CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022383Orig1s000

MEDICAL REVIEW(S)

Addendum #2, June 8, 2011
Indacaterol maleate, NDA 22-383

Cardiovascular safety data presented in the addendum dated April 4, 2011 were subsequently reviewed in two team meetings on June 1 and June 8, 2011 between the clinical and the biostatistical review teams. The sponsor's data of both cardiovascular serious adverse events and adverse events were organized using the MedDRA 13.0 hierarchical terms, high level group term (HLGT) and high level term (HLT). As well, the standard MedDRA queries (SMQ) of 'ischemic heart disease' and 'other ischemic heart disease' provided by the sponsor were also reviewed by the team. The outcome of the meetings is that the data presented do not demonstrate a clear safety signal for the indacaterol 150 mcg once daily dose. This was primarily arrived upon due to: the likelihood of the data representing noise or statistical artifact resulting from the pooling of safety data across multiple trials; serious adverse events with small numbers heavily influencing the rates of higher level terms; lack of credibility in the data due to a lack of consistency in the dose response effect for the 600 mcg dose data and where applicable, overlapping and wide confidence intervals.
The addition of this addendum to the clinical review of the data presented in NDA 22-383 continues to result in a recommendation of approval for indacaterol 75 mcg once daily dose in the maintenance treatment of COPD. An efficacy advantage of the higher 150 mcg dose in more severe patients with COPD was not demonstrated and my regulatory recommendation is a complete response for the 150 mcg once daily dose. Based on the evaluation of these additional data included in the addendum by the clinical and biostatistics review teams, I no longer recommend a post marketing commitment to evaluate the cardiovascular disorder adverse events in patients with ≥ 1 risk factors.

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/s/

ANYA C HARRY
06/08/2011

THERESA M MICHELE
06/08/2011
Review noted. See CDTL addendum for additional review of CV events.

4/4/11

6.3.4 Submission Specific Primary Safety Concerns- Addendum

6.3.4.1 Cardiovascular and cerebrovascular events

As described in the primary review, the safety evaluation during the first cycle highlighted a higher frequency of combined CCV events. During the clinical review of the second cycle trends of possible higher rates of CCV for certain indacaterol treatment groups were recognized but due to a lack of consistency across treatment groups and across safety datasets, interpretation was difficult. At this time, a secondary review was initiated in this addendum due to ongoing concern over the current data. No new data was reviewed for this addendum.

Review Cycle One [S0000, December 17, 2008]:

The percentage of patients with ≥1 CCV SAE for the COPD 3-, 6- and 12-month safety populations is presented in Table 1 below. For the COPD 3-month safety group the highest rates of patients with ≥ 1 CCV SAE were seen in the tiotropium group, 1.45% followed by indacaterol 150 and 300 mcg treatment groups at 0.96 and 0.94, respectively. The rate of CCV SAEs for placebo was 0.66. In the COPD 6-month safety group the highest rates were seen in the indacaterol 150 mcg and tiotropium treatment groups, both at 2.2% versus placebo at 1.1%. In the COPD 12-month safety dataset, the rates were highest in the 300 mcg indacaterol group, 3.4% versus placebo, 0.9%. Overall, the SAE rates for the three safety databases were primarily influenced by the following preferred terms: acute myocardial infarction, angina pectoris, atrial fibrillation, CAD and myocardial infarction.

Table 1 Cardiovascular and cerebrovascular SAEs (% of patients) by preferred term in the COPD 3-, 6- and 12- month safety population

	Indacaterol treatment groups (%)			Control treatment groups (%)		
	150 mcg	300 mcg	600 mcg	For	Tio	Pbo
COPD 3-month	N=627	N=853	N=547	N=556	N=415	N=1055
Pts with ≥1 CCV SAE	0.96	0.94	0.55	0.18	1.45	0.66
Acute myocardial infarction	0.16	0.12	0	0	0	0
Angina pectoris	0.16	0.12	0	0	0	0.19
Atrial fibrillation	0.16	0	0	0	0.48	0.09
CAD	0.16	0.12	0.18	0	0	0
Myocardial infarction	0.16	0.12	0.18	0	0	0.28
COPD 6-month	N=416	N=853	N=547	N=556	N=415	N=850
Pts with ≥1 CCV SAE	2.2	1.4	1.3	0.5	2.2	1.1
Atrial fibrillation	0.7	0	0	0	0.72	0.24
Angina pectoris	0.5	0.1	0.2	0	0	0.2
Acute myocardial infarction	0.24	0.12	0	0	0	0
CAD	0.24	0.23	0.37	0	0	0.12
Myocardial infarction	0.24	0.12	0.18	0.18	0	0.24
COPD 12- month	---	N=437	N=425	N=434	---	N=432
Pts with ≥1 CCV SAE	---	3.4	2.6	1.4	---	0.9
Atrial fibrillation	---	0.7	0	0.2	---	0.2
Cardiac failure congestive	---	0.5	0	0	---	0.2
Myocardial ischemia	---	0.5	0	0	---	0
Acute myocardial	---	0.2	0	0	---	0

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infarction						
Angina pectoris	---	0.2	0.2	0	---	0.2

Source: Adapted from Tables 2-82, 2-84 and 2-86 CTD 2.7.4 Summary of Clinical Safety

The percentage of patients with ≥1 CCV AE for the COPD 3-, 6-, and 12- month safety populations is presented in Table 2 below. For the COPD 3- month safety population the highest rates were observed in the Tiotropium and indacaterol 300 mcg treatment groups, 4.3% and 3.5%, respectively versus 2.5% in the placebo group. In the COPD 6-month safety group the highest rates were seen in the indacaterol 150 mcg and Tio treatment groups, both at 5.8% versus placebo at 3.7%. In the COPD 12-month safety population the rates were comparable across the active treatment groups ranging from 6.1 to 6.6 but higher than the rate for placebo at 3.9%. The preferred terms that appeared to influence these higher rates across the different safety populations included: ventricular tachycardia, ECG QT prolongation, angina pectoris and atrial fibrillation. In the 12 month safety group, the lowest proposed dose during that submission of 150 mcg was not evaluated for this time duration. These AE rates were not adjusted for exposure.

Table 2 Cardiovascular and cerebrovascular AEs (% of patients) by preferred term in the COPD 3, 6 and 12- month safety population

	Indacaterol treatment groups (%)			**Control treatment groups (%)**		
	150 mcg	300 mcg	600 mcg	For	Tio	Pbo
COPD 3-month	N=627	N=853	N=547	N=556	415	N=1055
Pts with ≥1 CCV AE	3	3.5	2	2	4.3	2.5
Ventricular tachycardia	0.8	0	0	0	0.48	0
ECG QT prolonged	0.48	0.47	0.91	0.54	0.48	0.85
Angina Pectoris	0.32	0.59	0	0.18	0.24	0.28
Atrial fibrillation	0.32	0.59	0.37	0	0.72	0.28
COPD 6-month	N=416	N=853	N=547	N=556	415	N=850
Pts with ≥1 CCV AE	5.8	5	3.3	4	5.8	3.7
ECG QT prolonged	1.4	0.6	0.9	0.5	0.96	1.1
Atrial fibrillation	1.2	0.6	0.4	0	1.45	0.6
Ventricular tachycardia	1.2	0	0	0	0.48	0.1
COPD 12-month	---	N=437	N=425	N=434	---	N=850
Pts with ≥1 CCV AE	---	6.6	6.1	6.5	---	3.9
Atrial fibrillation	---	1.4	0.5	0.5	---	0.7
Myocardial ischemia	---	0.9	0	0.2	---	0
Angina pectoris	---	0.7	0.5	0.2	---	0.2

Source: Adapted from Tables 2-81, 2-83 and 2-85 CTD 2.7.4 Summary of Clinical Safety

Review Cycle Two [S0027, September 28, 2010]:

Table 3 below shows the relationship between the percentage of patients with CCV AEs and the presence (yes) or absence (no) of cardiovascular risk factors at baseline. For the COPD 3-month safety population, the percentage of patients without cardiovascular risk factors who experienced a CCV AE was consistent across the active and placebo treatment groups with a range of 1.72% to 2.7% across the indacaterol doses and 2.15% for placebo. For those with baseline cardiovascular risk factors in the COPD 3-month safety population, the percentage of CCV AE ranged between 2.63% in the highest indacaterol dose of 600 mcg and 5.13% in the 300 mcg indacaterol treatment groups, with placebo at 4.45%. There was not a clear dose response relationship. In the COPD 6-month safety and the COPD 12-month safety populations, there were higher rates of CCV AEs observed in those with baseline cardiovascular risk factors across all active treatment groups as well as placebo. In the COPD 12-month safety population, the largest

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percentage of CCV AEs in those without cardiovascular risk factors was seen in the 150 mcg indacaterol treatment group, 8% and the placebo group at 4%. In those patients with baseline cardiovascular risk factors, again, the 150 mcg indacaterol group had the largest percentage of CCV AE at 21% followed by indacaterol 300 mcg at 14% and placebo at 11%. A consistent dose response relationship with the CCV AEs across the indacaterol treatment groups was not apparent. As well, greater percentages of CCV AEs emerged over the longer duration of time as seen across the different safety populations.

Table 3 Percentage of patients with CCV AEs by baseline cardiovascular risk factors

		Indacaterol treatment groups (%)				Control treatment groups (%)			
AE: CCV condition		75 mcg	150 mcg	300 mcg	600 mcg	For	Tio	Sal	Pbo
3 month safety		N=449	N=2611	N=1157	N=547	N=556	N=1214	N=895	N=2012
	No	1.72	1.87	2.70	1.85	1.36	1.95	1.96	2.15
	Yes	2.97	4.62	5.13	2.63	4.39	3.31	3.87	4.45
6 month safety		N=127	N=933	N=1041	N=547	N=556	N=415	N=333	N=1371
	No	4.72	4.39	3.82	3.23	2.71	5.26	3.76	3.18
	Yes	4.76	11.32	9.66	3.51	8.77	7.61	8.96	8.37
12 month safety		---	N=144	N=583	N=425	N=434	---	---	N=556
	No	---	8.00	7.35	5.42	4.62	---	---	4.03
	Yes	---	21.05	14.02	8.6	13.64	---	---	11.01

Source: Adapted from Appendix 1 Tables 4.3-13, H-4.3-13 and L-4.3-13 Summary of Clinical Safety

Novartis examined the relationship between the occurrence of AEs specific to cardiac disorders and baseline cardiovascular risk factors at baseline. The number of cardiac disorder AEs adjusted based on exposure (per 1000 pt-yr) was evaluated based on the number of cardiovascular risk factors present at baseline in the COPD Safety population and is presented in Table 4 below. Again, no consistent dose response relationship was apparent across the doses of indacaterol studied. The number of cardiac disorder AEs increases with the number of baseline cardiovascular risk factors from 0 to ≥3. In those patients without baseline cardiovascular risk factors, no events occurred in the indacaterol 75 mcg group and a limited number of events occurred in the indacaterol 150 mcg and 300 mcg treatment groups, 15/1000 pt-yr for the two and 71 cardiac disorder AE/1000 pt-yr for placebo. In those patients with ≥3 baseline cardiovascular risk factors, the greatest number of cardiac disorder AEs occurred in the 75 mcg treatment group (183/1000 pt-yr) with the fewest number of patients. The lowest number of cardiac disorder AEs were seen in the indacaterol 600 mcg treatment group (46/1000 pt-yr) which had the same number of patients as the 75 mcg group, 217. The number of cardiac disorder AE in the placebo group for those with ≥3 cardiovascular risk factors was lower at 115/1000 pt-yr.

Table 4 Number of Cardiac Disorder AEs adjusted for exposure per 1000 py (n/1000 py) based on number of cardiovascular (CV) risk factors in the COPD safety population

	Indacaterol treatment groups (n/1000 py)				Control treatment groups (n/1000 py)			
AE: Cardiac Disorders COPD Safety	75 mcg	150 mcg	300 mcg	600 mcg	For	Tio	Sal	Pbo
Total Population 0 CV risk factor	N=15 0	N=185 15	N=104 15	N=37 0	N=44 62	N=81 39	N=60 55	N=145 71
Total Population 1 CV risk factor	N=78 53	N=605 74	N=317 74	N=140 74	N=129 21	N=262 37	N=241 40	N=536 44

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Total Population 2 CV risk factor	N=139 60	N=737 113	N=329 96	N=153 98	N=158 51	N=357 111	N=226 57	N=531 52
Total Population ≥3 CV risk factor	N=217 183	N=1084 118	N=407 157	N=217 46	N=225 145	N=514 118	N=368 142	N=800 115

Source: Adapted from Appendix 1 Tables 4.3-13, H-4.3-13 and L-4.3-13 Summary of Clinical Safety

Examination of the percent of patients with ≥1 CCV SAE for the COPD 3-, 6- and 12- month safety populations is presented in Table 5 below. For the COPD 3-month safety population the rates were comparable across the indacaterol treatment groups as well as placebo ranging from 0.5% to 0.9%. In the COPD 6-month safety population the highest rates were seen in the indacaterol 75 mcg, 150 mcg and tiotropium treatment groups, at 2.4%, 1.7% and 2.2% respectively. The rate of CCV SAE in the placebo group was 1.2%. In the COPD 12-month safety population, the rates were highest in the 300 mcg and 600 mcg indacaterol groups, 3.1% and 2.6%, respectively versus placebo, 1.4%. Overall, the SAE rates for the three safety databases were primarily influenced by the following preferred terms: angina pectoris, atrial fibrillation, CAD and acute myocardial infarction.

Table 5 Cardiovascular and cerebrovascular SAEs by preferred term in COPD 3-, 6- and 12- month safety population

	Indacaterol treatment groups (%)				**Control treatment groups (%)**			
COPD 3-month safety	75 N=449 n (%)	150 N=2611 n (%)	300 N=1157 n (%)	600 N=547 n (%)	For N=556 n (%)	Tio N=1214 n (%)	Sal N=895 n (%)	Pbo N=2012 n (%)
Patients with ≥ 1 CCV SAE	0.5	0.9	0.7	0.6	0.2	0.9	0.7	0.7
Angina pectoris	0	0.2	0.1	0	0	0	0	0.1
Acute myocardial infarction	0	0.1	0.1	0	0	0	0.1	0
CAD	0	0.1	0.1	0.2	0	0.1	0.1	0
Myocardial infarction	0	0.1	0.1	0.2	0	0	0.1	0.2
Atrial fibrillation	0	0.1	0	0	0	0.3	0.1	0.1
CVA	0.2	0.1	0	0	0	0.2	0	0
COPD 6-month safety	75 N=127	150 N=933	300 N=1041	600 N=547	For N=556	Tio N=415	Sal N=333	Pbo N=1371
Patients with ≥ 1 CCV SAE	2.4	1.7	1.2	1.3	0.5	2.2	1.5	1.2
Angina pectoris	0.8	0.3	0.1	0.2	0	0	0.3	0.2
Atrial fibrillation	0.8	0.3	0	0	0	0.7	0.3	0.2
Acute Myocardial Infarction	0	0.2	0.1	0	0	0	0.3	0
CVA	0	0.1	0	0	0	0	0	0
COPD 12-month safety	75 ---	150 N=144	300 N=583	600 N=425	For N=434	Tio ---	Sal ---	Pbo N=556
Patients with ≥ 1 CCV SAE	---	0.7	3.1	2.6	1.4	---	---	1.4
Atrial fibrillation	---	0.7	0.5	0	0.2	---	---	0.2
Angina pectoris	---	0	0.3	0.2	0	---	---	0.2
Myocardial infarction	---	0	0.3	0.5	0.2	---	---	0.4
CVA	---	0	0	0.2	0.2	---	---	0
Cerebral infarction	---	0	0.2	0	0	---	---	0

Source: Adapted from Tables 2.82, 2.84 and 2.86 CTD 2.7.4 Summary of Clinical Safety

Examination of the percent of patients with ≥1 CCV AE for the COPD 3-, 6- and 12- month safety populations is presented in Table 6 below. For the COPD 3-month safety population the highest rates of patients with ≥1 CCV AE were seen in the indacaterol 300 mcg group, 3.11% versus placebo at 2.58%. In the COPD 6-month safety population the highest rates were seen in the

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tiotropium and indacaterol 150 mcg treatment groups, at 5.8% and 5.6% respectively. The rate of CCV AEs in the placebo group was 4.1%. In the COPD 12-month safety population, the rates were highest in both the 150 mcg and 300 mcg indacaterol groups, 9.7% and 8.6%, respectively versus placebo, 5.4%. Overall, the CCV AE rates for the three safety populations were primarily influenced by the following preferred terms: ECG QT prolonged, angina pectoris, atrial fibrillation and CAD.

Table 6 Cardiovascular and cerebrovascular AEs by preferred term in COPD 3-, 6- and 12-month safety population

	Indacaterol treatment groups (%)				Control treatment groups (%)			
COPD 3-month safety	75 mcg N=449	150 mcg N=2611	300 mcg N=1157	600 mcg N=547	For N=556	Tio N=1214	Sal N=895	Pbo N=2012
Patients with ≥ 1 CCV AE	2	2.37	3.11	2.01	1.98	2.2	2.35	2.58
ECG QT prolonged	0	0.3	0.4	0.9	0.5	0.3	0.3	0.6
Angina pectoris	0	0.3	0.5	0	0.2	0.2	0.3	0.2
Atrial fibrillation	0	0.2	0.4	0.4	0	0.4	0.5	0.3
CAD	0	0.2	0.1	0.2	0.4	0.2	0.1	0.4
Ventricular extrasystoles	0.22	0.23	0.52	0.18	0.36	0.16	0.11	0.35
COPD 6-month safety	N=127	N=933	N=1041	N=547	N=556	N=415	N=333	N=1371
Patients with ≥ 1 CCV AE	4.7	5.6	4.8	3.3	4	5.8	4.8	4.1
ECG QT prolonged	0	1.1	0.5	0.9	0.5	1	0.6	0.7
Angina pectoris	0.8	0.8	0.7	0.2	0.2	0.2	0.3	0.2
Atrial fibrillation	0.8	0.8	0.5	0.4	0	1.5	0.6	0.5
Ventricular tachycardia	1.6	0.5	0	0	0	0.5	0	0.1
CAD	0	0.3	0.3	0.4	0.4	0	0.6	0.2
Acute Myocardial Infarction	0	0.2	0.1	0	0	0	0.3	0
COPD 12-month safety	---	N=144	N=583	N=425	N=434	---	---	N=556
Patients with ≥ 1 CCV AE	---	9.7	8.6	6.1	6.5	---	---	5.4
Atrial fibrillation	---	0.7	1.4	0.5	0.5	---	---	0.9
ECG QT prolonged	---	4.2	1.4	0.9	0.7	---	---	0.9
Angina pectoris	---	0.7	1.0	0.5	0.2	---	---	0.2
Myocardial ischemia	---	0	0.7	0	0.2	---	---	0.2
Ventricular extrasystoles	---	0	0.7	0.5	0.5	---	---	0.2
Cardiac failure	---	0	0.5	0.9	1.38	---	---	0.2

Source: Adapted from Tables 2-81, 2-83 and 2-85 CTD 2.7.4 Clinical Summary of Safety

Novartis also examined the CCV SAEs and AEs for a fourth safety population, the COPD safety population. This data was presented only adjusted for exposure with the preferred terms of the most frequently occurring CCV SAEs displayed in Table 7 and Table 8 below. There was no apparent dose response relationship between the cardiovascular and cerebrovascular SAEs and indacaterol. The most notable events occurring more frequently in the indacaterol treatment groups than the placebo groups were angina pectoris, acute myocardial infarction, coronary artery disease and cerebral vascular accident.

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Table 7 Cardiovascular and cerebrovascular SAE episodes adjusted for exposure by primary system organ class and preferred term

	Indacaterol treatment groups (n/1000 pt-yr)				Control treatment groups (n/1000 pt-yr)			
COPD Safety Population	75 mcg N=449	150 mcg N=2611	300 mcg N=1157	600 mcg N=547	For N=556	Tio N=1214	Sal N=895	Pbo N=2012
Patients with ≥ 1 CCV SAE	4	30	23	11	6	14	8	24
Total patient years	105	860	737	394	396	358	275	924
# CCV AE per 1000 py	57	43	39	35	23	56	36	28
Angina Pectoris	10	7	3	3	0	0	4	2
AMI	0	5	1	0	0	0	4	1
Atrial fibrillation	10	5	5	0	3	11	4	5
CAD	0	3	3	8	0	3	11	1
MI	0	3	3	5	5	0	4	5
Cerebral infarction	0	2	1	0	0	0	0	0
CVA	10	2	0	3	3	6	0	0
TIA	10	2	0	0	0	0	0	2

Source: Adapted from Appendix 1 Table O-4.3-12a

The CCV AEs occurring most frequently and adjusted for exposure are presented in Table 8. There was no apparent dose response relationship. The most notable events occurring more frequently in the indacaterol treatment groups than the placebo groups were angina pectoris, coronary artery disease, ventricular tachycardia, atrial flutter and cardiac failure congestive.

Table 8 Cardiovascular and cerebrovascular AE episodes adjusted for exposure by primary system organ class and preferred term

	Indacaterol treatment groups (n/1000 pt-yr)				Control treatment groups (n/1000 pt-yr)			
COPD Safety Population	75 mcg N=449	150 mcg N=2611	300 mcg N=1157	600 mcg N=547	For N=556	Tio N=1214	Sal N=895	Pbo N=2012
Patients with ≥ 1 CCV AE	11	89	73	28	28	33	27	77
Total patient years	105	860	737	394	396	358	275	924
# CCV AE per 1000 py	133	131	137	99	101	131	113	112
Angina pectoris	10	16	12	5	3	6	15	4
Atrial fibrillation	10	13	18	8	5	22	15	12
CAD	0	10	4	8	5	3	11	2
Ventricular extrasystoles	10	7	12	5	8	6	7	10
Ventricular tachycardia	19	6	0	0	0	6	0	1
AMI	0	5	1	0	0	0	4	1
BBB left	0	5	3	0	3	0	4	0
Atrial flutter	19	3	3	3	5	3	0	1
Cardiac failure congestive	10	3	5	0	0	6	0	2

Source: Appendix 1 Table O-4.3-11a Summary of Clinical Safety

Due to the granular nature of MedDRA there were many different preferred terms (PTs) representing verbatim descriptors that described the same overall AE (i.e. acute myocardial

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infarction and myocardial infarction or cerebrovascular accident and cerebral infarction). To further evaluate the cardiovascular data, the MedDRA 13.0 preferred terms were organized into the high level general term (HLGT) of Coronary Artery Disorder which includes the particular high level terms (HLT) of Ischemic Coronary Artery Disorders and Coronary Artery Disorders, NEC. See Table 9 below for details.

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Table 9 Cardiovascular AEs by HLGT, HLT and PT in the COPD safety population

	Indacaterol treatment groups									*Control treatment groups*					
	75 mcg (N = 449)			*150 mcg (N = 2611)*			*300 mcg (N = 1157)*			*For (N = 547)*			*Placebo (N = 2012)*		
HLGT	*Events*	*n*	*Proportion (%)*	*Events*	*n*	*Proportion (%)*	*Events*	*n*	*Proportion (%)*	*Events*	*n*	*Proportion (%)*	*Events*	*n*	*Proportion (%)*
Coronary artery disorders	2	1	0.22	42	33	1.26	27	23	1.99	9	7	1.28	17	14	0.7
HLT	*Events*	*n*	*Proportion (%)*	*Events*	*n*	*Proportion (%)*	*Events*	*n*	*Proportion (%)*	*Events*	*n*	*Proportion (%)*	*Events*	*n*	*Proportion (%)*
Ischaemic coronary artery disorders	2	1	0.22	30	27	1.03	22	20	1.73	6	6	1.1	13	12	0.6
Coronary artery disorders NEC	0	0	0	12	9	0.34	5	5	0.43	3	3	0.55	4	3	0.15
PT	*Events*	*n*	*Proportion (%)*	*Events*	*n*	*Proportion (%)*	*Events*	*n*	*Proportion (%)*	*Events*	*n*	*Proportion (%)*	*Events*	*n*	*Proportion (%)*
Acute myocardial infarction	0	0	0	4	4	0.15	1	1	0.09	0	0	0	1	1	0.05
Angina pectoris	1	1	0.22	15	15	0.57	10	10	0.86	2	2	0.37	4	4	0.2
Angina unstable	1	1	0.22	0	0	0	3	2	0.17	1	1	0.18	1	1	0.05
Acute coronary syndrome	0	0	0	1	1	0.04	0	0	0	0	0	0	0	0	0
Myocardial infarction	0	0	0	7	7	0.27	2	2	0.17	2	2	0.37	7	7	0.35
Myocardial ischaemia	0	0	0	3	3	0.11	5	5	0.43	0	0	0	0	0	0
Stress cardiomyopathy	0	0	0	0	0	0	1	1	0.09	0	0	0	0	0	0
Microvascular angina	0	0	0	0	0	0	0	0	0	1	1	0.18	0	0	0
Coronary artery disease	0	0	0	9	8	0.31	5	5	0.43	3	3	0.55	2	2	0.1
Coronary artery occlusion	0	0	0	1	1	0.04	0	0	0	0	0	0	0	0	0

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A similar organization of the cardiovascular SAEs at the higher level MedDRA terms is presented in Table 10 below. At the HLGT level of coronary artery disorders there is a dose response relationship from 75 mcg to 300 mcg indacaterol. The smallest rate was seen in the indacaterol 75 mcg group at 0.22%. The largest rate was seen in the indacaterol 300 mcg group at 0.95% versus placebo at 0.5%.

Table 10 Cardiovascular SAEs by HLGT, HLT and PT in the COPD Safety Population

			Indacaterol treatment groups			Control treatment groups	
			75 mcg	150 mcg	300 mcg	For	Placebo
	HLGT	N	449	2611	1157	556	2012
Event	Coronary artery disorders	47	2	18	15	2	10
Subject	Coronary artery disorders	38	1	15	11	1	10
Proportion (%)	Coronary artery disorders		0.22	0.57	0.95	0.18	0.50
	HLT						
Event	Ischaemic coronary artery disorders	41	2	15	13	2	9
Subject	Ischaemic coronary artery disorders	35	1	13	11	1	9
Proportion (%)	Ischaemic coronary artery disorders		0.22	0.50	0.95	0.18	0.45
Event	Coronary artery disorders NEC	6	0	3	2	0	1
Subject	Coronary artery disorders NEC	6	0	3	2	0	1
Proportion (%)	Coronary artery disorders NEC		0.00	0.67	0.45	0.00	0.22
	PT						
Event	Acute coronary syndrome	1	0	1	0	0	0
Subject	Acute coronary syndrome	1	0	1	0	0	0
Proportion (%)	Acute coronary syndrome		0.00	0.22	0.00	0.00	0.00
Event	Acute myocardial infarction	6	0	4	1	0	1
Subject	Acute myocardial infarction	6	0	4	1	0	1
Proportion (%)	Acute myocardial infarction		0.00	0.89	0.22	0.00	0.22
Event	Angina pectoris	12	1	6	3	0	2
Subject	Angina pectoris	12	1	6	3	0	2
Proportion (%)	Angina pectoris		0.22	1.34	0.67	0.00	0.45
Event	Angina unstable	5	1	0	3	0	1
Subject	Angina unstable	4	1	0	2	0	1
Proportion (%)	Angina unstable		0.22	0.00	0.45	0.00	0.22
Event	Coronary artery disease	6	0	3	2	0	1
Subject	Coronary artery disease	6	0	3	2	0	1
Proportion (%)	Coronary artery disease		0.00	0.67	0.45	0.00	0.22
Event	Myocardial infarction	12	0	3	2	2	5
Subject	Myocardial infarction	11	0	3	2	1	5
Proportion (%)	Myocardial infarction		0.00	0.67	0.45	0.22	1.11
Event	Myocardial ischaemia	4	0	1	3	0	0
Subject	Myocardial ischaemia	4	0	1	3	0	0
Proportion (%)	Myocardial ischaemia		0.00	0.22	0.67	0.00	0.00
Event	Stress cardiomyopathy	1	0	0	1	0	0

Reference ID: 2925943

Subject	Stress cardiomyopathy	1	0	0	1	0	0
Proportion (%)	Stress cardiomyopathy		0.00	0.00	0.22	0.00	0.00

Evaluation of the data at the HLGT and HLT level of MedDRA for the COPD safety population reveal a dose response relationship. The rate of events in the HLGT Coronary Artery Disorder as well as the corresponding HLTs Ischaemic Coronary Artery Disorders and Coronary Artery Disorders, NEC increase in patients treated with increasing doses of indacaterol from 75 mcg to 300 mcg once daily. In the HLGT Coronary Artery Disorders the proportion of events increases from 0.22% in the 75 mcg indacaterol group and 1.26% in the 150 mcg group to 1.99% in the 300 mcg group. The proportion of events in the placebo group was 0.7%. These events were primarily influenced by ischaemic coronary artery disorders with rates of 0.22%, 1.03% and 1.73% in the 75 mcg, 150 mcg and 300 mcg indacaterol groups, respectively. The proportion of events in the placebo group was 0.6%.

Reviewer Comment:
The 5 levels of the hierarchy of MedDRA include the lower level term (LLT), a granular level used to code verbatim terms; the preferred term (PT) represents "single medical concepts"; the high level term (HLT); the high level group term (HLGT) and the system organ class (SOC). Multiple PTs have the limitation of allowing important safety signals to go undetected when AEs are coded in only PT and SOCs. It is recommended to summarize AE rates at the HLT and HLGT level or to take advantage of the SMQs provided by MedDRA.

A similar organization of the cardiovascular SAEs at the higher level MedDRA terms is presented in Table 10 below. At the HLGT level of coronary artery disorders there is a dose response relationship from 75 mcg to 300 mcg indacaterol. The smallest rate was seen in the indacaterol 75 mcg group at 0.22%. The largest rate was seen in the indacaterol 300 mcg group at 0.95% versus placebo at 0.5%.

Table 10 Cardiovascular SAEs by HLGT, HLT and PT in the COPD Safety Population

			Indacaterol treatment groups			Control treatment groups	
			75 mcg	150 mcg	300 mcg	For	Placebo
	HLGT	N	449	2611	1157	556	2012
Event	Coronary artery disorders	47	2	18	15	2	10
Subject	Coronary artery disorders	38	1	15	11	1	10
Proportion (%)	Coronary artery disorders		0.22	0.57	0.95	0.18	0.50
	HLT						
Event	Ischaemic coronary artery disorders	41	2	15	13	2	9
Subject	Ischaemic coronary artery disorders	35	1	13	11	1	9
Proportion (%)	Ischaemic coronary artery disorders		0.22	0.50	0.95	0.18	0.45
Event	Coronary artery disorders NEC	6	0	3	2	0	1
Subject	Coronary artery disorders NEC	6	0	3	2	0	1
Proportion (%)	Coronary artery disorders NEC		0.00	0.67	0.45	0.00	0.22
	PT						
Event	Acute coronary syndrome	1	0	1	0	0	0
Subject	Acute coronary syndrome	1	0	1	0	0	0
Proportion (%)	Acute coronary syndrome		0.00	0.22	0.00	0.00	0.00
Event	Acute myocardial infarction	6	0	4	1	0	1
Subject	Acute myocardial infarction	6	0	4	1	0	1

Reference ID: 2925943

Proportion (%)	Acute myocardial infarction		0.00	0.89	0.22	0.00	0.22
Event	Angina pectoris	12	1	6	3	0	2
Subject	Angina pectoris	12	1	6	3	0	2
Proportion (%)	Angina pectoris		0.22	1.34	0.67	0.00	0.45
Event	Angina unstable	5	1	0	3	0	1
Subject	Angina unstable	4	1	0	2	0	1
Proportion (%)	Angina unstable		0.22	0.00	0.45	0.00	0.22
Event	Coronary artery disease	6	0	3	2	0	1
Subject	Coronary artery disease	6	0	3	2	0	1
Proportion (%)	Coronary artery disease		0.00	0.67	0.45	0.00	0.22
Event	Myocardial infarction	12	0	3	2	2	5
Subject	Myocardial infarction	11	0	3	2	1	5
Proportion (%)	Myocardial infarction		0.00	0.67	0.45	0.22	1.11
Event	Myocardial ischaemia	4	0	1	3	0	0
Subject	Myocardial ischaemia	4	0	1	3	0	0
Proportion (%)	Myocardial ischaemia		0.00	0.22	0.67	0.00	0.00
Event	Stress cardiomyopathy	1	0	0	1	0	0
Subject	Stress cardiomyopathy	1	0	0	1	0	0
Proportion (%)	Stress cardiomyopathy		0.00	0.00	0.22	0.00	0.00

Standardized MedDRA queries (SMQs), or groupings of MedDRA PTs that relate to a defined medical condition or area of interest were also performed on the COPD safety population. In this case, the SMQ was "Other Ischemic Heart Disease" narrow scope. This SMQ revealed a similar pattern as seen when the data was evaluated at the HLGT and HLT levels. The rates of 'other ischemic heart disease' in the 75 mcg, 150 mcg and 300 mcg treatment groups were 0.22%, 1.26% and 2.16%, respectively versus placebo at 0.7%. As well, a dose response relationship was apparent.

6.3.4.2 Summary

1. Cardiovascular AEs evaluated at the higher level group term of coronary artery disorders reveal higher rates in the higher indacaterol treatment groups of 150 mcg and 300 mcg over placebo in the COPD safety population.
2. These rates were not elevated at the 75 mcg indacaterol treatment group, however the duration of exposure to this dose was only for 3 months.
3. Cardiovascular AEs evaluated by the standard MedDRA query of ischaemic heart disease also reveal higher rates at the higher indacaterol treatment groups of 150 mcg and 300 mcg over placebo in the COPD safety population. These rates were not elevated for the 75 mcg indacaterol treatment group, again only treated for the 3 month duration of time.
4. There was a dose response relationship between the specific cardiovascular toxicities and the indacaterol doses studied.
5. The number of cardiac disorder AEs increased with increasing number of predisposing cardiovascular risk factors.

6.3.4.3 Addendum to Recommendation on Regulatory Action

Reference ID: 2925943

The addition of this addendum to the clinical review of the data presented in NDA 22-383 results in a recommendation of approval for indacaterol 75 mcg once daily in the maintenance treatment of COPD. There is substantial evidence from 6 adequate and well controlled clinical trials submitted to the complete response in support of efficacy for two proposed doses of indacaterol 75 mcg and 150 mcg once daily. However, there is not sufficient data demonstrating an efficacy advantage of the higher dose in more severe patients with COPD.

The primary bronchodilator assessment was trough FEV1 (tFEV1) at various time points. This was further supported by other measures of bronchodilation i.e. peak FEV1, FEV1 AUC (0 – 4 hr), FEV1 AUC (0-12 hr) as well as patient or evaluator reported outcome measures for rescue medication use and the health related quality of life, SGRQ.

The safety profile of indacaterol 75 mcg is acceptable. Patients with increasing number of cardiovascular risk factors appear to have higher rates of cardiovascular disorder AEs. Therefore, a large simple trial of 12 months duration in patients with COPD to evaluate the cardiovascular AEs in patients with ≥1 cardiovascular risk factors is recommended by this reviewer as a post marketing commitment.

Reference ID: 2925943

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/s/

ANYA C HARRY
04/04/2011

THERESA M MICHELE
04/04/2011
Review addendum noted and discussed with management. Disagree with conclusions and recommendation for a post-marketing commitment. Secondary review addedendum will be submitted.

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22-383
Priority or Standard	Standard-resubmission
Submit Date(s)	September 28, 2010
Received Date(s)	September 28, 2010
PDUFA Goal Date	April 1, 2011
Division / Office	DPARP/ODE II
Reviewer Name(s)	Anya C. Harry M.D., Ph.D.
Review Completion Date	February 14, 2011
Established Name	Indacaterol maleate
(Proposed) Trade Name	Arcapta Neohaler
Therapeutic Class	Long acting β2 agonist
Applicant	Novartis Pharmaceuticals
Formulation(s)	Single dose dry powder inhaler
Dosing Regimen	Once daily
Indication(s)	The long term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.
Intended Population(s)	Patients with COPD

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1 Recommendations//Risk Benefit Analysis

1.1 Recommendation on Regulatory Action

Clinical review of the data presented in NDA 22-383 results in a recommendation of **approval** for indacaterol 75 mcg q.d in the maintenance treatment of COPD. There is substantial evidence from 6 adequate and well controlled clinical trials submitted to the complete response in support of efficacy for two proposed doses of indacaterol 75 mcg and 150 mcg once daily. However, there is not sufficient data demonstrating an efficacy advantage of the higher dose in more severe patients with COPD. Therefore, in advance of input from an upcoming Pulmonary Allergy Drugs Advisory Committee meeting, the 150 mcg indacaterol dose will not be approved.

The primary bronchodilator assessment was trough FEV1 (tFEV1) at various time points. This was further supported by other measures of bronchodilation i.e. peak FEV1, FEV1 AUC $_{(0-4\ hr)}$, FEV1 AUC $_{(0\text{-}12\ hr)}$ as well as patient or evaluator reported outcome measures for rescue medication use and the health related quality of life, SGRQ.

The safety profile of indacaterol 75 mcg is acceptable. The safety database includes adverse events (AEs) typical for long acting beta2 adrenergic agents with the exception of a short lasting post inhalation cough. Additional information was requested by FDA for an analysis of externally adjudicated serious adverse events (SAEs) primarily, respiratory related death, intubation and hospitalization. A review of this analysis is pending.

1.2 Risk Benefit Analysis

The new safety data presented in the complete response for the lower proposed dose of indacaterol support the risk benefit assessment. No new safety concerns were apparent for patients with COPD, however there were 2 asthma related deaths in the asthma population from the original cycle. These two deaths brought up the overriding concern of LABA safety in asthmatics. While the target population for marketing will not be patients with asthma but instead, COPD the concern is carried over to this population for many reasons. 1). Many COPD patients as noted in this safety database have a significant degree of reversible bronchospasm and may therefore be at greater risk for LABA associated respiratory SAEs 2). The respiratory related events appear to be dose related and therefore it was critical to explore the complete dose response profile in conjunction to dose related toxicities for indacaterol and identify the most appropriate dose. 3). Unique to indacaterol is the long half life of ~49 hours and therefore evaluation of dosing frequencies was important to minimize the potential for SAEs due to systemic accumulation over chronic administration. Still, as many of these concerns are not apparent for the 75 mcg indacaterol dose in patients with COPD, the major safety concern for asthma related death will be reflected as a boxed warning. Finally, the increased frequencies of combined cardio- and cerebrovascular events observed with the higher doses in the original cycle were not as apparent in the 75 mcg indacaterol treatment groups. A final risk-benefit determination is pending the results of a respiratory-related event meta-analysis and discussion at the Pulmonary Allergy Drug Advisory Committee meeting.

1.3 Recommendations for Postmarket Risk Management Activities

The risk management activity for indacaterol will include the REMS elements: medication guide, communication plan; timetable for submission of assessments as well as an enhanced adverse event surveillance program. This will include evaluation of designated medical events of concern such as respiratory and cardiac deaths, the collection of additional safety data in non-caucasian populations, monitoring the off-label use of indacaterol in patients with asthma, and the conduct of post-marketing studies in order to further assess the safety of indacaterol in COPD and asthma populations.

1.4 Recommendations for Postmarket Studies/Clinical Trials

The mean exposure of 75 mcg indacaterol was 85.5 days and for 150 mcg indacaterol it was 120 days. As mentioned in more detail in the Safety Summary, the [1]E1A-Guideline for Industry, The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life Threatening Conditions, recommends that the number of patients in the safety data base treated for 6 months at dosage levels intended for clinical use should be 300 to 600 and 100 patients exposed for a minimum of one-year. An adequate number of patient exposures is available for higher doses (150 and 300 mcg). These numbers were not achieved in the indacaterol 75 mcg data base and while no new safety signals were apparent for the duration of exposure evaluated, a postmarketing clinical trial of adequate size and duration may be necessary to determine the risk of fatal and life-threatening respiratory events associated with the long term use of Arcapta Neohaler. If the results of the meta-analysis are supportive of safety, additional trials may not be necessary.

2 Introduction and Regulatory Background

2.1 Product Information

The proposed product is indacaterol maleate inhalation powder (QAB149), and the proposed trade name is Arcapta™ Neohaler™. The established name, indacaterol (Ind) without specification of the salt will be used throughout the review to refer to the product. Indacaterol is a new molecular entity in the beta-2 adrenergic agonist class of drugs. It is a dry powder for inhalation that is pre-metered with the formulation of approximately 25 mg of lactose monohydrate contained in hard gelatin capsules. A capsule is inserted into the Neohaler device, also called the Concept 1. The device pierces both ends of the capsule, then inhalation causes the capsule to spin and the formulation powder to be entrained into the airstream.

The proposed indication for indacaterol is for once daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. The proposed dose is one inhalation of a 75 mcg capsule once daily, with a qualifier that administration of a 150 mcg capsule once daily has been shown to provide additional clinical benefit in some patients.

2.2 Currently Available Treatments for Proposed Indications

Currently available drugs for the treatment of COPD are listed in Table 1. The list includes many pharmcotherapeutics that are used for the treatment of acute bronchospasm.

[1] E1A- The Extent of Population Exposure to Assess Clinical Safety: for Drugs Intended for Long-term Treatment of Non-Life Threatening Conditions March, 1995. Available at the website http://www.fda.gov/cder/guidance/index.htm

Table 1 Currently available pharmacologic treatment for COPD

Class		Generic name	Brand name
Beta2-adrenergic agonists	Short-acting† (SABA)	Albuterol Albuterol sulfate	Accuneb, ProAir HFA, Proventil HFA, Ventolin HFA
		Levalbuterol Levalbuterol tartrate	Xopenex HFA
		Pirbuterol	Maxair Autohaler
		Terbutaline sulfate	
	Long-acting (LABA)	Salmeterol	Serevent Diskus
		Formoterol	Foradil Aerolizer
		Arformoterol	Brovana
		Formoterol solution	Perforomist
Anti-cholinergics	Short-acting	Ipratropium bromide	Atrovent HFA
	Long-acting	Tiotropium bromide	Spiriva Handihaler
Combination	SABA/anti-cholinergic	Albuterol/ipratropium	Combivent, Duoneb
	Corticosteroid/LABA	Fluticasone/salmeterol	Advair Diskus, Advair HFA
		Budesonide/formoterol	Symbicort
Xanthines		Theophylline	multiple

†Products with a general bronchodilator claim, not COPD specific.

2.3 Availability of Proposed Active Ingredient in the United States

Indacaterol is currently not marketed in the US. According to the sponsor, it is approved in 30 countries worldwide, including the EU at a dose of 150mcg or 300 mcg once daily.

2.4 Important Safety Issues With Consideration to Related Drugs

Indacaterol belongs to a subclass of beta-2 agonists termed long-acting beta agonists or LABAs that include the marketed drugs Foradil and Perforomist (formoterol), Brovana (R,R formoterol), and Serevent (salmeterol). The use of LABAs has come under scrutiny as a result of a safety signal of increased risk of severe exacerbations including death in patients with asthma. The increased risk was demonstrated in the Salmeterol Multicenter Asthma Research Trial (SMART) in 1996. SMART was a randomized, double-blind study that enrolled patients with asthma not currently using LABAs to assess the safety of salmeterol (42 mcg twice daily for 28 weeks) compared to placebo when added to usual asthma therapy. The primary endpoint was the combined number of respiratory-related deaths or respiratory-related life-threatening experiences (intubation and mechanical ventilation). The study was prematurely terminated in January 2003 after a total of approximately 30,000 patients had been enrolled because a planned interim analysis suggested that salmeterol may be associated with an increased risk of severe asthma exacerbations including death.

As a result of the findings described above as well findings in smaller safety studies conducted with another LABA, formoterol, the safety of LABAs was the topic of discussion at a July 13, 2005, Pulmonary Allergy Drugs Advisory Committee Meeting (PADAC). Subsequent to the meeting, in November, 2005, the FDA released a Public Health Advisory to alert healthcare professionals and patients that LABAs may increase the chance of severe asthma episodes and death. Based on this meeting and a follow up PADAC meeting on December 10, 2008, the existing product labels have been revised and now include a Boxed Warning and a Medication Guide for all marketed LABA products. In addition, the paradigm for

asthma treatment has now changed, contraindicating the use of a LABA without a concomitant asthma controller medication, such as an inhaled corticosteroid (ICS)[2].

Because it is unclear if addition of an inhaled corticosteroid mitigates the risk of LABAs in asthma, sponsors of LABA products indicated for asthma are being required to perform large safety trials to evaluate serious asthma outcomes in patients receiving concomitant ICS and LABA. The design of these trials was discussed at a PADAC meeting held March 10-11, 2010.

While no such safety signal has been observed in patients with COPD, dose-related class effects of beta agonists, especially those affecting the cardiac and central nervous systems, can be deleterious to older patients with COPD, many of whom have increased cerebral and cardiovascular risk factors.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Novartis initially submitted NDA 22-383 on December 15, 2008, requesting approval of two doses, 150 and 300 mcg once daily, for COPD. To support this application, Novartis submitted three pivotal COPD studies: a 26-week adaptive design dose ranging study (with continuing doses of 150 and 300 mcg), a one-year efficacy and safety study (300 and 600 mcg), and a 12 week study (150 mcg). FDA took a complete response action for this application on October 16, 2009. Key issues were unacceptable higher frequencies of cardiovascular and cerebrovascular adverse events (AEs) compared to placebo and to formoterol in patients with COPD and possible asthma related deaths compared to salmeterol in patients with asthma. In addition, the dose and dosing frequency were not adequately explored, with no clinically meaningful difference between 75 mcg once daily and the proposed doses of 150 and 300 mcg.

A post action meeting was held on November 24, 2009. The highlights of the meeting included review of FDA's comments to questions from the November 5, 2009 package as well as a general discussion of the path forward. FDA reviewed recommendations for the use of patients with a significant degree of bronchoresponsiveness to define the dose response profile and for selection of the lowest dose with a tolerable safety profile to be carried forward to patients with COPD.

In a complete response to regulatory action, Novartis now submits 6 new pivotal studies in addition to 10 Phase 3 supportive studies. The key pivotal studies include dose ranging and dose regimen studies in a bronchodilator-responsive asthma population, a dose ranging study in COPD, two replicative 12-week confirmatory studies in COPD with the 75 mcg dose, and one 26 week confirmatory study in COPD with the 150 mcg dose. Important long-term safety data for the 150 mcg dose comes from a 26 week extension to the adaptive design study, for a total duration of 1 year.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The Division requested an audit by the Division of Scientific Investigations (DSI) for this NDA since indacaterol is a new molecular entity. An efficacy by center analysis of the new dose finding and confirmatory trials was performed by the biostatistician, Dr. Dongmei Liu. Overall, most sites had too few patients to detect any significant deviation in efficacy. No particular outlier sites were identified. The sites therefore offered for a DSI audit included those based on the criteria of enrollment and death. DSI selected the following sites: Drs. Steven Weinstein #521, James Pearle #514 and James Meli #535. Only

[2] Chowdhury BA, Dal Pan G. FDA and safe use of long-acting beta-agonists in the treatment of asthma. 2010 N Engl J Med 362:1169-71

preliminary review is available at this time and there were no data integrity or scientific misconduct issues based on an early working draft by the ORA office.

3.2 Compliance with Good Clinical Practices

The Applicant has indicated that all clinical trials were conducted in full compliance with Good Clinical Practices [See CTD 2.5 Clinical Overview, pg 12]. The Applicant states that no debarred investigators participated in the trials [Module 1.3.3 Debarrment Certification, pg 1].

3.3 Financial Disclosures

Module 1, Section 1.3.4 Financial Disclosure addresses the Applicant's compliance with the Final Rule on Financial Disclosure by Clinical Investigators. The Applicant certifies that it did not enter into financial arrangements with any investigator whereby the value of compensation could be affected by the outcome of the study (Category 1), that no investigator received significant payments (Category 2), that none of the investigators disclosed a proprietary interest in the product (Category 3), or possessed a significant equity interest in the Applicant (Category 4) as defined in 21 CFR 54 with the following exceptions.

Five investigators were noted to receive significant payments from the Sponsor > $25,000: (b) (6) As mentioned in Section 3.1 most sites had too few patients to detect any significant deviation in efficacy, it is unlikely that financial interests could have influenced or biased the results of these trials.

4 Sources of Clinical Data

Between the original application [NDA 22383 12/17/08, S0000] and the resubmission [9/28/10, S0027], Novartis has conducted 21 Phase III controlled clinical trials with indacaterol in over 13,500 patients. There were 3 trials identified as pivotal in the original Phase III program: B2335S, B2334 and B2346 and 3 supportive profiling trials: B2305, B2307 and B2340. These trials were summarized in the reviews of the original application by Drs. Lynne Wu and Anthony Durmowicz and are not mentioned further in this review. There were 16 new Phase II and III trials submitted in the complete response. These new trials are summarized in Table 2. Of the 16 new trials, 6 are considered pivotal to the resubmission as they provide data in support of dose selection and dosing frequency as well as confirmation of safety and efficacy of the new proposed doses. The dose finding trials B2357, B2356 and B2223 were the trials submitted in response to concern over the dose and regimen selection described in the CR letter [October 16, 2009]. In addition, two confirmatory trials, B2355 and B2354 were reviewed to evaluate the safety and efficacy of the 75 mcg dose in patients with COPD over a 12 week treatment period. The trial B2336 was ongoing at the time of the initial submission, completed and included as part of the current resubmission. It was a pivotal efficacy and safety trial of indacaterol 150 mcg q.d. with the active comparator, salmeterol over 26 weeks and provides data the sponsor uses to support the SGRQ claim.

Ten additional supplementary controlled trials not included in the original submission were reviewed and briefly summarized as supportive towards efficacy and safety in patients with COPD. Trials B1302 and B2333 were long term studies performed in Asia evaluating the two higher doses of indacaterol 150 mcg and 300 mcg compared to placebo. Trials B2349 and B2350 recruited international patients and evaluated the efficacy of indacaterol 150 mcg and an active comparator, either salmeterol 50 mcg b.i.d or tiotropium 18 mcg q.d. respectively. B2335SE, also an international trial was a 26 week extension to the 26 week adaptive seamless design trial included in the original submission. Although the extension did not include the active control, tiotropium the trial provided long term safety data of indacaterol 150 mcg and 300 mcg compared to placebo after 52 weeks of treatment. Trials B2341 and B2351 compared the

efficacies of indacaterol 150 mcg given concurrently with tiotropium HandiHaler (18 mcg q.d.) to tiotropium alone and placebo. Two profiling studies were B2311 and B2331, the former evaluated indacaterol 300 mcg and placebo on exercise endurance time, the latter evaluated the two doses 150 mcg and 300 mcg versus placebo on the 24 hour lung function. The 24 week interim analysis of the ongoing Japanese trial B1303 was also included.

Novartis submitted a Periodic Safety Update Report (PSUR-1) for Onbrez® Breezhaler ® (indacaterol maleate) and related products which were first registered in the EU on November 30, 2009 at doses of 150 and 300 mcg covering the time frame of November 30, 2009 to May 31, 2010 that was reviewed. Furthermore, Medwatch reports submitted to the IND 48,649 were also reviewed.

4.1 Tables of Studies/Clinical Trials

Table 2 Clinical trials included in evaluation

Study	Objective, population	Planned patients	Treatment duration	Dosage	Efficacy endpoint	Safety endpoints
Dose finding trials						
B2335S	Adaptive design dose-ranging in COPD	1945	26 weeks	Indacaterol 75, 150, 300, 600 mcg q.d., Formoterol 12 mcg bid Tiotropium 18 mcg QD (open label) Placebo	FEV_1 trough at 24 hr at wk 2 FEV_1 AUC_{1-4} hr at wk 2 FEV_1 trough at 24 hr at wk 12	AE, SAEs, labs, ECGs, VS, PE, weight, COPD exacerbations, 24 hour Holter (subset)
B2357	Dose-ranging in asthma	558	2 weeks	Indacaterol 18.75, 37.5, 75, 150 mcg q.d. Salmeterol 50 mcg bid Placebo bid	tFEV1 after 14 days	AE (including asthma exacerbations), SAEs, labs, ECG, VS, PE, weight
B2223	Dosing regimens in asthma	192	2 weeks	Indacaterol 37.5 mcg bid, 75 mcg q.d., 150 mcg q.o.d	tFEV1 after 14 days	VS, ECG, labs, AEs
B2356	Dose-ranging in COPD	576	2 weeks	Indacaterol 18.75, 37.5, 75, 150 mcg q.d. Salmeterol 50 mcg bid Placebo bid	tFEV1 after 14 days	AE, SAEs, labs, ECG, VS, PE, rescue medication use
Key controlled efficacy trials-75 mcg						
B2355	Efficacy/safety in COPD	326	12 weeks	Indacaterol 75 mcg q.d. Placebo q.d.	tFEV1 at Week 12	AE, SAEs, labs, ECG, VS, PE
B2354	Efficacy/safety in COPD	326	12 weeks	Indacaterol 75 mcg q.d. Placebo q.d.	tFEV1 at Week 12	AE, SAEs, labs, ECG, VS, PE
Key controlled efficacy trials-≥ 150 mcg						
B2336	Efficacy/safety in COPD	972	26 weeks	Indacaterol 150 mcg q.d. Salmeterol 50 mcg b.i.d Placebo b.i.d	tFEV1 at Week 12	AE (including COPD exacerbations), SAEs, labs, ECG, VS, PE, medical resource utilization, post inhalation events

Supplementary controlled efficacy trials						
B1302	Efficacy/safety in COPD Hong Kong, India, Japan, Korea, Singapore and Taiwan	336	12 weeks	Indacaterol 150, 300 mcg q.d. Placebo q.d.	tFEV1 at Week 12	AE (including COPD exacerbations), SAEs, labs, ECG, VS, PE, weight, post inhalation events
B2333	Efficacy/safety in COPD, China, Australia and India	558	26 weeks	Indacaterol 150, 300 mcg q.d. Placebo q.d.	tFEV1 at Week 12	AEs, SAEs, VS, ECGs, labs, post inhalation events
B2349	Efficacy/safety in COPD	1084	12 weeks	Indacaterol 150 mcg q.d. Salmeterol 50 mcg b.i.d	AUC (5 min-11h 45 min for FEV1 at Week 12	ECG, labs, blood pressure, heart rate, AEs
B2350	Efficacy/safety in COPD	1568	12 weeks	Indacaterol 150 mcg q.d. Tiotropium 18 mcg q.d.	tFEV1 at Week 12	AEs, SAE, ECG, labs, blood pressure, heart rate, AEs
Long term controlled efficacy trials						
B2335SE	Efficacy/safety in COPD	417	26 weeks (additional to initial 26 weeks)	Indacaterol 150, 300 mcg q.d. Placebo q.d.	tFEV1 at Week 52	AE (including COPD exacerbations), SAEs, labs, ECG, VS, PE, weight
Trials with indacaterol given concurrently with tiotropium						
B2341	Efficacy/safety in COPD	1126	12 weeks	Indacaterol 150 mcg q.d. + tiotropium 18 mcg q.d. Placebo to indacaterol + tiotropium 18 mcg q.d.	AUC (5 min-8 h) for FEV1 at Week 12	AEs, COPD exacerbations, SAEs, labs, VS, PE, ECG
B2351	Efficacy/safety in COPD	1126	12 weeks	Indacaterol 150 mcg q.d. + tiotropium 18 mcg q.d. Placebo to indacaterol + tiotropium 18 mcg q.d.	AUC (5 min-8 h) for FEV1 at Week 12	AEs, COPD exacerbations, SAEs, labs, VS, PE, ECG
Short-term profiling trials						
B2311	Exercise endurance in COPD	83	3 weeks (2 treatment periods separated	Indacaterol 300 mcg q.d. Placebo q.d.	Exercise endurance time (measured	AEs, SAEs, labs, VS, ECG, PE

			by 2 weeks of wash out)		through constant-load cycle ergometry testing) after 3 weeks of treatment	
B2331	24 h lung function profile in COPD	148	14 days (3 treatment periods separated by 2 weeks of wash out)	Indacaterol 150, 300 mcg q.d. Tiotropium 18 mcg q.d. Placebo q.d.	tFEV1 on Day 15	AEs (including COPD exacerbations),, SAEs, labs, VS, ECG, PE
Interim analysis for Japanese trial						
B1303	Efficacy/safety in COPD (Japan)	180	52 weeks (interim analysis at Week 24)	Indacaterol 300 mcg q.d. Salmeterol 50 mcg b.i.d.	tFEV1 on Day 169 (Week 24)	AE (including COPD exacerbations), SAEs, labs, ECG, VS, PE, weight, post inhalation events

4.2 Review Strategy

The two new dose ranging trials (B2357 and B2356) and the dose regimen trial (B2223) were first reviewed for validity and appropriateness of the selected dose and regimen. B2357 and B2223 were conducted in the bronchoreactive population of asthmatics as recommended by FDA. Then the two confirmatory 12 week trials B2355 and B2354 were reviewed for efficacy and safety of the proposed 75 mcg dose. Next, the long term 26 week trial B2336 was examined for safety of the higher proposed dose which could be extrapolated to the lower proposed dose. Overall, safety was judged by the review of many sources including: the Overview of Safety, the PSUR-1 and postmarketing reports. Novartis submission of a meta-analysis of the incidence of respiratory related death is pending at the time of finalization of this background package. It is anticipated that this information will be available at the PADAC meeting

4.3 Discussion of Individual Studies/Clinical Trials

4.3.1 DOSE FINDING TRIAL IN PATIENTS WITH ASTHMA B2357

A Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Parallel-Group Study to Assess the Efficacy and Safety of Different Doses of Indacaterol in Adult Patients with Persistent Asthma, Using Salmeterol as an Active Control.

4.3.1.1 Trial Description

4.3.1.1.1 Design

This was a Phase III, multicenter (73), randomized, double-blind, double-dummy, placebo-controlled, parallel group trial conducted in patients with persistent asthma for 14 days with indacaterol once daily at doses of 18.75, 37.5, 75 or 150 mcg, salmeterol 50 mcg twice daily, or placebo. Initially, there was an open label period on Day 15 where all subjects would receive a single dose of indacaterol 300 mcg, this was removed in Amendment #2 dated 2/15/10 along with the associated study objectives and assessments.

Reviewer's Comment:
The intention of the Sponsor was that this study would supplement the data from Study CQAB149B2335S and support the selection of an appropriate dose of indacaterol for the treatment of COPD.

4.3.1.1.2 Duration

The treatment period was 2 weeks. A two week run-in time preceded the active treatment period.

Reviewer's Comment:
The time taken to reach pharmacokinetic steady state is 14 days for indacaterol when administered once daily.

4.3.1.1.3 Population

Males and females aged 18 years and older, diagnosed with persistent asthma (according to [3]GINA guidelines, update 2008) were enrolled. The randomization was stratified by asthma severity (GINA guidelines) based on data recorded in the patient's diary during the run-in period. The population was changed in Amendment #2 dated 2/15/10 to include a 24-hour spirometry profiling subgroup. All patients were offered the opportunity

Reviewer's Comment:
The targeted asthma population was at the recommendation of the Agency where the rationale was to test in the patient population most sensitive to both the bronchodilator and AE effects of LABAs.

4.3.1.1.4 Study Sites

This study was conducted at 73 sites in the United States

4.3.1.1.5 Investigational and Reference Therapy

The following drugs were used:

- Indacaterol 18.75 mcg dry powder capsules blister batch # VMLK/2009-3018, DP Batch # X223 0909
- Indacaterol 37.5 mcg dry powder capsules blister batch # VMLK/2009-3019, DP Batch # X224 0909
- Indacaterol 75 mcg dry powder capsules blister batch # VMLK/2009-2700, DP Batch # X173GF
- Indacaterol 150 mcg dry powder capsules blister batch # VMLK/2009-2826, DP Batch # X172GF
- Placebo to indacaterol blister batch # VMLK/2008-1409, DP Batch # X039BE
- Salmeterol 50 mcg Diskus® DP batch # R438216
- Placebo to salmeterol Diskus® DP batch # X2780807

[3] Global Initiative for Asthma (GINA) 2008, Available from the website http://www.ginasthma.org.

- Placebo to salmeterol Diskus® DP batch # X1650608

All indacaterol dry powder capsules and placebo-to-indacaterol were inhaled through the Concept1 SDDPI. Salmeterol and the placebo-to-salmeterol were inhaled through the Diskus®.

4.3.1.1.6 Objectives

The primary objective was to evaluate the dose response relationship among four doses of indacaterol (18.75, 37.5, 75, and 150 mcg q.d.), placebo and salmeterol 50 mcg b.i.d. as measured by the 24 hr post-dose FEV1 (trough) after 14 days (tFEV1 Day 14) of treatment in adult patients with persistent asthma.

Reviewer's Comment:
The doses selected were smaller than those evaluated in study B2335S in the original submission [NDA22-383 S000], 75, 150, 300 and 600 mcg.

The second secondary objectives were as follows:

- To evaluate the bronchodilator effect for all doses of indacaterol as compared to placebo as measured by:
  - 24-hour post-dose of (trough) FEV1 after 1 day (tFEV1 Day1) of treatment
  - Peak FEV1 on Day 1, this was changed from time to peak FEV1 on Day 1 in Amendment #1, dated 1/15/10
  - AUC for FEV1 5 minutes -11 hours 45 minutes on Days 1 and 14
  - AUC for FEV1 5 minutes-4 hours on Days 1 and 14
- To evaluate the effect of all doses of indacaterol and placebo on morning (premedication) and evening (pre-medication) PEF using data obtained from the eDiary over 14 days
- To evaluate day and night time rescue medication usage for all doses of indacaterol as compared to placebo over 14 days

An exploratory objective to assess the 24-hour (FEV1 and FVC) profile of indacaterol (18.75, 37.5, 75 and 150 mcg q.d.), salmeterol and placebo after 14 days of treatment was added in Amendment #2 dated 2/15/10.

4.3.1.1.7 Inclusion Criteria

Key inclusion criteria included:

- Male and female adults aged ≥ 18 years
- Diagnosis of persistent asthma per GINA 2008 guidelines
- Stable treatment with inhaled corticosteroid (ICS) for one month
- FEV1 ≥ 50 and ≤ 90% of predicted normal
- Reversibility with an increase FEV1 of ≥12% and ≥200 mL within 30 minutes of albuterol via MDI

The criterion for FEV1 had to be demonstrated after a washout period of at least 6 hours during which no use of short acting β2-agonist (SABA), and a minimum of 48 hours for a long acting β2-agonist (LABA). Patients using LABAs (i.e. formoterol or salmeterol) were switched to the PRN use of the SABA (albuterol) at least 48 hours prior to Visit 2, those taking fixed dose combination treatment with ICS plus a LABA were taken off the combined medication and given the equivalent ICS monotherapy replacement of the ICS plus the inhaled SABA (as needed) at least 48 hours prior to Visit 2. Those taking a fixed dose combination anti-cholinergic plus a SABA (i.e., Combivent®) were taken off the combination at least 8 hours prior to Visit 2. Instead, only albuterol was used. In either case where fixed dose combination products were discontinued, regular dosage regimens of albuterol as rescue medication were only permitted during the screening period however, during the treatment period albuterol was taken for rescue ("when required") purposes only. Reversibility could be demonstrated after a washout period of at least 6 hours prior to the evaluation for a SABA and at Visit 2 or between Visits 2 and 3.

