

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207923Orig1s000

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 207-923/0000

Drug Name: Seebri Neohaler (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
4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS.....	9
5 SUMMARY AND CONCLUSIONS	9
5.1 STATISTICAL ISSUES	9
5.2 CONCLUSIONS AND RECOMMENDATIONS	9
5.3 COMMENT ON THE PROPOSED LABEL	10

LIST OF TABLES

Table 1. Summary of Study Design and Primary Endpoints.....	6
Table 2. Summary of Patient Disposition in Study 2208.....	7
Table 3. Efficacy Results- Change from Baseline in Trough FEV ₁ (L) at Day 28- Study 2208 (FAS Population).....	7

LIST OF FIGURES

Figure 1. 24 Hour Profile of Least Square Means of FEV_1 (L) at Days 1/2 (FAS)	8
Figure 2. 24 Hour Profile of Least Square Means of FEV_1 (L) at Days 28/29 (FAS).....	9

1 EXECUTIVE SUMMARY

Dose-ranging study NVA237A2208 (2208) examined various once a day (qd) and twice a day (bid) doses of glycopyrrolate inhalation powder (NVA237). My analyses of the data is consistent with the results reported by the applicant and support the evaluation of NVA237 12.5 µg bid 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 2208. 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 NVA237A2208 (hereafter referred to as 2208).

2.2 Data Sources

The datasets from the phase 2 study are archived under the network path location \\cdsesub1\evsprod\nda207923\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 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)
NVA237A2208	Two period-28 days each	NVA 12.5 qd	96	Moderate to severe COPD	Trough FEV ₁ after 28 days
		NVA 25 qd	99		
		NVA 12.5 bid	99		
		NVA 50 qd	96		
		NVA 25 bid	100		
		NVA 100 qd	98		
		NVA 50 bid	94		
		Placebo	94		

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

Source: Reviewer

Study 2208 was a phase 2, randomized, double-blind, placebo-controlled, balanced incomplete block design, multi-center, two period (29 days each) study. Study drug was administered once (qd) or twice daily (bid). Patients were randomized to sixteen independent sequences that resulted from this design. The treatments studied were qd (12.5 µg qd, 25 µg qd, 50 µg qd and 100 µg qd), bid (12.5 µg bid, 25 µg bid, and 50 µg bid), and placebo administered over 28 days each.

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 trough FEV₁, calculated as the average of 2 measurements taken at 23 hours 15 minutes and 23 hours 45 minutes after dosing. The change from baseline in trough FEV₁ was analyzed using an analysis of covariance (ANCOVA) model with treatment, patient effect, period effect, (period) baseline FEV₁, smoking status at baseline, and baseline ICS use. Period baseline FEV₁ was defined as the mean of two values taken at 45 minutes and 15 minutes prior to study drug administration in the treatment period. Patient was treated as a random effect in the model.

3.2.2 Patient Disposition

The summary of the patient disposition in study 2208 is given in Table 2. Approximately 52% of the patients discontinued due to adverse events (AE).

Table 2. Summary of Patient Disposition in Study 2208

	NVA 12.5 qd n (%)	NVA 25 qd n (%)	NVA 12.5 bid n (%)	NVA 50 qd n (%)	NVA 25 bid n (%)	NVA 100 qd n (%)	NVA 50 bid n (%)	Placebo n (%)
Randomized	96	99	99	96	100	98	94	9494
FAS	89 (93)	96 (97)	95 (96)	92 (96)	96 (96)	96 (98)	87 (93)	91 (97)
Completed	80 (83)	91 (92)	93 (94)	89 (93)	89 (89)	92 (94)	82 (87)	82 (87)
Discontinued	11 (12)	5 (5)	2 (2)	3 (3)	7 (7)	4 (4)	6 (6)	9 (10)
Adverse Event	6 (55)	3 (60)	1 (50)	0	6 (86)	3 (75)	2 (33)	4 (44)
Patient withdrew consent	1 (9)	2 (20)	0	2 (67)	0	0	1 (17)	4 (44)
Protocol deviation	2 (18)	0	0	0	0	0	2 (33)	1 (11)
Lost to follow up	2 (18)	0	0	0	0	1 (25)	1 (17)	0
Administrative problems	0	1 (20)	1 (50)	0	0	0	0	0
Abnormal Laboratory value(s)	0	0	0	0	1 (14)	0	0	0
Death	0	0	0	1 (33)	0	0	0	0

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 CNVA237A2208 Table 10-1, page 107

3.2.4 Results and Conclusions

All doses of NVA237 demonstrated a statistically significant improvement in trough FEV₁ at day 28 compared to placebo, (Table 3). There was a 0.14 L improvement for the dose of interest, 12.5 µg bid compared to placebo at day 28.

