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Indacaterol (QAB149) in Chronic Obstructive Pulmonary Disease

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Addendum to Briefing Document

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List of abbreviations and definition of terms

AC	Adjudication Committee
b.i.d.	bis in diem / twice a day
CI	confidence intervals
COPD	Chronic Obstructive Pulmonary Disease
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in one second
GOLD	Global Initiative for Chronic Obstructive Pulmonary Disease
HR	Hazard ratio
ICS	Inhaled corticosteroid
LABA	Long-acting β_2-agonist
o.d.	omni die / once a day
q.o.d.	Quiaque alternis die/every other day
SABA	short-acting β_2-agonist
SAE	serious adverse event

1 Executive Summary

Introduction

Further to a request from the FDA in December 2010 to provide additional information to facilitate the safety review of indacaterol, this Addendum to the Briefing Document dated February 1, 2011 provides the methodology and results of an additional comprehensive analysis evaluating the incidence of a respiratory-related composite endpoint consisting of death, intubation and hospitalization related to asthma, chronic obstructive pulmonary disease (COPD) or pneumonia.

Objectives of analysis

To obtain the most comprehensive and objective assessment of the respiratory safety of indacaterol based upon a review of serious adverse event reports and patient narratives by an independent external expert panel.

Description of analysis

Each serious adverse event (SAE) reported in the indacaterol development program was reviewed by an independent external expert panel (Adjudication Committee (AC)), to determine whether it included a hospitalization, intubation or death, and if the cause was primarily related to asthma, COPD or pneumonia.

This Addendum describes the methodology and the statistical methods used for the analysis, and provides a summary of the results of the adjudicated data. The AC charter and statistical analysis plan were submitted to FDA and refined as requested before implementation.

The safety database used for this review included 13,669 patients exposed to study drug across 30 studies with 8170 treated with indacaterol. The majority of these patients (86%) were treated for COPD (23 studies), with the remainder treated for asthma (7 studies), in study durations ranging from 7 days up to 1 year. Per the FDA request, this SAE review was performed on patient narratives blinded to treatment.

Results

For the All-treated COPD safety population I (which included active and placebo controlled studies), a time to event analysis for the acute respiratory-related (hospitalization, intubation, and death) composite endpoint demonstrated an overall risk for the indacaterol combined treatment group (in the to-be-marketed device) that was not statistically significantly different to placebo (HR = 0.93, 95% CI 0.69-1.24).

For the All-treated asthma safety population I (both active and placebo controlled studies), a time to event analysis for the acute respiratory-related composite endpoint showed a difference in hazard ratios between the indacaterol combined treatment group (in the to-be-marketed device) and the salmeterol treatment group which was not statistically significant (HR=1.26, 95% CI 0.55-2.91). In this population, hazard ratios compared to placebo could not be calculated due to zero events in the placebo treatment group.

Conclusions

This analysis demonstrates that the risk of SAEs, namely the composite endpoint of hospitalizations, intubations, and death, whether related to asthma, COPD or pneumonia, in patients treated with indacaterol was similar to that of patients treated with placebo.

The data, along with the overall safety assessments submitted as part of the NDA application, and described in the Advisory Committee Briefing Document, support the overall positive safety profile of indacaterol across all doses studied.

2 Introduction

The FDA requested additional information to facilitate the safety review of indacaterol. Specifically, FDA requested Novartis to conduct an analysis evaluating the incidence of respiratory-related composite endpoint consisting of death, intubation and hospitalization related to asthma, COPD or pneumonia in indacaterol-treated patients compared to control. This review was to be similar in methodology to a meta-analysis of pooled data from all long-acting β_2-agonist (LABA)-containing products marketed in the US carried out by the FDA in 2008. That review focused specifically on LABA use in asthma and used a composite endpoint of serious asthma-related outcomes, including death, intubation and hospitalization.

Novartis implemented an Adjudication Committee (AC) to provide an independent, external, systematic, standardized and unbiased assessment of all SAEs occurring during the development of indacaterol (COPD and asthma). Reference is made to Section 6.5.2 (Respiratory-related deaths, hospitalizations and intubations) of the Briefing Document dated February 1, 2011, where it is noted that an Addendum detailing the methodology and results of this analysis will be provided.

3 Adjudication procedure

Studies for adjudication

The FDA requested that all blinded, controlled studies in COPD and in asthma of at least 7 days duration using the single dose dry powder inhaler of the to-be-marketed product (Concept1), or devices similar to the Concept1, be included. This analysis included studies in which indacaterol was administered as randomized treatment, either with or without a concomitant inhaled corticosteroid (ICS) or other adjunctive therapy, and studies conducted with indacaterol combination products that had an indacaterol-only treatment arm. Studies could be parallel group or crossover designs, but for the latter, only the first treatment period was evaluated.

For studies where subjects were exposed to both blinded and open-label treatments, only blinded treatment arms were included in the analysis.

In total, there were 7 asthma studies ranging in duration from 7 days to 26 weeks and 23 COPD studies ranging in duration from 7 days to 52 weeks which met the criteria for the analysis.

Adjudication Committee

The Adjudication Committee (AC) consisted of five members, all medical professionals in the field of pulmonary medicine. The AC was split into two groups of two to review the patient narratives, i.e. each narrative would be reviewed by two AC members. The fifth member of the AC was the Chair.

Within each group of two, the AC members, blinded to treatment and disease under study, independently assessed patient narratives to categorize whether any deaths, hospitalizations, and intubation events described in the narratives were respiratory- related or not, and if they were respiratory-related events, whether the respiratory event was related to asthma, COPD or pneumonia. For the purposes of the adjudication, the following disease-related definitions were used:

- Asthma-related event - the primary cause for hospitalization, intubation or death was an acute worsening of the patient's underlying asthma
- COPD-related event - the primary cause for hospitalization, intubation or death was an acute worsening of the patient's underlying COPD
- Pneumonia-related event - the primary cause for hospitalization, intubation or death was pneumonia, related to a viral, bacterial, fungal or other infection. Assignment of pneumonia as a cause of the event could be based on chest x-ray findings, the presence of fever or leukocytosis, or other aspects included in the patient narrative.

In addition:

- Hospitalization was defined as a hospital admission or an emergency room visit greater than 24 hours in duration (± systemic corticosteroid treatment)
- Intubation was defined as endotracheal intubation for mechanical ventilation for the treatment of acute hypoxemic or hypercapneic respiratory failure.

If there was a difference (including the day on which the event occurred) in adjudication of any event within a team of two AC members, a meeting with the adjudication committee chair took place to resolve the adjudication of the event.

4 Analysis plan

4.1 Analysis populations

The analyses were performed on data that had already been integrated for the September 2010 submission to the NDA.