4.3.1.1.8 Exclusion Criteria

Notable exclusion criteria included:

- Pregnant or lactating women
- Women of child-bearing potential unless use of one or more acceptable method of contraception
- Smoking history of >10 pack years or current smokers who smoke more than 10 cigarettes a day
- Diagnosis of COPD as defined by the [4]Global Initiative for Chronic Obstructive Lung Disease (GOLD guidelines for 2008)
- Patients with seasonal allergic rhinitis whose asthma was likely to deteriorate during the study
- Severe asthma exacerbation requiring hospitalization in the 6 months prior to Visit 1, previous intubation
- Emergency room visit for an asthma attack within 6 weeks prior to Visit 1 or anytime between Visit 1 and 3
- Use of ≥8 inhalations per day of SABA (90 mcg albuterol via MDI) on any 2 consecutive days from screening to randomization
- Respiratory tract infection within 6 weeks prior to Visit 2 however, in Amendment #3, this was changed so that these patients were permitted to reenroll at a later date of at least 6 weeks
- Respiratory tract infection between Visit 2 and Visit 3 must discontinue from the trial
- Concomitant pulmonary disease, pulmonary tuberculosis (unless confirmed by chest x-ray to be no longer active), or clinically significant bronchiectasis
- Patients with diabetes Type I or uncontrolled diabetes Type II including patients with a of blood glucose levels consistently outside the normal range of glycosylated A1c > 8.0% of total hemoglobin measured at Visit 2.
- Clinically relevant laboratory abnormality or a clinically significant condition such as unstable ischemic heart disease, arrhythmia, or other clinically significant ECG findings, uncontrolled hypertension and other significant cardiac disease or conduction defect, uncontrolled thyroid disease, hypokalemia, hyperadrenergic state
- History (or family history) of long QT syndrome or QTc interval (Fridericia) measured at Visit 2 and 3 >450 ms (males) or >470 ms
- Any patient with lung cancer, any active cancer or a history of lung cancer or other cancer with less than 5 years of disease free survival time

4.3.1.1.9 Conduct

Table 3 and Table 4 below outline the overall design of the study and the schedule of study procedures. At the pre-screening visit (Visit 1), informed consent was obtained and current asthma medications were reviewed. Arrangements were made to adjust prohibited asthma therapy prior to Visit 2, and all patients were provided with a SABA (albuterol) which they were to use throughout the study as rescue medication. During the treatment period albuterol was to be taken as rescue (when required) medication only and no other rescue treatment was permitted. The interval between Visits 2 and 3, the 14 day run-in period was used to assess eligibility of patients and to collect baseline patient characteristics and data on PEF measurements and rescue medication use via patient diary entries.

Patients who met inclusion/exclusion criteria at the screening visit returned for the randomization, Visit 3. At Visit 3, patient eligibility was confirmed and the patient was randomized (1:1:1:1:1:1) to one of the 6 blinded treatments as follows:

1. Indacaterol (18.75 mcg) delivered via SDDPI q.d. in the morning and placebo to salmeterol via Diskus® in the morning and placebo to salmeterol via Diskus® in the evening, or
2. Indacaterol (37.5 mcg) delivered via SDDPI q.d. in the morning and placebo to salmeterol via Diskus® in the morning and placebo to salmeterol via Diskus® in the evening, or
3. Indacaterol (75 mcg) delivered via SDDPI q.d. in the morning and placebo to salmeterol via Diskus® in the morning and placebo to salmeterol via Diskus® in the evening, or

[4] Global Initiative for Chronic Obstructive Lung Disease (2001, updated 2007) Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. Available from the GOLD website http://www.goldcopd.com.

4. Indacaterol (150 mcg) delivered via SDDPI q.d. in the morning and placebo to salmeterol via Diskus® in the morning and placebo to salmeterol via Diskus® in the evening, or
5. Placebo to indacaterol delivered via SDDPI q.d. in the morning and placebo to salmeterol via Diskus® in the morning and placebo to salmeterol via Diskus® in the evening, or
6. Placebo to indacaterol delivered via SDDPI once daily in the morning and salmeterol 50 mcg via Diskus® in the morning and salmeterol 50 mcg via Diskus® in the evening.

Patients received their first dose of study medication in the clinic on the morning of Day 1 (Visit 3) and were assessed in the clinic on Days 2, 14 and 15.

Table 3 Protocol B2357 Study Design

Period	Pre-screen	Screen/ Run-in	14-Day Randomized Treatment			
Visits	1	2	3	4	5	6
Day	-30 to -14	-14	1	2	14	15
			Patients are randomized (1:1:1:1:1:1) to receive one of the following six blinded treatments: Indacaterol 18.75 µg o.d. via SDDPI and placebo to salmeterol 50 µg b.i.d. via Diskus®, or Indacaterol 37.5 µg o.d. via SDDPI and placebo to salmeterol 50 µg b.i.d. via Diskus®, or Indacaterol 75 µg o.d. via SDDPI and placebo to salmeterol 50 µg b.i.d. via Diskus®, or Indacaterol 150 µg o.d. via SDDPI and placebo to salmeterol 50 µg b.i.d. via Diskus®, or Placebo to indacaterol o.d. via SDDPI and placebo to salmeterol 50 µg b.i.d. via Diskus®, or Placebo to indacaterol via SDDPI and salmeterol 50 µg b.i.d. via Diskus®			
		Daily ICS monotherapy will be mandatory for all patients to remain stable throughout the duration of the study. Albuterol will be available for rescue use throughout the study.				

Source: Table 3-1 Study No. CQAB149B2357 Amendment #3

The sequence of measurements were to be done in the following order when multiple assessments were required: ECG, vital signs, samples for hematology/blood chemistry, and then spirometry, starting in time to ensure spirometry measurements take place as close as possible to the scheduled time point. The screen period was changed in the Amendment #1 dated January 15, 2010 to only -14 days and an open label period was removed in Amendment #2 dated February 15, 2010.

Table 4 Protocol B2357 Assessment Schedule

	Pre-Screen	Screening/ Run-in	Treatment Period			
Treatment period			Double blind treatment			
Visit	1	2	3	4	5	6
Day	-30 to -14	-14	1	2	14	15
Informed consent	XS					
Current medication review	XS					
Inclusion/exclusion Criteria	S	XS	XS			
Medical History	XS					
Demographics	XS					
Smoking History	XS					
Pregnancy Test (serum)[2]		XS				XS
Physical Examination[2]		S[#]				S[#]
Record height (Visit 2 only) and weight[2]		XS				XS
FEV_1 reversibility (β_2 agonist) and FEV_1/FVC		XS				
Contact IVRS/IVRS[2]	S	S	S			S
Randomization via the IVRS[6]			XS			
Provide rescue medication as needed	S	S	S	S	S	
Review/record β_2 agonist use[2]		XS	XS	XS	XS	XS
ECG[2,3]		XS	XS		XS	XS
Systolic & diastolic blood pressure & radial pulse rate[2,3]		XS	XS		XS	XS
Urinalysis[2,3]		XS	XS		XS	XS
Hematology/blood chemistry[2,3]		XS	XS		XS	XS
Spirometry[2,3]		XS	XS	XS	XS	XS
24-hour spirometry profiling (subset of patients)					XS	XS
AE recording[2]	XS	XS	XS	XS	XS	XS
Concomitant medication[2]	XS	XS	XS	XS	XS	XS
Device training[1]	XS	XS	XS			
PEF & Diary training		XS				
Dispense PEF/Diary		XS				
Review, collect and download PEF/Diary[2, 5]			XS	XS	XS	XS
Telephone patient 1 day prior to Visit[4]					S	
Administer study drug at visit			XS	XS	XS	
Dispense study drug[7]			X			
Collect unused study drug[2]						XS

X = assessment to be recorded on clinical data base
S = assessment to be recorded on source documentation
Source: Table 6-1 Study No. CQAB149B2357 Amendment #3

Efficacy Assessments

The scheduling of serial measurements is presented in Table 5 below. Serial spirometry was performed on Days 1 (Visit 3) and Day 14 (Visit 5), at 50 and 15 minutes predose, then 5, 15, 30 minutes, 1, 2, 4, 8 hours and 11 hours 10 min, 11 hours 45 minutes post dose, then on Day 2 (Visit 4) and Day 15 spirometry was performed at 23 hours 10 min and 23 hours 45 minutes post dose. The serial spirometry subgroup continued to have spirometry taken during 14, 20 and 22 hours post dose. Baseline FEV1 was defined as the average of the FEV1 value at 50 and 15 minutes prior to dosing on Day 1. Patients were advised to avoid caffeine, chocolate, ice-cold beverages, strenuous physical activity and alcohol intake for at least 24 hour prior to scheduled study visits. Spirometry was read by a central laboratory.

Patients were provided with a Peak Flow meter and a diary device (Visit 2) to perform morning and evening peak expiratory flow (PEF) measurements, and record clinical symptoms and rescue medication usage (the number of inhalations used of albuterol via MDI) between morning and evening study medication inhalations. Compliance with the diary during the run-in period was encouraged.

Patients were instructed to avoid rescue albuterol within 6 hours of the start of each visit unless absolutely necessary. If rescue medication was taken within 6 hours prior to spirometry at Screening, or prior to the spirometry at Days 1 and 15 (Visits 3 and 6), the visit was rescheduled for the next day. If rescue medication was taken within 6 hours prior to the post-dose spirometry measurements (relative to the previous day's dose) at Days 2 and 14 (Visits 4 and 5 the spirometry measurements were considered invalid). Daily use of rescue medication was recorded once in the morning and once in the evening using their electronic diary.

Table 5 Protocol B2357 Timed Assessments

Visit (Day)	Timepoint[1]	Urinalysis	ECG[2]	Vital Signs[3]	Hematology/ blood chemistry	Spirometry (expiratory maneuver FEV_1)[4]
Visit 3 (Day 1)	-50 min	X				X
	-25 min		XX	X	X	
	-15 min					X
	5 min					X
	15 min					X
	30 min					X
Visit (Day)	**Timepoint[1]**	**Urinalysis**	**ECG[2]**	**Vital Signs[3]**	**Hematology/ blood chemistry**	**Spirometry (expiratory maneuver FEV_1)[4]**
	1 h		XX	X	X	X
	2 h					X
	4 h					X
	8 h					X
	11 h 10 min					X
	11 h 45 min					X
Visit 4[5] (Day 2)	23 h 10 min					X
	23 h 45 min					X
Visit 5[6] (Day 14)	-50 min	X				X
	-25 min		XX	X	X	
	-15 min					X
	5 min					X
	15 min					X
	30 min					X
	1 h		XX	X	X	X
	2 h					X
	4 h					X
	8 h					X
	11 h 10 min					X
	11 h 45 min					X
24-hour spirometry subgroup (Day 15)	14 h					X
	20 h					X
	22 h					X
Visit 6[5] (Day 15)	23 h 10 min	X				X
	23 h 35 min		XX	X	X	
	23 h 45 min					X

Source: Table 6-2 Study No. CQAB149B2357 Amendment #3

Safety Assessments

ECG, vitals and laboratory evaluations were performed 25 minutes predose and 1 hour post dose on Visits 3 and 5 and then again on Visit 6 at 23 hours 35 minutes. Urinalysis was performed 3 times on Visits 3 and 5 at 50 minutes predose and Visit 6 at 23 hours 10 minutes. AE and concomitant medications were recorded during all clinic visits. Physical exam and serum pregnancy test were performed during the screening and Day 15.

4.3.1.1.10 Concomitant Treatments

Inhaled corticosteroids were required and the dose was to be stable for at least 1 month prior to screening and throughout the study. Other allowed medications included pure SSRIs, inactivated vaccine,

nasal corticosteroids and antihistamines. As mentioned above, only albuterol was to be used as a rescue medication. The following medications were prohibited: non-potassium sparing diuretics (unless administered as a fixed-dose combination with a potassium conserving drug), non-selective systemic beta-blocking agents, cardiac anti-arrhythmics Class Ia and Class III, amiodarone, any other drug with potential to significantly prolong the QT interval (i.e. astemizole, terfenadine, mizolastin, macrolides), all antidepressants (except pure SSRI's), anti-psychotics, monoamino-oxidase inhibitors, macrolides and other investigational drugs, mast cell stabilizers, leukotriene antagonists, Varenicline, live attenuated vaccine and intraarticular depot corticosteroids. Prohibited asthma-related medications included: long acting anticholinergics, short acting anticholinergics, fixed combinations of beta2 agonists and ICS, fixed combinations of SABA and short acting anticholinergics, LABAs, SABAs (other than study rescue medication), xanthines, parenteral or oral corticosteroids and intra-muscular depot corticosteroids.

4.3.1.1.11 Ethical Aspects

The trial was designed, implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki. Eligible patients were included in the study after providing written, IRB/IEC-approved informed consent or, if incapable of doing so, after such consent was provided by a legally acceptable representative of the patient.

4.3.1.1.12 Data Analysis

Efficacy Variables

Full details of the statistical analysis of this as well as the other 5 relevant trials will be reviewed by the biostatistician, Dr. Dongmei Liu. Briefly, there were four sets defined for analyses: the randomized set, the full analysis set (FAS), the per-protocol set (PPS) and the safety set. The primary analysis set for efficacy was the FAS and this included all randomized patients who received at least one dose of study drug. The safety set was used in the analysis of all safety variables. In addition, a subset of patients in the FAS with 24 hour serial spirometry was defined. The estimated treatment differences for all treatment comparisons were summarized along with the associated 95% confidence intervals (CIs) and two-sided p-values.

Reviewer comment:
For the purposes of this review, only data from the FAS are presented in the efficacy summary.

Primary endpoint- tFEV1 Day 15

The primary efficacy endpoint was "trough FEV1" (tFEV1) at Day 15 in the full analysis set (FAS), with trough being defined as the average of the 23 hour 10 minute and the 23 hour 45 minute values taken in the clinic on Day 15.

Reviewer Comment:
The trough value characterizes the residual treatment effect prior to the next dose of drug.

The primary variable with missing values imputed with last observation carried forward (LOCF) was analyzed using a mixed model for the FAS. The model included treatment as a fixed effect with the baseline FEV1 measurement (defined as the average of the FEV1 measurements taken in the clinic at 50 minutes and 15 min prior to first dose of study drug at Visit 3), FEV1 prior to inhalation and FEV1 within 30 minutes post inhalation of albuterol (components of SABA reversibility at Visit 2) all as covariates. The model also included asthma severity (mild persistent/moderate persistent/severe persistent) as a fixed effect and center as a random effect.

The sample size was based on the widths of the two-sided 95% confidence interval (CI) between any pair of treatments. A 95% CI of expected width 200 mL was considered by the sponsor an acceptable level of precision in this dose ranging study. Analysis from a previous indacaterol asthma dose ranging study QAB149A2216 suggested an appropriate standard deviation of trough FEV1 to assume was 320 mL. This led to an estimate of 79 evaluable patients per treatment group required to detect a 95% confidence

interval (two-sided) of expected width 200 mL wide, assuming a standard deviation of 320 mL. A drop out rate of 15% was assumed over 2 weeks of treatment; therefore, a sample size of 558 randomized patients or 93 per treatment group was required.

For the indacaterol and placebo treatment groups, if any of the 23 hour 10 minute and 23 hour 45 minute values contributing to the tFEV1 were collected within 6 hours of rescue medication or if actual measurement times were outside the 22-25 hour post-morning dose time window then the individual FEV1 value was set to missing. This was also done for the salmeterol treatment group. If one of the two values was missing (or set to missing) then the remaining non-missing value was taken as tFEV1. If both values were missing, or if the patient withdrew from the study, regardless of the reason for discontinuation, then tFEV1 was regarded as missing in which case the patient would not contribute to the primary analysis. Other secondary efficacy variables were summarized and analyzed using a similar model to that described for the primary efficacy variable for the FAS only and the estimated treatment difference for all treatment comparisons was displayed along with the associated 95% confidence intervals. In addition to the above, the exploratory efficacy variables were to explore the 24 hour (FEV1 and forced vital capacity (FVC)) profile of indacaterol (18.75, 37.5, 75 and 150 mcg QD), salmeterol and placebo after 14 days of treatment.

Several supportive analyses were conducted: A supportive analysis employing LOCF was performed for the PPS. In addition an analysis employing LOCF was repeated for the log transformed trough FEV1. This analysis was used to assess percentage change from baseline in tFEV1. And as well, a supportive analysis was conducted using a model-based approach to provide a quantitative characterization of the dose-response relationship after 14 days of treatment. This analysis was performed on the FAS and included trough FEV1 values obtained on Day 14 and Day 15. An Emax model was employed to characterize the dose-response relationship:

$$\text{Expected Trough FEV1} = E0 + \frac{Emax \times dose}{ED50 + dose}$$

Reviewer Comment:
The approach of LOCF for missing (or set to missing) trough at Day 15 but not missing at Day 14 was applied as a change in planned analysis pre-database lock. Changes made post-database lock include:

1. *Due to the data observed the estimate of an indacaterol dose which yielded the same estimated increase in tFEV1 at Day 15 as treatment with salmeterol 50 mcg b.i.d., and the indacaterol dose which yielded an increase in tFEV1 of 0.2 L, was not possible. Therefore these values were dropped from the analysis outputs.*
2. *Additional subgroup analyses by a) SABA reversibility (< 12%, 12 - < 15%, 15 - < 20% and ≥ 20%) and b) age group more appropriate to asthma (age < 40 years and ≥ 40 years) for tFEV1 at Day 15 were added to the analysis plan.*
3. *Responder analyses in tFEV1 at Day 15 for both FAS and PPS were added to the analysis plan. Responders were defined as subjects who had an increase from baseline in tFEV1 of a) ≥ 12 % and ≥ 0.2 L, b) ≥ 15 % and ≥ 0.2 L c) ≥ 20 % and ≥ 0.2 L.*

These changes were discussed with the Biostatistics team who felt overall, they did not change the conclusions.

Secondary endpoints- tFEV1 Day 2 and Day 14

Trough FEV1 1 day post treatment and at Day 14 (after 13 days of treatment) was analyzed in the same manner and using the same mixed model as specified for trough at 2 weeks. Missing trough FEV1 were not imputed. For Day 2 trough FEV1 was defined as the average of the 23 hour 10 minute and the 23 hour 45 minute values taken in the clinic and for Day 14 as the average of the 50 minute and 15 minute pre-dose values taken at the clinic.

Secondary endpoints- Peak FEV1 over 5mins-4hours

Peak FEV1 was defined as the maximum FEV1 during the first 4 hours post morning dosing. It was calculated at Day 1 and Day 14 for all patients in the FAS. FEV1 measurements taken within 6 hours of rescue medication use were set to missing before the peak FEV1 was calculated. If FEV1 measurements were missing at 30 minutes and following time-points up to 4 hours, then the peak FEV1 was not calculated. A similar mixed model to that specified for the primary analysis was used at each visit.

Secondary endpoints- AUC FEV1 5mins-4hours

AUC FEV1 was calculated between 5 min and 4 h post morning dose at Day 1 and Day 14 as the sum of trapezoids divided by the length of time for all patients in the FAS. FEV1 measurements taken within 6 h of rescue use were set to missing before the AUC was calculated.

Secondary endpoints- AUC for FEV1 5 mins – 11 hrs 45 mins

The AUC for FEV1 will be calculated between 5 minutes and 11 hours 45 minutes post morning dose at Visit 3 (Day 1) and Visit 5 (Day 14). Calculation of AUC and statistical analyses were done in the same way as specified for AUC(5 minutes - 4 hours).

Secondary endpoints- FEV1 and FVC at all other post-baseline time points

FEV1 and FVC at each scheduled time-point (5, 15 and 30 minutes, 1, 2, 4, 8 hours, 11 hour 10 minutes, 11 hour 45 minutes, 14, 20, 22 hours, 23 hour 10 minutes and 23 hour 45 minutes after the dose taken at Day 14 (Visit 5)) was analyzed at each post-baseline time point at each visit using the same mixed model as specified for the primary analysis. Least squares means for FEV1 were displayed by treatment group. The estimated treatment difference along with the 95% confidence interval was also displayed.

Secondary endpoints- AUC for FEV1 5 mins – 23 h 45 min and FEV1 11h 45 min – 23 h 45 min for serial spirometry subgroup

The AUC for FEV1 was calculated between 5 min and 23 hour 45 min and between 11hour 45 min and 23 hour 45 min post morning dose at Visit 5 (Day 14) for the serial spirometry subgroup. Calculation of AUC and statistical analyses was performed in the same way as specified for AUC(5 min - 4 hour).

Secondary endpoints- Daily rescue use (number of puffs) over 2 weeks

The number of puffs of rescue medication taken in the previous 12 hr was recorded in the diary in the morning and evening. The mean change from baseline in the daily number of puffs of rescue medication was analyzed using a similar mixed model to that specified for the primary analysis.

Secondary endpoints- Daytime and nighttime rescue medication use (number of puffs) over 2 weeks

The total number of puffs of rescue used over the last 12 hr was recorded in the morning (nighttime use) and in the evening (daytime use) over the two weeks study duration was divided by the total number of days with non-missing rescue data (after imputation was applied) to derive the mean daytime and nighttime number of puffs of rescue medication. Diary data recorded during the 14 day run-in period were used to calculate the baseline values. Change from baseline in mean daytime and nighttime number of puffs of rescue medication was analyzed in the same way as change from baseline in mean daily number of puffs of rescue medication.

Secondary endpoints- Percentage of days with no rescue use

A ‘day with no rescue use’ was defined as any day where the patient did not use any puffs of rescue medication. The total number of ‘days with no rescue use’ over the 2 week treatment period was divided by the total number of days in order to derive the percentage of ‘days with no rescue use’. The percentage of ‘days with no rescue use’ was summarized by treatment and analyzed using a mixed model similar to that specified for the primary analysis.

Secondary endpoints- Morning and evening PEF over 2 weeks

Morning and evening (pre-medication) PEF, as recorded in the diary, were averaged separately over the two week study duration for each patient. Diary data recorded during the 14 day run-in period was used to calculate the baseline. Change from baseline in the mean morning and evening PEF was analyzed using a similar mixed model to that specified for the primary analysis.

Safety Variables

All safety data was summarized for the Safety set. The safety assessments included monitoring and recording all AEs, including asthma exacerbations, serious adverse events (SAEs), clinical laboratory (hematology, blood chemistry and urinalysis), and regular assessments of vital signs, physical examination and ECG as well as pregnancy. Asthma exacerbations were recorded on the asthma exacerbation episode eCRF and not on the adverse event eCRF. They were included in the summaries of AEs and additionally summarized separately from other AEs.

Asthma exacerbation was defined as:

- The use of ≥ 8 inhalations per day of SABA (90 mcg albuterol via MDI) on any 2 consecutive days from screening to randomization or
- New onset or worsening of respiratory symptoms that required change or increase in asthma related treatment (i.e., use of systemic corticosteroids) or
- Asthma-related hospitalization or emergency room visit that required medical intervention or change to regular treatment

Deaths were summarized by primary system organ class (SOC) and preferred term (PT), also adjusted for exposure. Summaries by primary SOC, high level term and PT were also presented for AEs and SAEs. The summary of all treatment emergent AEs (TEAEs) and of SAEs were repeated by age group. The number and percentage of patients with any asthma exacerbations, with asthma exacerbations requiring treatment with systemic glucocorticosteroids, with asthma exacerbations resulting in an emergency room visit and with asthma exacerbations meeting SAE criteria were displayed.

Adverse Events

Adverse events starting on or after the time of the first inhalation of study drug but not later than 7 days (30 days in the case of a serious adverse event) after the last inhalation were classified as a TEAE. Any AEs that started during the study but before the time of the first inhalation of study drug were classified as a prior adverse event and not summarized in tables, but only included in listings. The same procedure was followed for AEs which start more than 7 days (30 days in the case of a SAE) after last inhalation of study drug; these were classified as post treatment adverse events. Adverse events were also analyzed using Standard MedDRA queries (version13.0), restricting to more specific “narrow” terms. The number and percentage of patients with each standardized MedDRA query (SMQ) level were presented for all TEAEs and hepatic disorders AEs. Additionally the number and percentage of patients with cardiac or cerebrovascular (CCV) SAEs were presented by MedDRA primary system organ class and preferred term.

Laboratory Data

All data were included regardless of rescue medication usage. Serum potassium and blood glucose were summarized by treatment and time-point at Days 1, 14, and 15. The baseline measurement was the measurement taken at 25 minutes pre-dose at Day 1. The maximum (blood glucose) and minimum (serum potassium) post first dosing (i.e. post baseline value) were summarized. Changes from baseline were also summarized by treatment. Summary statistics, standard descriptive statistics including changes from baseline, and shift tables of frequencies (n (%) of patients) relative to the normal ranges between baseline and post baseline time points and between baseline and worst post baseline values were performed. To evaluate potential drug-induced liver injury the numbers of patients with newly occurring or worsening elevations in liver function tests at any time post baseline were summarized. No interim analyses were performed.

Vital Signs, Weight, ECG Data

All vital signs, body weight and ECG data were included in the analysis regardless of rescue medication usage. All were also summarized with descriptive statistics. Vitals and ECG were also analyzed using a similar mixed model as for the primary analysis.

4.3.1.2 Patient Disposition and Demographics

Disposition

There were a total of 1200 screening visits, and interestingly, despite planned enrollment, only 511 patients were randomized. A total of 502 (98.2%) patients were exposed to study drug, 500 (97.8%) were included in the FAS and 483 completed the trial as planned. See Table 6. The 511 patients were randomized in a ratio of 1:1:1:1:1:1 to the following treatment groups: 85 in indacaterol 18.75 mcg; 85 in indacaterol 37.5 mcg; 84 in indacaterol 75 mcg;, 86 in indacaterol 150 mcg; 86 in Salmeterol 50 mcg bid; and 85 in placebo. Refer to Table 6 for further details. Overall, 384 patients (75.1%) were included in the PPS. The FAS, including the subset of patients who participated in the 24-hour serial spirometry subgroup, included 279 patients (54.6%). Eleven patients were excluded from the FAS: two were randomized to treatment more than once and the remaining 9 patients were randomized to treatment but discontinued before any study treatment was administered.

Table 6 Protocol B2357 Patient Disposition

	Ind 18.75 µg n (%)	Ind 37.5 µg n (%)	Ind 75 µg n (%)	Ind 150 µg n (%)	Salm n (%)	Pbo n (%)	Total n (%)
Screening visits	-	-	-	-	-	-	1200
Patients							
Randomized	85 (100.0)	85 (100.0)	84 (100.0)	86 (100.0)	86 (100.0)	85 (100.0)	511 (100.0)
Exposed	84 (98.8)	81 (95.3)	84 (100.0)	85 (98.8)	84 (97.7)	84 (98.8)	502 (98.2)
Completed	83 (97.6)	78 (91.8)	83 (98.8)	81 (94.2)	78 (90.7)	80 (94.1)	483 (94.5)
Discontinued	2 (2.4)	7 (8.2)	1 (1.2)	5 (5.8)	8 (9.3)	5 (5.9)	28 (5.5)
Primary reason for premature discontinuation							
Adverse event(s)	1 (1.2)	1 (1.2)	0 (0.0)	1 (1.2)	5 (5.8)	1 (1.2)	9 (1.8)
Administrative problems	1 (1.2)	3 (3.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	5 (1.0)
Subject withdrew consent	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	1 (1.2)	3 (3.5)	5 (1.0)
Protocol deviation	0 (0.0)	2 (2.4)	1 (1.2)	2 (2.3)	0 (0.0)	0 (0.0)	5 (1.0)
Abnormal test procedure results(s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	1 (0.2)
Unsatisfactory therapeutic effect	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.3)	0 (0.0)	0 (0.0)	2 (0.4)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	1 (0.2)

Patients who have screen failed and re-screened under a new patient number will be counted twice in the number of screening visits.

Source: Table 10-1 Study No. CQAB149B2357 Clinical Study Report

The largest percentage of patients discontinued from the salmeterol group (9.3%) and the indacaterol 37.5 mcg (8.2%) groups. The most common reason for discontinuation was AE(s) (1.8%), followed by administrative problems and withdrawal of subject's consent and protocol deviation (1.0% each). The majority of the patients who discontinued due to AE(s) were in the salmeterol treatment group (i.e. 5.8% patients). No patient discontinued from the indacaterol 75 mcg treatment group due to AEs.

Protocol Deviation

A total of 116 patients (23.2%) in the FAS had at least one major protocol deviation leading to their exclusion from the PPS. The proportion of patients with a protocol deviation leading to exclusion from the PPS ranged from 18.8% of patients in the indacaterol 37.5 mcg treatment group to 28.2% of patients in the indacaterol 150 mcg treatment group. Overall, the most common major protocol deviations leading to

exclusion from the PPS were: postbronchodilator FEV1 < 12% or < 200 mL of the pre-bronchodilator value at screening (5.0% across the 6 treatment groups), non compliance with the morning Dosing of study medication scheduled at the primary endpoint dosing visit (4.0% across the 6 treatment groups), patients not taking inhaled ICS ≥ 1 month pre-screening (3.8% across the 6 treatment groups) and < 80% of study medication doses taken prior to the primary endpoint visit (3.4%).

Four major protocol deviations, reported in 3 patients before the trial database was locked, were retracted by the investigative sites. The sites provided additional information to the sponsor after database lock in order to remove these protocol deviations. Therefore, these patients should have been included in the per protocol (PP) analysis (B2357-0567-00017 [Placebo], B2357-0567-00008 [Indacaterol 75 mcg], and B2357-0578-00014 [Indacaterol 75 mcg]).

Demographics

While the mean age of the patients with COPD in Study B2356 was 63, the demographics for those with asthma is very different as evidenced by the mean age of 41 years with a range of 18-82 years. Table 7 below summarizes key demographics across treatment groups. There were similar proportions in the 18 – 39 year age range and the 40 – 64 year age range. The majority of the patients were caucasian (78.9%); however, more than half (55.4%) were female.

Table 7 Protocol 2357 Demographic Summary (Safety Set)

		Ind 18.75 µg N = 84	Ind 37.5 µg N = 81	Ind 75 µg N = 84	Ind 150 µg N = 85	Salm N = 84	Pbo N = 84	Total N = 502
Age (years)	n	84	81	84	85	84	84	502
	Mean	42.0	41.9	40.2	41.0	40.9	40.6	41.1
	SD	14.64	14.96	14.71	15.20	14.56	14.17	14.65
	Median	43.5	42.0	38.5	42.0	41.0	41.0	41.0
	Min - Max	18 - 74	19 - 74	18 - 77	18 - 82	18 - 75	18 - 70	18 - 82
Age group – n (%)	18 – 39 years	38 (45.2)	34 (42.0)	45 (53.6)	39 (45.9)	39 (46.4)	38 (45.2)	233 (46.4)
	40 – 64 years	41 (48.8)	39 (48.1)	35 (41.7)	42 (49.4)	39 (46.4)	42 (50.0)	238 (47.4)
	65-74 years	5 (6.0)	8 (9.9)	3 (3.6)	3 (3.5)	5 (6.0)	4 (4.8)	28 (5.6)
	≥75 years	0 (0.0)	0 (0.0)	1 (1.2)	1 (1.2)	1 (1.2)	0 (0.0)	3 (0.6)
Sex – n (%)	Male	42 (50.0)	35 (43.2)	35 (41.7)	30 (35.3)	38 (45.2)	44 (52.4)	224 (44.6)
	Female	42 (50.0)	46 (56.8)	49 (58.3)	55 (64.7)	46 (54.8)	40 (47.6)	278 (55.4)
Race – n (%)	Caucasian	68 (81.0)	63 (77.8)	63 (75.0)	69 (81.2)	65 (77.4)	68 (81.0)	396 (78.9)
	Black	13 (15.5)	14 (17.3)	17 (20.2)	11 (12.9)	19 (22.6)	12 (14.3)	86 (17.1)
	Asian	2 (2.4)	0 (0.0)	1 (1.2)	3 (3.5)	0 (0.0)	1 (1.2)	7 (1.4)
	Pacific Islander	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
	Other	1 (1.2)	3 (3.7)	3 (3.6)	2 (2.4)	0 (0.0)	3 (3.6)	12 (2.4)
Weight (kg)	n	84	81	84	85	84	84	502
	Mean	81.0	84.5	83.2	80.0	82.2	83.9	82.5
	SD	17.25	17.71	18.94	17.22	18.60	18.23	17.98
	Median	81.1	82.1	83.0	79.4	83.7	82.7	82.0
	Min - Max	45.5-124.1	45.9-131.5	44.4-125.0	46.7-112.0	44.0-128.0	40.0-139.5	40.0 - 139.5
BMI (kg/m²)	n	84	81	84	85	84	84	502
	Mean	28.1	29.5	28.9	28.2	28.2	28.7	28.6
	SD	5.46	5.47	5.75	5.94	5.62	5.24	5.58
	Median	27.5	29.1	28.0	26.9	27.5	28.6	27.8
	Min - Max	17.8 - 39.8	20.1 - 46.7	16.7 - 41.6	17.5 - 42.9	18.3 - 39.5	16.6 - 39.9	16.6 - 46.7

Source: Adapted from Table 11-2 Study No. CQAB149B2357 Clinical Study Report

Baseline disease characteristics overall were similar across the treatment groups, see Table 8 below. The population represented patients with a significant history of disease burden and distribution of severity. All

patients had persistent asthma as defined in GINA guidelines (updated 2008) with 68.3% of the patients presenting with moderate persistent asthma and 24.5% presenting with mild persistent asthma. The overall mean duration of asthma was 26.8 years (range, 0.5 – 68.7 years), and most patients (308 patients, 61.4%) had asthma for more than 20 years. All 502 (100%) patients were using ICS at baseline.

Across all treatment groups, the majority of the patients had never smoked (79.7%), 17.7% were ex-smokers and the remainder were current smokers (2.6%). The number of pack years (± SD) was 3.6 (± 2.58) and ranged from 1.0 to 10.0, refer to Table 8. The screening spirometric measurements were comparable across the treatment groups. At Visit 2, the mean percentage of predicted FEV1 before SABA bronchodilation ranged from 68.9% to 71.4% across the treatment groups. The mean percentage of predicted FEV1 after SABA bronchodilation ranged from 83.7% to 86.9%. Overall, the mean FEV1/FVC ratio after bronchodilation was 71.3%. The mean percentage increase in FEV1 after SABA bronchodilator was 22.4%. Baseline values were comparable across the six treatment groups. The mean FEV1 for all patients was 2.36 L and mean FVC was 3.55 L.

Table 8 Protocol B2357 Disease Characteristics at Screening (Safety Set)

		Ind 18.75 mcg N=84	Ind 37.5 mcg N=81	Ind 75 mcg N=84	Ind 150 mcg N=85	Salm N=84	Placebo N=84
Asthma Duration (years) n (%)	<10 years	7	8	8	12	10	7
	10-20 years	20	19	22	30	24	27
	>20 years	57	54	54	43	50	50
Asthma Severity (years) n (%)	Mild persistent	19	20	22	21	21	20
	Moderate persistent	59	55	56	58	57	58
	Severe persistent	6	6	6	6	6	6
Smoking History n (%)	Never smoker	63	70	67	68	67	65
	Ex-smoker	19	8	15	17	13	17
	Current smoker	2	3	2	0	4	2

Source: Adapted from Table 11-3 Study No. CQAB1492357 Clinical Study Report

4.3.1.3 Efficacy Review

4.3.1.3.1 Primary Endpoint

The primary efficacy variable was tFEV1 at Day 15 which is presented as LS mean and estimated treatment differences in Table 9. The efficacy analysis of the FAS included 500 of the 511 randomized patients (97.8%). Two patients were excluded from the FAS as they were randomized to treatment more than once and the remaining 9 patients were randomized to a treatment group and discontinued before any study treatment was administered. The most common reason for discontinuation was AEs (1.8%), followed by administrative problems, withdrawal of patient's consent and protocol deviation (1% each). None of the treatment differences between an active treatment group and the placebo group reached the pre-specified minimal clinically important difference (MCID) of 0.20 L for asthma. The table below summarizes the treatment group comparisons for the primary efficacy endpoint, tFEV1 Day 15.

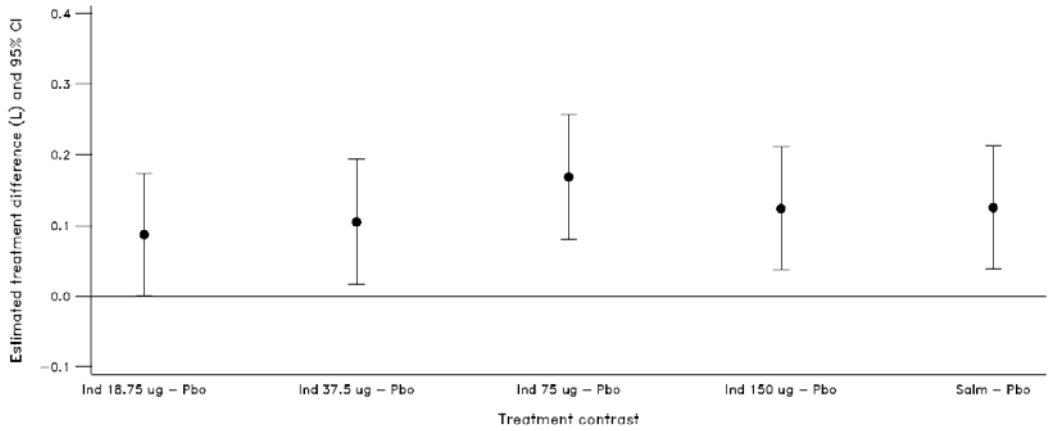
Table 9 Protocol B2357 Trough FEV1 at Day 15: treatment comparisons (FAS, imputed with LOCF)

	------- Treatment -------				------ Treatment difference ----			
Treatment	**n**	**LS Mean**	**SE**	**Comparison**	**LS Mean**	**SE**	**95% CI**	**p-value**
Full analysis set								
Ind 18.75 µg	82	2.50	0.036	Ind 18.75 µg - Pbo	0.09	0.044	(0.00, 0.17)	0.048*
Ind 37.5 µg	77	2.52	0.037	Ind 37.5 µg - Pbo	0.11	0.045	(0.02, 0.19)	0.020*
Ind 75 µg	82	2.59	0.036	Ind 75 µg - Pbo	0.17	0.045	(0.08, 0.26)	<.001*
Ind 150 µg	80	2.54	0.037	Ind 150 µg - Pbo	0.12	0.045	(0.04, 0.21)	0.006*
Salm µg	78	2.54	0.037	Salm - Pbo	0.13	0.045	(0.04, 0.21)	0.005*
Pbo	81	2.42	0.036					

Source: Adapted from Table 11-5 Study No. CQAB149B2357 Clinical Study Report

All treatment groups on this variable were superior to placebo with the greatest treatment difference in LS mean tFEV1 Day 15 was observed in the indacaterol 75 mcg treatment group (0.17L), p <0.001 as depicted in the graph below. However, the 150 mcg dose was not superior to the active comparator, Salmeterol 50 mcg bid.

Figure 1 Protocol B2357 Estimated treatment differences and associated 95% CI of tFEV1 Day 15 (FAS, imputed with LOCF)



Source: Figure 14.2-1.2 Study no CQAB149B2357 Clinical Study Report

Analysis of the subgroups reveal most patients were caucasian (n=396) versus black (n= 86), asian (n= 7), Pacific Islander (n= 1), or other (n= 12). Most had moderate asthma severity (n= 343) versus mild persistent (n= 123) or severe persistent (n=36). Most never smoked (n=65) versus ex-smoker (n=17) or current smoker (n= 2). Age and gender were generally evenly distributed. Regarding those factors that were unevenly distributed, such as race, it is difficult to comment on the generalizability of any clinically relevant treatment differences. However, some of the key subgroup analyses included the treatment differences found between the three doses of 37.5, 75 and 150 mcg indacaterol amongst mild, moderate and severe asthmatics; never smokers, ex-smokers and current smokers and SABA reversibility. See Table 10.

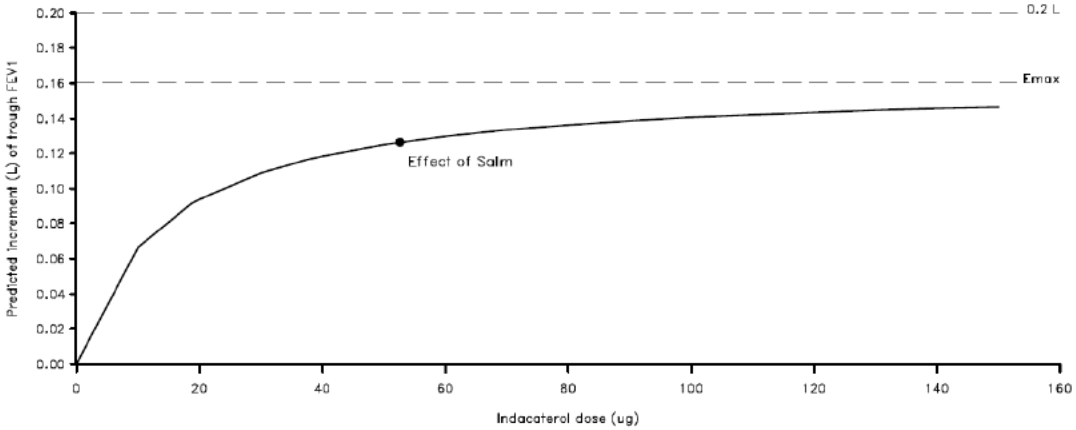
Table 10 Protocol B2357 Select subgroup analysis of trough FEV1 at Day 15 (imputed with LOCF, FAS)

		LS mean of treatment differences (n)							
Indacaterol dose		37.5 mcg (n)	p-value	75 mcg (n)	p-value	150 mcg (n)	p-value	Salmeterol (n)	p-value
Severity of asthma	Mild	0.06 (19)	0.482	0.17 (21)	0.054	0.10 (20)	0.29	0.12 (19)	0.177
	Moderate	0.13 (52)	0.022	0.17 (55)	0.002	0.13 (54)	0.018	0.11 (53)	0.042
	Severe	0.06 (6)	0.707	0.16 (6)	0.337	0.19 (6)	0.264	0.27 (6)	0.105
Smoking status	Never smoker	0.09 (67)	0.069	0.18 (65)	<0.001	0.13 (64)	0.009	0.16 (61)	0.002
	Ex-smoker	0.24 (8)	0.053	0.17 (15)	0.097	0.09 (16)	0.367	0.01 (13)	0.934
	Current smoker	0.10 (2)	0.739	-0.09 (2)	0.753	N/A	N/A	0.04 (4)	0.879
SABA reversibility	<12%	0.09 (2)	0.733	0.14 (2)	0.588	0.07 (7)	0.733	0.11 (4)	0.615
	12- <15%	0.12 (20)	0.186	0.15 (17)	0.099	0.13 (16)	0.169	0.11 (19)	0.237
	15- <20%	0.04 (19)	0.620	0.16 (24)	0.059	0.07 (24)	0.374	0.15 (17)	0.100
	> 20%	0.13 (36)	0.077	0.19 (39)	0.006	0.15 (33)	0.031	0.14 (38)	0.044

Source: Table 14.2-1.1Study no CQAB149B2357 Clinical Study Report

The findings of the Emax model were not supported by the actual data, for example, the largest treatment difference in tFEV1 Day 15 was observed with 150 mcg indacaterol at 0.15 (0.08, 0.24) followed by both indacaterol 75 mcg and salmeterol both at 0.13, refer to. However, results from the trial depict 75 mcg indacaterol exhibiting the largest treatment difference of 0.17 (0.08, 0.26) followed by salmeterol (0.13) and 150 mcg indacaterol (0.12).). Refer to Figure 2.

Figure 2 Protocol B2357 Estimated dose response curve (Emax model) for increase in tFEV1 on Day 15 (imputed LOCF, FAS)



Source: Figure 14.2-2.1 Study No. CQAB149B2357 Clinical Study Report

Three responder groups were defined post-database lock:

- subjects with an increase in tFEV1 from baseline to day 15 of ≥ 12% and 200 mL (called the 12% group)
- those with a ≥ 15% and 200 mL increase (15% group)
- those with an increase of ≥ 20% and 200 mL (20% group)

The results for the FAS for the 3 groups defined above are given in Table 11. The odds ratios generated were for comparisons of treatment drug with placebo. The highest odds of response were seen in the 75 mcg indacaterol group across the subgroups.

Table 11 Protocol B2357 Responder analysis of trough FEV1 at Day 15

	Response by increase from baseline in trough FEV1, n (%), odds ratio, p-value								
	≥ 12%, 200 mL			≥ 15%, 200 mL			≥ 20%, 200 mL		
Indacaterol dose (N)	n (%)	OR	p-value	n (%)	OR	p-value	n (%)	OR	p-value
18.75 mcg (82)	23 (28%)	1.49	0.323	15 (18.3%)	1.07	0.893	11 (13.4%)	6.25	0.002
37.5 mcg (77)	20 (26%)	1.48	0.343	15 (19.5%)	1.24	0.649	7 (9.1%)	3.79	0.033
75 mcg (82)	30 (36.6%)	2.64	0.016	22 (26.8%)	1.88	0.168	15 (18.3)	9.86	< 0.001
150 mcg (80)	24 (30%)	2.09	0.071	18 (22.5%)	1.94	0.159	12 (15%)	8.94	< 0.001
Salmeterol (78)	25 (32.1%)	2.16	0.056	16 (20.5%)	1.29	0.596	12 (15.4%)	6.77	0.002
Placebo (81)	17 (21%)	N/A	N/A	14 (17.3%)	N/A	N/A	4 (4.9%)	N/A	N/A

Source: Table 14.2-1.6 Study No. CQAB149B2357 Clinical Study Report
Odds ratio comparison with placebo
n= the number of patients with a response, N= the number of patients included in the analysis

The highest odds of response in the FAS were achieved in the indacaterol 75 mcg (odds ratio [OR] = 2.64 (12%), OR = 1.88 (15%)) and indacaterol 150 mcg (OR = 2.09 (12%), OR = 1.94 (15%)) treatment groups. In the majority of cases the treatment effects in the indacaterol 75 mcg and 150 mcg treatment groups were similar to the salmeterol group. The smallest treatment differences from placebo were

observed in the indacaterol 18.75 and 37.5 mcg treatment groups. The 20% group had few subjects meeting this definition in the placebo group and this makes the results difficult to interpret.

4.3.1.3.2 Secondary Endpoints

tFEV1 Day2 and Day 14

The dose with the largest treatment difference in tFEV1 after 1 day of treatment (Day 2) was observed with salmeterol with the LS mean of 0.21 (0.14, 0.27) and for indacaterol it was the 150 mcg dose with 0.16 L (0.09, 0.22). However, a different profile was observed after 13 days of treatment (Day 14) where the largest treatment difference was observed with the 75 mcg dose, 0.17 L (0.08, 0.26) while salmeterol and the 150 mcg indacaterol dose were 0.13 (0.05, 0.22). Again, none of the treatment differences between an active treatment group (i.e. indacaterol or salmeterol) and the placebo group achieved the pre-defined MCID set by the sponsor of 0.20 L for asthma. See Table 12 for summary.

Reviewer Comment:
The 150 mcg dose does not appear to offer benefit over the 75 mcg dose at Day 14 or 15, although a difference is shown on Day 1. Since FEV1 profiles for indacaterol show that 14 days is required for steady state, this suggests that the 150 mcg dose is already on the flat portion of the dosage curve.

Table 12 Protocol B2357 Analysis of tFEV1 (L) at Day2 and Day 14 (FAS)

		--- Treatment ----			---- Treatment difference -----			
Treatment	n	LS Mean	SE	Comparison	LS Mean	SE	95% CI	p-value
Day 2								
Ind 18.75 µg	83	2.46	0.026	Ind 18.75 µg - Pbo	0.02	0.034	(-0.05, 0.08)	0.623
Ind 37.5 µg	77	2.52	0.027	Ind 37.5 µg - Pbo	0.08	0.035	(0.01, 0.15)	0.027
Ind 75 µg	81	2.54	0.026	Ind 75 µg - Pbo	0.09	0.034	(0.03, 0.16)	0.006
Ind 150 µg	82	2.60	0.026	Ind 150 µg - Pbo	0.16	0.034	(0.09, 0.22)	<.001
Salm	79	2.65	0.027	Salm - Pbo	0.21	0.034	(0.14, 0.27)	<.001
Pbo	80	2.45	0.027					
Day 14								
Ind 18.75 µg	72	2.51	0.034	Ind 18.75 µg - Pbo	0.10	0.044	(0.02, 0.19)	0.019
Ind 37.5 µg	70	2.51	0.034	Ind 37.5 µg - Pbo	0.10	0.045	(0.02, 0.19)	0.020
Ind 75 µg	69	2.57	0.035	Ind 75 µg - Pbo	0.17	0.045	(0.08, 0.26)	<.001
Ind 150 µg	68	2.54	0.035	Ind 150 µg - Pbo	0.13	0.045	(0.05, 0.22)	0.003
Salm	67	2.54	0.035	Salm - Pbo	0.13	0.045	(0.05, 0.22)	0.003
Pbo	64	2.41	0.035					

Source: Table 11-9 Study No. CQAB149B2357 Clinical Study Report

Peak FEV1

At Day1, the greatest treatment difference between the indacaterol groups and the placebo group was observed in the indacaterol 150 mcg treatment group (0.15 L) and was smaller than the treatment difference observed between the salmeterol treatment group and the placebo group (0.23 L). At Day 14, the greatest treatment difference was observed in the 75 mcg indacaterol group. The treatment differences at Day 14 for indacaterol 75, 150 mcg and salmeterol compared to placebo were as follows: 0.23 (95% CI 0.15, 0.30), 0.20 (95% CI 0.13, 0.27) and 0.22 (95% CI 0.15, 0.30).

AUC FEV1 ***5 minutes-4 hours***

The results observed for the standardized FEV1 $AUC_{(5min-4h)}$ (Table 13) were very similar to those seen for peak FEV1. The LS mean FEV1 $AUC_{(5min-4\ h)}$ at Day 1 was significantly greater in all indacaterol treatments groups than in the placebo group. The greatest treatment difference at Day1 was observed with salmeterol treatment group 0.26 (0.22, 0.31) followed by indacaterol 150 mcg dose with 0.18 (0.14, 0.23) and indacaterol 75 mcg dose 0.15 (0.10, 0.20). Consistent with the previous patterns, on Day 14,

the greatest difference was observed with the indacaterol 75 mcg dose 0.26 (0.19, 0.33) with both salmeterol and indacaterol 150 mcg dose both at 0.24 (0.17, 0.31).

AUC FEV1 *5 minutes-11 hours 45 minutes*

The results observed for the standardized FEV1 $AUC_{(5min-11h45min)}$ were very similar to those for standardized FEV1 $AUC_{(5min-4h)}$ (Table 13). At Day 1, there was a dose response between the indacaterol treatment groups (37.5 mcg up to 150 mcg) for the LS mean FEV1 AUC(5min-11h45min). The LS mean FEV1 $AUC_{(5min-11h45min)}$ at Day1 was greater in all indacaterol treatments groups than in the placebo group. The greatest treatment difference was observed for salmeterol at 0.23 L (0.18, 0.29) followed by indacaterol 150 mcg dose 0.18 (0.13, 0.23) and indacaterol 75 mcg dose 0.14 (0.09, 0.20). Again, at Day 14, the treatment differences in LS mean FEV1 $AUC_{(5min-11h45min)}$ compared with the placebo group were greatest in the indacaterol 75 mcg dose 0.22 (0.15, 0.30) followed by salmeterol 0.21 (0.14, 0.28) and indacaterol 150 mcg 0.19 (0.11, 0.26).

Table 13 Protocol B2357 Analysis of secondary endpoints

	Treatment difference LS mean in Liters (95% CI)				
	Ind 18.75 mcg	Ind 37.5 mcg	Ind 75 mcg	Ind 150 mcg	Salmeterol
Peak FEV1 Day 1	0.04 (-0.01, 0.09)	0.04 (-0.01, 0.09)	0.12 (0.07, 0.17)	0.15 (0.10,0.20)	0.23 (0.18, 0.28)
Peak FEV1 Day 14	0.12 (0.05, 0.20)	0.14(0.06,0.21)	0.23 (0.15, 0.30)	0.20 (0.13, 0.27)	0.22(0.15, 0.30)
AUC FEV1 $_{5\ min-4hr}$ Day 1	0.07 (0.02, 0.11)	0.07 (0.02, 0.12)	0.15 (0.10, 0.20)	0.18 (0.14, 0.23)	0.26 (0.22, 0.31)
AUC FEV1 $_{5\ min-4\ hr}$ Day14	0.15 (0.08, 0.22)	0.17 (0.10, 0.24)	0.26 (0.19, 0.33)	0.24 (0.17, 0.31)	0.24 (0.17, 0.31)
AUC FEV1 $_{5\ min-12\ hr}$ Day 1	0.06 (0.01, 0.12)	0.06 (0.00, 0.11)	0.14 (0.09, 0.20)	0.18 (0.13, 0.23)	0.23 (0.18, 0.29)
AUC FEV1 $_{5\ min-12\ hr}$ Day 14	0.11 (0.04, 0.18)	0.14 (0.07, 0.21)	0.22 (0.15, 0.30)	0.19 (0.11, 0.26)	0.21 (0.14, 0.28)

Source: Adapted from Tables 11-10, 11-11, 11-12 Study No. CQAB149B2357 Clinical Study Report

FEV1 and FVC

Analysis of FEV1 at the following serial time points was conducted: 5, 15, 30 min, 1, 2, 4, 8 hours, 11 hr 10 min, 11 hr 45 min, 23 hr 10 min, 23 hr 45 min. Select values are represented in Table 14 below. Evidence of a dose response relationship was observed with increasing doses as demonstrated in the table below. At the 5 minute time-point on Day 1, the magnitude of the improvements in FEV1 compared with baseline were 0.15 L in the indacaterol 150 mcg treatment group, 0.11 L in the indacaterol 75 mcg treatment group, 0.08 L in the indacaterol 37.5 mcg treatment group and 0.06 L in the indacaterol 18.75 mcg treatment group. These results are consistent with a dose response effect at the early time points measured. As well, the treatment difference for 75 mcg indacaterol at 5 minutes represents 79% of the difference seen at 4 hours, by which time Cmax has been achieved. At 5 minutes, the 150 mcg dose represents 83% of the treatment difference seen at 4 hours. For FVC, overall, a dose response relationship was also evident and the maximum value was reached by 4 hours.

Table 14 Protocol B2357 Serial FEV1 (FAS)

	Treatment difference (L) from placebo (95% CI) at Day 1, (FAS)					
	5 min	p-value	4 hr	p-value	8 hr	p-value
Ind 18.75 mcg	0.06 (0.01, 0.11)	0.011	0.05 (0.00, 0.11)	0.071	0.07 (0.01, 0.14)	0.026
Ind 37.5 mcg	0.08 (0.03, 0.12)	0.002	0.05 (-0.11, 0.11)	0.112	0.08 (0.01, 0.14)	0.022
Ind 75 mcg	0.11 (0.06, 0.16)	< 0.001	0.14 (0.08, 0.20)	< 0.001	0.14 (0.07, 0.20)	< 0.001
Ind150 mcg	0.15 (0.10, 0.19)	< 0.001	0.18 (0.12, 0.24)	< 0.001	0.19 (0.12, 0.25)	< 0.001
Salmeterol	0.10 (0.06, 0.15)	< 0.001	0.27 (0.21, 0.33)	< 0.001	0.20 (0.13, 0.26)	< 0.001

Source: Table 14.2-5.1 Study No. CQAB149B2357 Clinical Study Report

Reviewer Comment:
In the proposed label, there is language describing the rapid onset of action at 5 minutes for indacaterol which appears to be supported by this data.

Patient Diary Data

- ***Use of rescue medication over 2 weeks***

Indacaterol at all doses showed a statistically significant benefit in the mean daily number of puffs, the mean daytime and nighttime number of puffs and the percentage of days with no rescue medication use. Refer to Table 15.

Table 15 Protocol B2357 Rescue medication use over 14 days: treatment comparisons (FAS)

		-- Treatment --			------- Treatment difference -------			
Treatment	**n**	**LSM**	**SE**	**Comparison**	**LSM**	**SE**	**95% CI**	**p-value**
Change from baseline in the mean daily number of puffs of rescue medication								
Ind 18.75 µg	84	-1.12	0.120	Ind 18.75 µg - Pbo	-0.49	0.155	(-0.79, -0.18)	0.002
Ind 37.5 µg	77	-1.33	0.124	Ind 37.5 µg - Pbo	-0.70	0.159	(-1.01, -0.38)	<.001
Ind 75 µg	82	-1.34	0.120	Ind 75 µg - Pbo	-0.71	0.156	(-1.01, -0.40)	<.001
Ind 150 µg	84	-1.23	0.119	Ind 150 µg - Pbo	-0.59	0.155	(-0.89, -0.29)	<.001
Salm	81	-1.18	0.121	Salm - Pbo	-0.55	0.156	(-0.85, -0.24)	<.001
Pbo	82	-0.64	0.121					
Change from baseline in the mean daytime number of puffs of rescue medication								
Ind 18.75 µg	83	-0.71	0.068	Ind 18.75 µg - Pbo	-0.29	0.089	(-0.46, -0.11)	0.001
Ind 37.5 µg	77	-0.81	0.070	Ind 37.5 µg - Pbo	-0.39	0.091	(-0.57, -0.21)	<.001
Ind 75 µg	82	-0.76	0.068	Ind 75 µg - Pbo	-0.34	0.089	(-0.52, -0.17)	<.001
Ind 150 µg	83	-0.76	0.068	Ind 150 µg - Pbo	-0.33	0.089	(-0.51, -0.16)	<.001
Salm	79	-0.68	0.069	Salm - Pbo	-0.26	0.089	(-0.43, -0.08)	0.004
Pbo	81	-0.42	0.069					
Change from baseline in the mean nighttime number of puffs of rescue medication								
Ind 18.75 µg	83	-0.43	0.060	Ind 18.75 µg - Pbo	-0.20	0.078	(-0.35, -0.05)	0.011
Ind 37.5 µg	77	-0.54	0.062	Ind 37.5 µg - Pbo	-0.31	0.080	(-0.47, -0.15)	<.001
Ind 75 µg	82	-0.59	0.060	Ind 75 µg - Pbo	-0.36	0.079	(-0.52, -0.21)	<.001
Ind 150 µg	84	-0.48	0.060	Ind 150 µg - Pbo	-0.25	0.078	(-0.40, -0.10)	0.001
Salm	80	-0.53	0.061	Salm - Pbo	-0.30	0.079	(-0.45, -0.14)	<.001
Pbo	82	-0.23	0.061					
Percentage of "days with no rescue use"								
Ind 18.75 µg	82	68.60	3.302	Ind 18.75 µg - Pbo	14.70	4.149	(6.5, 22.8)	<.001
Ind 37.5 µg	76	73.81	3.367	Ind 37.5 µg - Pbo	19.90	4.252	(11.5, 28.2)	<.001
Ind 75 µg	82	69.39	3.269	Ind 75 µg - Pbo	15.50	4.177	(7.3, 23.7)	<.001
Ind 150 µg	83	69.44	3.254	Ind 150 µg - Pbo	15.50	4.139	(7.4, 23.6)	<.001
Salm	78	70.04	3.327	Salm - Pbo	16.10	4.183	(7.9, 24.3)	<.001
Pbo	81	53.93	3.299					

Source: Table 11-13 Study No. CQAB149B2357 Clinical Study Report

- ***Asthma symptoms***

The percentage of "days with no daytime asthma symptoms" during the 14 days of treatment was reduced in all treatment groups when compared to baseline. The reduction was numerically greater in the active treatment groups than in the placebo group, but the difference was not statistically significant. The mean change from baseline in percentage of days was -24.8 in the indacaterol 18.75 mcg treatment group, -26.7 in the indacaterol 37.5 mcg treatment group, -22.3 in the indacaterol 75 mcg treatment group, -23.3 in the indacaterol 150 mcg treatment group, -23.0 in the salmeterol treatment group and -13.5 in the placebo group. Similar results were observed for "days with no nighttime asthma symptoms" with the following values: -15.4, -16.6, -13.0, -12.7, -15.9 and -8.2 respectively.

- ***Peak expiratory flow (PEF) over 2 weeks***

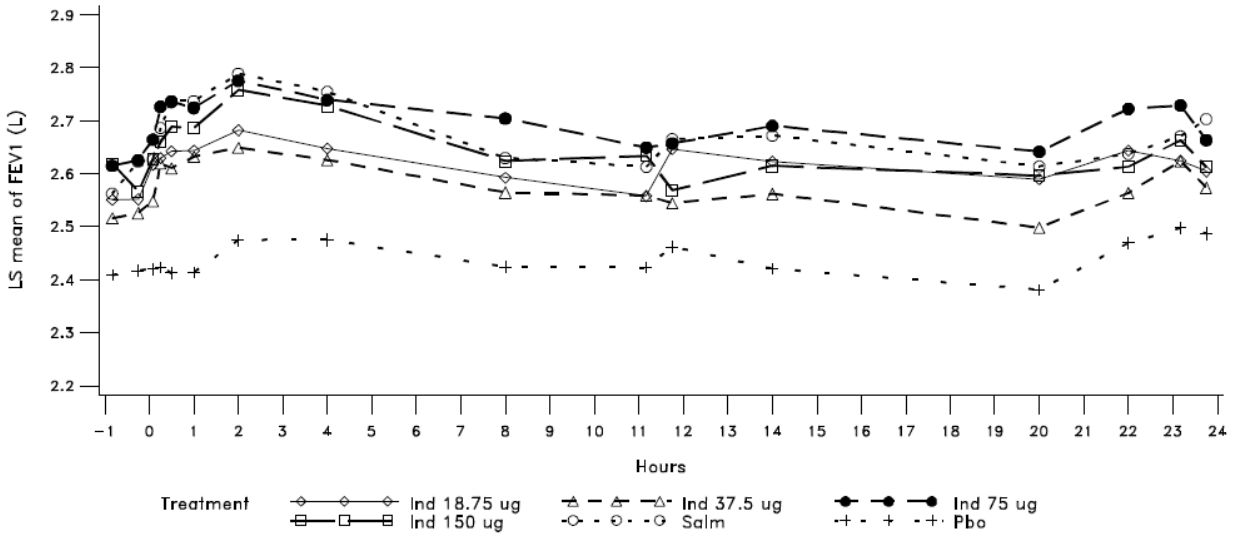
In all indacaterol and salmeterol treatment groups, an increase from baseline in morning and evening PEF was observed compared with the placebo group. All active treatment groups were statistically significantly greater than placebo.