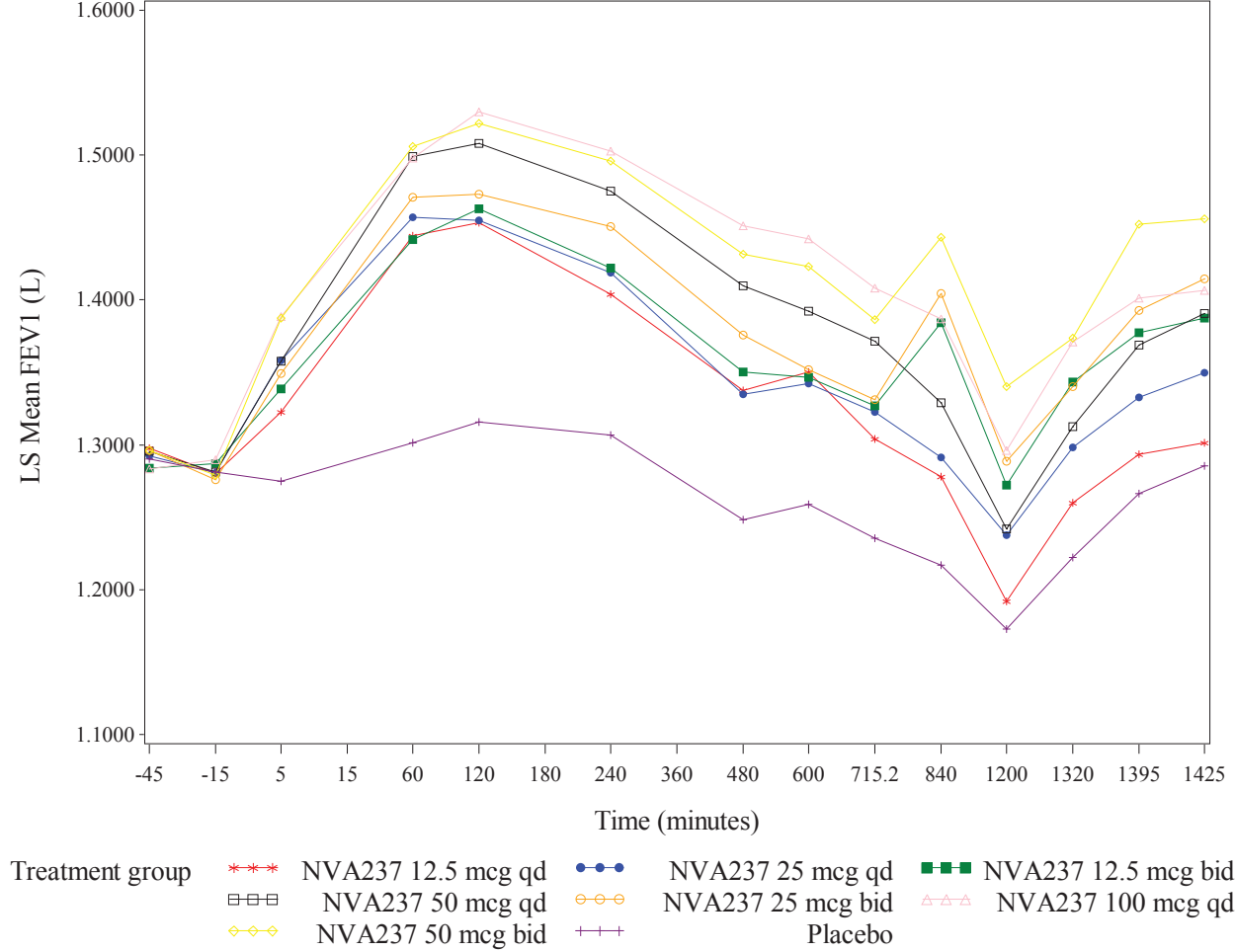
Table 3. Efficacy Results- Change from Baseline in Trough FEV₁ (L) at Day 28- Study 2208 (FAS Population)

Treatment	n	Mean at day 28	Mean Treatment Δ from placebo		
			Mean	95 % CI	p-value
NVA 12.5 µg qd	81	1.33	0.08	0.03, 0.14	0.0023
NVA 25 µg qd	81	1.34	0.09	0.05, 0.15	0.0001
NVA 12.5 µg bid	90	1.39	0.14	0.09, 0.19	<0.0001
NVA 50 µg qd	88	1.34	0.09	0.04, 0.14	0.0007
NVA 25µg bid	87	1.41	0.17	0.12, 0.23	<0.0001
NVA 100 µg qd	90	1.42	0.18	0.13, 0.22	<0.0001
NVA 50 µg bid	81	1.42	0.18	0.13, 0.22	<0.0001
Placebo	82	1.25	-	-	-

Source: Full Clinical Study Report-Protocol Number CNVA237A2208 Table 16.1.9-1.27, page 3947