Six populations of interest were defined:

- All-treated safety population I - patients entered into **any** study, i.e. active and placebo controlled, COPD or asthma studies, who took at least one study dose
- All-treated safety population II - patients who took at least one study dose in the COPD and asthma studies **that were placebo-controlled only**
- All-treated COPD safety population I - patients who took at least one study dose in the COPD studies

- All-treated COPD safety population II - patients who took at least one study dose in the COPD studies **that were placebo-controlled only**
- All-treated asthma safety population I - patients who took at least one study dose in the asthma studies
- All-treated asthma safety population II - patients who took at least one study dose in the asthma studies **that were placebo controlled only**

In all cases, only the blinded treatments were included in the population. For crossover studies, only treatments in the first period were included.

As well as reporting each individual indacaterol dose inhaled through the Concept1 device, placebo and active comparators (formoterol, salmeterol, tiotropium), the following grouped treatment arms were defined:

- Any indacaterol dose inhaled through the Concept1 device, labeled as **Ind CON** in tables
- Any indacaterol dose inhaled through other devices similar to the Concept1, labeled as **Ind OTH** in tables
- All indacaterol doses administered through inhalation, labeled as **Ind ALL** in tables

To reflect the FDA request, only events of interest that took place while on study drug were included.

4.2 Subgroups of interest

Subgroups based on nominal trial duration and SABA reversibility were defined as follows:

1. Trials of 7 days of treatment vs trials >7 days of treatment
2. Trials with less than 12 weeks of treatment vs trials with 12 or more weeks of treatment
3. FEV_1 increase post-SABA of >12% and >200 mL (Pellegrino et al, 2005) at baseline: yes vs. no

Analyses for subgroup 1 (above) were performed for the All-treated asthma safety populations and for subgroups 1 to 3 for the All-treated COPD safety populations.

4.3 Respiratory related events

4.3.1 Endpoints

The endpoints of interest were hospitalization, intubation or death. All endpoint events were classified by the Adjudication Committee as follows:

1. Asthma-related
2. COPD-related
3. Pneumonia-related
4. Other respiratory-related, e.g. pulmonary embolus, lung cancer
5. Non-respiratory

Events classified as asthma-, COPD- or pneumonia-related were further classified as acute respiratory-related.

In addition to analyzing the data for each endpoint individually, composite endpoints were created:

- Total, i.e. any cause, and defined using classifications 1-5 above
- respiratory-related i.e. any respiratory cause, and defined using classifications 1-4 above
- acute respiratory events, i.e. any acute respiratory cause, and defined using classifications 1-3 above
- not respiratory-related, defined using classification 5 only

Patients who experienced one or more hospitalizations or one or more intubations or died in the categories above were included in the composite endpoints.

Finally, all-cause mortality was also defined as an endpoint.

4.3.2 Statistical Analysis

This section describes the planned statistical analyses. Not all model-based analyses were actually performed due to the small number of events.

4.3.2.1 Incidence

Incidence was based on the number and percentage of patients who reported the endpoints described in Section 4.3.1. All analyses were performed at the patient level. This analysis does not adjust for time on study, whereas the time to event analysis does.

4.3.2.2 Time to event

The primary analysis method was time to first event based on the following endpoints:

- Hospitalization due to: asthma, COPD, pneumonia, any acute respiratory cause, any respiratory cause
- Intubation due to: asthma, COPD, pneumonia, any acute respiratory cause, any respiratory cause
- Death due to: asthma, COPD, pneumonia, any acute respiratory cause, any respiratory cause, any cause
- Composite (hospitalization, intubation or death) due to: asthma, COPD, pneumonia, any acute respiratory cause, any respiratory cause

The time to first endpoint event was analyzed using a Cox regression model. The model was stratified by study with treatment included as a factor for the analysis populations described in Section 4.1 (and the SABA reversibility subgroup for the All-treated COPD safety populations I and II).

In the analyses by SABA reversibility, an interaction between treatment and reversibility was included.

Please note that many of the endpoint events occurred rarely. In cases where there were zero events in either of the treatment groups being compared, a hazard ratio could not be calculated. These are presented as n.e. (not estimable) in the tables.

4.3.2.3 Risk difference

A sensitivity analysis based on risk difference was performed. The risk difference (with its associated confidence interval) was calculated using the Mantel-Haenszel method with the results presented as forest plots. Analyses were performed for the three placebo-controlled populations alone, and only indacaterol versus placebo treatment comparisons are presented in a forest plot in Figure 5-1.

5 Results

5.1 Data sets analyzed

Thirty studies were included in the analyses. A summary of the number of subjects in each analysis population broken down by treatment received is given in Table 5-1.

The total number of narratives adjudicated in the All-treated safety population I is given in Table 5-2, including the main disease-relationship categories to which the events were adjudicated. Across the studies, 746 subjects in the indacaterol clinical development program experienced at least one SAE and therefore had a patient narrative available for review by the AC. Of the 746 narratives adjudicated, 420 were from indacaterol-treated patients, and 326 from patients treated with an active control or placebo.

Table 5-1 Analysis populations

	Indacaterol dose (µg) and dose regimen										Indacaterol totals			Control groups			
Population	**18.75 o.d.**	**37.5 o.d.**	**37.5 b.i.d.**	**75 o.d.**	**150 o.d.**	**150 q.o.d.**	**150 + Tio**	**300 o.d.**	**400 o.d.**	**600 o.d.**	**CON**	**OTH**	**ALL**	**For**	**Tio**	**Sme**	**Pbo**
All-treated safety I [1]	173	171	48	674	2830	48	1142	1690	7	852	7635	535	8170	556	842	1363	2738
All-treated safety II [2]	173	171	48	674	1477	48	0	1422	7	584	4604	535	5139	556	43	532	2738
All-treated asthma safety I [3]	84	81	48	131	85	48	0	268	7	268	1020	287	1307	0	0	353	254
All-treated asthma safety II [4]	84	81	48	131	85	48	0	0	7	0	484	287	771	0	0	84	254
All-treated COPD safety I [5]	89	90	0	543	2745	0	1142	1422	0	584	6615	248	6863	556	842	1010	2484
All-treated COPD safety II [6]	89	90	0	543	1392	0	0	1422	0	584	4120	248	4368	556	43	448	2484

1. Patients entered into active or placebo controlled, COPD or asthma study who took at least one study dose
2. Patients who took at least one study dose in those COPD and asthma studies that are placebo-controlled only
3. Patients who took at least one study dose in Asthma studies
4. Patients who took at least one study dose in asthma studies that were placebo controlled
5. Patients who took at least one study dose in COPD studies
6. Patients who took at least one study dose in COPD studies that were placebo controlled

Abbrev: Ind = indacaterol, For=formoterol, Tio=tiotropium, Sme=salmeterol, Pbo=placebo, Ind CON = total patients in studies using the Concept1 device, Ind OTH = total patients in studies using other devices, Ind ALL = total patients in studies using any device o.d.=once-daily, b.i.d.= twice daily, q.o.d.=once every other day

