Clinical Review Addendum

Application Type	NDA
Application Number(s)	207-070
Priority or Standard	Standard
Submit Date(s)	August 15, 2014
Received Date(s)	August 15, 2014
PDUFA Goal Date	September 15, 2014
Division / Office	DPARP / ODE II
Reviewer Name(s)	Stacy Chin, MD
Review Addendum Date	September 04, 2015
Established Name	Tiotropium Respimat
(Proposed) Trade Name	Spiriva Respimat
Therapeutic Class	long-acting muscarinic antagonist
Applicant	Boehringer Ingelheim
Formulation(s)	Inhalation Solution
Dosing Regimen	2.5 µg once daily
Indication(s)	Asthma
Intended Population(s)	12 years and older

1. Introduction

This is an addendum to the medical officer primary review of NDA 207-070, dated May 21, 2015, to provide additional information regarding the secondary efficacy endpoints of asthma exacerbations and asthma control and quality of life instruments used in the asthma clinical program and the subsequent labeling discussions involving this topic.

In their asthma development program, Boehringer Ingelheim (BI) measured secondary endpoints of asthma exacerbations and asthma control and symptoms which were important to placing the primary efficacy outcomes on lung function (as assessed by FEV_1 $peak_{(0\text{-}3hr)}$ and FEV_1 trough) in context given that anticholinergic drugs have not yet been established as an effective drug class for maintenance treatment of asthma.

For the asthma exacerbation endpoint, the only additional information included in this addendum are individual study results from the replicate studies in adults with moderate asthma (Trials 418 and 419) for which pooled data was presented in the primary review and individual study results will be presented here. To measure the impact of Spiriva Respimat treatment on subjects' quality of life and perception of health, BI used two instruments: the Asthma Quality of Life Questionnaire (AQLQ) and the Asthma Control Questionnaire (ACQ). Both of these tools were described in the original primary review, however, this addendum also includes additional analyses requested by the Division and a more detailed interpretation of the results. A copy of the questionnaires are provided at the end of this document.

2. Asthma Exacerbations

Given that the FEV_1 treatment response for the primary endpoint(s) was consistently numerically better for Spiriva Respimat 2.5 mcg than for Spiriva Respimat 5 mcg across multiple studies, it was important to determine if there was a differential treatment effect on asthma exacerbations as well. Although trials 416 and 417 were longer in duration (48 weeks) and enriched with patients who experienced frequent exacerbations, the results from these trials were not as relevant to the review of Spiriva Respimat for asthma for reasons discussed in the primary review (patient population required to have fixed obstruction to the same degree as nonsmokers with COPD and lack of data for the 2.5 mcg dose). Therefore, results from the replicate 24-week trials in patients with moderate asthma (418 and 419) became of greater importance even though exacerbations were not designated as a primary endpoint in these studies. Of note, however, exacerbations were defined and captured similarly among studies in the asthma program. As in the primary review, asthma exacerbations in this addendum refer to those that were defined as "severe" by BI (i.e., the subgroup of all asthma worsenings that required treatment with systemic corticosteroids for at least 3 days). Individual trial results shown in Table 1 demonstrate that the rate of asthma exacerbations with the 2.5 mcg dose was half the rate with the 5 mcg dose in trial 418, while the rates were similar in trial 419. Because patients remained in the studies after experiencing an exacerbation, the rate of exacerbations rather than the time to first exacerbation was the more

clinically relevant measure of exacerbations. These results support the effectiveness of the 2.5 mcg dose for asthma.

Table 1. Asthma exacerbation data from Trials 418 and 419

	Trial 418			Trial 419		
	SR 2.5 (N=259)	**SR 5 (N=261)**	**Placebo (N=265)**	**SR 2.5 (N=256)**	**SR 5 (N=252)**	**Placebo (N=253)**
Number of patients with at least 1 event, n (%)	9 (3.5)	17 (6.5)	24 (9.1)	13 (5.1)	14 (5.6)	19 (7.5)
Rate of exacerbations per patient year						
Mean rate of events	0.08	0.19	0.24	0.13	0.14	0.18
Comparison to Placebo, Rate ratio (95% CI) p-value	0.32 (0.20, 0.51) <0.001	0.78 (0.55, 1.10) 0.16	--	0.70 (0.46, 1.08) 0.10	0.76 (0.50, 1.16) 0.20	--
Time to first exacerbation						
Compared to Placebo, Hazard ratio (95% CI) p-value	0.37 (0.17, 0.80) 0.01	0.72 (0.39, 1.35) 0.31	--	0.66 (0.33, 1.34) 0.26	0.72 (0.36, 1.43) 0.35	--
Abbreviations: SR=Spiriva Respimat Source: CSR 205.418, Tables 15.2.1.4:16 and 15.2.1.4:19; CSR 205.419, Tables 15.2.1.4:16 and 15.2.1.4:19						