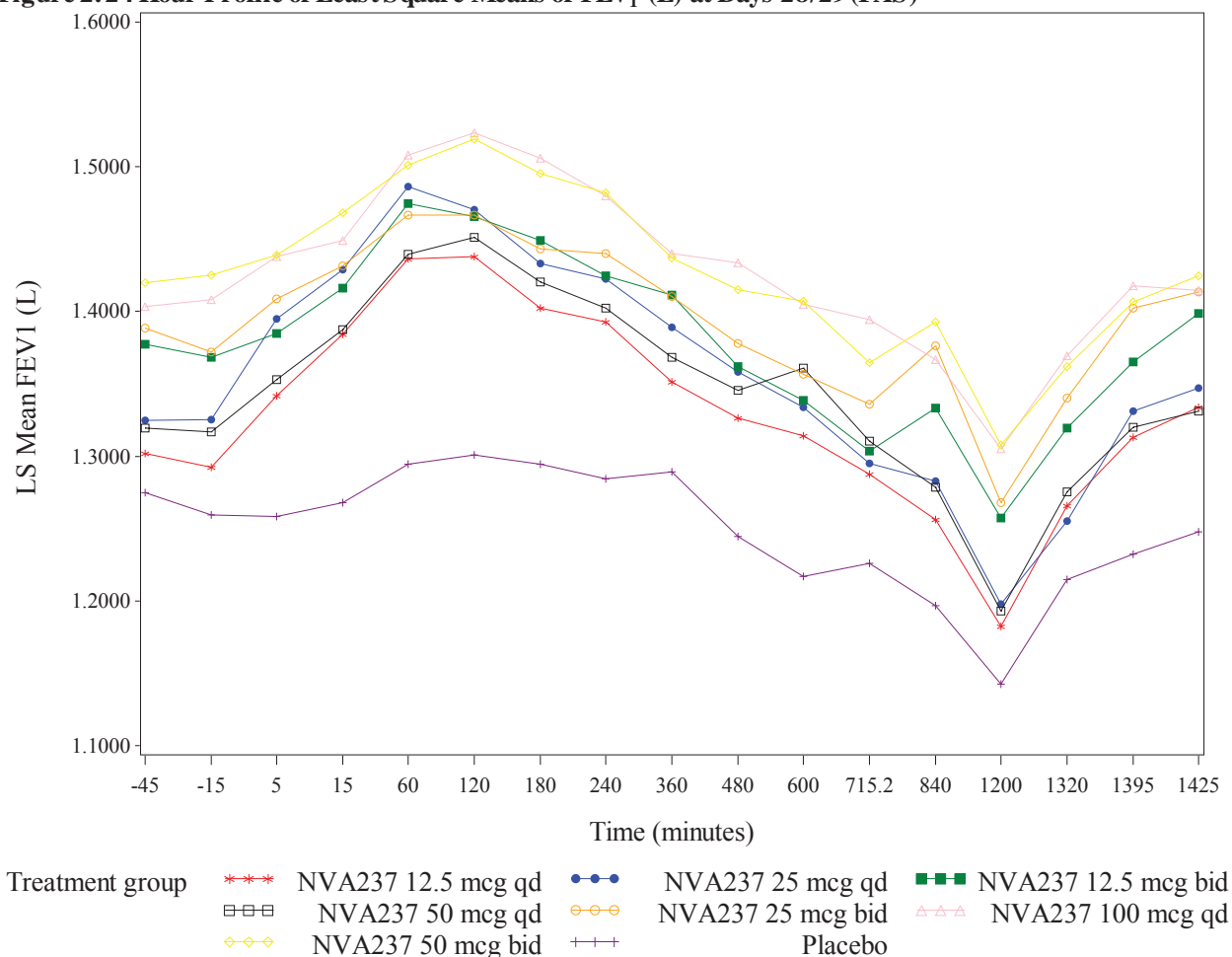
Figures 1 and 2 show the 24 hour profile least squares means of FEV₁ for all eight treatments for days 1/2 and 28/29, respectively. All eight doses were numerically better than placebo.

Figure 1. 24 Hour Profile of Least Square Means of FEV₁ (L) at Days 1/2 (FAS)



Source: Reviewer

Figure 2. 24 Hour Profile of Least Square Means of FEV₁ (L) at Days 28/29 (FAS)



Source: Reviewer

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 improvements by NVA237 compared to placebo for mean change in baseline for trough FEV₁ after day 28. Significant differences were seen for all NVA237 doses for trough FEV₁ at day 28 compared to

placebo. There was a 0.14 L improvement for the dose of interest, 12.5 µg bid compared to placebo at day 28.

5.3 Comment on the Proposed Label

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

- Insert 24 hour profile of LS mean FEV₁ at day 1 and day 28 (not corrected for placebo) from study A2208 in 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
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 207-923/0000

Drug Name: Seebri Neohaler (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>	7
3.2.3 <i>Patient Disposition, Demographic and Baseline Characteristics</i>	8
3.2.4 <i>Results and Conclusions</i>	10
3.3 EVALUATION OF SAFETY	12
4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS	12
4.1 GENDER, RACE, AND AGE	12
4.2 OTHER SPECIAL/SUBGROUP POPULATIONS	13
5 SUMMARY AND CONCLUSIONS	14
5.3 COMMENT ON THE PROPOSED LABEL	14

