	Number of Patients	Study Population	Primary Efficacy Endpoint(s)
2336	12 weeks DB period	QVA149	258	Moderate to severe airflow limitation	FEV ₁ AUC ₀₋₁₂ hours at week 12
		27.5/12.5 bid	260		
		QAB149 27.5 bid	261		
		NVA 12.5 bid	261		
2337	12 weeks DB period	QVA149	250	Moderate to severe airflow limitation	FEV ₁ AUC ₀₋₁₂ hours at week 12
		27.5/12.5 bid	251		
		QAB149 27.5 bid	250		
		NVA 12.5 bid	247		
2340	52 weeks DB period	QVA149	204	Moderate to severe airflow limitation	Safety: Overall AE rate
		27.5/12.5 bid	204		
		QVA149 27.5/25 bid	206		
		QAB149 75 od	206		

Source: Reviewer

* bid: Twice a day, od: Once a day

3.2.1.1 Studies 2336 and 2337

Studies 2336 and 2337 were phase 3, randomized, double-blind, parallel-group, placebo- and active-controlled, multi-center, 12 week studies. These studies were designed to evaluate the efficacy and safety of QVA149 27.5/12.5 µg administered twice daily (b.i.d.) versus the monotherapy components QAB149 27.5 µg b.i.d and NVA237 12.5 µg b.i.d. as well as placebo in COPD patients with moderate to severe airflow limitation. Patients were randomized in a 1:1:1:1 ratio and stratified by smoking (current / ex-smoker) status.

The primary endpoint for both studies was change from baseline in FEV₁ AUC_{0-12h} post morning dose at week 12. Baseline FEV₁ was defined as the mean of the pre-dose FEV₁ measured at -45 minutes and -15 minutes at day 1. The key secondary endpoints are St. George's Respiratory Questionnaire (SGRQ) total score at week 12 and percentage of patients with clinically significant improvement in SGRQ total score at week 12.

3.2.1.2 Study 2340

Study 2340 was a multi-center, double-blind, active controlled, parallel-group, randomized 52-week treatment efficacy and safety study of QVA149 27.5/12.5 µg b.i.d. in patients with COPD with moderate to severe airflow limitations. Patients were permitted COPD background therapy in this long-term safety study. Patients were randomized in a 1:1:1 ratio to either QVA149 27.5/12.5 µg b.i.d., QVA149 27.5/25 µg b.i.d, or QAB149 75 µg o.d. Note, QAB149 is an approved bronchodilator. Treatment randomization was stratified by smoking (current or ex-smoker), ICS use (yes or no), and severity of airflow limitation (moderate or severe).

The secondary efficacy endpoints, change from baseline in pre-dose trough FEV₁ (average of the two FEV₁ measurements 45 and 15 minutes pre-dose) at days 29, 57, 85, 141, 197, 253, 309, and 365, time to first moderate or severe COPD exacerbation, and annual rate of moderate or severe COPD exacerbation, will be discussed in this review. A COPD exacerbation was defined as a worsening of the following two or more major symptoms for at least two consecutive days: dyspnea, sputum volume and sputum purulence, or a worsening of any one major symptom together with an increase in any one of the following minor symptoms for at least two consecutive days: sore throat, colds (nasal discharge and/or nasal congestion), fever without other cause, cough and wheeze. A COPD exacerbation was considered of moderate severity if treatment with systemic corticosteroids or antibiotics or both was required and severe, if hospitalization was required. An emergency room visit of longer than twenty-four hours was considered a hospitalization. The primary endpoint was overall adverse event (AE) rate, a safety endpoint and is not discussed further in this review.

3.2.2 Statistical Methodologies

All efficacy analyses were performed using the full analysis set (FAS), which was defined as all randomized patients who received at least one dose of study drug.

3.2.2.1 Studies 2336 and 2337

Missing FEV₁ measurements were not imputed when deriving AUC_{0-12h}. FEV₁ measurements within 6 hours of rescue medication use or within 7 days of systemic corticosteroid use were considered missing.

In both studies the pre-specified analysis of the primary efficacy endpoint, change from baseline in FEV₁ AUC_{0-12h} post morning dose at week 12, was a mixed model for repeated measures (MMRM) with treatment, baseline FEV₁, smoking status at baseline, baseline ICS use, region, visit, treatment-by-visit interaction, and baseline FEV₁-by-visit interaction. The null hypothesis of no difference in FEV₁ AUC_{0-12h} in patients treated with the combination product and each monotherapy was tested at a significance level of 0.05. The key secondary endpoint, change from baseline in SGRQ total score was analyzed using a linear mixed model with treatment, baseline SGRQ score, smoking status at baseline, and history of ICS use as fixed effects. Center nested within region was included as a random effect. The proportion of patients who achieved a clinically important improvement of at least 4 units in the SGRQ total score was compared using logistic regression with treatment, baseline SGRQ score, smoking status at baseline, and history of ICS use as fixed effects. Center nested within region was included as a random effect in the model.

A gate keeping procedure was used to protect the overall type I error for the primary and key secondary endpoints.

- If superiority of QVA149 27.5/12.5 µg b.i.d. over each of its monotherapy components: QAB149 27.5 and NVA237 12.5 µg b.i.d. was established for FEV₁ AUC_{0-12h} at week 12 at the 0.05 level (for each component)

- Then the test for SGRQ total score was performed. If superiority of QVA149 27.5/12.5 µg b.i.d. over placebo in SGRQ total score was statistically significant at the 0.05 level
- Then QVA149 27.5/12.5 µg b.i.d. was compared to placebo for percentage of patient with clinically significant improvement of at least 4 units in SGRQ total score at the 0.05 level.

The trapezoidal rule was used to calculate FEV₁ AUC_{0-12h} similar to a time weighted average. For each patient, an AUC was calculated based on the existing FEV₁ measurements (i.e., the missing FEV₁ measurements were not to be interpolated). The following is an excerpt from the clinical study report.

Specifically, for those patients who had a FEV₁ assessment at only one time point, their AUC was approximated by the observed FEV₁. For those patients who had more than one FEV₁ assessment, their AUC was approximated by $\sum_{k=2}^m w_k \tilde{y}_k$, where $\tilde{y}_k = 0.5(y_k + y_{k-1})$, $w_k = (t_k - t_{k-1}) / (t_m - t_1)$, and y_j is the FEV₁ value at time t_j , for $j = 1, \dots, m$, in which $t_1 < \dots < t_m$ are the time points when FEV₁ are measured. Scheduled measurement times t_j rather than actual times were used. If FEV₁ AUC_{0-12h} was missing at week 12, then the FEV₁ AUC_{0-12h} measured at day 1 was not carried forward.