3. Asthma Quality of Life Questionnaire

The AQLQ is an asthma-specific health-related quality of life instrument that assesses both the physical and emotional impacts of disease. There are a total of 32 items in 4 domains covering a 2-week recall period. The domains include: symptoms (11 items), activity limitation (12 items), emotional function (5 items), and environmental exposure (4 items). Scores range from 1 to 7 with higher scores indicating better quality of life. The standardized version, which BI used in their trials and is the most widely used, incorporates five generic activities under the domain "activity limitation" rather than five individualized activities. The minimally important difference (MID) has been determined to be a difference in score of 0.5 for overall quality of life and for each of the individual domains.

4. Asthma Control Questionnaire

The ACQ is an asthma-specific questionnaire designed to measure the adequacy of asthma control and change in asthma control which occurs either spontaneously or as a result of treatment. There are a total of 7 items: 5 items assessing symptoms, 1 item assessing rescue bronchodilator use, and 1 item assessing FEV_1%. Items 1 through 6 are self-administered while item 7 is completed by clinic staff. Each item is scored on a 7-point scale with 0=no impairment and 6=maximum impairment for symptoms and rescue medication use. Likewise, there are 7 categories for FEV_1%. Scores range between 0 and 6 with lower scores indicating better asthma control. The test has been validated against the AQLQ and the Medical Outcomes Survey Short Form-36 (SF-36), and has a high reported intraclass correlation coefficient (=0.90). The MID has

also been determined to be a change in score of 0.5. Shortened versions using symptoms alone (ACQ-5) or symptoms plus rescue bronchodilator use (ACQ-6) have been validated. Although the measurement properties of the shorter versions are not quite as good as those of the complete ACQ-7, they have utility in certain settings in which one is trying to separate the benefit of a bronchodilator such as Spiriva Respimat from the effects on asthma symptoms.

5. Analysis of AQLQ and ACQ Scores

For each questionnaire, a change in ≥ 0.5 units has been identified as the minimally important difference and was used as the cutoff to define a "responder".[1,2] While a change in ≥ 0.5 units in the overall mean score when different from placebo suggests a beneficial treatment effect, this analysis fails to capture individual treatment responses and appears falsely optimistic if scores in the placebo group worsen. Therefore, an evaluation of the ACQ and AQLQ responder rates were of greater interest and clinical relevance. The following table (**Error! Reference source not found.**) lists the results of both the mean scores and the responder rates for the AQLQ, ACQ-7, and ACQ-5 for all phase 3 efficacy trials in adults and adolescents. In general, there were greater improvements and more responders in the Spiriva Respimat groups with no clear and consistent difference between the 5 mcg and 2.5 mcg doses. In both of the 24-week trials (418 and 419), treatment with Spiriva Respimat resulted in more favorable AQLQ(S) and ACQ responder rates over placebo with similar trends observed for the 5 mcg and 2.5 mcg dose, again supporting the effectiveness of the lower 2.5 mcg dose in asthma. Because the ACQ consists of two questions directly related to bronchodilator treatment effects (rescue medication use and FEV_1), the Division also considered responder rates to the ACQ-5 which eliminated the two aforementioned components. The responder rates to the ACQ-5 were similar to the complete ACQ (ACQ-7), indicating that the results were not solely driven by Spiriva Respimat's bronchodilatory activity. Although few of the comparisons to placebo were statistically significant, for the purposes of this review, the data from these secondary endpoints were sufficient to support the efficacy of Spiriva Respimat for asthma and the selection of the lower 2.5 mcg dose in asthma.