LIST OF TABLES

Table 1. Summary of Study Design and Primary Endpoints	7
Table 2. Summary of Patient Disposition in Studies 2317 and 2318	9
Table 3. Demographics in Studies 2317 and 2318- Randomized Set.....	9
Table 4. Primary Efficacy Results-Change from Baseline in FEV ₁ (L) AUC _(0-12h) at week 12- Study 2317 (FAS Population).....	10
Table 5. Primary Efficacy Results-Change from Baseline in FEV ₁ (L) AUC _(0-12h) at Week 12- Study 2318 (FAS Population).....	10
Table 6. Tipping Point Analysis at Day 85 Change from Baseline FEV ₁ AUC _{0-12h}	10
Table 7. SGRQ Total at Week 12- Study 2317 (FAS)	11
Table 8. SGRQ Total at Week 12- Study 2318 (FAS)	11
Table 9. Analysis of the Proportion of Patients with a Clinically Important Improvement of ≥ 4 Units in the SGRQ Total Score at Week 12- Study 2317 (FAS)	11
Table 10. Analysis of the Proportion of Patients with a Clinically Important Improvement of ≥ 4 Units in the SGRQ Total Score at Week 12- Study 2318 (FAS)	11

LIST OF FIGURES

Figure 1. Forest Plot Subgroup Analysis of FEV ₁ (L) AUC _{0-12h} at Week 12- Study 2317	12
Figure 2. Forest Plot Subgroup Analysis of FEV ₁ (L) AUC _{0-12h} at Week 12- Study 2318.....	13
Figure 3. Forest Plot Other Subgroup Analysis of FEV ₁ (L) AUC _{0-12h} at Week 12- Study 2317.....	13
Figure 4. Forest Plot Other Subgroup Analysis of FEV ₁ (L) AUC _{0-12h} at Week 12- Study 2318.....	14

1 EXECUTIVE SUMMARY

Novartis proposes glycopyrrolate inhalation powder (NVA237), 12.5 µg twice daily for the long term maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

There were two 12-week, phase 3, multi-center, double-blind, placebo-controlled, parallel-group, randomized efficacy and safety studies, CNVA237A2317 (2317) and CNVA237A2318 (2318), that evaluated NVA237 12.5 µg twice daily in patients with COPD that had moderate to severe airflow limitation. These patients were permitted to use inhaled corticosteroids along with the study treatment. There was also a long term safety study NVA237A2319 (2319) that compared NVA237 to indacaterol (QAB149). This 52-week treatment study was a multi-center, double-blind, parallel-group, randomized efficacy and safety study of NVA237 12.5 µg in patients with COPD with moderate to severe airflow limitations.

In studies 2317 and 2318, compared to placebo, NVA237 12.5 µg demonstrated a statistically significant improvement in the primary endpoint, FEV₁ AUC_{0-12h} at week 12. The secondary endpoint of interest, St George's Respiratory Questionnaire (SGRQ), demonstrated a significant improvement for NVA237 12.5 µg over placebo in both studies 2317 and 2318. However, there were no pre-specified multiplicity corrections in place for this secondary endpoint.

Results from study 2319 indicated there were no statistically significant differences in the treatment differences between NVA237 12.5 µg b.i.d. and QAB149 75 µg o.d. in the change from baseline in pre-dose trough FEV₁ at any visit over the 52 weeks, time to first moderate or severe COPD exacerbation, or annual rate of moderate or severe COPD exacerbation in study 2319. As expected, there was not enough evidence to conclude the NVA237 was any different from QAB149 with respect to lung function. Study 2319 will not be discussed further in this review.

2 INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Novartis developed glycopyrrolate inhalation powder, hereafter referred to as NVA237, a long-acting muscarinic antagonist for twice-daily use in a dry powder formulation, inhalation powder hard capsules administered via a single-dose dry powder inhaler (Neohaler). The applicant proposes NVA237 12.5 µg for the long term maintenance (b) (4) 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

Novartis had several interactions with the Division of Pulmonary, Allergy, and Rheumatology Products regarding NVA237 under IND 48,655. Pertinent parts of the communications and interactions relevant to statistical review are summarized herein.

There was a Type A meeting held on May 4, 2009 to discuss the Special Protocol Assessment (SPA) that Novartis sent on February 13, 2009. The Division issued a “No Agreement” letter dated March 26, 2009. The Division did not agree that (b) (4)

. On July 13, 2009 there was a post SPA denial clarification meeting to discuss the clinical and non-clinical development program for NVA237 prior to initiating the phase 3 program. The Division stated that they could not give specific responses to their questions at the time due to the information needed to make decisions at that stage where not available yet. In a pre-NDA meeting on September 28, 2011, the Division again expressed concern regarding the (b) (4). Written responses provided to the sponsor on November 21, 2013 indicated the company had sufficient information to submit an application.

2.1.3 Specific Studies Reviewed

This review will focus on the results from studies NVA237A2317, NVA237A2318, and NVA237A2319 (hereafter referred to as 2317, 2318, and 2319 respectively).