To evaluate the impact of missing data at day 85 for the primary endpoint, change from baseline in FEV₁ AUC_{0-12h}, tipping point analyses were provided by the applicant. This included the possibility that patients with missing data in the active arms had worse outcomes than patients with missing data in the placebo arm. Using a multiple imputation approach, values for the active arm were decreased by a specific delta and primary analysis was repeated. If the conclusions did not change, i.e. there was still a significant treatment effect, the delta was increased and the analysis was repeated. This process continued until significance was no longer noted, i.e. the analysis tipped.

3.2.2.2 Study 2340

The change from baseline in pre-dose trough FEV₁ at weeks 4 and 52 was analyzed using a repeated measures analysis of covariance (ANCOVA) model with treatment, baseline FEV₁, visit, treatment by visit interaction, visit by baseline FEV₁ interaction, smoking status at baseline, baseline ICS use, airflow limitation severity, and region as fixed effects. Time to first moderate or severe COPD exacerbation was analyzed using Cox regression model with treatment, baseline total symptom score, baseline COPD exacerbation history (i.e. number of COPD exacerbations during 12 months prior to study), smoking status at baseline, baseline ICS use, airflow limitation severity, and region as fixed effects. The rate of moderate or severe COPD exacerbations was analyzed using a generalized linear model assuming a negative binomial distribution. The model included with treatment, baseline FEV₁, visit, treatment by visit interaction, visit by baseline FEV₁ interaction, smoking status at baseline, baseline ICS use, airflow limitation severity, and region as fixed effects.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Study 2336 and 2337

The summary of the patient disposition in studies 2336 and 2337 are given in Tables 2 and 3. Approximately 1%-6% of the patients discontinued study medication in both studies over 12 weeks. The primary reason for discontinuation in both groups was patient/guardian decision.

Table 2. Summary of Patient Disposition in Study 2336

	QVA149 27.5/12.5 bid	QAB149 27.5 bid	NVA237 12.5 bid	Placebo
Randomized	260	260	261	261
FAS	258 (99)	260 (100)	261 (100)	261 (100)
Completed	255 (98)	251 (97)	258 (98)	246 (94)
Discontinued	5 (2)	9 (4)	3 (1)	15 (6)
Patient/guardian decision	4 (2)	4 (2)	2 (1)	11 (4)
Protocol deviation	1 (<1)	1 (<1)	0	1 (<1)
Death	0	1 (<1)	1 (<1)	1 (<1)
Physician decision	0	1 (<1)	0	2 (1)
Lost to follow-up	0	2 (1)	0	0

Source: Full Clinical Study Report-Protocol Number QVA149A2336 Table 10-1, page 92

Table 3. Summary of Patient Disposition in Study 2337

	QVA149 27.5/12.5 bid	QAB149 27.5 bid	NVA237 12.5 bid	Placebo
Randomized	250	251	251	249
FAS	250 (100)	251 (100)	250 (99)	247 (99)
Completed	244 (98)	241 (96)	245 (98)	236 (95)
Discontinued	6 (2)	10 (4)	6 (2)	13 (5)
Patient/guardian decision	3 (1)	9 (4)	3 (1)	9 (4)
Protocol deviation	1 (<1)	0	1 (<1)	0
Death	0	1 (<1)	0	0
Technical problems	0	0	2 (1)	1 (<1)
Lost to follow-up	0	0	2 (1)	1 (<1)

Source: Full Clinical Study Report-Protocol Number QVA149A2337 Table 10-1, page 88

Demographics and baseline characteristics for all randomized patients in studies 2336 and 2337 are given in Tables 4 and 5. The patients' mean age was approximately 64 years and most of the patients were White (88%-94%). These factors were generally well-balanced across the treatment groups.

Table 4. Demographics in Study 2336 - Randomized Set

	QVA149 27.5/12.5 bid N=260	QAB149 27.5 bid N=260	NVA237 12.5 bid N=261	Placebo N=261
Age (years)				
Mean (SD)	64 (9)	64 (8)	64 (9)	64 (8)
Sex n (%)				
Female	90 (35)	74 (29)	78 (30)	92 (35)
Male	170 (65)	186 (72)	183 (70)	169 (65)
Race n (%)				
White	241 (93)	239 (92)	230 (88)	244 (94)
Black	10 (4)	8 (3)	15 (6)	8 (3)
Asian	8 (3)	10 (4)	13 (5)	8 (3)
Native American	0	0	1 (<1)	1 (<1)
Pacific Islander	0	0	0	0
Unknown	0	1 (<1)	0	0
Other	1 (1)	2 (1)	2 (1)	0
Height				
Mean (SD)	169 (9)	170 (9)	170 (8)	168 (10)
Weight (kg)				
Mean (SD)	77 (17)	80 (17)	80 (18)	78 (17)

Source: Reviewer Analysis

Table 5. Demographics in Study 2337 - Randomized Set

	QVA149 27.5/12.5 bid N=250	QAB149 27.5 bid N=251	NVA237 12.5 bid N=251	Placebo N=249
Age (years)				
Mean (SD)	63 (9)	64 (9)	63 (9)	63 (8)
Sex n (%)				
Female	96 (38)	101 (40)	107 (43)	111 (45)
Male	154 (62)	150 (60)	144 (57)	138 (55)
Race n (%)				
White	230 (92)	224 (89)	222 (88)	227 (91)
Black	7 (3)	11 (4)	9 (4)	11 (4)
Asian	0	1 (<1)	0	0
Native American	12 (5)	15 (6)	19 (8)	10 (4)
Pacific Islander	0	0	0	0
Unknown	0	0	0	0
Other	1 (<1)	0	1 (<1)	1 (<1)
Height				
Mean (SD)	170 (9)	169 (10)	169 (10)	169 (9)
Weight (kg)				
Mean (SD)	79 (18)	80 (18)	79 (20)	76 (18)

Source: Reviewer Analysis

3.2.3.2 Study 2340

The summary of the patient disposition in study 2340 is given in Table 6. Approximately 11% of the patients discontinued study medication over 52 weeks. The primary reason for discontinuation in each group was patient/guardian decision.