Exploratory efficacy results

- ***FEV1 and FVC by time-point analyses***

The protocol included exploratory objectives which were to evaluate the 24-hour (FEV1 and forced vital capacity [FVC]) profile of indacaterol (18.75, 37.5, 75, and 150 mcg q.d.), salmeterol and placebo after 14 days of treatment. At each Day 14/15 time-point of the 24 hour FEV1 profile the LS mean FEV1 was greater in all active treatment groups than in the placebo group, see Figure 3. At the majority of time-points, the LS mean FEV1 was similar in the indacaterol 75, 150 mcg and salmeterol treatments groups and smaller in the indacaterol 18.75 mcg and 37.5 mcg treatment groups.

Figure 3 Protocol B2357 24 hour profile of least squares means of FEV1 (L) after 14 days treatment (FAS)



Source: Figure 14.2-3.1 Study No. CQAB149B2357 Clinical Study Report

- ***Standardized (with respect to time) AUC FEV1*** $_{5\ min\text{-}23\ hr\ 45\ min}$***; AUC FEV1*** $_{11\ hr\ 45\ min\text{-}\ 23\ hr\ 45\ min}$

At Day 14/15 the LS mean $AUC_{(5min–23hr\ 45min)}$ FEV1 and FEV1 $AUC_{(11hr\ 45min\text{-}23hr\ 45min)}$ were greater in all active treatment groups (i.e. indacaterol and salmeterol) than in the placebo group. For both spirometry assessments, the FEV1 $AUC_{(5min\text{-}23hr\ 45\ min)}$ and FEV1 $AUC_{(11hr\ 45\ min\text{-}23\ hr\ 45\ min)}$, the indacaterol 75 mcg treatment group had the greatest magnitude of treatment difference (0.27 L for both). The smallest treatment differences compared with the placebo group were observed in the indacaterol 18.75 and 37.5 mcg treatment groups (0.19 L and 0.15 L, respectively).

4.3.1.4 Safety Results

4.3.1.4.1 Extent of exposure

All treatment groups had similar exposure to indacaterol with a median of 15 days and a range of 1 to 28 days. Compliance with the Concept1 SDDPI device, assessed as the percentage of doses taken over the whole treatment period, was consistently high across all treatment groups (mean 98.5 - 102.3%).

4.3.1.4.2 Concomitant medication

Concomitant medications and significant non-drug therapies (asthma-related and non asthma-related) were taken by more than 70% of patients in any treatment group in the safety set. All patients in the salmeterol and placebo groups and most patients (98.8% to 100%) in the indacaterol treatment groups were taking asthma-related concomitant therapy, mostly as inhaled formulations. The most frequently used medications were the corticosteroids. Non asthma-related concomitant medications and significant non-drug therapies were used by 73.8% to 83.5% of all patients in the indacaterol groups and by 78.6% and 81.0% in the salmeterol and placebo group, respectively. Most frequent was the use of ibuprofen, loratadine, mometasone furoate, paracetamol and multivitamins.

4.3.1.4.3 Adverse events

Details regarding AEs will be included in the ISS, however a brief summary will be mentioned here. The overall incidence of AEs was higher in the indacaterol 75 mcg treatment group (26.2%), compared with the indacaterol 37.5 mcg treatment group (22.2%) and the salmeterol treatment group (21.4%). Respiratory, thoracic and mediastinal disorders were the most commonly affected system organ classes (SOC) followed by nervous system disorders and infections and infestations. The most frequently reported AE in the total safety set was headache, which occurred at similar frequencies in all treatment groups, but was highest in the indacaterol 75 mcg treatment group (6%). Cough was the second most frequent event and was observed in 9.5% of the patients in indacaterol 75 mcg treatment group, 4.7% in the indacaterol 150 mcg treatment group, and 2.4% in the indacaterol 18.75 mcg treatment group. See Table 16 below for a summary.

Table 16 Protocol B2357 Most frequent AEs, including exacerbations, (as least 2% in any treatment group) by preferred term, n (%) of patients (Safety set)

	Ind 18.75 µg N = 84 n (%)	Ind 37.5 µg N = 81 n (%)	Ind 75 µg N = 84 n (%)	Ind 150 µg N = 85 n (%)	Salm N = 84 n (%)	Pbo N = 84 n (%)
Patients with any AE(s)	10 (11.9)	18 (22.2)	22 (26.2)	16 (18.8)	18 (21.4)	14 (16.7)
Preferred term						
Cough	2 (2.4)	0 (0.0)	8 (9.5)	4 (4.7)	1 (1.2)	0 (0.0)
Headache	2 (2.4)	2 (2.5)	5 (6.0)	3 (3.5)	4 (4.8)	4 (4.8)
Asthma	1 (1.2)	2 (2.5)	0 (0.0)	1 (1.2)	3 (3.6)	4 (4.8)
Blood triglycerides increased	0 (0.0)	2 (2.5)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.4)	0 (0.0)
Oropharyngeal pain	0 (0.0)	3 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Preferred terms are sorted in descending order of frequency in the Ind 18.75 µg treatment group. Only treatment emergent adverse events are summarized. Adverse events starting on or after the time of the first inhalation of study drug but not later than 7 days (30 days in the case of a serious adverse event) after the last inhalation were classified as a treatment emergent.
Source: Table 12-3 Study No. CQAB149B2357 Clinical Study Report

Reviewer comment:
Cough appears to be dose-related in the indacaterol groups, occurring much more frequently in the 75 and 150 mcg dose groups. Given the large difference from placebo and salmeterol, it is likely that post-inhalational cough is a drug-related side effect. The sponsor specifically evaluates the incidence of cough as part of the Integrated Summary of Safety.

Asthma exacerbations
In total, 10 patients had asthma exacerbations: one patient (1.2%) in the indacaterol 18.75 mcg treatment group; 2 patients (2.5%) in the indacaterol 37.5 mcg treatment group; 3 patients (3.6%) in the salmeterol treatment group and 4 patients (4.8%) in the placebo group]. Six of the 10 patients with asthma exacerbation required treatment; all with systemic glucocorticosteroids. Three patients had to permanently discontinue study drug due to the exacerbation; 2 patients in the salmeterol treatment group and the one patient in the indacaterol 18.75 mcg treatment group.

Deaths/SAEs
There were no deaths and one SAE (substance abuse) which led to premature discontinuation. However, a total of 8 patients discontinued prematurely due to an AE: 3 among the indacaterol treatment groups (1 patient each in indacaterol 18.75 mcg, 37.5 mcg and 150 mcg treatment group); 4 patients in the salmeterol treatment group and 1 patient in the placebo group.

Adverse events leading to discontinuation
A total of 8 patients discontinued prematurely due to an AE, 3 patients among the indacaterol treatment groups (1 patient or 1.2% each in indacaterol 18.75 mcg, 37.5 mcg and 150 mcg, respectively), 4 patients

(4.8%) in the salmeterol treatment group and one patient in the placebo group. The AEs leading to discontinuation were asthma exacerbation (indacaterol 18.75 mcg treatment group); ventricular extrasystoles (indacaterol 37.5 mcg treatment group); bronchitis, and sinusitis (salmeterol); headache, nausea and vomiting (salmeterol); asthma exacerbation (salmeterol), flank pain (salmeterol) and sinusitis (placebo). Of note, in the cardiac disorders SOC, there was 1 ventricular extrasystole.

4.3.1.4.4 Laboratory findings

In the hematology assessment, less than 5% had an abnormal value. The most frequently reported notable value was low hematocrit in the indacaterol 75 mcg treatment group (4 patients, 4.8%) and in the salmeterol treatment group (3 patients, 3.6%).Focus will be on glucose, potassium and liver function assessments within the clinical chemistry assessment. No clinically significant differences were seen in the LS mean serum potassium and mean blood glucose levels between all treatment groups. No patients had a clinically notable low potassium (< 3mmol/L). One patient in salmeterol treatment group had a clinically high (> 6 mmol/L) value for potassium. Notably low (< 2.78 mmol/L) or high (>9.99 mmol/L) glucose levels (non-fasting) were recorded in one patient in the indacaterol 18.75 mcg treatment group, 2 patients in the indacaterol 37.5 mcg treatment group, 1 patient in the indacaterol 75 mcg treatment group, 3 patients in the salmeterol treatment group and for 4 patients in the placebo group. Elevations of liver function tests were reported in 4 patients; one in the indacaterol 75 mcg treatment group, one in the indacaterol 150 mcg treatment group and two in the placebo group.

4.3.1.4.5 ECG findings

There were no clinically significant abnormal overall ECG interpretations. The incidence of a maximum increase from baseline of 30 ms to 60 ms in Fridericia's QTc was higher in the indacaterol 18.75 mcg treatment group (3 cases) and in the placebo group (2 cases). No patient was recorded with an increase in Fridericia's QTc of > 60ms. Overall, the most frequently recorded ECG abnormalities were changes in rhythm. These occurred more frequently in the salmeterol treatment group (16%) and occurred at a similar frequency in all other treatment groups except for the indacaterol 37.5 mcg treatment group and the indacaterol 150 mcg treatment groups in which the frequency was lower (2.7% and 5.1%, respectively).

4.3.1.4.6 Physical examination (this should be mostly BP and pulse)

Focus was limited to BP and pulse for the physical examination assessment. There were no clinically relevant differences between treatment groups with respect to LS mean pulse rate or post baseline systolic or diastolic blood pressure. A dose relationship was observed for those with a post-baseline pulse rate above 90 bpm: 2 (2.4%) patients in the indacaterol 18.75 mcg treatment group: 1 (1.2%) patient in the indacaterol 37.5 mcg treatment group; 4 (4.8%) patients in the indacaterol 75 mcg treatment group, 9 (10.6%) patients in the indacaterol 150 mcg treatment group, 8 (9.5%) patients in the salmeterol treatment group and 7 (8.3%) patients in the placebo group. There was not a dose response relationship with SBP > 140 mmHg: 9 (10.7%) in the 18.75mcg treatment group; 11 (13.6%) in 37.5 mcg; 10 (11.9%) in 75 mcg; 8 (9.4%) in 150 mcg; 8 (9.5%) in salmeterol and 16 (19%) in the placebo group. For DBP> 90 mmHg 6 (7.1%) in the 18.75 mcg treatment group; 9 (11.1%) in 37.5 mcg; 11 (13.1%) in 75 mcg; 7 (8.2%) in 150 mcg; 8 (9.5%) in salmeterol and 10 (11.9%) in the placebo group.

4.3.1.5 Summary of Study

This was a two week, multicenter, randomized, placebo-controlled trial comparing different doses of indacaterol, 18.75 mcg, 37.5 mcg, 75 mcg and 150 mcg, to placebo in adults with persistent asthma. In addition, salmeterol 50 mcg bid was used as an active comparator. There was a dose response in the primary endpoint of tFEV1 at Day 15. The sponsor's predefined minimum clinically important difference (MCID) of 200 ml was not met for any dose of indacaterol. Although this difference is used as a marker of bronchodilator response, an accepted value has not been established. For the primary endpoint, tFEV1 Day 15, the 75 mcg indacaterol dose provided the largest treatment difference of 0.17 L. The key secondary endpoints of tFEV1 at Day 2 and Day 14 demonstrated a larger treatment difference amongst the indacaterol doses compared to placebo. On Day 2, the 150 mcg indacaterol dose group showed the

largest difference (0.16 L) although salmeterol was superior with a treatment difference of 0.21 L. However, by Day 14 the 75 mcg dose exhibited the largest treatment difference of 0.17 L. There was a dose response for other secondary endpoints such as peak FEV1 and AUC. Furthermore, the secondary endpoints such as peak FEV1 Day1 and Day 14, AUC FEV1 (5min-4 hr) Day 1 and Day 14, and AUC FEV1 (5 min- 12 hr) Day 1 and Day 14 all exhibited the same pattern with the largest treatment seen early with the 150 mcg indacaterol dose and any superiority lost by Day 14 to the 75 mcg dose.

The most frequent reported AEs were headache and cough. Six of 10 patients with an asthma exacerbation required treatment, all with systemic glucocorticosteroids. Three patients permanently discontinued study drug due to the exacerbation, only one of whom was in an indacaterol group (18.75 mcg). There were no deaths and only one SAE reported (substance abuse) which led to premature discontinuation. There were no clinically meaningful effects of treatment at any of the doses of indacaterol studied on pulse, blood pressure and QTc interval, and no unexpected effects on clinical laboratory parameters were observed.

4.3.2 DOSE FINDING TRIAL IN PATIENTS WITH COPD-B2356

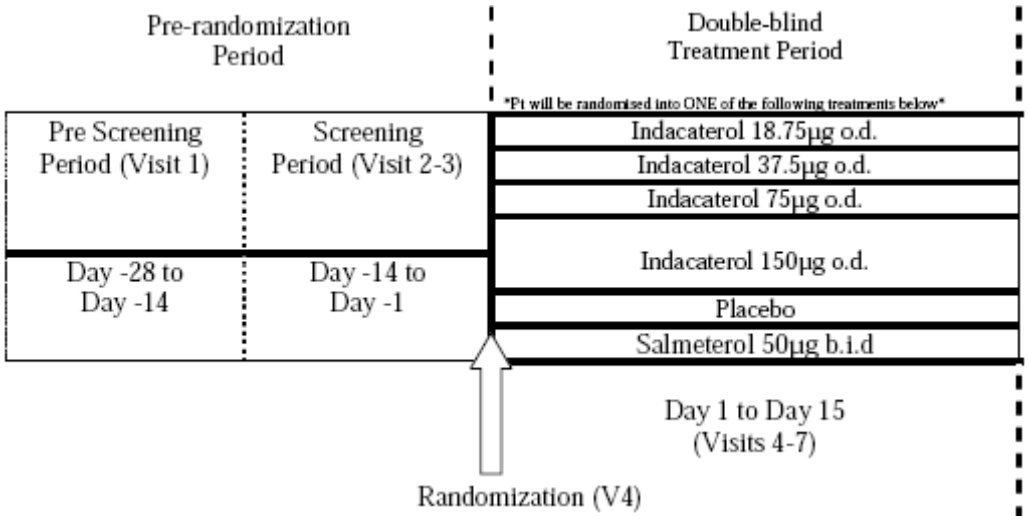
A Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Parallel-Group Study to Assess the Efficacy and Safety of Different Doses of Indacaterol in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD), Using Salmeterol as an Active Control.

4.3.2.1 Trial Description

4.3.2.1.1 Design

Like the dose ranging Study B2357 in asthmatics, this Phase III multicenter trial was designed as a randomized, double-blind, double-dummy, placebo-controlled, parallel group trial. The study design is represented in Figure 4 below and was very similar to the dose finding study carried out in asthmatics however, ICS therapy was not mandatory for all COPD patients as it was for asthma patients. In addition, PK parameters were collected at the end of the 14-day dosing period.

Figure 4 Protocol B2356 Study Design



Source: Figure 3-1, Appendix 16.1.1, Clinical Study Report QAB149B2356

Protocol Amendments (Appendix 16.1,1 pg. 1845-6, CSR QAB149B2356):

- Amendment #1 dated February 16, 2010 (prior to study start):
  1). Additional spirometry time points were added on Day 14 through Day 15 (at 14 hr, 20 hr and 22 hr post morning dose of Day 14) in the study in order to further characterize the 24-hour bronchodilatory profile of indacaterol at the end of the randomized treatment period. All patients were offered the opportunity to participate in the 24 hour spirometry
  2). The open label single dose of indacaterol 300 mcg at Visit 7 was removed
  3). Visit 8 (Day16) was removed from the study.
- Amendment #2 dated May 17, 2010:
  1). Repeatability criteria at Visit 2 were clarified.
  2). Exclusion criteria were amended to give patient s who were eligible to enroll in the study at Visit 2, but had a COPD exacerbation between Visit 2 and Visit 4 (randomization), the ability to re-screen and enroll in the study.
  3) Patients who had a respiratory tract infection between Visits 2 and 4 could also re-enroll at a later time of at least 6 weeks after start of infection.

4.3.2.1.2 Duration

The treatment period was 2 weeks. A 2 week run-in time preceded the active treatment period.

4.3.2.1.3 Population

Males and females aged 40 years and older, with a clinical diagnosis of moderate to severe COPD (as classified by the Global Initiative for Chronic Obstructive Lung Disease; GOLD guidelines 2008), and a smoking history of at least 10 pack years were enrolled. The randomization was stratified by the patients' current smoking status (current/ex-smoker) and current ICS use.

4.3.2.1.4 Study Sites

The study was conducted at 67 centers in the United States.

4.3.2.1.5 Investigational and Reference Therapy

The following drugs were used:

- Indacaterol 18.75 mcg blister batch # VMLK/2009-3018, DP batch # X223 0909
- Indacaterol 37.5 mcg blister batch # VMLK/2009-3019, DP batch # X224 0909
- Indacaterol 75 mcg blister batch # VMLK/2009-2700, DP batch # X173GF
- Indacaterol 150 mcg blister batch # VMLK/2009-2826, DP batch # X172GF
- Placebo to indacaterol blister batch # VMLK/2009-1409, DP batch # X039BE
- Salmeterol 50 mcg Diskus DP batch # R438216, R438396
- Placebo to salmeterol DP batch # X278 0807, X165 0608

All indacaterol dry powder capsules and placebo to indacaterol were inhaled through the Concept1 SDDPI device. Salmeterol (50 mcg b.i.d.) and placebo to salmeterol were inhaled through a single Diskus® device.

4.3.2.1.6 Objectives

The primary objective was to evaluate the dose response relationship among four doses of indacaterol (18.75, 37.5, 75, and 150 mcg q.d.), placebo and salmeterol 50 mcg b.i.d. as measured by the 24 h post-dose Forced Expiratory Volume in 1 second (FEV1) (trough) after 14 days of treatment in patients with moderate to severe COPD.

The secondary objective was to evaluate the dose response relationship in the following lung function assessments:

- tFEV1 after 1 day of treatment
- Peak FEV1 on Day 1
- AUC for FEV1 5min-11h 45min on Day 1 and Day 14
- AUC for FEV1 5min-4 h on Day 1 and Day 14
- To evaluate day and night time rescue medication usage for all doses of indacaterol as compared to placebo and salmeterol 50 mcg b.i.d. over 14 days
- To evaluate the pharmacokinetic (PK) profiles of indacaterol in a subset of patients after 14 days of treatment

The safety objective was: to evaluate safety (AEs, ECGs, laboratory tests, vital signs) and tolerability of indacaterol over the course of treatment.

The exploratory objective of this study was: to explore the 24 hour (FEV1 and FVC) profile of indacaterol (18.75, 37.5, 75 and 150 mcg q.d.), salmeterol and placebo after 14 days of treatment.

4.3.2.1.7 Inclusion Criteria

- Male and female adults aged ≥ 40 years
- Moderate to severe diagnosis of COPD as per GOLD guidelines, 2008
- Patients must have a post-bronchodilator FEV1 <80% and ≥ 30% of predicted
- Post bronchodilator FEV1/FVC <70%.
- Smoking history of at least 10 pack years

4.3.2.1.8 Exclusion Criteria

Key exclusion criteria were:

- Pregnancy or lactating women
- Women of child-bearing potential unless using two birth control methods
- History of COPD exacerbation requiring glucocorticoid treatment, antibiotics, hospitalization or a respiratory tract infection in the 6 weeks prior to screening
- Concomitant pulmonary disease, pulmonary tuberculosis (unless confirmed by chest x-ray to be no longer active), clinically significant bronchiectasis or history of lung cancer
- O2 requirement for chronic hypoxia of >15 hours per day (excluding acute COPD exacerbation)
- History of long QT syndrome
- Patients with a history of asthma indicated by (but not limited to): onset of respiratory symptoms (such as cough, wheezing, shortness of breath) suggestive of asthma prior to 40 years of age or a history of a diagnosis of asthma
- Patients involved in the active phase of a supervised pulmonary rehabilitation program or any patients planning to undertake a supervised pulmonary rehabilitation program during the study
- Patients with a known diagnosis of Alpha-1 Antitrypsin deficiency

If there was an exacerbation during the run-in period the patient would be discontinued however, he could be re-screened at a later time.

4.3.2.1.9 Conduct

At the pre-screening visit (Visit 1), informed consent was obtained, current COPD medications were reviewed and, if necessary, arrangements were made to adjust prohibited COPD therapy to allowable COPD therapy. Patients using LABAs were switched to the “as needed” use of the SABA, albuterol via MDI, at least 48 hours prior to Visit 2. The steroid component of any fixed combination therapy (ICS and β2-agonist) were replaced with the equivalent ICS monotherapy plus the “as needed” use of a SABA, albuterol via MDI, at least 48 hours prior to Visit 2. A baseline spirometry assessment was to be performed after a washout period of at least 6 hours for SABAs, 48 hours for LABAs and 48 hours for long-acting anticholinergics. However, longer washout periods were acceptable depending on exclusion criteria.

At Visit 2, spirometry measurements were taken to assess eligibility. At Visit 2 FEV1 and FVC were assessed prior to and 10- 15 minutes after inhalation of 4 x 90 mcg puffs of albuterol via MDI and FEV1 and FVC within 10-15 min after inhalation of 4 x 90 mcg albuterol via MDI. These FEV1 assessments were the components of ß2-agonist FEV1 reversibility.

At Visit 3 the patient was to return in the morning to assess FEV1 and FVC prior to inhalation of 2 x 21 mcg ipratropium bromide (equivalent to 2 x 17 mcg ipratropium bromide) and FEV1 and FVC 1 hour post inhalation of the specified anticholinergic medication. The FEV1 assessments were the components of the anti-cholinergic FEV1 reversibility. In order to avoid the suggestion of bias in efficacy analysis, the statistical models were to be adjusted with respect to the reversibilities of both anti-cholinergic and beta agonist mechanisms of action so both reversibilities were collected for this purpose and reported. Reversibility was calculated as:

$$100 \times \frac{FEV_1\text{ (post bronchodilator)} - FEV_1\text{ (baseline)}}{FEV_1\text{ (baseline)}}$$

At Visit 4, eligibility was confirmed and patients were randomized to treatment. The period between Visits 4 to 6 was a 14 day treatment period. Patients were randomized 1:1:1:1:1:1 to one of the six blinded treatments as follows:

1. Indacaterol (18.75 mcg) delivered via SDDPI q.d. in the morning and placebo to salmeterol via Diskus® in the morning and placebo to salmeterol via Diskus® in the evening, or
2. Indacaterol (37.5 mcg) delivered via SDDPI q.d. in the morning and placebo to salmeterol via Diskus® in the morning and placebo to salmeterol via Diskus® in the evening, or
3. Indacaterol (75 mcg) delivered via SDDPI q.d. in the morning and placebo to salmeterol via Diskus® in the morning and placebo to salmeterol via Diskus® in the evening, or
4. Indacaterol (150 mcg) delivered via SDDPI q.d. in the morning and placebo to salmeterol via Diskus® in the morning and placebo to salmeterol via Diskus® in the evening, or
5. Placebo to indacaterol delivered via SDDPI q.d. in the morning and placebo to salmeterol via Diskus® in the morning and placebo to salmeterol via Diskus® in the evening, or
6. Placebo to indacaterol delivered via SDDPI once daily in the morning and salmeterol 50 mcg via Diskus® in the morning and salmeterol 50 mcg via Diskus® in the evening

Patients were also randomized to inhale their morning dose of study medication in one of two possible sequences if possible:

- Indacaterol/placebo SDDPI, followed by salmeterol/placebo Diskus® inhaler
- Salmeterol/placebo Diskus® inhaler, followed by indacaterol/placebo SDDPI

The dosing scheme is depicted in Table 17 below.

Table 17 Protocol B2356 Study treatments (dosing scheme)

Treatment	Morning		Evening
	Concept1 SDDPI	Salmeterol proprietary inhaler (Diskus®)	Salmeterol proprietary inhaler (Diskus®)
Group 1	Indacaterol 18.75 µg	Placebo	Placebo
Group 2	Indacaterol 37.5 µg	Placebo	Placebo
Group 3	Indacaterol 75 µg	Placebo	Placebo
Group 4	Indacaterol 150 µg	Placebo	Placebo
Group 5	Placebo	Placebo	Placebo
Group 6	Placebo	Salmeterol 50 µg	Salmeterol 50 µg

Source: Table 9-3 Study CQAB149B2356 Clinical Study Report

Efficacy Assessments

The scheduling of serial measurements were similar to that seen in Study B2357 with the addition of an assessment for FEV1 anticholinergic reversibility at screening and PK profile blood sampling at Days 14 and 15. See Table 18 below for details.

Table 18 Protocol B2356 Timed Assessments

Visit (Day)	Timepoint[1]	Urinalysis	ECG[2]	Vital Signs[3]	Hematology/ blood chemistry	PK profile blood sample[6]	Spirometry (expiratory maneuver FEV_1)[4]
Visit 4 (Day 1)	-50 min	X					X
	-25 min		XX	X	X		
	-15 min						X
	5 min						X
	15 min						X
	30 min						X
	1 h		XX	X	X		X
	2 h						X
	4 h						X
	8 h						X
	11 h 10 min						X
	11 h 45 min						X
Visit 5[5] (Day 2)	23 h 10 min						X
	23 h 45 min						X
Visit 6[7,8] (Day 14)	-50 min	X					X
	-25 min		XX	X	X	X	
	-15 min						X
	5 min						X
	10 min					X	
	15 min						X
	20 min					X	
	30 min						X
	1 h		XX	X	X	X	X
	2 h					X	X
	4 h					X	X
	8 h					X	X
	11 h 10 min						X
	11 h 45 min					X	X
24 h spirometry subgroup (Day 15)	14 h						X
	20h						X
	22h						X
Visit 7 (Day 15)	23 h 10 min[5]	X					X
	23 h 35 min		XX	X	X		
	23h 45 min[5]					X	X

Source: Table 9-5 Study No. CQAB2356 Clinical Study Report

Spirometry measurements:

As shown in Table 18 serial spirometry was performed on Day1 (Visit 4) and Day 14 (Visit 6) at 50 and 15 minutes predose, then 5, 15, 30 minutes, 1, 2, 4, 8 hours and 11 hours 10 minutes, 11 hours 45 minutes post dose. On Day 2 (Visit 5) and Day 15 spirometry was performed at 23 hours 10 min and 23 hours 45 minutes post dose. The 24 hour spirometry subgroup continued to have spirometry taken during 14, 20 and 22 hours post dose. These assessments were all similar to the schedule in the B2357 asthma dose finding trial. As in the prior study, patients were advised to avoid caffeine, chocolate, ice-cold beverages, strenuous physical activity and alcohol intake for at least 24 hours prior to scheduled study visits. All spirometry was read at a central laboratory.

Number of inhalations of albuterol rescue medication
No rescue medication was permitted other than study-provided albuterol. Patients were instructed to abstain from taking rescue albuterol via MDI within 6 hours of the start of each visit unless absolutely necessary. If rescue medication was taken within 6 hours prior to spirometry at Screening, or the pre-dose spirometry at Day 1 or prior to spirometry at Day 15 (Visits 2, 4 and 7 respectively), the visit was to be rescheduled to the next possible day. The investigator reminded the patients to continue to take their study medication as prescribed. If rescue medication was taken within 6 hours prior to the post-dose spirometry measurements (relative to the previous day's dose) at Days 2 and 14 (Visits 5 and 6), the patient still attended the visit; however, the spirometry measurements taken within the 6 hours of the rescue medication dose were considered invalid for all spirometry analyses. In the event that a patient used a dose of rescue medication after taking study medication at a visit then the visit continued as planned. The time the rescue medication was taken was recorded in the eCRF. All daily usage of rescue medication was recorded once in the morning and once in the evening by the patient using their electronic diary.

COPD Exacerbations
COPD exacerbations were defined as:
worsening of 2 or more of the following major symptoms for at least 2 consecutive days:

- Dyspnea
- Sputum volume
- Sputum purulence

or
worsening of any 1 major symptom together with any 1 of the following minor symptoms for at least 2 consecutive days:

- sore throat
- colds (nasal discharge and/or nasal congestion)
- fever without other cause
- increased cough
- increased wheeze

and
requiring treatment with systemic (oral or parenteral) corticosteroids and/or antibiotic

COPD exacerbations were considered of moderate severity if treatment with systemic corticosteroids and/or antibiotic was required and severe if hospitalization was required. An ER visit of longer than 24 hours was considered a hospitalization. An increase in ICS dose was not counted as an exacerbation. In the event of a COPD exacerbation matching the above definition occurring at any time after signing of informed consent, patients were to be treated for the exacerbation as deemed necessary by the investigator. All COPD exacerbations, regardless of treatment, was to only be recorded on the COPD exacerbation episode eCRF and not on the AE eCRF.

Safety Assessments
ECG, vitals and laboratory evaluations were performed 25 minutes predose and 1 hour post dose on Visits 4 and 6 and then again on Visit 7 at 23 hours 35 minutes. Urinalysis was performed 3 times on Visits 4 and 6 at 50 minutes predose and Visit 7 at 23 hours 10 minutes.

PK Assessments
All blood samples (4 mL) will be collected at each of the following time points into polypropylene tubes spray coated with silica (for serum preparation): Day 14/15: 25 minutes predose and 10, 20 minutes, 1, 2, 4, 8 hours and 11 hour 45 minutes and 23 hour 45 minutes post dose.

4.3.2.1.10 Concomitant Treatments

Allowed medications included pure SSRIs, inactivated vaccines, ICS, nasal corticosteroids and antihistamines. Prohibited medications include: long acting anticholinergics, short acting anticholinergics, fixed combinations of β2 agonists and ICS; fixed combinations of SABAs and short-acting anticholinergics: LABAs; short acting β2 agonists; xanthines; parenteral or oral corticosteroids and intra-muscular depot corticosteroids. In the event of a COPD exacerbation, the patient was withdrawn from the trial with treatment initiated by the physician.

Reviewer's Comment:
Inhaled corticosteroids were permitted but not required as in the dose finding study in asthmatics because the same concerns of adverse respiratory events associated with the use of LABAs in patients with asthma are not evident for LABAs in the COPD population as described in the [5]TORCH1 study are not evident for LABAs in COPD.

4.3.2.1.11 Ethical Aspects

This clinical study was designed, implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations,(US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

4.3.2.1.12 Data Analysis

Sample size calculation

The sample size was based on the widths of the two-sided 95% confidence interval (CI) between any pair of treatments for the primary endpoint, trough FEV1. A 95% CI of expected width 120 mL (the sponsor assigned clinically important difference in COPD patients) was considered an appropriate level of precision in this dose ranging study. The estimate for the standard deviation for tFEV1 was 200 mL. This estimate was based on a review of the analysis outputs from the phase III indacaterol studies: QAB149B2334, QAB149B2346, QAB149B2335S and data from the phase IIIb study QAB149B2349. Eighty six evaluable patients per treatment group were required to detect a 95% confidence interval (two-sided) of expected width 120 mL wide, assuming a standard deviation of 200 mL. With a drop- out rate of 10% over 2 weeks of treatment, a sample size of 576 randomized patients (96 per treatment group) in total was required.

Efficacy Variables

The same four sets defined for analysis in Study B2357; the randomized set, the full analysis set (FAS), the per-protocol set (PPS) and the safety set were defined in addition to a PK set which included all patients with at least one evaluable drug concentration data. The planned analysis of some of the efficacy variables were modified post database lock:

- To estimate an indacaterol dose which yields the same estimated increase in trough FEV1 as the treatment with salmeterol 50 µg b.i.d., and the indacaterol dose which yields an increase in tFEV1 by 0.12L, were dropped from the analysis plan.
- Responder analyses in tFEV1 at Day 15 were added to the analysis plan. Responders were defined as patients who had an increase from baseline in trough FEV1 a) = 12 % or = 0.2 L, b) = 12 % or = 0.12 L.

Primary endpoint- tFEV1 Day 15

The primary efficacy objective was to evaluate the dose response relationship among the four doses of indacaterol (18.75, 37.5 75, and 150 mcg q.d.), placebo and salmeterol as measured by the tFEV1 after 14 days of treatment in patients with COPD and was summarized by treatment group for the FAS.
The same statistical analysis and handling of missing data conducted for the B2357 asthma dose ranging trial was carried out for this COPD dose ranging trial. Most of the same supportive analyses were also performed; however, in this case exploratory subgroup analyses were conducted for severity of COPD

[5] Calverley PD, Anderson JA. Et al. Salmeterol and fluticasone propionate and survival in Chronic Obstructive Pulmonary Disease. NEJM, 2007 Feb; 356(8): 775-789

based on GOLD criteria instead of severity of asthma. As well, the same Emax model was employed to characterize the dose response relationship.

Secondary endpoints- tFEV1 after one day

Trough FEV1 after one day of treatment was analyzed the same as above and missing data was not imputed. Peak FEV1 5 mins-4 hrs post morning dose; AUC FEV1 $_{5\ mins\text{-}4\ hrs}$; AUC FEV1 $_{5\ mins\text{-}11hrs\ 45\ mins}$; FEV1 and FVC at all other post baseline time points; 24 hour serial spirometry; AUC for FEV1 $_{5\ mins\ –\ 23\ h\ 45\ min}$ and AUC for FEV1 $_{11h\ 45\ min\ –23\ h\ 45\ min}$ for serial spirometry subgroup; daily rescue medication use; daytime and nighttime rescue medication use; percentage of days with no rescue medication use were all defined and analyzed similarly as for the B2357 asthma dose ranging study.

Safety Variables

All data was summarized for the Safety set. The safety variables included monitoring and recording all treatment emergent AEs, including COPD exacerbations. The same description for prior AE and post treatment AEs were conducted in this trial as performed in the AE section of 5.3.1.1.12. And as mentioned in the COPD Exacerbation Section 5.3.2.1.9, COPD exacerbations were recorded on the COPD exacerbation episode eCRF and not on the AE eCRF. They were included in the summaries of AEs and additionally summarized separately from other AEs. Laboratory data, vital signs and body weight and ECG were all analyzed in a similar manner as in the previous study.

Pharmacokinetic Variables

Descriptive statistics of pharmacokinetic parameters included mean, SD, and CV, min, median and max. When a geometric mean was presented it was to be stated that way. Since Tmax is generally evaluated by a nonparametric method, only median values and ranges were given for those parameters. An exploratory analysis of the relationship between dose and Cmax as well as AUCtau was carried out on the basis of dose-normalized Cmax and AUCtau values using log transformed geometric means fitted to a “dose-division” model: Log(PK parameter/Dose) = LogB +(C-1)*log(Dose), where B was the gradient of the PK parameter versus a possible linear trend and C was the power term. Confidence intervals (90%) was produced for the PK parameters. Changes made in the PK analysis post data lock included the exclusion of the 18.75 mcg treatment group from the exploratory analysis because many patients in the 18.75 mcg treatment group had sample concentration levels which were below the LLOQ and therefore set to zero. This was done in attempt to avoid bias due to the LLOQ artifact.

4.3.2.2 Patient Disposition and Demographics

Disposition

Approximately 576 patients (96 per treatment group) were to be randomized with the goal of at least 516 patients (86 per treatment group) to complete the study. Dropouts were not replaced. A total of 1110 screening visits were performed and 552 patients were randomized to the 6 treatment groups (92 in the indacaterol 18.75 mcg group, 91 in the indacaterol 37.5 mcg group, 94 in the indacaterol 75 mcg group, 92 in the indacaterol 150 mcg group, 92 in the salmeterol group and 91 in the placebo group. There were 547 patients exposed to treatment and 531 (96.2%) completed the study as planned (84 in the indacaterol 18.75 mcg group, 86 in the indacaterol 37.5 mcg group, 92 in the indacaterol 75 mcg group, 91 in the indacaterol 150 mcg group, 90 in the salmeterol group and 88 in the placebo group. The percentage of patients who discontinued prematurely was highest in the indacaterol 18.75 mcg group (8.7%) and the next in the 37.5 mcg group (5.5%). Overall, the most common reason for discontinuation was for adverse events, however there was no dose response. Refer to Table 19 below for details. Randomization was stratified by patient’s current smoking status and ICS use.

Table 19 Protocol B2356 Patient disposition (All patients)

	Ind 18.75 ug n (%)	Ind 37.5 ug n (%)	Ind 75 ug n (%)	Ind 150 ug n (%)	Salm n (%)	Pbo n (%)	Total n (%)
Screening visits	-	-	-	-	-	-	1110
Patients							
Randomized	92 (100.0)	91 (100.0)	94 (100.0)	92 (100.0)	92 (100.0)	91 (100.0)	552 (100.0)
Exposed	89 (96.7)	90 (98.9)	94 (100.0)	92 (100.0)	91 (98.9)	91 (100.0)	547 (99.1)
Completed	84 (91.3)	86 (94.5)	92 (97.9)	91 (98.9)	90 (97.8)	88 (96.7)	531 (96.2)
Discontinued	8 (8.7)	5 (5.5)	2 (2.1)	1 (1.1)	2 (2.2)	3 (3.3)	21 (3.8)
Primary reason for premature discontinuation							
Adverse event(s)	5 (5.4)	1 (1.1)	1 (1.1)	0 (0.0)	0 (0.0)	1 (1.1)	8 (1.4)
Subject withdrew consent	0 (0.0)	1 (1.1)	1 (1.1)	1 (1.1)	0 (0.0)	2 (2.2)	5 (0.9)
Abnormal test procedure results(s)	2 (2.2)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.5)
Lost to follow-up	1 (1.1)	1 (1.1)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	3 (0.5)
Protocol deviation	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	2 (0.4)

Patients who have screen failed and rescreened under a new patient number were counted twice in the number of screening visits.

Source: Table 10-1 Study No. CQAB149B2356 Clinical Study Report

Protocol Deviations

A total of 81 patients (14.8%) in the FAS had at least one major protocol deviation resulting in exclusion from the per-protocol set. The proportion of patients with a protocol deviation leading to exclusion from the PPS included: 11.1% in the indacaterol 37.5 mcg treatment group, 12.8% in the 75 mcg group; 20.7% in the indacaterol 150 mcg group; 15.4% in the salmeterol group and 13.2% in the placebo group. No patient had a non-protocol deviation leading to exclusion. The two most frequent reasons for protocol deviation were:

- "study medication taken < 80% doses prior to the primary endpoint (PEP) visit" (the largest was in placebo, 5.5% and the smallest, indacaterol doses 18.75 and 37.5 mcg at 2.2%) and
- "spirometry for SABA reversibility not acceptable as per American Thoracic Society/ European Respiratory Society (ATS/ERS) criteria" (the largest was in the 18.75 mcg indacaterol dose, 7.9% and the smallest in 37.5, 150 mcg indacaterol and placebo at 1.1%)

The breakdown of the analysis sets show that for the FAS group the range is from 96.7% (18.75 mcg indacaterol) to 100% (75 mcg, 150 mcg indacaterol and placebo) of all randomized patients were included in the analyses.

Demographics

Similar to most of the trials reviewed, the majority of patients were caucasian (94%) and male (54%) with a mean age of 62.6 years (range of 40 to 87 years) as depicted in Table 20 below. The low numbers of other races, limits any generalizability to non-caucasian demographics.

Table 20 Protocol B2356 Demographic summary (Safety set)

		Ind 18.75 ug N=89	Ind 37.5 ug N=90	Ind 75 ug N=94	Ind 150 ug N=92	Salm N=91	Pbo N=91	Total N=547
Age (years)	n	89	90	94	92	91	91	547
	Mean	62.8	61.9	62.6	62.3	62.4	63.6	62.6
	SD	8.95	9.61	9.30	9.50	9.52	8.44	9.20
	Median	62.0	63.5	63.0	62.0	63.0	63.0	63.0
	Min - Max	43 - 84	43 - 83	44 - 87	40 - 84	43 - 83	47 - 85	40 - 87
Age group – n (%)	40-64 years	53 (59.6)	51 (56.7)	52 (55.3)	52 (56.5)	51 (56.0)	54 (59.3)	313 (57.2)
	65-74 years	27 (30.3)	31 (34.4)	33 (35.1)	34 (37.0)	31 (34.1)	26 (28.6)	182 (33.3)
	>= 75 years	9 (10.1)	8 (8.9)	9 (9.6)	6 (6.5)	9 (9.9)	11 (12.1)	52 (9.5)
Sex – n (%)	Male	50 (56.2)	47 (52.2)	54 (57.4)	53 (57.6)	44 (48.4)	48 (52.7)	296 (54.1)
	Female	39 (43.8)	43 (47.8)	40 (42.6)	39 (42.4)	47 (51.6)	43 (47.3)	251 (45.9)
Race – n (%)	Caucasian	86 (96.6)	84 (93.3)	91 (96.8)	84 (91.3)	82 (90.1)	86 (94.5)	513 (93.8)
	Black	2 (2.2)	6 (6.7)	2 (2.1)	6 (6.5)	8 (8.8)	5 (5.5)	29 (5.3)
	Asian	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	1 (0.2)
	Native American	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	1 (1.1)	0 (0.0)	2 (0.4)
	Pacific Islander	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
	Other	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)

Source: Table 11-2 Study No. CQAB149B2356 Clinical Study Report

The population included mainly patients with a short duration of disease with a mean duration of COPD of 6.9 years and approximately 48% of patients diagnosed with COPD for ≤ 5 years. Approximately 53% were in the moderate severity category and 46% were in the severe category, no patients had mild COPD. The mean FEV1 for all patients was 1.29 L and the mean FVC was 2.46 L. Across the different treatment groups, the mean baseline FEV1 was similar with the lowest in the placebo group (1.21 L) and the highest in the 75 mcg indacaterol group (1.37 L). The remaining breakdown is as follows: 18.75 mcg with 1.30 L, 37.5 mcg with 1.31 L, 150 mcg with 1.32 L, salmeterol with 1.26 L. Less than half of patients were using ICS on entry to the study. A greater proportion of patients were current smokers than ex-smokers and the overall smoking history in terms of the mean number of pack years for all patients was 51.5. Regarding reversibility, the mean FEV1 before SABA was 1.30 L and after SABA it was 1.47 L. The mean post SABA FEV1 for all patients was 52% of predicted and the mean FEV1/FVC was 52.9%. The mean percentage increase in FEV1 after SABA bronchodilator was 15.7% including a range of 14.2% in the 150 mcg group to 16.7% in the salmeterol group.

Refer to Table 21 below.

Table 21 Protocol B2356 Baseline disease characteristics (Safety set)

		Treatment group						
		Ind 18.75 mcg	Ind 37.5 mcg	Ind 75 mcg	Ind 150 mcg	Salmeterol	Pbo	Total
Duration of COPD (years)	n	89	90	94	92	91	91	547
	Mean	6.6	6.6	6.8	6.7	7	7.9	6.9
	SD	5.61	5.88	6.27	5.75	6	6.72	6.04
Duration of COPD (years)-n	<1-5 yrs	43	48	46	43	46	38	264
	>5-10 yrs	28	28	27	30	24	29	166
	>10-20 yrs	17	12	19	16	18	19	101
	> 20 yrs	1	2	2	3	3	5	16
Severity of COPD n (%)	Mild	0	0	0	0	0	0	0
	Moderate	47	52	54	45	45	49	292
	Severe	42	37	39	45	46	41	250
	Very Severe	0	1	1	2	0	1	5
FEV1, mean	Pre-BD (L)	1.31	1.32	1.37	1.32	1.26	1.22	1.30
	Pre-BD (%P)	47.2	47.1	47.5	46.5	46.2	45.3	46.6
	Post-BD (L)	1.48	1.50	1.54	1.48	1.44	1.39	1.47
	Post-BD (%P)	53.4	53.8	53.9	52.2	52.7	51.5	52.9
ICS use-n(%)	No	57	55	60	56	59	59	346
	Yes	32	35	34	36	32	32	201
Smoking history-n(%)	Ex smoker	42	40	44	40	39	42	247
	Current smoker	47	50	50	52	52	49	300
Number of pack years	Mean	52.2	51.2	51	50.8	53	51	51.5
	SD	25.19	25.82	21.72	29.34	30.23	25.01	26.25

Legend: Ind: Indacaterol; pbo: placebo; BD: bronchodilator (albuterol)
Source: Adapted from Table 11-3 Study No. CQAB2356 Clinical Study Report

4.3.2.3 Pharmacokinetics

Across all treatment groups indacaterol peak serum levels were consistently observed at a median Tmax of 0.33 hours post dose. PK parameters were biased by the fact numerous samples were below LLOQ and therefore the PK parameters calculated for the indacaterol 18.75 mcg treatment group were not included in the statistical analysis of dose-proportionality. Average Cmax increased with increasing dose from 24.80 pg/mL in the 18.75 mcg treatment group, 51.36 in the 37.5 mcg group, 100.36 in the 75 mcg group and 250.53 pg/mL in the 150 mcg treatment group. Average AUC0-23.75hr values increased from 183.8 pg*hr/mL in the 18.75 mcg treatment group to 2606.3 pg*hr/mL in the 150 mcg treatment group.

4.3.2.4 Efficacy Review

4.3.2.4.1 Primary Endpoint

The primary efficacy variable was tFEV1 at Day 15 which is presented as LS mean and estimated treatment differences as done for Protocol B2357. The overall results are summarized in Table 22 below. The Sponsor predefined MCID for the targeted population was 120 mL. The largest treatment difference was observed for the 150 mcg dose of indacaterol (0.12 L). Salmeterol, and the two lower doses of indacaterol 37.5 and 75 mcg all had the same treatment effect with a treatment difference of 0.10 L.

Reviewer Comment:
Although the Sponsor prespecified a MCID for the targeted population of patients with COPD as 120 mL, this value is not supported.

Table 22 Protocol B2356 Trough FEV1 (L) at Day 15: treatment comparisons (FAS and PPS, imputed with LOCF)

	------- Treatment -------				------ Treatment difference ----			
Treatment	**n**	**LS Mean**	**SE**	**Comparison**	**LS Mean**	**SE**	**95% CI**	**p-value**
Full analysis set								
Ind 18.75 ug	82	1.35	0.020	Ind 18.75 ug - Pbo	0.07	0.027	(0.02, 0.12)	0.008*
Ind 37.5 ug	84	1.38	0.019	Ind 37.5 ug - Pbo	0.10	0.027	(0.05, 0.16)	<.001*
Ind 75 ug	87	1.38	0.019	Ind 75 ug - Pbo	0.10	0.026	(0.04, 0.15)	<.001*
Ind 150 ug	90	1.40	0.019	Ind 150 ug - Pbo	0.12	0.026	(0.07, 0.17)	<.001*
Salm	88	1.39	0.019	Salm - Pbo	0.10	0.026	(0.05, 0.16)	<.001*
Pbo	86	1.28	0.019					

Source: Table 11-5 Study No. CQAB149B2356 Clinical Study Report

The pre-planned Emax model assumed the absolute increase in trough FEV1 would be at least 0.12L but this was not reflected in the actual data. This resulted in the model producing uninterpretable estimates. Therefore the two estimates were dropped from the analysis plan.

Subgroup analysis is presented in Table 23 below. Most notable findings are that current smokers treatment differences for tFEV1 Day 15 appears to trend lower for all doses. Based on COPD severity those with more severe disease appear to have larger treatment differences in tFEV1 Day15 for doses 37.5, 75 and 150 mcg indacaterol than those with moderate COPD.

Table 23 Protocol B2356 Summary statistics of change from baseline trough FEV1 (L) at Day 15 imputed with LOCF, FAS

	Ind 18.75 ug		Ind 37.5 ug		Ind 75 ug		Ind 150 ug		Salm		Pbo	
Subgroup	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Age												
< 65 years	50	0.04 (0.170)	48	0.08 (0.284)	47	0.09 (0.271)	50	0.13 (0.206)	48	0.10 (0.203)	50	-0.01 (0.205)
≥ 65 years	32	0.12 (0.101)	37	0.08 (0.179)	40	0.09 (0.124)	40	0.09 (0.160)	40	0.10 (0.110)	36	0.01 (0.181)
Sex												
Male	45	0.06 (0.177)	43	0.06 (0.309)	50	0.10 (0.248)	52	0.15 (0.203)	44	0.13 (0.189)	45	0.03 (0.217)
Female	37	0.08 (0.114)	42	0.10 (0.149)	37	0.08 (0.164)	38	0.06 (0.150)	44	0.07 (0.135)	41	-0.04 (0.160)
Race												
Caucasian	79	0.07 (0.153)	79	0.09 (0.243)	85	0.09 (0.218)	82	0.12 (0.184)	79	0.09 (0.169)	82	-0.00 (0.194)
Black	2	0.06 (0.018)	6	0.00 (0.239)	2	0.03 (0.025)	6	0.13 (0.225)	8	0.08 (0.094)	4	0.04 (0.232)
Asian	0		0		0		1	-0.22 ( )	0		0	
Other	1	0.21 ( )	0		0		1	0.14 ( )	1	0.43 ( )	0	
Inhaled corticosteroid (ICS) use at baseline												
No ICS use	52	0.09 (0.143)	53	0.10 (0.270)	57	0.08 (0.242)	55	0.12 (0.208)	56	0.09 (0.180)	56	-0.02 (0.187)
ICS use	30	0.05 (0.165)	32	0.05 (0.189)	30	0.12 (0.152)	35	0.09 (0.148)	32	0.10 (0.142)	30	0.03 (0.206)
Smoking history												
Ex-smoker	37	0.09 (0.114)	39	0.14 (0.216)	42	0.10 (0.121)	39	0.12 (0.183)	39	0.13 (0.137)	41	0.01 (0.196)
Current smoker	45	0.05 (0.175)	46	0.03 (0.253)	45	0.08 (0.277)	51	0.11 (0.191)	49	0.07 (0.183)	45	-0.01 (0.194)
COPD severity												
Moderate or less	45	0.08 (0.142)	49	0.07 (0.288)	51	0.07 (0.252)	44	0.10 (0.204)	44	0.14 (0.173)	48	0.02 (0.192)
Severe or worse	37	0.06 (0.163)	36	0.09 (0.165)	36	0.12 (0.146)	46	0.12 (0.170)	44	0.06 (0.150)	38	-0.03 (0.197)

Source: Adapted from Table 11-7 Study No. CQAB149B2356 Clinical Study Report

A post hoc analysis was performed after database lock. The responder analysis defined responders as ≥ 12% or ≥ 0.2 L and ≥12% or >0.12 L in the increase in trough FEV1 at Day 15. The odds ratios generated were treatment drug compared to placebo. The highest odds of response were seen in the indacaterol 75 mcg and 150 mcg for both subgroups.

Table 24 Protocol B2356 Analysis of responders in trough FEV1 at Day 15 (FAS)

	Response by increase from baseline in trough FEV1, n (%), odds ratio, p-value					
	≥ 12%, 0.2 L			≥ 12%, 0.12 L		
Indacaterol dose (N)	n (%)	OR	p-value	n (%)	OR	p-value
18.75 mcg (82)	29 (35%)	2.52	0.071	39 (48%)	3.45	0.002
37.5 mcg (84)	34 (41%)	4.26	0.005	40 (48%)	4.51	< 0.001
75 mcg (87)	39 (43%)	4.48	0.003	45 (52%)	4.98	< 0.001
150 mcg (90)	32 (43%)	4.28	0.004	46 (51%)	4.71	< 0.001
Salmeterol (88)	25 (36%)	1.09	0.862	41 (47%)	1.09	0.812
Placebo (86)	17 (20%)	N/A	N/A	20 (23%)	N/A	N/A

Source: Table 14.2-1.6 Study No. CQAB149B2356 Clinical Study Report

4.3.2.4.2 Secondary Endpoints

- ***tFEV1 Day 2 and Day 14***

The largest treatment difference in tFEV1 after 1 day of treatment (Day2) was observed with both indacaterol 150 mcg and salmeterol with a LS mean of 0.13 (0.09, 0.17). At Day 14, again, any advantage demonstrated by the 150 mcg indacaterol dose was lost. The numerical values between the two highest indacaterol doses were similar: indacaterol 75 mcg 0.09 (0.04, 0.13), indacaterol 150 mcg 0.10 (0.05, 0.15) and salmeterol 0.08 (0.03, 0.13). See Table 25 for a summary of the treatment differences.

Table 25 Protocol B2356 Analysis of trough FEV1 (L) at Day 2 and Day 14 (FAS)

		--- Treatment ---			---- Treatment difference -----			
Treatment	n	LS Mean	SE	Comparison	LS Mean	SE	95% CI	p-value
Day 2								
Ind 18.75 ug	85	1.33	0.015	Ind 18.75 ug - Pbo	0.05	0.021	(0.01, 0.09)	0.016
Ind 37.5 ug	86	1.34	0.015	Ind 37.5 ug - Pbo	0.06	0.021	(0.02, 0.10)	0.004
Ind 75 ug	88	1.38	0.015	Ind 75 ug - Pbo	0.11	0.021	(0.06, 0.15)	<.001
Ind 150 ug	91	1.40	0.014	Ind 150 ug - Pbo	0.13	0.021	(0.09, 0.17)	<.001
Salm	88	1.41	0.015	Salm - Pbo	0.13	0.021	(0.09, 0.17)	<.001
Pbo	86	1.28	0.015					
Day 14								
Ind 18.75 ug	72	1.35	0.018	Ind 18.75 ug - Pbo	0.05	0.025	(0.01, 0.10)	0.027
Ind 37.5 ug	78	1.38	0.018	Ind 37.5 ug - Pbo	0.09	0.025	(0.04, 0.14)	<.001
Ind 75 ug	82	1.38	0.017	Ind 75 ug - Pbo	0.09	0.024	(0.04, 0.13)	<.001
Ind 150 ug	84	1.39	0.017	Ind 150 ug - Pbo	0.10	0.024	(0.05, 0.15)	<.001
Salm	80	1.37	0.017	Salm - Pbo	0.08	0.024	(0.03, 0.13)	0.001
Pbo	79	1.29	0.017					

Source: Table 11-9 Study No. CQAB149B2356 Clinical Study Report

A summary of the results of key secondary endpoints is presented in Table 26 below. A brief description of each is presented in the subsequent sections.

Table 26 Protocol B2356 Treatment differences for secondary endpoints

	Treatment difference LS mean (95% CI)				
	18.75 mcg	37.5 mcg	75 mcg	150 mcg	Salmeterol
Peak FEV1 1st 4 hrs Day 1	0.03 (-0.00, -0.06)	0.05 (0.02, 0.08)	0.09 (0.06, 0.12)	0.12 (0.09, 0.15)	0.12 (0.09, 0.15)
Peak FEV1 1st 4 hrs Day 14	0.09 (0.04, 0.13)	0.12 (0.08, 0.17)	0.13 (0.08, 0.18)	0.13 (0.08, 0.18)	0.12 (0.07, 0.17)
AUC FEV1 $_{5\ min-4hr}$ Day 1	0.05 (0.02, 0.08)	0.07 (0.04, 0.10)	0.11 (0.08, 0.14)	0.14 (0.11, 0.17)	0.14 (0.11, 0.18)
AUC FEV1 $_{5\ min-4\ hr}$ Day14	0.10 (0.05, 0.15)	0.14 (0.09, 0.19)	0.13 (0.09, 0.18)	0.15 (0.11, 0.20)	0.14 (0.10, 0.19)
AUC FEV1 $_{5\ min-12\ hr}$ Day 1	0.04 (0.01, 0.08)	0.06 (0.03, 0.09)	0.10 (0.06, 0.13)	0.13 (0.10, 0.17)	0.14 (0.10, 0.17)
AUC FEV1 $_{5\ min-12\ hr}$ Day 14	0.08 (0.04, 0.13)	0.14 (0.10, 0.19)	0.13 (0.08, 0.17)	0.14 (0.09, 0.18)	0.13 (0.09, 0.18)

Source: Adapted from Tables 11-10, 11-11 and 11-12

- ***Peak FEV1***

At Day 1 the treatment difference in LS mean peak FEV1 in the indacaterol 150 mcg treatment group achieved the MCID (0.12L); the same as observed in the salmeterol treatment group. The treatment difference compared to placebo for the indacaterol 37.5 and 75 mcg treatment groups at Day 1 were 0.05L and 0.09L, respectively. However, at Day 14, the LS mean peak FEV1 treatment differences compared with placebo were similar for most indacaterol treatment groups: indacaterol 37.5 mcg 0.12 (0.08, 0.17); indacaterol 75 mcg 0.13 (0.08, 0.18); indacaterol 150 mcg 0.13 (0.08, 0.18) and salmeterol 0.12 (0.07, 0.17).

- ***AUC for FEV1*** $_{5\ min\ –\ 4\ hr}$ ***and FEV1*** $_{5\ min\ –\ 11\ hr\ 45\ min}$

The largest treatment differences for AUC for FEV1 $_{5\ min-4\ hr}$ and FEV1 $_{5\ min-11\ hr\ 45\ min}$ at Day 1 were largest for the 150 mcg indacaterol group, however, by Day 14 for the same assessments, the difference between 37.5 mcg, 75 mcg and 150 mcg indacaterol were negligible.

- ***FEV1 and FVC***

At the 5 min time point on Day 1, the magnitude of the improvements in FEV1 compared with baseline are 0.11L for indacaterol 150 mcg, 0.10L for indacaterol 75 mcg and 0.07L for salmeterol. See Table 27 below for a summary. At this same time point on Day 14 the 75 mcg indacaterol dose is observed to have the largest treatment difference. The values are: 0.14L for indacaterol 150 mcg, 0.16L for indacaterol 75 mcg and 0.14L for salmeterol. Consistent with the findings in B2357, at the 5 minute time point on Day 1 indacaterol has achieved 77% of the effect seen at 4 hours when steady state is reached. These results indicate a faster onset of action for the 150 mcg and 75 mcg indacaterol treatment groups compared with the 18.75 mcg and 37.5 mcg treatment groups and salmeterol.

Table 27 Protocol B2356 Summary statistics of FEV1 (L) at each time point for Days 1 and 14

	Treatment difference from baseline (L) at Day 1 and 14					
	Day 1			Day 14		
Time point	75 mcg	150 mcg	salmeterol	75 mcg	150 mcg	salmeterol
-0:50	N/A	N/A	N/A	0.1	0.1	0.1
-0:15	N/A	N/A	N/A	0.09	0.11	0.11
0:5	0.10	0.11	0.07	0.16	0.14	0.14
0:15	0.12	0.14	0.11	0.15	0.18	0.18
0:30	0.13	0.15	0.13	0.15	0.17	0.17
1:00	0.12	0.15	0.14	0.15	0.17	0.17
2:00	0.12	0.15	0.16	0.16	0.17	0.17
4:00	0.13	0.16	0.17	0.14	0.15	0.15
8:00	0.09	0.12	0.12	0.09	0.09	0.09
11:10	0.06	0.09	0.08	0.08	0.11	0.11
11:45	0.06	0.1	0.08	0.08	0.09	0.09
11:10	0.09	0.11	0.12	0.08	0.11	0.11
23:45	0.11	0.13	0.13	0.09	0.12	0.12

Source: Adapted from Table 14.2-5.2 Study No. CQAB149B2356 Clinical Study Report

Reviewer Comment:
B2356 represents the second trial providing supportive data for the claim of rapid onset of action within 5 minutes, consistent with language included in the clinical section of the proposed label.

- ***Rescue medication use***

All rescue medication assessments including: daily number of puffs of rescue medication; daytime and nighttime number of puffs of rescue medication; and percentage of days with no rescue use statistically significantly improved with all doses of indacaterol as well as salmeterol. Refer to Table 28 below.