2.2 Data Sources

The submission of NDA 207923 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\nda207923\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)
NVA237A2317	12 weeks DB period	NVA 12.5 b.i.d Placebo	222 219	Moderate to severe airflow limitation	FEV ₁ AUC ₀₋₁₂ hours at week 12
NVA237A2318	12 weeks DB period	NVA 12.5 b.i.d Placebo	216 216	Moderate to severe airflow limitation	FEV ₁ AUC ₀₋₁₂ hours at week 12

Source: Reviewer

* b.i.d: Twice a day, o.d.: Once a day, QAB149: indacaterol

3.2.1.1 Studies 2317 and 2318

Studies 2317 and 2318 were phase 3, randomized, double-blind, parallel-group, placebo-controlled, multi-center 12 week studies. These studies were designed to evaluate the efficacy and safety of NVA237 12.5 µg administered twice daily (b.i.d.) in COPD patients with moderate to severe airflow limitation. Patients were allowed to take COPD background therapy with inhaled corticosteroids (ICS) along with the study treatments. Albuterol or salbutamol, a short-acting β₂-adrenergic agonist (SABA), was provided as rescue medication for use as necessary during the study.

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 and 15 minutes prior to dosing on day 1.

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 2317 and 2318

Missing FEV₁ AUC_{0-12h} data was not imputed. Measurements within 6 hours of rescue medication use or within 7 days of systemic corticosteroid use were not included in the analysis.

The protocol pre-specified that in both studies the primary endpoint change from baseline in FEV₁ AUC_{0-12h} post morning dose at week 12, was analyzed using a mixed model for repeated measures (MMRM) with treatment, baseline FEV₁, smoking status at baseline, baseline ICS use, visit, treatment-by-visit interaction, baseline FEV₁-by-visit interaction. Treatment, smoking status at baseline, ICS use at baseline and visit were treated as categorical variables. The null hypothesis of no difference in FEV₁ AUC_{0-12h} in patients treated with NVA237 12.5 µg compared to placebo versus the alternative hypothesis of there is a difference in the FEV₁ AUC_{0-12h} for COPD patients treated with NVA237 12.5 µg compared to placebo at week 12 was tested at a significance level of 0.05. No adjustments for any secondary endpoints were made for multiplicity.

The trapezoidal rule was used to calculate FEV_1 AUC_{0-12h} similar to a time weighted average. For each patient, an AUC was calculated based on the existing FEV_1 measurements (i.e., the missing FEV_1 measurements were not to be interpolated). The following is an excerpt from the clinical study report.

Specifically, for those patients who had a FEV_1 assessment at only one time point, their AUC was approximated by the observed FEV_1 . For those patients who had more than one FEV_1 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 FEV_1 value at time t_j , for $j = 1, \dots, m$, in which $t_1 < \dots < t_m$ are the time points when FEV_1 are measured. Scheduled measurement times t_j rather than actual times were used. The first (possible) time point t_1 was 5 minutes post dose and last (possible) time point t_m was 11 hours 55 minutes post dose just before evening dosing, so the AUC was over 11 hours and 50 minutes.

To evaluate the impact of missing data at day 85 for the primary endpoint, change from baseline in FEV_1 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.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Study 2317 and 2318

The summary of the patient disposition in studies 2317 and 2318 are given in Table 2. Approximately 3%-5% 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 Studies 2317 and 2318

	Study 2317		Study 2318	
	NVA 12.5 (bid) n (%)	Placebo n (%)	NVA 12.5 (bid) n (%)	Placebo n (%)
Randomized	222	219	216	216
FAS	222(100)	216 (98.6)	215 (99)	214 (99)
Completed	211 (89)	202 (91)	209 (97)	205 (95)
Discontinued	7 (3)	11 (9)	7 (3)	11 (5)
Adverse Event	0	2 (0.9)	0	0
Patient/guardian Decision	5 (2)	6 (3)	7 (3)	9 (4)
Death	0	1 (0.5)	0	0
Physician decision	0	1 (0.5)	0	0
Non-compliant with study treatment	1 (0.5)	1 (0.5)	0	0
Lost to Follow- Up	1 (0.5)	0	0	2 (1)

Source: Full Clinical Study Report-Protocol Number CNVA237A2317 Table 10-1, page 93 and Full Clinical Study Report-Protocol Number NVA237A2318 Table 10-1, page 94

Demographics and baseline characteristics for all randomized patients in studies 2317 and 2318 are given in Table 3. The patients' mean age was about 63 years. Most of the patients were White (88%-92%) in these studies. These factors were generally well-balanced across the treatment groups.