Table 6. Summary of Patient Disposition Study 2340

	QVA149 27.5/12.5 bid n (%)	QVA149 27.5/25 bid n (%)	QAB149 75 od n (%)
Randomized	204	204	207
FAS			
Completed	177 (87)	187 (92)	183 (88)
Discontinued	27 (13)	17 (8)	24 (12)
Patient/guardian			
Decision	19 (9)	12 (6)	10 (5)
Lost to follow-up	5 (3)	1 (1)	6 (3)
Protocol deviation	1 (1)	0	1 (1)
Death	1 (1)	3 (2)	4 (2)
Physician decision	0	0	1 (1)
Adverse event	0	1 (1)	2 (1)
Technical problems	1 (1)	0	0

Source: Full Clinical Study Report-Protocol Number QVA149A2340 Table 10-1, page 98

Demographics and baseline characteristics for all randomized patients in study 2340 are given in Table 7. The patients' mean age was approximately 64 years and most of the patients were White (98%) in this study. These factors were generally well-balanced across the treatment groups.

Table 7. Demographics in Study 2340- Randomized Set

	QVA149 27.5/12.5 bid N=204	QVA149 27.5/25 bid N=204	QAB149 75 od N=207
Age (years)			
Mean (SD)	64 (8)	64 (9)	63 (9)
Sex n (%)			
Female	73 (36)	81 (40)	58 (28)
Male	131 (64)	123 (60)	149 (72)
Race n (%)			
White	199 (98)	202 (99)	200 (97)
Black	3 (2)	2 (1)	4 (2)
Asian	0	0	0
Native American	1 (1)	0	1 (1)
Other	1 (1)	0	2 (1)
Height			
Mean (SD)	168 (9)	168 (9)	170 (9)
Weight (kg)			
Mean (SD)	78 (17)	78 (18)	80 (18)
At United States site, n (%)			
No	110 (54)	112 (55)	127 (61)
Yes	94 (46)	92 (45)	80 (39)

Source: Full Clinical Study Report-Protocol Number QVA149A2340 Table 11-2, page 103

3.2.4 Results and Conclusions

3.2.4.1 Studies 2336 and 2337

In both studies, QVA149 27.5/12.5 µg demonstrated a statistically significant improvement in the FEV₁ AUC_{0-12h} at week 12 compared to each monotherapy, QAB149 27.5 µg and NVA237 12.5 µg. Results are shown in Tables 8 and 9. This statistically significant improvement in both studies supports the demonstration of the benefit of QVA149 27.5/12.5 µg over each its monotherapy components with respect to lung function. In both studies compared to placebo, QVA149 27.5/12.5 µg and each of its monotherapy components demonstrated a statistically significant improvement in the primary endpoint in both studies.

Table 8. Primary Efficacy Results-Change from Baseline in FEV₁ (L) AUC_(0-12h) at Week 12- Study 2336 (FAS Population)

	QVA149 27.5/12.5 bid N=258	QAB149 27.5 mcg bid N=260	NVA237 12.5 bid N=261	Placebo N=261
Mean at week 12	0.21	0.12	0.11	-0.02
Mean treatment Δ QVA149 27.5/12.5 vs QAB 27.5	0.094			
95% CI	0.06, 0.13			
p-value	<0.001			
Mean treatment Δ QVA149 27.5/12.5 vs NVA 12.5	0.10			
95% CI	0.06, 0.14			
p-value	<0.001			
Mean treatment Δ Drug vs Placebo	0.23	0.14	0.13	
95% CI	0.19, 0.27	0.10, 0.18	0.09, 0.17	
p-value	<0.001	<0.001	<0.001	

N: Number of observations used in the analysis

Source: Full Clinical Study Report-Protocol Number QVA1492336 Table 11-7, page 104

Table 9. Primary Efficacy Results-Change from Baseline in FEV₁ (L) AUC_(0-12h) at Week 12- Study 2337 (FAS Population)

	QVA149 27.5/12.5 bid N=249	QAB149 27.5 mcg bid N=251	NVA237 12.5 bid N=250	Placebo N=246
Mean at week 12	0.23	0.12	0.16	-0.03
Mean treatment Δ QVA149 27.5/12.5 vs QAB 27.5	0.11			
95% CI	0.07, 0.15			
p-value	<0.001			
Mean treatment Δ QVA149 27.5/12.5 vs NVA 12.5	0.08			
95% CI	0.04, 0.12			
p-value	<0.001			
Drug vs Placebo	0.26	0.15	0.18	
95% CI	0.22, 0.30	0.11, 0.19	0.15, 0.22	
p-value	<0.001	<0.001	<0.001	

N: Number of observations used in the analysis

Source: Full Clinical Study Report-Protocol Number QVA1492337 Table 11-7, page 101

Tipping point analyses conducted for both studies (Table 10) support the primary analyses. Values of delta at which the analyses tipped, i.e. treatment effect was no longer significant, were considered large and not likely to occur. Hence, the primary analysis was considered robust with respect to missing data at Day 85.

Table 10. Tipping Point Analysis at Day 85 Change from Baseline FEV₁ AUC_{0-12h}

Study	Comparison	Tipping Point (L)
QVA149A2336	QVA vs. QAB	1.00
	QVA vs. NVA	1.09
	QVA vs. Placebo	3.16
QVA149A2337	QVA vs. QAB	1.46
	QVA vs. NVA	0.86
	QVA vs. Placebo	4.03

Source: Response to Information Request – Statistics Table 2-1, page 4

In both studies the by-treatment group comparison for the first primary efficacy endpoint, FEV₁ AUC_{0-12h} at week 12 was statistically significant for the QVA149 27.5/12.5 µg group, therefore; according to the pre-specified multiplicity plan, inferential statistical analysis proceeded to the first key secondary efficacy endpoint, SGRQ total score at week 12 for QVA149 27.5/12.5 µg versus placebo.

SGRQ total is shown in Table 11 for study 2336 and Table 12 for study 2337. QVA149 27.5/12.5 µg demonstrated a statistically significant improvement in the SGRQ total at week 12 compared to placebo for both studies.