Table 28 Protocol B2356 Rescue medication use over 14 days: treatment comparisons, FAS

	- Treatment -				- Treatment difference -			
Treatment	n	LS Mean	SE	Comparison	LS Mean	SE	95% CI	p-value
Change from baseline in the mean daily number of puffs of rescue medication								
Ind 18.75 ug	85	-1.58	0.227	Ind 18.75 ug - Pbo	-1.04	0.309	(-1.65, -0.44)	<.001
Ind 37.5 ug	83	-2.07	0.230	Ind 37.5 ug - Pbo	-1.54	0.312	(-2.15, -0.92)	<.001
Ind 75 ug	86	-1.72	0.227	Ind 75 ug - Pbo	-1.18	0.308	(-1.79, -0.58)	<.001
Ind 150 ug	85	-1.84	0.227	Ind 150 ug - Pbo	-1.30	0.309	(-1.91, -0.70)	<.001
Salm	89	-1.72	0.224	Salm - Pbo	-1.19	0.304	(-1.79, -0.59)	<.001
Pbo	89	-0.54	0.223					
Change from baseline in the mean daytime number of puffs of rescue medication								
Ind 18.75 ug	81	-1.00	0.133	Ind 18.75 ug - Pbo	-0.56	0.180	(-0.91, -0.20)	0.002
Ind 37.5 ug	82	-1.31	0.133	Ind 37.5 ug - Pbo	-0.87	0.180	(-1.22, -0.51)	<.001
Ind 75 ug	84	-1.11	0.132	Ind 75 ug - Pbo	-0.66	0.179	(-1.01, -0.31)	<.001
Ind 150 ug	82	-1.17	0.133	Ind 150 ug - Pbo	-0.72	0.180	(-1.08, -0.37)	<.001
Salm	86	-1.11	0.131	Salm - Pbo	-0.66	0.177	(-1.01, -0.32)	<.001
Pbo	89	-0.45	0.128					
Change from baseline in the mean nighttime number of puffs of rescue medication								
Ind 18.75 ug	83	-0.61	0.110	Ind 18.75 ug - Pbo	-0.49	0.149	(-0.78, -0.20)	0.001
Ind 37.5 ug	83	-0.79	0.110	Ind 37.5 ug - Pbo	-0.67	0.149	(-0.96, -0.38)	<.001
Ind 75 ug	86	-0.64	0.109	Ind 75 ug - Pbo	-0.53	0.148	(-0.82, -0.24)	<.001
Ind 150 ug	85	-0.67	0.109	Ind 150 ug - Pbo	-0.56	0.148	(-0.85, -0.26)	<.001
Salm	88	-0.62	0.108	Salm - Pbo	-0.50	0.146	(-0.79, -0.22)	<.001
Pbo	89	-0.12	0.107					
Percentage of 'days with no rescue use'								
Ind 18.75 ug	81	39.41	3.413	Ind 18.75 ug - Pbo	13.70	4.583	(4.7, 22.7)	0.003
Ind 37.5 ug	82	44.44	3.389	Ind 37.5 ug - Pbo	18.70	4.581	(9.7, 27.7)	<.001
Ind 75 ug	85	36.07	3.349	Ind 75 ug - Pbo	10.40	4.523	(1.5, 19.3)	0.022
Ind 150 ug	83	44.66	3.361	Ind 150 ug - Pbo	19.00	4.554	(10.0, 27.9)	<.001
Salm	86	40.06	3.336	Salm - Pbo	14.40	4.499	(5.5, 23.2)	0.001
Pbo	89	25.69	3.260					

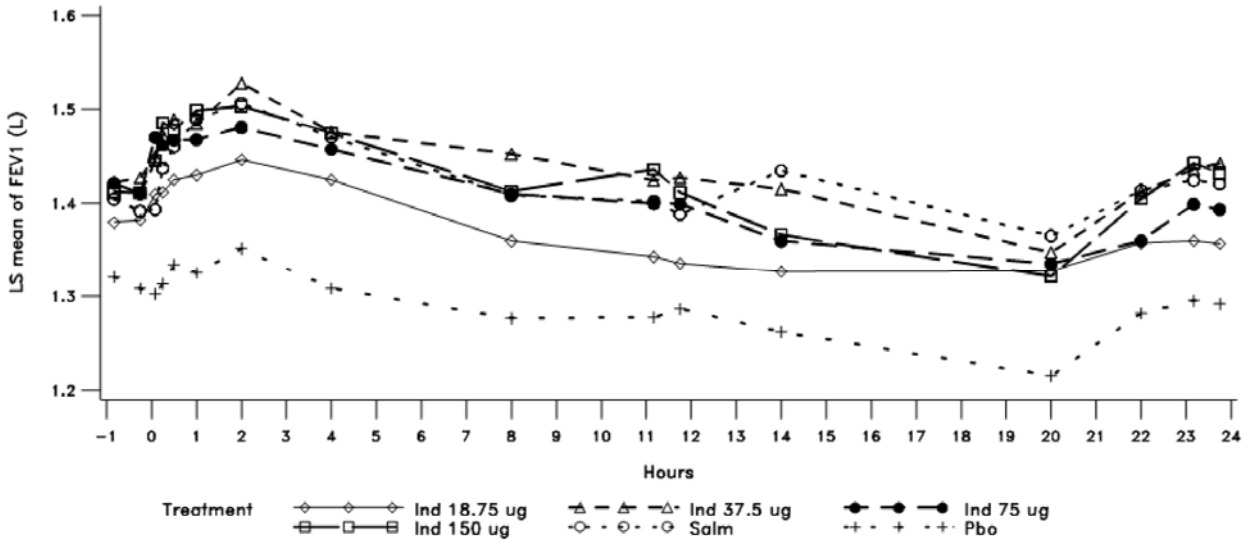
Source: Table 11-13 Study No. CQAB149B2356 Clinical Study Report

Exploratory efficacy results:

- ***Serial spirometry assessments***

After the final dose on Day 14, a subset of 369 patients took part in serial spirometry assessments over 24 hours. The LS mean FEV1 was lower in the 18.75 mcg treatment group at all time points up to 24 hour post-starting on Day 14. While the time points for the 18.75 mcg treatment group during the first half of the dose-response-time curve (5 min-8 hours) were significantly larger than placebo, there were many time points between 11 hr 10 min to 23 hr 45 min that were not. The remaining indacaterol treatment groups, 37.5 mcg, 75 mcg and 150 mcg were statistically greater than placebo at all time points up to 24 hours post dose starting on Day 14. Refer to Figure 5 for a graphical display of the data.

Figure 5 Protocol B2356 24 hour profile of LS mean of FEV1 after 14 days of treatment (FAS, 24 hour serial spirometry subsets)



Source: Figure 11-1 Study No. CQAB149B2356 Clinical Study Report

Pharmacokinetic analysis

Pharmacokinetic assessments were carried out in 135 patients with calculations obtained from 123: 24 patients in the 18.75 mcg dose, 24 the 37.5 mcg, 38 the 75 mcg, and 38 in the 150 mcg dose. Some had too few data points above LLOQ to allow PK parameter calculation. An increase in Cmax (24.8 pg/mL for 18.75 mcg to 250.53 pg/mL for 150 mcg) and AUC (145 pg*hr/mL for 18.75 to 2606.3 pg*hr/mL for 150 mcg was observed with increasing doses. All indacaterol treatment groups demonstrated peak serum levels at a median Tmax of 0.33 hours post dose. Some bias was introduced due to numerous samples being below the LLOQ for the 18.75 mcg treatment group and was not included in the statistical analysis.

4.3.2.5 Safety Review

4.3.2.5.1 Extent of exposure

The mean number of days of exposure were similar across all treatment groups (14.4 to 15.5). Compliance over the two week treatment period ranging from 88% of doses taken in the indacaterol 18.75 mcg group to 94% in the 75 mcg group and were identical between the Concept 1 SDDPI and the proprietary device.

4.3.2.5.2 Concomitant medications

Concomitant medications and significant non-drug therapies (COPD-related and non-COPD-related) were taken by greater than 80% of patients in any treatment group in the safety set as follows: indacaterol 18.75 mcg (77 patients, 86.5%), indacaterol 37.5 mcg (80 patients, 88.9%), indacaterol 75 mcg (79 patients, 84.0%), indacaterol 150 mcg (83 patients, 90.2%), salmeterol (74 patients, 81.3%) and placebo (80 patients, 87.9%).

COPD-related concomitant medications were taken by greater than 35% of patients in any treatment group. The most common medications taken were ICSs which were used by a similar percentage of patients in each treatment group (ranging from 35.1% to 38.9%). COPD-related concomitant medications were changed after the start of study medication by a low percentage of patients; 1 patient (1.1%) in the indacaterol 18.75 mcg group, 2 patients (2.2%) in the indacaterol 37.5 mcg group, and 2 patients (2.2%) in the placebo group. Non-COPD-related concomitant medications were taken by a similar percentage of patients in each treatment group. The most commonly used medications overall were acetylsalicylic acid, simvastatin, lisinopril, and multivitamins.

4.3.2.5.3 Adverse events

The overall incidence of AEs (including COPD exacerbations) was higher in the placebo group (23.1%) than in any active treatment group (14.6% for indacaterol 18.75 mcg, 18.9% for indacaterol 37.5 mcg, 18.1% for indacaterol 75 mcg, 10.9% for indacaterol 150 mcg, and 15.4% for salmeterol). The system organ classes most frequently affected by AEs were respiratory, thoracic and mediastinal disorders, infections and infestations, gastrointestinal disorders and investigations.

Table 29 Adverse events overall and by primary system organ class - n (%) of patients (Safety set)

	Ind 18.75 ug N=89 n (%)	Ind 37.5 ug N=90 n (%)	Ind 75 ug N=94 n (%)	Ind 150 ug N=92 n (%)	Salm N=91 n (%)	Pbo N=91 n (%)
Patients with any AE(s)	13 (14.6)	17 (18.9)	17 (18.1)	10 (10.9)	14 (15.4)	21 (23.1)
Primary system organ class						
Respiratory, thoracic and mediastinal disorders	2 (2.2)	6 (6.7)	7 (7.4)	2 (2.2)	3 (3.3)	4 (4.4)
Infections and infestations	3 (3.4)	2 (2.2)	4 (4.3)	4 (4.3)	2 (2.2)	7 (7.7)
Gastrointestinal disorders	2 (2.2)	3 (3.3)	1 (1.1)	3 (3.3)	4 (4.4)	4 (4.4)

Source: Table 12-2 Study No. CQAB149B2356 Clinical Study Report

The most frequently reported AE in the total safety set was cough, which occurred at similar frequencies in the indacaterol 37.5 and 75 mcg groups (6.7% and 7.4%, respectively) and at lower frequencies in the other treatment groups (none in the indacaterol 18.75 mcg group, 1.1% in the indacaterol 150 mcg group, 1.1% in the salmeterol group and 2.2% in the placebo group). Of the 17 patients with cough, 5 of the 6 in the indacaterol 37.5 mcg group, and 4 of the 7 in the indacaterol 75 mcg group reported the event as occurring after study drug inhalation. No patient in any treatment group discontinued the study drug due to cough.

Table 30 Most frequent AEs, including COPD exacerbations (at least 2 patients in any treatment group) by preferred term-n (%) of patients (Safety set)

	Ind 18.75 ug N=89 n (%)	Ind 37.5 ug N=90 n (%)	Ind 75 ug N=94 n (%)	Ind 150 ug N=92 n (%)	Salm N=91 n (%)	Pbo N=91 n (%)
Patients with any AE(s)	13 (14.6)	17 (18.9)	17 (18.1)	10 (10.9)	14 (15.4)	21 (23.1)
Preferred term						
Cough	0 (0.0)	6 (6.7)	7 (7.4)	1 (1.1)	1 (1.1)	2 (2.2)
Chronic obstructive pulmonary disease	1 (1.1)	1 (1.1)	1 (1.1)	0 (0.0)	0 (0.0)	2 (2.2)
Blood creatine phosphokinase increased	0 (0.0)	0 (0.0)	1 (1.1)	1 (1.1)	2 (2.2)	1 (1.1)
Headache	1 (1.1)	1 (1.1)	0 (0.0)	0 (0.0)	1 (1.1)	2 (2.2)
Vomiting	0 (0.0)	1 (1.1)	0 (0.0)	1 (1.1)	1 (1.1)	2 (2.2)
Dermatitis contact	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.2)

Source: Table 12-3 Study No. CQAB149B2356 Clinical Study Report

Deaths and SAEs

No deaths occurred in any treatment group during the study or 30 day follow up period. SAEs (including COPD exacerbations) were observed in 8 patients in total. Briefly, 1 patient in the indacaterol 18.75 mcg group was a 65 year old male with an AMI, symptoms started one day after drug initiation he underwent

PTCA two days later. One patient in the indacaterol 75 mcg group, a 55 year old male hospitalized for dyspnea and chest pain 29 days after the last dose.

Three patients in the indacaterol 150 mcg group: a 58 year old female with a history of anemia developed symptomatic anemia 12 days after onset of treatment; a 66 year old female who developed a deep venous thrombosis 23 days after study completion and a 55 year old female hospitalized for a COPD exacerbation 2 weeks after study completion. Three patients in the placebo group reported SAEs: hyperkalemia, COPD exacerbation and esophageal obstruction. There were no significant differences of SAEs by age group (<65 years, ≥ 65 years).

Adverse events leading to discontinuation
The AEs leading to permanent discontinuation of study drug were observed for 4 patients (4.5%) in the indacaterol 18.75 mcg group, and 1 patient in each of the indacaterol treatment groups. Brief descriptions of the 4 discontinuations in the 18.75 mcg treatment group are as follows: a 56 year old male with atrial fibrillation with rapid ventricular response; a 65 year old male with a myocardial infarction; a 69 year old female with a COPD exacerbation and upper respiratory tract infection and a 62 year old male with increased liver enzymes. One patient in the 37.5 mcg treatment group was a 66 year old male who developed chills, nausea and syncope leading to discontinuation. A 58 year old male in the 75 mcg treatment group developed polycythemia. The one discontinuation in the placebo treatment group was in a 59 year old male with a COPD exacerbation. The 1 patient with the myocardial infarction in the 18.75 mcg group and the one with a COPD exacerbation in the placebo group were also captured in the above SAEs section.

4.3.2.5.4 Laboratory findings
The notable criteria for the hematology laboratories are for hematocrit, males < 0.37 L/L, and for female < 0.32 L/L. The number of patients with recorded abnormal values was: 3, 3, 4, 2, 2 and 4 in 18.75, 37.5, 75, 150 mcg, salmeterol and placebo respectively. There were no abnormal platelet values and few numbers of patients with white blood cell counts outside of the notable range. Focus will be placed on potassium and glucose levels for the chemistry findings. The numbers of patients with a shift from normal at baseline to low (< 3 mmol/L) post baseline were: 6 patients in the 18.75 mcg, 1 in 37.5 mcg, 4 in 75 mcg, 3 in 150 mcg and 5 each in salmeterol and placebo treatment groups. Notably high glucose levels > 9.99 mmol/L and based on the maximum post-baseline value, the proportion of patients with shifts from normal at baseline to high post-baseline was: 14.8% for indacaterol 18.75 mcg, 11.2% for indacaterol 37.5 mcg, 20.2% for indacaterol 75 mcg, 13.0% for indacaterol 150 mcg, 25.6% for salmeterol and 12.1% for placebo.

4.3.2.5.5 ECG findings
There were no clinically significant abnormal overall ECG interpretations. The incidence of a maximum increase from baseline of 30 ms to 60 ms in Fridericia's QTc was highest in the indacaterol 75 mcg treatment group (6 cases) and in the 18.75 mcg indacaterol and placebo groups (5 cases in each). Two patients were recorded with an increase in Fridericia's QTc of > 60ms, one in 37.5 mcg and one in salmeterol. Overall, the most frequently recorded ECG abnormalities were ectopy. This occurred the most in the 18.75 and 37.5 mcg treatment groups (23% in each).

4.3.2.5.6 Physical examination
Focus was placed on systolic and diastolic blood pressure and pulse changes. Low SBP or ≤ 75 mm Hg or ≤ 90 mm Hg and ≥ 20 decrease from baseline was recorded in 1 in the 18.75 mcg and 1 in the salmeterol group. High SBP or >200 mm Hg, or ≥ 180 mm Hg and increase from baseline ≥ 20 mm Hg was observed in: 1 in 18.75 mcg, 1 in 37.5 mcg and 2 in salmeterol groups. Low DBP <40 mm Hg, or ≤ 50 mmHg and decrease from baseline ≥ 15 mm Hg was observed in: 1 in 18.75 mcg, 1 in 37.5 mcg and 1 in salmeterol groups. High DBP or >115 mm Hg, or ≥ 105 mm Hg and increase from baseline ≥ 15 mmHg was observed in: 1 in 37.5 mcg, 1 in 150 mcg and 1 in salmeterol treatment groups.

4.3.2.5.7 Summary of Study

This was a two week, multicenter, randomized, placebo-controlled trial comparing different doses of indacaterol, 18.75 mcg, 37.5 mcg, 75 mcg and 150 mcg to placebo in adults with COPD. In addition, salmeterol 50 mcg bid was used as an active comparator. There was a dose response in the primary endpoint of tFEV1 at Day 15. The largest magnitude of treatment difference compared to placebo for the primary endpoint was observed for the 150 mcg indacaterol dose with a value of 0.12 L. This value was statistically significant. The treatment differences observed for indacaterol 37.5 mcg, 75 mcg and salmeterol were all 0.10 L, also statistically significant. For the secondary endpoints of tFEV1 at Day 2 and Day 14, peak FEV1 and AUC, there was a dose response in the LS mean treatment differences for indacaterol doses of 18.75 to 150 mcg. Indacaterol doses 75 mcg and 150 mcg and salmeterol were statistically significant, 0.11, 0.13 and 0.13 L respectively on Day 2 and 0.09, 0.10 and 0.08 L respectively on Day 14. By Days 14/15 the magnitude of effect between the 150 mcg indacaterol and 37.5 mcg, 75 mcg indacaterol and salmeterol treatments for the primary and key secondary endpoints were undetectable.

There were some differences based on subgroup analysis apparent with the primary endpoint. Because of the few numbers of blacks and asians, no quantitative assessments can be made based on race. However, no differences based on age can be concluded. At the higher doses of indacaterol, 75 mcg and 150 mcg males exhibited larger treatment differences than females. Overall, those that were ex smokers had larger treatment differences than current smokers. The higher doses of indacaterol, 75 mcg and 150 mcg displayed larger treatment differences in those who were on ICS at baseline. Those with more severe COPD in the 75 mcg and 150 mcg treatment groups had larger treatment differences of tFEV1 (0.12 each) at Day 15 than the two lower indacaterol 18.75 mcg and 37.5 mcg treatment groups.

Indacaterol demonstrated a rapid onset of action with a treatment difference of 0.10 L for 75 mcg and 0.11 L for 150 mcg indacaterol at the 5 minute post treatment time point on Day1. For the peak FEV1 within 4 hours of the first dose assessment the 150 mcg indacaterol dose along with salmeterol achieved the largest treatment differences of 0.12 L followed by 75 mcg with 0.09 L and 37.5 mcg with 0.05 L. All assessments of rescue medication use showed improvements from baseline for all indacaterol treatment groups and with salmeterol after 14 days of treatment; and all were statistically significantly greater than those seen in the placebo group.

The most frequent reported AE was cough. which occurred at similar frequencies in the indacaterol 37.5 and 75 mcg groups (6.7% and 7.4%,respectively) and at lower frequencies in the other treatment groups (none in the indacaterol 18.75 mcg group, 1.1% in the indacaterol 150 mcg group, 1.1% in the salmeterol group and 2.2% in the placebo group). There were no deaths and 8 patients with SAEs reported. AEs (including COPD exacerbations) leading to permanent discontinuation of study drug were reported for 4.5% of patients in the indacaterol 18.75 mcg group, and 1.1% of patient in the 37.5 mcg and 75 mcg indacaterol treatment groups. There were no clinically meaningful effects of treatment at any of the doses of indacaterol studied on pulse, blood pressure and QTc interval, and no unexpected effects on clinical laboratory parameters were observed.

4.3.3 DOSE REGIMEN TRIAL B2223

A Multi-center, Randomized, Double-blind, Placebo-controlled, Parallel group, Repeated-dose Study to Evaluate the Efficacy, Safety, Tolerability and Pharmacokinetics of Three Different Dosing Regimens of Inhaled Indacaterol Maleate in Patients with Persistent Asthma

4.3.3.1 Trial Description

4.3.3.1.1 Design

This was a Phase II international multicenter, randomized, double-blind, multiple dose, placebo-controlled, parallel group trial. Patients with persistent asthma were randomized to receive either twice daily 37.5 mcg, once daily 75 mcg, alternate day indacaterol 150 mcg or twice daily placebo from Day 1 to Day 16.

Reviewer Comment:
The dose regimens were selected with a bias of using the mean daily dose of 75 mcg indacaterol.

Reviewer Comment:
A dosing regimen trial was requested by the FDA to address deficiencies included in the dose selection process of the first cycle.

4.3.3.1.2 Duration

A 21 day screening period was followed by a 2 week run-in period and a 19 day treatment period. The end of study evaluation occurred 3 days following the last treatment drug, Day 16. The total study duration per patient was approximately 54 days.

4.3.3.1.3 Population

Male and female patients aged 18 years or above, who had a diagnosis of persistent asthma diagnosed according to GINA guidelines 2008 (FEV1 at screening of 50-90% predicted normal) were included. Patients had to be on a stable dose of ICS one month prior to first study visit and had to demonstrate reversibility albuterol with an increase in FEV1 ≥12% and ≥200 mL.

Reviewer Comment:
As in trial B2357, an asthmatic population was selected at the recommendation of the Agency where the rationale was to test in the patient population most sensitive to both the bronchodilator and AE effects of LABAs.

Study Sites

This trial was conducted at 19 sites in the United States, 3 sites in the United Kingdom, 2 in France, 2 in Jordan, 1 in Germany and 1 in the Netherlands.

Reviewer's Comment:
The two dose finding studies, B2357 and B2356 were carried out solely in the United States. It is unclear if this different population has introduced any unexpected results.

4.3.3.1.4 Investigational and Reference Therapy

Investigational therapy was indacaterol capsules as maleate salt in three dose strengths: 37.5 mcg batch number X224 0909, 75 mcg batch number X173GF and 150 mcg batch number X172GF. Matching placebo capsules for inhalation with the batch number X123DF were used. All dry powder capsules were inhaled through the Concept 1 SDDPI device.

4.3.3.1.5 Objectives

Primary Objectives:

- To evaluate the bronchodilator effect of three different indacaterol dosing regimens (once-daily/q.d., alternate day/q.o.d. and twice daily/b.i.d.) on tFEV1 after two-weeks of treatment in patients with persistent asthma

- To assess the bronchodilator effect of q.d. and b.i.d. indacaterol dosing regimens on FEV1 AUC(0-24hr)
- To assess the bronchodilator effect of q.o.d. and q.d. indacaterol dosing regimens on FEV1 AUC(0-48hr) and FEV1 AUC(24-48hr).

Key Secondary Objectives:

- To assess FEV1 and FVC at each post-dose time-point on days 1/2 and days 16/17/18/19 (q.d. and b.i.d. treatment)
- To assess FEV1 and FVC at each post-dose time-point on days 1/2/3 and days 15/16/17/18/19 (q.o.d. treatment)
- Peak FEV1 on day 1 and 16

Additional Secondary Objectives:

- To assess the bronchodilator effect of three indacaterol dosing regimens on:
  - FEV1 AUC $_{(0\text{-}12hr)}$ and FEV1 AUC $_{(12\text{-}24hr)}$ for b.i.d. and q.d. treatment regimens
  - FEV1 AUC $_{(0\text{-}24hr)}$ and FEV1 AUC $_{(36\text{-}48hr)}$ for q.d. and q.o.d. treatment regimens
  - Trough FEV1 after 1 day of treatment
  - Time to peak FEV1 on day 1 and day 16
  - FVC (trough, peak and AUCs corresponding to key secondary objective variables defined for FEV1)
  - FEF $_{25\text{-}75}$ (trough, peak and AUCs corresponding to key secondary objective variables defined for FEV1)
- Morning and evening Peak Expiratory Flow (PEF)
- To assess day and night time rescue medication usage.

Exploratory Objectives:

To explore the relationships between systemic PK (AUCtau and Cmax) and heart rate, QTcF interval, serum potassium and plasma glucose of three different indacaterol dosing regimens.

4.3.3.1.6 Inclusion Criteria

Patients had to be on a stable regimen of ICS for the month prior to the first study visit. The FEV1 at screening had to be ≥50% and ≤90% of the predicted normal value. As well, patients had to demonstrate reversibility with an increase of ≥12% and ≥200 mL in FEV1 over their prebronchodilator value within 30 minutes after having inhaled a total of 360 mcg of albuterol MDI (or equivalent dose of DPI) (the reversibility test). This criterion for FEV1 was demonstrated after a washout period of at least 6 hours during which no SABA has been inhaled and a minimum of 48 hours for a LABA and 7 days for tiotropium.

4.3.3.1.7 Exclusion Criteria

Key exclusion criteria were:

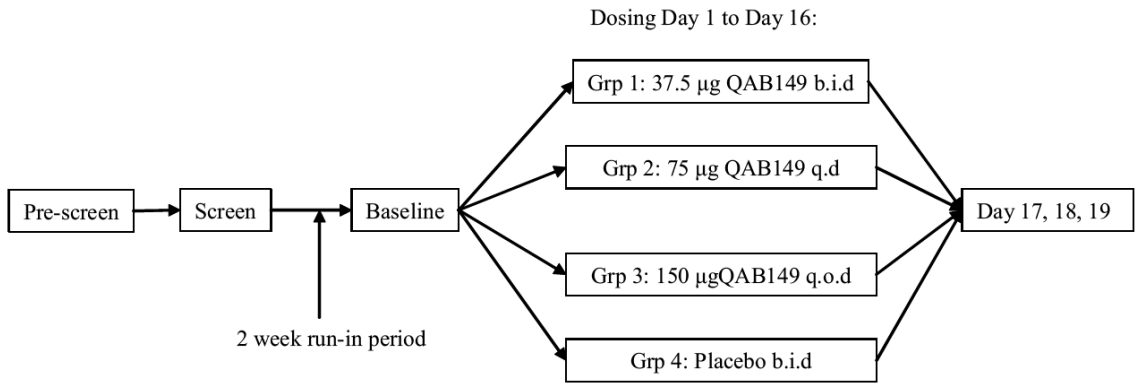
- Prior intubation for a severe asthma attack/exacerbation, a severe asthma attack/exacerbation requiring hospitalization in the 6 months prior to the first study visit or an ER visit for an asthma attack/exacerbation within 6 weeks prior to the first study visit or any time between the first study visit and pre-dose Day 1
- Lower respiratory tract infection within 6 weeks prior to the first study visit or any time between the first study visit and pre-dose day 1
- Seasonal allergy whose asthma was likely to deteriorate during the study period
- Patients who required the use of ≥8 inhalations per day of the SABA (90 mcg albuterol MDI or equivalent dose of DPI) on any 2 consecutive days from screening to randomization
- Smoking history of greater than 10 pack years, current smokers who smoked greater than 10 cigarettes per day. Smokers had to maintain their usual smoking habits throughout the course of the study
- Patients diagnosed with COPD
- Significant illness within 4 weeks prior to the first study visit

The remainder of the exclusion criteria were similar to the B2357 asthma dose ranging study.

4.3.3.1.8 Conduct

Figure 6 and Table 31 below display the overall design and schedule of study procedures. Patients were pre-screened to review their current asthma medication and have it adjusted as appropriate and sign the informed consent. During the pre-screening visit patients were provided with a PEF meter (PiKo®-1 Home Monitoring System) and diary in which they recorded their morning and evening PEF, asthma symptoms and the use of rescue medication throughout the study. Patient eligibility assessments were performed at either the pre-screening or screening visit which included an FEV1 reversibility test to total dose of 400 mcg albuterol. Patients were admitted to the study site by the morning of Day -1. At Visit 3 (Day 1) all eligible patients were randomized to one of the following 4 treatment arms in a ratio of 1:1:1:1 as seen in Figure 6.

Figure 6 Protocol B2223 Study Design



Source: Figure 9-1 Study No. CQAB149 B2223 Clinical Study Report

Efficacy Assessments:

Serial spirometry assessments were performed on a different schedule from the previous dosing ranging studies, B2357 and B2356. The spirometry time points were:

- **Day -1:** 50 and 15 min pre-dose, 10, 30 mins, 1, 2, 3, 4, 8 hrs, 11hrs 10mins, 11hrs 45mins, 12hrs 10mins, 12hrs 30mins, 13, 14, 16, 20 and 22 hrs post dose
- **Day 1:** 50 and 15 min pre-dose, 10, 30 mins, 1, 2, 3, 4, 11hrs 10mins, 11hrs 45mins post dose
- **Day 2:** pre-dose
- **Day 15 and 16:** 50 and 15 min pre-dose, 10, 30 mins, 1, 2, 3, 4, 8 hrs, 11hrs 10mins, 11hrs 45mins, 12hrs 10mins, 12hrs 30mins, 13, 14, 16, 20 and 22hrs post dose
- **Day 17:** 50 and 15 mins pre-dose, 6 hrs post dose
- **Day 18 and 19:** pre-dose

Peak Expiratory Flow Rates were obtained twice daily. Patients were permitted to leave the clinic following the completion of the all post-dose assessments on day 1. Patients returned to the clinic on the morning of days 2, 3, 9, 13, 15, 16, 17, 18 and 19. Patients returned at least 1 hour prior to scheduled dosing for spirometric final study assessments which were performed on day 19.

Placebo capsules were administered to maintain the blind in the 75 mcg q.d. dosing regimen (an evening dose) and 150 mcg q.o.d dosing regimen (an evening dose every other day and morning and evening doses on non-treatment days).

Safety Assessments:

Blood pressure, heart rate, ECG, potassium and glucose measurements were performed as follows:

- **Day 1:** 50 mins pre-dose, 15 and 30 mins, 1, 2 hrs post dose
- **Day 2 and 3:** pre-dose
- **Day 15, 16:** 50 mins pre-dose, 15 and 30 mins, 1, 2, 13 and 14 hrs post dose

- **Day 17, 18 and 19:** pre-dose

PK Assessments:
Timed PK samples were collected on:

- Day 1 at : pre-dose, 0.25, 0.5, 1, 2, 4, 12 hours post dose (before evening dose)
- Day 2, 3, 9, 13 at : pre-morning dose (15 minutes before dosing)
- Day15 at: pre-dose, 0.25, 0.5, 1, 2, 4, 12 hours post dose (before evening dose)
- Day16 at : pre-morning dose (15 minutes before dosing)
- Day17 at : 24 hours post morning dose on day 16

Table 31 Protocol B2223 Evaluation and visit schedule

	Screening		Baseline	Treatment Period												Study Completion
Visit numbers [1]		*Visit 1*	*Visit 2*	*Visit 3*	*Visit 4*	*Visit 5*		*Visit 6*		*Visit 7*		*Visit 8*	*Visit 9*	*Visit 10*	*Visit 11*	*Visit 777*
Day	D-35 to D-14		D-1	D1	D2	D3	D4-8	D9	D10-12	D13	D14	D15	D16	D17	D18	D19
Inclusion /Exclusion criteria		X	X													
Informed consent	X															
Relevant med. History/Current med. Conditions (incl smoking history)		X	X													
Concomitant meds/Therapies	X	X	As required													
Demography		X														
Physical examination		X	X													X
Device instruction			X													
FEV_1 Reversibility test		X														
Hepatitis and HIV screen		X														
Alcohol test & drug screen		X	X													
Pregnancy test (Females only)		X	X													X
FSH testing (post-menopausal females only)		X														
Drug administration at clinic				X	X[2]	X[2]		X[2]		X[2]		X	X			
Drug administration at home					X[2]	X[2]	X	X[2]	X	X[2]	X					
Diary completion					X[2]	X[2]	X	X[2]	X	X[2]	X					
Study completion information																X
Comments	As required															
Vital signs and body measurements																
Body height		X														
Body weight		X	X													X
Body temperature		X	X													
Blood pressure/pulse rate[4]		X	X	X[4]	X[4]	X[4]						X[4]	X[4]	X[4]	X[4]	X[4]
ECG evaluation (12 leads)[4]		X	X	X[4]	X[4]	X[4]						X[4]	X[4]	X[4]	X[4]	X[4]
Spirometry[3]		X	X[3]	X[3]	X[3]	X[3]						X[3]	X[3]	X[3]	X[3]	X[3]
Urine																
Urinalysis		X	X													X
Blood																
Haematology, Biochemistry		X	X													X
Serum Potassium & Plasma Glucose[4]		X	X	X[4]	X[4]	X[4]						X[4]	X[4]	X[4]	X[4]	X[4]
PK Samples[5]				X[5]	X[5]	X[5]		X[5]		X[5]		X[5]	X[5]	X[5]		
PEFR	X[6]															
Adverse Events				As required												

X = visits at which all assessments were performed.
Source: Table 9-4 Study CQAB149B2223 Clinical Study Report

4.3.3.1.9 Concomitant Treatments

Prohibited medications were similar to those in B2357, the asthma dose ranging study. The acceptable medications were also similar; primarily a stable dose of ICS was required. However, differences were that inhaled nasal cromolyn was permitted and maintenance immunotherapy was permitted.

4.3.3.1.10 Ethical Aspects

This clinical trial was designed, implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

4.3.3.1.11 Data Analysis

Sample size calculation

A sample size of 40 completed patients per treatment arm was planned; with over-recruitment by 20% to allow for drop-outs, 48 patients per treatment arm were to be recruited. The sample size was based on estimating the precision of the treatment contrasts for the primary endpoints tFEV1 and FEV1 AUC 0-24hr, and was based on variability data from study CQAB149A2218 of 290 mL for tFEV1, and 245 mL for AUC 0-24hr, expressed in terms of 95% CI width for treatment differences.

A 95% CI of expected width approximately 250 mL for tFEV1 was considered an acceptable level of precision by the Sponsor in this trial. With the assumption of a standard deviation of 290 mL, Forty (40) evaluable patients per treatment group were required to detect a 95% confidence interval (two-sided) of expected width 250 mL. Over-recruiting by 20% resulted in a total sample size of 192 randomized patients (48 per treatment group) required. This sample size would also allow a 95% CI of expected width of 215 mL for time-standardized FEV1 AUC $_{0\text{-}24}$ to be detected assuming a standard deviation of 245 mL

Efficacy Variables

The primary efficacy variables were tFEV1 after 2 weeks of study treatment and AUCs for FEV1 change from baseline over the time period 0-24 hr, 0-48 hr and 24-48 hr.

Reviewer's Comment:
Data for the remaining primary endpoints FEV1 AUC $_{0\text{-}48\ hr}$ and AUC $_{24\text{-}48\ hr}$ were not available from previous studies.

The analysis sets were defined as follows: all patients who were randomized and received at least one dose of study drug were included in the safety and tolerability data set. Different from the dose ranging studies, there was no per protocol analysis. All patients who were dosed, with evaluable data were included in the data analysis set and all patients with evaluable PK data were included in the PK data analysis set.

The analyses of primary endpoints were performed using an analysis of covariance with treatment as a fixed effect and baseline value as a continuous covariate. Baseline values were determined from the baseline spirometry profile (Day -1 and pre-dose Day 1). Treatment contrasts between dosing regimens, and between dosing regimens and placebo, and their 95% confidence intervals, were also derived. Similar analyses were used for secondary endpoints. Change from baseline was analyzed separately for each post-dose time point.

Key secondary endpoints were the FEV1 and FVC change from baseline vs. time over the time periods 0-48 hr, and peak FEV1 on Days 1 and 16. Other endpoints of interest included values of FEV1 and FVC at each time point on Days 1/2/3 and Days 15/16/17/18/19, time-standardized AUC $_{0\text{-}12\ hr}$, AUC $_{12\text{-}24\ hr}$ and AUC $_{36\text{-}48\ hr}$; tFEV1 at Day 1; peak and time to peak FEV1 on Day 1 and Day 16; FVC derived endpoints as for FEV1; FEF $_{25\text{-}75}$ derived endpoints as for FEV1.

The analysis of secondary derived endpoints was the same as for the primary endpoints. Specific treatment contrasts of interest for specified variables are as follows:

- $AUC_{36\text{-}48\ hr}$ for indacaterol b.i.d and q.o.d
- $AUC_{9\text{-}12\ hr}$ and $AUC_{12\text{-}24\ hr}$ for indacaterol b.i.d and q.d.

For the key secondary endpoints, the corresponding confidence interval widths for contrasts between pairs of treatments were: FEV1 at each post-dose time-point on Days 1/2/3 and Days 15/16/17/18/19 would range between 245mL and 408mL. FVC at each post-dose time-point on Days 1/2/3 and Days 15/16/17/18/19 would range between 230mL and 315mL. Peak FEV1 on Day 1 and Day 16 expected confidence interval width was 290mL. A similar approach will be used to analyze other secondary endpoints. Data from the PiKo® device will be listed and summarized only.

PK data were listed and summarized by treatment group.

Safety Variables
Safety data, including adverse events data, vital signs/ECG, chemistry, hematology, and use of rescue and concomitant medications, were and summarized by treatment group. Selected safety data were analyzed formally, including heart rate, QTcF, serum potassium and plasma glucose, using a repeated measures analysis.

Pharmacokinetic Variables
Samples for PK analysis were collected during a dosing interval tau (tau = 12hr, 24hr, and 48hr for 37.5 mcg b.i.d., 75 mcg q.d. and 150 mcg q.o.d. respectively) after the first dose (Day 1) and the dose on Day 15. Trough samples were collected over the treatment period. Indacaterol concentrations in serum were measured by a validated LC/MS/MS method. Pharmacokinetic parameters AUCtau, AUClast, Cmax, Cmin, Tlast and Tmax were calculated after dosing on Day 1 and Day 15.

Protocol Amendments
Amendment 1 (September 9, 2010), issued before study start (February 23, 2010 – first patient consented), introduced the following changes based on recommendations from Health Authorities:

- The hierarchy of FEV1-based efficacy endpoints was changed, with promotion of AUCs over the dosing intervals of the three regimens to co-primaries to reflect the importance of characterizing the entire FEV1-time course in addition to the residual effect at the dosing interval i.e. trough, when comparing different dosing regimens.
- The addition of spirometry time points, 20 and 22 hours post-dose on days -1, 15 and 16, allowed this time course to be more fully characterized.
- The primary and key secondary efficacy endpoints were analyzed using analysis of covariance of change from baseline at Day 16, with baseline values as a continuous covariate, and treatment as a fixed effect. Treatment contrasts were constructed to compare pairs of treatments, and results expressed as estimates and their 95% confidence intervals, without adjustment for multiple testing.

Amendment 2 (January 20, 2010), provided clarification for spirometry assessments, urinalysis requirements, device training and on timing of ICS treatment. It also provided small corrections (i.e., correction to the assessment schedule foot note for spirometry and correction to an error in the blood log and estimated total volume of blood). The criteria of two effective methods of contraception for women of child-bearing potential was also changed.

***Amendment* 3** (January 20, 2010), clarified the grammar of inclusion 3; acceptable methods of contraception for women of child-bearing potential.

Amendment 4 (March 31, 2010), issued 37 days after the start of the study when only 7 patients had received their first dose was requested by a Health Authority. An additional exclusion criteria was added

that related to patients being hypersensitive or allergic to indacaterol or other similar drugs in its class or to the excipients (including lactose) of the drug product.

Amendment 5 (January 20, 2010), clarified the timing of the screening reversibility test to be performed between screening and Day -2.

4.3.3.2 Patient Disposition and Demographics

As indicated in Table 32 below, larger numbers of patients discontinued in the indacaterol 150 mcg and placebo (12.5 and 12.8% respectively) treatment groups which also had the largest numbers discontinue due to either abnormal test or subject withdrawal of consent. Few patients used rescue medication in the active treatment groups and most patients used it on a few days. Rescue medication use was higher in the placebo group with up to 19 patients using it on any one day

Table 32 Protocol B2223 Patient disposition (Safety data set)

	Indacaterol 37.5 µg b.i.d N=48 n (%)	**75 µg q.d N=48 n (%)**	**150 µg q.o.d N=48 n (%)**	**Placebo N=47 n (%)**	**All patients N=191 n (%)**
Completed	46 (95.8%)	46 (95.8%)	42 (87.5%)	41 (87.2%)	175 (91.6%)
Discontinued	2 (4.2%)	2 (4.2%)	6 (12.5%)	6 (12.8%)	16 (8.4%)
Main cause of discontinuation					
Adverse Event(s)	0 (0.0%)	0 (0.0%)	1 (2.1%)	1 (2.1%)	2 (1.0%)
Abnormal test procedure result(s)	0 (0.0%)	1 (2.1%)	2 (4.2%)	2 (4.3%)	5 (2.6%)
Subject withdrew consent	0 (0.0%)	0 (0.0%)	2 (4.2%)	2 (4.3%)	4 (2.1%)
Lost to follow-up	0 (0.0%)	0 (0.0%)	1 (2.1%)	0 (0.0%)	1 (0.5%)
Administrative problems	0 (0.0%)	1 (2.1%)	0 (0.0%)	1 (2.1%)	2 (1.0%)
Protocol deviation	2 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.0%)

Source: Table 10-1 CQAB149B2223 Clinical Study Report

Review of the patient demographics in Table 33 reveal a lack of equal distribution of patients across dosing regimens. For example, there were fewer males in the indacaterol 75 mcg q.d. dose group and fewer blacks in the 37.5 mcg b.i.d dose group. The majority of patients were caucasian. Baseline disease pulmonary function characteristics also appeared to be different for the 75 mcg q.d. regimen with a mean FEV1 of 2.51 L where as the FEV1 for the 37.5 mcg bid regimen was 2.84 L, for 150 mcg q.o.d it was 2.61 L and placebo was 2.72 L.

Reviewer Comment:
Any differences in baseline FEV1 were corrected by using baseline as a covariate in the analysis model.

Table 33 Protocol B2223 Demographic summary by treatment group (Safety data set)

		Indacaterol			Placebo N=46
		37.5 mcg b.i.d N=48	75 mcg q.d N=47	150 mcg q.o.d N=48	
Age (years)	Mean (SD)	37 (11)	41 (14.7)	42 (12.2)	41 (12.7)
	Range	18-68	19-80	19-70	21-73
Gender-N (%)	Male	27 (56%)	23 (49%)	32 (67%)	28 (61%)
	Female	21 (44%)	24 (51%)	16 (33%)	18 (39%)
Race-N (%)	Caucasian	42 (88%)	37 (79%)	29 (60%)	43 (94%)
	Black	3 (6%)	8 (17%)	13 (27%)	2 (4%)
	Asian	1 (2%)	0 (0%)	2 (4%)	0 (0%)
	Pacific Islander	0 (0%)	0 (0%)	1 (2%)	0 (0%)
	Other	2 (4%)	2 (4%)	3 (6%)	1 (2%)
Baseline FEV1 (L)	Mean (SD)	2.84 (0.643)	2.51 (0.624)	2.61 (0.723)	2.72 (0.658)
	Range	1.22-4.59	1.40-3.89	1.22-3.94	1.20-4.19
Reversibility FEV1 (%)	Mean (SD)	22.1 (11.06)	21.4 (8.07)	20.4 (12.75)	22.5 (9.25)
	Range	12.0-49.2	11.7-47.1	-20.1-50.0	11.9-47.1

Source: Adapted from Tables 11-1 and 11-2 CQAB149B2223 Clinical Study Report

Protocol deviations

The majority of protocol deviations listed related to missed PK assessments or missed spirometry assessments. For example, one of the protocol deviations included patients not being withdrawn when their PEF readings met the stopping criteria. This impacted 1 patient in the 37.5 mcg b.i.d group, 2 in the 75 mcg q.d. group, 5 patients in the 150 mcg group and 7 patients in the placebo group.

Reviewer Comment:
The protocol deviations described would not change the overall results of the trial.

4.3.3.3 Efficacy Review

4.3.3.3.1 Primary Endpoint

As mentioned earlier in the Efficacy Variables section, the hierarchy of FEV1 related endpoints was changed with the FEV1 AUCs over the three time points being promoted to co-primary endpoints along with tFEV1 after two weeks. However, there was no mention of a multiplicity adjustment made in the analysis of the data. As summarized in Table 34, evaluation of primary endpoints, the treatment differences for all dosing regimens of indacaterol were greater than placebo. The tFEV1 on Days 15/16 for the dosing regimens of 0.197 for 75 mcg q.d. and 0.199 for 150 mcg q.o.d (contrast with placebo 0.202 and 0.203 L, respectively) were larger than 0.156 L for 37.5 mcg bid (contrast from placebo, 0.16 L). The actual values of change from baseline were very similar across treatment regimens ranging from 0.197 to 0.218 however when the widely varied placebo values were subtracted from the treatment differences the resultant values were all also widely spread.

Table 34 Protocol B2223 Summary of the statistical analysis of change from baseline in trough FEV1 and time-standardized AUCs on Days 15/16 (PD analysis set)

		Change from baseline		
PD parameter	**Treatment**	**Mean**	**Lower 90% CI**	**Upper 90% CI**
Trough FEV_1 (L)	37.5 µg b.i.d	0.156	0.083	0.228
	75 µg q.d	0.197	0.125	0.269
	150 µg q.o.d	0.199	0.125	0.272
	Placebo	-0.005	-0.080	0.071
AUC 0-24h (L)	37.5 µg b.i.d	0.196	0.127	0.266
	75 µg q.d	0.198	0.127	0.269
	Placebo	0.030	-0.044	0.103
AUC 0-48h (L)	75 µg q.d	0.218	0.148	0.288
	150 µg q.o.d	0.198	0.135	0.260
	Placebo	0.059	-0.012	0.129
AUC 24-48h (L)	75 µg q.d	0.216	0.144	0.288
	150 µg q.o.d	0.201	0.138	0.265
	Placebo	0.085	0.013	0.156

Source: Table 11-3 CQAB149B2223 Clinical Study Report

Reviewer's Comment: Unclear why the placebo mean values varied widely across the different primary endpoints ranging from -0.005-0.08 which when subtracted from the treatment differences demonstrated different trends.

Here the MCID, predefined as 200 ml was achieved by the 75 mcg q.d. and 150 mcg q.o.d. dosing regimens as demonstrated in Table 35 below of the treatment differences.

Table 35 Study B2223 Summary of the statistical analysis of contrasts with placebo for change from baseline in trough FEV1 and time-standardized AUCs on days 15/16 (PD analysis set)

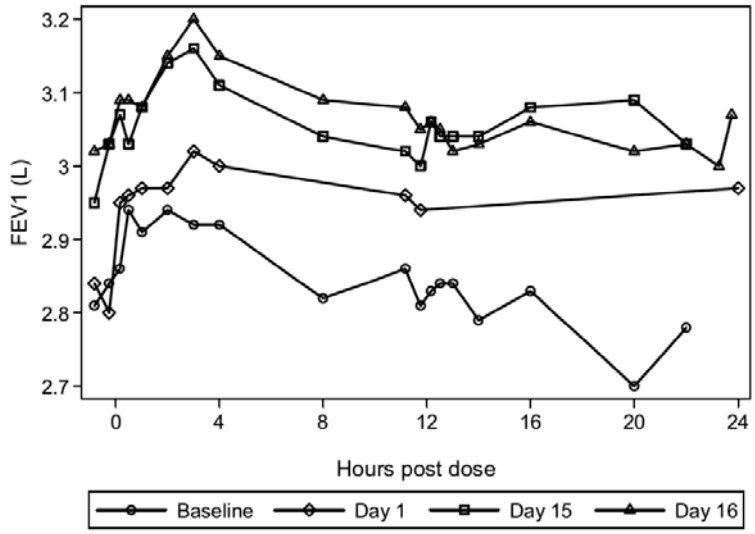
		Contrast with placebo		
PD parameter	**Treatment**	**Mean**	**Lower 95% CI**	**Upper 95% CI**
Trough FEV_1 (L)	37.5 µg b.i.d	0.160	0.036	0.284
	75 µg q.d	0.202	0.077	0.327
	150 µg q.o.d	0.203	0.077	0.329
AUC 0-24h (L)	37.5 µg b.i.d	0.167	0.046	0.287
	75 µg q.d	0.168	0.046	0.291
AUC 0-48h (L)	75 µg q.d	0.159	0.040	0.279
	150 µg q.o.d	0.139	0.026	0.252
AUC 24-48h (L)	75 µg q.d	0.131	0.009	0.253
	150 µg q.o.d	0.117	0.002	0.231

Source: Table 2 CQAB149B2223 Clinical Study Report

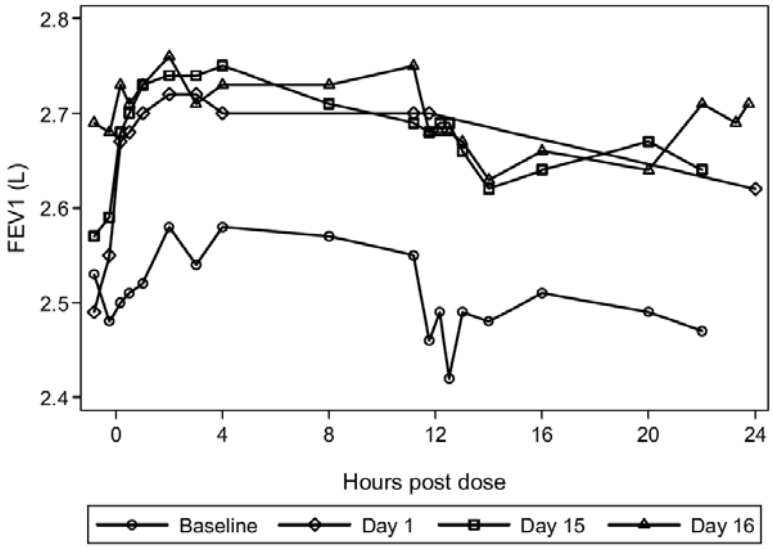
In the 37.5 mcg b.i.d dosing regimen seen in Figure 7 below the Day 1 curve falls in between baseline and Days 15/16. The difference between the Day 1 and Day 15 curves is less marked for the other regimens, 75 mcg q.d. and 150 mcg q.o.d., suggesting that 37.5 mcg b.i.d takes longer to reach maximal benefit than the other regimens.

Figure 7 Protocol B2223 Mean FEV1 over time for 37.5 mcg b.i.d, 75 mcg q.d. and 150 mcg q.o.d at baseline, Days 1, 15 and 16 (PD analysis set)

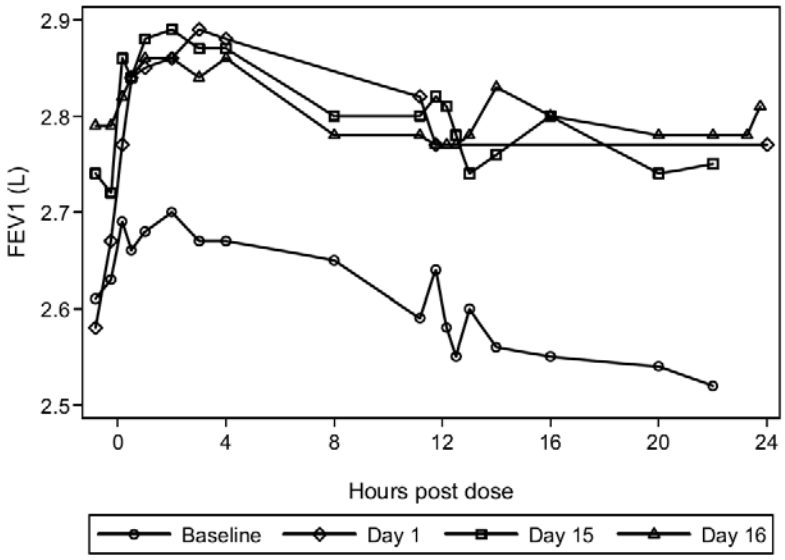
37.5 mcg indacaterol b.i.d



75 mcg indacaterol q.d.



150 mcg q.o.d



Sources: Figures 11-1, 11-2, 11-3 CQAB149B2223 Clinical Study Report

Reviewer Comment:
An interesting observation is the baseline between the different dose finding trials conducted in patients with asthma. In B2357 the mean FEV1 for all asthmatic patients was 2.36 L with a tight range of 2.32-2.46 L. In B2223 the mean FEV1 was 2.67 with a wide range from 2.51 L in the 75 mcg q.d group to 2.84 L for the 37.5 mcg b.i.d group. This represents a difference of ~ 0.300 L between the two trial populations. This large difference in baseline FEV1 may perhaps be due to different patient demographics. This absence of homogeneity must be kept in mind when assessing the validity of data from the dose regimen trial, B2223. These patients at baseline already appear to be at a higher level of FEV1 and therefore may not have much room for improvement. Differences between the indacaterol regimens may not be demonstrated due entirely to different baseline FEV1 characteristics.

Reviewer Comment:
No adjustments were made for multiple comparisons or multiplicity, and also of note, in Amendment 1 2/19/10, the hierarchy of FEV1-based efficacy endpoints was changed, with promotion of AUCs over the dosing intervals of the three regimens to co-primaries. This was done, according to the Sponsor, to reflect the importance of characterizing the entire FEV1-time course in addition to the residual effect at the dosing interval i.e. trough, when comparing different dosing regimens.

4.3.3.3.2 Secondary Endpoints

A summary of the secondary endpoint analyses is provided in Table 36 below. The largest change from baseline in peak FEV1 at Day 1 was observed with indacaterol 150 mcg q.o.d (0.423 L) followed by 75 mcg q.d. (0.357 L) and 37.5 mcg b.i.d (0.127 L). The largest change from baseline for AUC $_{(0\text{-}4\ hr)}$ after 2 weeks was observed with indacaterol 150 mcg b.i.d (0.270 L), followed by 37.5 mcg b.i.d (0.256 L) and 75 mcg q.d. (0.249 L). The range of changes from baseline for AUC $_{(0\text{-}24\ hr)}$ at Day 1 was 0.197 for 75 mcg q.d. to 0.142 L for 37.5 mcg b.i.d. The range of changes from baseline for AUC $_{(0\text{-}48\ hr)}$ was 0.157 L for 150 mcg q.o.d to 0.144 L for 75 mcg q.d. The largest changes from baseline are seen with either 75 mcg q.d or 150 mcg q.o.d across the different secondary endpoints

.

Table 36 Protocol B2223 Select secondary endpoints

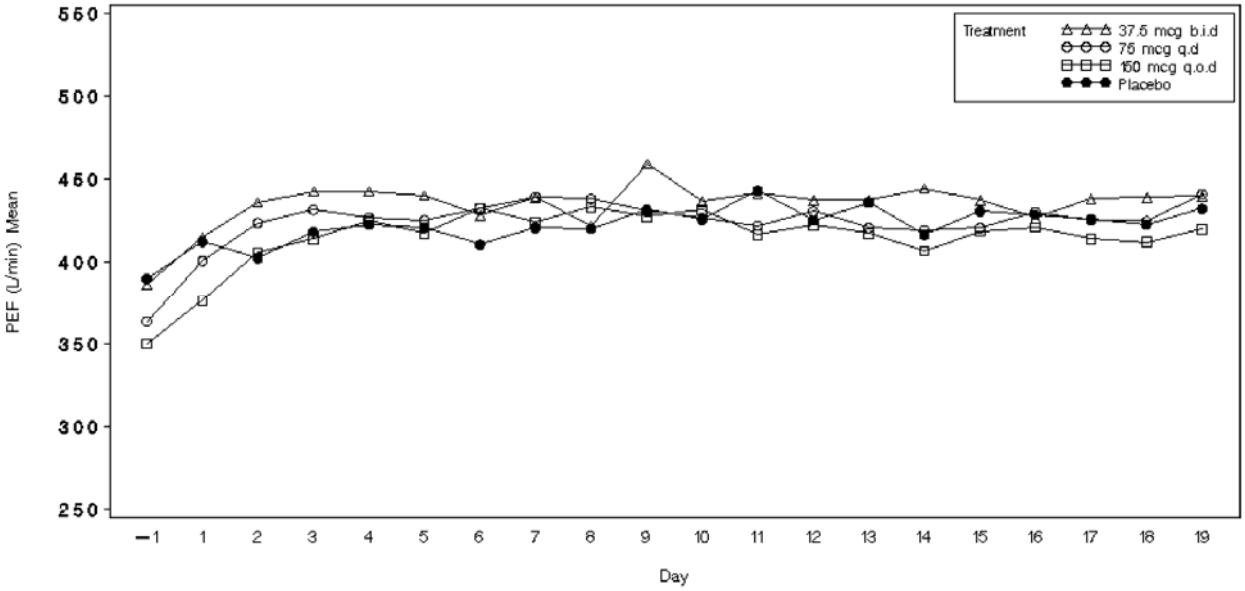
	Change from baseline (90% CI)			
	37.5 mcg b.i.d	75 mcg q.d.	150 mcg q.o.d	Placebo
tFEV1 Day 1	0.120 (0.058, 0.181)	0.115 (0.052, 0.177)	0.126 (0.064, 0.188)	-0.044 (-0.106, 0.018)
Peak FEV1 Day 1	0.127 (0.065, 0.190)	0.357 (0.294, 0.421)	0.423 (0.361, 0.485)	0.273 (0.209, 0.336)
Peak FEV1 Day 15, 16	0.364 (0.293, 0.435)	0.447 (0.376, 0.518)	0.529 (0.457, 0.602)	0.261 (0.187, 0.336)
$AUC_{0\text{-}4hr}$ Day 15/16	0.256 (0.185, 0.327)	0.249 (0.178, 0.320)	0.270 (0.197, 0.344)	0.042 (-0.032, 0.116)
$AUC_{0\text{-}12hr}$ Day 1	0.138 (0.088, 0.188)	0.193 (0.145, 0.242)	N/A	0.051 (0.001, 0.101)
$AUC_{0\text{-}12hr}$ Day 15/16	0.245 (0.170, 0.319)	0.243 (0.168, 0.317)	N/A	0.059 (-0.018, 0.137)
$AUC_{0\text{-}24hr}$ Day 1	0.142 (0.090, 0.194)	0.197 (0.143, 0.251)	0.194 (0.144, 0.245)	0.044 (-0.011, 0.098)
$AUC_{0\text{-}48hr}$ Day 1	N/A	0.144 (0.087, 0.202)	0.157 (0.109, 0.206)	0.020 (-0.034, 0.074)
$AUC_{12\text{-}24hr}$ Day 1	0.130 (0.072, 0.187)	0.188 (0.128, 0.249)	N/A	0.033 (-0.027, 0.093)
$AUC_{12\text{-}24hr}$ Day 15/16	0.163 (0.082, 0.244)	0.165 (0.082, 0.247)	N/A	-0.012 (-0.098, 0.073)
$AUC_{24\text{-}48hr}$ Day 1	N/A	0.149 (0.079, 0.22)	0.144 (0.089, 0.198)	-0.006 (-0.068, 0.055)

Source: Adapted from Table 14.2-2.2.1 CQAB149B2223 Clinical Study Report

Reviewer Comment:
The peak to trough ratio was close to 1 however, this value has a limited role here with the presence of diurnal variations.

PEF
Peak flow values increased progressively for all three indacaterol dosing regimens through Day 8. After Day 9, all curves including the placebo plateau together, See Figure 8 below for graphical representation of the data.

Figure 8 Protocol B2223 Mean PEF over time



Source: Figure 14.2-2.5 CQAB149B2223 Clinical Study Report

Pharmacokinetic Assessments

Indacaterol was absorbed rapidly following inhalation and the rate of absorption was similar for Day 1 and Day 15 across all regimens. The mean Tmax was similar across dosing regimens, 15 to 18 min post-dose on Day 1 and Day 15. The mean Cmax increased with dose regimen on Day 1 (18.8 pg/mL for 37.5 mcg b.i.d, 59.6 pg/mL for 75 mcg q.d and 138 pg/mL for 150 mcg q.o.d) and Day 15 (76.2 pg/mL for 37.5 mcg b.i.d, 143 pg/mL for 75 mcg q.d. and 220 pg/mL for 150 mcg q.o.d). Minimum serum indacaterol concentrations on day 15 (Cmin), however, were similar for the three dosing regimens, with means ranging from 34.3 pg/mL to 39.8 pg/mL. Refer to Table 37 and Table 38 for summary of data.

Table 37 Protocol B2223 Summary statistics of indacaterol PK parameters- Day 1

Regimen	Statistic	[1]Tmax (hr)	Cmax (pg/mL)	[1]Tlast (hr)	AUClast (pg.hr/mL)	AUCtau (pg.hr/mL)
37.5 µg	N	39	39	39	39	12
b.i.d	Mean	0.250	18.8	4.00	73.1	162
	SD	0.167-4.00	9.24	0.50-12.0	69.3	59.4
	CV%	-	49.3	-	94.8	36.6
75 µg	N	45	45	45	45	34
q.d.	Mean	0.300	59.6	23.8	389	423
	SD	0.150-23.9	26.9	2.03-25.6	168	137
	CV%	-	45.2		43.2	32.5
150 µg	N	42	42	42	42	40
q.o.d	Mean	0.300	138	47.8	1110	1120
	SD	0.183-2.00	48.8	23.8-48.5	293	300
	CV%	-	35.3	-	26.3	26.7

Source: Table 11-8 CQAB149B2223 Clinical Study Report

Table 38 Protocol B2223 Summary statistics of indacaterol PK parameters- Day 15

Regimen	Statistic	[1]Tmax (hr)	Cmax (pg/mL)	Cmin (pg/mL)	[1]Tlast (hr)	AUClast (pg.hr/mL)	AUCtau (pg.hr/mL)
37.5 µg	N	43	43	43	43	43	39
b.i.d	Mean	0.267	76.2	34.4	12.0	565	604
	SD	0.217-2.08	37.0	18.5	2.00-12.1	277	255
	CV%	-	48.6	53.8	-	49	42.2
75 µg	N	40	40	40	40	40	40
q.d.	Mean	0.283	143	39.8	23.8	1440	1450
	SD	0.200-4.02	54.2	16.6	22.3-23.8	553	556
	CV%	-	38.0	41.9		38.5	38.4
150 µg	N	35	35	35	35	36	34
q.o.d	Mean	0.25	220	34.3	48.0	2920	2970
	SD	0.233-4.03	61.4	12.1	23.8-48.6	774	749
	CV%	-	27.9	35.3	-	26.5	25.2

Source: Table 11-9 CQAB149B2223 Clinical Study Report

4.3.3.4 Safety Results

4.3.3.4.1 Extent of exposure

All patients who completed the trial received 16 days of dosing except for one patient in the 37.5 mcg b.i.d group who received 15 days. The range of treatment duration was the lowest in placebo with 89% of patients taking 16 days of treatment drug to the highest in indacaterol 75 mcg q.d. with 98% taking 16 days of trial drug. A summary of the duration of exposure to trial drug is shown in Table 39.

Table 39 Overall exposure by treatment duration (Safety data set)

	Indacaterol			
	37.5 µg b.i.d	75 µg q.d	150 µg q.o.d	Placebo
Exposure duration	N=48	N=47	N=48	N=46
<15 days, n (%)	1 (2)	1 (2)	5 (10)	5 (11)
15 days, n (%)	2 (4)	0 (0)	0 (0)	0 (0)
16 days, n (%)	45 (94)	46 (98)	43 (90)	41 (89)

Source: Table 12-1 CQAB149B2223 Clinical Study Report

4.3.3.4.2 Concomitant medication

Most of the medications used throughout the trial were for asthma and were ongoing from baseline. Few patients used rescue medication in the active treatment groups and most patients used it on a few days. Rescue medication use was much higher in the placebo group with up to 19 patients using it on any one day.

4.3.3.4.3 Adverse events

Adverse events were reported by 10 (21%) patients in the 37.5 mcg b.i.d group, 12 (26%) patients in the 75 mcg q.d group, 19 (40%) patients in the 150 mcg q.o.d group and 14 (30%) in the placebo group. The most common reported AEs were headache and cough. Headaches were observed in 6%, 4%, 6% and 13% in indacaterol 37.5 mcg b.i.d, 75 mcg q.d., 150 mcg q.o.d and placebo, respectively. The largest incidence of cough was observed in 150 mcg q.o.d (15%) and the smallest incidence in placebo (2%).

Headache and cough were the most common AEs reported by patients in this study with a total of 14 patients experiencing each of these AEs. Headache was experienced by patients in all four treatments but more so for patients when receiving placebo [6/46 (13%)] than with the indacaterol dosing regimens (Table 12-3). Cough was mainly experienced by patients when receiving indacaterol with only 1/46 (2%)

patients in the placebo group reporting a cough. The incidence of cough was greatest for the 150 mcg q.o.d group affecting 7/48 patients with 3 (6%) patients affected in the other two dosing regimens. Dizziness and nasopharyngitis were seen with highest incidences of 4% for both in the 75 mcg q.d. group.

Deaths and SAEs
There were no deaths during the study. Three patients experienced a SAE during the study; two prior to randomization. A third patient in the indacaterol 150 mcg q.o.d group was a 43 year old male, Polynesian, who received a total of three doses of 150 mcg q.o.d and the corresponding 7 matching placebo doses developed flu-like symptoms following exposure to pollen precipitating an asthma exacerbation 5 hours after receiving inhaled placebo requiring hospitalization.

Adverse events leading to discontinuation
In addition to the above mentioned, a patient in the placebo group was withdrawn due to elevated transaminases.