Table 2. AQLQ and ACQ scores from phase 3 trials

Trial	N	AQLQ(S)				ACQ-7				ACQ-5			
		Baseline	Δ from baseline	Mean difference from placebo (95% CI) p-value	Responders* Odds ratio (95% CI) p-value	Baseline	Δ from baseline	Mean difference from placebo (95% CI) p-value	Responders* Odds ratio (95% CI) p-value	Baseline	Δ from baseline	Mean difference from placebo (95% CI) p-value	Responders* Odds ratio (95% CI) p-value
205.416													
Spiriva Respimat 5 mcg	237	4.60	0.50	0.04 (-0.10, 0.19) 0.56	41% 0.89 (0.61, 1.31) 1.00	2.67	-0.69	-0.12 (-0.25, 0.01) 0.07	55% 1.07 (0.73, 1.57) 0.79	2.44	-0.75	-0.11 (-0.27, 0.04) 0.16	58% 1.08 (0.73, 1.59) 0.75
Placebo	222	4.58	0.44	--	44%	2.66	-0.56	--	54%	2.42	-0.61	--	56%
205.417													
Spiriva Respimat 5 mcg	216	4.63	0.46	0.17 (0.02, 0.33) 0.03	44% 1.41 (0.95, 2.10) 0.09	2.60	-0.60	-0.20 (-0.33, -0.06) <0.01	52% 1.61 (1.09, 2.38) 0.02	2.36	-0.64	-0.19 (-0.34, -0.03) 0.02	56% 1.68 (1.14, 2.48) 0.01
Placebo	232	4.65	0.28	--	36%	2.58	-0.38		41%	2.33	-0.42	--	43%
205.418													
Spiriva Respimat 5 mcg	242	4.78	0.71	0.07 (-0.06, 0.20) 0.30	57% 1.32 (0.92, 1.89) 0.13	2.23	-0.77	-0.13 (-0.25, -0.02) 0.03	67% 1.76 (1.22, 2.45) <0.01	2.22	-0.90	-0.09 (-0.22, 0.05) 0.22	68% 1.34 (0.92, 1.95) 0.13
Spiriva Respimat 2.5 mcg	246	4.87	0.67	0.07 (-0.06, 0.20) 0.27	58% 1.34 (0.94, 1.93) 0.11	2.18	-0.82	-0.2 (-0.32, -0.09) <0.01	63% 1.47 (1.02, 2.11) 0.04	2.19	-0.93	-0.13 (-0.27, 0.002) 0.05	65% 1.18 (0.81, 1.70) 0.42
Placebo	247	4.83	0.60	--	50%	2.15	-0.60	--	53%	2.16	-0.78	--	62%
205.419													
Spiriva Respimat 5 mcg	240	4.76	0.74	-0.003 (-0.14, 0.13) 0.96	58% 1.09 (0.76, 1.58) 0.68	2.19	-0.80	-0.08 (-0.20, 0.03) 0.16	62% 0.98 (0.67, 1.42) 1.00	2.22	-0.93	-0.01 (-0.15, 0.12) 0.86	67% 1.01 ((0.69, 1.49) 1.00
Spiriva Respimat 2.5 mcg	245	4.77	0.75	0.01 (-0.12, 0.14) 0.87	57% 1.09 (0.76, 1.57) 0.70	2.17	-0.83	-0.13 (-0.24, -0.01) 0.03	66% 1.19 (0.81, 1.74) 0.40	2.20	-0.94	-0.03 (-0.17, 0.11) 0.67	67% 1.02 (0.69, 1.50) 1.00
Placebo	240	4.88	0.70	--	55%	2.21	-0.72	--	63%	2.24	-0.93	--	67%
205.442													

Trial	N	AQLQ(S)				ACQ-7				ACQ-5			
		Baseline	Δ from baseline	Mean difference from placebo (95% CI) p-value	Responders* Odds ratio (95% CI) p-value	Baseline	Δ from baseline	Mean difference from placebo (95% CI) p-value	Responders* Odds ratio (95% CI) p-value	Baseline	Δ from baseline	Mean difference from placebo (95% CI) p-value	Responders* Odds ratio (95% CI) p-value
Spiriva Respimat 5 mcg	152	--	--	--	--	2.08	-0.70	0.01 (-0.12, 0.15) 0.83	58% 0.97 (0.60, 1.57) 1.00	2.18	-0.82	0.09 (-0.06, 0.24) 0.24	59% 0.85 (0.52, 1.38) 1.00
Spiriva Respimat 2.5 mcg	149	--	--	--	--	2.12	-0.68	0.06 (-0.07, 0.19) 0.36	59% 1.02 (0.63, 1.64) 1.00	2.16	-0.79	0.13 (-0.02, 0.29) 0.09	62% 0.96 (0.59, 1.57) 1.00
Placebo	154	--	--	--	--	2.10	-0.70	--	59%	2.15	-0.88	--	63%
205.444													
Spiriva Respimat 5 mcg	132	5.34	0.61	0.08 (-0.09, 0.25) 0.35	53% 1.60 (0.96, 2.66) 0.07	2.02	-0.94	-0.10 (-0.26, 0.07) 0.25	75% 1.47 (0.84, 2.58) 0.19	2.15	-1.00	-0.06 (-0.26, 0.14) 0.55	74% 1.20 (0.68, 2.11) 0.60
Spiriva Respimat 2.5 mcg	120	5.43	0.63	0.14 (-0.04, 0.31) 0.12	47% (1.27 (0.76, 2.13) 0.40	2.05	-1.03	-0.16 (-0.33, 0.01) 0.07	76% 1.58 (0.89, 2.83) 0.13	2.19	-1.11	-0.15 (-0.35, 0.05) 0.14	74% 1.23 (0.69, 2.20) 0.55
Placebo	136	5.35	0.54	--	41%	2.02	-0.86	--	67%	2.15	-0.95	--	70%
205.456													
Spiriva Respimat 5 mcg	--	--	--	--	--	2.10	-0.97	0.04 (-0.12, 0.20) 0.66	73% 0.99 (0.55, 1.76) 1.00	2.18	-1.05	0.06 (-0.13, 0.25) 0.53	74% 1.03 (0.57, 1.84) 1.00
Spiriva Respimat 2.5 mcg	--	--	--	--	--	2.15	-0.96	0.06 (-0.10, 0.22) 0.48	75% 1.08 (0.60, 1.95) 0.90	2.24	-1.02	0.12 (-0.07, 0.31) 0.20	71% 0.88 (0.50, 1.57) 1.00
Placebo	--	--	--	--	--	2.15	-1.03	--	73%	2.24	-1.15	--	73%