Table 11. SGRQ Total at Week 12- Study 2336 (FAS)

	QVA149 27.5/12.5 bid N=246	QAB149 27.5 mcg bid N=244	NVA237 12.5 bid N=243	Placebo N=223
Mean at week 12	-6.4	-4.6	-4.8	-2.7
Mean treatment Δ QVA149 27.5/12.5 vs QAB 27.5	-1.9			
95% CI	-3.8, 0.0			
p-value	0.052			
Mean treatment Δ QVA149 27.5/12.5 vs NVA 12.5	-1.7			
95% CI	-3.6, 0.2			
p-value	0.083			
Mean treatment Δ Drug vs Placebo	-3.8	-1.9	-2.1	
95% CI	-5.7, -1.8	-3.8, 0.1	-4.0, -0.1	
p-value	<0.001	0.058	0.036	

N: Number of observations used in the analysis

Source: Full Clinical Study Report-Protocol Number QVA1492336 Table 11-9, page 112

Table 12. SGRQ Total at Week 12- Study 2337 (FAS)

	QVA149 27.5/12.5 bid N=238	QAB149 27.5 mcg bid N=234	NVA237 12.5 bid N=237	Placebo N=226
Mean at week 12	-7.5	-5.9	-6.0	-1.1
Mean treatment Δ QVA149 27.5/12.5 vs QAB 27.5	-1.5			
95% CI	-3.6, 0.6			
p-value	0.158			
Mean treatment Δ QVA149 27.5/12.5 vs NVA 12.5	-1.4			
95% CI	-3.5, 0.7			
p-value	0.190			
Mean treatment Δ Drug vs Placebo	-6.4	-4.8	-4.9	
95% CI	-8.5, -4.2	-7.0, -2.7	-7.1, -2.8	
p-value	<0.001	<0.001	<0.001	

N: Number of observations used in the analysis

Source: Full Clinical Study Report-Protocol Number QVA1492337 Table 11-9, page 108

Again, for both studies, the comparison for change in baseline in SGRQ total score was statistically significant so the inferential statistical analysis proceeded to the next key secondary endpoint, proportion of patients who achieved a clinically important improvement of at least 4 in the SGRQ total score at week 12, shown in Tables 13 and 14. Compared to placebo, QVA149 27.5/12.5 µg demonstrated a statistically significant improvement over placebo in the analysis of the proportion of patients with a clinically meaningful improvement of at least 4 units in the SGRQ total score in both studies 2336 and 2337. In study 2336, QAB149 27.5 µg and NVA237

12.5 µg did not demonstrate significance difference compared to placebo. However, in study 2337, each monotherapy was significantly different from placebo. In neither study, was the combination product significantly different from the monotherapies. Note these comparisons were not pre-specified in the multiplicity plan. Therefore, the results of the key secondary analyses are only considered supportive of the primary analysis.

Table 13. Proportion of patients with a clinically important improvement of at least 4 units in the SGRQ Total Score at Week 12- Study 2336 (FAS)

	QVA149 27.5/12.5 bid N=258	QAB149 27.5 mcg bid N=260	NVA237 12.5 bid N=261	Placebo N=261
n/M (%)	141/246 (57)	117/244 (48)	112/243 (46)	87/223 (39)
Odds Ratio QVA149 27.5/12.5 / QAB 27.5	1.53			
95% CI	1.06, 2.22			
p-value	0.024			
Odds Ratio QVA149 27.5/12.5 / NVA 12.5	1.60			
95% CI	1.10, 2.32			
p-value	0.014			
Odds Ratio Drug/ Placebo	2.20	1.44	1.38	
95% CI	1.50, 3.24	0.98, 2.10	0.94, 2.02	
p-value	<0.001	0.062	0.101	

n: Number of patients who achieved an improvement of at least 4 units, i.e. a decrease ≥ 4

M: Number of patients with a SGRQ total score (included in the analysis)

N: Number of patients in the analysis set

Source: Full Clinical Study Report-Protocol Number QVA1492336 Table 11-10, page 114

Table 14. Proportion of Patients with a Clinically Important Improvement of at Least 4 Units in the SGRQ Total Score at Week 12- Study 2337 (FAS)

	QVA149 27.5/12.5 bid N=250	QAB149 27.5 mcg bid N=251	NVA237 12.5 bid N=250	Placebo N=247
n/M (%)	141/238 (59)	133/234 (57)	122/237 (52)	78/226 (35)
Odds Ratio QVA149 27.5/12.5 / QAB 27.5	1.13			
95% CI	0.78, 1.65			
p-value	0.520			
Odds Ratio QVA149 27.5/12.5 / NVA 12.5	1.40			
95% CI	0.96, 2.04			
p-value	0.081			
Odds Ratio Drug/ Placebo	2.85	2.52	2.04	
95% CI	1.93, 4.21	1.70, 3.73	1.38 3.01	
p-value	<0.001	<0.001	<0.001	

n: Number of patients who achieved an improvement of at least 4 units, i.e. a decrease ≥ 4

M: Number of patients with a SGRQ total score (included in the analysis)

N: Number of patients in the analysis set

Source: Full Clinical Study Report-Protocol Number QVA1492337 Table 11-10, page 110

3.2.4.2 Study 2340

There were no multiplicity adjustments made for any of the secondary endpoints evaluated in this study. The results are described for descriptive purposes only. The primary endpoint for study 2340 was AE rate, a safety endpoint and was not included in this efficacy review. However, the results for the secondary efficacy endpoint, pre-dose trough FEV₁ are shown in Table 15 by visit was included. A difference was demonstrated in the pre-dose trough FEV₁ at each visit over the 52 weeks for both doses of QVA149, 27.5/12.5 µg b.i.d. and 27.5/25 µg b.i.d compared to one of its monotherapy components, QAB149 75 µg o.d. This improvement supports the demonstration of the benefit of QVA149 over one of its monotherapy components, QAB149 75 µg o.d.

Table 15. Change from Baseline Pre-dose Trough FEV1 (L), by visit- study 2340 (FAS)