Table 3. Demographics in Studies 2317 and 2318- Randomized Set

	Study 2317		Study 2318	
	NVA 12.5 (bid) N=222	Placebo N=219	NVA 12.5 (bid) N=216	Placebo N=216
Age (years)				
Mean (SD)	63 (8)	62 (8)	64 (9)	64 (8)
Sex n (%)				
Female	98 (44)	87 (40)	88 (41)	90 (42)
Male	124 (56)	132 (60)	128 (59)	126 (58)
Race n (%)				
White	205 (92)	193 (88)	190 (88)	185 (86)
Black	12 (5)	19 (9)	19 (9)	27 (13)
Asian	2 (1)	2 (1)	1 (0.5)	1 (0.5)
Pacific Islander	0	0	1 (0.5)	0
Native American	0	1 (0.5)	2 (1)	3 (1)
Other	3 (1)	4 (2)	3 (1)	0
Height (cm)				
Mean (SD)	170 (10)	170 (10)	171 (9)	170 (9)
Weight (kg)				
Mean (SD)	82 (18)	80 (19)	83 (19)	82 (18)
Smoking status at baseline, n (%)				
Current smoker	137 (62)	132 (60)	115 (53)	115 (53)
Ex-smoker	85 (38)	87 (40)	101 (47)	101 (47)
Mean pack years (SD)	54 (27)	56 (30)	51 (25)	51 (24)

Source: Reviewer Analysis

3.2.4 Results and Conclusions

3.2.4.1 Studies 2317 and 2318

In both studies, NVA237 12.5 µg demonstrated a statistically significant improvement in the FEV₁ AUC_{0-12h} at week 12 compared to placebo, with a 0.14 L improvement in study 2317 (Table 4) and 0.12 L in study 2318 (Table 5).

Table 4. Primary Efficacy Results-Change from Baseline in FEV₁ (L) AUC_(0-12h) at week 12- Study 2317 (FAS Population)

	NVA 237 12.5 bid N=222	Placebo N=216
Mean at week 12	0.13	-0.01
Mean Treatment Δ from placebo		0.14
95% CI		0.10, 0.18
p-value		<0.001

N: Number of observations used in the analysis

Source: Clinical Trial Report-Protocol Number CNVA237A2317 Table 11-6, page 102

Table 5. Primary Efficacy Results-Change from Baseline in FEV₁ (L) AUC_(0-12h) at Week 12- Study 2318 (FAS Population)

	NVA 237 12.5 bid N=215	Placebo N=213
Mean at week 12	0.12	-0.008
Mean Treatment Δ from placebo		0.12
95% CI		0.08, 0.17
p-value		<0.001

N: Number of observations used in the analysis

Source: Clinical Trial Report-Protocol Number CNVA238A2318 Table 11-6, page 103

Tipping point analyses conducted for both studies (Table 6) 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 6. Tipping Point Analysis at Day 85 Change from Baseline FEV₁ AUC_{0-12h}

Study	Comparison	Tipping Point (L)
NVA237A2317	NVA vs. Placebo	1.16
NVA237A2318	NVA vs. Placebo	0.68

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

Per clinical request the results for the secondary endpoint, SGRQ are included. There were no pre-specified multiplicity corrections in place for any secondary endpoints, including SGRQ. The results are described for descriptive purposes only. SGRQ total score is shown in Table 7 for study 2317 and Table 8 for study 2318. NVA237 12.5 µg demonstrated a statistically significant improvement in the SGRQ total at week 12 compared to placebo for both studies 2317 and 2318. These results are considered supportive of the primary analyses.

Table 7. SGRQ Total at Week 12- Study 2317 (FAS)

	NVA 237 12.5 bid N=210	Placebo N=192
Mean at week 12	-4.4	-1.7
Mean Treatment Δ from placebo		-2.8
95% CI		-5.0, -0.50
p-value		0.016

N: Number of observations used in the analysis

Source: Clinical Trial Report-Protocol Number CNVA237A2317 Table 11-10, page 106

Table 8. SGRQ Total at Week 12- Study 2318 (FAS)

	NVA 237 12.5 bid N=195	Placebo N=196
Mean at week 12	-6.4	-1.2
Mean Treatment Δ from placebo		-5.2
95% CI		-7.7, -2.7
p-value		<0.0001

N: Number of observations used in the analysis

Source: Clinical Trial Report-Protocol Number CNVA237A2318 Table 11-10, page 108

Compared to placebo, there was no statically significant improvement demonstrated in the analysis of the proportion of patients with a clinically meaningful improvement of ≥ 4 units in the SGRQ total score for the NVA237 12.5 μg in study 2317. However, there were a higher proportion of patients with a clinically meaningful improvement in the NVA237 group than in the placebo group. In study 2318 there was a significant treatment effect in favor of NVA 237 12.5 μg . See Tables 9 and 10.