Table 5-2 Summary of narratives adjudicated – All-treated safety population I

	Indacaterol dose (µg) and dose regimen										Indacaterol totals			Control groups			
Variable	**18.75 o.d.**	**37.5 o.d.**	**37.5 b.i.d.**	**75 o.d.**	**150 o.d.**	**150 + tio**	**150 q.o.d.**	**300 o.d.**	**400 o.d.**	**600 o.d.**	**CON**	**OTH**	**ALL**	**For**	**Tio**	**Sme**	**Pbo**
Total patients N	173	171	48	674	2830	1142	48	1690	7	852	7635	535	8170	556	842	1363	2738
Patients with adjudicated narratives n (%)	1 (0.6)	0	0	19 (2.8)	142 (5.0)	46 (4.0)	1 (2.1)	135 (8.0)	0	68 (8.0)	412 (5.4)	8 (1.5)	420 (5.1)	76 (13.7)	34 (4.0)	45 (3.3)	171 (6.2)
Adjudicated to contain: n (%)																	
Any Non Respiratory related events	1 (0.6)	0	0	9 (1.3)	60 (2.1)	16 (1.4)	0	50 (3.0)	0	36 (4.2)	172 (2.3)	2 (0.4)	174 (2.1)	29 (5.2)	14 (1.7)	16 (1.2)	63 (2.3)
Any Respiratory related events	0	0	0	6 (0.9)	43 (1.5)	16 (1.4)	0	57 (3.4)	0	18 (2.1)	140 (1.8)	1 (0.2)	141 (1.7)	32 (5.8)	7 (0.8)	16 (1.2)	52 (1.9)
Acute Respiratory related	0	0	0	6 (0.9)	37 (1.3)	15 (1.3)	0	50 (3.0)	0	18 (2.1)	126 (1.7)	1 (0.2)	127 (1.6)	31 (5.6)	6 (0.7)	14 (1.0)	50 (1.8)
Asthma related	0	0	0	0	0	0	0	2 (0.1)	0	2 (0.2)	4 (0.1)	1 (0.2)	5 (0.1)	0	0	1 (0.1)	0
COPD related	0	0	0	5 (0.7)	36 (1.3)	14 (1.2)	0	42 (2.5)	0	13 (1.5)	110 (1.4)	0	110 (1.3)	30 (5.4)	5 (0.6)	10 (0.7)	47 (1.7)
Pneumonia related	0	0	0	3 (0.4)	6 (0.2)	6 (0.5)	0	11 (0.7)	0	3 (0.4)	29 (0.4)	0	29 (0.4)	4 (0.7)	4 (0.5)	3 (0.2)	7 (0.3)
Other Respiratory related	0	0	0	0	6 (0.2)	2 (0.2)	0	7 (0.4)	0	0	15 (0.2)	0	15 (0.2)	1 (0.2)	1 (0.1)	2 (0.1)	2 (0.1)

Abbrev: Ind = indacaterol, For=formoterol, Tio=tiotropium, Sme=salmeterol, Pbo=placebo; Indacaterol totals- CON = total patients in studies using the Concept1 device, OTH = total patients taking any indacaterol dose in studies using other devices, ALL = total patients in studies using any device; o.d.=once-daily, b.i.d.= twice daily, q.o.d.=once every other day

5.2 Demographic and other baseline characteristics

The All-treated safety population I contains 1,914 patients diagnosed with asthma and 11,755 patients with COPD.

In the All-treated asthma safety population I, the treatment groups were broadly similar as were the treatment groups in the All-treated COPD safety population I.

The demographic and baseline characteristics of the All-treated safety, All-treated asthma and All-treated COPD safety populations II (limited to placebo-controlled trials) were similar to those above. All-treated safety populations in this analysis were similar to the safety population described in the Advisory Committee Briefing Document.

Demographic and baseline characteristics were also analyzed by subgroup and showed no clinically relevant differences between treatments within subgroups compared to the full population analyses.

Disposition of patients

A total of 11,923 of 13,669 (87.2%) patients in the All-treated safety population I completed the studies as planned.

Discontinuations from the studies overall occurred more frequently for patients treated with placebo than for the Ind CON-treated patients. The discontinuation rates in all indacaterol dose groups were lower or similar to placebo in all cases. This was similar to the safety population described in the Advisory Committee Briefing Document.

The patient disposition showed a similar pattern in the subgroups of the All-treated asthma safety populations I and II and in the All-treated COPD safety populations I and II by study duration (7 days vs >7 days and <12 weeks vs ≥12 weeks), and by reversibility (>12% and >200 mL vs ≤12% or ≤200 mL).

5.3 Event incidence rates and associated analysis

In this section, the presentation begins with a display of incidence data for the All-treated COPD safety population I, which is a key population that reflects the focus of the indacaterol development program and the target indication in studies including placebo and/or active controls. The All-treated asthma safety population is much smaller than COPD, but carries relevant safety information for a patient population of particular interest for respiratory safety in a more bronchoreactive population. The 'All-treated safety population' is a large population that combines both COPD and asthma patients, so comparisons between treatment groups might be less relevant from a clinical standpoint. The adjudicated results are thus presented in this document in the following order: All-treated COPD safety population, All-treated asthma safety population, All-treated safety population (includes asthma and COPD).

The discussions that follow will focus on the acute respiratory-related events, although incidence data for all event types (individually and as composites) and adjudicated causes are presented in the tables. Note that the incidence data is not adjusted for exposure and data for the 300 µg and 600 µg indacaterol treatment groups are from studies of longer duration and

the data from tiotropium and salmeterol are from studies of shorter duration. However, the time to event analyses do adjust for time spent on study.

5.3.1 Incidence of events

5.3.1.1 All-treated COPD safety population

In the All-treated COPD safety population I, there were 23 trials in which a total of 513 of 11,755 patients had at least one composite event, the majority (274/513, 53%) of which were non-respiratory related. A summary of the composite events of interest in this population is given in Table 5-3. Note that the treatment groups Ind 18.75, Ind 37.5, and Ind OTH had an exposure duration of 2 weeks or less.

The composite total of acute respiratory related events was 1.8% for the Ind CON group compared to 2.0% in the placebo group, the indacaterol events being more prevalent in the 300 µg and 600 µg treatment groups, probably due to the longer duration of exposure in the studies that included the 300 µg and 600 µg treatments. These treatments were generally given at durations of 26 weeks to 1 year. There were no asthma-related events recorded. For SABA reversibility, event rates in general were slightly higher for the less reversible patients (FEV_1 reversibility ≤12% or ≤200 mL) when compared with those that are more reversible (>12% and >200 mL).

In the All-treated COPD safety population II, which excluded any studies that were not placebo-controlled, there were no relevant differences compared to the safety profile seen in the COPD safety population I.

