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 OUTCOME ASSESSMENTS

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|---|---|
| **NDA/BLA #:** | NDA 207070 |
| **Drug Name:** | Spiriva Respimat (Tiotropium Bromide) Inhalation Spray |
| **Indication(s):** | Long-term, once daily, add-on maintenance treatment of asthma in patients who remain symptomatic on at least inhaled corticosteroids |
| **Applicant:** | Boehringer Ingelheim |
| **Date(s):** | Receipt date: August 15, 2014 |
| | PDUFA date: September 15, 2015 |
| **Review Priority:** | Standard |
| | |
| **Biometrics Division:** | Division of Biometrics II |
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| **Concurring Reviewers:** | Davis Petullo, M.S., Team Leader |
| | |
| | |
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**Keywords:** NDA review, clinical studies

## Table of Contents

# LIST OF TABLES

# 1  EXECUTIVE SUMMARY

Analyses from two randomized studies, studies 418 and 419, included assessments of patient reported outcomes or often referred to as clinical outcome assessments. Improvements in Spiriva Respimat compared to placebo for mean change from baseline standardized asthma quality of life questionnaire (AQLQ), AQLQ response rate, mean change from baseline asthma control questionnaire (ACQ)-5, ACQ-5 response rate, mean change from baseline ACQ-7, and ACQ-7 response rate. Rate of severe asthma exacerbation was also included. These analyses were conducted without consideration of multiplicity and were not pre-specified.

There were some numeric differences seen in ACQ-7 in both studies. However, there were no differences seen for ACQ-5 for mean change from baseline or response rate. A numeric difference was seen in Spiriva Respimat 2.5 mcg over placebo for rate of severe asthma exacerbation in study 418.

# 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 June 10, 2015.

### 2.1.2  History of Drug Development

The Division of Pulmonary, Allergy and Rheumatology requested additional analyses for the endpoints standardized asthma quality of life questionnaire (AQLQ), asthma control questionnaire (ACQ)-5 and ACQ-7 (ACQ total), and exacerbation rate for both studies 418 and 419. These endpoints were analyzed based on claims made in the label. This review addresses the Division's analyses for these endpoints.

## 2.2  Data Sources

The additional datasets from the phase 3 study data for AQLQ, ACQ5, and ACQ7 are archived under the network path location \\CDSESUB1\evsprod\NDA207070\0023.

# 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 review analyses generally matched those in the submission.

## 3.2 Evaluation of Efficacy

### 3.2.1 Study Design and Endpoints

A summary of the study design and endpoints for the two efficacy studies are shown in Table 1. Each study is discussed below. AQLQ, ACQ, and rate of severe asthma exacerbation were secondary endpoints without pre-specified multiplicity corrections. The results are described for descriptive purposes only and the p-values reported are not adjusted for multiplicity.

**Table 1: Summary of Study Design and Primary Endpoints**

| Study ID | Length of the Study | Treatment Arms* | Number of Patients | Study Population | Efficacy Endpoint(s) |
|---|---|---|---|---|---|
| 418 | 24 weeks DB period | SR 2.5 mcg<br>SR 5 mcg<br>Salmeterol 50 mcg<br>Placebo | 262<br>265<br>275<br>269 | Moderate persistent asthma | Primary:<br>Peak $FEV_1$ 0-3 hours after 24 weeks<br>Trough $FEV_1$ after 24 weeks<br>Secondary after 24 weeks:<br>AQLQ, ACQ-5, ACQ-7, Rate of severe exacerbation |
| 419 | 24 weeks DB period | SR 2.5 mcg<br>SR 5 mcg<br>Salmeterol 50 mcg<br>Placebo | 258<br>254<br>266<br>259 | Moderate persistent asthma | Primary:<br>Peak $FEV_1$ 0-3 hours after 24 weeks<br>Trough $FEV_1$ after 24 weeks<br>Secondary after 24 weeks:<br>AQLQ, ACQ-5, ACQ-7, Rate of severe exacerbation |

Source: Reviewer
* SR = Spiriva Respimat, DB: double blind

### 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 the study medication and had at least one on-treatment efficacy measurement.