*Responders defined as patients with an improvement of 0.5 units.
Results are from the 24 week timepoint except for trials 442 and 456 which were at 12 weeks.
AQLQ not assessed in 12-week trials 442 and 456.
Source: BI response to IR submitted August 4, 2015

6. Labeling Considerations

The secondary endpoints of asthma exacerbations and asthma control and symptoms are important to providing context for the primary outcomes on lung function. (b) (4)

Therefore, exacerbation data from the replicate 24-week trials (418 and 419) will be included in the label with results from individual studies presented separately since pooling was not pre-specified.

To date, the ACQ has been used primarily as a patient selection tool for entry into clinical trials, but has not been included as an outcome to support efficacy in asthma drug product labels. On the other hand, the AQLQ has been described in the clinical trials section of a few products such as Advair. During the labeling review, the Agency felt that the results from these tools provided further support to the asthma exacerbation data which primarily demonstrated a benefit in the need for oral corticosteroids rather than a reduction in hospitalizations or asthma-related intubations or deaths. Both questionnaires are commonly used in clinical practice and are referred to in asthma treatment guidelines, and therefore, information related to improvement in subjective symptoms and disease control might be informative to patients and health care providers. Because the two questionnaires are related, information from the ACQ and AQLQ will be included in the clinical trials section for asthma in the Spiriva Respimat label.

Figure 1. Standardized Asthma Quality of Life Questionnaire (AQLQ(S))

(b) (4)