Table 5-3 Number and percentage of patients with events of interest – Composite event totals, All-treated COPD safety population I

Type of Event	Ind 18.75µg N=89	Ind 37.5µg N=90	Ind 75µg N=543	Ind 150µg N=2745	Ind 150µg +tio N=1142	Ind 300µg N=1422	Ind 600µg N=584	Ind CON N=6615	Ind OTH N=248	Ind ALL N=6863	For N=556	Tio N=842	Sme N=1010	Pbo N=2484
Composite event														
Total n (%)	1 (1.1)	0	15 (2.8)	100 (3.6)	32 (2.8)	100 (7.0)	46 (7.9)	294 (4.4)	0	294 (4.3)	61 (11.0)	21 (2.5)	26 (2.6)	111 (4.5)
Total respiratory related	0	0	6 (1.1)	43 (1.6)	16 (1.4)	54 (3.8)	15 (2.6)	134 (2.0)	0	134 (2.0)	32 (5.8)	7 (0.8)	14 (1.4)	52 (2.1)
Acute respiratory related	0	0	6 (1.1)	37 (1.3)	15 (1.3)	47 (3.3)	15 (2.6)	120 (1.8)	0	120 (1.7)	31 (5.6)	6 (0.7)	12 (1.2)	50 (2.0)
Asthma related	0	0	0	0	0	0	0	0	0	0	0	0	0	0
COPD related	0	0	5 (0.9)	36 (1.3)	14 (1.2)	41 (2.9)	13 (2.2)	109 (1.6)	0	109 (1.6)	30 (5.4)	5 (0.6)	10 (1.0)	47 (1.9)
Pneumonia related	0	0	3 (0.6)	6 (0.2)	6 (0.5)	11 (0.8)	2 (0.3)	28 (0.4)	0	28 (0.4)	4 (0.7)	4 (0.5)	2 (0.2)	7 (0.3)
Other respiratory related	0	0	0	6 (0.2)	2 (0.2)	7 (0.5)	0	15 (0.2)	0	15 (0.2)	1 (0.2)	1 (0.1)	2 (0.2)	2 (0.1)
Non-respiratory related	1 (1.1)	0	9 (1.7)	59 (2.1)	16 (1.4)	49 (3.4)	32 (5.5)	166 (2.5)	0	166 (2.4)	29 (5.2)	14 (1.7)	12 (1.2)	63 (2.5)

Abbrev: Ind = indacaterol, For=formoterol, Tio=tiotropium, Sme=salmeterol, Pbo=placebo; Ind CON = total patients using the Concept1 device, OTH = total patients using other devices, ALL = total patients using any device
- A subject with multiple occurrences of an event is counted only once in the category for that treatment.
- A subject with multiple events (death, intubation, hospitalization) is counted only once in the summary row.
- Composite total includes all respiratory and non-respiratory events; Total respiratory includes acute and other respiratory events; Acute respiratory includes asthma, COPD or pneumonia

The individual events of interest (death, hospitalization, and intubation) and their adjudicated cause are shown for the All-treated COPD safety population I in Table 5-4. Relatively few intubations and very few deaths were recorded on treatment with indacaterol or placebo. While the incidence of total intubations was slightly higher in the 600 μg treatment group versus placebo, the incidence in the Ind ALL treatment group was similar to that of the placebo group. Most of the events derived from hospitalization, slightly less than half being for respiratory-related reasons. The total incidence of acute respiratory related events in the Ind CON and Ind ALL-treatment groups was slightly lower than the incidence in the placebo treatment group. In the All-treated COPD safety population II the results were similar to those of the All-treated COPD safety population I.

Table 5-4 Number and percentage of patients with events of interest – Death, hospitalization, intubation, All-treated COPD safety population I

Type of Event	Ind 18.75µg N=89	Ind 37.5µg N=90	Ind 75µg N=543	Ind 150µg N=2745	Ind 150µg +Tio N=1142	Ind 300µg N=1422	Ind 600µg N=584	Ind CON* N=6615	Ind OTH N=248	Ind ALL* N=6863	For N=556	Tio N=842	Sme N=1010	Pbo N=2484
Composite n (%)														
Death -Total	0	0	0	1 (0.0)	1 (0.1)	0	0	2 (0.0)	0	2 (0.0)	2 (0.4)	0	0	4 (0.2)
Total respiratory related	0	0	0	0	0	0	0	1 (0.0)	0	1 (0.0)	1 (0.2)	0	0	0
Acute respiratory related	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Asthma related	0	0	0	0	0	0	0	0	0	0	0	0	0	0
COPD related	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Pneumonia related	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Other respiratory related	0	0	0	0	1 (0.1)	0	0	1 (0.0)	0	1 (0.0)	1 (0.2)	0	0	0
Non-respiratory related	0	0	0	1 (0.0)	0	0	0	1 (0.0)	0	1 (0.0)	1 (0.2)	0	0	4 (0.2)
Hospitalization -Total	1 (1.1)	0	15 (2.8)	99 (3.6)	32 (2.8)	100 (7.0)	46 (7.9)	293 (4.4)	0	293 (4.3)	61 (11.0)	21 (2.5)	26 (2.6)	109 (4.4)
Total respiratory related	0	0	6 (1.1)	43 (1.6)	16 (1.4)	53 (3.7)	15 (2.6)	133 (2.0)	0	133 (1.9)	32 (5.8)	7 (0.8)	14 (1.4)	52 (2.1)
Acute respiratory related	0	0	6 (1.1)	37 (1.3)	15 (1.3)	46 (3.2)	15 (2.6)	119 (1.8)	0	119 (1.7)	31 (5.6)	6 (0.7)	12 (1.2)	50 (2.0)
Asthma related	0	0	0	0	0	0	0	0	0	0	0	0	0	0
COPD related	0	0	5 (0.9)	36 (1.3)	14 (1.2)	40 (2.8)	13 (2.2)	108 (1.6)	0	108 (1.6)	29 (5.2)	5 (0.6)	10 (1.0)	47 (1.9)
Pneumonia related	0	0	3 (0.6)	6 (0.2)	6 (0.5)	11 (0.8)	2 (0.3)	28 (0.4)	0	28 (0.4)	4 (0.7)	4 (0.5)	2 (0.2)	7 (0.3)
Other respiratory related	0	0	0	6 (0.2)	1 (0.1)	7 (0.5)	0	14 (0.2)	0	14 (0.2)	1 (0.2)	1 (0.1)	2 (0.2)	2 (0.1)
Non-respiratory related	1 (1.1)	0	9 (1.7)	58 (2.1)	16 (1.4)	49 (3.4)	32 (5.5)	165 (2.5)	0	165 (2.4)	29 (5.2)	14 (1.7)	12 (1.2)	60 (2.4)