4.3.3.4.4 Laboratory findings
In the hematology assessment, the mean hematocrit values during screening ranged from 0.434 to 0.445 (corresponding hemoglobin values, 142.4 g/L to 146.2 g/L). The mean hematocrit value during end of study ranged from 0.423 to 0.437 (corresponding hemoglobin values, 135.8 g/L to 141.1 g/L). All of the patients had at least one clinical laboratory test result outside of the normal range during conduct of the trial. There were no clinically meaningful events reported for glucose and potassium assessments. There was a reduction in creatinine kinase values over the treatment period as represented by a mean value of 228 U/L on screening to a mean of 161 U/L at the end of the trial in the 150 mcg q.o.d treatment group. Clinically significant effects on transaminases were reported for one patient in placebo with high values at baseline with an increase during the trial leading to discontinuation as mentioned above.

4.3.3.4.5 ECG findings
There were no QTcF values flagged as > 500 ms. In the 37.5 mcg b.i.d group, 1 patient had in increase of > 30 msec on Days 1, 2 on Day 15; in the 75 mcg q.d. group there was 1 patient on each Day 1 and Day2, 2 patients at the end of trial and 7 on Day 15 and 3 on Day 16. The 150 mcg group had the greatest numbers of patients with an increase of > 30 msec with the largest number of 8 on Day 15. Values > 60 msec were observed in one patient in the 37.5 mcg b.i.d group, 2 in the 75 mcg q.d. and 1 in the 150 mcg q.o.d group.

4.3.3.4.6 Physical examination
There was one patient reported with elevated BP resulting in an AE. The patient was a 68 year old black female with a history of hypertension, elevated BP at baseline and increased to a maximum of 209/119 mmHg. This was recorded as an AE. Increases in pulse > 90 bpm were reported in 5 patients in 37.5 mcg b.i.d ranging from 91-102 bpm; 10 patients in the 75 mcg q.d. group ranging from 91-101 bpm; 10 in the 150 mcg q.o.d group ranging from 91-107 bpm and 7 in the placebo group ranging from 91-101 bpm. There were two episode of bradycardia recorded, one in the 75 mcg q.d. group (39 bpm) and the other in the placebo group (37-39 bpm).

4.3.3.5 Summary of Study
This trial along with B2356 and B2357 were not included in the Sponsor's summary of safety due to the short duration and different target population. This was a two week, multicenter, international, randomized, placebo-controlled trial comparing different dosing regimens of indacaterol, 37.5 mcg b.i.d, 75 mcg q.d. and 150 mcg q.o.d. to placebo in adults with persistent asthma. Evaluation of the bronchodilatory effects of the different regimens were carried out with spirometry and the systemic levels were measured through the pharmokinetic assessments. The treatment differences from placebo for the 75 mcg q.d and 150 mcg q.o.d regimens were similar (0.202 L and 0.203 L) and exceeded the Sponsor's predefined MCID of 0.200 L in patients with asthma. The 37.5 mcg b.i.d. regimen had the smallest treatment difference of 0.16 L. The magnitude of mean change from baseline in peak FEV1, FEV1 AUCs

0-24 hr, 1-12 hr and 12-24 hr were greatest for the 75 mcg q.d. regimen when compared to the 37.5 mcg b.i.d regimen. After two weeks of treatment, FEV1 AUC 0-24hr for the 75 mcg q.d, 150 mcg q.o.d and 37.5 mcg b.i.d dosing regimens were similar. The 150 mcg q.o.d regimen had the greatest magnitude of mean change from baseline in the peak FEV1 at Days 1 and 14.

The mean Tmax was similar across dosing regimens; 15 to 18 min post-dose. The mean Cmax increased with dose regimen on Day 1 as well as Day 15. The AUC last and tau increased with dose regimen and from Day 1 to Day 15. Based on the mean AUC tau values the average steady state concentrations of indacaterol were similar for the three dosing regimens. With average steady state concentrations similar across the regimens, the total systemic exposure was similar. Pharmacokinetic steady state was achieved by day 15 for all three dosing regimens as indicated by the trough serum concentrations of indacaterol.

The baseline demographics were generally comparable however the disease characteristics showed the lowest mean baseline FEV1 for the 75 mcg q.d. group (2.51 L) and highest for the 37.5 mcg b.i.d group (2.84 L) a difference of approximately 0.300 L. The degree of reversibility was comparable across groups.

The most frequent reported AEs were cough and headache. There were no deaths during the trial and the one SAE of an asthma exacerbation in the 150 mcg q.o.d. treatment regimen group. There were reports of expected pharmacodynamic effects in glucose, potassium levels, ECG and one event of elevated blood pressure recorded as an AE.

4.3.4 CONFIRMATORY TRIAL B2355

A 12-Week Treatment, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Efficacy and Safety of Once Daily Indacaterol in Patients with Chronic Obstructive Pulmonary Disease

4.3.4.1 Trial Description

4.3.4.1.1 Design

This was a Phase III, multicenter, randomized double-blind, placebo-controlled, parallel group study using 75 mcg indacaterol once daily via an SDDPI for 12 weeks in patients with moderate to severe COPD. The patients were stratified for smoking status and ICS use. The study design is presented in Table 40 below.

Table 40 Protocol B2355 Study design

Period	Pre-screen	Screen/ Run-in	Screen/Run -in	12-week Randomized Treatment
Visits	1	2	3	4-9
Day/Week	≥ Day -28 to ≤ -14	Day -14	Day -13	Week 1 – Week 12 (Day 1-85)
				Patients were randomized (1:1) to receive one of the following two blinded treatments: Indacaterol 75 µg o.d. via SDDPI or Placebo to indacaterol o.d. via SDDPI
		Daily ICS monotherapy allowed, if needed, was to remain stable throughout study albuterol was available for rescue use throughout study		

Source: Table 9-1 Study No. CQAB149B2355 Clinical Study Report

4.3.4.1.2 Duration

A 14 day run in period was followed by a 12 week treatment period.

4.3.4.1.3 Population

Male and female adults aged ≥ 40 years, outpatients with a diagnosis of COPD, moderate to severe as classified by the GOLD Guidelines 2008. The study also had a 24 hour serial spirometry profiling subgroup, with all patients offered the opportunity to participate.

4.3.4.1.4 Study Sites

The trial was conducted at 54 centers in the United States.

4.3.4.1.5 Investigational and Reference Therapy

Investigational product: indacaterol 75 mcg formulation #6002142.003, batch # X173GF, X297LF and X231KF. Placebo to indacaterol formulation #3760253.004, batch #X123DF. All indacaterol dry powder capsules and placebo to indacaterol were inhaled through the Concept 1 SDDPI device.

4.3.4.1.6 Objectives

The primary objective of the study was to evaluate the efficacy of indacaterol (75 mcg q.d.) in terms of tFEV1 as compared to placebo after 12 weeks of treatment. Trough FEV1 was defined as the mean of FEV1 measurements at 23hr 10 min and 23hr 45 min after the previous morning's dose.

The key secondary objective was to evaluate the efficacy of indacaterol (75 mcg q.d.) in terms of transition dyspnea index (TDI) focal score after 12 weeks of treatment as compared to placebo.

Other secondary objectives were:

- To evaluate the efficacy of indacaterol (75 mcg q.d.) in terms of 24 hour post-dose (trough) FEV1 after a single dose (Day 2) of treatment as compared to placebo

- To evaluate the efficacy of indacaterol (75 mcg q.d.) versus placebo for the standardized AUC of FEV1 5 minutes-4 hours after a single dose (Day 1) and 12 weeks of treatment
- To evaluate the efficacy of indacaterol (75 mcg q.d.) in terms of health-related quality-of-life as measured by the St George's Respiratory Questionnaire (SGRQ) total score after 12 weeks of treatment compared to placebo
- To evaluate the efficacy on indacaterol (75 mcg q.d.), and placebo in terms of rescue medication use over the 12 week treatment period using data obtained from the eDiary
- To evaluate the efficacy of indacaterol (75 mcg q.d.) and placebo in terms of patient reported symptoms over the 12 week treatment period using data obtained from the eDiary
- To compare indacaterol (75 mcg q.d.) to placebo on spirometry assessments in terms of FEV1 measured at all time points, including approximate peak response (Day 1 and after 12 weeks treatment) and trough response
- To evaluate the safety (in particular regarding ECG, laboratory tests, vital signs, adverse events) of indacaterol (75 mcg q.d.) over 12 weeks, in patients with COPD

Exploratory objectives were:

- To evaluate the effect of indacaterol (75 mcg q.d.) on COPD exacerbations over the 12 week treatment period
- To evaluate the pharmacokinetic profile of indacaterol in a subset of patients after 84 days of treatment. This was added in Amendment 1 dated 2/10/10.
- To explore the 24 hour FEV1 and FVC profile of indacaterol (75 mcg q.d.) and placebo after 12 weeks of treatment
- To explore individual genetic variation in genes relating to drug metabolism, COPD, and the drug target pathway, and how these differences may confer a differential response to indacaterol through pharmacogenetic analysis.

4.3.4.1.7 Inclusion Criteria

Inclusion criteria were the same as in B2356, the dose ranging study in patients with COPD. Briefly, patients included had a smoking history of at least 10 pack years, post-bronchodilator FEV1 <80% and ≥30% of predicted and post bronchodilator FEV1/FVC <70% of the value at screening. Post bronchodilator refers to within 10-15 minutes of inhalation of 4 x 90 mcg albuterol delivered at the mouthpiece.

4.3.4.1.8 Exclusion Criteria

The exclusion criteria were the same as in Study B2356, the dose ranging study performed in patients with COPD.

4.3.4.1.9 Conduct

At prescreening visit (Visit 1) informed consent was obtained and current COPD medications were reviewed. For suitable patients, arrangements were made to adjust prohibited COPD therapy to allowable COPD therapy. The adjustments for patients taking LABAs or combinations containing LABAs or SABAs were carried out in the same manner as in Study B2356, the dose ranging trial in patients with COPD. The interval between Visit 1 and Visit 2 was based on the washout period of the prohibited medication that the patient was on. The interval between Visits 2 and 4 was a 14 day run-in period used to assess eligibility of patients for the study and to collect baseline information. The interval between Visits 4 and 9 was the 12-week randomized blinded treatment period. Collection of blood samples for PK measurements after 12 weeks of study treatment was included into the protocol in Amendment 1 dated February 10, 2010. See Table 41 for a schedule of assessments.

Table 41 Protocol B2355 Assessment schedule

Period	Pre-screen	Screen / Run-in	Screen / Run-in	12- week Randomized Treatment						
Visit	1	2	3	4	5	6	7	8	9	-
Wk – start of wk (**last day of week*)		-2	-2	1	1	5	9	12*	13	13
Day		- 14	- 13	1	2	29	57	84	85	86
Informed consent	XS									
Current medication review/ adjustment	XS	XS								
Incl./Excl. criteria	S	S	S	S						
Medical History, Demographics	XS									
Smoking history/status	XS								XS	
PG Blood (consenting pts)				XS						
Pregnancy Test (serum) [#]		XS							XS	
Concom. Meds[#]		XS	XS	XS	XS	XS	XS	XS	XS	XS
Physical Exam. [#]		S							XS	
ECG [1#]		XS		XS		XS	XS	XS		
Systolic and diastolic BP and radial pulse rate[1#]		XS		XS		XS	XS	XS		
Record Height, waist and hip measurements (Visit 2 only) and Weight [#]		XS							XS	
Review/record β_2-agonist use		XS		XS	XS	XS	XS	XS	XS	XS
FEV_1 Reversibility (β_2 agonist)		XS								
FEV_1 Reversibility (Anti-cholinergic)			XS							
Spirometry [1#]		XS	XS	XS	XS	XS	XS	XS	XS	XS
Urinalysis [1#]		XS		XS		XS	XS	XS		
Hematology/ Blood Chemistry [1#]		XS		XS		XS	XS	XS		
PG sample[5]				XS						
Device training[3]	S	S		S						
AE Recording [#]	XS	XS	XS	XS	XS	XS	XS	XS	XS	XS

Period	Pre-screen	Screen / Run-in	Screen / Run-in	12- week Randomized Treatment						
Visit	1	2	3	4	5	6	7	8	9	-
Wk – start of wk (*last day of week*)		-2	-2	1	1	5	9	12*	13	13
Day		- 14	- 13	1	2	29	57	84	85	86
Provide rescue medication as necessary	S	S	S	S	S	S	S	S		
Issue Patient Diary		S								
Review, collect and download Patient Diary #				S	S	S	S	S	S	
SGRQ #				XS		XS		XS		
BDI				XS						
TDI #						XS		XS		
Randomization				S						
Telephone patients 1 day prior to visit						S	S	S		
Administer study drug at visit				XS	XS	XS	XS	XS	XS[4]	
Dispense study medication [2]				S		S	S			
Collect study medication #						S	S	S		
Call IVRS #	S	S		S		S	S		S	
Record number of capsules taken since previous dispensing visit #						XS	XS		XS	
24 hr profiling at end of study (subset of patients only)[4]										XS
Study completion eCRF #									XS	

S (recorded in source documents only); XS (recorded in database and source documents)
Source: Table 6-1 Study No. CQAB149B23B2355

Efficacy Assessments

Spirometry measurements

Serial spirometry was performed on:

- Day 1 (Visit 4) at 50 and 15 minutes predose, then 5, 30 minutes, 1, 2 and 4 hours post dose
- Day 2 (Visit 5) at 23 hr 10 min and 23 45 min
- Day 29 (Visit 6) at 50 and 15 minutes predose, then 5, 30 minutes, 1 hour post dose
- Day 57 (Visit 7) at 50and 15 minutes predose, then 5, 30 minutes, 1 hour post dose
- Day 84 (Visit 8) at 50and 15 minutes predose, then 5, 30 minutes, 1, 2 and 4 hours post dose
- Day 85 (Visit 9) at 23 hr 10 min and 23 hr 45 min
- Day 85/86 (Visit 9) at 5 and 30 minutes, 1, 2, 4, 6, 12, 16, 22 and 24 hours post dose

Daily clinical symptoms and Rescue Medication Use

At Visit 2 all patients were provided with an electronic Patient Diary to record daily (morning and evening) clinical symptoms and rescue medication (albuterol) use. Questions, which covered the preceding 12

hours included: number of puffs of rescue medication; how would you rate your respiratory symptoms last night: how was your cough; how was your wheeze; how much sputum did you produce; what color was the sputum you produced; and during what activities did you first feel breathless in the past.

Baseline and Transitional Dyspnea Indices

Dyspnea was measured at baseline using the baseline dyspnea index (BDI) and during the treatment period using the transition dyspnea index (TDI), which captures changes from baseline. The BDI and TDI each have three domains: functional impairment, magnitude of task, and magnitude of effort. The BDI domains are rated from 0 (severe) to 4 (unimpaired), and the domain scores are summed for the baseline focal score ranging from 0 to 12. Lower scores represented worse dyspnea severity. The TDI domains are rated from -3 (major deterioration) to 3 (major improvement), and the domain scores are summed for the transition focal score ranging from - 9 to 9 with minus scores indicating deterioration. Patients were interviewed by an independent, trained assessor who graded the degree of impairment due to dyspnea at Visit 4 (baseline dyspnea index) and Visits 6 and 8 (transition dyspnea index). The same assessor completed both the BDI and TDI assessments for an individual patient, which was undertaken prior to dosing at these visits.

Reviewer comment:
The use of the Mahler Baseline Dyspnea Index/Transitional Dyspnea Index (BDI/TDI) to support a dyspnea indication was discussed in a Pulmonary Allergy Drug Advisory Committee (PADAC) meeting held on September 6, 2002 for tiotropium HandiHaler. The committee identified a number of issues with the instrument, making it inappropriate for use to support labeling claims.

COPD Exacerbations

COPD exacerbations were defined as:

worsening of 2 or more of the following major symptoms for at least 2 consecutive days:

- Dyspnea
- sputum volume
- sputum purulence

or

worsening of any 1 major symptom together with any 1 of the following minor symptoms for at least 2 consecutive days:

- sore throat
- colds (nasal discharge and/or nasal congestion)
- fever without other cause
- increased cough
- increased wheeze

and

requiring treatment with systemic corticosteroids and/or antibiotic

COPD exacerbations were considered of moderate severity if treatment with systemic corticosteroids and/or antibiotic was required and severe if hospitalization was required. An ER visit of longer than 24 hours was considered a hospitalization. An increase in ICS dose was not counted as an exacerbation. COPD exacerbations were recorded on the COPD exacerbation episode eCRF page only.

Safety Assessments

ECG, vitals and laboratory evaluations were performed 25 minutes predose and 1 hour post dose on Days1, 29, 57 and 84. Urinalysis was performed 50 minutes prior to dose on the same days as ECG,

vitals and laboratory evaluations. Serum pregnancy test was performed during screening and again on Day 85 or premature discontinuation visit. AE were recorded at each study visit. A complete physical exam was performed at screening and at Day 85.

An SAE was defined as an event which:

- was fatal or life-threatening
- resulted in persistent or significant disability/incapacity
- constituted a congenital anomaly/birth defect
- required inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - social reasons and respite care in the absence of any deterioration in the patient's general condition
- was medically significant, i.e., defined as an event that jeopardized the patient or may have required medical or surgical intervention to prevent one of the outcomes listed above.

Other Assessments

SGRQ

The SGRQ was self-administered on paper by the patient at the investigator's site at baseline (Visit 4) and Visit 6 and 8 or at the time of discontinuation for patients who discontinue prematurely. The one month recall version of the SGRQ was used and the questionnaire was to be completed before all other assessments were made to avoid influencing the responses. The completed questionnaires were reviewed and examined by the investigator, before the clinical examination, for responses which may have indicated potential AEs or SAEs. The investigator reviewed the responses as well as the comments written by the patient and then transcribed the answers into the eCRFs.

Reviewer's Comment:
The SGRQ contains 50 items divided into three sections: "Symptoms" concerned with respiratory symptoms, their frequency and severity; "Activity" concerned with activities that caused or were limited by breathlessness; and "Impacts" which covered different aspects of social functioning and psychological disturbances resulting from airway disease. Scores for each section and a "Total" score were calculated, ranging from 0 to 100. Higher values correspond to greater impairment of health-related quality of life. The MCID for the SGRQ is a change from baseline of 4 points over placebo. ([6]Jones PW, 2002, and [7]Jones PW, 2005).

PK Assessments

Blood samples (4 mL) were collected at each of the following time points:

- Day 84: -25 min pre-dose, 30 min, 1 hr and 4hr post dose
- Day 85: 23 hr 35 min post the previous days dose

Biofluid concentrations were expressed in mass per volume units. Missing data were labeled as such in the concentration data listings. Data below LLOQ were set to zero and treated as such in the PK analysis and in summary statistics.

4.3.4.1.10 Concomitant Treatments

[6] Jones PW, Eur Resp J 2002; 19:398-404
[7] Jones PW, COPD: Journal of Chronic Obstructive Pulmonary Disease 2005; 2: 75-79

The prohibited medications, prohibited COPD-related medications and medications allowed under certain conditions were the same as in Studies B2357 and B2356, the dose ranging studies carried out in patients with asthma and COPD.

4.3.4.1.11 Ethical Aspects

This clinical trial was designed, implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations, US Code of Federal Regulations Title 21, and with the ethical principles laid down in the Declaration of Helsinki.

4.3.4.1.12 Data Analysis

Efficacy variables

The primary variable was 'trough FEV1' after 12 weeks of treatment (Visit 9). Trough FEV1 was defined as the average of the 23 hr 10 min and the 23 hr 45 min values taken in the clinic at Visits 5 and 9 only. At all other visits tFEV1 was defined as the average of the 50 min and 15 min pre-dose values taken at the clinic. The baseline measurement was defined as the average of the FEV1 values taken in the clinic 50 and 15 min prior to dosing at Visit 4 (Day 1/week1). The primary variable (imputed with LOCF) was analyzed using a mixed model for the full analysis set (FAS) which included all randomized patients who received at least one dose of study drug. Following the intent-to-treat principle, patients were analyzed according to the treatment they were assigned to at randomization. The per-protocol set (PPS) included all patients in the FAS without any major protocol deviations. The safety set included all patients who received at least one dose of study drug. The FAS and safety set are the same except that the safety set allows the inclusion of non-randomized patients who received study drug in error, and the FAS assigns randomized treatment while the safety set assigns received treatment.

The sponsor-defined MCID of 120 mL in the tFEV1 was the same MCID used as in prior trials with patients with COPD. An estimate of the standard deviation of tFEV1 of 225 ml at 12 weeks was obtained from other phase III indacaterol studies, QAB149B2334, QAB149B2346 and QAB149B2335S. Based on these values, the Sponsor calculated 75 evaluable patients per treatment group were required to detect a difference in tFEV1 of 120 mL at Week 12, using a 5% significance level (two-sided) with 90% power, assuming a standard deviation of 225 mL. Assuming a drop out rate of 15% over 12 weeks of treatment, a sample size of 178 randomized patients (89 per treatment group) in total was required.

Missing values and discontinuations were handled as in Studies B2357 and B2356, the dose ranging trials. Furthermore, as in these previous trials, any value contributing to the tFEV1 that were collected within 6 hours of rescue medication or actual measurement times were outside the 22-25 hour post-dose time window then the individual FEV1 value was not analyzed.

Superiority of indacaterol 75 mcg to placebo was demonstrated if the two-sided p-value was less than the 5% significance level and the 95% confidence interval for the mean FEV1 difference of indacaterol minus placebo lay entirely to the right of (higher than) 0 mL.

Supportive analyses include tFEV1 for the PPS imputed with LOCF as well as both FAS and PPS without LOCF. There were numerous exploratory subgroup analyses such as age < 65 and ≥ 65; gender; race; severity of disease; smoking status at baseline; use of ICS; BMI and waist to hip ratio. Analysis of the log-transformed tFEV1 (imputed with LOCF) after 12 weeks of treatment for the FAS was also performed using the same mixed model.

The key secondary variable was the TDI focal score after 12 weeks treatment. This score was analyzed using the same mixed model as specified for the primary analysis with the BDI focal score as baseline. If data was missing or insufficient for any one of the domains a focal score was not calculated. The Sponsor did have a hierarchical testing approach to handle multiplicity for the primary and key secondary comparisons:

1. tFEV1 after 12 weeks treatment - Superiority of indacaterol 75 mcg over placebo. If indacaterol 75 mcg was superior to placebo then;
2. TDI focal score after 12 weeks treatment - Superiority of indacaterol 75 mcg over placebo.

The treatment comparisons for the other secondary variables were for supportive evidence and no adjustment for multiplicity were made.

Other secondary variables:

- Trough FEV1 following a single dose (Day 2) of treatment
- Standardized AUC (5 min – 4 h) for FEV1 following a single dose and after 12 weeks of treatment
- Peak FEV1 over 5 min - 4 hours post morning dose on Day 1 (single dose) and after 12 weeks of treatment
- FEV1 and FVC at each post-baseline time point
- FEV1 trough response over 12 weeks- rate of change in tFEV1 defined as the average of the 50 min and 15 min pre-dose values from Visit 6 (Day 29) onwards was analyzed using a random coefficients model
- 24 hour Serial Spirometry- FEV1 and FVC at each scheduled time-point (6, 12, 16, 22 and 24 hours) was analyzed using the same mixed model for all patients in the FAS in the 24 hr profiling subgroup. The baseline was defined as the trough measurement at Visit 9 prior to the 24 profiling spirometry
- Daily rescue medication use (number of puffs) over 12 weeks
- Daytime and nighttime rescue medication use (number of puffs) over 12 weeks
- Daily, daytime and nighttime rescue medication use (number of puffs) at approximately 4 weekly intervals
- Percentage of ‘days with no rescue use’ over 12 weeks
- Percentage of nights with ‘no nighttime awakenings’ over 12 weeks
- Percentage of days with ‘no daytime symptoms’ over 12 weeks
- Percentage of ‘days able to perform usual daily activities’ over 12 weeks
- Symptom scores over 12 weeks
- Percentage of patients with a clinically important improvement of at least 1 in the TDI focal score after 12 weeks treatment
- SGRQ total score after 4 weeks and 12 weeks treatment, percentage of patients with a clinically important improvement of at least 4 units in the total SGRQ score after 4 weeks and 12 weeks treatment.

Exploratory variables:

- COPD exacerbations- For COPD exacerbation related endpoints the comparison between indacaterol and placebo were exploratory endpoints.

All variables were summarized and analyzed by treatment for the FAS unless otherwise specified and where appropriate, utilized the mixed model for analysis.

Safety variables
All safety endpoints were summarized for the safety set. Safety data, including AEs data, vital signs, ECG, chemistry, hematology, and use of rescue and concomitant medications, were listed and summarized by treatment group. Selected safety data were analyzed formally, including heart rate, QTcF, serum potassium and plasma glucose, using a repeated measures analysis. Treatment emergent AEs, prior and post-treatment AE were classified as in Studies B2357 and B2356, the dose ranging studies.

Health-related quality of life variables

SGRQ total score after 12 weeks of treatment

The scoring and handling of missing item data for the SGRQ were conducted in accordance with the user guide. The SGRQ total score at Week 12 (Visit 9) were summarized by treatment and analyzed using a mixed model for the FAS. The same model as specified for the primary analysis was used, however, with baseline SGRQ total score instead of baseline FEV1 as covariate.

Missing data of the SGRQ total score were imputed by using LOCF. Scores were carried forward from the last evaluable visit within the previous 8 weeks. Similar analysis as for the SGRQ total score were performed for the symptoms, activities, and impacts component scores.

Percentage of patients with a clinically important improvement of at least 4 units in the total SGRQ score after 12 weeks treatment

The proportion of patients who achieved a clinically important improvement of at least 4 units in the total SGRQ was analyzed using logistic regression for the FAS. The model included terms for treatment, baseline smoking status and country as fixed effects with center nested within country as a random effect. The model also contained as fixed effects the baseline total SGRQ score, FEV1 prior to inhalation and FEV1 10-15 min post inhalation of albuterol (components of SABA reversibility at Visit 2), FEV1 prior to inhalation and FEV1 1 hour post inhalation of ipratropium (components of anticholinergic reversibility at Visit 3), and inhaled corticosteroid use at baseline as covariates. The estimated adjusted odds ratios were displayed along with associated 95% confidence interval and two-sided p-values.

4.3.4.2 Patient Disposition and Demographics

Disposition

Table 42 below outlines the numbers of patients screened, randomized and completed by treatment group. A total of 597 patients were screened, and 318 were randomized equally to the two treatment groups. One hundred forty-eight (93%) of the patients in the indacaterol 75 mcg treatment group and 142 (89%) of patients in the placebo treatment group completed the study. The primary reason for discontinuation in both treatment groups was ‘subject withdrew consent’, occurring in 5 patients in the indacaterol treatment group and 6 in the placebo group. Overall, the proportion of patients discontinuing for each reason was similar for both treatment groups, with the exception of ‘unsatisfactory therapeutic effect’ where all (2.5%) the affected patients were in the placebo group. The proportion of patients who discontinued due to AEs was the same in each treatment group and these patients are discussed in Section 4.3.4.3.3.

Table 42 Protocol B2355 Patient disposition (All patients)

	Ind 75 µg n (%)	Pbo n (%)	Total n (%)
Patients			
Screened	-	-	597
Randomized	159 (100.0)	159 (100.0)	318 (100.0)
Exposed	159 (100.0)	159 (100.0)	318 (100.0)
Completed	148 (93.1)	142 (89.3)	290 (91.2)
Discontinued	11 (6.9)	17 (10.7)	28 (8.8)
Primary reason for premature discontinuation			
Subject withdrew consent	5 (3.1)	6 (3.8)	11 (3.5)
Adverse event(s)	3 (1.9)	3 (1.9)	6 (1.9)
Abnormal laboratory value(s)	1 (0.6)	0 (0.0)	1 (0.3)
Lost to follow-up	1 (0.6)	2 (1.3)	3 (0.9)
Protocol deviation	1 (0.6)	1 (0.6)	2 (0.6)
Unsatisfactory therapeutic effect	0 (0.0)	4 (2.5)	4 (1.3)
Administrative problems	0 (0.0)	1 (0.6)	1 (0.3)

Source: Table 10-1 Study No. CQAB149B2355 Clinical Study Report

Protocol Deviations
A total of 69 patients in the FAS had at least one major protocol deviation resulting in exclusion from the PPS, 40 (25%) in the indacaterol treatment group and 29 (18%) in the placebo group. The most frequent protocol deviation resulting in exclusion from the PPS was ‘spirometry for SABA reversibility not acceptable as per American Thoracic Society/ European Respiratory Society (ATS/ERS) criteria’ and this occurred in a higher proportion of patients in the indacaterol 75 mcg (18%) group than in the placebo (13%) group.

A slightly higher proportion of patients in the placebo group (5%) than in the indacaterol 75 mcg group (2.5%) were ‘not compliant with dosing scheduled at the primary endpoint dosing visit(s)’. Other major protocol deviations occurred in 7 patients or fewer overall.

Demographics
Table 43 summarizes the demographics for the two treatment groups which were generally well matched. Overall the majority of patients were caucasian, approximately 54% were male, and the mean age was 61.4 years, with a range of 40 to 86 years.

Table 43 Protocol B2355 Demographic summary (Safety set)

		Ind 75 µg N=159	Pbo N=159	Total N=318
Age (years)	N	159	159	318
	Mean	61.3	61.5	61.4
	SD	9.83	9.85	9.83
	Median	61.0	62.0	62.0
	Min – Max	40 - 82	42 - 86	40 – 86
Age group - n (%)	19-39 years	0 (0.0)	0 (0.0)	0 (0.0)
	40-64 years	96 (60.4)	94 (59.1)	190 (59.7)
	≥65 years	63 (39.6)	65 (40.9)	128 (40.3)
Sex - n (%)	Male	83 (52.2)	89 (56.0)	172 (54.1)
	Female	76 (47.8)	70 (44.0)	146 (45.9)
Race - n (%)	Caucasian	151 (95.0)	147 (92.5)	298 (93.7)
	Black	7 (4.4)	9 (5.7)	16 (5.0)
	Native American	0 (0.0)	1 (0.6)	1 (0.3)
	Other	1 (0.6)	2 (1.3)	3 (0.9)
Weight (kg)	n	159	159	318
	Mean	79.6	82.2	80.9
	SD	17.68	19.17	18.46
	Median	78.0	82.1	80.0
	Min – Max	40.9 - 130.5	35.0 - 132.0	35.0 - 132.0

Source: Adapted from Table 11-2 Study No. CQAB149B2355 Clinical Study Report

Baseline disease characteristics were comparable between treatment groups (Table 44). Overall, the median duration of COPD was 5.0 years, with a range of 0 to 31.2 years. Overall, the severity of COPD was moderate in approximately 62% of patients and severe in 38% of patients. Specifically, in the indacaterol 75 mcg group, 109 (69%) patients were categorized as moderate in severity and in the placebo group, 87 (55%) were moderate. Less than half of patients were using inhaled corticosteroids (ICS) on entry to the study. A greater proportion of patients were current smokers (58.8%) than ex-smokers (41.2%).

Reviewer Comment:
Although, more patients in the placebo group 72 (45%) than in the indacaterol group 48 (30%) were in the severe category, the baseline FEV1 was similar between the groups with an overall pre-bronchodilator FEV1 of 1.30 L, suggesting a more moderate population. This is consistent with the proposed marketing population.

Table 44 Protocol B2355 Baseline disease characteristics (Safety set)

		Ind 75 µg N=159	Pbo N=159	Total N=318
Duration of COPD (years)	n	159	159	318
	Mean	6.7	6.8	6.8
	SD	6.10	6.10	6.09
	Median	5.6	4.7	5.0
	Min - Max	0.0 - 31.2	0.0 - 30.0	0.0 - 31.2
Duration of COPD - n (%)	< 1 year	17 (10.7)	12 (7.5)	29 (9.1)
	1 - 5 years	60 (37.7)	71 (44.7)	131 (41.2)
	>5 - 10 years	46 (28.9)	45 (28.3)	91 (28.6)
	>10 - 15 years	24 (15.1)	18 (11.3)	42 (13.2)
	>15 - 20 years	5 (3.1)	7 (4.4)	12 (3.8)
	> 20 years	7 (4.4)	6 (3.8)	13 (4.1)
Severity of COPD (GOLD 2008) - n (%)	Mild	0 (0.0)	0 (0.0)	0 (0.0)
	Moderate	109 (68.6)	87 (54.7)	196 (61.6)
	Severe	48 (30.2)	72 (45.3)	120 (37.7)
	Very severe	2 (1.3)	0 (0.0)	2 (0.6)
ICS use - n (%)	No	96 (60.4)	103 (64.8)	199 (62.6)
	Yes	63 (39.6)	56 (35.2)	119 (37.4)
Smoking history - n (%)	Ex-smoker	67 (42.1)	64 (40.3)	131 (41.2)
	Smoker	92 (57.9)	95 (59.7)	187 (58.8)
Number of pack years	n	159	159	318
	Mean	52.4	52.4	52.4
	SD	28.06	28.39	28.18
	Median	45.0	45.0	45.0
	Min - Max	11.0 - 180.0	10.0 - 204.0	10.0 - 204.0

Source: Table 11-3 Study No. CQAB149B2355 Clinical Study Report

4.3.4.3 Efficacy Review

4.3.4.3.1 Primary Endpoint

The prespecified primary efficacy endpoint was the 'trough FEV1' after 12 weeks of treatment. For the FAS, the LS mean in the indacaterol 75 mcg group was statistically greater than placebo. The number randomized was 318, however, 295 were analyzed. The treatment difference was 0.140 L (0.10, 0.18, p-value of <0.001) consistent with a clinically important bronchodilator effect.

Subgroup analyses for age, sex, COPD severity, smoking history, SABA reversibility and ICS use at baseline were performed for tFEV1 after 12 weeks of treatment. The treatment differences are displayed below in Table 45. Consistent with Study B2354, indacaterol 75 mcg dose had a larger treatment difference in the ≥ 65 age group with 0.16 L as opposed to the < 65 age group with 0.13 L. The treatment difference for indacaterol 75 mcg based on severity were consistent with that seen in B2354 and B2336, larger differences were seen in patients with moderate or less severe COPD (0.16 L) than in those with severe or worse disease with a treatment difference of only 0.13 L. For those who were not on ICS at baseline, the treatment difference was 0.18 L vs. those on a stable ICS regimen with 0.07 L.

Table 45 Protocol B2355 Analysis of trough FEV1 after 12 weeks treatment (imputed with LOCF), select subgroup analyses

	Trough FEV1 (L)				
	Ind 75 mcg N=145	Placebo N=150	Treatment difference	95% CI	p-value
Full analysis set	1.49	1.35	0.14	0.10, 0.18	<0.001
Subgroup analyses					
Age					
< 65	1.48	1.35	0.13	0.07, 0.18	<0.001
≥ 65	1.51	1.35	0.16	0.10, 0.23	<0.001
Gender					
Male	1.51	1.34	0.17	0.11, 0.23	<0.001
Female	1.47	1.36	0.11	0.05, 0.17	<0.001
COPD Severity					
Moderate or less	1.49	1.33	0.16	0.10, 0.21	<0.001
Severe or worse	1.49	1.37	0.13	0.05, 0.20	<0.001
Smoking status					
Ex smoker	1.50	1.35	0.14	0.08, 0.21	<0.001
Current smoker	1.49	1.34	0.14	0.09, 0.20	<0.001
SABA reversibility					
≤ 12%	1.49	1.37	0.12	0.06, 0.19	<0.001
>12%	1.49	1.34	0.16	0.10, 0.21	<0.001
ICS					
No	1.51	1.33	0.18	0.13, 0.23	<0.001
Yes	1.46	1.39	0.07	0.01, 0.14	0.035

Source: Adapted from Tables 14.2-1.1b and 14.2-1.1c Study No. CQAB149B2355 Clinical Study Report

4.3.4.3.2 Secondary Endpoint

The key secondary efficacy endpoint, the TDI was prespecified by the Sponsor such that a difference of 1 unit was considered a MCID for COPD patients. At Week 12, the difference between treatment groups in LS mean TDI focal score was not statistically significant nor did it meet the MCID of 1 unit. The LS mean TDI treatment difference was 0.45 (-0.18, 1.09).

Reviewer comment:
The Applicant has not included any labeling claims regarding dyspnea or the Mahler TDI instrument.

Other Endpoints

- Trough FEV1 on days other than the primary endpoint

The trough FEV1 showed a significant improvement over placebo at all time points tested. A smaller effect was demonstrated after the first dose, consistent with other indacaterol studies.

Table 46 Protocol B2355 Analysis of tFEV1 over 12 weeks of treatment at visits other than the primary endpoint (FAS)

tFEV1 alternate visits	Treatment difference Ind 75 mcg – pbo (L)	95% CI	p-value
Day 2	0.08	0.05, 0.11	<0.001
Day 29	0.15	0.11, 0.19	<0.001
Day 57	0.15	0.11, 0.19	<0.001
Day 84	0.12	0.07, 0.16	<0.001

Source: Table 14.2-3.1 Study No. CQAB149B2355 Clinical Study Report

- FEV1 AUC 5 min- 4hr following a single dose (Day 1) and Week 12

The FEV1 AUC 5 min- 4 hr after the first dose and week 12 of study medication was analyzed for the full analysis set. The LS mean AUC 5 min- 4 hr at Day 1 and Week 12 were statistically significantly greater in the indacaterol 75 mcg group than in the placebo group. The treatment difference between indacaterol and placebo after Day 1 was 0.12 L (95% CI 0.10, 0.15; p<0.001) and after 12 weeks of treatment, it was 0.18 L (95% CI 0.14, 0.23; p<0.001).

- Peak FEV1 over 5 min- 4 hrs Day 1 and Week 12

The maximum FEV1 during the first 4 hours post morning dosing was calculated at Day 1 (Visit 4) and Week 12 (Visit 8). The treatment difference for the peak FEV1 5min- 4 hrs was statistically significant for both time points: for Day1 the value was 0.11 (0.08, 0.13) and Week 12 the value was 0.17 (0.13, 0.22).

- FEV1 at post-baseline time points

To evaluate the onset of action, FEV1 was measured at multiple time points on Days 1, 2, 29, 57, 84 and 85. At 5 minutes, the treatment difference represents of 75 mcg indacaterol on FEV1 compared to placebo was 0.10 L which was statistically significant and represented 69% of the mean trough value on Day 85. See Table 47.

Table 47 B2355 Trough FEV1 at multiple post baseline time points

Analysis of FEV1 for Indacaterol 75 mcg at multiple time points (FAS)				
		Treatment difference (L)	95% CI	p-value
Day 1	5 min	0.10	(0.08, 0.12)	< 0.001
	30 min	0.12	(0.10, 0.15)	< 0.001
	1 hr	0.12	(0.09, 0.15)	< 0.001
	2 hr	0.12	(0.09, 0.15)	< 0.001
	4 hr	0.13	(0.09, 0.16)	< 0.001
Day 2	23 hr 10 min	0.08	(0.04, 0.11)	< 0.001
	23 hr 45 min	0.07	(0.04, 0.11)	< 0.001
Day 29	-50 min	0.14	(0.11, 0.18)	< 0.001
	-15 min	0.15	(0.11, 0.18)	< 0.001
	5 min	0.18	(0.15, 0.22)	< 0.001
	30 min	0.20	(0.16, 0.23)	< 0.001
	1 hr	0.20	(0.16, 0.24)	< 0.001
Day 57	-50 min	0.15	(0.11, 0.19)	< 0.001
	-15 min	0.14	(0.10, 0.18)	< 0.001
	5 min	0.18	(0.14, 0.22)	< 0.001
	30 min	0.20	(0.15, 0.24)	< 0.001
	1 hr	0.21	(0.17, 0.25)	< 0.001
Day 84	-50 min	0.11	(0.07, 0.15)	< 0.001
	-15 min	0.11	(0.06, 0.15)	< 0.001
	5 min	0.16	(0.11, 0.20)	< 0.001
	30 min	0.19	(0.14, 0.23)	< 0.001
	1 hr	0.18	(0.14, 0.23)	< 0.001
	2 hr	0.19	(0.15, 0.24)	< 0.001
	4 hr	0.17	(0.12, 0.21)	< 0.001
Day 85	23 hr 10 min	0.15	(0.10, 0.19)	< 0.001
	23 hr 45 min	0.14	(0.10, 0.19)	< 0.001

Source: Table 14.2-5.1 Study No. CQAB149B2355 Clinical Study Report

- FEV1 trough response over 12 Weeks

To evaluate potential tachyphylaxis over this 12 week study, the protocol called for comparisons of the rate of change in tFEV1 for indacaterol 75 mcg group and placebo from Day 29 to 12 weeks. There was no statistically significant difference in the estimate of the rate of change in tFEV1 from Day 29 to 12 weeks of treatment between the treatment groups. The rate of change (slope) per month was -3.42 for indacaterol 75 mcg group and 4.51 for placebo. The treatment difference was -7.93 (95% CI -25.94, 10.075; p=0.387).

- 24 hr serial spirometry

A subset of 239 patients took part in serial spirometry assessments after the final dose of study medication at Week 12. Spirometry measurements were made pre-dose and serially up to 24 hours post-dose. At each time point, both pre-dose and post-dose, the LS mean FEV1 value was statistically significantly greater in the indacaterol 75 mcg group than in the placebo group. The LS mean treatment difference was 0.13 L at all time points, consistent with a bronchodilator effect over the 24 hour dosing period.

- Rescue medication use

All patients were provided with albuterol for use as rescue medication from Visit 1. Rescue medication use over 12 weeks of treatment is summarized below in Table 48. The protocol stated that the number of puffs of rescue medication taken in the previous 12 hours would be recorded twice daily in the electronic patient diary. The value was obtained by calculating the total number of puffs of rescue medication per day (over 12 weeks) and dividing that by the total number of days with non-missing rescue medication. The indacaterol 75 mcg group had statistically significant improvement in the LS mean change from baseline over placebo in:

- daily number of puffs of rescue medication
- number of puffs during the day and night compared with placebo over 12 weeks of treatment, and
- days with no rescue medication use

Table 48 Protocol B2355 Rescue medication use over 12 weeks: treatment comparisons (FAS)

		-- Treatment --			---------- Treatment difference ----------			
Treatment	**n**	**LSM**	**SE**	**Comparison**	**LSM**	**SE**	**95% CI**	**p-value**
Change from baseline in the mean daily number of puffs of rescue medication								
Ind 75 µg	150	-1.15	0.186	Ind 75 µg - Pbo	-0.66	0.247	(-1.15, -0.18)	0.008
Pbo	154	-0.49	0.184					
Change from baseline in the mean daytime number of puffs of rescue medication								
Ind 75 µg	147	-0.75	0.109	Ind 75 µg - Pbo	-0.41	0.140	(-0.68, -0.13)	0.004
Pbo	152	-0.34	0.107					
Change from baseline in the mean nighttime number of puffs of rescue medication								
Ind 75 µg	149	-0.45	0.091	Ind 75 µg - Pbo	-0.32	0.124	(-0.56, -0.07)	0.011
Pbo	151	-0.13	0.091					
Percentage of 'days with no rescue use'								
Ind 75 µg	149	39.3	2.40	Ind 75 µg - Pbo	8.4	2.91	(2.7,14.1)	0.004
Pbo	150	30.9	2.38					

Source: Table 11-11 Study No. CQAB149B2355 Clinical Study Report

- Symptoms

The only symptom category to reach statistical significance was "days able to perform usual daily activities" with a treatment LS mean value of 39 for indacaterol 75 mcg treatment group vs. 30.3 for placebo. The treatment difference was 8.7 with a p-value of <0.001. See Table 49.

Table 49 Protocol B2355 Percentage of nights with "no nighttime awakenings", percentage of days with "no daytime symptoms" and percentage of "days able to perform usual daily activities" over 12 weeks: treatment comparisons (FAS)

		- Treatment -			- Treatment difference -			
Treatment	**n**	**LS Mean**	**SE**	**Comparison**	**LS Mean**	**SE**	**95% CI**	**p-value**
Percentage of nights with 'no nighttime awakenings'								
Ind 75 µg	149	63.4	1.82	Ind 75 µg - Pbo	1.9	2.44	(-2.9, 6.7)	0.430
Pbo	151	61.5	1.81					
Percentage of days with 'no daytime symptoms'								
Ind 75 µg	147	8.0	1.20	Ind 75 µg - Pbo	2.8	1.66	(-0.5, 6.1)	0.091
Pbo	152	5.2	1.19					
Percentage of 'days able to perform usual daily activities'								
Ind 75 µg	147	39.0	1.97	Ind 75 µg - Pbo	8.7	2.53	(3.7, 13.7)	<0.001
Pbo	152	30.3	1.94					

Source: Table 11-12 Study No. CQAB149B2355 Clinical Study Report

- **Health related quality of life**

The SGRQ was used to provide health-related quality of life measurements during the course of the study. The protocol specified that the SGRQ would be administered at Visits 4, 6 and 8 (Days 1, 29 and 84). Negative changes in scores indicate improvement in health-related quality of life. Comparisons between the indacaterol 75 mcg treatment group and placebo were to be based on the total score, with a difference of 4 points pre-specified as representing a clinically meaningful difference.

The LS mean SGRQ total score treatment difference at Week 12 (imputed with LOCF) was statistically significantly lower in the indacaterol 75 mcg group than in the placebo group. However, the treatment difference of -3.6 (-6.4, -0.9) did not reach the MCID of 4 units. The SGRQ total score treatment difference at Week 4 was -2.0 (-4.3, 0.2). The proportion of patients with a MCID of ≥ 4 units in the SGRQ was 51% for the indacaterol 75 mcg group and 37% for the placebo group. Analysis of the individual SGRQ domains was also performed with the only significant findings seen in the symptoms and impact domain as seen in Table 50 below.

Table 50 Protocol B2355 Analysis of SGRQ component scores after 12 weeks

	LS Mean score		Treatment difference	95% CI	p-value
	Ind 75 mcg N=148	Placebo N=145			
Symptoms score	56.0	61.9	-6	(-9.8, -2.1)	0.003
Activity score	62.3	65.1	-2.3	(-5.7, 1.1)	0.179
Impacts score	32.8	36.4	-3.6	(-6.7, -0.4)	0.026
Total score	45.9	49.5	-3.6	(-6.4, -0.9)	0.010

Adapted from data in Tables 14.2-9.4, 14.2-9.6 and 14.2-9.8

- **COPD exacerbation frequency**

The exploratory efficacy variable of COPD exacerbation frequency was also measured. The mean number of exacerbations over 12 weeks (without imputation) was 0.9 for both the indacaterol 75 mcg group and placebo group. Only one patient had more than 1 COPD exacerbation during the 12 week treatment (1 patient in the placebo group had 2 exacerbations). The rate of exacerbations per year was comparable between the treatment groups (0.39 indacaterol 75 mcg, 0.40 placebo). Imputation was done by adding one exacerbation to the total number of exacerbations for patients who discontinued prematurely unless they had an exacerbation in the 7 days prior to discontinuation. The mean number of exacerbations over 12 weeks with imputation was 0.14 for the indacaterol 75 mcg group and 0.16 for the placebo group and the corresponding rates of exacerbations were 0.64 and 0.74 respectively.

Reviewer comment:
COPD exacerbation frequency is difficult to determine in a 3 month study, so results should be interpreted with caution. The recommended duration for a study designed to show a difference in COPD exacerbations is 12 months.

4.3.4.3.3 Safety Review

All relevant long term trials will be reviewed collectively in the Integrated Summary of Safety. However, a brief synopsis of the safety findings from this trial will be provided here.

4.3.4.3.4 Extent of Exposure

The extent of exposure was identical between the indacaterol and placebo groups with a median number of days of exposure as 85 in both. As well, both groups exhibited a high level of compliance with 97 % of the indacaterol 75 mcg doses taken and 98% of placebo doses taken.

4.3.4.3.5 Concomitant medication

Most patients were taking both non COPD and COPD related medications. The most commonly taken COPD related medication taken was ICS used in approximately 39% of those on indacaterol and 35% on placebo. The most common non COPD related medications were aspirin, lisinopril, multivitamins and ibuprofen with similar rates in both.

4.3.4.3.6 Adverse events

There were more incidences of AEs in the indacaterol group (44.7%) than in placebo (40.9%).The most frequently reported SOCs reported were infections and infestations and respiratory, thoracic and mediastinal. The most common AE was COPD and was reported with similar frequencies in the indacaterol 75 mcg (8.8%) and placebo (8.2%) groups. However, cough, the second most frequent AE overall, was 3x higher in the indacaterol group (9.4%) than placebo (3.1%). Nasopharyngitis, oropharyngeal pain, bronchitis, headache, hypertension were reported in >2% of those on indacaterol and was higher than placebo.

Deaths and SAEs

There were no deaths in the trial. SAEs occurred with the same rate across the two treatment groups. The proportion of SAEs leading to discontinuations in either treatment group are summarized in Table 51 below. Using the preferred terms, there were more events of non cardiac chest pain, bronchitis, pneumonia, CVA, COPD and hemoptysis reported in the indacaterol treated groups than placebo.

Adverse events leading to discontinuation

Two patients in the indacaterol treatment group discontinued, one for hospitalization due to bronchitis and hemoptysis and the other due to hospitalization due to a CVA. One patient discontinued on placebo due to hospitalization for a limb crushing injury.

Table 51 Protocol B2355 Deaths, other serious adverse events (including COPD exacerbations) and adverse events leading to permanent discontinuation of study drug- n% of patients (Safety set)

	Ind 75 µg N=159 n (%)	Pbo N=159 n (%)
Patients with any AE(s)	71 (44.7)	65 (40.9)
Serious AEs or AE discontinuations		
Deaths	0 (0.0)	0 (0.0)
SAEs	4 (2.5)	4 (2.5)
Discontinued due to AE(s)	3 (1.9)	3 (1.9)
Discontinued due to SAE(s)	2 (1.3)	1 (0.6)
Discontinued due to non-SAE(s)	2 (1.3)	2 (1.3)

Source: Table 12-4 Study No. CQAB149B2355 Clinical Study Report

4.3.4.3.7 Laboratory findings

There were no meaningful differences between groups nor any clinically meaningful shifts from baseline for hematology or chemistry laboratory assessments. Glucose levels greater than 9.99 mmol/L were found in 9 (5.7%) patients in the indacaterol group and 15 (9.4%) in the placebo group. For potassium levels < 3 mmol/L there was 1 patient in each treatment group. There was 1 patient in each the AST, ALT and Gamma GTT with levels > 3x the upper limit of normal (ULN) and 2 patients in placebo with a gamma GT level >3 x the ULN.

4.3.4.3.8 ECG findings

There were no events of QTc > 500 ms in either treatment group reported. A maximum increase from baseline of 30-60 ms was observed in 15 patients in the indacaterol group and 12 in the placebo group.

There were no > 60 ms increases from baseline in either group. ECG changes were comparable however there were more conduction abnormalities in the indacaterol group (16.5%) than placebo (10%).

4.3.4.3.9 Physical examination

Physical examination findings will focus on blood pressure and pulse abnormalities. There were no pulse rates > 130 bpm observed in the indacaterol groups, there was one in the placebo group. There were 2 patients with SBP >200 mm Hg, 1 in placebo, however for diastolic blood pressure, there were 5 with a DBP >115 mm Hg in the indacaterol group and 1 in placebo.

4.3.4.4 Summary of Study

This was a twelve week, multicenter, randomized, placebo-controlled trial comparing indacaterol 75 mcg q.d. to placebo in adults with moderate to severe COPD. The selected dose of indacaterol 75 mcg achieved the primary endpoint, demonstrating a statistically significant treatment difference of 0.14 L in trough FEV1 from placebo after twelve weeks. Subgroup analyses of the primary endpoint demonstrated larger treatment differences for patients aged ≥ 65, those with moderate or less severe disease and those not on ICS at baseline.

Indacaterol 75 mcg failed to show a statistically significant improvement in the key secondary endpoint, TDI focal score over placebo. Other spirometry based endpoints did demonstrate superiority of indacaterol 75 mcg over placebo including tFEV1 on Days 2, 29, 57 and 84;FEV1 AUC5min- 4hr; and peak FEV1 over 5 min-4hr on Days 1 and week 12. At 5 minutes post first dose, the treatment difference was 0.10 L, which was statistically significant and represented 69% of the treatment difference achieved on Day 85. There was no difference in the rate of change in tFEV1 for indacaterol 75 mcg from Day 29 to Week 12, indicating that there was no tachphylaxis. Rescue medication use was also statistically significantly reduced after 12 weeks of treatment with indacaterol 75 mcg.

Only one category of the patient diary symptoms assessment, ‘days able to perform usual daily activities’ improved significantly on indacaterol. The quality of life questionnaire, SGRQ, did not meet the predefined clinically meaningful difference of -4 for the total score. However, both the symptom component as well as the impact component achieved statistical significance after 12 week treatment with indacaterol 75 mcg.

COPD and cough were the most frequent reported AEs. There were no deaths reported during the trial and the 3 SAEs 2 in the indacaterol treatment group and the remaining in placebo that led to discontinuation. There were no clinically meaningful differences between treatment groups observed in the hematology, chemistry laboratory or urinalysis assessments, vitals or ECG. There were reports of expected pharmacodynamic effects in glucose, potassium levels, ECG and one event of elevated blood pressure recorded as an AE.

4.3.5 CONFIRMATORY TRIAL B2354

A Twelve-Week Treatment, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Efficacy and Safety of Once Daily Indacaterol in Patients with Chronic Obstructive Pulmonary Disease

4.3.5.1 Trial Description

4.3.5.1.1 Design

This was a Phase III randomized double-blind, placebo-controlled, parallel group trial using 75 mcg indacaterol once daily in patients with moderate to severe COPD. Patients were stratified based on smoking status and ICS use.

4.3.5.1.2 Duration

The treatment period was 12 weeks following a 14 day run-in period.

4.3.5.1.3 Population

The population consisted of male and female adults aged ≥ 40 years, who were outpatients with a diagnosis of moderate to severe COPD, as classified by the GOLD Guidelines 2008.

4.3.5.1.4 Study Sites

There were sixty-three centers in the United States

4.3.5.1.5 Investigational and Reference Therapy

- Investigational product: indacaterol 75 mcg formulation # 6002142.003 batch # X173GF, X297LF, X231KF.
- Placebo to indacaterol formulation # 3760253.004 batch # X171CD, X123DF. Indacaterol and placebo both were delivered via SDDPI, Concept 1 device (Neohaler).

4.3.5.1.6 Objectives

The primary objective of the study was to evaluate the efficacy of indacaterol (75 mcg q.d.) in terms of 24 hour post-dose tFEV1 as compared to placebo after 12 weeks of treatment. Trough FEV1 was defined as in the previous trial B2355.

The key secondary objective was to evaluate the efficacy of indacaterol (75 mcg q.d.) in terms of the TDI focal score after 12 weeks of treatment as compared to placebo.

Other secondary objectives were:

- To evaluate the efficacy of indacaterol (75 mcg q.d.) in terms of t FEV1 after a single dose (Day 2) of treatment as compared to placebo
- To evaluate the efficacy of indacaterol (75 mcg q.d.) versus placebo for the standardized area under the curve (AUC) of FEV1 5 minutes-4 hours after a single dose (Day 1) and 12 weeks of treatment
- To evaluate the efficacy of indacaterol (75 mcg q.d.) in terms of health-related quality-of-life as measured by St. George's Respiratory Questionnaire (SGRQ) total score after 12 weeks of treatment compared to placebo
- To evaluate the efficacy on indacaterol (75 mcg q.d.), and placebo in terms of rescue medication use over the 12 week treatment period using data obtained from the electronic diary (eDiary)
- To evaluate the efficacy of indacaterol (75 mcg q.d.) and placebo in terms of patient reported symptoms over the 12 week treatment period using data obtained from the eDiary
- To compare indacaterol (75 mcg q.d.) to placebo on spirometry assessments in terms of FEV1 measured at all time points, including approximate peak response (Day 1 and after 12 weeks treatment) and trough response
- To evaluate the safety (in particular regarding ECG, laboratory tests, vital signs, AEs) of indacaterol (75 mcg q.d.) over 12 weeks, in patients with COPD

The Exploratory objectives were:

- To evaluate the effect of indacaterol (75 mcg q.d.) on COPD exacerbations over the 12- week treatment period
- To evaluate the PK profile of indacaterol in a subset of patients after 84 days of treatment was added in Amendment 1 dated 2/10/10.

4.3.5.1.7 Inclusion Criteria

The inclusion criteria were the same as those used in trials B2355 and B2356

4.3.5.1.8 Exclusion Criteria

The exclusion criteria were the same as those used in trials B2355 and B2356

4.3.5.1.9 Conduct

The trial was conducted almost identically to Study B2355, with the exceptions of no 24 hour spirometry profiling at the end of study as seen in B2355 and the addition of PK profiling obtained on Days 84 and 85. Briefly, the scheduled visits included both a prescreen to obtain informed consent and review and adjust COPD medications that were prohibited. Again, albuterol was to be used during the treatment period for rescue purposes only and rescue use was to be abstained within 6 hours of the start of each visit. The 14 day run-in was to assess eligibility and baseline information which was followed by the interval between Visits 4 and 9, the 12 week randomized blinded treatment period. The assessment schedule was similar with Study B2355.

Efficacy Assessments

The efficacy assessments included spirometry, daily clinical symptoms and rescue medication use, daily clinical symptoms, number of inhalations of albuterol rescue medication, BDI/TDI, and COPD exacerbations. The scheduling of spirometry measurements were the same as in Study B2355 except for the 24 hour profiling. Daily symptoms and rescue medication were captured with an electronic patient diary provided at Visit 2. Baseline and TDI scores were obtained on a similar schedule. COPD exacerbations were defined and recorded in the same manner as in Study B2355. Furthermore, as in B2355, COPD exacerbations were considered of moderate severity if treatment with systemic corticosteroids and/or antibiotic was required and severe if hospitalization was required. An ER visit of longer than 24 hours was considered a hospitalization. An increase in ICS dose was not be counted as an exacerbation. COPD exacerbations were recorded on the COPD exacerbations episode eCRF page only.

Safety Assessment

The safety assessment was the same as conducted in Study B2355.

Other Assessments

SGRQ

Similar to the conduct of Study B2355, the SGRQ was self-administered on paper by the patient at the investigator's site at baseline (Visit 4) and Visit 6 and 8 or at the time of discontinuation for patients who discontinue prematurely. The one month recall version of the SGRQ was used in this study. The questionnaire was to be completed before any other assessments were made.

PK Assessments

The collection of blood samples for PK as well as pharmacogenetic measurements after 12 weeks of study treatment was introduced in Amendment 1 dated February 10, 2010.

4.3.5.1.10 Concomitant Treatments

The prohibited medications, prohibited COPD-related medications and medications allowed under certain conditions were the same as in Studies B2357 and B2356, the dose ranging studies carried out in patients with asthma and COPD **Section 4.3.2.1.10** and **4.3.1.1.10**

4.3.5.1.11 Ethical Aspects

This clinical study was designed, implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

4.3.5.1.12 Data Analysis

The primary variable was 'trough FEV1' after 12 weeks of treatment (Visit 9) with LOCF as in B2355. Five populations were defined for analysis:

- The randomized set, included all randomized patients, whether they received study medication or not, grouped according to the treatment to which they were randomized.
- The full analysis set (FAS), included all randomized patients who received at least one dose of study drug. Patients were analyzed according to the treatment to which they were randomized.
- The per-protocol set (PPS), included all patients of the FAS without any major protocol deviations or non-protocol deviations. Patients were analyzed according to the treatment they received in the dispensing period prior to the primary endpoint visit except if a patient incorrectly took more than one treatment in the dispensing period prior to the primary endpoint visit. If this occurred the patient was excluded from the PPS. Major protocol deviations were defined prior to database lock and unblinding of the study.
- The safety set, included all patients who received at least one dose of study drug. Patients were analyzed according to the treatment they received except if a patient incorrectly took more than one treatment. If this occurred the patients was analyzed according to the treatment they were randomized to.
- The PK set included all patients with at least one evaluable drug concentration data sample who consented to participate in the PK subgroup. Patients were analyzed according to the treatment they received.

Note that the FAS and safety set are the same except that the safety set allows the inclusion of non-randomized patients who receive study drug in error. Also, the FAS assigned randomized treatment and the safety set assigned received treatment. The primary analysis set for efficacy was the FAS and was analyzed using the same mixed model as specified in Study B2355. The PPS was used for supportive analysis of the primary objective. The FAS was used for the analysis of all other efficacy variables. The PK set was used for the analysis of all PK data. The safety set was used in the analysis of all safety variables.

For the key secondary objective, the TDI focal score was analyzed using the same mixed model as specified for the primary analysis with the BDI focal score as baseline. If data was missing or insufficient for any one of the domains, the focal score was not calculated. A hierarchical testing approach of the primary and secondary comparisons was the procedure used to handle multiplicity.

1. Trough FEV1 after 12 weeks treatment - Superiority of indacaterol 75 mcg over placebo. If indacaterol 75 mcg is superior to placebo then;
2. TDI focal score after 12 weeks treatment - Superiority of indacaterol 75 mcg over placebo.

The treatment comparisons for the other secondary variables/comparisons were for supportive evidence and no adjustment for multiplicity was made.

4.3.5.2 Patient Disposition and Demographics

Disposition

Table 52 below outlines the numbers of patients screened, randomized and completed by treatment group. A total of 755 screenings took place, and 323 patients were randomized into the two treatment groups. The proportion of patients who completed the study was higher in the indacaterol 75 mcg group (88.3%) than in the placebo group (81.3%). The primary reason for discontinuation in both treatment

groups was AEs, primarily COPD exacerbations and pneumonia. A lower proportion of patients in the indacaterol 75 µg group withdrew consent than in the placebo group. Two deaths were reported in the placebo group.

Table 52 Protocol B2354 Patient disposition (All patients)

	Ind 75 µg n (%)	Pbo n (%)	Total n (%)
Screenings	-	-	755
Patients			
Randomized	163 (100.0)	160 (100.0)	323 (100.0)
Exposed	163 (100.0)	160 (100.0)	323 (100.0)
Completed	144 (88.3)	130 (81.3)	274 (84.8)
Discontinued	19 (11.7)	30 (18.8)	49 (15.2)
Primary reason for premature discontinuation			
Adverse event(s)	9 (5.5)	10 (6.3)	19 (5.9)
Subject withdrew consent	4 (2.5)	9 (5.6)	13 (4.0)
Protocol deviation	3 (1.8)	4 (2.5)	7 (2.2)
Abnormal test procedure result(s)	1 (0.6)	0 (0.0)	1 (0.3)
Unsatisfactory therapeutic effect	1 (0.6)	3 (1.9)	4 (1.2)
Lost to follow-up	1 (0.6)	1 (0.6)	2 (0.6)
Abnormal laboratory value(s)	0 (0.0)	1 (0.6)	1 (0.3)
Death	0 (0.0)	2 (1.3)	2 (0.6)

Source: Table 10-1 Study No. CQAB149B2354 Clinical Study Report

Protocol deviations

A total of 39 patients in the FAS had at least one major protocol deviation resulting in exclusion from the per-protocol set. The most frequent protocol deviation resulting in exclusion from the PPS was ‘spirometry for SABA reversibility not acceptable as per ATS/ERS criteria’ and this occurred in a similar proportion of patients in the indacaterol 75 mcg and the placebo groups. In general, the number of patients with each type of protocol deviation was similar between treatment groups.