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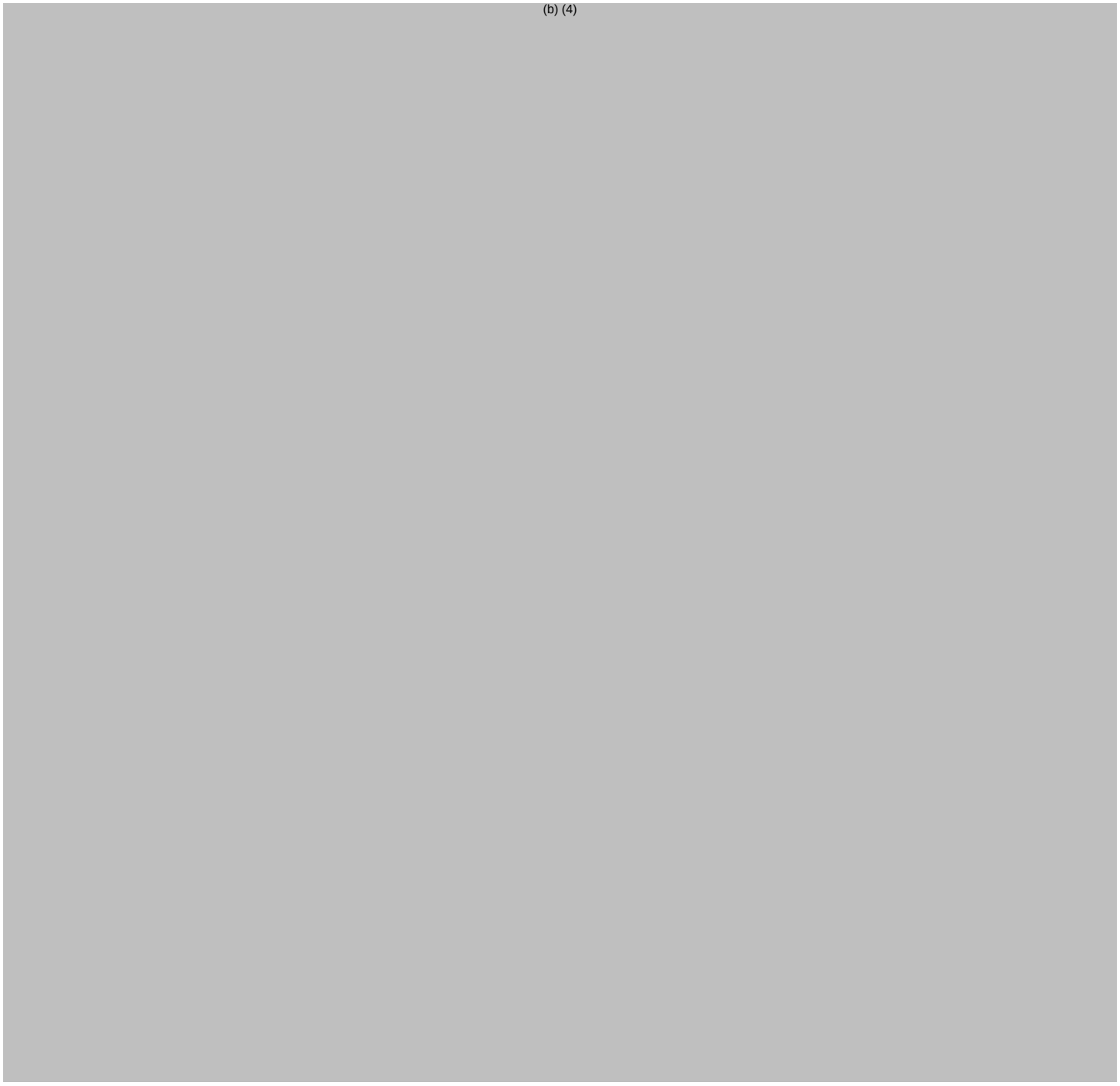