Type of Event	Ind 18.75µg N=89	Ind 37.5µg N=90	Ind 75µg N=543	Ind 150µg N=2745	Ind 150µg +Tio N=1142	Ind 300µg N=1422	Ind 600µg N=584	Ind CON* N=6615	Ind OTH N=248	Ind ALL* N=6863	For N=556	Tio N=842	Sme N=1010	Pbo N=2484
Intubation -Total	0	0	1 (0.2)	14 (0.5)	3 (0.3)	16 (1.1)	15 (2.6)	49 (0.7)	0	49 (0.7)	8 (1.4)	0	1 (0.1)	16 (0.6)
Total respiratory related	0	0	0	1 (0.0)	1 (0.1)	2 (0.1)	0	4 (0.1)	0	4 (0.1)	4 (0.7)	0	0	1 (0.0)
Acute respiratory related	0	0	0	1 (0.0)	0	1 (0.1)	0	2 (0.0)	0	2 (0.0)	3 (0.5)	0	0	1 (0.0)
Asthma related	0	0	0	0	0	0	0	0	0	0	0	0	0	0
COPD related	0	0	0	1 (0.0)	0	1 (0.1)	0	2 (0.0)	0	2 (0.0)	3 (0.5)	0	0	1 (0.0)
Pneumonia related	0	0	0	1 (0.0)	0	0	0	1 (0.0)	0	1 (0.0)	1 (0.2)	0	0	0
Other respiratory related	0	0	0	0	1 (0.1)	1 (0.1)	0	2 (0.0)	0	2 (0.0)	1 (0.2)	0	0	0
Non-respiratory related	0	0	1 (0.2)	13 (0.5)	2 (0.2)	15 (1.1)	15 (2.6)	46 (0.7)	0	46 (0.7)	4 (0.7)	0	1 (0.1)	15 (0.6)

Abbrev: Ind = indacaterol, Pbo=placebo; Ind CON = total patients using the Concept1 device, ALL = total patients using any device
- A subject with multiple occurrences of an event is counted only once in the category for that treatment.
- A subject with multiple events (death, intubation, hospitalization) is counted only once in the summary row.
- Composite total includes all respiratory and non-respiratory events; Total respiratory includes acute and other respiratory events; Acute respiratory includes asthma, COPD or pneumonia

5.3.1.2 All-treated asthma safety population

In the All-treated asthma safety population I, there were 7 trials in which a total of 21 of 1,914 patients had at least one composite event, 12 of which were non-respiratory related. A summary of the events of interest in this population is given in Table 5-5. The composite total of acute respiratory events was 0.6% for the Ind CON group, 0.6% for the Sme (Salmeterol) group, compared to none in the placebo group, the indacaterol events being concentrated in the 300 µg and 600 µg treatment groups. This disparity is due to the inclusion in this population of Study B2338, a large study of much longer duration (26 weeks) than the other asthma studies (max 28 days), which did not have a placebo arm, and included only indacaterol dose groups of 300 µg and 600 µg. Study B2338 used ICS doses that were not co-randomized, and not aligned with severity of asthma.

The All-treated asthma safety population II, excluded any studies that were not placebo-controlled, so it excluded the important Study B2338, and only included studies of short duration, i.e. two weeks or less. Therefore, little meaningful interpretation can be put on this population for asthma.

One patient in the indacaterol 300 µg group who died was adjudicated as having a COPD related event resulting in hospitalization, intubation, and death. This death occurred off treatment, and, as per the FDA request, was not included in this population analysis. Another patient in the indacaterol 300 µg group died from an event adjudicated to be asthma related. These cases are further discussed in Section 6.1.

Table 5-5 Number and percentage of patients with events of interest – All-treated asthma safety population I

Type of Event	Ind 18.75µg N=84	Ind 37.5µg N=81	Ind 37.5 b.i.d. µg N=48	Ind 75µg N=131	Ind 150µg N=85	Ind 150µg q.o.d. N=48	Ind 300µg N=268	Ind 400µg N=7	Ind 600µg N=268	Ind CON N=1020	Ind OTH N=287	Ind ALL N=1307	Sme N=353	Pbo N=254
Composite event														
Total n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	4 (1.5)	0 (0.0)	7 (2.6)	12 (1.2)	3 (1.0)	15 (1.1)	6 (1.7)	0
Total respiratory related	0	0	0	0	0	0	3 (1.1)	0	3 (1.1)	6 (0.6)	1 (0.3)	7 (0.5)	2 (0.6)	0
Acute respiratory related	0	0	0	0	0	0	3 (1.1)	0	3 (1.1)	6 (0.6)	1 (0.3)	7 (0.5)	2 (0.6)	0
Asthma related	0	0	0	0	0	0	2 (0.7)	0	2 (0.7)	4 (0.4)	1 (0.3)	5 (0.4)	1 (0.3)	0
COPD related	0	0	0	0	0	0	1 (0.4)	0	0	1 (0.1)	0	1 (0.1)	0	0
Pneumonia related	0	0	0	0	0	0	0	0	1 (0.4)	1 (0.1)	0	1 (0.1)	1 (0.3)	0
Other respiratory related	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Non-respiratory related	0	0	0	0	1 (1.2)	0	1 (0.4)	0	4 (1.5)	6 (0.6)	2 (0.7)	8 (0.6)	4 (1.1)	0
Death -Total	0	0	0	0	0	0	1 (0.4)	0	0	1 (0.1)	0	1 (0.1)	0	0
Total respiratory related	0	0	0	0	0	0	1 (0.4)	0	0	1 (0.1)	0	1 (0.1)	0	0
Acute respiratory related	0	0	0	0	0	0	1 (0.4)	0	0	1 (0.1)	0	1 (0.1)	0	0
Asthma related	0	0	0	0	0	0	1 (0.4)	0	0	1 (0.1)	0	1 (0.1)	0	0
COPD related	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Pneumonia related	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Other respiratory related	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Non-respiratory related	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hospitalization -Total	0	0	0	0	1 (1.2)	0	4 (1.5)	0	7 (2.6)	12 (1.2)	3 (1.0)	15 (1.1)	6 (1.7)	0
Total respiratory related	0	0	0	0	0	0	3 (1.1)	0	3 (1.1)	6 (0.6)	1 (0.3)	7 (0.5)	2 (0.6)	0
Acute respiratory related	0	0	0	0	0	0	3 (1.1)	0	3 (1.1)	6 (0.6)	1 (0.3)	7 (0.5)	2 (0.6)	0
Asthma related	0	0	0	0	0	0	2 (0.7)	0	2 (0.7)	4 (0.4)	1 (0.3)	5 (0.4)	1 (0.3)	0
COPD related	0	0	0	0	0	0	1 (0.4)	0	0	1 (0.1)	0	1 (0.1)	0	0
Pneumonia related	0	0	0	0	0	0	0	0	1 (0.4)	1 (0.1)	0	1 (0.1)	1 (0.3)	0
Other respiratory related	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Non-respiratory related	0	0	0	0	1 (1.2)	0	1 (0.4)	0	4 (1.5)	6 (0.6)	2 (0.7)	8 (0.6)	4 (1.1)	0