Day		QVA149 27.5/12.5 bid N=192	QVA149 27.5/25 mcg bid N=196	QAB149 75 mcg od N=199
Day 29	Mean	0.164	0.19	0.11
	Mean treatment Δ			
	QVA149 27.5/12.5 vs QAB149 75	0.06		
	95% CI	0.02, 0.09		
	p-value	0.006		
	Mean treatment Δ			
Day 57	QVA149 27.5/25 vs QAB149 75		0.09	
	95% CI		0.05, 0.12	
	p-value		<0.001	
	Mean	0.18	0.20	0.11
	Mean treatment Δ			
	QVA149 27.5/12.5 vs QAB149 75	0.07		
Day 85	95% CI	0.03, 0.11		
	p-value	<0.001		
	Mean treatment Δ			
	QVA149 27.5/25 vs QAB149 75		0.09	
	95% CI		0.05, 0.13	
	p-value		<0.001	
Day 141	Mean	0.17	0.20	0.10
	Mean treatment Δ			
	QVA149 27.5/12.5 vs QAB149 75	0.07		
	95% CI	0.03, 0.11		
	p-value	0.001		
	Mean treatment Δ			
Day 197	QVA149 27.5/25 vs QAB149 75		0.11	
	95% CI		0.06, 0.15	
	p-value		<0.001	
	Mean	0.14	0.20	0.09
	Mean treatment Δ			
	QVA149 27.5/12.5 vs QAB149 75	0.09		
Day 197	95% CI	0.04, 0.13		
	p-value	<0.001		
	Mean treatment Δ			
	QVA149 27.5/25 vs QAB149 75		0.11	
	95% CI		0.06, 0.16	
	p-value		<0.001	
Day 197	Mean	0.14	0.18	0.08
	Mean treatment Δ			
	QVA149 27.5/12.5 vs QAB149 75	0.06		
	95% CI	0.01, 0.10		
	p-value	0.012		

Day 253	Mean treatment Δ			
	QVA149 27.5/25 vs			
	QAB149 75		0.10	
	95% CI		0.06, 0.15	
	p-value		<0.001	
Day 309	Mean	0.14	0.15	0.10
	Mean treatment Δ			
	QVA149 27.5/12.5			
	vs QAB149 75	0.070		
	95% CI	0.02, 0.11		
Day 365	p-value	0.004		
	Mean treatment Δ			
	QVA149 27.5/25 vs			
	QAB149 75		0.08	
	95% CI		0.03, 0.13	
Day 309	p-value		<0.001	
	Mean	0.10	0.12	0.05
	Mean treatment Δ			
	QVA149 27.5/12.5			
	vs QAB149 75	0.05		
Day 365	95% CI	0.002, 0.09		
	p-value	0.041		
	Mean treatment Δ			
	QVA149 27.5/25 vs			
	QAB149 75		0.07	
Day 309	95% CI		0.03, 0.12	
	p-value		0.001	
	Mean	0.12	0.12	0.04
	Mean treatment Δ			
	QVA149 27.5/12.5			
Day 365	vs QAB149 75	0.08		
	95% CI	0.03, 0.13		
	p-value	<0.001		
	Mean treatment Δ			
	QVA149 27.5/25 vs			
Day 309	QAB149 75		0.08	
	95% CI		0.03, 0.13	
	p-value		<0.001	

Source: Full Clinical Study Report-Protocol Number QVA149A2340 Table 11-7, pages 112-113

A graph of the change from baseline pre-dose trough FEV₁ over the post-baseline visits is shown below, see Figure 1. A separation in the curves is seen between both doses of QVA149 and QAB149 75 µg.

Figure 1. Change from Baseline in Pre-dose Trough FEV₁ (L) over Post-baseline Visits-Study 2340 (FAS)

Time to first moderate or severe COPD exacerbation and annual rate of moderate and severe COPD exacerbations, are included in this review.

Time to first moderate or severe COPD exacerbation is shown in Table 16. There were about the same number of patients in both QVA149 27.5/12.5 µg b.i.d. and QVA149 27.5/25 µg b.i.d groups that had experienced a moderate or severe COPD exacerbation. There were no differences noted between the treatment groups with respect to COPD exacerbations.

Table 16. Results Time to First Moderate or Severe COPD Exacerbation- Study 2340 (FAS)

	QVA149 27.5/12.5 bid N=204	QVA149 27.5/25 mcg bid N=204	QAB149 75 mcg od N=206
n/M (%)	47/200 (24)	50/201 (25)	54/200 (27)
Hazard Ratio QVA149 27.5/12.5 QAB149 75	0.88		
95% CI	0.59, 1.30		
p-value	0.516		
Hazard Ratio QVA149 27.5/12.5 QVA149 27.5/25	1.00		
95% CI	0.67, 1.49		
p-value	0.0.993		
Hazard Ratio QVA149 27.5/25 QAB149 75		0.88	
95% CI		0.60, 1.29	
p-value		0.502	

n: Number of patients with a moderate or severe COPD exacerbation

M: Number of patients included in the analysis

N: Number of patients in the analysis set

Source: Full Clinical Study Report-Protocol Number QVA149A2340 Table 11-8, pages 116

The results for the annual rate of moderate or severe COPD exacerbations are shown in Table 17. There were no significant differences demonstrated between the two treatment groups.

Table 17. Rate of Moderate or Severe COPD Exacerbations During Treatment-Study 2340 (FAS)

	QVA149 27.5/12.5 bid N=204	QVA149 27.5/25 mcg bid N=204	QAB149 75 mcg od N=206
N	200	201	200
Rate Ratio QVA149 27.5/12.5 QAB149 75	0.75		
95% CI	0.51, 1.12		
p-value	0.163		
Rate Ratio QVA149 27.5/12.5 QVA149 27.5/25	0.87		
95% CI	0.58, 1.30		
p-value	0.497		
Rate Ratio QVA149 27.5/25 QAB149 75		0.87	
95% CI		0.69, 1.27	
p-value		0.464	

n: Number of patients included in the analysis

N: Number of patients in the analysis set

Source: Full Clinical Study Report-Protocol Number QVA149A2340 Table 11-9, pages 117

3.3 Evaluation of Safety

Safety evaluations for this submission will be evaluated by the Medical Reviewer, Erika Torjusen, M.D. Refer to her review for more details regarding the safety findings of QVA149.