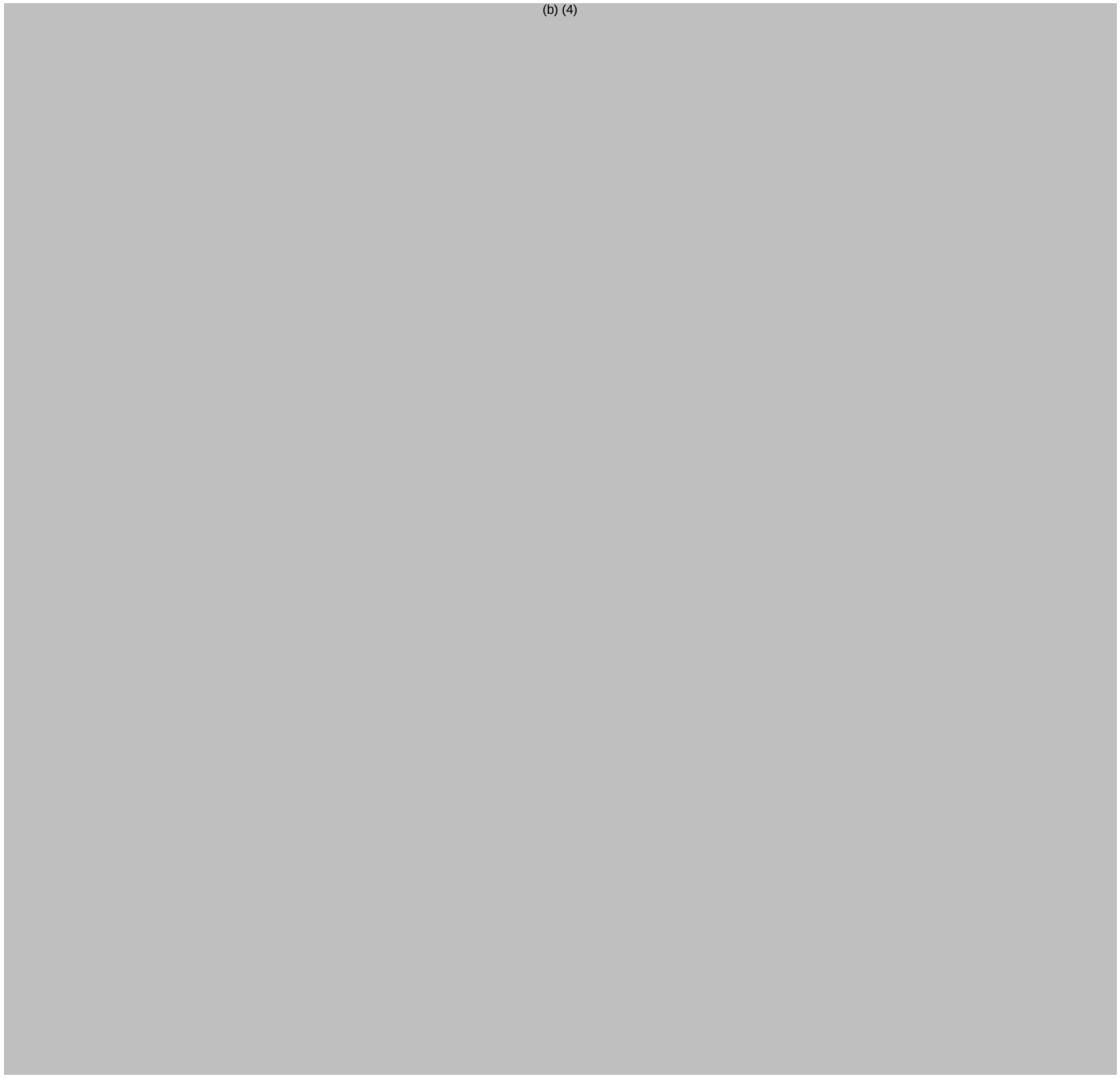
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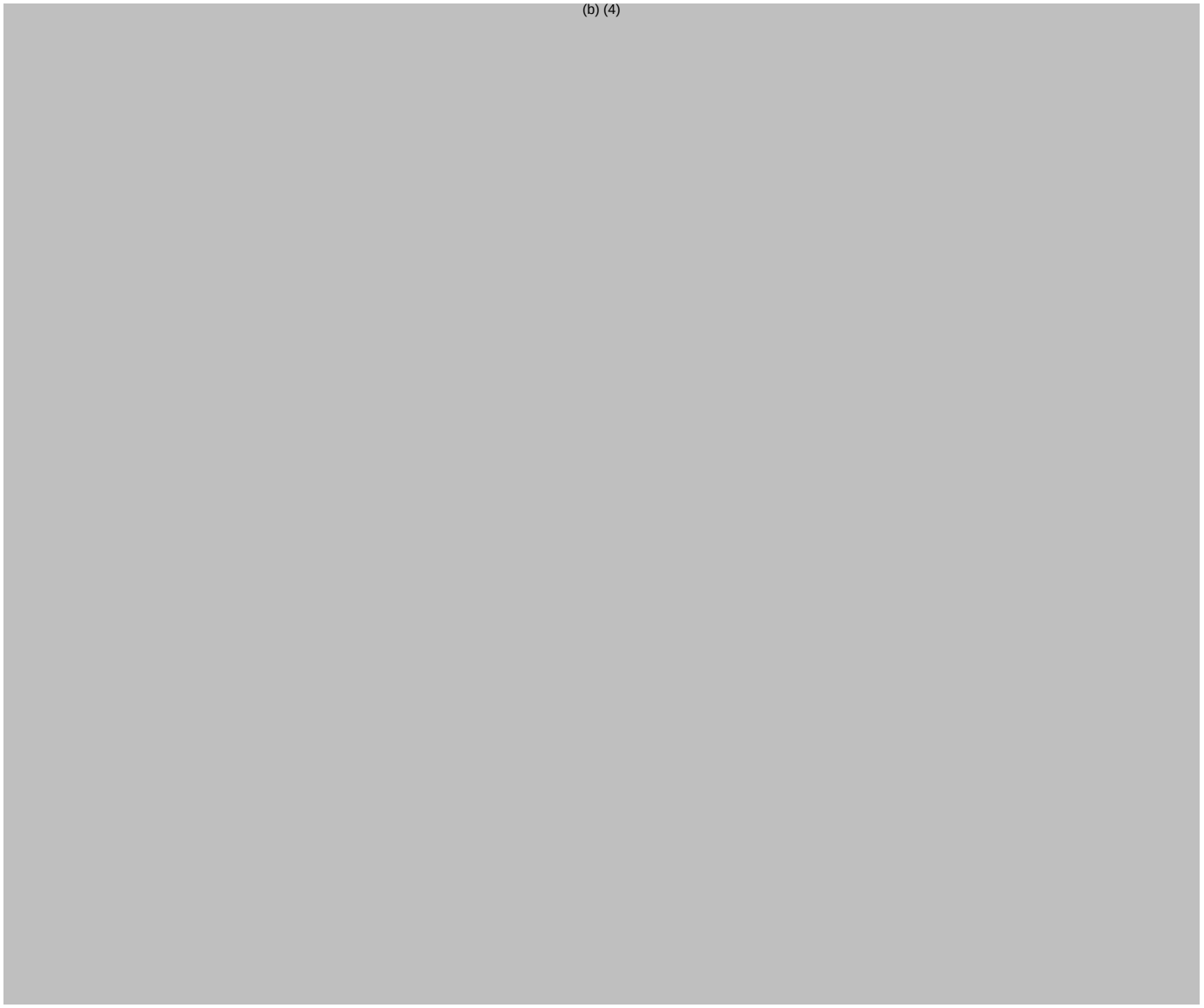