Type of Event	Ind 18.75µg N=84	Ind 37.5µg N=81	Ind 37.5 b.i.d. µg N=48	Ind 75µg N=131	Ind 150µg N=85	Ind 150µg q.o.d. N=48	Ind 300µg N=268	Ind 400µg N=7	Ind 600µg N=268	Ind CON N=1020	Ind OTH N=287	Ind ALL N=1307	Sme N=353	Pbo N=254
Intubation -Total	0	0	0	0	0	0	2 (0.7)	0	3 (1.1)	5 (0.5)	0	5 (0.4)	1 (0.3)	0
Total respiratory related	0	0	0	0	0	0	1 (0.4)	0	0	1 (0.1)	0	1 (0.1)	0	0
Acute respiratory related	0	0	0	0	0	0	1 (0.4)	0	0	1 (0.1)	0	1 (0.1)	0	0
Asthma related	0	0	0	0	0	0	0	0	0	0	0	0	0	0
COPD related	0	0	0	0	0	0	1 (0.4)	0	0	1 (0.1)	0	1 (0.1)	0	0
Pneumonia related	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Other respiratory related	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Non-respiratory related	0	0	0	0	0	0	1 (0.4)	0	3 (1.1)	4 (0.4)	0	4 (0.3)	1 (0.3)	0

Abbrev: Ind = indacaterol, Sme=salmeterol, Pbo=placebo; Indacaterol totals- CON = total patients using the Concept1 device, OTH = total patients using other devices, ALL = total patients in studies using any device
- A subject with multiple occurrences of an event e.g. intubation is counted only once in the category.
- A subject with multiple events (death, intubation, hospitalization) is counted only once in the summary row.
- Total includes all respiratory and non-respiratory events. Total respiratory includes acute and other respiratory events. Acute respiratory includes asthma, COPD or pneumonia.

5.3.1.3 All-treated safety population

Thirty trials were included in the All-treated safety population I. At least one respiratory related composite event was observed in 248 of 13,669 (1.8%) patients. The results for the composite respiratory and acute respiratory endpoints for the combined indacaterol doses, active controls and placebo are given in Table 5-6. The numbers of both respiratory- and acute respiratory-related events were balanced between the Ind CON and placebo groups. Similar event rates were seen in the All-treated safety population II which excluded any studies that were not placebo-controlled.

Overall, the All-treated safety population I and II summaries of composite events do not show any findings of interest over and above those noted for the All-treated COPD and All-treated asthma safety populations and therefore in Tables 5-6 and 5-7, only the All-treated safety population I is shown. In these tables, only indacaterol (Ind CON and Ind ALL), the active controls and placebo are provided.

Table 5-6 Number (%) of patients with composite endpoints – All-treated safety population I

Type of event	Ind CON N=7635	Ind ALL N=8170	For N=556	Tio N=842	Sme N=1363	Pbo N=2738
Composite	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total	306 (4.0)	309 (3.8)	61(11.0)	21 (2.5)	32 (2.3)	111 (4.1)
Total respiratory related	140 (1.8)	141 (1.7)	32 (5.8)	7 (0.8)	16 (1.2)	52 (1.9)
Acute respiratory related	126 (1.7)	127 (1.6)	31 (5.6)	6 (0.7)	14 (1.0)	50 (1.8)
Other respiratory related	15 (0.2)	15 (0.2)	1 (0.2)	1 (0.1)	2 (0.1)	2 (0.1)
Non-respiratory related	172 (2.3)	174 (2.1)	29 (5.2)	14 (1.7)	16 (1.2)	63 (2.3)

- Total has any cause. Acute respiratory is any event adjudicated as asthma, COPD, pneumonia related. Other respiratory is any event that is respiratory in nature but not asthma, COPD or pneumonia related.
- Non-respiratory includes all other causes. - A subject with multiple occurrences of an event is counted only once in the category for that treatment.
- A subject with multiple events (death, intubation, hospitalization) is counted only once in composite total row.

Event rates in the All-treated safety population I for death, hospitalization and intubation are summarized in Table 5-7. Event rates in the Ind CON group were similar to those seen with placebo.

Table 5-7 Number (%) of patients with endpoints death, hospitalization and intubation – All-treated safety population I

	Ind CON N=7635	Ind ALL N=8170	For N=556	Tio N=842	Sme N=1363	Pbo N=2738
Type of event	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Death -Total	3 (0.0)	3 (0.0)	2 (0.4)	0	0	4 (0.1)
Total respiratory related	2 (0.0)	2 (0.0)	1 (0.2)	0	0	0
Acute respiratory related	1 (0.0)	1 (0.0)	0	0	0	0
Non-respiratory related	1 (0.0)	1 (0.0)	1 (0.2)	0	0	4 (0.1)
Hospitalization –Total	305 (4.0)	308 (3.8)	61(11.0)	21 (2.5)	32 (2.3)	109 (4.0)
Total respiratory related	139 (1.8)	140 (1.7)	32 (5.8)	7 (0.8)	16 (1.2)	52 (1.9)
Acute respiratory related	125 (1.6)	126 (1.5)	31 (5.6)	6 (0.7)	14 (1.0)	50 (1.8)
Non-respiratory related	171 (2.2)	173 (2.1)	29 (5.2)	14 (1.7)	16 (1.2)	60 (2.2)
Intubation -Total	54 (0.7)	54 (0.7)	8 (1.4)	0	2 (0.1)	16 (0.6)
Total respiratory related	5 (0.1)	5 (0.1)	4 (0.7)	0	0	1 (0.0)
Acute respiratory related	3 (0.0)	3 (0.0)	3 (0.5)	0	0	1 (0.0)
Non-respiratory related	50 (0.7)	50 (0.6)	4 (0.7)	0	2 (0.1)	15 (0.5)

- Total has any cause. Acute respiratory is any event adjudicated as asthma, COPD, pneumonia related. Other respiratory is any event that is respiratory in nature but not asthma, COPD or pneumonia related.
- Non-respiratory includes all other causes.- A subject with multiple occurrences of an event is counted only once in the category for that treatment.
- A subject with multiple events (death, intubation, hospitalization) is counted only once in composite total row.

5.3.2 Time to event analyses

Time to event analyses were performed as described in Section 4.3.2.2. A summary of the risk (based on the hazard ratio) of an acute respiratory composite event for the All-treated safety, All-treated COPD safety, and All-treated asthma safety population I is presented in Table 5-8.

Table 5-8 Hazard ratio (95% confidence interval) for the acute respiratory composite endpoint – All-treated safety population I, All-treated COPD safety population I, All-treated asthma safety population I

	Ind CON vs Pbo	For vs Pbo	Tio vs Pbo	Sme vs Pbo
Population	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
All-treated safety population I	0.93 (0.69-1.23)	1.30 (0.80-2.13)	0.62 (0.19-2.01)	0.83 (0.40-1.74)
All-treated COPD safety population I	0.93 (0.69-1.24)	1.28 (0.78-2.09)	0.64 (0.20-2.07)	0.94 (0.41-2.12)
All-treated asthma safety population I	n.e.	n.e.	n.e.	n.e.