Demographics

Table 53 below summarizes the key demographics of the two treatment groups. Overall, very similar to Study B2355, the majority of patients were caucasian, approximately 55% were male, and the mean age was 64 years.

Table 53 Protocol B2354 Demographic summary (Safety set)

		Ind 75 µg N=163	Pbo N=160	Total N=323
Age (years)	n	163	160	323
	Mean	64.0	64.1	64.0
	SD	8.29	9.43	8.86
	Median	64.0	64.0	64.0
	Min - Max	44 - 85	40 - 90	40 - 90
Age group – n (%)	19–39 years	0 (0.0)	0 (0.0)	0 (0.0)
	40–64 years	85 (52.1)	84 (52.5)	169 52.3)
	≥ 65 years	78 (47.9)	76 (47.5)	154 47.7)
Sex – n (%)	Male	89 (54.6)	87 (54.4)	176 (54.5)
	Female	74 (45.4)	73 (45.6)	147 (45.5)
Race – n (%)	Caucasian	145 (89.0)	146 (91.3)	291 (90.1)
	Black	10 (6.1)	10 (6.3)	20 (6.2)
	Asian	5 (3.1)	3 (1.9)	8 (2.5)
	Other	3 (1.8)	1 (0.6)	4 (1.2)

Source: Adapted from Table 11-2 Study No. CQAB149B2354 Clinical Study Report

Baseline disease characteristics were comparable between treatment groups (Table 54). Overall, the median duration of COPD was 5.1 years, with a range of 0 to 35.7 years. Approximately 50% of patients had a diagnosis of COPD for >5 years. The severity of COPD was moderate in approximately 57% of patients overall and the majority of the remaining patients had severe COPD with a balanced distribution between treatment groups. This was also different between the two studies, B2355 and B2354. While both had comparable distribution of severity i.e., B2355 61.6% vs. 37.7% moderate to severe, while in B2354 it was 57.3% vs. 42.1%, Study B2355 had a different pattern of distribution between indacaterol and placebo with 68.6% moderate disease in indacaterol treatment group and 54.7% in placebo; for severe it was 30.2% and 45.3% respectively, however for B2354 both moderate and severe patients were more equally distributed between indacaterol and placebo treatment groups. Overall, approximately 45% patients were using inhaled corticosteroids (ICS) on entry to the study. In contrast to Study B2355, a slightly greater proportion of patients were ex-smokers than current smokers. Overall smoking history in terms of the mean number of pack years for all patients was 52.

Prebronchodilator FEV1 for the combined treatment groups was 1.3 L (47% predicted). The overall mean FEV1 after albuterol was 53.5% of predicted normal, and the FEV1/FVC ratio was 52.4%. The overall mean reversibility of FEV1 after albuterol at Visit 2 and after ipratropium at Visit 3 was approximately 16% in each case.

Table 54 Protocol B2354 Baseline disease characteristics (Safety set)

		Ind 75 µg N=163	Pbo N=160	Total N=323
Duration of COPD (years)	n	163	160	323
	Mean	7.2	7.3	7.3
	SD	6.31	6.43	6.36
	Median	5.5	4.7	5.1
	Min - Max	0.0 - 30.7	0.1 - 35.7	0.0 - 35.7
Duration of COPD – n (%)	<1 yrs	13 (8.0)	13 (8.1)	26 (8.0)
	1–5 yrs	65 (39.9)	70 (43.8)	135 (41.8)
	>5–10 yrs	44 (27.0)	39 (24.4)	83 (25.7)
	>10–15 yrs	23 (14.1)	19 (11.9)	42 (13.0)
	>15–20 yrs	10 (6.1)	10 (6.3)	20 (6.2)
	>20 yrs	8 (4.9)	9 (5.6)	17 (5.3)
Severity of COPD (GOLD 2008) – n (%)	Mild	0 (0.0)	0 (0.0)	0 (0.0)
	Moderate	96 (58.9)	89 (55.6)	185 (57.3)
	Severe	67 (41.1)	69 (43.1)	136 (42.1)
	Very severe	0 (0.0)	2 (1.3)	2 (0.6)
ICS use – n (%)	Yes	70 (42.9)	76 (47.5)	146 (45.2)
	No	93 (57.1)	84 (52.5)	177 (54.8)
Smoking history – n (%)	Ex-smoker	92 (56.4)	89 (55.6)	181 (56.0)
	Smoker	71 (43.6)	71 (44.4)	142 (44.0)
Number of pack years	n	163	160	323
	Mean	52.9	51.2	52.0
	SD	26.79	24.82	25.81
	Median	48.0	45.0	45.0
	Min - Max	10.0 - 150.0	10.0 - 148.0	10.0 - 150.0

Source: Table 11-3 Study No. CQAB149B2354 Clinical Study Report

4.3.5.3 Efficacy Review

All of the 323 randomized patients were included in the Safety set and FAS. Overall, 87.9% of patients were included in the PP set. Approximately 15% of patients in the indacaterol 75 mcg group were included in the PK set.

4.3.5.3.1 Primary Endpoint

The primary variable was 'tFEV1' after 12 weeks of treatment (Visit 9). Of the 323 randomized patients included in the FAS set 297 were evaluated for the primary endpoint. Patients were included in the analysis if a tFEV1 value was available at Day 29 (Visit 6) or later, and values for Week 12 were imputed with a LOCF approach. For the FAS, the LS mean tFEV1 at Week 12 in the indacaterol 75 mcg group was statistically significantly greater to that in the placebo group (Table 55), with a LS mean treatment difference of 0.12 L equal to the pre-defined MCID. This result was comparable to the treatment difference of 0.14 L observed in B2355 and 0.17 L in B2336 which both had less severe COPD patients.. The sensitivity analysis in the per-protocol set showed the same treatment difference in tFEV1 as the FAS.

Table 55 Protocol B2354 Trough FEV1 (L) at Week 12: treatment comparisons (Full analysis set and per-protocol set, imputed with LOCF)

		--- Treatment ----			---------- Treatment difference ----------			
Treatment	**n**	**LS Mean**	**SE**	**Comparison**	**LS Mean**	**SE**	**95% CI**	**p-value**
Full analysis set								
Ind 75 µg	149	1.38	0.013	Ind 75 µg - Pbo	0.12	0.019	(0.08, 0.15)	<.001*
Pbo	148	1.26	0.013					
Per-protocol set								
Ind 75 µg	133	1.39	0.014	Ind 75 µg - Pbo	0.12	0.019	(0.08, 0.16)	<.001
Pbo	129	1.27	0.014					

Source: Table 11-5 No. CQAB149B2354 Clinical Study Report

Subgroup analyses for age, sex, smoking history, COPD severity, SABA reversibility and ICS use at baseline were performed for tFEV1 after 12 weeks of treatment. The treatment differences of select subgroups are displayed below in Table 56. Identical to B2355, but in contrast to B2336, indacaterol 75 mcg dose had a larger treatment difference in the ≥ 65 age group with 0.15 L as opposed to the < 65 age group with 0.09 L. However, the treatment difference for indacaterol 75 mcg based on severity was consistent with that in B2336, where larger differences were seen in patients with moderate or less severe COPD (0.14 L) than in those with severe or worse disease (treatment difference = 0.09 L). Patients who were not on ICS at baseline had a higher the treatment difference of 0.14 L vs. those on a stable ICS regimen with 0.10 L.

Table 56 Protocol B2354 Analysis of trough FEV1 after 12 weeks treatment (imputed with LOCF), select subgroup analyses

		Treatment difference (L)		
		Ind 75 mcg	95% CI	p-value
Age	< 65	0.09	0.04, 0.14	< 0.001
	≥ 65	0.15	0.09, 0.20	< 0.001
Gender	Male	0.13	0.08, 0.18	< 0.001
	Female	0.11	0.05, 0.16	< 0.001
COPD Severity	Moderate/less	0.14	0.09, 0.19	< 0.001
	Severe/worse	0.09	0.04, 0.15	= 0.001
Smoking status	Ex smoker	0.13	0.08, 0.18	< 0.001
	Current smoker	0.10	0.05, 0.16	<0.001
SABA reversibility	>12%	0.12	0.07, 0.16	<0.001
	≤ 12%	0.12	0.06, 0.18	<0.001
ICS	No	0.14	0.09, 0.19	< 0.001
	Yes	0.10	0.04, 0.15	< 0.001

Source: Adapted from Tables 14.2-1.1 Study No. CQAB149B2354 Clinical Study Report

4.3.5.3.2 Secondary Endpoints

The key secondary objective was to demonstrate that indacaterol (75 mcg q.d.) was superior to placebo with respect to TDI focal score following 12 weeks of treatment. The sponsor considered a difference of 1 unit in TDI to be the MCID for COPD patients. At Week 12, the difference between treatment groups in LS mean TDI focal score was statistically significantly greater in the indacaterol 75 mcg group compared with

the placebo group (p<0.001), with a treatment difference of 1.23 units. The LS mean TDI focal score was statistically significantly higher in the indacaterol 75 mcg group than in the placebo group at Week 4 (LS mean difference 0.97, p=0.001)., A responder analysis of the proportion of patients with a MCID of ≥ 1 revealed that at Weeks 4 and 12, 42% and 48 % of patients, respectively in the 75 mcg treatment group had a MCID ≥ 1.

A summary of the treatment differences seen between indacaterol and placebo for select secondary endpoints is presented in Table 57 below. Trough FEV1, FEV1 AUC (5 min-4 hr), and peak FEV1 showed a statistically significant difference from placebo at all time points, consistent with the bronchodilator action of the drug.

Table 57 Protocol B2354 Select secondary efficacy endpoints (FAS)

		Treatment difference (L)		
		Ind 75 mcg	95% CI	p-value
Trough FEV1	Day 2	0.08	(0.06, 0.1)	< 0.001
	Day 29	0.11	(0.08, 0.15)	< 0.001
	Day 57	0.10	(0.05, 0.14)	< 0.001
	Day 84	0.11	(0.07, 0.15)	< 0.001
FEV1 AUC (5 min-4 hr)	Week 12	0.17	(0.14, 0.21)	< 0.001
Peak FEV1 1st 4 hr	Day 1	0.11	(0.09, 0.13)	< 0.001
	Week 12	0.16	(0.13, 0.20)	< 0.001

Source: Adapted from Tables 14.2-3.1, 14.2-3.2, 14.2-4.1, 14.2-4.2, 14.2-4.3, 14.2-4.4 Study No. CQAB149B2354 Clinical Study Report

As described in the protocol, FEV1 was measured at multiple time points on Days 1, 2, 29, 57, 84 and 85. All values were statistically significantly larger than placebo as seen in Table 58. The difference from placebo in FEV1 was 0.09L, consistent with the onset of action claims the sponsor proposes in the label. The values on Day 84 were all larger than the corresponding time points on Day 1. At each time point measured, FVC values in the indacaterol 75 mcg group were also statistically significantly greater than in the placebo group (all, p=0.007), with LS mean differences ranging from 0.10 L to 0.25 L across all time points.

Table 58 Protocol B2354 Analysis of FEV1 (L) at each time point, by visit (FAS)

		Treatment differences (L)		
		Ind 75 mcg	95% CI	p-value
Day 1	5 min	0.09	(0.07, 0.10)	< 0.001
	30 min	0.12	(0.10, 0.14)	< 0.001
	1 hr	0.11	(0.09, 0.13)	< 0.001
	2 hr	0.13	(0.10, 0.15)	< 0.001
	4 hr	0.12	(0.10, 0.15)	< 0.001
Day 2	23 hr 10 min	0.08	(0.05, 0.10)	< 0.001
	23 hr 45 min	0.08	(0.06, 0.11)	< 0.001
Day 29	-50 min	0.12	(0.08, 0.15)	< 0.001
	-15 min	0.12	(0.08, 0.15)	< 0.001
	5 min	0.16	(0.13, 0.20)	< 0.001
	30 min	0.17	(0.14, 0.21)	< 0.001
	1 hr	0.17	(0.14, 0.20)	< 0.001
Day 57	-50 min	0.10	(0.05, 0.14)	< 0.001
	-15 min	0.11	(0.06, 0.15)	< 0.001
	5 min	0.15	(0.10, 0.19)	< 0.001
	30 min	0.14	(0.10, 0.19)	< 0.001
	1 hr	0.15	(0.11, 0.20)	< 0.001
Day 84	-50 min	0.12	(0.08, 0.16)	< 0.001
	-15 min	0.13	(0.09, 0.17)	< 0.001
	5 min	0.18	(0.15, 0.22)	< 0.001
	30 min	0.18	(0.14, 0.22)	< 0.001
	1 hr	0.18	(0.14, 0.21)	< 0.001
	2 hr	0.17	(0.14, 0.21)	< 0.001
	4 hr	0.15	(0.11, 0.19)	< 0.001
Day 85	23 hr 10 min	0.11	(0.07, 0.15)	< 0.001
	23 hr 45 min	0.12	(0.07, 0.16)	< 0.001

Source: Adapted from Table 14.2-5.1 Study No. CQAB149B2354 Clinical Study Report

- FEV1 trough response

Similar to Study B2355, the protocol called for comparisons of the rate of change in tFEV1 by indacaterol 75 mcg and placebo from Day 29 to Week 12 of treatment to evaluate for evidence of tachyphylaxis. The estimate value for the slope for indacaterol was positive, consistent with no loss of efficacy over time.

- Rescue medication use

All patients were provided with albuterol for use as rescue medication from Visit 1 and an electronic diary to record use on Visit 2. The indacaterol 75 mcg group had statistically significant decreases in the LS mean change from baseline in daily number of puffs of rescue medication and the LS mean change from baseline in number of puffs during the day and night compared with placebo over 12 weeks of treatment. The percentage of 'days with no rescue medication use' was statistically significantly higher in the indacaterol 75 mcg group compared with the placebo group. Summary statistics of the mean daily number of puffs of rescue medication, mean number of daytime puffs and mean number of nighttime puffs of rescue medication over 12 weeks of treatment are presented in Table 59 below.

Table 59 Protocol B2354 Rescue medication use over 12 weeks: treatment comparisons (FAS)

		-- Treatment --			---------- Treatment difference ----------			
Treatment	n	LS Mean	SE	Comparison	LS Mean	SE	95% CI	p-value
Change from baseline in the mean daily number of puffs of rescue medication								
Ind 75 µg	153	-1.58	0.186	Ind 75 µg - Pbo	-1.16	0.261	(-1.67, -0.65)	<.0001
Pbo	153	-0.42	0.185					
Change from baseline in the mean daytime number of puffs of rescue medication								
Ind 75 µg	151	-0.97	0.106	Ind 75 µg - Pbo	-0.64	0.149	(-0.93, -0.35)	<0.001
Pbo	146	-0.33	0.107					
Change from baseline in the mean nighttime number of puffs of rescue medication								
Ind 75 µg	152	-0.65	0.092	Ind 75 µg - Pbo	-0.52	0.129	(-0.77, -0.27)	<0.001
Pbo	151	-0.13	0.091					
Percentage of 'days with no rescue use'								
Ind 75 µg	152	42.4	2.34	Ind 75 µg - Pbo	13.7	3.25	(7.3, 20.0)	<0.001
Pbo	149	28.8	2.36					

Source: Table 11-10 Study No. CQAB149B2354 Clinical Study Report

- Symptoms

In contrast to Study B2355 where the only symptom category to reach statistical significance was 'days able to perform usual daily activities', in Study B2354, that category did not reach statistical significance, but instead the category, 'no daytime symptoms' reached statistical significance with a LS mean treatment difference of 4.6 (95% CI 1.5, 7.6; p=0.003).

- Health related quality of life

The SGRQ was used to provide health-related quality of life measurements during the course of the trial. The protocol specified that the SGRQ would be administered at Visits 4, 6 and 8 (Days 1, 29 and 84). The LS mean SGRQ total score at Week 12 (imputed with LOCF) was statistically significantly lower in the indacaterol 75 mcg group than in the placebo group, although the treatment difference of -3.8 (95% CI -6.2, -1.4; p=0.002) did not achieve the MCID of 4 units. Analyses of the SGRQ total scores at Week 4 (LS mean difference -2.9, p=0.005) and without LOCF imputation at Week 12 (LS mean difference -3.7, p=0.003) were consistent.

In a responder analysis, the proportion of patients with a clinically important improvement of 4 units in the SGRQ total score at Week 12 (imputed with LOCF) was 47.6% for the indacaterol 75 mcg group and 34.5% for the placebo group, and the odds ratio (1.80) was statistically significant (p=0.024). Analysis of SGRQ components scores after 12 weeks, demonstrated significant improvement in symptoms and activity. See Table 60. This was a different pattern than that seen in B2355 where the symptoms and impact components reached statistical significance but, not the activity component.

Table 60 SGRQ total score at Week 12 (imputed with LOCF): treatment comparisons (Full analysis set)

		--- Treatment ----			---------- Treatment difference ----------			
Treatment	n	LS Mean	SE	Comparison	LS Mean	SE	95% CI	p-value
Ind 75 µg	147	43.4	0.86	Ind 75 µg - Pbo	-3.8	1.21	(-6.2, -1.4)	0.002
Pbo	142	47.2	0.87					

Source: Table 11-12 No. CQAB149B2354 Clinical Study Report

- COPD exacerbation frequency

The exploratory efficacy endpoint of number of COPD exacerbations over 12 weeks treatment was also examined. The mean number of exacerbations per patient (without imputation) was 0.2 for the indacaterol 75 mcg group and 0.3 for the placebo group. No patient had more than 1 COPD exacerbation during the 12 week treatment. The rate of exacerbations per year was lower in the indacaterol 75 mcg group than the placebo group (0.8 vs. 1.3).

4.3.5.4 Pharmacokinetic analyses

PK assessments were measured for a subgroup of 25 patients. Peak serum levels were achieved with a median Tmax of 0.53 hours. The average (±SD) Cmax was 150.44 pg/mL (±68.26 pg/mL) and average AUClast was 2163.3 pg*hr/mL)

4.3.5.5 Safety Review

4.3.5.5.1 Extent of exposure

The overall exposure and compliance was similar across the two treatment groups. The mean number of days patients in the indacaterol group were exposed to drug was 78.9 and for placebo it was 77 days. Compliance of percent of doses taken over the whole treatment period was over 97% for both groups.

4.3.5.5.2 Concomitant medication

Concomitant medications and non drug therapies were taken by the majority of patients in both groups. COPD medications were taken by more than half of patients on indacaterol and placebo. The most common COPD related medications were ICSs used by 44.2% of patients in the indacaterol group and 47.5% in the placebo. Non COPD medications were taken by 92.6% of patients in the indacaterol group and 91.9% in the placebo group. The most common were acetylsalicylic acid, multivitamins, simvastatin and lisinopril.

4.3.5.5.3 Adverse events

The incidence of adverse events reported in the indacaterol group was 49/1% and 46.35 for the placebo group. Similar to other trials the most frequently affected SOCs were: infections and infestations, respiratory, thoracic and mediastinal disorders and gastrointestinal disorders. The most commonly reported AE was COPD (8.6% versus 11.1%) for indacaterol vs. placebo treatment groups, respectively. Headache, urinary tract infection nasopharyngitis were observed in higher levels in the indacaterol group than placebo. Cough and dyspnea were also common but had similar rates across treatment groups.

Deaths and SAEs

There were 2 deaths reported in the trial, both in the placebo group. One patient was a 68 year old female with a history of hypertension, hypercholesterolemia and type II diabetes mellitus died of a myocardial infarction. The other patient, was a 71 year old male with a history of hyperlipidemia, hypertension, anemia and type II diabetes mellitus, died due to a ruptured aortic aneurysm. There were 4 SAEs captured in the indacaterol group (2.5%) and 9 (5.6%) in the placebo group. The SAEs in the indacaterol group include: COPD exacerbation, worsening of chronic anemia, mycosis fungoides and atypical non-cardiac chest pain.

Adverse events leading to discontinuation

The AEs leading to discontinuation were reported at a lower rate in the 75 mcg indacaterol (4.9%) group than in the placebo (6.9%) group. The most common AE leading to discontinuation was COPD which was higher in the placebo (2.5%) group than in the indacaterol (1.8%) group. Dyspnea was reported more than once and greater in the indacaterol group.

4.3.5.5.4 Laboratory findings

There were no clinically meaningful changes in the hematology laboratories. Evaluation of the chemistry laboratories revealed a maximum mean change from baseline of creatinine kinase levels higher in the indacaterol 75 mcg group than placebo (65.1 vs. 47.0). Notable elevations of glucose > 9.99 mmol/L were observed in 6.3% of placebo treated patients and 4.9% of indacaterol treated patients. However, based

on the maximum post-baseline value, 19.1% of patients in the indacaterol 75 mcg group and 11.3% of the patients in the placebo group had shifts from normal at baseline to high (above the normal range) post-baseline.

There were no reports of notable potassium < 3 mmol/L in either indacaterol or placebo treatment groups. However, based on the minimum post-baseline value, 6.8% (11 patients) in the indacaterol 75 mcg group and 8.8% (14 patients) in the placebo group had a shift from normal at baseline to low post-baseline.

4.3.5.5.5 ECG findings

No events of QTc > 500 ms were reported in either treatment group. A maximum increase from baseline of 30- 60 ms in QTc was seen in 8 (4.9%) patients in the indacaterol 75 mcg group and 6 (3.8%) patients in the placebo group. There were no reports of a maximum increase from baseline > 60 ms in either treatment group. Qualitative ECG changes occurred at similar rates between the two groups. Ectopy was reported with the greatest rates of 25.5% in the indacaterol group and 21.8% in the placebo group.

4.3.5.5.6 Physical examination

There were no reports of pulse rates > 130 bpm in either treatment group. There was 1 event of SBP > 200 mm Hg in the placebo group and 3 events in the placebo group and 1 in the indacaterol group of DBP> 115 mm Hg.

4.3.5.6 Summary of Study

This was a twelve week, multicenter, randomized, placebo-controlled trial comparing indacaterol 75 mcg q.d. to placebo in adults with moderate to severe COPD. The selected dose of indacaterol 75 mcg achieved the primary endpoint of tFEV1, demonstrating a statistically significant treatment difference from placebo after twelve weeks, 0.12 L.

Consistent with the expected response for a bronchodilator drug, other spirometry based endpoints also demonstrated superiority of indacaterol 75 mcg over placebo including tFEV1 on Days 2, 29, 57 and 84;FEV1 AUC5min- 4hr; peak FEV1 over 5 min-4hr on Days 1 and week 12. As well, at 5 minutes post first dose, the treatment difference was 0.09 L, statistically significant and representing 78% of the treatment difference achieved on Day 85. There was no difference in the rate of change in tFEV1 for indacaterol 75 mcg from Day 29 to Week 12. Rescue medication use was also statistically significantly reduced after 12 weeks of treatment with indacaterol 75 mcg.

A different category from that seen in B2355 of the patient diary symptoms assessment, ‘no daytime symptoms’ improved significantly to indacaterol. The quality of life questionnaire, SGRQ total score, showed a treatment difference of -3.8, which did not meet the predefined clinically meaningful difference of -4. As seen in B2355, the symptom component reached statistical significance over placebo, however, in this trial the activities component and not the impact component achieved statistical significance after 12 week treatment with indacaterol 75 mcg.

Peak serum levels of indacaterol after administration of a 75 mcg dose reached maximum in approximately 30 minutes

The most frequent AE was COPD with a lower incidence in the indacaterol treatment group than in placebo. Headache, urinary tract infections, nasopharyngitis and arthralgia were also frequently reported AEs. There were two deaths in the placebo group reported during the trial; one due to a myocardial infarction, the other a ruptured aortic aneurysm. There were 7 patients (1 patient in the indacaterol 75 mcg treatment group and 6 patients in the placebo group) with SAEs leading to discontinuation from the trial. There were no clinically meaningful differences reported between treatment groups in the hematology, chemistry laboratory (including serum potassium, blood glucose and transaminases) or urinalysis assessments, vitals or ECG.

4.3.6 LONG TERM TRIAL B2336

A 26-Week Treatment, Multicenter, Randomized, Double Blind, Double Dummy, Placebo Controlled, Parallel Group Study to Assess the Efficacy and Safety of Indacaterol (150 mcg q.d.) in Patients with Chronic Obstructive Pulmonary Disease, Using Salmeterol (50 mcg b.i.d.) as an Active Control

4.3.6.1 Trial Description

4.3.6.1.1 Design

This was a Phase III, multi center, double blind, double dummy, parallel group study of indacaterol 150 mcg once daily in patients with moderate-to-severe COPD. Eligible patients were randomized 1:1:1 to receive indacaterol 150 mcg q.d., salmeterol 50 mcg b.i.d., or placebo for 26 weeks as detailed in Table 61 below.

Table 61 Protocol B2336 Study design

Period	Pre-screen	Screen/ Run-in	26- week Randomized Treatment
Visits		1* and 2	3-13
Day/Week		Day -14 to 1	1-26
			↓ Patients were randomized (1:1:1) to receive one of the following three blinded treatments: indacaterol 150 µg o.d. via SDDPI and placebo to salmeterol 50 µg b.i.d. via a proprietary dry powder inhaler, or salmeterol 50 µg b.i.d. via a proprietary dry powder inhaler and placebo to indacaterol via SDDPI, or placebo to indacaterol via SDDPI and placebo to salmeterol 50 µg b.i.d. via a proprietary dry powder inhaler
		Daily ICS monotherapy, if needed, was to remain stable throughout study **Salbutamol/albuterol was available for rescue use throughout study**	

Source: Table 9-1 Study No. CQAB149B2336 Clinical Study Report

4.3.6.1.2 Duration

A 14 day run in period was followed by a 26 week treatment period.

4.3.6.1.3 Population

The population included male and female patients aged ≥40 years with a clinical diagnosis of moderate to severe COPD and a smoking history of at least 20 pack years.

Reviewer Comment:
Study B2356 recruited patients with at least 10 pack year history. In this trial only patients with a 20 pack year history were included.

4.3.6.1.4 Study Sites

The trial was conducted at 142 centers in 15 countries: Canada (4), Colombia (3), Czech Republic (6), Denmark (10), Germany (43), Finland (6), France (4), Hungary (5), India (11), Iceland (1), Italy (15), Peru (6), Russia (15), Slovakia (5), and Taiwan (8).

4.3.6.1.5 Investigational and Reference Therapy

The active comparator was salmeterol 50 mcg b.i.d. delivered via a proprietary drug power inhaler. The indacaterol (150 mcg) placebo product was delivered via SDDPI and the placebo to salmeterol (50 mcg) was delivered via a proprietary dry powder inhalation device. A large number of different batch numbers

were utilized for this trial, which differed by country. These numbers are provided in the Clinical Study Report.

4.3.6.1.6 Objectives

The primary objective was to confirm the superiority of indacaterol 150 mcg q.d. via SDDPI in patients with COPD compared to placebo with respect to 24 hr post dose tFEV1 after 12 weeks of treatment..

The key secondary objectives were to: 1) evaluate the effect of indacaterol (150 mcg q.d.) on the total score of the SGRQ after 12 weeks compared with placebo; and 2) evaluate the effect of indacaterol (150 mcg q.d.) on the percentage of "days of poor control" reported over the 26-week randomized treatment period compared with placebo.

Other secondary objectives were to:

- Compare salmeterol with placebo and indacaterol (150 mcg) with salmeterol with respect to all other secondary variables and the tFEV1 at week 12
- Evaluate the effect of indacaterol (150 mcg q.d.) on the total score of the SGRQ, after 4, 8, and 26 weeks compared with placebo
- Evaluate the effect of indacaterol (150 mcg q.d.) on health related quality of life assessments compared with placebo after 12 and 26 weeks of treatment
- Evaluate the effect of indacaterol (150 mcg q.d.) on exacerbation during the 26 week randomized treatment period compared with placebo with respect to:
    - time to first COPD exacerbation
    - COPD exacerbation rate
- Evaluate the effect of indacaterol (150 mcg q.d.) on the TDI focal score compared with placebo measured after 4, 8, 12 and 26 weeks of treatment
- Compare indacaterol (150 mcg q.d.) with placebo on spirometry assessments in terms of:
    - tFEV1 measured on Day 2 and after 26 weeks of treatment
    - FEV1 and FVC measured at all time points, including approximate peak response (Day 1 and after 2, 12 and 26 weeks of treatment) and trough response
    - the standardized AUC for FEV1 $_{(5\ min\ –\ 1hr)}$ for all patients and 5 min – 4hr for a sub group) on Day 1 and after 2 (5 min – 1hr), 12 and 26 weeks of treatment
- Evaluate the effect of indacaterol (150 mcg q.d.) vs. placebo on other clinical variables such as morning (pre-medication) and evening (pre-medication) PEF, clinical symptoms and use of rescue medication over 26 weeks of treatment
- Evaluate the effect of indacaterol (150 mcg q.d.) versus placebo on post inhalation events (especially cough) measured over 26 weeks of treatment
- Assess the long-term safety (particularly with regard to ECG, laboratory tests, blood pressure and adverse events) of indacaterol (150 mcg q.d.)
- Evaluate the 24 hour spirometry (FEV1 and FVC) profile of the 150 mcg q.d. dose of indacaterol, placebo and salmeterol after 26 weeks treatment
- Evaluate the response to the patient end of study questionnaire for the 150 mcg q.d. dose of indacaterol, placebo and salmeterol after 26 weeks of treatment

Exploratory objectives were to:

- Conduct (in subjects signing an additional PG consent form) exploratory PG research studies on the effects of human genetic variation on indacaterol (150 mcg q.d.) response and exposure.
- Assess the effect of indacaterol (150 mcg q.d.) on the BODE index (total and individual components) after 12 and 26 weeks of treatment compared to placebo
- Explore the impact of indacaterol (150 mcg) on medical resource utilization
- Evaluate the performance and properties of a new COPD quality of life measure, Living with Chronic Obstructive Pulmonary Disease questionnaire (LCOPD)
- Evaluate the rate of change in trough FEV1 and FVC of indacaterol (150 mcg q.d.) and placebo over 26 weeks of treatment.

4.3.6.1.7 Inclusion Criteria

Post bronchodilator criteria remained the same as in Study B2355 and B2356.

4.3.6.1.8 Exclusion Criteria

These were the same as in Study B2355 and B2356 with the addition of further qualification of the diagnosis of asthma for exclusion: blood eosinophil count > 400/mm. However, the protocol did not exclude patients with Alpha-1 Antitrypsin deficiency or those who have ever received omalizumab as in B2355.

4.3.6.1.9 Conduct

During the prescreening visit, informed consent was obtained, current COPD medications were reviewed and if necessary arrangements were made to adjust prohibited COPD therapy to allowable COPD therapy. At Visit 1, eligible patients underwent assessments, including ß2-agonist reversibility testing, and started the 14-day run-in period. At Visit 2, patients underwent anti-cholinergic reversibility testing. At Visit 3 (study day 1), eligible patients were randomized 1:1:1 to receive indacaterol 150 mcg q.d., salmeterol 50 mcg b.i.d., or placebo for 26 weeks. Visits 3 to 12 comprised the 26-week randomized treatment period. Randomization was stratified by smoking status. See Table 62 for details.

Table 62 Protocol B2336 Assessment Schedule

Period	**Categ-ory[1]**	**Pre-screen**	**Screen / Run-in**		**26-week randomized treatment**								
Visit			**1**	**2**	**3**	**4**	**5**	**6, 7**	**8**	**9**	**10, 11**	**12[2]**	**13[2,10]**
Week – start of week ***(*last day of wk)***			**- 2**	**- 2**	**1**	**1**	**3**	**5, 9**	**12 ***	**13**	**17, 22**	**26***	**27**
Day			**- 14**	**- 13**	**1**	**2**	**15**	**29,57**	**84**	**85**	**113,148**	**182**	**183/184**
Informed consent	DS	X											
PG Informed Consent	DS	X											
Current Medication review	DS	X											
Incl./Excl. criteria	S		X		X								
Medical History, Demographics	DS		X										
Smoking History	DS		X						X			X	
Pregnancy Test (serum)	DS		X						X				X
Physical exam.	S		X							X			X
Record height (Visit 1 only) and weight	DS		X						X				X
Contact IVRS to register patient	DS		X										
FEV_1 Reversibility (β_2 -agonist)	DS		X										
FEV_1 Reversibility (anti-cholinergic)	DS			X									
PG Blood (consenting pts)	DS				X								
Issue Patient Diary	S		X		X			X		X	X		
Review/collect Patient Diary	DS[7]				X	X	X	X	X	X	X	X	X
Randomization	DS				X								
Provide Rescue Medication as necessary	S		X	X	X	X	X	X	X	X	X	X	
Review/record β_2-agonist use	DS		X	X	X	X	X	X	X	X	X	X	X

Period	**Categ-ory[1]**	**Pre-screen**	**Screen / Run-in**		**26-week randomized treatment**								
Visit			**1**	**2**	**3**	**4**	**5**	**6, 7**	**8**	**9**	**10, 11**	**12[2]**	**13[2,10]**
Week – start of week ***(*last day of wk)***			**- 2**	**- 2**	**1**	**1**	**3**	**5, 9**	**12 ***	**13**	**17, 22**	**26***	**27**
Day			**- 14**	**- 13**	**1**	**2**	**15**	**29,57**	**84**	**85**	**113,148**	**182**	**183/184**
ECG[3]	DS		X		X		X		X			X	X
Systolic & diastolic blood pressure & radial pulse rate[3]	DS		X		X		X		X			X	X
Urinalysis[3]	DS		X		X		X		X				X
Hematology/Blood Chemistry[3]	DS		X		X		X		X			X	X
C-reactive protein[3]	DS				X				X			X	
24 h Spirometry Profiling[8]													X
Spirometry[3]	DS		X	X	X	X	X	X	X	X	X	X	X
Record post inhalation events[4]	DS				X	X	X	X	X	X	X	X	X
AE recording	DS		X	X	X	X	X	X	X	X	X	X	X
Concom. Meds	DS		X	X	X	X	X	X	X	X	X	X	X
Record medical resource utilization	DS		X	X	X	X	X	X	X	X	X	X	X
EQ-5D	DS				X				X			X	
SGRQ	DS				X			X	X			X	
LCOPD	DS				X				X			X	
BDI	DS				X								
TDI	DS							X	X			X	
MMRC dyspnea scale	DS				X				X			X	
Pt end of study questionnaire	DS												X
6 min walk test5	DS				X				X			X	
Device training	S		X		X								
Telephone patient[1] day prior to Visit6	S						X	X	X		X	X	
Administer study drug at visit	DS				X	X	X	X	X	X	X	X	X[9]
Dispense (excluding Visit 13) and review use of study drug	DS				X			X		X	X		X
Collect unused study drug	S							X		X	X		X
Record total number of capsules taken since the last dispensing visit	DS							X		X	X		X

Period	Categ-ory[1]	Pre-scree n	Screen / Run-in		26-week randomized treatment								
Visit			**1**	**2**	**3**	**4**	**5**	**6, 7**	**8**	**9**	**10, 11**	**12[2]**	**13[2,10]**
Week – start of week ***(*last day of wk)***			**- 2**	**- 2**	**1**	**1**	**3**	**5, 9**	**12 ***	**13**	**17, 22**	**26***	**27**
Day			**- 14**	**- 13**	**1**	**2**	**15**	**29,57**	**84**	**85**	**113,148**	**182**	**183/184**
Study completion eCRF	DS												X

Source: Table 9-4 Study No. CQAB149B2336 Clinical Study Report

Efficacy Assessments

Spirometry assessments

At Visit 1 (Day -14) spirometry was measured to assess eligibility as well as beta agonist reversibility and on the next day anti-cholinergic reversibility testing was performed.

Serial spirometry assessments were performed on a schedule as follows:

- Day 1: 50 and 15 min pre-dose, 5, 30 min, 1 hr post- dose
- Day 2: 23 hr 10 min, 23 hr 45 min post- dose
- Day 15: 50 and 15 min pre-dose, 5, 30 min and 1 hr post- dose
- Day 57: 50 and 15 min pre-dose, 5 min and 30 min post- dose
- Day 84: 50 and 15 min pre-dose, 5, 30 min and 1 hr post- dose
- Day 85: 23 hr 10 min and 23 hr 45 min post- dose
- Day 148: 50 and 15 min pre-dose and 5 and 30 min post- dose
- Day 182: 50 and 15 min pre-dose and 5, 30 min and 1 hr post- dose
- Day 183: 23 hr 10 min and 23 hr 45 min post-dose

As part of Amendment 1 dated 8/7/08, a 24 hr spirometry profiling assessment period (Visit 13 or Day183) was added. For those in the 24 hr serial spirometry subgroup their assessments were extended into Days 183 and 184 to include time points at 6, 12, 16, 22 and 24 hrs post-dose. A subgroup of patients at designated centers also underwent spirometry testing at 2 and 4 hr post- dose at Day 1, 84 and 182.

Patient diaries

All patients were provided with a Patient Diary to record morning and evening PEF, daily clinical symptoms, rescue medication (albuterol) use, any AEs, and any changes in concomitant medication throughout the study, number of 'days of poor control'. Patient diaries were given out on Days -14, 1, 29, 57, 85, 113 and 148 and patients were instructed to complete the diary twice daily, before taking study drug and again each evening.

Peak expiratory flow (PEF)

A Peak Flow Meter was given to each patient at Visit 1 (Day -14) for the measurement of morning and evening PEF.

Dyspnea indices

Patients were interviewed by an independent, trained assessor who graded the degree of impairment due to dyspnea at Visit 3 (Day 1), baseline dyspnea index and at Days 29, 57, 84 and 149 to obtain the transition dyspnea index. The same assessor completed all the BDI/TDI assessments for an individual patient. These assessments were undertaken after completing the EQ-5D, SGRQ and COPDQOL but prior to completion of the MMRC dyspnea scale and the 6 min walk test.

MMRC dyspnea scale

Investigators assessed patients according to the modified [8]MMRC dyspnea scale at Days 1, 84 and 149. The assessment was performed prior to the 6 min walk test. The MMRC dyspnea score (0-4), together

[8] Mahler DA, et al., (1984) The measurement of dyspnea. Chest; 85:751-8.

with the 6 min walk test, FEV1 (% predicted) and the body mass index were used to calculate the BODE index.

Reviewer's Comment:
The BODE index, a multidimensional 10 point grading system has been shown to be a predictor of the risk of death from any cause and from respiratory causes among patients with COPD ([9]Celli BR et al., 2004).The four factors include: the body-mass index (B), the degree of airflow obstruction (O) and dyspnea (D), and exercise capacity (E), measured by the six-minute–walk test. The higher scores indicate a higher risk of death.

Six min walk test
The 6 min walk test was conducted pre-dose at Day 1 and 90 min post-dose at Days 84 and 182.

Safety Assessments
Vitals, laboratory and ECG were taken at 25 min pre-dose and 1 hr post-dose on Days 1, 15, 84, 182 and Day 183 at 23 hr 35 min post-dose. Urinalysis was performed 2 hrs pre-dose on Days 1 and 84, on Day 15 it was performed 35 min pre-dose and on Day 183 23 hrs post-dose. AEs were recorded at all visits and a serum pregnancy test was taken on Days -14, 84 and 183. PE was performed on Days -14, 85 and 183.

All COPD exacerbations, regardless of treatment were recorded on the COPD exacerbation episode eCRF and not on the AE eCRF unless in the opinion of the investigator it should be classified as a SAE (not requiring hospitalization) at which point both the SAE form and the COPD exacerbation episode eCRF was to be completed. A COPD exacerbation was defined as:

- A new onset or worsening of more than one respiratory symptom (i.e. dyspnea, cough, sputum purulence or volume, or wheeze) present for more than 3 consecutive days
- Plus at least one of the following:
    - Documented change or increase in COPD related treatment due to worsening symptoms (e.g., steroids/antibiotics/oxygen)
    - Documented COPD-related hospitalizations or ER visits

Other Assessments
Health-related quality of life questionnaires (EQ-5D, SGRQ and LCOPD), assessment of health care resource utilization, and a patient end-of-study questionnaire were used in this study. The EuroQol (EQ-5D) and SGRQ were completed at the investigator's site on the day of randomization and at Days 84 and 182 (or early discontinuation visit), before any treatment had been given or other assessments performed. In addition the new Living with COPD Questionnaire (LCOPD) measure was administered following the EQ-5D and SGRQ. The SGRQ was also completed on Days 29 and 57.

The EQ-5D contained 5 questions asking the patient about their current health and also a visual analogue scale of 0-100 (0= worst imaginable health state; 100 = best imaginable health state) on which the patient marked their health status. The EQ-5D was administered to collect data on health-related quality of life in order to calculate utilities to support economic evaluation.

The SGRQ is divided into three sections: "Symptoms" concerns with respiratory symptoms, their frequency and severity; "Activity" concern activities that caused or were limited by breathlessness; and "Impacts" which cover different aspects of social functioning and psychological disturbances resulting from airway disease. Scores for each section and a "Total" score were calculated, ranging from 0 to 100. Higher values corresponded to greater impairment of health-related quality of life. The LCOPD consisted of 22 statements designed to measure the impact of COPD on patient's lives. Data were collected to

[9] Celli BR, Cote CG, Marin JM, et al., (2004) The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med; 350:1005-12.

support ongoing evaluation of the performance and psychometric properties of available language translations of the LCOPD.

Reviewer's Comment:
Details of the EQ-5D will not be included as economic evaluation is not part of the FDA review and evaluation.

4.3.6.1.10 Concomitant Treatments
Prohibited and allowed medications were the same as in Study B2355 and B2356.

4.3.6.1.11 Ethical Aspects
This clinical trial was designed, implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

4.3.6.1.12 Data Analysis

Three populations were defined for analysis:

- The intention-to-treat (ITT) population, including all randomized patients who received at least one dose of study drug. Patients were analyzed according to the treatment to which they were randomized.
- The per-protocol (PP) population, including all patients of the ITT population who had no major protocol deviations. Patients were analyzed according to the treatment they received except if a patient incorrectly received more than one treatment before the primary end point visit. If this occurred the patient was excluded from the PP population. Major protocol deviations were defined prior to database lock and unblinding of the study.
- The safety population, including all patients who received at least one dose of study drug.

The ITT population was used for the primary analysis of efficacy. The PP population was used for supportive analyses of the primary variable. The safety population was used in the analysis of all safety variables. In Amendment 1 dated August 7, 2008, changes were made to the statistical analysis plan, including updating the analyses planned for EQ-5D, post-inhalation events, BODE index, 24 hr spirometry profiling, association of post-inhalation events with a decrease = 20% FEV1 from pre-dose in first 30 min after dosing, and elevating the analysis of SGRQ total score at Visit 8 to an important secondary objective. The amendment also introduced a patient end of study questionnaire to be completed at the end of the study (Visit 13) or at early discontinuation.

There were no changes to the planned analyses post database lock and unblinding. To handle the issue of multiplicity, a hierarchical testing approach to the analyses of primary and important secondary variables was used as follows:

1. Trough FEV1 after 12 weeks treatment - Superiority of indacaterol 150 mcg q.d. over placebo. If indacaterol 150 mcg q.d. was superior to placebo then;
2. SGRQ total score after 12 weeks treatment – Superiority of indacaterol 150 mcg q.d. over placebo. If indacaterol 150 mcg q.d. was superior to placebo then;
3. Percentage of 'days of poor control' over 26 weeks treatment - Superiority of indacaterol 150 mcg q.d. over placebo.

The other treatment comparisons for the other secondary variables/comparisons were for supportive evidence and no adjustment for multiplicity were made.

Efficacy Variables
Primary Efficacy Variables
The primary efficacy variable was to demonstrate the superiority of indacaterol 150 mcg q.d. over placebo with respect to 24 hour tFEV1 after 12 weeks of treatment measured at Day 85. A difference of 120 mL in

tFEV1 was predefined by the Sponsor to be the MCID for COPD patients. The standard deviation of 270 mL for tFEV1 was based on the weighted average of the estimates from two Foradil pivotal studies, protocols 056 and 058. A sample size of 108 evaluable patients in each treatment group was needed to detect this difference between indacaterol 150 mcg and placebo as statistically significant at the 5% significance level (2 sided) with 90% power. The primary variable was analyzed using a mixed model using the ITT population. The model contained treatment as a fixed effect with the baseline FEV1 measurement, FEV1 prior to inhalation and FEV1 30 min post inhalation of albuterol, FEV1 prior to inhalation and FEV1 one hour post inhalation of ipratropium as covariates. Like with the previous studies, any values contributing to the tFEV1 taken within 6 hours of rescue medication use or the actual measurement times were outside the 22 hr to 25 hr post- dose time window, then the individual FEV1 value was set to missing. For the primary analysis, a missing tFEV1 value at Week 12 was replaced by LOCF as long as the visit was not prior to Day 15.

Exploratory subgroup analyses of trough FEV1 after 12 weeks of treatment (imputed with LOCF) were performed for the ITT population to explore the treatment effect by age (< 65 years / = 65 years), sex (male, female), race (caucasian, black, asian, other), smoking history (current smoker, ex-smoker), severity of disease (moderate or less, severe or worse based on the GOLD Guidelines (GOLD 2005), and the use of ICS at baseline.

Secondary Efficacy Variables
The important secondary objectives were to determine if indacaterol 150 mcg q.d. was superior to placebo with respect to the SGRQ total score after 12 weeks treatment and if indacaterol 150 mcg q.d. was superior to placebo with respect to percentage of COPD 'days of poor control' during 26 weeks treatment. In Amendment 2 dated January 6, 2009, the Sponsor changed the order of testing of secondary efficacy objectives so that the SGRQ total score at Week 12 would be tested after the primary objective had been achieved. In turn, the percentage of 'days of poor control' after 26 weeks of treatment would be tested if the SGRQ total score at Week 12 objective was achieved. The second amendment also elevated comparisons between salmeterol and indacaterol from exploratory to secondary.

SGRQ at 12 weeks
A detailed description of the statistical analysis will be included in Dr Dongmei Liu's review. The SGRQ total score at 12 weeks was analyzed using a mixed model for the ITT population. The model contained treatment as a fixed effect, baseline total score of SGRQ, smoking status, FEV1 prior to inhalation and FEV1 30 min post inhalation of albuterol, FEV1 prior to inhalation and FEV1 one hour post inhalation of ipratropium as covariates. Missing data was imputed using LOCF.

COPD 'days of poor control'
A 'day of poor control' was defined as any day in the Patient Diary where a score = 2 (i.e. moderate or severe symptoms) was recorded for at least two out of five symptoms (cough, wheeze, production of sputum, color of sputum, breathlessness). Either the worst of two scores was taken or if one was missing then the existing score was used. If both were missing, then the daily score for that individual symptom was imputed as 0 but otherwise set to missing. The total number of 'days of poor control' over the 26 week treatment period was divided by the total number of evaluable days to calculate the percentage of 'days of poor control'. Diary data recorded during the 14 day run-in period were used to calculate the baseline. The percentage of 'days of poor control' was summarized by treatment and analyzed using the same mixed model as specified for the primary analysis using the ITT population. For the percentage of COPD 'days of poor control', a difference of 8% was considered clinically important. An estimate of 28% for the standard deviation was based on data from the foradil pivotal trials, protocols 056 and 058, over 12 weeks, protocol F2402 over 6 months and protocol 058 over 12 months. A sample size of 259 evaluable patients in each treatment group was needed to detect this difference between indacaterol 150 mcg and placebo as statistically significant at the 5% significance level (2 sided) with 90% power. Assuming a drop out rate of 20% over 26 weeks of treatment and 15% over the first 12 weeks of treatment, a minimum sample size of 972 patients (324 indacaterol 150 mcg: 324 placebo: 324

salmeterol) was chosen that provided >99% power for the primary endpoint (trough FEV1). Since this was so high, the hierarchical procedure only caused a negligible reduction in the unconditional 90% power for the secondary endpoint of the percentage of 'days of poor control'.

Reviewer's Comment:
The sample size above was driven by percentage of 'days of poor control' which was a key secondary endpoint in the original protocol; however, in Amendment 2, SGRQ total score at Week 12 was elevated above the percentage of 'days of poor control' in the hierarchical testing procedure. Recruitment was already complete, so the protocol amendment did not change the sample size or conduct of the trial. According to the Sponsor, this was done because of data coming from other indacaterol pivotal trials. Based on the original hierarchical testing procedure, since 'days of poor control' did not meet statistical significance, SGRQ would not have been measured.

Spirometry assessments

Assuming a drop-out rate of 15%, a subgroup of 330 randomized patients (110 indacaterol 150 mcg: 110 placebo: 110 salmeterol) was needed to detect a clinically important difference of 120 mL in FEV1 at any serial spirometry time point at the 5% significance level (2 sided) with 80% power. A standard deviation of 290 mL had been assumed based on two Foradil pivotal studies, protocols 056 and 058. No adjustment for multiplicity was carried out for these variables. All spirometry assessments were analyzed using the same mixed model as specified for the primary analysis.

COPD exacerbations

The time to the first COPD exacerbation was displayed for each treatment group with a Kaplan-Meier curve. For COPD exacerbation rate, the number of COPD exacerbations during the 26 week treatment period was analyzed using Poisson regression.

Dyspnea

For the TDI Focal Score after 4, 8, 12, and 26 weeks of treatment, the score was analyzed at each time point (Visits 6, 7, 8, and 12) using the same mixed model as specified for the primary analysis with the BDI focal score as baseline. Missing scores were imputed using LOCF. For percentage of patients with a clinically important improvement of at least 1 in the TDI Focal Score after 4, 8, 12, and 26 weeks of treatment, the proportion of patients who achieved this was analyzed using logistic regression.

Symptoms

The following symptom scores were calculated over the 26 week period. A night with 'no nighttime awakenings' was defined from the diary data as any night where the patient did not wake up due to symptoms. The percentage of nights with 'no nighttime awakenings' was derived and analyzed as for the percentage of 'days of poor control'. That included the imputation of missing nighttime awakening data with a score of 0 (= no awakening) when other symptom data, rescue use, or PEF were available at that morning. A day with 'no daytime symptoms' was defined from the diary data as any day where the patient had recorded in the evening no cough, no wheeze, no production of sputum and no feeling of breathless (other than when running) during the past 12 hours. The percentage of days with 'no daytime symptoms' was derived and analyzed as for the percentage of 'days of poor control'. A 'day able to perform usual daily activities' was defined from the diary data as any day where the patient was not prevented from performing their usual daily activities due to respiratory symptoms (i.e. the question 'Did your respiratory symptoms stop you performing your usual daily activities today?' was answered 'Not at all'). The percentage of 'days able to perform usual daily activities' was derived and analyzed as for the percentage of 'days of poor control' including the imputation of missing data. The mean total symptom scores and individual symptom scores for the patient were calculated for the full 26 weeks. Diary data recorded during the 14 day run-in period were used to calculate the baseline value. The mean change from baseline in the total scores and in the individual scores was summarized with descriptive statistics by treatment. Separate analyses were performed for nighttime, daytime, and the full 24 hours.

Rescue medication

For the daily rescue use or the number of puffs of rescue medication over 26 weeks, the total number of puffs of rescue medication per day over the full 26 weeks was calculated and then divided by the total number of days with non-missing rescue data to derive the mean daily number of puffs of rescue medication taken for the patient. The total number of puffs of rescue medication used over the last 12 hr as recorded in the morning (nighttime use) and in the evening (daytime use) over the full 26 weeks was divided by the total number of days with non-missing rescue data to derive the mean daytime and nighttime number of puffs of rescue medication. The mean daily, daytime and nighttime number of puffs of rescue medication use were calculated for 4 weekly intervals prior to tFEV1 measurements at 12 weeks and 26 weeks and the change from baseline was displayed graphically over time. For the percentage of 'days with no rescue use' over 26 weeks, a 'day with no rescue use' was defined from the diary data as any day where the patient used no puffs of rescue medication. The percentage of 'days with no rescue use' was derived and analyzed as the percentage of 'days of poor control'. The mean change from baseline for all the rescue medication use variables was analyzed using the same mixed model as specified for the primary analysis. Diary data recorded during the 14 day run-in period were used to calculate the baseline.

Peak expiratory flow (PEF)

Morning and evening (pre-medication) PEF, as recorded in the Patient Diary, was averaged separately over the full 26 weeks for each patient. Diary data recorded during the 14 day run-in period were used to calculate the baseline. Change from baseline in the mean morning and evening PEF was analyzed using the same mixed model as specified for the primary analysis.

Health related quality of life

The SGRQ total score at Weeks 4, 8, and 26 was analyzed using the same model as for the total score after 12 weeks. Missing data of the SGRQ total score were imputed by using LOCF. For the percentage of patients with a clinically important improvement of at least 4 in the total SGRQ after 4, 8, 12 and 26 weeks treatment, the proportion of patients who achieved a score of at least 4 in the total SGRQ was analyzed using logistic regression. For the EQ-5D after 12 and 26 weeks of treatment, the questionnaire contained 5 questions (regarding mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each with 3 categories (no problem, moderate problem, severe problems) and a health state assessment from 0 (worst possible health state) to 100 (best possible health state). The number and percentage of patients in each of the three categories for each question was presented by visit. Standard summary statistics were shown for the self-rated health state assessment.

Patient end of study questionnaire

A patient end of study questionnaire was required to be completed by all patients who completed the study or discontinued early. This questionnaire contained two questions regarding the patients' overall satisfaction with the study drug and their willingness to take the same study medication again in future. Descriptive summary statistics for each item on the patient end of study questionnaire were presented by treatment group.

Exploratory variables

FEV1 and FVC trough response over 26 weeks

The rate of change in trough FEV1 defined as the average of the 50 min and 15 min pre-dose values from Day 15 (Visit 5) onwards to the end of study was analyzed using a random coefficients model. The random coefficients model was fitted with the same covariates as specified for the primary analysis with the additional fixed effects of time and time by treatment interaction and random effects of patient and patient by time.

LCOPD

This questionnaire was done at baseline, Week 12 and 26. The number and percentage of patients who agree to a statement was presented by visit for each statement.

BODE index after 12 and 26 weeks of treatment
The BODE index was calculated at baseline (Day 1, Visit 3) and at Weeks 12 (Visit 8) and 26 (Visit 12). The BODE index at each time point was analyzed using the same mixed model as specified for the primary analysis.

Safety Variables
All treatment emergent AEs, including COPD exacerbations, were summarized and listed. Treatment emergent AEs were summarized with incidences overall, by primary SOC, and by PT. Summaries were provided for all AEs, most frequent AEs, all AEs by maximum severity, suspected drug-related AEs, SAEs, and adverse events leading to permanent discontinuation of study drug.

The assessment of safety was based on the incidence of AEs and abnormal laboratory values as well as on the statistical analysis of vital signs, post-inhalation events, ECG measurements, and time to premature discontinuation due to AE and unsatisfactory therapeutic effect. All safety analyses were based on the safety population and most were summarized with descriptive statistics and listed. However, for VS and ECG changes from baseline were analyzed using a similar mixed model as specified for the primary efficacy variable. Separate analyses were performed for time to premature discontinuation due to the primary reason of adverse event (as some evidence of long-term tolerability) and for time to premature discontinuation due to the primary reason of unsatisfactory therapeutic effect (as some evidence of persistency of efficacy). Kaplan-Meier curves were displayed for each treatment group using the safety population.

4.3.6.2 Patient Disposition and Demographics

Disposition
A total of 1518 patients worldwide were screened and 1002 were randomized to study treatment in 142 centers from 15 countries. Approximately 84% of patients completed the study as planned. Of the 3 groups, discontinuation was the highest in the placebo group with 21% compared to 13% in the indacaterol 150 mcg treatment group and 15% in the salmeterol group. The difference in discontinuation rates was largely driven by patients who withdrew consent and had unsatisfactory therapeutic effect, which occurred more frequently in the placebo group. See Table 63.

Table 63 Protocol B2336 Patient disposition

	Ind 150 µg n (%)	Salm n (%)	Pbo n (%)	Total n (%)
Patients				
Screened	-	-	-	1518
Randomized	333 (100.0)	334 (100.0)	335 (100.0)	1002 (100.0)
Exposed	330 (99.1)	333 (99.7)	335 (100.0)	998 (99.6)
Completed	289 (86.8)	284 (85.0)	265 (79.1)	838 (83.6)
Discontinued	44 (13.2)	50 (15.0)	70 (20.9)	164 (16.4)
Primary reason for premature discontinuation				
Adverse event(s)	18 (5.4)	16 (4.8)	13 (3.9)	47 (4.7)
Protocol deviation	9 (2.7)	11 (3.3)	13 (3.9)	33 (3.3)
Subject withdrew consent	8 (2.4)	12 (3.6)	22 (6.6)	42 (4.2)
Abnormal lab value(s)	2 (0.6)	1 (0.3)	2 (0.6)	5 (0.5)
Abnormal test procedure result(s)	2 (0.6)	1 (0.3)	1 (0.3)	4 (0.4)
Lost to follow-up	2 (0.6)	5 (1.5)	2 (0.6)	9 (0.9)
Unsatisfactory therapeutic effect	1 (0.3)	2 (0.6)	15 (4.5)	18 (1.8)
Administrative problems	1 (0.3)	1 (0.3)	0	2 (0.2)
Death	1 (0.3)	0	2 (0.6)	3 (0.3)
Patient's inability to use the device	0	1 (0.3)	0	1 (0.1)

Source: Table 10-1 Study No. CQAB149B2336 Clinical Study Report

Protocol Deviation

Major protocol deviations as well as non-protocol deviations leading to exclusion from the per-protocol (PP) population were reported for 11.5% of patients, with similar frequencies across the treatment groups: 11.2% in indacaterol, 12% in salmeterol and 11.3% in placebo. The most common protocol deviation across all treatment groups was eosinophil count above 400/mm3 at screening, which was reported in 3.9% of the salmeterol group, 3.0% of the indacaterol and 3.3% of those in the placebo group. The percentage of patients taking <80% of doses of study medication between randomization and the visit of the primary endpoint was highest in the salmeterol, 3.0% and indacaterol, 2.7% groups than in the placebo group with 1.8%. Regarding compliance with dosing schedule, more patients in the indacaterol treated group (1.5%) were not compliant with the dosing schedule. The lower levels of noncompliance were seen in the salmeterol (0.6%) and placebo (0.6%) groups. More patients treated with placebo (2.4%) had a post-bronchodilator FEV1 < 30% or ≥ 80% of predicted normal value at screening than indacaterol (0.6%) or salmeterol (0.9%).

Demographics

Overall, the mean age was 63.5 years, the majority were male (75%) and caucasian (76%). Regarding the disease status, the median duration of COPD was 5 years and most patients had moderate (53.6%) or severe (42.6%) COPD based on the GOLD criteria. Mean post- bronchodilator FEV1 was 1.47 L (53.4% of predicted) and mean FEV1/FVC ratio was 52.8%. Mean pre-bronchodilator FEV1 was 1.34 L Approximately 44% were using ICS at baseline while 54% were ex-smokers with the remaining as active smokers. The mean number of pack years was 40. Mean FEV1 reversibility after SABA inhalation at Visit1 was 11.8% and after anticholinergics inhalation at Visit 2 it was 12.5%. Furthermore, nearly 74% of all patients discontinued at least one COPD-related medication prior to the start of study drug, with very similar frequency across the treatment groups. These medications included SABAs (39.9%), predominantly inhaled albuterol (36.2%); LABAs (20.5%), mainly inhaled formoterol (17.6%); combination beta-agonist and steroid (21.8%); long-acting anti-cholinergics (19.2%), mainly inhaled tiotropium (18.3%); combination beta-agonist and anti-cholinergic (12.4%) and xanthines (11.7%). Refer to Table 64 and Table 65 for details.

Table 64 Protocol B2336 Demographic summary (Safety population)

		Ind 150 µg N=330	Salm N=333	Pbo N=335	Total N=998
Age (years)	n	330	333	335	998
	Mean	63.2	63.4	63.9	63.5
	SD	8.67	9.19	8.56	8.81
	Median	63.5	64.0	64.0	64.0
	Min - Max	41 - 85	41 - 86	42 - 89	41 - 89
Age group - n (%)	19-39 years	0	0	0	0
	40-64 years	181 (54.8)	178 (53.5)	180 (53.7)	539 (54.0)
	>= 65 years	149 (45.2)	155 (46.5)	155 (46.3)	459 (46.0)
Sex - n(%)	Male	238 (72.1)	249 (74.8)	258 (77.0)	745 (74.6)
	Female	92 (27.9)	84 (25.2)	77 (23.0)	253 (25.4)
Race - n (%)	Caucasian	250 (75.8)	258 (77.5)	251 (74.9)	759 (76.1)
	Black	1 (0.3)	0	1 (0.3)	2 (0.2)
	Asian	53 (16.1)	52 (15.6)	56 (16.7)	161 (16.1)
	Native American	1 (0.3)	0	1 (0.3)	2 (0.2)
	Other	25 (7.6)	23 (6.9)	26 (7.8)	74 (7.4)
Weight (kg)	n	330	332	335	997
	Mean	73.5	73.7	72.0	73.1
	SD	17.06	18.16	17.24	17.49
	Median	72.0	72.0	71.0	72.0
	Min - Max	38.0 - 130.0	34.0 - 138.2	37.0 - 160.0	34.0 - 160.0

Source: Adapted from Table 11-2 Study No. CQAB149B2336 Clinical Study Report

Table 65 Protocol B2336 Baseline disease characteristics (Safety population)

		Indacaterol 150 mcg N= 330	Salmeterol N= 333	Placebo N= 335	Total N= 998
Duration of COPD (years)	Mean	6.5	6.4	6.6	6.5
	SD	5.65	5.69	5.79	5.71
Duration of COPD n (%)	< 5 yrs	174 (52.7)	168 (50.4)	158 (47.1)	500 (50.1)
	5-10 yrs	88 (26.7)	109 (32.7)	111 (33.1)	308 (30.9)
	10- 20 yrs	62 (18.7)	47 (14.1)	55 (16.4)	164 (16.4)
	> 20 yrs	6 (1.8)	9 (2.7)	11 (3.3)	26 (2.6)
Severity of COPD n (%)	At risk	2 (0.6)	3 (0.9)	8 (2.4)	13 (1.3)
	Mild	7 (2.1)	7 (2.1)	5 (1.5)	19 (1.9)
	Moderate	182 (55.2)	179 (53.8)	174 (51.9)	535 (53.6)
	Severe	139 (42.1)	141 (42.3)	145 (43.3)	425 (42.6)
	Very severe	0	2 (0.6)	3 (0.9)	5 (0.5)
	Missing	0	1 (0.3)	0	1 (0.1)
ICS use n (%)	No	181 (54.8)	181 (54.4)	200 (59.7)	562 (56.3)
	Yes	149 (45.2)	152 (45.6)	135 (40.3)	436 (43.7)
Smoking history	Ex-smoker	178 (53.9)	179 (53.8)	185 (55.2)	542 (54.3)
	smoker	152 (46.1)	154 (46.2)	150 (44.8)	456 (45.7)
Post bronchodilator (SABA) FEV1 at Visit 1 (% predicted)	Mean	54	53	53	53
	SD	14.0	13.6	14.2	14.0
FEV1 reversibility after SABA at Visit 1 (% increase)	Mean	11.7	11	12.7	11.8
	SD	15.3	13.9	16.4	15.2

Source: Adapted from Tables 11-3 and 11-4 Study No. CQAB149B2336 Clinical Study Report

4.3.6.3 Efficacy Review

4.3.6.3.1 Primary Endpoint

The prespecified primary efficacy endpoint was 24 hr post-dose tFEV1 after 12 weeks of treatment with the analysis based on the ITT population. The efficacy analysis was carried out on 953 of the 998 patients of the ITT population. Patients were excluded from the analysis if data were not available on D15 or later. Otherwise a LOCF was utilized for missing data.