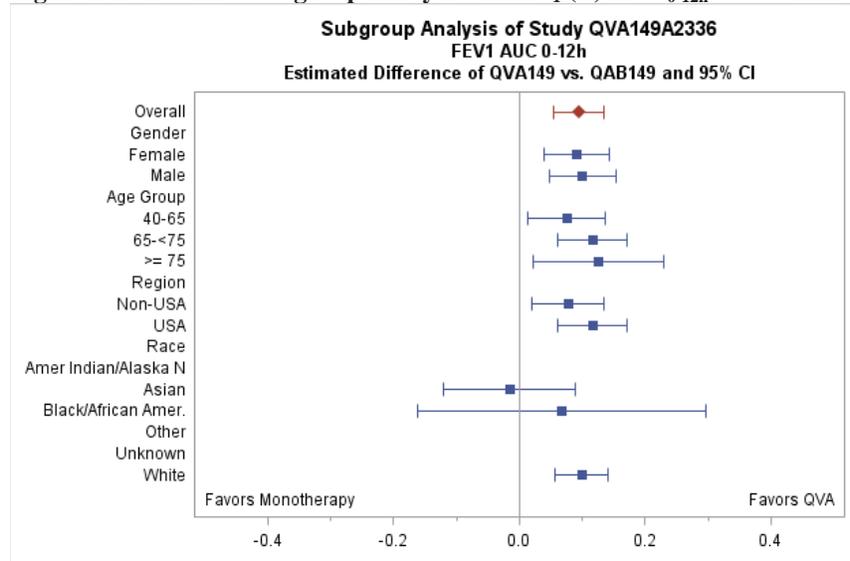
4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analysis on the primary and key secondary efficacy endpoints are shown by gender, age, race (Black or African American, American Indian or Alaskan Native, Asian, White, and Other), airflow limitation, smoking status, and ICS use in studies 2336 and 2337 only. The subgroups were examined by adding the relevant subgroup and treatment by subgroup interaction to the primary analysis model, with results evaluated at the nominal 0.05 level of significance. The subgroup analyses were performed using the FAS population.

Gender, Race, and Age

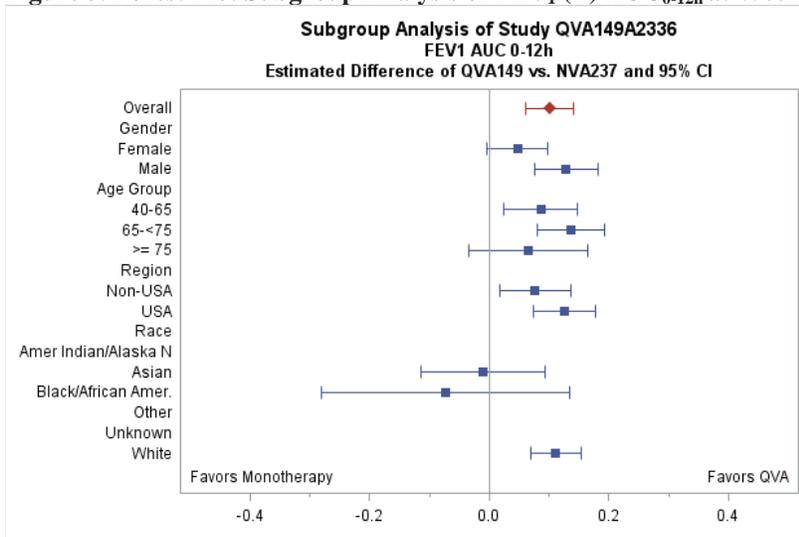
Figures 2-5 below summarize the efficacy results by subgroups for studies 2336 and 2337 for gender, race, and age. The figures are separated by the comparison of QVA149 versus each of its monotherapy components, QAB149 and NVA237. In general, the subgroup analyses were consistent with the primary and key secondary results from the overall population. However, these studies were not designed or powered to detect differences in these specific groups.

Figure 2. Forest Plot Subgroup Analysis of FEV₁ (L) AUC_{0-12h} at Week 12 QVA149 vs. QAB149- Study 2336



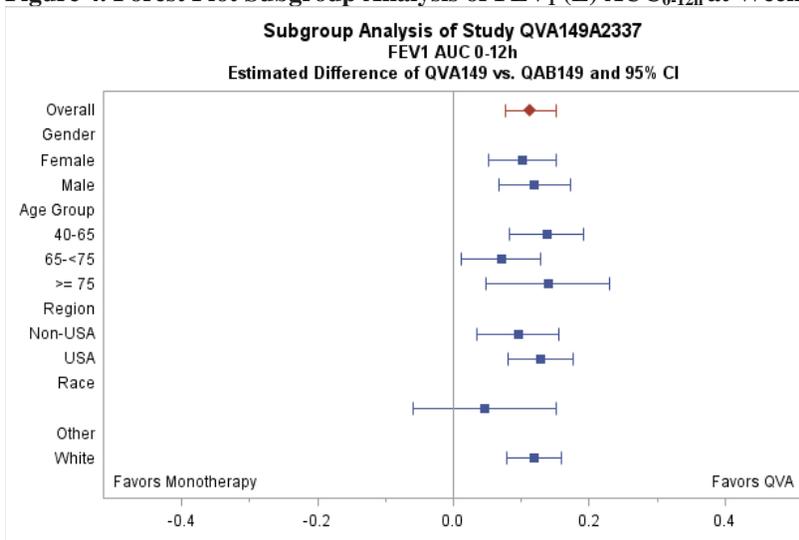
Source: Reviewer

Figure 3. Forest Plot Subgroup Analysis of FEV₁ (L) AUC_{0-12h} at Week 12, QVA149 vs. NVA237- Study 2336



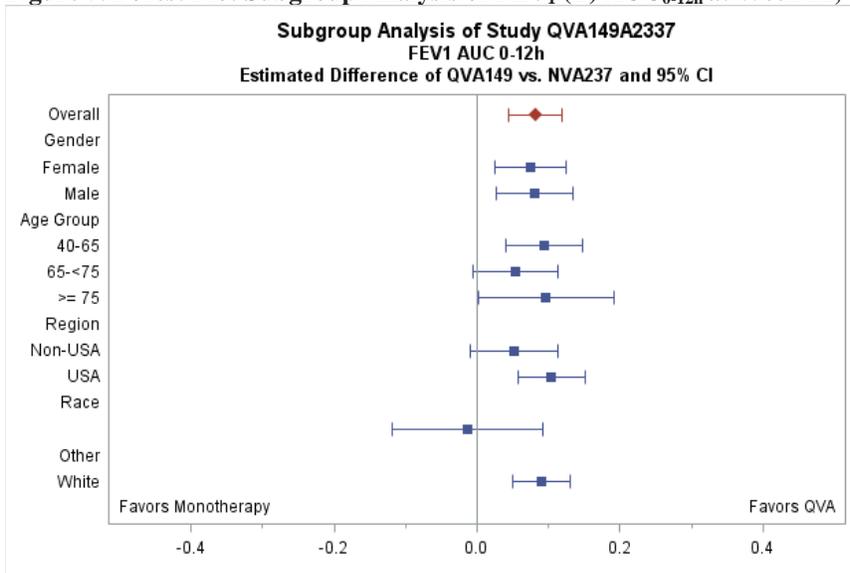
Source: Reviewer

Figure 4. Forest Plot Subgroup Analysis of FEV₁ (L) AUC_{0-12h} at Week 12, QVA149 vs. QAB149- Study 2337