- The hazard ratio/95% CI of treatment comparison (A vs B) is computed from a Cox proportional hazards regression model stratified by study. A hazard ratio <1 implies that an A-treated patient has a lower risk of having an event than a B-treated patient. The Ind Con hazard ratio is based on a weighted (by size) average of the individual doses given via Concept1
- acute events are those related to asthma, COPD or pneumonia
- n.e.=not estimable

5.3.2.1 All-treated COPD safety populations

For the All-treated COPD safety population I, the overall hazard ratio for Ind CON versus placebo for the any acute respiratory composite event was 0.93 (95% CI 0.69-1.24). It should be noted that hazard ratios could not be estimated for all treatment comparisons for all event categories. Notably, it was not possible to estimate hazard ratios for any indacaterol group versus placebo for any category of death or intubation. There were no asthma-related composite events in this population. When only patients from placebo-controlled studies (All-treated COPD safety population II) were considered, similar results were obtained.

Hazard ratios for all individual events as well as the composite event were not statistically significant versus placebo with one exception in one of the subgroups. When the 75 µg treatment group was compared to placebo, for the endpoint of time to first pneumonia related composite event by SABA reversibility ≤12% or ≤200 mL, for the All-treated COPD safety population I, the hazard ratio of 8.77 is statistically significant (95% CI 1.22, 62.86). The same is true for the endpoint of time to first pneumonia related hospitalization for the ≤12% or ≤200 ml treatment group. This observation was not seen for other indacaterol doses; when evaluating these endpoints for the entire COPD safety population I, the comparisons of the 75 µg treatment group to placebo are not statistically significant and the hazard ratios are <1. All of these patients had risk factors for developing pneumonia.

In the more reversible subgroup with SABA reversibility >12% and >200 ml, no difference was seen between treatments in the All-treated COPD safety populations I or II.

5.3.2.2 All-treated asthma safety populations

Hazard ratios for indacaterol versus placebo for any event category, could not be calculated due to zero incidence on placebo. There were a small number (7) of respiratory-related composite events in the All-indacaterol treatment group (n=1307) versus 2 on salmeterol (n=353). The difference between indacaterol inhaled via the Concept1 and salmeterol was not

statistically significant (HR=1.26, 95% CI 0.55-2.91, All-treated asthma safety population 1). When time to event analysis was conducted for the asthma safety population including only placebo-controlled studies, there was only a single respiratory-related composite event, in one of 771 patients treated with indacaterol, and hazard ratios could not be estimated for any treatment group comparison or category of events.

5.3.2.3 All-treated safety populations

Time to event analysis showed no statistically significant hazard ratios for any indacaterol group versus placebo for any category of event. In the All-treated safety population 1, the difference between indacaterol inhaled via the Concept1 and placebo was not statistically significant (HR= 0.93, 95% CI 0.69-1.23, All-treated safety population 1). It should be noted that hazard ratios could not be estimated for many indacaterol-placebo comparisons for a number of event categories, including deaths and intubations.

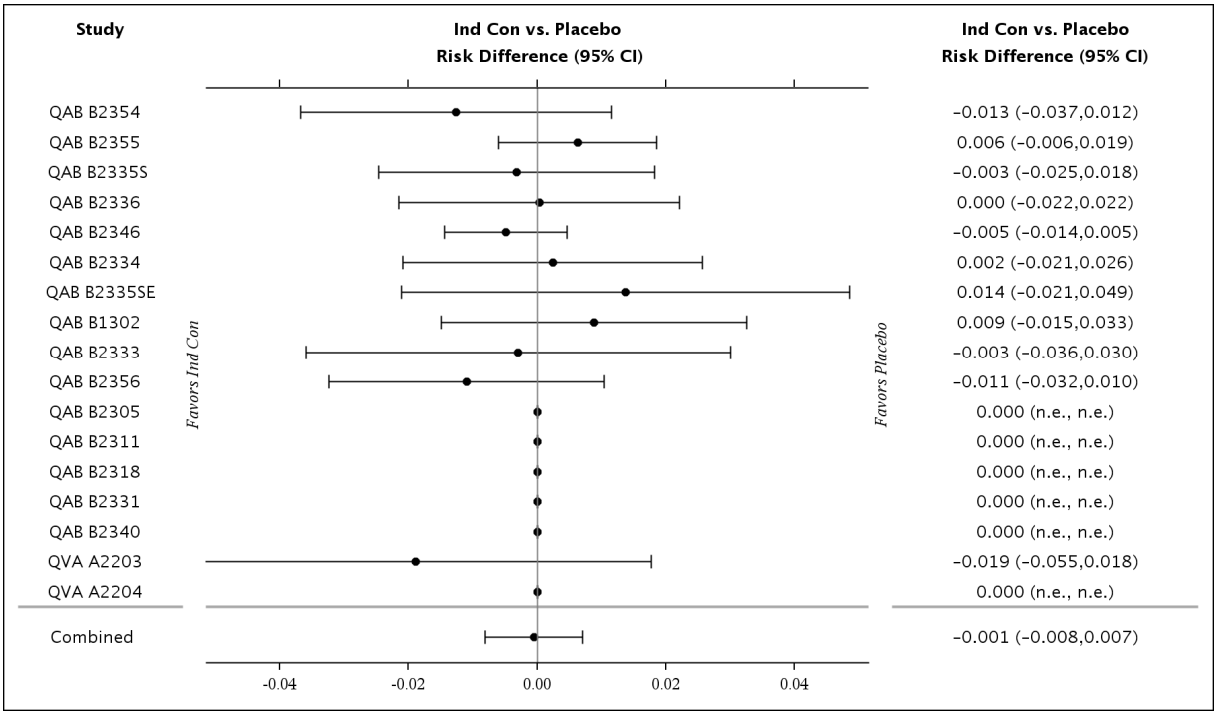
Similar results were obtained when the population was restricted to patients from placebo-controlled studies. As in the All-treated safety population 1, hazard ratios could not be estimated for many indacaterol-placebo comparisons for a number of event categories, including deaths and intubations, when the analysis was restricted to placebo-controlled studies.

5.4 Meta-analysis

The Mantel-Haenszel risk difference and associated confidence interval was used as a sensitivity analysis for the placebo-controlled studies. These analyses were planned for the All-treated asthma and COPD safety populations. However, due to the small number of events in the placebo controlled asthma studies, the asthma results are not informative.

The estimated risk differences and 95% confidence intervals (CI) for the acute respiratory related composite endpoint for the combined indacaterol doses given via Concept1 in the All-treated COPD safety population II is displayed by study and overall in the forest plot in Figure 5-1. A positive risk difference implies that the indacaterol group was associated with a higher rate of the endpoint than the placebo group. The figure shows that there is variability in the reporting of the composite endpoints of interest across studies as would be expected. All confidence intervals for the individual studies contained the value of 0, implying that there were no studies where the analysis suggested indacaterol resulted in a statistically significant increased risk for the acute respiratory composite. The combined Ind CON group shows a very small reduction of risk in the indacaterol group vs placebo. The risk difference estimate for indacaterol overall (Ind CON vs placebo) was -0.001 (95% CI: -0.008 – 0.007). The results of this analysis support those of the primary analysis.