Table 9. Analysis of the Proportion of Patients with a Clinically Important Improvement of ≥ 4 Units in the SGRQ Total Score at Week 12- Study 2317 (FAS)

	NVA 237 12.5 b.i.d N=222	Placebo N=216
n/M (%)	103/210 (49)	78/192 (41)
Odds Ratio		1.43
95% CI		0.95, 2.15
p-value		0.083

N: Number of observations used in the analysis

Source: Clinical Trial Report-Protocol Number CNVA237A2317 Table 11-11, page 107

Table 10. Analysis of the Proportion of Patients with a Clinically Important Improvement of ≥ 4 Units in the SGRQ Total Score at Week 12- Study 2318 (FAS)

	NVA 237 12.5 b.i.d N=215	Placebo N=214
n/M (%)	106/193 (55)	82/194 (42)
Odds Ratio		1.78
95% CI		1.17, 2.71
p-value		0.008

N: Number of observations used in the analysis

Source: Clinical Trial Report-Protocol Number CNVA237A2318 Table 11-11, page 108

3.3 Evaluation of Safety

Safety evaluations for this submission will be evaluated by the Medical Reviewer, Stacy Chin, M.D. Refer to her review for specific details regarding the safety findings of Spiriva Respimat.

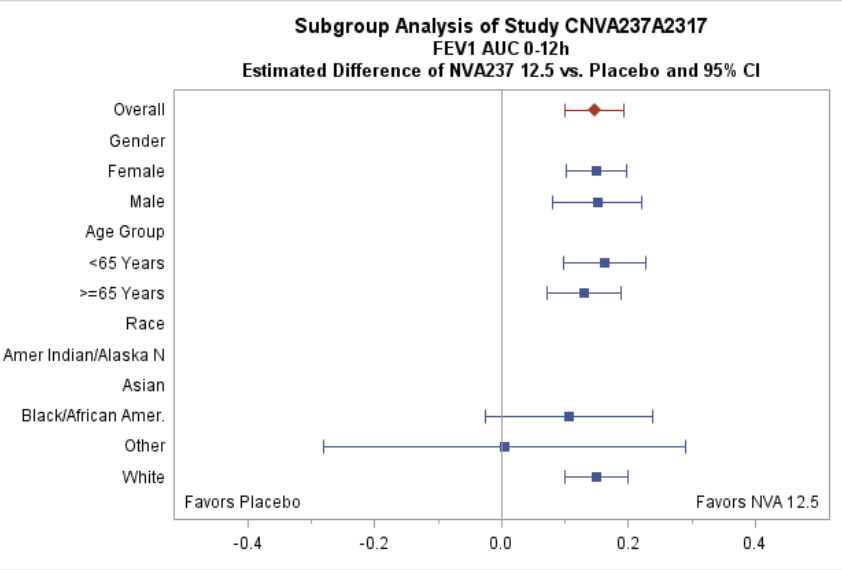
4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

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 2317 and 2318 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

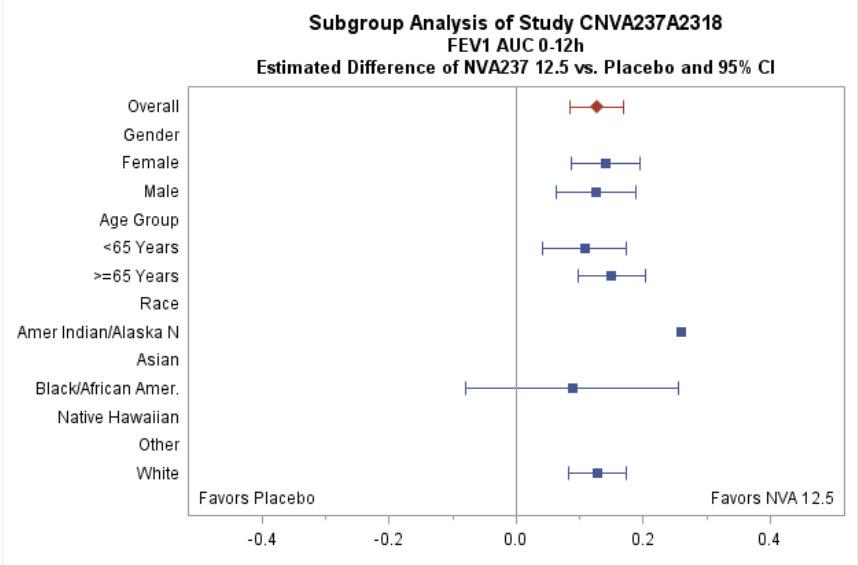
Figures 1-2 below summarize the efficacy results by subgroups for studies 2317 and 2318 for gender, race, and age. In general, the subgroup analyses were consistent with the primary and key secondary results from the overall population. However, these studies were not designed or powered to detect differences in these specific subgroups.