Source: Reviewer

Figure 5. Forest Plot Subgroup Analysis of FEV₁ (L) AUC_{0-12h} at Week 12, QVA149 vs. NVA237- Study 2337

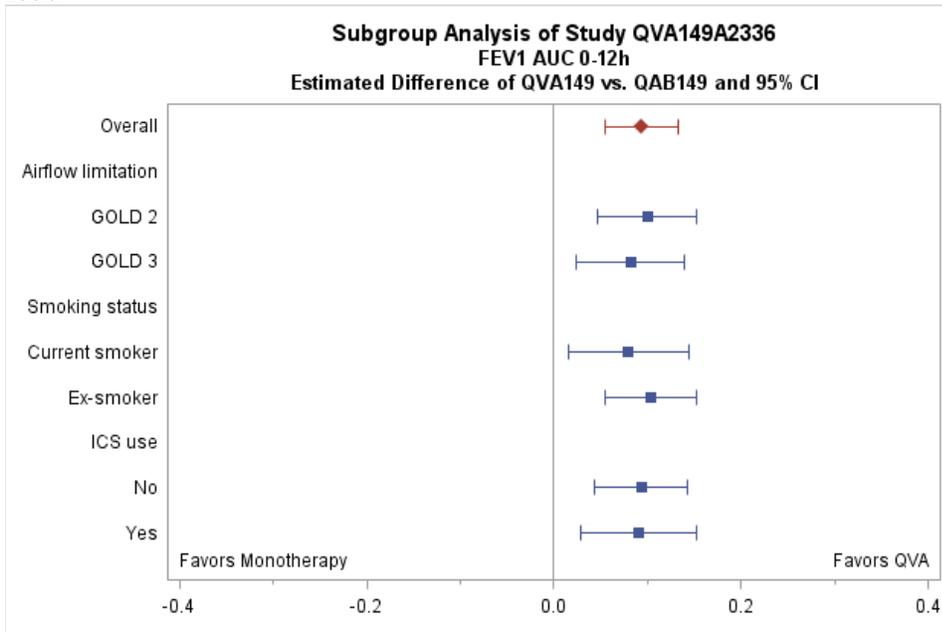


Source: Reviewer

4.2 Other Special/Subgroup Populations

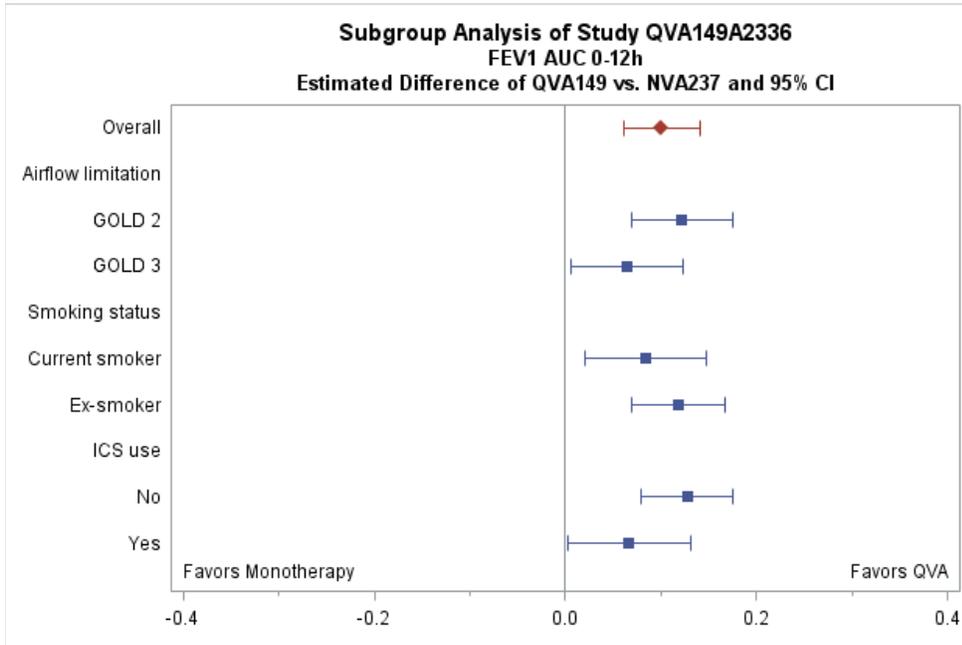
Figures 6-9 below summarize the efficacy results by subgroups for studies 2336 and 2337 for airflow limitation, smoking, and ICS use. The figures are separated by the comparison of QVA149 versus each of its mono-components, QAB149 and NVA237. In general, the subgroup analyses were consistent with the primary and key secondary results from the overall population. However, these studies were not designed or powered to detect differences in these specific groups.

Figure 6. Forest Plot Other Subgroup Analysis of FEV₁ (L) AUC_{0-12h} at Week 12 QVA149 vs. QAB149- Study 2336



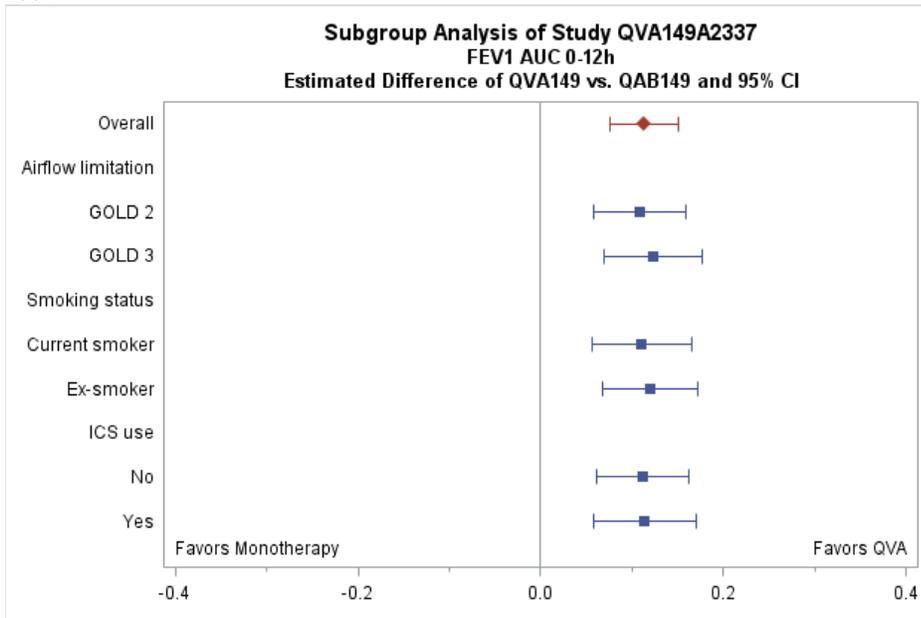
Source: Reviewer

Figure 7. Forest Plot Other Subgroup Analysis of FEV₁ (L) AUC_{0-12h} at Week 12 QVA149 vs. NVA237- Study 2336