Figure 5-1 Forest plot of acute respiratory related composite endpoint by study and overall (All-treated COPD safety population II)



Risk difference and 95% confidence interval based on the Mantel-Haenszel method

6 Discussion and conclusions

6.1 Discussion

This analysis summarizes the findings of an independent external unbiased review of serious adverse events (SAEs) that occurred during the development of indacaterol, using blinded narratives, to investigate the safety of indacaterol, in asthma and COPD patients. Analyses were performed and evaluated on the adjudicated outcomes using a composite endpoint of serious asthma and COPD related outcomes, namely death, intubation, and hospitalization. Pneumonia related outcomes were also assessed. This methodology was previously used by the FDA in a meta-analysis to review the safety of LABA use in asthma. It is used here, at the request of the FDA, to review the safety of indacaterol in a large population containing both COPD and asthma patients.

The clinical database used for the review was extensive, including indacaterol studies in both COPD and asthma at a wide range of doses from 18.75 µg up to 600 µg daily, and included 13,669 patients exposed to study drug across 30 studies. The majority of these patients were treated for COPD (23 studies), with the remainder treated for asthma (7 studies), in study durations ranging from 7 days up to 1 year. It should be noted that a few deaths in either the indacaterol or control treatment groups in the COPD population which are in the Novartis indacaterol safety database were not included in this adjudication database as per the criteria for study inclusion requested by the FDA. These occurred in studies where the treatment was either open label or off treatment. There was also one death which was not included in the

asthma safety population (see description further in this section). Overall, the findings from these studies do not demonstrate a statistically significant risk for indacaterol versus placebo for hospitalization, intubation, or death in either asthmatic or COPD patients. In addition, there was no statistically significant risk associated with indacaterol versus placebo for pneumonia-related events.

For the COPD safety populations, time to event analyses demonstrated no significant difference in risk between indacaterol and placebo for the composite endpoint of hospitalization, intubation, and death or for the individual events. There was no increased risk versus placebo for pneumonia-related events.

Subgroup analyses did not indicate that COPD patients exposed to indacaterol with documented reversibility (>12% and >200 mL) had a greater risk of events, as measured by the composite endpoint when compared to placebo. In the SABA reversibility ≤12% or ≤200 mL subgroup, for the endpoint of time to first pneumonia-related composite event, in the COPD safety populations, when comparing the 75 µg treatment group to placebo, the hazard ratio was statistically significant. The same was true for the endpoint of time to first pneumonia related hospitalization for the ≤12% or ≤200 mL treatment group. However, when looking at these endpoints for the entire COPD safety population I, the comparisons of the 75 µg treatment group to placebo were not statistically significant. In addition, this was not seen with increasing doses or duration of indacaterol so it is unlikely this would represent a drug-related effect. None of the cases of pneumonia were considered to be drug related and all patients had risk factors for pneumonia.

With regards to study duration, although there were more patients and events in studies of >7 days and ≥12 weeks when compared to studies of shorter duration, there was no increased risk within each of these subpopulations when comparing indacaterol and placebo.

For the COPD safety populations, hospitalizations contributed the largest number of events, compared to intubation and death, for the composite endpoint. There was no significant difference in risk between indacaterol and placebo for these events.

In the asthma safety populations, time to event analysis showed very few findings, and there were no significant difference in risk ratios. For both active and placebo controlled studies, a time to event analysis for the acute respiratory-related composite endpoint showed a difference in hazard ratios between the indacaterol combined treatment group (in the to-be-marketed device) and the salmeterol treatment group which was not statistically significant (HR=1.26, 95% CI 0.55-2.91).

Most events in the asthma population occurred among patients participating in Study B2338. In this study, patients were requested to continue their background treatment with inhaled corticosteroids, but ICS treatment was not co-randomized nor was it supplied by the study sites, and compliance with ICS was not monitored throughout the study. Two fatal events occurred in Study B2338. One 60 year old man died following an asthma exacerbation that was not treated with systemic corticosteroids. Both adjudicators felt the cause of death was asthma-related. The death of a 75 year old woman was judged by one adjudicator to have been secondary to a myocardial infarction and by the other adjudicator as being secondary to withdrawal of ventilator support. The final adjudication for this case noted that the likely cause of death was COPD (not asthma) and another respiratory event (not asthma or COPD).

This death occurred off treatment, and, as per the FDA request, was not included in the asthma safety population analysis.

The interpretation of the data in this report is limited by a number of factors. Firstly, the trials included in the study were generally not designed to address the specific research objectives requested by FDA. In particular, the trials were not designed to specifically evaluate the endpoints considered in this analysis. Post-hoc identification and adjudication of events were based on existing serious adverse event reports. In addition, only higher doses of indacaterol were evaluated in the longer term studies, i.e. time at risk for an event is confounded by dose, likely explaining the appearance of a dose response relationship with increasing dose. Importantly, the time-to-event analyses that consider time at risk, as well as event rate, do not support an association between indacaterol and the events of interest.

In summary, when considering all populations evaluated in this report, e.g. the COPD safety populations, the asthma safety populations, or both populations combined (total safety populations), the analyses demonstrate that the risk of serious adverse events, namely the composite endpoint of hospitalizations, intubations, and death whether related to asthma, COPD or pneumonia, in patients treated with indacaterol was similar to that of patients treated with placebo. This was also true for the individual events of hospitalizations, intubations, and death.

6.2 Conclusions

The purpose of this document is to analyze whether there is an increased risk of serious adverse events, specifically hospitalization, intubation, or death, associated with exposure to indacaterol in patients with COPD or asthma and to additionally analyze whether there exists an increased risk for pneumonia related events in these patients treated with indacaterol. The conclusions result from a systematic review of blinded information on serious adverse events from the Novartis safety database by an external independent panel of adjudicators, according to specified criteria for study inclusion requested by the FDA.

Based on this review, the following conclusions can be drawn:

- For the endpoint of interest, acute respiratory composite endpoint, there was no significant difference between any indacaterol groups and placebo or the active controls in the All-treated safety population (COPD and asthma combined)
- For the COPD safety population, acute respiratory composite endpoint, there was no significant difference between any indacaterol groups and placebo or the active controls, with no difference between patients who showed baseline reversibility greater than 12% and 200 mL, compared to those with reversibility <12% or <200 mL
- For the Asthma safety populations, acute respiratory composite endpoint, there was no significant difference between any indacaterol groups and placebo or the active controls, although the number of events in the asthma population was small.

This data, along with the overall safety assessments submitted as part of the NDA application, support the overall positive safety profile of indacaterol across all doses studied.

7 List of references

Pellegrino R, Viegi G, Brusasco RO, et al. Interpretative strategies for lung function tests. *Eur Respir J* 2005; 26:948-68.