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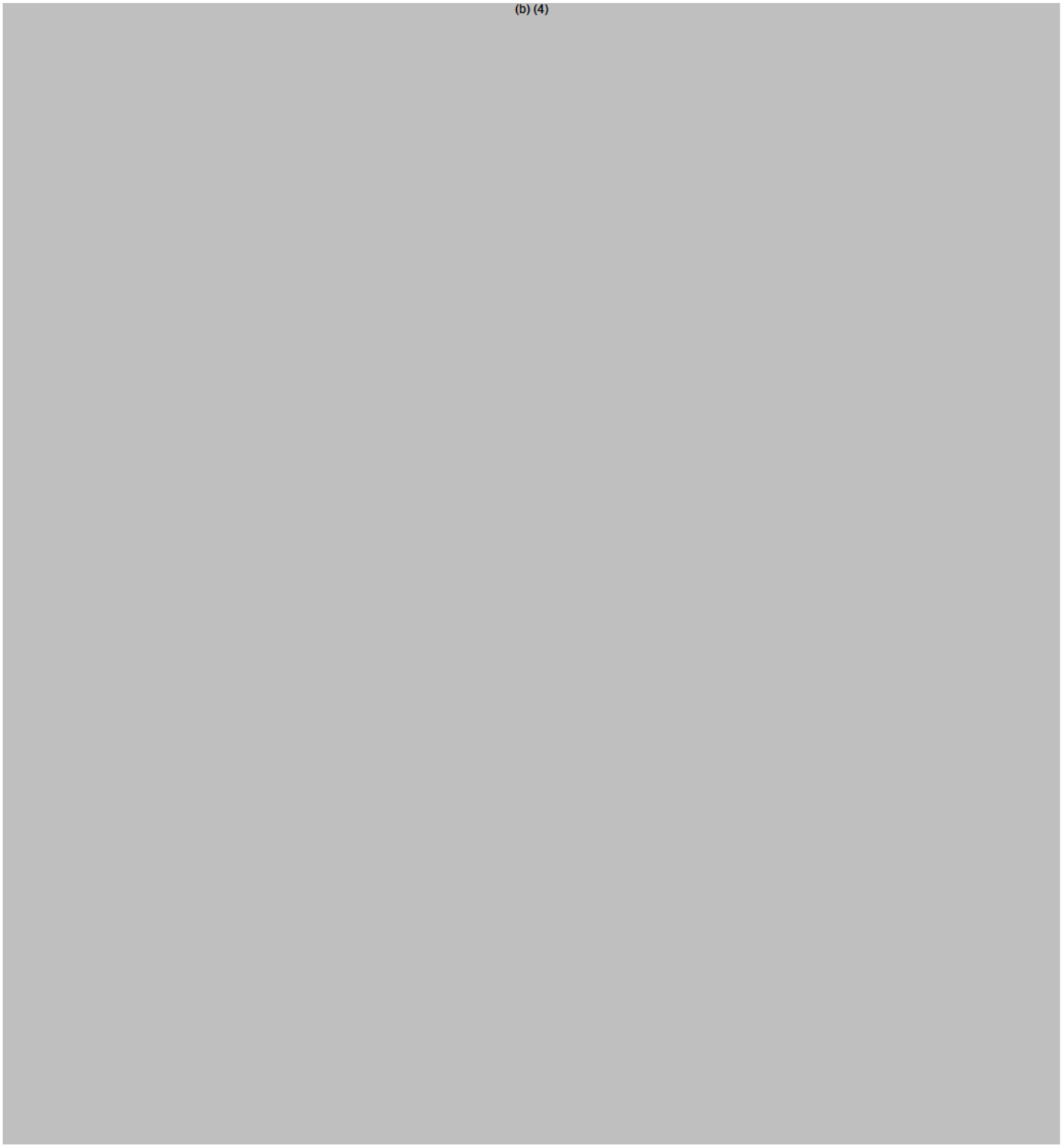
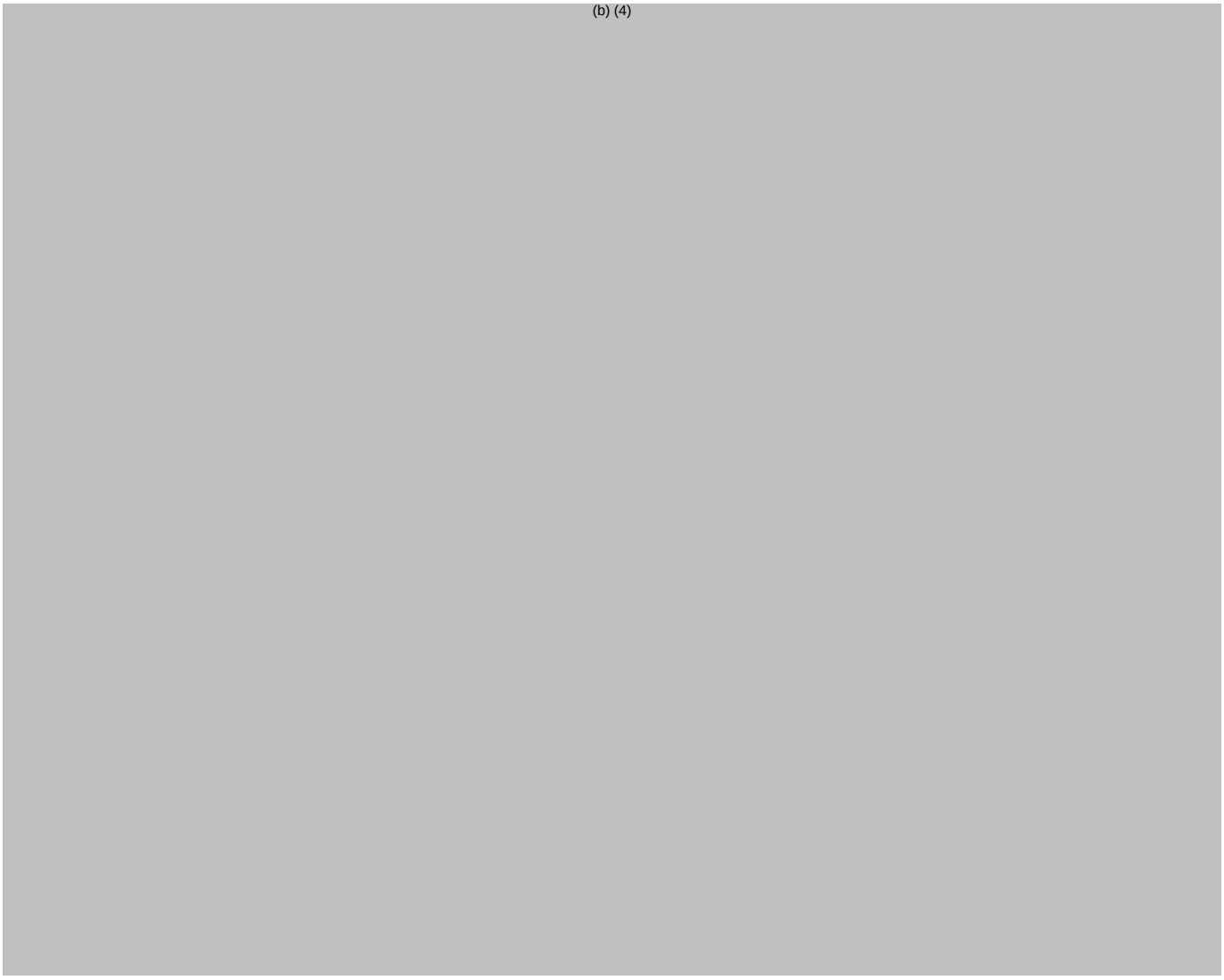
Figure 2. Asthma Control Questionnaire (ACQ)




(b) (4)

References

1. Juniper EF, Svensson K, Mork AC, Stahl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respir Med.* 2005;99(5):553-558.
2. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific Quality of Life Questionnaire. *J Clin Epidemiol.* 1994;47(1):81-87.

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