The mean percent change from baseline in tFEV1 after 12 weeks of treatment (imputed with LOCF) was 12.5%, 7.7% and -0.7% for indacaterol, salmeterol and placebo, respectively. The treatment differences were statistically significantly different from placebo for both active treatment groups and are summarized in Table 66 below. The numbers were almost identical for the PP group.

Table 66 Study B2336 Trough FEV1 at Week 12: treatment comparisons (ITT and PP populations with LOCF)

	Treatment				Treatment difference			
Treatment	n	LS mean	SE	Comparison	LS mean	SE	95% CI	p-value
ITT population								
Overall baseline	953	1.31						
Ind 150 µg	320	1.45	0.018	Ind 150 µg - Pbo	0.17	0.018	(0.13, 0.20)	<.001*
				Ind 150 µg - Salm	0.06	0.018	(0.02, 0.10)	<.001
Salm	317	1.39	0.018	Salm - Pbo	0.11	0.018	(0.07, 0.14)	<.001

Source: Adapted from Table 11-5 Study No. CQAB149B2336 Clinical Study Report

Subgroup analyses for age, sex, smoking history, COPD severity and ICS use at baseline were performed for tFEV1 after 12 weeks of treatment. Overall, indacaterol was superior to placebo in tFEV1 at Week 12 across all subgroups based on age, sex, smoking history, COPD severity and ICS use at baseline. The treatment differences are displayed below in Table 67. The only significant treatment by subgroup interaction was for age, for which the improvement in the indacaterol group over placebo was smaller in patients who were 65 years of age or older than for the younger age group.

Table 67 Protocol B2336 Treatment difference from placebo in trough FEV1 after 12 weeks treatment (imputed with LOCF), select subgroup analyses

		Ind150 mcg	95% CI	p-value	Salmeterol	95% CI	p-value
Age	< 65	0.21	0.16, 0.26	< 0.001	0.15	0.10, 0.19	< 0.001
	≥ 65	0.11	0.06, 0.17	< 0.001	0.06	0.01, 0.11	0.029
Gender	Male	0.17	0.13, 0.21	< 0.001	0.10	0.06, 0.14	< 0.001
	Female	0.14	0.07, 0.21	< 0.001	0.12	-0.04, 0.09	0.002
COPD Severity	Moderate/less	0.19	0.14, 0.23	< 0.001	0.13	0.08, 0.18	< 0.001
	Severe/worse	0.14	0.08, 0.19	< 0.001	0.08	0.02, 0.13	0.006
Smoking status	Ex smoker	0.17	0.12, 0.22	< 0.001	0.10	0.05, 0.15	< 0.001
	Current smoker	0.16	0.11, 0.22	<0.001	0.11	0.06, 0.17	< 0.001
ICS	No	0.18	0.14, 0.23	< 0.001	0.12	0.07, 0.17	< 0.001
	Yes	0.14	0.09, 0.20	< 0.001	0.09	0.03, 0.14	0.002

Source: Adapted from Tables 14.2-1 Study No. CQAB149B2336 Clinical Study Report

Reviewer comment:
This is the only indacaterol pivotal trial to have a significant subgroup interaction for age, making it most likely to represent a statistical anomaly of multiple testing rather than a real effect. Of note, there is no benefit of indacaterol 150 mcg for patients with severe COPD patients compared to patients with moderate COPD.

4.3.6.3.2 Secondary Endpoints

- **SGRQ after 12 weeks of treatment**

A detailed evaluation of this secondary endpoint is presented in the review by Dr. Dongmei Liu. At baseline, the SGRQ was similar across all treatment groups (43.6, 43.2 and 43.6 units for indacaterol, salmeterol and placebo, respectively). After 12 weeks of treatment the mean change from baseline in SGRQ total score was a decrease (improvement) of 7.7, 5.4 and 1.2 units for indacaterol, salmeterol and placebo, respectively. The LS mean difference between indacaterol and placebo was 6.3 units, which was statistically significant (p<0.001) and exceeded the MCID of 4 units for SGRQ total score. Salmeterol was also significantly different from placebo, with a difference of 4.2 units (p<0.001). Refer to Table 68.

Table 68 SGRQ total score at Week 12: treatment comparisons (ITT population)

		Treatment			Treatment difference			
Treatment	n	LS Mean	SE	Comparison	LS Mean	SE	95% CI	p-value
Ind 150 µg	309	36.4	1.04	Ind 150 µg - Pbo	-6.3	0.99	(-8.2,-4.3)	<.001*
				Ind 150 µg - Salm	-2.1	0.99	(-4.0,-0.2)	0.033
Salm	301	38.5	1.04	Salm - Pbo	-4.2	1.01	(-6.1,-2.2)	<.001
Pbo	294	42.6	1.05					

Source Table 11-7 Study No. CQAB149B2336 Clinical Study Report

Evaluation by responder analysis demonstrates that the percentage of patients with a clinically important improvement of 4 units or greater in SGRQ total score was highest in the indacaterol group (57.9%)

compared with the salmeterol (46.8%) and placebo (39.1%) groups. There was a statistically significant difference in the likelihood of achieving a clinically relevant improvement of at least 4 units in SGRQ total score with indacaterol vs. placebo (odds ratio, 2.41; 95% CI, 1.69- 3.42; p<0.001). The validity of this data may be called into question based on the change of sequence in the hierarchical testing that led SGRQ to be tested when originally it would not have been.

- **COPD 'days of poor control' over 26 weeks of treatment**

A 'day of poor control' was defined as any day in the Patient Diary where a score = 2 (i.e. moderate or severe symptoms) was recorded for at least two out of five symptoms (cough, wheeze, production of sputum, color of sputum, breathlessness). The total number of 'days of poor control' over the 26 week treatment period was divided by the total number of evaluable days (i.e. the days with 2 or more symptoms with scores) in order to derive the percentage of 'days of poor control'. Diary data recorded during the 14 day run-in period were used to calculate the baseline. Patients were considered as eligible for analysis of the percentage of 'days of poor control' if and only if they had at least 7 evaluable diary days in the baseline period and in the post baseline period they had at least 30% of their diary days evaluable and at least 20 evaluable diary days in total.

Treatment with either indacaterol or salmeterol did not result in a statistically significantly reduced percentage of 'days of poor control'. The treatment difference of indacaterol 150 mcg and placebo was -4, 95% CI (-8.0, 0.1), p-value 0.058, and for salmeterol it was -4, 95% CI (-8.1, 0.1), p-value 0.057.

- **COPD exacerbation**

The percentage of patients who experienced COPD exacerbations for the indacaterol, salmeterol and placebo groups were 18.2%, 15.3% and 19.4%, respectively. Although indacaterol treated patients exhibited a longer time to first COPD exacerbation compared with placebo treated patients, a Cox regression analysis showed no statistically significant difference between indacaterol and placebo (hazard ratio, 0.78; 95% CI, 0.55-1.12; p=0.177). Rate of exacerbations per year were numerically lower for the indacaterol (0.68) and salmeterol (0.69) groups compared with placebo (1.02); however no treatment comparisons in COPD exacerbation rate ratios were statistically significant.

Reviewer comment:
This analysis does not adjust for overdispersion, so the results presented may overestimate the efficacy of the drug. The default Poisson regression technique assumes that all patients are homogenous with respect to their rate of exacerbation. The correction for overdispersion takes into account that for COPD, the majority of exacerbations occur in a small portion of patients while the rest of the population has no exacerbations. The method of calculation of exacerbation rate and correction for overdispersion is critical as different statistical methodologies may give very different results.

- **Trough FEV1 at Day 2 and after 26 weeks of treatment**

The treatment differences of both indacaterol from placebo and salmeterol from placebo at Day 2 and after 26 weeks of treatment were all statistically significant. Specifically, at Day 2, the treatment difference for indacaterol and placebo was 0.13L, 95% CI (0.10, 0.15), p-value <0.001; after 26 weeks of treatment, the values were 0.18L, 95% CI (0.14, 0.22) p-value <0.001. The values for salmeterol are as follows: at Day 2, 0.12L, 95% CI (0.10, 0.15) p-value <0.001; 26 weeks of treatment, it was 0.11L, 95% CI (0.07, 0.15) p-value <0.001. Subgroup analyses for age, sex, smoking history, COPD severity, and ICS use at baseline were performed for tFEV1 after 26 weeks of treatment all showed a statistically significant difference from placebo. The treatment difference by age persisted.

Table 69 Protocol B2336 Subgroup analyses of trough FEV1 after 26 weeks treatment, imputed with LOCF, ITT population

		Indacaterol 150 mcg	95% CI	p-value	salmeterol	95% CI	p-value
Age	< 65 years	0.21	(0.16, 0.27)	< 0.001	0.14	(0.08, 0.19)	< 0.001
	≥ 65 years	0.13	(0.08, 0.19)	< 0.001	0.08	(0.02, 0.14)	0.007
Gender	Male	0.18	(0.13, 0.22)	< 0.001	0.10	(0.05, 0.14)	< 0.001
	Female	0.18	(0.10, 0.25)	< 0.001	0.14	(0.06, 0.22)	< 0.001
Smoking history	Ex-smoker	0.16	(0.11, 0.22)	< 0.001	0.12	(0.06, 0.17)	< 0.001
	Current smoker	0.19	(0.14, 0.25)	< 0.001	0.10	(0.05, 0.16)	< 0.001
COPD severity	Moderate/less	0.20	(0.15, 0.25)	< 0.001	0.14	(0.09, 0.20)	< 0.001
	Severe/worse	0.14	(0.08, 0.20)	< 0.001	0.07	(0.01, 0.13)	0.025
ICS use	No	0.17	(0.12, 0.23)	< 0.001	0.13	(0.07, 0.18)	< 0.001
	Yes	0.18	(0.12, 0.24)	< 0.001	0.10	(0.04, 0.15)	0.002

Source: Adapted from table 14.2-4 Study No. CQAB149B2336 Clinical Study Report

- **Peak FEV1 and AUC for FEV1**

The LS mean peak FEV1 in the first 4 hr post morning dose at Week 12 was 1.60 L, 1.59 L and 1.41 L for the indacaterol, salmeterol and placebo groups, respectively, based on a subset of the ITT population with 4 hr serial spirometry. The treatment difference for indacaterol compared to placebo was 0.19L, 95% CI (0.12, 0.25) p-value <0.001, and for salmeterol compared to placebo was 0.18L, 95% CI (0.12, 0.25) p-value <0.001. Similar results were seen for peak FEV1 at Day 1 and Week 26 and for $AUC_{(5min-1hr)}$ at Week 12. Benefit was demonstrated across all subgroups.

- **24 hour serial spirometry**

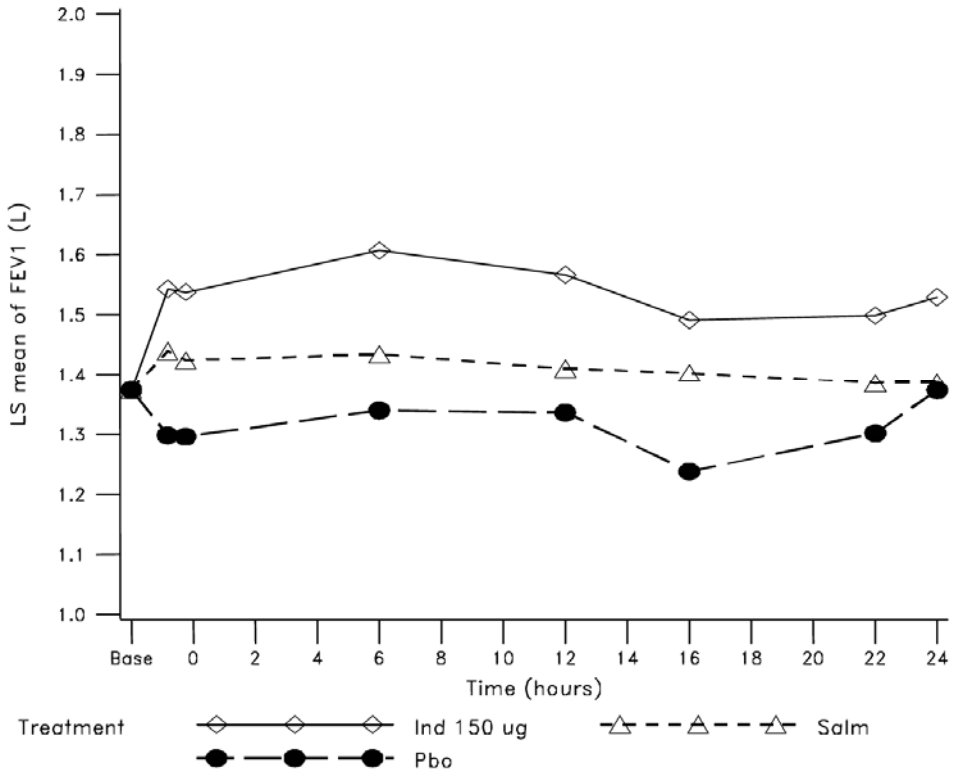
A subset of the ITT population participated in the 24 hr serial spirometry at Week 26. This subset included 53 patients taking indacaterol, 50 patients taking salmeterol, and 48 patients taking placebo. Analysis of FEV1 at each time point up to 24 hr post morning dose for ITT patients in the 24 hr serial spirometry subgroup at Week 26 is presented in Table 70, and the 24-hr profile of LS means of FEV1 is displayed in Figure 9. At all post morning dose evaluations over 24 hr, patients taking indacaterol had significantly higher LS mean FEV1 values compared with patients taking placebo. The difference between indacaterol and placebo was >0.20 L up to 22 hr (all p<0.001) and 0.16 L at 24 hr (p=0.002).

Table 70 Protocol B2336 FEV1 (L) at each time point up to 24 hours post morning dose at 26 weeks (ITT population, subset with 24 hour serial spirometry)

		Treatment				Treatment difference			
Time point	Treatment	n	LS mean	SE	Comparison	LS mean	SE	95% CI	p-value
Baseline	All	150	1.37						
-50 min	Ind 150 µg	53	1.54	0.060	Ind 150 µg - Pbo	0.24	0.052	(0.14, 0.35)	<.001
					Ind 150 µg - Salm	0.10	0.052	(0.00, 0.21)	0.051
	Salm	50	1.44	0.061	Salm - Pbo	0.14	0.054	(0.04, 0.25)	0.010
	Pbo	47	1.30	0.061					
-15 min	Ind 150 µg	52	1.54	0.063	Ind 150 µg - Pbo	0.24	0.051	(0.14, 0.34)	<.001
					Ind 150 µg - Salm	0.11	0.051	(0.01, 0.22)	0.030
	Salm	50	1.42	0.065	Salm - Pbo	0.13	0.053	(0.02, 0.23)	0.017
	Pbo	47	1.30	0.064					
6 hours	Ind 150 µg	49	1.61	0.060	Ind 150 µg - Pbo	0.27	0.059	(0.15, 0.38)	<.001
					Ind 150 µg - Salm	0.17	0.059	(0.05, 0.29)	0.005
	Salm	48	1.43	0.062	Salm - Pbo	0.09	0.062	(-0.03, 0.22)	0.128
	Pbo	43	1.34	0.062					
12 hours	Ind 150 µg	51	1.57	0.061	Ind 150 µg - Pbo	0.23	0.067	(0.10, 0.36)	<.001
					Ind 150 µg - Salm	0.16	0.065	(0.03, 0.29)	0.018
	Salm	48	1.41	0.063	Salm - Pbo	0.07	0.068	(-0.06, 0.21)	0.277
	Pbo	42	1.34	0.064					
16 hours	Ind 150 µg	51	1.49	0.068	Ind 150 µg - Pbo	0.25	0.058	(0.14, 0.37)	<.001
					Ind 150 µg - Salm	0.09	0.057	(-0.03, 0.20)	0.126
	Salm	48	1.40	0.069	Salm - Pbo	0.16	0.060	(0.05, 0.28)	0.007
	Pbo	43	1.24	0.070					
22 hours	Ind 150 µg	50	1.50	0.065	Ind 150 µg - Pbo	0.20	0.049	(0.10, 0.29)	<.001
					Ind 150 µg - Salm	0.11	0.050	(0.01, 0.21)	0.026
	Salm	47	1.39	0.067	Salm - Pbo	0.08	0.052	(-0.02, 0.19)	0.109
	Pbo	44	1.30	0.066					
24 hours	Ind 150 µg	50	1.53	0.056	Ind 150 µg - Pbo	0.16	0.048	(0.06, 0.25)	0.002
					Ind 150 µg - Salm	0.14	0.049	(0.05, 0.24)	0.004
	Salm	46	1.39	0.058	Salm - Pbo	0.01	0.051	(-0.09, 0.11)	0.789
	Pbo	44	1.37	0.057					

Source: Table 11-13 Study No. CQAB149B2336 Clinical Study Report

Figure 9 Protocol B2336 24 hour profile of least squares means of FEV1 (L) after 26 weeks of treatment (ITT population, subset with 24 hour serial spirometry



Source: Figure 11-4 Study No. CQAB149B2336 Clinical Study Report

- **Transitional Dyspnea Index**

The protocol called for the evaluation of dyspnea using the TDI. The TDI focal score, ranging from -9 to 9, is the sum of three domains (functional impairment, magnitude of task and magnitude of effort), with negative scores indicating deterioration. The prespecified MCID was 1.0 unit. Mean TDI focal scores increased between Week 4 and Week 26 for all treatment groups including placebo. As seen in Table 71 below, the 1.45 unit difference in LS mean TDI focal score between indacaterol and placebo was significant ($p<0.001$) and exceeded the MCID of 1.0. Indacaterol was also statistically superior to salmeterol in TDI focal score by a difference 0.55 units ($p=0.015$). The 0.90 unit difference between salmeterol and placebo was statistically significant ($p<0.001$) but did not reach the MCID. At Week 26, neither of the active treatments reached the MCID of 1.0 even though they were statistically significantly different from placebo.

Table 71 Protocol B2336 TDI focal score at Week 12 and Week 26 (LOCF): treatment comparisons (ITT population)

		Treatment			Treatment difference			
Treatment	n	LS Mean	SE	Comparison	LS Mean	SE	95% CI	p-value
Week 12								
Ind 150 µg	303	2.17	0.246	Ind 150 µg - Pbo	1.45	0.229	(1.00, 1.90)	<.001
				Ind 150 µg - Salm	0.55	0.226	(0.11, 1.00)	0.015
Salm	296	1.62	0.245	Salm - Pbo	0.90	0.231	(0.45, 1.35)	<.001
Pbo	286	0.72	0.250					
Week 26								
Ind 150 µg	297	2.03	0.294	Ind 150 µg - Pbo	0.99	0.244	(0.51, 1.47)	<.001
				Ind 150 µg - Salm	0.02	0.239	(-0.45, 0.49)	0.935
Salm	289	2.02	0.295	Salm - Pbo	0.97	0.247	(0.49, 1.46)	<.001
Pbo	272	1.04	0.300					

Source: Table 11-14 Study No. CQAB149B2336 Clinical Study Report

- **Daytime and nighttime symptoms**

The daytime and nighttime symptom treatment effect was evaluated. Specifically, the percentage of nights with 'no nighttime awakenings', percentage of days with 'no daytime symptoms' and percentage of 'days able to perform usual daily activities' over 26 weeks were all measured.

Patients taking either active treatment had a higher percentage of nights with 'no nighttime awakenings' compared with patients taking placebo. The LS mean percentage of nights with 'no nighttime awakenings' over 26 weeks of treatment was 71.6%, 70.8% and 65.3% for indacaterol, salmeterol and placebo, respectively. Differences in the percentage of nights with 'no nighttime awakenings' were statistically significant for comparisons between indacaterol and placebo (difference of 6.3%; p<0.001) and between salmeterol and placebo (difference of 5.5%; p=0.004).

Patients taking indacaterol had a higher percentage of days with 'no daytime symptoms' compared with patients taking either salmeterol or placebo. The LS mean percentage of days with 'no daytime symptoms' over 26 weeks of treatment was 10.5%, 8.9% and 6.2% for the indacaterol, salmeterol and placebo groups, respectively. Differences in the percentage of days with 'no daytime symptoms' were statistically significant for comparisons between indacaterol and placebo (difference of 4.2%; p=0.002) and between salmeterol and placebo (difference of 2.7%; p=0.049).

The LS mean percentage of 'days able to perform usual daily activities' over 26 weeks of treatment was 42.5%, 38.2% and 34.8% for the indacaterol, salmeterol and placebo groups, respectively. Differences in the percentage of 'days able to perform usual daily activities' were statistically significant, favoring indacaterol over placebo (difference of 7.7%; p<0.001) and over salmeterol (difference of 4.4%; p=0.032). Salmeterol provided 3.4% more 'days able to perform usual daily activities' compared with placebo, but this difference was not statistically significant.

- **Rescue medication use**

The protocol stated that the daily rescue medication use was calculated by the total number of puffs of rescue medication per day over the full 26 weeks divided by the total number of days of rescue medication use. Baseline rescue medication use was based on patient diary data from the 14 day interval between Visits 1 and 3. The LS mean change from baseline in mean daily number of puffs of rescue medication was a decrease of 1.34, 1.16, and 0.32 puffs for indacaterol, salmeterol and placebo, respectively. Patients taking either indacaterol or salmeterol required significantly fewer daily puffs of rescue medication over 26 weeks compared with placebo patients (both p<0.001).

The mean daytime and nighttime number of puffs of rescue medication was also measured. The LS mean change from baseline in mean daytime number of puffs of rescue medication was a decrease of 0.89, 0.74, and 0.22 puffs for indacaterol, salmeterol and placebo, respectively. The decrease from baseline in the mean daytime number of puffs of rescue medication over 26 weeks was significantly higher for indacaterol and salmeterol vs. placebo (both p<0.001). The LS mean change from baseline in mean nighttime number of puffs of rescue medication was a decrease of 0.47, 0.43, and 0.15 puffs for indacaterol, salmeterol and placebo, respectively. The decrease from baseline in mean nighttime number of puffs of rescue medication over 26 weeks was significantly higher for indacaterol and salmeterol vs. placebo (both p<0.001).

Finally, the percentage of 'days with no rescue use' was measured. A 'day with no rescue use' was defined from the diary data as any day where the patient used no puffs of rescue medication (after imputation of missing data). The percentage of 'days with no rescue use' was derived and analyzed as the percentage of 'days of poor control'. The LS mean percentage of 'days with no rescue use' was 59.7%, 54.7% and 42.2% for indacaterol, salmeterol and placebo, respectively. Compared with placebo, patients taking either active treatment had a significantly higher percentage of days (17.5% more days with indacaterol and 12.4% more days with salmeterol) with no use of rescue medication than patients taking placebo (both p<0.001). Indacaterol treated patients also had a significantly higher percentage of days without using rescue medication compared with salmeterol treated patients (difference of 5.1%; p=0.033).

- **Peak expiratory flow (PEF)**

Patients taking either indacaterol or salmeterol showed improvements from baseline in morning PEF compared with patients taking placebo. The LS mean change from baseline in morning PEF over 26 weeks of treatment was 25.3, 15.2 and -0.8 L/min for indacaterol, salmeterol and placebo, respective. The corresponding treatment differences were 26.2 (21.0, 31.4) for indacaterol and placebo; 16 (10.8, 21.3) for salmeterol and placebo. Compared with placebo, patients taking either indacaterol or salmeterol had significantly higher increases in change from baseline for morning PEF (both p<0.001). Indacaterol was also significantly superior to salmeterol in the improvement from baseline in morning PEF (p<0.001). Similar results were seen with the evening values and were also statistically significant for both indacaterol and salmeterol.

- **SGRQ total score and component scores over time**

The least squares mean treatment difference for indacaterol over placebo for SGRQ total score over Week 4, 8 and 26 were -3.6, -4.1 and -5.0, all statistically significant over placebo. The component scores are summarized in Table 72.

Table 72 Analysis of the SGRQ symptoms component score after 4, 8, 12 and 26 weeks of treatment (imputed with LOCF, ITT population)

	Treatment difference Indacaterol 150 mcg to placebo					
	Symptoms (95% CI)	p-value	Activity (95% CI)	p-value	Impact (95% CI)	p-value
Week 4	-5.6 (-8.1, -3.0)	<0.001	-2.5 (-4.9, -0.2)	0.037	-3.5 (-5.4, -1.6)	<0.001
Week 8	-5.9 (-8.6, -3.2)	<0.001	-3.4 (-6.0, -0.9)	0.008	-4.1 (-6.2, -2.0)	<0.001
Week 12	-7.8 (-10.6, -4.9)	<0.001	-5.4 (-7.9, -2.8)	<0.001	-6.4 (-8.5, -4.3)	<0.001
Week 26	-7.8 (-10.8, -4.7)	<0.001	-4.7 (-7.4, -2.1)	<0.001	-4.4 (-6.8, -2.1)	<0.001

Source: Adapted from Table 14.2-10.4 Study No. CQAB149B2336 Clinical Study Report

- **Rate of change in FEV1 and FVC response over 26 weeks**

Over the 26 week treatment duration, no statistically significant differences between treatment groups in the estimated rate of change per month in tFEV1 or FVC was apparent.

- **BODE index**

At Week 12, the LS mean BODE index score was 2.44, 2.58 and 2.87 for indacaterol, salmeterol and placebo, respectively. At Week 26, the LS mean BODE index score was 2.40, 2.55 and 2.86, respectively. BODE index scores were significantly lower with both indacaterol and salmeterol compared with placebo after 12 and 26 weeks (all p<0.01).

Reviewer's Comment:
It is unclear if a value has been defined as clinically significant for reduction in BODE score.

- **Six minute walk distance**

The LS mean distance walked in 6 min at Week 12 was 387.3 m, 384.4 m and 382.2 m for the indacaterol, salmeterol and placebo groups, respectively. There were no significant treatment differences at Week 12. The LS mean distance walked in 6 min at Week 26 increased to 395.4 m, 388.9 m and 383.6 m for the treatment groups, respectively. Patients taking indacaterol walked statistically significantly longer distances in 6 min at Week 26 compared with patients taking placebo (difference of 11.8 m; p=0.032). The clinical relevance of such a small improvement has not been demonstrated.

4.3.6.3.3 Safety Review

4.3.6.3.3.1 Extent of exposure

The extent of exposure was similar across treatment groups. The mean number of days of exposure for indacaterol 150 mcg was 169.2, for salmeterol the mean was 164.3 days and placebo, 155.4 days. Most patients were exposed for over 24 weeks, 88.8% of patients in the indacaterol treatment group and 78.8% in the placebo group. Compliance was demonstrated by > 98% of the planned doses for indacaterol with the SDDPI device and >96% with the proprietary device were taken.

4.3.6.3.3.2 Concomitant medications

Slightly more than half of the patients across the treatment groups were taking COPD-related medications, with the most common being ICS. Antibiotics were the second most common COPD-related medication. Non-COPD related medications were taken by 73.9% of patients in the indacaterol group and 69.4% in the salmeterol group and 65.4% in the placebo group. The most common non-COPD medications taken were acetylsalicylic acid, paracetamol, enalapril and simvastatin.

4.3.6.3.3.3 Adverse events

Consistent with many of the other trials, the SOC with the highest percent of events were infection and infestations (239 patients) and respiratory, thoracic and mediastinal (230 patients). The most frequent AEs were: COPD with higher rates in placebo (19.4%) than indacaterol (18.2%); nasopharyngitis with similar rates across treatment groups; upper respiratory tract infection, indacaterol (4.2%) higher than placebo (1.5%) lower respiratory tract infection, also with similar rates across treatment groups. Refer to Table 73 for a summary.

Table 73 Most frequent AEs, including COPD exacerbations, by preferred term (at least 1.0% in any treatment group) (Safety population)

	Ind 150 µg N=330 n (%)	Salm N=333 n (%)	Pbo N=335 n (%)
Patients with any AE(s)	169 (51.2)	152 (45.6)	156 (46.6)
Preferred term			
Chronic obstructive pulmonary disease	60 (18.2)	51 (15.3)	65 (19.4)
Nasopharyngitis	24 (7.3)	29 (8.7)	21 (6.3)
Upper respiratory tract infection bacterial	14 (4.2)	3 (0.9)	5 (1.5)
Viral upper respiratory tract infection	10 (3.0)	3 (0.9)	7 (2.1)
Lower respiratory tract infection	9 (2.7)	13 (3.9)	8 (2.4)
Cough	8 (2.4)	9 (2.7)	13 (3.9)
Back pain	7 (2.1)	12 (3.6)	6 (1.8)
Dyspnea	7 (2.1)	6 (1.8)	15 (4.5)
Hypertension	7 (2.1)	4 (1.2)	5 (1.5)
Influenza	7 (2.1)	5 (1.5)	4 (1.2)
Pyrexia	7 (2.1)	3 (0.9)	4 (1.2)
Upper respiratory tract infection	7 (2.1)	1 (0.3)	8 (2.4)

Source: Table 12-3 Study No. CQAB149B2336 Clinical Study Report

Deaths and SAEs

There were a total of 5 deaths in the trial, 4 occurring during treatment or within 30 of the last dose. One death occurred in a patient on indacaterol, this was reported as a cardiac arrest. There were 2 other deaths not included in the clinical database, 1 in the salmeterol group and 1 in placebo. There were 74 patients with SAEs, of which, 32 led to discontinuation. The most common SAE leading to discontinuation was COPD. In the indacaterol 150 mcg treatment group, 1 patient had a myocardial infarction, another a cardiac arrest, one with a tachyarrhythmia, and one with tachycardia. These events were not reported for salmeterol or placebo. As well, there was 1 patient with a cerebral infarction and 1 with cerebral vascular accident, and none of these events in salmeterol and placebo.

Adverse events leading to discontinuation

There were 5 SAEs in indacaterol, 9 in salmeterol and 2 in placebo categorized under the SOC of infections and infestations leading to discontinuation. There were more cardiac disorders leading to discontinuation (4) in indacaterol than placebo (2). AEs leading to discontinuation occurred at similar rates across treatment groups (5.2% in patients treated with indacaterol and 4.8% in patients taking salmeterol and 4.5% in patients treated with placebo.

4.3.6.3.3.4 Laboratory findings

There were no clinically significant changes in hematology or chemistry labs over the treatment groups. There were 1 patient (0.3%) in the indacaterol group, 2 (0.6%) in the salmeterol group and 0 in placebo with potassium levels < 3 mmol/L. For notable glucose levels > 9.99 mmol/L there were 19 (5.8%). 30 (9.0%) and 21 (6.3%) in the indacaterol, salmeterol and placebo groups, respectively.

4.3.6.3.3.5 ECG findings

One patient in the indacaterol treatment group developed a QTcF >500 ms, a 69 year old male who subsequently developed adenocarcinoma of the pancreas. A maximum increase from baseline of 30 – 60 ms in QTcF occurred in more indacaterol treated patients (31 patients, 9.1%) than salmeterol (15 patients, 4.5%) and placebo (21 patients, 6.3%). There were 2 patients who developed a maximum increase from baseline > 60 msec, 1 in the indacaterol group and one in the salmeterol group.

4.3.6.3.3.6 Physical examination

Focus was placed on blood pressure and pulse the with known beta2 adrenergic effect. There was a higher percentage of SBP > 200 mm Hg in patients in the placebo group (1.5%) than indacaterol (0.6%) or salmeterol (0.9%). DBP > 115 mm Hg occurred at equal rates in the indacaterol group and placebo group (0.3%). There were no events of notable pulse rate > 130 bpm.

4.3.6.3.3.7 Special safety topics

More patients taking indacaterol versus other treatments experienced a post inhalational (PI) cough event within 5 min after dosing, usually within 15 seconds after dosing with a median duration of 12 seconds. The incidence of PI cough events in the indacaterol group ranged from 17- 19.7% across visits, salmeterol ranged from 0.3- 2% and placebo ranged from 0.9- 3.3%.

4.3.6.3.4 Summary of Study

This was a 26 week, multicenter, international, randomized, placebo-controlled trial comparing the higher proposed dose indacaterol 150 mcg q.d. to placebo in adults with moderate to severe COPD. The selected dose of indacaterol 150 mcg achieved the primary endpoint demonstrating a statistically significant treatment difference from placebo after twelve weeks, 0.170 L.

Indacaterol 150 mcg treatment for 12 weeks achieved the important secondary endpoint, SGRQ, and met the minimum clinically important difference of 4 units. Indacaterol 150 mcg was not shown to be significantly different from placebo in the symptomatic diary assessment of ‘days of poor control’.

Consistent with the known bronchodilator mechanism of indacaterol, a significant difference was also shown over placebo for other spirometry based endpoints including tFEV1 on Day 2 and Week 26; peak FEV 5 min-4hr at Day 1, Week 12 and Week 26; FEV1 AUC 5min- 4hr and AUC 5min- 1hr at Day 1, Week 12 and Week 26. Indacaterol 150 mcg also showed benefit over placebo for FEV1 during all the measured time points over 24 hours.

TDI focal scores were statistically significantly improved with indacaterol 150 mcg by 12 and 26 weeks of treatment. Percentage of nights with ‘no nighttime awakenings’, days with ‘no daytime symptoms’ and ‘days able to perform usual daily activities’ over 26 weeks were statistically significant for comparisons between indacaterol and placebo. Patients taking indacaterol 150 mcg showed improvement for all rescue medication use assessments reported; patients required significantly fewer daily, daytime or nighttime puffs of rescue medication and had a significantly higher percentage of ‘days with no rescue use’ compared with patients taking placebo over 26 weeks of treatment.

The most frequent AEs were COPD, nasopharyngitis, upper respiratory tract infect, lower respiratory tract infection, cough, dyspnea and back pain. The percentage of patients with the AEs of COPD and dyspnea was higher in the placebo group than the indacaterol 150 mcg group. There were a total of 7 deaths in the trial, 4 occurring during treatment or within 30 of the last dose. One death occurred in a patient on indacaterol, this was reported as a cardiac arrest. There were 74 patients with SAEs, of which, 32 led to discontinuation. The most common SAE leading to discontinuation was COPD. In the indacaterol 150 mcg treatment group, 1 patient had a myocardial infarction, another a cardiac arrest, one with a tachyarrhythmia, and one with tachycardia. These events were not reported for salmeterol or placebo. As well, there was 1 patient with a cerebral infarction and 1 with cerebral vascular accident, and none of these events in salmeterol and placebo. There were 5 SAEs in indacaterol, 9 in salmeterol and 2 in placebo categorized under the SOC of infections and infestations leading to discontinuation. There were more cardiac disorders leading to discontinuation (4) in indacaterol than placebo (2).

There were no clinically meaningful differences reported between treatment groups for serum potassium or blood glucose. There were no significant differences between treatment groups regarding vital signs. An increase of >60 ms in Fridericia’s QTc was seen in 1 patient in each active treatment group. More

patients taking indacaterol versus other treatments experienced a post inhalational cough event within 5 min after dosing, typically starting within 15 seconds after dosing and lasting with a median duration of 12 seconds. The incidence of PI cough events in the indacaterol group was <20%.

Supplementary Trials

Trial B2341

Trial B2341 was a 12 week, randomized, double-blind, parallel group efficacy and safety comparison of indacaterol 150 mcg plus open-label tiotropium HandiHaler (18 mcg) versus placebo plus open-label tio HH18 in patients with COPD. The study was conducted in 186 different centers in 14 countries (including the United States, Central and South America, Europe, Asia, Africa, and Australia). The primary study endpoint was FEV1 $AUC_{5min-8hours}$ after 12 weeks of therapy. The key secondary endpoint was trough FEV1 after 12 weeks of therapy. Multiplicity for the key secondary endpoint was controlled by heirarchical testing. Other study efficacy endpoints included FEV_1 at other time points, inspiratory capacity (subset only), rescue medication use, and COPD symptoms.

A total of 1134 male and female subjects with moderate to severe COPD (post-bronchodilator FEV_1 30-65% predicted) were enrolled; 570 in the combination group and 564 in the tio alone group. Of these, 1060 (93.5%) completed the study. Demographics were generally balanced between the treatment groups. Overall, the mean age of patients in the trial was 63.7 years. Most patients were male (68.7%) and caucasian (77.5%). Patients had a mean post-bronchodilator FEV1 of 1.33L, with 46.7% having moderate COPD and 52.6% with severe disease. Nearly half of patients were taking concurrent inhaled corticosteroids (47.9%), and just over 1/3 were current smokers (38.4%). Six percent of patient had major protocol deviations, primarily not meeting the FEV1 enrollment criteria (2.4%), SABA reversibility not acceptable (1.1%), or compliance with <80% of study medication doses (0.8%). These deviations are not expected to bias the results significantly as they occurred equally in both treatment groups.

For the primary endpoint, FEV1 $AUC_{5min-8hours}$ after 12 weeks of therapy, the combination group was significantly higher than the tio alone group, with an AUC of 1.50L versus 1.38L. This demonstrated a treatment difference of 0.13L, 95% CI 0.10-0.15, $p<0.001$. Likewise, for the key secondary endpoint, trough FEV1, the combination group showed a significantly different treatment benefit over the tio alone group, with a difference of 0.08L, 95% CI (0.05, 0.10), $p<0.001$. Day 1 values also showed a significant benefit for the combination group over the tio alone group for all FEV1 endpoints measured, with separation demonstrated as early as the 5 minute time point. At Week 12, the FEV1 treatment difference varied from 100 to 140 ml. Rescue medication use, symptom scores, and inspiratory capacity also showed numerical benefit for the combination group over the tio alone group.

The most frequent adverse event was cough, which occurred more frequently in the combination group (10.4% versus 3.7%). Other adverse events occurring more frequently in the combination group were muscle spasms (2.3% versus 0) and abdominal pain (1.2% versus 0.2%). The most common serious adverse events were respiratory, cardiac, and infections. COPD exacerbations occurred more frequently in the combination group, with 6 (1.1%) versus 12 (2.1%). Likewise, discontinuations due to AEs occurred more frequently in the combination group, with 21 (3.7%) versus 9 (1.6%). There were two on-treatment deaths in the trial, both in the combination group. Cause of death was anaphylaxis 30 minutes after receiving ceftriaxone for a COPD exacerbation and myocardial infarction.

Reviewer comment:

This trial demonstrates that indacaterol provides additional bronchodilator benefit in patients receiving a long-acting anticholinergic (tiotropium), a common therapy in COPD. This benefit is tempered by an increased risk of cough and COPD exacerbation. There were also two deaths in the combination group, but the numbers are too small to draw safety conclusions regarding mortality.

Trial B2351

Trial B2351 was a 12 week, randomized, double-blind, parallel group efficacy and safety comparison of indacaterol 150 mcg plus open-label tiotropium HandiHaler (18 mcg) versus placebo plus open-label tio HH18 in patients with COPD. The trial design was the same as Protocol B2341. The trial was conducted in 182 different centers in 12 countries (including the United States, Canada, South America, Eastern and

Western Europe, India, and the Philippines). The primary endpoint was FEV1 AUC5min-8hours after 12 weeks of therapy. The key secondary endpoint was trough FEV1 after 12 weeks of therapy. Multiplicity for the key secondary endpoint was controlled by hierarchical testing. Other trial efficacy endpoints included FEV1 at other time points, inspiratory capacity (subset only), rescue medication use, and COPD symptoms.

A total of 1142 male and female subjects with moderate to severe COPD (post-bronchodilator FEV1 30-65% predicted) were enrolled; 572 in the combination group and 570 in the tio alone group. Of these, 1076 (94.2%) completed the trial. Demographics were generally balanced between the treatment groups. Overall, the mean age of patients in the trial was 62.9 years. Most patients were male (65.4%) and Caucasian (78.5%). Patients had a mean post-bronchodilator FEV1 of 1.31L, with 45.8% having moderate COPD and 53.2% with severe disease. Nearly half of patients were taking concurrent inhaled corticosteroids (45.9%), and 40% were current smokers. Seven percent of patients had major protocol deviations, primarily not meeting the FEV1 enrollment criteria (2.8%), compliance with <80% of study medication doses (1.1%), or SABA reversibility not acceptable (0.8%). These deviations are not expected to bias the results significantly as they occurred equally in both treatment groups.

For the primary endpoint, FEV1 AUC $_{5min-8hours}$ after 12 weeks of therapy, the combination group was significantly higher than the tio alone group, with an AUC of 1.46 L versus 1.34 L. This demonstrated a treatment difference of 0.12 L, 95% CI 0.09-0.14, p<0.001. Likewise, for the key secondary endpoint, trough FEV1, the combination group showed a significantly different treatment benefit over the tio alone group, with a difference of 0.07 L, 95% CI (0.05, 0.09), p<0.001. Day 1 values also showed a significant benefit for the combination group over the tio alone group for all FEV1 endpoints measured, with separation demonstrated as early as the 5 minute time point. At Week 12, the FEV1 treatment difference varied from 120 to 130 ml at various time points up to 8 hours. Rescue medication use, symptom scores, and inspiratory capacity also showed numerical benefit for the combination group over the tio alone group.

The most frequent adverse event was cough, which occurred more frequently in the combination group (9.1% versus 4.4%). Other adverse events occurring more frequently in the combination group were dry mouth and dyspnea (2.1% versus 0.5% for both AEs). The most common serious adverse events were respiratory and infections. In contrast to Trial B2341, COPD exacerbations and discontinuations due to AEs were balanced between treatment groups. Serious cardiovascular events were also balanced. There were three on-treatment deaths in the trial, one in the combination group and two in the tiotropium group. In the combination group cause of death was myocardial infarction, and in the tiotropium group cause of death was sudden death and cardiac arrest.

Reviewer comment:

This trial demonstrates that indacaterol provides additional bronchodilator benefit in patients receiving a long-acting anticholinergic (tiotropium), a common therapy in COPD, providing replicate data to Trial B2341. This benefit is tempered by an increased risk of cough. Mortality and serious adverse events were generally balanced between treatment groups.

Trial B2335SE

Trial B2335SE was a 26 week extension to a 26 week, randomized, double-blind, multicenter, placebo-controlled, adaptive design, parallel-group efficacy and safety comparison of indacaterol (150 mcg and 300 mcg) versus placebo in patients with COPD. The trial was conducted in 142 different centers in 9 countries (including the United States, Argentina, Canada, Germany, India, Italy, Spain, Sweden and Turkey). No primary efficacy endpoint was specified. The secondary efficacy endpoints were trough FEV1 at Week 52. Other efficacy endpoints included: FEV1 and FVC at other time points, time to first COPD exacerbation, COPD exacerbation rates, COPD symptoms, post-inhalational cough events, rescue medication use, PEF and SGRQ.

A total of 415 male and female patients with moderate to severe COPD (post bronchodilator FEV1 <80% and ≥ 30% of predicted) who completed stage 2 of the core trial (B2335S) were enrolled in the extension trial B2335SE. A total of 366 (88.2%) completed the extension trial (126 patients or 87.5%, indacaterol 150 mcg; 135 or 92.5%, indacaterol 300 mcg and 105 or 84% in placebo). Discontinuation was observed at a higher rate in the placebo group (16%) and ranged from 7.5% in indacaterol 300 mcg to 12.5% in the indacaterol 150 mcg group. The most common reasons for discontinuation were withdrawal of consent, lost to follow up and protocol deviations. Demographics were balanced between the treatment groups and consistent with many of the previous trials. The mean age was 62.6 (± 9.21 years), most were males (61.4%) and caucasian (81.4%). The patients had a mean post bronchodilator FEV1 of 1.49 L, with 54% having moderate COPD and 41% with severe disease. Inhaled corticosteroids were taken by 35-38% of patients and half were current smokers. Nineteen percent reported major protocol deviations, primarily time of dosing eosinophil count > 400/mm3 at screening and trough measurement timings not compliant with protocol. These deviations are unlikely to bias the results significantly as they occurred at similar rates across treatment groups.

The treatment difference of trough FEV1 at Week 52 was statistically significantly higher in the indacaterol treatment groups compared to placebo, 150 mcg indacaterol 0.17 L (0.11, 0.23) and 300 mcg indacaterol 0.18 L (0.12, 0.24) for the ITT population. Likewise, the tFEV1 at other time points, Week 12 (Day1), Week 26 (Day 2), and Week 36 and 44 were all statistically significantly higher than placebo with similar numeric values as Week 52.

The Cox regression analysis of time to first COPD exacerbation showed no statistically significant differences between groups. Likewise, there were no significant differences in number of exacerbations per patient and event free rates. The rates of COPD exacerbations over the 52 week total duration of the study for indacaterol 150 mcg, 300 mcg, and placebo were 0.39, 0.38 and 0.54, respectively. While the Sponsors analysis of ratio of rates meets statistical significance, this analysis is not corrected for overdispersion, so may overestimate the treatment effect.

Evaluation of the percentage of patients with “days of poor control” over 52 weeks as well as improvement in daytime and nighttime symptoms did not show any significant difference between indacaterol treatment groups and placebo. All assessments of rescue medication use as well as morning and evening PEF showed statistical significance in comparison between the indacaterol treatment groups and placebo. Assessment of health-related quality of life as measured by the SGRQ did not meet the MCID of -4 at week 52 (treatment difference of -3.2); however, at Weeks 26 and 44 the treatment differences were -4.47 and -5.7 for the 150 mcg indacaterol treatment group. The treatment difference was smaller for the 300 mcg indacaterol treatment group, with a difference of -1.9, -5.4, and -1.7 at Week 26, 44, and 52, respectively.

The most frequent AEs by preferred term were COPD, nasopharyngitis, cough, upper respiratory tract infection, headache, muscle spasms and oropharyngeal pain. The rates were similar between indacaterol and placebo for COPD and nasopharyngitis, and higher for cough, headache, and muscle spasms. Post inhalational cough occurred in 28.5%, 31.5% and 3.2% of patients in the 150 mcg, 300 mcg, and placebo groups, respectively. SAEs were reported at similar rates between indacaterol 150 mcg (10.4%), 300 mcg (13.0%) and placebo (10.5%). SAEs occurred most frequently in the respiratory, thoracic and mediastinal (14 patients), cardiac (9 patients) and infection and infestations (8 patients) SOCs. There were two deaths during the trial, one patient in the placebo group and one in the indacaterol 300 mcg group, both from myocardial infarctions.

Reviewer Comment:

The trial demonstrates that indacaterol 150 mcg and 300 mcg were effective bronchodilators in patients with COPD out to 12 months treatment duration. The safety profile was consistent with events described in the pivotal trials.

Trial B1302

Trial B1302 was a 12 week randomized, double-blind, multicenter, placebo-controlled, parallel-group efficacy and safety comparison of the two higher doses of indacaterol 150 mcg and 300 mcg versus placebo in patients with COPD. The trial was conducted at 73 centers in 6 countries (including Japan, Taiwan, Korea, India, Hong Kong and Singapore). The primary endpoint was tFEV1 at 12 weeks of treatment. Exploratory secondary endpoints included: FEV1 AUC at multiple time points; FEV1 and FVC during multiple time points, COPD symptoms, rescue medication use and health-related quality of life measurements.

A total of 347 patients with moderate to severe COPD (post bronchodilator FEV1 <80% and ≥ 30% of predicted) were enrolled. Three hundred and eight patients completed the trial. Overall demographics were balanced across the treatment groups. The mean age of patients in the trial was 66.7 years. The majority of patients were male (96.5%), and as this trial was designed to confirm efficacy and safety for the asian population, 100% were asian. Patients had a mean post bronchodilator FEV1 of 1.41 L, with 59.7% having moderate COPD, 40.3% having severe disease and 24.7% on concurrent ICS. One third (32%) of the patients were current smokers. At least one major protocol deviation occurred in 24 patients (6.9%), with the most common being that a leukotriene antagonist (1.4%) or other COPD medication (1.2%) was taken during 30 days prior to the screening visit. These deviations occurred at similar frequencies across all treatment groups and therefore are not expected to alter the results significantly.

For the primary endpoint, tFEV1 after 12 weeks both doses 150 mcg and 300 mcg indacaterol were significantly higher than the placebo group with a LS mean of tFEV1 of indacaterol (1.34 L for 150 mcg and 1.37 L for 300 mcg) compared to placebo (1.17 L) ($p<0.001$). This demonstrated a treatment difference compared to placebo of 0.17 L (95% CI 0.13, 0.21) and 0.20 L (0.16, 0.24) for the indacaterol 150 mcg and 300 mcg, respectively. There were no significant differences between the subgroups analyzed. The treatment comparisons of tFEV1 at different time points, Week 2, 4, 8 and 12 were also statistically significantly greater for the two doses with values of 0.16, 0.14, 0.16 and 0.21 for indacaterol 150 mcg, and 0.17, 0.15, 0.18 and 0.21 for indacaterol 300 mcg respectively, all with p-values < 0.001. There was no significant separation of the curves between the two indacaterol doses at any time point up to 13 weeks. The peak FEV1 and FEV1 AUC at multiple time points were also statistically significantly greater for the two indacaterol doses over placebo.

Evaluation of the clinical symptoms through “days of poor control” showed only the 150 mcg indacaterol dose as statistically significantly greater than placebo. The percentage of nights with “no nighttime awakenings” and the “days able to perform usual daily activities” were statistically significant for both indacaterol doses over placebo however, the percentage of days with “no daytime symptoms” was not. The TDI score after 12 weeks was statistically significant for the two doses over placebo, however, none of the assessments for rescue medication use reached statistical significance. The health-related quality of life measure, SGRQ was evaluated at Week 12 and shown not only to be statistically significant with the two indacaterol doses over placebo, but also exceeded the MCID of 4 units, indacaterol 150 mcg, -4.8 (p-value = 0.005) and 300 mcg -5.7 (p-value = 0.001).

The most frequent adverse event was COPD, which occurred more frequently in the placebo group (12.8%) than either 150 mcg (9.6%) or 300 mcg (9.5%) indacaterol doses. Adverse events occurring more frequently in the indacaterol groups were cough (4.4%, 9.5% versus 2.6% for indacaterol 150 mcg, 300 mcg and placebo, respectively), headache (2.6, 0.0 versus 0.9%) and muscle spasms (1.8%, 0.9% versus 0). The most common serious adverse events by SOC were respiratory, cardiac, and infections with COPD exacerbations occurring less frequently in the 150 mcg and 300 mcg indacaterol groups (9.6%, 9.5% respectively) than placebo (12.8%). There were no deaths reported during the trial.

Reviewer Comment:

The trial demonstrates that indacaterol 150 mcg and 300 mcg were effective bronchodilators in asian patients with COPD out to 12 weeks treatment duration. The safety profile was consistent with events described in the pivotal trials.

Trial B2333

Trial B2333 was a 26 week randomized, double-blind, multicenter, placebo-controlled, parallel-group efficacy and safety comparison of the two higher doses of indacaterol 150 mcg and 300 mcg versus placebo in patients with COPD. The trial was conducted at 29 centers in 3 countries (including Australia, China and India). The primary endpoint was tFEV1 at 12 weeks of treatment. Secondary endpoints included: tFEV1 at different time points; FEV1 at multiple baseline points; COPD exacerbations; symptoms, rescue medication use; morning and evening PEF over 26 weeks and health-related quality of life measurements.

A total of 563 patients with moderate to severe COPD (post bronchodilator FEV1 <80% and ≥ 30% of predicted) were enrolled and 482 (85.6%) completed the trial. Overall demographics were balanced across the treatment groups. The mean age of patients in the trial was 65.4 years. The majority of patients were male (94%), and as this trial was conducted to support regulatory submission in China, the majority (89.8%) were Chinese. Patients had a mean post bronchodilator FEV1 of 1.30 L, with 46.9% having moderate COPD, 52.6% having severe disease and 34.8% on concurrent ICS. One quarter (22.3%) of the patients were current smokers. At least one major protocol deviation occurred in 63 patients (11.2%), with the most common being “not compliant with dosing scheduled at primary endpoint dosing visits” which occurred at a higher frequency in the indacaterol 150 mcg group (2.7%) than the 300 mcg group (1.6%) or placebo (1.1%). Although, the numerical value was slightly higher for indacaterol 150 mcg group, its unlikely to have altered the results significantly. Since there were a greater number of non-compliant patients in the indacaterol groups, if there were an effect, it would have been to bias away from the drug.

For the primary endpoint, tFEV1 after 12 weeks both doses 150 mcg and 300 mcg indacaterol were significantly higher than the placebo group with a LS mean of tFEV1 of indacaterol (1.32 L for 150 mcg and 1.29 L for 300 mcg) compared to placebo (1.17 L) (p<0.001). This demonstrated a treatment difference compared to placebo of 0.15 L (95% CI 0.11, 0.19) and 0.13 L (0.09, 0.17) for the indacaterol 150 mcg and 300 mcg, respectively. Secondary endpoints such as the LS means for tFEV1 were generally comparable between the subgroups analyzed. The treatment comparisons of tFEV1 at different time points, Day 2 and after 26 weeks of treatment were also statistically significantly greater for the two doses with values of 0.15 and 0.14 for indacaterol 150 mcg at Day 2 and 0.13 and 0.14 for indacaterol 300 mcg on Week 26, all with p-values < 0.001. There is no significant separation of the curves between the two indacaterol doses at any time point up to 26 weeks. FEV1 was measured at Days 1, 15, 29, 57, 84, 85, 113, 182 and 183. All other time points measured for indacaterol 150 mcg and 300 mcg were significantly greater compared to placebo (all p-values <0.001). As well, there were no statistically significant difference in the rate of change in tFEV from 15 days to 26 weeks of treatment. Morning and evening PEF over 26 weeks of treatment with indacaterol were statistically significantly greater over placebo. The LS mean difference for morning PEF of indacaterol 150 mcg and 300 mcg were 30.4 and 26.9 and the evening values were 29.1 and 25.7, respectively (all p-values < 0.001).

The SGRQ scores were lower for the two indacaterol doses over placebo however, the difference was neither statistically significant nor exceeded the MCID for any of the time points evaluated.

Time to first COPD exacerbation was also evaluated and was not statistically significantly different from placebo. The COPD exacerbation rate as measured by the ratio of rates was significantly lower for indacaterol 150 mcg but not for the 300 mcg group. Other measures such as TDI at Weeks 8, 12 and 26; percentage of nights with “no nighttime awakenings”; percentage of “days able to perform usual daily activities” and all assessments of rescue medication use over 26 weeks all had treatment differences that were statistically significant over placebo.

The most frequent adverse event was COPD, which occurred at similar rates across treatment groups: indacaterol 150 mcg (18.7%), 300 mcg (22.9%) and placebo group (21.0%). Adverse events occurring more frequently in the indacaterol groups were cough (2.1%, 3.7% versus 1.6% for indacaterol 150 mcg, 300 mcg and placebo, respectively) and eosinophilia (2.7, 2.1 versus 0.5%). The most common serious adverse events by SOC were respiratory thoracic and mediastinal disorders with 3.2%, 5.3% and 3.8% for 150 mcg, 300 mcg indacaterol and placebo, respectively. Infections and infestations were the second most common (0.5%, 1.6% and 2.7%, respectively). The frequency of SAEs were similar across subgroups analyzed. There were no deaths reported during the trial.

Reviewer Comment:

The trial demonstrates that indacaterol 150 mcg and 300 mcg were effective bronchodilators in Chinese patients with COPD out to 26 weeks treatment duration. The safety profile was consistent with events described in the pivotal trials with the addition of more reports of eosinophilia in the indacaterol groups over placebo.

Trial B2349

Trial B2349 was a 12 week randomized, double-blind, multicenter, placebo-controlled, parallel-group to show the superiority of indacaterol 150 mcg versus an active comparator, salmeterol (50 mcg b.i.d) in patients with COPD. The trial was conducted at 142 centers in 8 countries (including United States, Czech Republic, Germany, Hungary, India, Slovakia, Spain and Turkey). The primary endpoint was FEV1 AUC between 5 min and 11 hr 45 min after 84 days of treatment. The key secondary endpoint was the tFEV1 after 84 days of treatment. Multiplicity for the key secondary endpoint was controlled by a heirarchical testing approach. Spirometry assessments at other time points, TDI focal score and rescue medication use were other efficacy endpoints.

A total of 1,123 patients with moderate to severe COPD (post bronchodilator FEV1 <80% and ≥ 30% of predicted) were enrolled. One thousand thirty four (92.1%) patients completed the trial. Overall demographics were balanced across the treatment groups. The mean age of patients in the trial was 63 years. The majority of patients were male (70%) and caucasian (84%) with a significant proportion of asians (12.4%). Patients had a mean post bronchodilator FEV1 of 1.46 L, with 53.2% having moderate COPD, and 45.9% having severe disease and 45.9% on concurrent ICS. Nearly half (44.5%) of the patients were current smokers. At least one major protocol deviation occurred in 193 patients (17.2%) of the two groups, with the most common being that SABA reversibility was not acceptable (10.7%). This deviation occurred at similar frequencies across all treatment groups and therefore is not expected to alter the results significantly.

For the primary endpoint, FEV1 AUC (5 min- 11hr 45 min) indacaterol (1.47 L) had a larger numerical value over baseline (1.28 L) versus salmeterol (1.41 L). The treatment difference between indacaterol and salmeterol after 12 weeks was statistically significant (0.06 L, 95% CI 0.04, 0.08 p-value= <0.001). Most subgroups did not show any major differences in LS mean values, with indacaterol 150 mcg q.d. generally consistently showing numerically higher values than salmeterol. No conclusions can be made about race given the small numbers of noncauscasian patients. The secondary efficacy endpoint showed similar results. The treatment differences of indacaterol 150 mcg over 50 mcg salmeterol at Week 12 was statistically significant (LS mean 0.06 L, 95% CI 0.04, 0.08 p-value= <0.001). The treatment differences for the other endpoints such as FEV1 AUC (5min-4 hr), AUC (5 min-8 hr) and AUC (8 hr- 11 hr 45 min) were also consistent with indacaterol values statistically greater than salmeterol. The treatment difference between indacaterol and salmeterol for the TDI focal score was statistically significant (0.63 95% CI 0.30, 0.97 p-value<0.001); however, it did not meet the Sponsor's predefined clincical importance level of ≥1. Evaluation of rescue medication use by change from baseline in the mean daily number of puffs of rescue medication and percentage of "days with no rescue use" also revealed indacaterol 150 mcg with a larger LS mean -1.64 versus salmeterol 50 mcg, -1.45. The treatment difference between the two groups was -0.18 (95% CI -0.36, 0 p-value= 0.048)

Adverse events occurred at almost identical rates between the two groups, indacaterol 150 mcg 33.8% versus salmeterol 50 mcg 33.5%. The most frequent adverse event was COPD, which occurred more frequently in the salmeterol group (5.7%) than the 150 mcg indacaterol group (4.5%). Other AEs such as headache, nasopharyngitis and oropharyngeal pain occurred at similar rates between the two groups. However, cough (3.4% versus 2.5%) and muscle spasms (2.0% versus 1.4%) occurred more frequently in the indacaterol groups than the salmeterol groups, respectively. Serious adverse events occurred at slightly higher rates in the indacaterol group (3.6%) versus the salmeterol group (2.8%). The most common serious adverse events by SOC were respiratory, thoracic and mediastinal, cardiac disorders and infections and infestations with COPD exacerbations occurring less frequently in the 150 mcg indacaterol group than in the 50 mcg salmeterol group (0.7%, 1.2% respectively). There were a total of 4 deaths reported during the trial. One (cardiac arrest) occurred during the run-in period and therefore the patient did not receive any trial medication. Two occurred in the 150 mcg indacaterol group: one of a suspected myocardial infarction and the second with a newly diagnosed stomach cancer. The fourth patient death, which occurred in the salmeterol group was reported as a respiratory failure.

Reviewer Comment:

The trial demonstrates that indacaterol 150 mcg q.d. had numerically larger spirometry values than salmeterol 50 mcg b.i.d. However, an important factor is that the 150 mcg indacaterol dose was selected from the interim analysis of the adaptive design trial B2335S based on criteria that the dose chosen be numerically higher than tiotropium and formoterol in terms of FEV1 AUC (1- 4 hr). The safety profile was consistent with events described in the pivotal trials.

Trial B2350

Trial B2350 was a 12 week randomized, double-blind, multicenter, active controlled, parallel-group to show non-inferiority of indacaterol 150 mcg q.d. with tiotropium 18 mcg q.d. in patients with COPD. The trial was conducted at 223 centers in 22 countries (including United States, Austria, Belgium, Canada, Colombia, Denmark, Finland, France, Germany, Greece, Hungary, Israel, Italy, Mexico, Norway, Poland, Russia, Slovakia, Spain, Switzerland, Turkey and the United Kingdom). The primary endpoint was tFEV1 at 12 weeks of treatment to show that indacaterol 150 mcg was non-inferior to tiotropium 18 mcg. The key secondary endpoint was to demonstrate superiority of indacaterol 150 mcg q.d. versus tiotropium 18 mcg q.d. with respect to tFEV1 after 12 weeks of treatment. A hierarchical testing approach was taken for the primary and key secondary comparisons. Other secondary endpoints included tFEV1 assessments, spirometry assessments at other time points, AUC (5min – 4hr) for FEV1 at other time points, rescue medication usage, measurements of TDI focal score and health related quality of life using St. George's respiratory questionnaire.