In both studies 418 and 419 ACQ-7 (ACQ total score) was calculated as the mean of the responses to all 7 questions in the ACQ. The ACQ-5 score was calculated as the mean of the responses to all 5 questions of the ACQ that were completed by the patient. Note that question 7 concerning pre-bronchodilator $FEV_1$ was not considered. The AQLQ total score was calculated as the mean of the responses to all 32 questions and was analyzed as an absolute value. The changes from baseline in ACQ-7, ACQ-5, and AQLQ at week 24 were analyzed using MMRM with fixed effects of baseline, center, visit, treatment, treatment-by-visit interaction, and baseline-by-visit interaction. A responder analysis was also conducted for ACQ and AQLQ.

5

Patients were considered responders if they had an improvement (decrease) in the endpoint of interest of at least 0.5 points, which is the minimal important difference compared to baseline. Both ACQ responder and AQLQ were analyzed using Fisher's Exact Test. Rate of severe asthma exacerbation was analyzed using the Poisson regression model.

### 3.2.3   Results and Conclusions

### 3.2.3.1   ACQ

Table 2 shows the results for ACQ-7 and ACQ-5 in studies 418 and 419. Compared to placebo, both doses of Spiriva Respimat provided significant reductions in the change from baseline ACQ-7 in study 418 and only for Spiriva Respimat 2.5 mcg in study 419. Spiriva Respimat showed a significant improvement over placebo for ACQ-7 response in only study 418. There was no difference in response rates or change from baseline for ACQ-5 in either study 418 or 419.

6

**Table 2 Summary of ACQ Results at 24 Weeks (FAS)**

| | Study 418 | | | Study 419 | | |
|---|---|---|---|---|---|---|
| | SR 5 | SR 2.5 | Placebo | SR 5 | SR 2.5 | Placebo |
| **ACQ-7** | | | | | | |
| N-observations at week 24 | 242 | 246 | 247 | 240 | 245 | 240 |
| Mean at week 24 | -0.77 | -0.82 | -0.60 | -0.80 | -0.83 | -0.72 |
| Mean Treatment Δ from placebo | -0.13 | -0.20 | | -0.08 | -0.13 | |
| 95% CI | -0.25, -0.02 | -0.32, -0.09 | | -0.20, 0.03 | -0.24, -0.01 | |
| p-value | 0.0262 | 0.0007 | | 0.1602 | 0.0305 | |
| Number of responders (%) | 174 (67) | 162 (63) | 141 (53) | 156 (62) | 170 (66) | 158 (63) |
| Active vs. Placebo Odds Ratio | 1.76 | 1.47 | | 0.98 | 1.19 | |
| 95% CI | 1.22, 2.45 | 1.02, 2.11 | | 0.67, 1.42 | 0.81, 1.74 | |
| p-value | 0.0022 | 0.0377 | | 1.0000 | 0.4012 | |
| **ACQ-5** | | | | | | |
| N-observations at week 24 | 242 | 247 | 247 | 240 | 245 | 240 |
| Mean at week 24 | -0.90 | -0.93 | -0.78 | -0.93 | -0.94 | -0.93 |
| Mean Treatment Δ from placebo | -0.09 | -0.13 | | -0.01 | -0.03 | |
| 95% CI | -0.22, 0.05 | -0.27, 0.002 | | -0.15, 0.12 | -0.17, 0.11 | |
| p-value | 0.2183 | 0.0535 | | 0.8608 | 0.6704 | |
| Number of responders (%) | 178 (68) | 169 (65) | 163 (62) | 169 (67) | 172 (67) | 169 (67) |
| Active vs. Placebo Odds Ratio | 1.34 | 1.18 | | 1.01 | 1.02 | |
| 95% CI | 0.92, 1.95 | 0.81, 1.70 | | 0.69, 1.49 | 0.69, 1.50 | |
| p-value | 0.1296 | 0.4249 | | 1.0000 | 1.0000 | |

Source: Response Document Table 6, page 11

### 3.2.3.2 AQLQ

Table 3 shows the results for AQLQ in studies 418 and 419. There was no difference in response rates or change from baseline for AQLQ in either study 418 or 419.