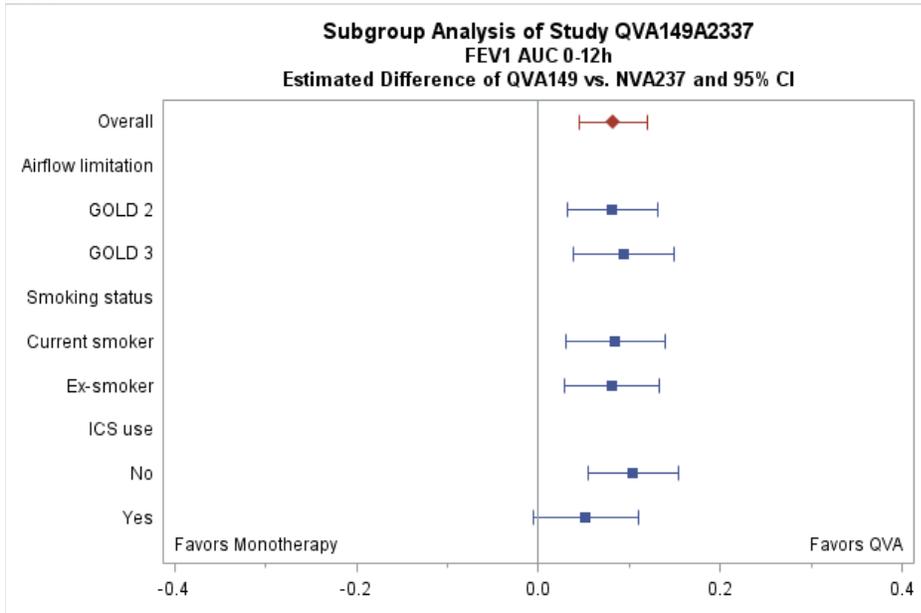
Source: Reviewer

Figure 8 Forest Plot Other Subgroup Analysis of FEV₁ (L) AUC_{0-12h} at Week 12 QVA149 vs. QAB149- Study 2337



Source: Reviewer

Figure 9 Forest Plot Other Subgroup Analysis of FEV₁ (L) AUC_{0-12h} at Week 12 QVA149 vs. NVA237- Study 2337



Source: Reviewer

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

During the course of this review, an information request (IR) was sent to the applicant. The IR requested tipping point sensitivity analyses in the two efficacy studies 2336 and 2337 to examine the impact of missing data on primary analyses. The applicant submitted a detailed description of the tipping point analyses for the primary endpoint, FEV₁ AUC_{0-12h} to address this concern. No other statistical concerns were noted.

5.2 Conclusions and Recommendations

In studies 2336 and 2337, QVA149 27.5/12.5 µg b.i.d. demonstrated a statistically significant improvement in the primary endpoint, FEV₁ AUC_{0-12h} at week 12 compared to each of its monotherapy components, QAB149 37.5 µg b.i.d. and NVA237 12.5 µg b.i.d. In addition, the combination product and each monotherapy were significantly better than placebo with respect to improvement in lung function at week 12. For SGRQ, a secondary endpoint that was not adjusted for multiplicity, when compared to placebo, the combination product, as well as, each monotherapy was better than placebo in study 2337. The benefit of the combination product over the monotherapies was not consistent. In study 2336, treatment with QVA149 27.5/12.5 µg b.i.d. demonstrated a significant improvement in SGRQ scores when compared to each monotherapy. In general, the analyses of SGRQ related endpoints were considered supportive of the primary endpoint.

Study 2340 demonstrated a significant difference in the treatment differences between both doses of QVA149 over one of its monotherapy components, QAB149 75 µg o.d. in the change from baseline in pre-dose trough FEV₁ at each visit over the 52 weeks. This statistically significant improvement supports the demonstration of the benefit of QVA149 over one of its monotherapy components, QAB149 75 µg o.d. in support of lung function. However, time to first moderate or severe COPD exacerbation and annual rate of moderate or severe COPD exacerbation did not demonstrate any significant differences QVA149 at any dose compared to QAB149 75 µg o.d.

Based on the results from the two efficacy studies and the one long term study comparing the study drug to its monotherapies, the efficacy of QVA149 27.5/12.5 µg b.i.d for the long-term, twice daily maintenance treatment of airflow obstruction in patients with COPD including chronic bronchitis and/or emphysema was demonstrated. For studies 2336 and 2337, the results of the tipping point analyses to evaluate the impact of missing data on primary analysis were considered robust and support the efficacy of the combination product.

5.3 Comment on the Proposed Label

The following suggestions have been made for Section 14 of the label.

- Removal of Figure 1
- Removal of (b) (4)
- Suggest that (b) (4). Show the individual study reports.

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

/s/

KIYA HAMILTON
09/24/2015

DAVID M PETULLO
09/25/2015
I concur.

STATISTICS FILING CHECKLIST FOR A NDA 207-930

NDA Number: 207-930

Applicant: Novartis

Stamp Date: 12/29/2014

Drug Name:

NDA/BLA Type: Standard

Indacaterol/Glycopyrrolate

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

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			

Comments to be included in 74-Day letter: No comments

Statistics Filing Checklist for NDA 207-930

STATISTICS FILING CHECKLIST FOR A NDA 207-930

Brief Summary of Studies Reviewed

Novartis has submitted two pivotal clinical studies in support of an indication for COPD, studies qva149a2336 and qva149a2337. Both studies are randomized, multi-center, double-blind, placebo and active controlled, parallel group 12 week efficacy and safety studies. Patients were randomized to QVA149 27.5/12.5 mcg twice a day (b.i.d.), QAB149 27.5 mcg b.i.d, NVA237 12.5 mcg b.i.d or placebo.

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

/s/

KIYA HAMILTON
02/27/2015

DAVID M PETULLO
03/01/2015