Figure 1. Forest Plot Subgroup Analysis of FEV₁ (L) AUC_{0-12h} at Week 12- Study 2317



Source: Reviewer

Figure 2. Forest Plot Subgroup Analysis of FEV₁ (L) AUC_{0-12h} at Week 12- Study 2318

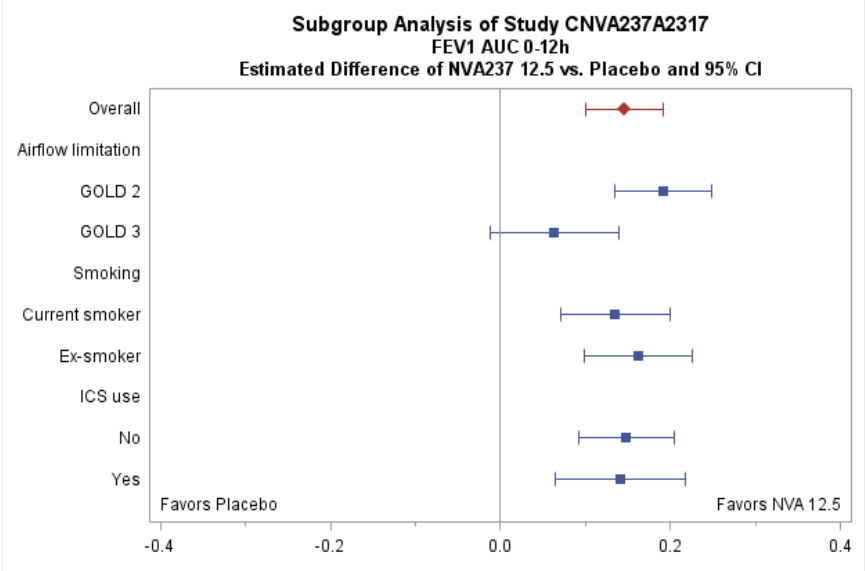


Source: Reviewer

4.2 Other Special/Subgroup Populations

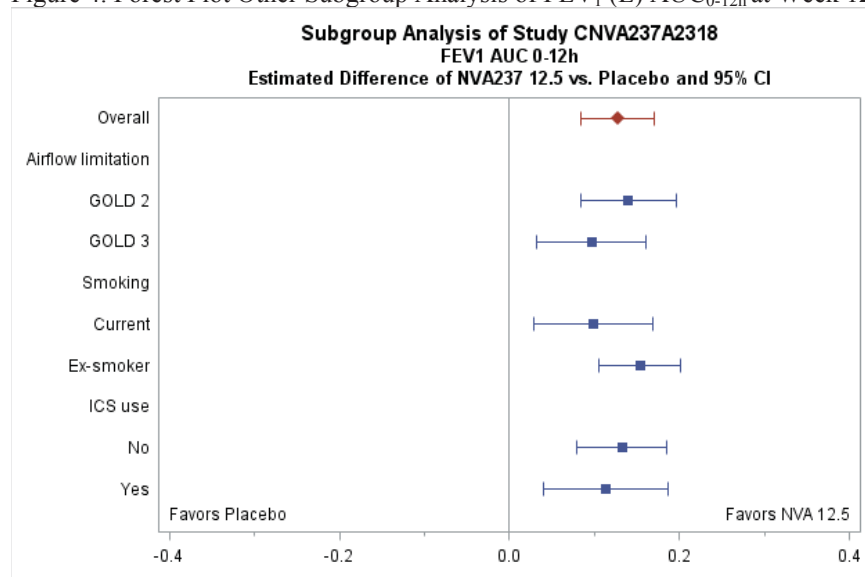
Figures 3 and 4 below summarize the efficacy results by subgroups for studies 2317 and 2318 for airflow limitation, smoking, and ICS use. In general, the subgroup analyses were consistent with the primary and key secondary results from the overall population. However, these studies were not designed or powered to detect differences in these specific groups.

Figure 3. Forest Plot Other Subgroup Analysis of FEV₁ (L) AUC_{0-12h} at Week 12- Study 2317



Source: Reviewer

Figure 4. Forest Plot Other Subgroup Analysis of FEV₁ (L) AUC_{0-12h} at Week 12- Study 2318



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 2317 and 2318 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 2317 and 2318, NVA237 12.5 µg demonstrated a statistically significant improvement in the pre-specified primary endpoint, FEV₁ AUC_{0-12h} at week 12 compared to placebo. The secondary endpoint SGRQ total demonstrated a statistically significant improvement in the FEV₁ AUC_{0-12h} for NVA237 12.5µg over placebo in both studies 2317 and 2318 and was considered supportive of the primary endpoint.

Based on the results from the two efficacy studies comparing the study drug to an already approved drug, the efficacy of NVA237 12.5 µg b.i.d for the long-term, twice daily maintenance (b) (4) treatment of airflow obstruction in patients with COPD including chronic bronchitis and/or emphysema was demonstrated. For studies 2317 and 2318, 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 NVA237 12.5 µg b.i.d.

5.3 Comment on the Proposed Label

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

- Remove (b) (4) from the label

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 207-923

NDA Number: 207923

Applicant: Novartis

Stamp Date: 12/29/2014

Drug Name: Glycopyrrolate

NDA/BLA Type: Standard

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

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

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? YES

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			

STATISTICS FILING CHECKLIST FOR A NDA 207-923

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

Brief Summary of Studies Submitted

Novartis has submitted 2 pivotal clinical studies in support of an indication for COPD, studies nva237a2317 and nva237a2318. Both studies were randomized, multi-center, double-blind, parallel-group, placebo-controlled 12 week efficacy and safety studies. Patients were randomized to NVA237 12.5 mcg twice a day 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