**Table 3 Summary of AQLQ Results at Week 24 (FAS)**

| | Study 418 | | | Study 419 | | |
|---|---|---|---|---|---|---|
| | SR 5 N=242 | SR 2.5 N=246 | Placebo N=247 | SR 5 N=240 | SR 2.5 N=245 | Placebo N=240 |
| Mean at week 24 | 0.071 | 0.67 | 0.60 | 0.74 | 0.75 | 0.70 |
| Mean Treatment Δ from placebo | 0.07 | 0.07 | | -0.003 | 0.01 | |
| 95% CI | -0.06, 0.20 | -0.06, 0.20 | | -0.14, 0.13 | -0.12, 0.14 | |
| p-value | 0.2956 | 0.2717 | | 0.9612 | 0.8700 | |
| Number of responders (%) | 149 (57) | 149 (57) | 133 (50) | 145 (58) | 147 (57) | 140 (55) |
| Active vs. Placebo | | | | | | |
| Odds Ratio | 1.32 | 1.34 | | 1.09 | 1.09 | |
| 95% CI | 0.92, 1.89 | 0.94, 1.93 | | 0.76, 1.58 | 0.76, 1.57 | |
| p-value | 0.1338 | 0.1101 | | 0.6821 | 0.7002 | |

N: Number of observations used in the analysis
Source: Response Document Table 6, page 11

### 3.2.3.3 Rate of Severe Asthma Exacerbation

Rate of severe asthma exacerbation is shown in Table 4. There was a significant improvement in Spiriva Respimat 2.5 mcg over placebo in Study 418. There was 68% reduction in the annual rate of severe asthma exacerbations for Spiriva 2.5 mcg. There were no other differences between Spiriva Respimat and placebo.

**Table 4 Results Rate of Severe Asthma Exacerbation- 24 weeks (FAS)**

| | Study 418 | | | Study 419 | | |
|---|---|---|---|---|---|---|
| | SR 5 N=261 | SR 2.5 N=259 | Placebo N=265 | SR 5 N=252 | SR 2.5 N=256 | Placebo N=253 |
| Mean rate of events | 0.19 | 0.08 | 0.24 | 0.14 | 0.13 | 0.18 |
| Active vs. Placebo | | | | | | |
| Rate Ratio | 0.78 | 0.32 | | 0.76 | 0.70 | |
| 95% CI | 0.551, 1.103 | 0.20, 0.51 | | 0.50, 1.16 | 0.46, 1.08 | |
| p-value | 0.5194 | <0.0001 | | 0.1974 | 0.1033 | |

Source: Clinical Trial Report Protocol Number- 205.418 Table 15.2.1.4:19, page 406 and Clinical Trial Report Protocol Number- 205.419 Table 15.2.1.4:19, page 406

## 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

No subgroup analyses were conducted. This submission includes exploratory endpoints only.

## 5 SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues

No outstanding statistical issues were identified in this review.

## 5.2    Conclusions and Recommendations

Analyses from phase 3, randomized, double-blind, double-dummy, active- and placebo-controlled, parallel-group 24 week studies were conducted to examine improvements by Spiriva Respimat compared to placebo for mean change in baseline AQLQ, AQLQ response rate, mean change from baseline in ACQ-7, ACQ-7 response rate, mean change from baseline in ACQ-5, ACQ-5 response rate, and rate of severe asthma exacerbation in studies 418 and 419. Note there was not adequate control of the type I error for these analyses and the significance level at which the statistical tests were conducted may underestimate the false discovery rate.

Significant differences were seen in study 418 for mean change in baseline ACQ-7 between both Spiriva doses and placebo and a significant difference in study 419 for Spiriva Respimat 2.5 mcg. Neither mean change from baseline or response rates for ACQ-5 or AQLQ showed any differences between the treatment groups. In study 418 there was a significant improvement in Spiriva Respimat 2.5 mcg over placebo for rate of severe asthma exacerbation.

## 5.3    Comment of the Proposed Label

Results for AQLQ, ACQ-7, ACQ-5, and rate of severe asthma exacerbation were added to the label in section 14 for studies 418 and 419. We have no issues with this addition to the label.

9