The Sponsor defined non-inferiority of indacaterol to tiotropium if the 95% CI for the mean FEV1 difference of indacaterol minus tiotropium lay entirely to the right of (higher than) -55 mL. Superiority was demonstrated if the two-sided p-value was less than 0.05 and the 95% confidence interval lay entirely to the right of (higher than) 0 mL.

A total of 1598 patients with moderate to severe COPD (post bronchodilator FEV1 <80% and ≥ 30% of predicted) were enrolled. One thousand four hundred seventy seven (92.4%) completed the trial. Overall demographics were balanced across the treatment groups. The mean age of patients in the trial was 63.5 years. Two thirds of the patients were male (68.6%) and the majority were caucasian (95.4%). Patients had a mean post bronchodilator FEV1 of 1.52 L, with 62% having moderate COPD and 37% having severe disease and 54.6% on concurrent ICS. Just under half (44.6%) of the patients were current smokers. At least one major protocol deviation occurred in 369 patients (23.2%), with the most common being spirometry for SABA reversibility not acceptable 15.9% and trial medication taken < 80% doses prior to primary endpoint visit (3.1%). These deviations occurred at similar frequencies across all treatment groups and therefore are not expected to alter the results significantly.

The LS mean for the primary endpoint, tFEV1 at 12 weeks of treatment was 1.44 L for both indacaterol 150 mcg and tiotropium 18 mcg with a treatment difference of 0. The 95% CI values were -0.02, 0.02 (p-value= <0.001) which were greater than the Sponsor's predefined non-inferiority margin of – 0.055. The key secondary endpoint of superiority of indacaterol over tiotropium was not supported as the 95% CI was not greater than 2.

The secondary endpoint of FEV1 AUC (5 min- 4 hr) at Week 12 showed a LS mean value for indacaterol 150 mcg of 1.51 L, slightly less than tiotropium 18 mcg of 1.52 L with a treatment difference of -0.01 (95% CI -0.03, 0.01 p-value= 0.18). The trough FEV1 on Day 2 for indacaterol 150 mcg was the same as tiotropium 18 mcg, 1.45 L, and on Day 29 it was 1.46 L for the indacaterol 150 mcg group and 1.44 L for the tiotropium 18 mcg group. The treatment difference of indacaterol over tiotropium was statistically significant only on Day 29 with a value of 0.03 (0.01, 0.04 p-value= 0.001). The treatment difference of indacaterol and tiotropium was statistically significant for the FEV1 values obtained at 5 minutes (0.07 L, 95% CI 0.06, 0.08), 30 minutes (0.03 L, 95% CI 0.02, 0.04) and 1 hour (0.02 L 95% CI 0.00, 0.03) post dose on Day 1. However, there is no significant difference from hour 2 and on. Overall, there were no significant differences across subgroups analyzed between the two treatment groups.

Evaluation of rescue medication use demonstrated that for all assessments: mean daily number of puffs; mean daytime number of puffs; mean nighttime number of puffs and percentage of days with no rescue use, the treatment difference of indacaterol 150 mcg over tiotropium was statistically significant (-0.54 p-value= <0.001, -0.32 p-value= <0.001, -0.24 p-value= <0.001 and 4.8 p-value= 0.004, respectively). The LS mean TDI focal score after 12 weeks of treatment in the indacaterol 150 mcg group was 2.01 and 1.43 in the tiotropium group. The comparison of the treatment difference for the TDI focal score of indacaterol over tiotropium showed a statistically significant value of 0.58 L (0.28, 0.87 p < 0.001). The health-related quality of life measure, SGRQ was evaluated at Week 12 and indacaterol demonstrated a statistically significant LS mean treatment difference compared to tiotropium, -2.1 (-3.3, -1.0). The MCID of 4 units was not achieved.

The frequency of AEs was comparable between the two treatment groups, indacaterol 39.7% and tiotropium 37.2%. The most frequent adverse event was COPD, which occurred at a numerically higher rate in the indacaterol group (12.8%) than in the tiotropium group (8.3%). Adverse events occurring more frequently in the indacaterol groups were cough (4.7% versus 3.4% for indacaterol and tiotropium respectively), bronchitis (2.0% versus 0.9%) and sinusitis (1.0% versus 0.3%). Serious adverse events occurred more frequently in the indacaterol group (2.8%) versus tiotropium (3.8%). The most common serious adverse events by SOC were respiratory, thoracic and mediastinal and infections and infestations. There were two deaths reported during the trial, both in the tiotropium group (one from a cardiac arrest and the other from septic shock).

Reviewer comment:

This trial demonstrates that indacaterol is non-inferior, but not superior to tiotropium and the AEs were comparable between the two. In addition, while the applicant provided some justification of the 0.055 L margin based upon historical studies with tiotropium and placebo, from a clinical standpoint the 0.055 L margin is quite large and not acceptable.

Trial B2311

Trial B2311 was a 3 week randomized, double-blind, multicenter, placebo controlled, 2 period cross-over comparison of indacaterol 300 mcg and placebo in exercise endurance in patients with COPD. The trial was conducted at 18 centers in 6 countries (including United States, Belgium, Canada, Italy, Denmark and Spain). The primary endpoint was exercise duration time measured through constant-load cycle ergometry. Secondary endpoints included spirometry and body plethysmography conducted pre-dose and post-dose at rest, spirometry during constant load cycle ergometry, leg discomfort scale and dyspnea scale (Borg CR10 Scale), daily symptom scores, rescue medication use, and COPD exacerbations.

A total of 90 patients with moderate to severe COPD (post bronchodilator FEV1 <80% and ≥ 30% of predicted) were enrolled. Seventy four (82.2%) completed the trial. Overall demographics were balanced across the treatment groups. The mean age of patients in the trial was 62.8 years. Just under two thirds of the patients were male (62.8%) and the majority were caucasian (98.9%). Patients had a mean post bronchodilator FEV1 of 1.71 L with 76.4% having moderate COPD and 19.1% having severe disease. A little over one third (37.1%) of the patients were current smokers. Major protocol deviations occurred in 6 patients (6.7%), and the two most common were: "data from treatment periods with major protocol deviations which were considered only to affect that period, were excluded from the per protocol analysis" (2.2% of patients) and "invalid Wmax" also known as maximum work rate (2.2% of patients).

Indacaterol 300 mcg treatment was statistically significantly superior to placebo in exercise endurance time after 3 weeks of treatment. The LS mean treatment difference was 111 sec although the confidence intervals were wide (95% CI 27, 195 p-value of 0.011). Indacaterol 300 mcg resulted in a significant improvement over placebo for most of the spirometry tests measured (IC, SVC, FEV1, FVC, SGaw as well as IRV) at rest, 60 minutes pre-dose after 3 weeks of treatment. No significant treatment differences in exertional dyspnea or leg discomfort were reported at peak (end of exercise) and 5 min after exercise completion after 3 weeks of treatment. Many of the rescue medication use assessments such as the mean change in: daily number of puffs, daytime number of puffs, nighttime number of puffs of rescue medication use and percentage of days with no rescue medication use were all statistically significant for indacaterol 300 mcg over placebo.

The frequency of AEs was comparable between the two treatment groups, indacaterol 300 mcg 22.9% and placebo 27.4%. The most frequent adverse event was nasopharyngitis, bronchitis, COPD, cough and upper respiratory tract infection. Bronchitis and upper respiratory tract infection occurred at a higher frequency in the indacaterol treatment group than placebo. Serious AEs occurred more frequently in the indacaterol group (3.6%) versus placebo (1.2%). The SAEs in the indacaterol group included single events of breast cancer, COPD exacerbation and a femur fracture. There were no deaths reported during the trial.

Reviewer comment:

This trial demonstrates that indacaterol 300 mcg significantly increased the exercise duration time, although the clinical importance of the demonstrated change is unclear. The safety profile was consistent with the pivotal trials.

Trial B2331

Trial B2331 was a 2 week randomized, double-blind, multicenter, placebo controlled, 3 period incomplete block, multidose crossover comparison of indacaterol 150 mcg and 300 mcg q.d. and placebo in patients with COPD. The trial was conducted at 21 centers in 7 countries (including Australia, Germany, Netherlands, Poland, South Africa, Spain and New Zealand). The primary endpoint was tFEV1 at 2 weeks of treatment. To allow for multiplicity (two superiority comparisons with the two doses of indacaterol) for the primary efficacy variable, a Bonferroni adjustment was applied so that each contrast was tested at the 2.5% (two-sided) significance level. Superiority of indacaterol (either dose) over placebo was demonstrated if the two-sided p-value was less than the 2.5% significance level (in other words, the 97.5% confidence interval lies entirely to the right of 0 mL).The key secondary endpoint was to demonstrate non-inferiority of indacaterol versus tiotropium 18 mcg q.d. with respect to tFEV1 after 2 weeks of treatment using the per protocol group. The Sponsor stated that indacaterol was considered to be non-inferior to tiotropium if the lower 97.5% CI of the treatment difference was above -55 mL for the PP population. A hierarchical testing approach was taken for the primary and key secondary comparisons. If non-inferiority was established then the superiority was tested in the mITT and the PP populations. Superiority over tiotropium was declared if the 97.5% CI was entirely above zero and in favor of indacaterol in the mITT population.

Other secondary endpoints included tFEV1 assessments at other time points, peak FEV1 during 4 hr post dosing on Day 1 and FEV1 at multiple time points and FEV1 AUC over the 24 hour time period, clinical symptoms, COPD exacerbations and health related quality of life using St. George's respiratory questionnaire.

A total of 169 patients with moderate to severe COPD (post bronchodilator FEV1 <80% and ≥ 30% of predicted) were enrolled. One hundred fifty three (90.5%) completed the trial. Overall demographics were balanced across the treatment groups. The mean age of patients in the trial was 64.5 years. Three quarters of the patients were male (76.6%) and the majority were caucasian (98.8%). Patients had a mean post bronchodilator FEV1 of 1.61 L, with 67.1% having moderate COPD and 31.1% having severe disease and 59.9% on concurrent ICS. Just under half (43.1%) of the patients were current smokers. At least one major protocol deviation occurred in 8 patients (4.8%), with the most common being eosinophil count > 400/mm3 at screening (1.8%) and other excluded non-indication medication as specified in the exclusion criteria (1.2%). These deviations occurred at similar frequencies across all treatment groups and therefore are not expected to alter the results significantly.

The LS mean treatment difference for the primary endpoint, tFEV1 at 2 weeks of treatment was statistically significant with a value of 0.17 L (0.12, 0.22 p-value= <0.001) between indacaterol 150 mcg and placebo and 0.15 L (0.10, 0.20 p-value= <0.001) for indacaterol 300 mcg and placebo. For the key secondary endpoint in the PP population, indacaterol 150 mcg and indacaterol 300 mcg met the Sponsor's non-inferiority margin to tiotropium. Mean FEV1 values were approximately 0.030 to 0.040 L higher in the indacaterol groups than in the tiotropium group. However, superiority of either indacaterol doses above tiotropium was not achieved as the 97.5% CIs for the treatment differences in the mITT population included the value zero.

Trough FEV1 assessments at Day 1 also demonstrated the statistical significance of both indacaterol 150 mcg (0.10 L 95% CI 0.06, 0.15) and 300 mcg (0.13 L 95% CI 0.09, 0.17) over placebo. Peak FEV1 in the first 4 hr post morning dose on Day 1 was also statistically significantly greater for both doses of indacaterol over placebo as was for the FEV1 AUC (5 min- 4 hr), AUC (5 min- 12 hr) and AUC (5 min- 23 hr 45 min) after Days 1 and 14. The LS mean treatment difference for the two doses of indacaterol over placebo was statistically significant for all FEV1 time points measured between 5 min and 24 hr.

Evaluation of rescue medication use demonstrated that for all assessments: mean daily number of puffs; mean daytime number of puffs; mean nighttime number of puffs and percentage of days with no rescue use, the treatment difference of indacaterol 150 mcg over tiotropium was statistically significant (-0.54 p-value= <0.001, -0.32 p-value= <0.001, -0.24 p-value= <0.001 and 4.8 p-value= 0.004, respectively). The LS mean TDI focal score after 12 weeks of treatment in the indacaterol 150 mcg group was 2.01 and 1.43 in the tiotropium group. The comparison of the treatment difference for the TDI focal score of indacaterol over tiotropium showed a statistically significant value of 0.58 L (0.28, 0.87 p < 0.001). The health-related quality of life measure, SGRQ was evaluated at Week 12 and indacaterol demonstrated a statistically significant LS mean treatment difference compared to tiotropium, -2.1 (-3.3, -1.0). The MCID of 4 units was not achieved.

The frequency of AEs was comparable across all treatment groups, indacaterol 150 mcg 31.4%, indacaterol 300 mcg 29.5%, tiotropium 28.3% and placebo 28.5%. The most frequent adverse event was COPD, which occurred at a numerically higher rate in the placebo group (8.9%) than in the indacaterol group (5.1% and 3.3% for 150 mcg and 300 mcg doses, respectively) but comparable to tiotropium group (8.3%). The only adverse event occurring more frequently in the indacaterol groups was cough (6.8% and 4.9% for indacaterol 150 mcg and 300 mcg respectively and 2.5 for the tiotropium group and 2.4 for placebo). Few SAEs occurred overall: 2 patients (1.7%) in indacaterol 150 mcg; 1 patient (0.8%) in indacaterol 300 mcg group; 4 patients (3.3%) in tiotropium group and 1 patient (0.8%) in the placebo group. There were no deaths reported during the trial.

Reviewer comment:

This trial demonstrates that indacaterol is non-inferior, but not superior to tiotropium and the AEs were comparable between the two. In addition, while the applicant provided some justification of the 0.055 L margin based upon historical studies with tiotropium and placebo, from a clinical standpoint the 0.055 L margin is quite large and not acceptable.

5 Review of Efficacy

Efficacy Summary

There is substantial evidence in support of the efficacy of indacaterol as a maintenance bronchodilator in patients with COPD. Both the original submission and the complete response present adequate and well controlled trials showing the superiority of indacaterol to placebo in the change from baseline in 24 hour tFEV1. However the original dose selections of 150 mcg and 300 mcg, currently marketed in the 40 countries were not significantly different from 75 mcg once daily. Furthermore, the 300 mcg doses were associated with cardiac and cerebrovascular events as well as two suspected asthma deaths. The use of an adaptive design trial as well as other supportive data were acceptable approaches towards dose selection however, the criteria used for dose selection to carry forward were flawed. The doses were chosen among four (75 mcg, 150 mcg, 300 mcg and 600 mcg) from the interim analysis of the adaptive design trial B2335s. The Data Monitoring Committee was charged to select dose (s) that were:

- Greater than placebo in trough FEV1 by 120 mL (proposed MCID) and numerically higher than tiotropium and formoterol
- Numerically higher than tiotropium and formoterol in terms of FEV1 standardized AUC (1- 4 hr)

The new supportive evidence comes from 5 simultaneously conducted trials, 3 dose finding and 2 confirmatory (B2357, B2356, B2223, B2355 and B2354). In addition, Novartis now submits one long term safety and efficacy trial, (B2336) which was initiated, but not completed during the original submission. All demonstrate the superiority of indacaterol to placebo in the primary endpoint of tFEV1. The two dose ranging trials B2357 and B2356 demonstrate superiority of the two lower doses, 37.5 mcg and 75 mcg as well as the 150 mcg indacaterol dose over placebo on the primary endpoint. These trials also demonstrate benefit of indacaterol 37.5 mcg, 75 mcg and 150 mcg over placebo for other standard measures of airflow obstruction with only one exception, 37.5 mcg dose in B2357 did not reach statistical significance for peak FEV1 at Day 1 (p-value 0.101). Both dose ranging trials demonstrated benefit of indacaterol compared to placebo in rescue medication use, providing supportive efficacy data.

The trial B2357 conducted in bronchoreactive asthmatic patients revealed two findings:

1. Indacaterol 75 mcg daily showed the greatest numerical benefit compared to placebo than either the 37.5 mcg or 150 mcg indacaterol doses in the primary endpoint –tFEV1 on Day 14
2. Although 150 mcg indacaterol had a larger improvement than the two lower doses after 1 day of treatment in all of the spirometry based secondary endpoints, this advantage is lost by Day 14. At Day 14, 75 mcg indacaterol showed a larger improvement than the other doses.

Trial B2356 was conducted in the predominantly moderate to severe COPD population (mean prebronchodilator FEV1 1.3 L) with a mean percent increase in FEV1 after SABA ranging from 14.2-16.7%. The trial demonstrated superiority of indacaterol to placebo in the primary efficacy endpoint tFEV1. Numerically, the largest treatment difference in tFEV1 after two weeks compared to placebo was observed with indacaterol 150 mcg; however, the values were similar to tFEV1 in the 37.5 mcg and 75 mcg indacaterol treatment groups. The key secondary endpoints, tFEV1 at Day 2 and Day 14 also demonstrated, significant benefit of the 37.5 mcg, 75 mcg, and 150 mcg group. Although the tFEV1 was marginally higher in the 150 mcg dose group, the difference of 20 ml is within the variability of the test and is not likely to be clinically important. The loss of any advantage of 150 mcg indacaterol over 37.5 mcg and 75 mcg doses by Day 14 for the other spirometry based secondary endpoints was apparent.

Overall, the dose regimen trial, B2223 did not reveal significant differences after two weeks between the three regimens evaluated, 37.5 mcg b.i.d, 75 mcg q.d. and 150 mcg q.o.d. The greatest magnitude in treatment differences from placebo in tFEV1 on Days 15/16 was observed with the 75 mcg q.d and 150 mcg q.o.d regimens which were almost identical in value. The magnitude of mean change from baseline in peak FEV1, FEV1 AUCs $_{0\text{-}24\ hr}$, AUC $_{1\text{-}12\ hr}$ and AUC $_{12\text{-}24\ hr}$ were greatest for the 75 mcg q.d. regimen when compared to the 37.5 mcg b.i.d regimen. The mean Tmax was similar across dosing regimens

ranging from 15 to 18 minutes with pharmacokinetic steady state being achieved by all three regimens by Day 15 as indicated by the trough serum concentrations of indacaterol.

The two 12 week confirmatory trials (B2355 and B2354) evaluating only the 75 mcg indacaterol dose compared to placebo demonstrated statistically significant benefit of indacaterol on the primary endpoint of tFEV1 after 12 weeks as well as other standard measures of airflow obstruction. However, the results of measurements intended to assess disease control using patient or evaluator reported outcome questionnaires were less consistent between trials. Superiority of indacaterol over placebo was observed using the TDI only in trial B2354, not B2355. While the two trials demonstrated superiority of indacaterol to placebo for all assessments of rescue medication use, there was no consistency in superiority for improvement in symptoms. Trial B2355 demonstrated statistically significant improvement in only the percent of 'days able to perform usual daily activities', while B2354 demonstrated statistical significance for indacaterol instead in the percent of days with 'no daytime symptoms'. The MCID of -4 for SGRQ was not achieved in either trial.

The single 26 week efficacy and safety trial, B2336 evaluating solely the indacaterol 150 mcg dose compared to placebo demonstrated statistically significant benefit of this higher proposed dose in the primary endpoint of tFEV1 after 12 weeks. In addition, indacaterol 150 mcg was superior to placebo in other measures of airflow obstruction. In contrast to the other trials measuring SGRQ, in B2336, indacaterol 150 mcg was statistically superior to placebo and also exceeded the MCID of 4. However, there is a concern that the amended protocol resulted in a change in the interpretation of the data. Amendment 2 dated 1/6/09 submitted towards the completion of the trial, called for the elevation of SGRQ over the original key secondary endpoint, percentage of 'days of poor control' in the hierarchical testing procedure. While it is unlikely that the change would alter the final result (change in the "N" needed to detect the significant difference or the MCID), SGRQ would not have been tested originally as 'days of poor control' did not meet statistical significance. The other secondary endpoints such as COPD exacerbation rates and the 6 minute walk, did not demonstrate superiority of indacaterol 150 mcg over placebo. The remaining secondary endpoints of TDI, all rescue medication use assessments, change from baseline in the mean morning and evening PEF, the BODE index after 12 and 26 weeks, daytime and nighttime symptoms and percentage of 'days able to perform usual daily activities' all supported the benefit of indacaterol 150 mcg over placebo. These secondary endpoints provide supportive evidence of efficacy.

The proposed label includes language describing the 'onset of action within 5 minutes' as well as 'no evidence of loss of efficacy (tachyphylaxis)'. A specific definition of 'onset of action' is not provided by the Sponsor. However, two of the pivotal trials reviewed, B2355 and B2354 provide data to support this claim, with significant improvement in FEV1 at 5 minutes after the first dose for both the indacaterol 75 mcg and 150 mcg doses over placebo. As well, these same two trials also provide data of no statistically significant difference in the rate of change in trough FEV1 from 29 days to 12 weeks of treatment between the treatment groups in support of the claim for no evidence of tachyphylaxis.

5.1 Indication

As a bronchodilator, the therapeutic aim sought for Arcapta Neohaler is to provide benefit through relief of reversible airflow obstruction. The specific labeling claim proposed by Novartis in the product label includes the following language:

> *"The long term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema."*

5.1.1 Methods

Dose finding trials:
To support the complete response, Novartis submitted 3 two week dose finding trials to address the deficiencies in dose selection and dosing frequency in the original NDA. The original trials exploring the dose response profile of indacaterol included: B2201, B2205, B2212, B1202 and B2335S. These trials will not be reviewed here. The three new trials listed in Figure 10 below explored lower doses to identify a dose with an acceptable balance of observed undesired effects and beneficial effects. The designs of the dose finding trials were similar - parallel, randomized, double-blind, placebo controlled, fixed multiple dose, dose response trials assessing trough FEV1 after two weeks to evaluate the efficacy of indacaterol in bronchodilation. An interesting note is that all were carried out concomitantly along with the two 3 month confirmatory trials.

Figure 10 Relevant dose finding trials

Study	Objective, population	n	Treatment duration	Treatment Groups	Efficacy endpoint	Safety endpoints	Study year	Countries
Dose finding trials								
B2357	Dose-ranging in asthma	558	2 wks	Ind 18.75 mcg qd Ind 37.5 mcg qd Ind 75 mcg qd Ind 150 mcg qd Salm 50 mcg bid Placebo bid	tFEV1 after 14 days	AE (including asthma exacerbations), SAEs, labs, ECG, VS, PE, weight	2/22/10-7/14/10	United States
B2223	Dosing regimens in asthma	192	2 wks	Ind 37.5 mcg bid Ind 75 mcg q. Ind 150 mcg qod placebo bid	tFEV1 after 14 days	VS, ECG, labs, AEs	3/10/10-7/12/10	France, Germany, Jordan, Netherlands, United Kingdom, United States
B2356	Dose-ranging in COPD	576	2 wks	Ind 18.75 mcg qd Ind 37.5 mcg qd Ind 75 mcg qd Ind 150 mcg q.d. Salm 50 mcg bid Placebo bid	tFEV1 after 14 days	AE, SAEs, labs, ECG, VS, PE, rescue medication use	3/5/10-7/9/10	United States

Protocol B2357 was a multi-center, randomized, double-blind, double-dummy, placebo-controlled, parallel-group trial in a representative broncho-reactive population, those with persistent asthma, classified by GINA guidelines, 2008. The patients were male and female adults age ≥ 18 years with a FEV1 ≥ 50 and ≤ 90% of the predicted and on a stable dose of ICS for at least one month. Consistent with their diagnosis, patients had to demonstrate an increase of ≥ 12% and ≥ 200 mL in FEV1 over their pre-bronchodilator value within 30 minutes after inhaling a total of 360 mcg of albuterol via a metered dose inhaler. Randomization was stratified by asthma severity. Those patients excluded had: a smoking history greater than 10 pack years; a diagnosis of COPD defined by GOLD, 2008 guidelines; an exacerbation requiring hospitalization 6 months prior, previous intubation for severe asthma exacerbation; ER visits for an asthma attack/exacerbation within 6 weeks; patients with uncontrolled asthma represented by the use of ≥ 8 inhalations per day of SABA (90 mcg albuterol via MDI) on any 2 consecutive days; respiratory tract infection within 6 weeks; other pulmonary disease, pulmonary TB or clinically significant bronchiectasis; history of lung cancer and history or family history of long QT syndrome.

Protocol B2223, a Phase II trial was a multi-center, randomized, double-blind, placebo-controlled, parallel group study also in patients with persistent asthma comparing three different indacaterol dosing regimens (75 mcg once daily, 150 mcg on alternate days and 37.5 mcg twice daily). Patients were dosed

for a total of 16 days following a 2 week run-in period to allow and monitor patient stability. The inclusion criteria were the same as in B2357, notably patients had to be on a stable dose of ICS for one month and demonstrate reversibility to SABA with an increase in FEV1 ≥ 12% and 200 mL. The key exclusion criteria were identical to B2357.

Protocol B2356 was a randomized, double-blind, double-dummy, placebo-controlled, parallel group trial. Patients were stratified for smoking status and ICS use. Patients with moderate to severe COPD as per GOLD, 2008 guidelines were treated for 14 days with indacaterol once daily (18.75, 37.5, 75 or 150 mcg), salmeterol 50 mcg twice daily or placebo. Patients were male or female adults aged ≥ 40 years with a smoking history of at least 10 pack years, a post bronchodilator FEV1 <80% and ≥30% of the predicted normal and FEV1/FVC <70% of the value. Key exclusion criteria were: COPD exacerbation requiring systemic glucocorticosteroid treatment and/or antibiotics and/or hospitalization in the 6 weeks prior to screening; the requirement of oxygen therapy for chronic hypoxemia (excluding acute COPD exacerbation); patients who had a respiratory tract infection within 6 weeks; patients with concomitant pulmonary disease, pulmonary tuberculosis (unless confirmed by chest x-ray to be no longer active), or clinically significant bronchiectasis; patients with a history of asthma indicated by (but not limited to) onset of respiratory symptoms suggestive of asthma prior to 40 years of age or a history of a diagnosis of asthma.

Long term efficacy and safety trials:
Protocols B2355 and B2354 were identical, Phase III trials, multi-center, randomized, double-blind, placebo-controlled, parallel-group design, using 75 mcg indacaterol once daily via an SDDPI for 12 weeks in patients with moderate to severe COPD with stratification for smoking status and inhaled corticosteroid (ICS) use. There was a 14 day run-in period, and a 12 week treatment period. The study was designed to allow further characterization of the efficacy and safety of the 75 mcg dose of indacaterol in COPD, using placebo as a control. The patients were male or female adults aged ≥ 40 years, with smoking history of at least 10 pack years; a post-bronchodilator FEV1 < 80% and ≥ 30% of the predicted normal and FEV1/FVC < 70%. Key exclusion criteria included: patients who had a COPD exacerbation requiring systemic glucocorticosteroid treatment and/or antibiotics and/or hospitalization in the 6 weeks prior to screening, patients requiring oxygen therapy for chronic hypoxemia (excluding acute COPD exacerbation), patients who had a respiratory tract infection within 6 weeks, concomitant pulmonary disease, pulmonary tuberculosis (unless confirmed by chest x-ray to be no longer active), or clinically significant bronchiectasis, patients with a history of asthma indicated by (but not limited to) onset of respiratory symptoms suggestive of asthma prior to 40 years of age or a history of a diagnosis of asthma.

Figure 11 Twelve week placebo-controlled efficacy/safety trials

Key controlled efficacy trials-75 mcg								
Study	Objective, population	n	Treatment duration	Treatment Groups	Efficacy endpoint	Safety endpoints	Study year	Countries
B2355	Efficacy/safety in COPD	326	12 wks	Ind 75 mcg q.d. Pbo q.d.	tFEV1 at Week 12	AE, SAEs, labs, ECG, VS, PE	1/27/10-6/14/10	United States
B2354	Efficacy/safety in COPD	326	12 wks	Ind 75 mcg q.d. Pbo q.d.	tFEV1 at Week 12	AE, SAEs, labs, ECG, VS, PE	1/22/10-7/14/10	United States
B2336	Efficacy/safety in COPD	972	26 wks	Ind150 mcg qd Salm 50mcg bid Pbo b.i.d	tFEV1 at Week 12	AE (including COPD exacerbations), SAEs, labs, ECG, VS, PE, medical resource utilization, post inhalation events	11/27/07-1/28/09	Canada, Colombia, Czech Republic, Denmark, Germany, Finland, France, Hungary, India, Iceland, Italy, Peru, Russia, Slovakia, Taiwan

Protocol B2336, a multi center, double blind, double dummy, parallel group trial of the higher proposed indacaterol dose of 150 mcg q.d. in patients with moderate-to-severe COPD. Eligible patients were randomized and stratified based on smoking status 1:1:1 to receive indacaterol 150 mcg q.d., salmeterol 50 mcg b.i.d., or placebo for 26 weeks. The main criteria for inclusion were male or female adults aged ≥ 40 years, with smoking history of at least 10 pack years; a post-bronchodilator FEV1 < 80% and ≥ 30% of the predicted normal and FEV1/FVC < 70%. They were somewhat different from the above COPD trials in that their smoking history was greater with at least 20 pack years. The exclusion criteria were the same as Protocols B2355 and B2354.

Supplementary trials
Submitted under this NDA were 10 supplementary trials that were either trials for registration in other countries or for profiling. These were only briefly reviewed and a summary is listed in Figure 12 below.

Figure 12 Supplementary controlled trials in patients with COPD

Supplementary controlled efficacy trials								
Study	Objective, population	n	Treatment duration	Drug	Efficacy endpoint	Safety endpoints	Study year	Countries
B1302	Efficacy/safety in COPD, Asia	336	12 weeks	Ind150, 300 mcg q.d. Pbo q.d.	tFEV1 at Week 12	AE (including COPD exacerbations), SAEs, labs, ECG, VS, PE, weight, post inhalation events	11/17/08-10/7/09	Hong Kong, India, Japan, Korea, Singapore, Taiwan
B2333	Efficacy/safety	558	26 weeks	Ind 150,	tFEV1 at	AEs, SAEs, VS,	11/13/08-	Australia,

	in COPD, Primarily China			300 mcg q.d. Pbo q.d.	Week 12	ECGs, labs, post inhalation events	2/26/10	China, India
B2349	Efficacy/safety in COPD	1084	12 weeks	Ind150 mcg q.d. Salm 50 mcg b.i.d	AUC (5 min- 11h 45 min for FEV1 at Week 12	ECG, labs, blood pressure, heart rate, AEs	1/23/09-10/9/09	Czech Republic, Germany, Hungary, India, Slovakia, Spain, Turkey, United States
B2350	Efficacy/safety in COPD	1568	12 weeks	Ind150 mcg q.d. Tiotropium 18 mcg q.d.	tFEV1 at Week 12	AEs, SAE, ECG, labs, blood pressure, heart rate, AEs	6/1/09-3/25/10	Austria, Belgium, Canada, Colombia, Denmark, Finland, France, Germany, Greece, Hungary, Israel, Italy, Mexico, Norway, Poland, Russia, Slovakia, Spain, Switzerland, Turkey, United Kingdom, United States
Long term controlled efficacy trials								
B2335SE	Efficacy/safety in COPD	417	26 weeks (additional to initial 26 weeks)	Ind 150, 300 mcg q.d. Pbo q.d.	tFEV1 at Week 52	AE (including COPD exacerbations), SAEs, labs, ECG, VS, PE, weight	5/14/08-3/2/09	Argentina, Canada, Germany, India, Italy, Spain, Sweden, Turkey and United States
Trials with indacaterol given concurrently with tiotropium								
B2341	Efficacy/safety in COPD	1126	12 weeks	Ind 150 mcg q.d. + tiotropium 18 mcg q.d. Pbo to ind + tiotropium 18 mcg q.d.	AUC (5 min- 8 h) for FEV1 at Week 12	AEs, COPD exacerbations, SAEs, labs, VS, PE, ECG	3/5/09-3/17/10	Argentina, Australia, Colombia, Denmark, Germany, Greece, Guatemala, Mexico, Peru, Philippines, South

								Africa, Spain, Turkey, United States.
B2351	Efficacy/safety in COPD	1126	12 weeks	Ind 150 mcg q.d. + tiotropium 18 mcg q.d. Pbo to ind + tiotropium 18 mcg q.d.	AUC (5 min- 8 h) for FEV1 at Week 12	AEs, COPD exacerbations, SAEs, labs, VS, PE, ECG	4/8/09-2/9/10	Argentina Canada, Colombia, Czech Republic, Hungary, India, Netherlands, Philippines, Slovakia, Spain, United States
Short-term profiling trials								
B2311	Exercise endurance in COPD	83	3 weeks (2 treatment periods separated by 2 weeks of wash out)	Ind 300 mcg q.d. Pbo q.d.	Exercise endurance time (measured through constant-load cycle ergometry testing) after 3 weeks of treatment	AEs, SAEs, labs, VS, ECG, PE	4/30/08-1/13/09	Belgium, Canada, Denmark, Italy, Spain, United States
B2331	24 h lung function profile in COPD	148	14 days (3 treatment periods separated by 2 weeks of wash out)	Ind 150, 300 mcg q.d. Tiotropium 18 mcg q.d. Pbo q.d.	tFEV1 on Day 15	AEs (including COPD exacerbations),, SAEs, labs, VS, ECG, PE	2/14/08-12/30/08	Australia, Germany, Poland, South Africa, Spain, The Netherlands, New Zealand
Interim analysis for Japanese trial								
B1303	Efficacy/safety in COPD (Japan)	180	52 weeks (interim analysis at Week 24)	Indacaterol 300 mcg q.d. Salmeterol 50 mcg b.i.d.	tFEV1 on Day 169 (Week 24)	AE (including COPD exacerbations), SAEs, labs, ECG, VS, PE, weight, post inhalation events	3/3/09-3/31/10 (last patient completes 24 weeks treatment)	Japan

5.1.2 Demographics

The populations reviewed were either asthmatics (as recommended by the FDA for evaluation of dose response) to test for bronchodilator efficacy in this known responsive group or patients with COPD, the ultimate marketing target. As such, the different disease characteristics require separate discussions of the demographic data.

The population of patients with asthma used in the dose ranging trial, B2357 and the dose regimen trial, B2223 were comparable in the breakdown of demographic characteristics as well as disease status. Caucasians made up the overwhelming predominate race, > 80% in both trials, however gender distribution varied as there were more males in B2223 (49%-67%) than B2357 (35%-52%). The mean age was consistent at 40-41 in both trials. Although the baseline disease characteristics were not provided in B2223, in B2357, the disease burden for asthma appears adequate with the mean duration of diagnosis of 27 years. Regarding reversibility, the main feature of this pathology, the mean predicted pre SABA FEV1 was 70-71% and post SABA was 85-86% with a high degree of mean reversibility of 22% for both trials. Overall, most patients in B2357 were mild to moderate in severity and approximately 80% never smoked.

The other 4 controlled trials conducted in patients with COPD, B2356, B2355, B2354 and B2336 were reviewed for the distribution of demographics, disease characteristics and generalizability. Overall, the majority, 85% to 94% were caucasian and most studies had between 52-63% males, however, B2356 had a lower range of 48-58% male patients and B2336 had a greater proportion of males 72-77%. The age was expectedly older with a mean ranging from 61 to 64 years. B2355 had a lower percentage of ex-smokers, 41% while B2354 had the highest percentage of ex-smokers, 55%. The median pack years of smoking ranged from 38 in B2336 to 45 pack years in B2356, B2354 and B2355. Across all 4 trials, >95% of the patients fell into the moderate to severe category according to GOLD, 2008 criteria. The trial with the lowest percent increase after SABA was B2336 with a mean percent increase of 11.8% seen for all treatment groups, while B2356, B2354 and B2355 had similar, high percent increases after SABA ranging from 15.7 -16.9%. Baseline ICS use was recorded for a low of 36% in B2355 and a high of 45% in B2354.

5.1.3 Subject Disposition

Patient disposition is described in detail in Sections 5.3 and 7.2 9. An evaluation of the pooled data includes the two dose finding trials in asthmatics which will be analyzed separately from the 4 trials conducted in patients with COPD. Refer to Figure 13.

Figure 13 Disposition in Trials B2357 and B2223

	B2357-(n)							B2223- (n)				
	Ind 18.75 mcg	Ind 37.5 mcg	Ind 75 mcg	Ind 150 mcg	Salm	Pbo	Total	Ind 37.5 b.i.d	Ind 75 q.d.	Ind 150 q.o.d	pbo	total
Randomized	85	85	84	86	86	85	511	48	48	48	47	191
Discontinued	2	7	1	5	8	5	28	2	2	6	6	16
Analyzed for prim efficacy	82	77	82	80	78	81	480	48	47	48	46	189

In B2357, 1200 patients were screened and 511 were randomized. The top four reasons for screening failure include: failure to meet reversibility criteria; prebronchodilator FEV1 >90%; withdrawal of consent and lost to follow-up. Of the 511 randomized, 502 were exposed to treatment drug, 500 were included in the FAS, 483 completed the trial as planned and 480 analyzed. For B2223, the number screened was not provided however 191 patients were enrolled and 189 were analyzed.

Figure 14 Disposition in Trials B2356 and B2355

	B2356- (n)							B2355- (n)		
	Ind 18.75 mcg	Ind 37.5 mcg	Ind 75 mcg	Ind 150 mcg	Salm	Pbo	Total	Ind 75 mcg	Pbo	Total
Randomized	92	91	94	92	92	91	552	159	159	318
Discontinued	8	5	2	1	2	3	21	11	17	28
Analyzed for prim efficacy	82	84	87	90	88	86	517	159	158	317

Figure 15 Disposition in Trials B2354 and B2336

	B2354 (n)			B2336 (n)			
	Ind 75 mcg	Pbo	Total	Ind 150 mcg	salm	Pbo	Total
Randomized	163	160	323	333	334	335	1002
Discontinued	19	30	49	44	50	70	164
Analyzed for prim efficacy	149	148	297	320	317	316	953

In Protocol B2356, 1110 patients were screened, 552 randomized and 96.2% (531) completed the trial. In the two confirmatory studies, B2355 and B2354 the breakdown was different. In B2355, 597 screenings occurred 318 patients were randomized and 91% completed the trial as planned. In B2354, 755 screenings occurred with 323 patients randomized into the protocol and a lower percentage, 84.8% (274) completed the trial. The top reasons for screening failures were similar across the three trials B2355, B2354 and B2356: 'unacceptable test procedure result'; 'did not meet diagnosis/severity criteria' and 'subject withdrew consent'. The reasons for screen failures were not provided in trial B2336. The percentage of discontinuations was greatest in the placebo group of Studies B2355, B2354, B2336 and B2223. Refer to Figure 14 and Figure 15 for further details.

5.1.4 Analysis of Primary Endpoint(s)

The selection of efficacy endpoints chosen by Novartis includes a wide breadth of objective physiological assessments as well as patient or evaluator reported outcome measures. As described in the [10]FDA Draft Guidance for Industry, Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment, the recommended measure of improvement in airflow obstruction is the change in post-dose FEV1. The 24 hour trough FEV1 was chosen as the primary endpoint with the specific aim of characterizing the end of the dosing interval in their once daily dosing LABA. In addition, several secondary and exploratory endpoints including multiple time points characterizing the entire FEV1 AUC were also evaluated and will be reviewed in the next section.

Reviewer Comment:
Novartis proposed the MCID of 200mL tFEV1 compared to placebo for the asthma trials and 120mL for the COPD trials. Support for their choice of a clinically meaningful improvement as the MCID of 200 ml in tFEV1 compared to placebo for the asthma trials and 120 ml for the COPD trials was provided by two referenced COPD review articles, [11]Cazzola, M et al., 2008 and [12]Donahue, JF 2005. Although this difference is used as a marker of bronchodilator response, it is intended to demonstrate peak effect, and does not apply to 24 hour trough, where smaller differences may also be clinically important. While an accepted MCID for FEV1, has yet to be established, the limitations in use of this value is evidenced by a

[10] November, 2007 available at the website http://www.fda.gov/cder/guidance/index.htm
[11] Cazzola M. et al., Eur Respir J 2008; 31: 416–468
[12] Donahue JF. COPD: Journal of Chronic Obstructive Pulmonary Disease 2005; 2: 111-124

quote from Donahue, "an MCID for FEV1 must be anchored to a global or overall assessment when evaluating dose-response". Not only efficacy should go into the balancing equation but the associated toxicities seen with the dose response profile. This concept corresponds appropriately with the ICH E4 guideline on dose-response information where a great emphasis on dose selection is placed on defining the relationship of drug dosage to clinical beneficial as well as undesirable effects. Therefore, the sponsor defined MCID of 120 ml is not further discussed or used in clinical decision making for this review.

Novartis has submitted significant data in support of the efficacy of indacaterol. In the original submission, doses ranging from 150 mcg to 600 mcg were supported by adequate and well controlled trials with significant p-values for the primary endpoint, trough FEV1 at week 12. See Figure 16 below.

Figure 16 Summary of primary efficacy endpoint (trough FEV1 at week 12) in pivotal studies, original submission

Study	Treatment	Mean (L)	SE (L)	Treatment difference	Mean (L)	SE (L)	95% CI (L)	p-value
B2335s Stage 2	Ind 150 mcg	1.46	0.02	Ind 150-Pbo	0.18	0.02	(0.15, 0.21)	<0.001
	Ind 300mcg	1.46	0.02	Ind 300-Pbo	0.18	0.02	(0.15, 0.21)	<0.001
	Tio 18mcg	1.42	0.02	Tio-Pbo	0.14	0.02	(0.11, 0.17)	<0.001
	Placebo	1.28	0.02					
B2334	Ind 300 mcg	1.48	0.01	Ind 300-Pbo	0.17	0.02	(0.13, 0.20)	<0.001
	Ind 600 mcg	1.48	0.01	Ind 600-Pbo	0.17	0.02	(0.13, 0.20)	<0.001
	For 12 mcg	1.38	0.01	For-Pbo	0.07	0.02	(0.04, 0.10)	<0.001
	Placebo	1.31	0.01					
B2346	Ind 150 mcg	1.49	0.02	Ind 150-Pbo	0.13	0.02	(0.09, 0.18)	<0.001
	Placebo	1.35	0.02					

Source: Table 4, from review of Biostatistician, Dr Dongmei Liu

However, these doses were associated with higher toxicities seen in the combined cardiac and cerebrovascular SMQs as well as unacceptable asthma deaths. Since there was not a significant difference between these doses and the 75 mcg dose in the efficacy for the primary endpoint, it was apparent the selected doses were on or approaching the plateau of the dose response profile. The new adequate and well controlled dose finding studies also show a significant difference of lower doses of indacaterol over placebo in the trough FEV1 primary endpoint at two weeks. Furthermore, the new long term trials, B2336, B2355 and B2354 were all designed to provide a reasonable assessment of benefit and the duration was consistent with FDA guidelines. See Figure 17 for summary.

Figure 17 Summary of primary efficacy endpoint (trough FEV1 at week 12) in pivotal studies, resubmission

Study	Treatment	Mean (L)	SE (L)	Treatment difference	Mean (L)	SE (L)	95% CI (L)	p-value
B2336	Ind 150 mcg	1.45	0.02	Ind 150-Pbo	0.17	0.02	(0.13, 0.20)	<0.001
	Salmeterol	1.39	0.02	Sal-Pbo	0.06	0.02	(0.02, 0.10)	<0.001
	Placebo	1.28	0.02	Ind-Sal	0.11	0.02	(0.07, 0.14)	<0.001
B2354	Ind 75 mcg	1.38	0.01	Ind 75-Pbo	0.12	0.02	(0.08, 0.15)	<0.001
	Placebo	1.26	0.01	---	---	---	---	---
B2355	Ind 75 mcg	1.49	0.02	Ind 75-Pbo	0.14	0.02	(0.10, 0.18)	<0.001
	Placebo	1.35	0.02	---	---	---	---	---

Source: Adapted from the review of Biostatistician, Dr Dongmei Liu

The Applicant proposes two doses of indacaterol for marketing, 75mcg and 150mcg, which would be novel for a LABA, as typically only one dose level is approved for use. The rationale for including a higher dose is "to provide additional benefit in patients with more severe bronchial obstruction." In addition, the Applicant proposes that the 150mcg dose provides meaningful improvement in SGRQ, which is discussed in the next section. The Applicant would need to provide substantial evidence that the higher dose provides clinically meaningful benefit over the lower dose and that the higher dose has an acceptable safety profile.

Other than two-week dose ranging studies, there are no direct comparisons of 75mcg and 150mcg and thus comparison of the doses at the 12 week time period is cross study comparison, which has some limitations. In the dose ranging studies, the 150 mcg dose provided no meaningful clinical benefit over the 75 mcg dose. Similarly, a comparison drawn from the pooled 3 month efficacy data from all double-blind, placebo and active controlled trials of at least 12 weeks duration, consisting of 10 trials, does not demonstrate a clinically meaningful benefit in the primary bronchodilator endpoint of tFEV1 at 12 weeks, with difference of only 10 ml between the two dose groups. A subgroup analysis of this data by Global initiative for chronic Obstructive Lung Disease (GOLD) stage likewise did not demonstrate a benefit of the 150 mcg dose over the 75 mcg dose for patients with severe disease.

5.1.5 Analysis of Secondary Endpoints(s)

SGRQ

The Applicant seeks a labeling claim for improvement in SGRQ, which would be a novel labeling claim for any drug approved for COPD in the United States. The medical literature has suggested a difference of 4 units as the value corresponding to a clinically meaningful improvement of SGRQ. The SGRQ was evaluated in five pivotal studies—two reviewed in the initial submission (Trials B2346 and B2335S) and three reviewed in this complete response submission (Trials B2336, B2354, and B2355). None of these trials included both the 150 mcg and 75 mcg dose groups, so direct comparisons between the doses cannot be made.

The table below shows the results for the SGRQ for the doses proposed by the Applicant. At 12 weeks, the 150 mcg dose group met the minimally clinically important difference (MCID) of -4 points change from baseline compared to placebo in the SGRQ total score in two studies. In Protocol B2346 the LS mean difference was -4.8, and in Protocol B2336 the LS mean difference was -6.3, forming the basis of the sponsor's claim that indacaterol 150 mcg improves SGRQ.

See Figure 18 for a summary of the results.

Figure 18 SGRQ total score at Week 12, treatment comparisons (imputed with LOCF, ITT)

		n	LS mean	SE	Comparison	LS mean	SE	95% CI	p-value
B2334	Ind 300 mcg	372	37.5	0.70	Ind 300 mcg – Pbo	-3.8	0.90	(-5.6, -2.1)	<.001
	Ind 600 mcg	354	37.2	0.70	Ind 600 mcg – Pbo	-4.1	0.90	(-5.9, -2.3)	<.001
	Form	359	38.1	0.70	For – Pbo	-3.2	0.90	(-5.0, -1.5)	<.001
	Placebo	347	41.3	0.70	---	---	---	---	---
B2335 S	Ind 150 mcg	368	38.3	0.70	Ind 150 mcg – Pbo	-2.8	0.90	(-4.5, -1.1)	0.001
	Ind 300 mcg	375	38.6	0.70	Ind 300 mcg – Pbo	-2.5	0.90	(-4.2, -0.8)	0.003
	Tio	374	40.1	0.70	Tio – Pbo	-1.1	0.90	(-2.8, 0.6)	0.195
	Placebo	347	41.2	0.70	---	---	---	---	---
B2336	Ind 150 mcg	309	36.4	1.04	Ind 150 mcg-Pbo	-6.3	0.99	(-8.2, -4.3)	<0.001
	Salm	301	38.5	1.04	Ind 150 mcg-Salm	-2.1	0.99	(-4.0, -0.2)	0.033
	Pbo	294	42.6	1.05	Salm- Pbo	-4.2	1.01	(-6.1, -2.2)	<0.001
B2346	Ind 150 mcg	199	43.4	0.86	Ind 150 mcg-Pbo	-4.8	1.22	(-7.1, -2.4)	<0.001
	Pbo	187	48.1	0.89	---	---	---	---	---
B2354	Ind 75 mcg	147	43.4	0.86	Ind 75 mcg-Pbo	-3.8	1.21	(-6.2, -1.4)	0.002
	Pbo	142	47.2	0.87	---	---	---	---	---
B2355	Ind 75 mcg	148	45.9	1.00	Ind 75 mcg-Pbo	-3.6	1.40	(-6.4, -0.9)	0.01
	Pbo	145	45.9	1.02	---	---	---	---	---

Source: Adapted from Tables 3-120, 3-121, 3-122 and 3-123 Summary of Clinical Efficacy and adapted from the review of Biostatistician, Dr Dongmei Liu

As shown in the table above, the SGRQ did not reach the proposed MCID for doses higher than 150 mcg in Trial B2334 (300 and 600 mcg) and Trial B2335S, which calls into question any dose response with SGRQ. In Trial B2336, the active comparator salmeterol also reached the MCID at -4.2. Since salmeterol has not been demonstrated to consistently benefit SGRQ, this suggests that the trial may have resulted in larger differences from placebo than expected.

Evaluating the SGRQ for the 75 mcg dose in Trials B2354 and B2355 shows a treatment difference of -3.8 and -3.6, respectively. The confidence intervals were wide, and between trial comparisons show marked overlap between the 75 and 150 mcg dose groups, suggesting that the results are statistically similar despite different point estimates. Likewise, as discussed in Dr. Dongmei Liu's statistical review, a responder analysis showed little difference between 75 mcg and 150 mcg, with similar percentages of patients meeting the MCID in both dose groups.

5.1.6 Other Endpoints

There were a multitude of nonprimary endpoints evaluated for indacaterol, notably tFEV1 at Day 2, tFEV1 after 12 and 26 weeks, peak FEV1 in first 4 hours, serial FEV1 over 24 hours, morning and evening PEF and these endpoints provided supportive evidence of the efficacy of indacaterol. However any conclusions regarding the validity of the data must be examined qualitatively as no statistical adjustments were made for the multiple comparisons of the many endpoints.

FEV1 AUC

The standardized AUC measurements for FEV1 (between 5 min- 1 hr and between 5 min-4 hr) after 12 weeks were significantly greater with indacaterol 75 mcg (B2354 and B2355) and 150 mcg (B2336) compared with placebo (both p<0.001). AUC values were also significantly higher with salmeterol vs. placebo (p<0.001).

Rescue Medication Use
Both indacaterol 75 mcg and 150 mcg demonstrated statistically significant improvements over placebo in rescue medication use.

TDI
Both the indacaterol 75 mcg and 150 mcg treatments in B2354 and B2336, respectively demonstrated statistically significant improvements in the TDI. In B2355 the TDI score difference was not statistically significant.

5.1.7 Subpopulations

Subgroup analyses for age, sex, race, COPD severity, smoking history, and ICS use at baseline, were performed for trough FEV1 after 12 weeks of treatment for trials B2355, B2354 and B2336. Since the population for the studies was about 80- 94% caucasian, it was difficult to make conclusions about the racial subgroups.

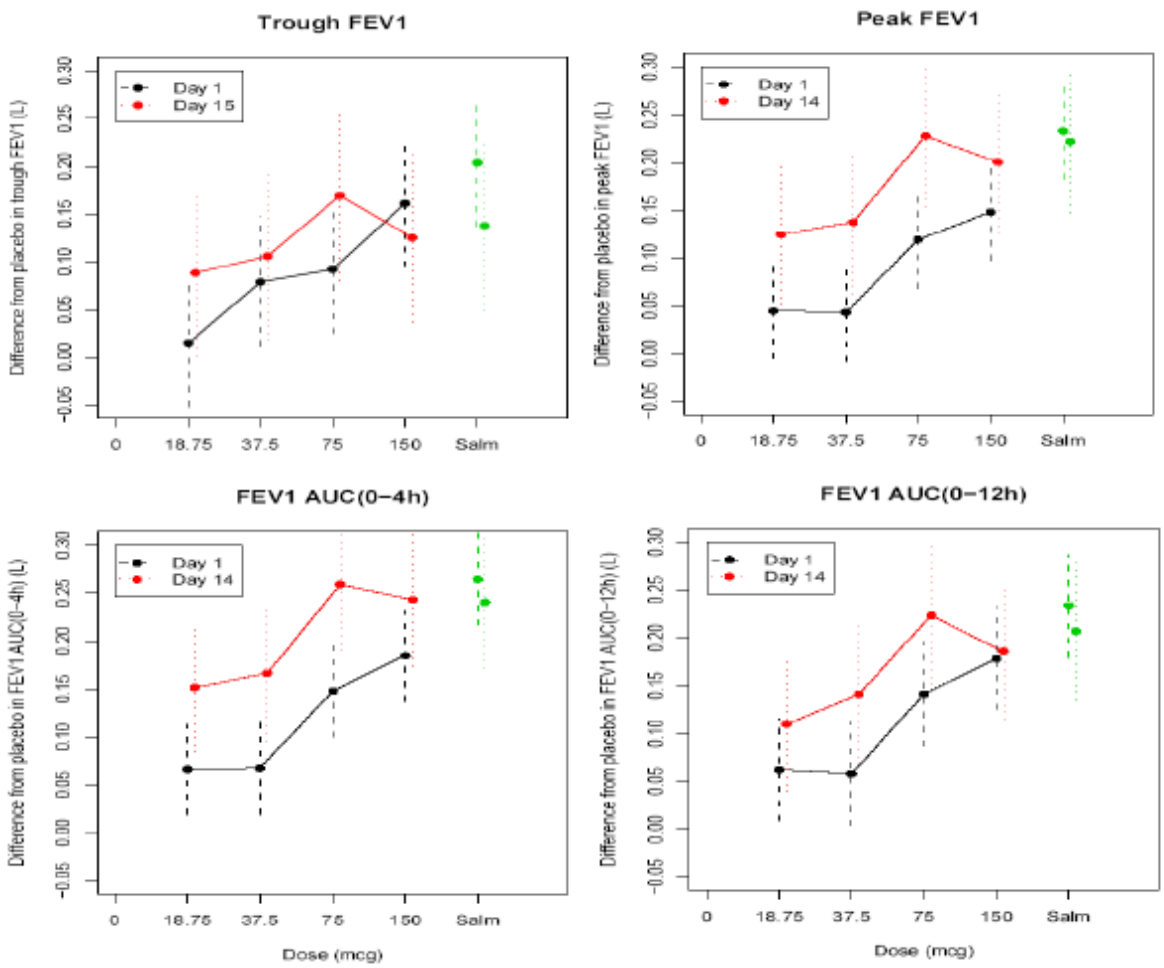
Males had higher trough FEV1 values at Week 12 than for females in the indacaterol 75 mcg and indacaterol 150 mcg treatment groups by approximately 30 mL. Patients without ICS use had a higher trough FEV1 at Week 12 in the indacaterol, 75 mcg (0.04 L) and indacaterol 150 mcg (0.03 L) treatment groups.

There was little difference in FEV1 response based on COPD severity (moderate/mild versus severe), age < 65 vs. ≥ 65, and ex-smokers versus current smokers. The results do not support the Sponsor's claim that the higher dose, indacaterol 150 mcg may provide additional benefit in severe patients. See individual study reviews for additional information.

5.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Dose selection
In addition to the data for trough FEV1, review of other FEV1 variables can inform dose selection. Using the data from Trial B2357 (dose ranging trial in patients with asthma), trough FEV1, peak FEV1, FEV1 AUC0-4hr, FEV1 AUC0-12hr, and serial FEV1 measurements were evaluated. As demonstrated in Figure 19 below, the 75 mcg dose has the largest effect on all four bronchodilator assessments highlighted. The Day 1 (black) curves show a characteristic dose response profile with the largest effect seen with the highest dose (150 mcg). By steady state however, the Day 14/15 curves reveal a maximum effect with the 75 mcg dose and the highest dose not exhibiting the peak effect. The two lowest doses, 18.75 and 37.5 are not very different (slope) in their bronchodilatory effects with the exception of tFEV1 on Day 1.

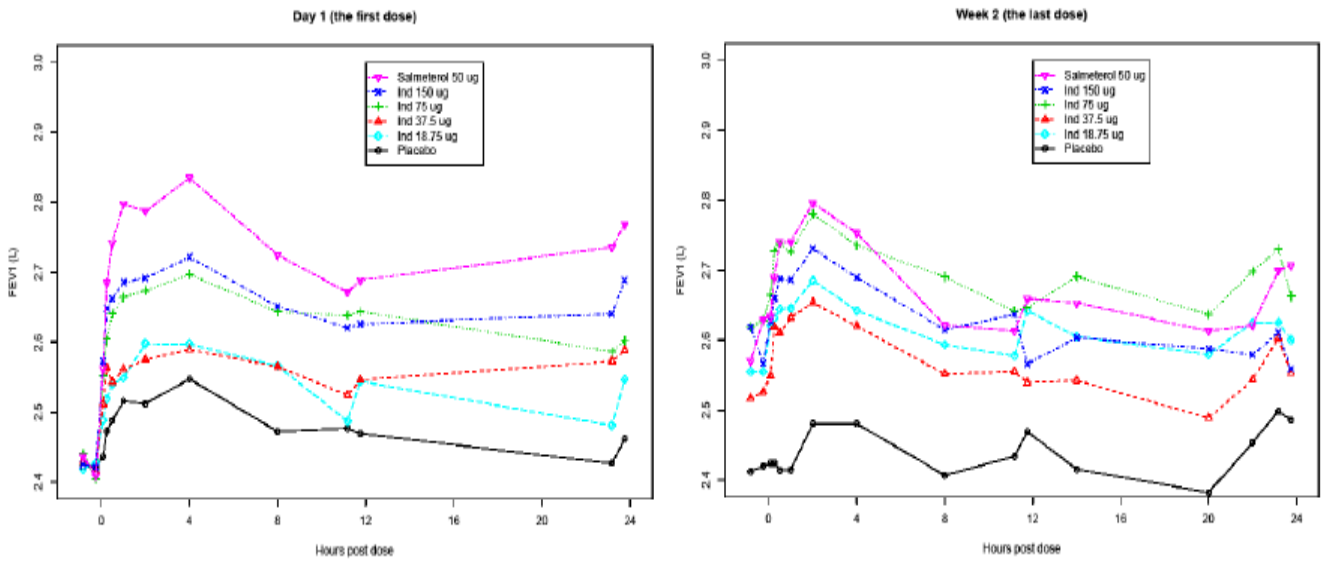
Figure 19 Protocol B2357, Dose response curves



Source: Adapted from the review of Biostatistician, Dr Dongmei Liu

The figure below shows the dose response curves over time generated by our biostatistician, Dr. Liu. The curves measuring FEV1 on Day 1 demonstrate the greatest magnitude of effect for most time points, particularly after the first hour by salmeterol. In terms of indacaterol, the 150mcg dose and the 75mcg dose had similar FEV1 profiles on Day 1, while the two lowest doses of indacaterol (18.75mcg and 37.5mcg) have a noticeably smaller effect of FEV1. Similar to the discussion above, by week 2 the FEV1 profile of 75mcg dose was numerically greater than the 150 mcg dose. Also of note, the dose response over time curves for the two lower doses at two weeks also changed their pattern as shown in Figure 20, now with both curves shifting upwards consistent with a greater bronchodilatory effect.

Figure 20 B2357 FEV1 profiles comparison



Source: Adapted from the review of Biostatistician, Dr Dongmei Liu

These data show that the indacaterol 75 mcg dose showed the most benefit compared to placebo for the primary endpoint, trough FEV1 (tFEV1) at Day 15. Although the 150 mcg indacaterol dose had a larger improvement than 75 or 37.5 mcg after 1 day of treatment, this advantage was lost by Day 14. In this trial, the 37.5 mcg and 18.75 mcg doses offered suboptimal bronchodilator effect on Day 1.

Dosing frequency

As indacaterol is proposed for once daily dosing, which is novel for a LABA, sufficient data is necessary to support to once daily dosing. The Agency requested the Applicant explore alternate dosing intervals. Study B2223 compared QD, BID, and QOD dosing regimens for the same nominal dose in patients with asthma. Data from Study B2223 demonstrated no statistical difference between the three dosing regimens examined and supports the proposed once daily dosing interval. The results for trough FEV1 are shown in the table below.

Table 74 Protocol B2223 Change from baseline in trough FEV1 on Days 15/16 (PD analysis set)

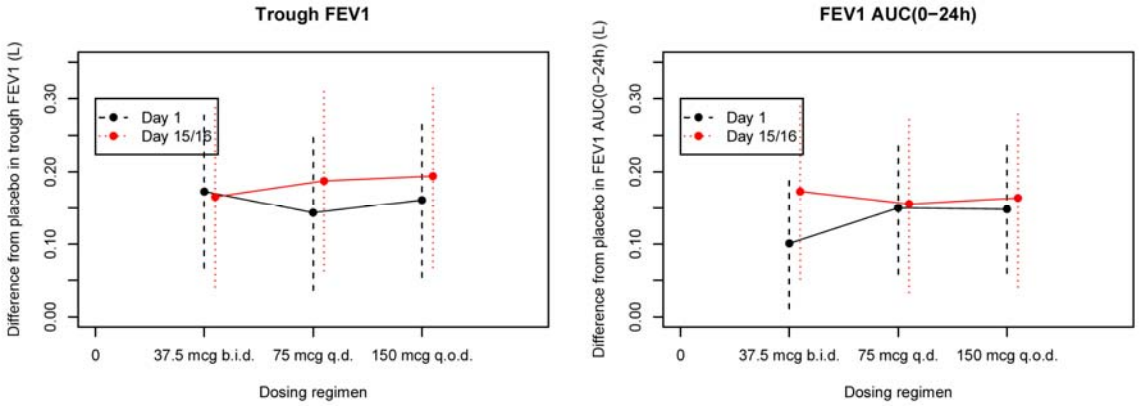
		Contrast with placebo		
PD parameter	**Treatment**	**Mean**	**Lower 95% CI**	**Upper 95% CI**
Trough FEV_1 (L)	37.5 µg b.i.d	0.160	0.036	0.284
	75 µg q.d	0.202	0.077	0.327
	150 µg q.o.d	0.203	0.077	0.329

Source: Table 2 CQAB149B2223 Clinical Study Report

Refer to the Figure 21 which displays the trough FEV1 as well as the FEV1 AUC (0-24 hr) for the different dosing regimens and suggests the once daily dosing regimen is supported. The peak/trough ratio for the 37.5 mcg b.i.d regimen was close to 1.0 on day 1 with the 90% CI including 1.0, on days 15/16 it was 1.08 with 90% CI above 1.0. The peak/trough ratio was 1.10 for 75 mcg q.d dosing and 1.13 for 150 mcg q.o.d dosing on both day 1 and days 15/16.

Reviewer Comment:
Limitations to the peak-to-trough analysis are due to the trough FEV1 measures influenced by the normal diurnal rhythm of pulmonary fluctuations resulting in an increase in FEV1 in the early waking hours in addition to the drug effect.

Figure 21 B2223 Dosing frequency

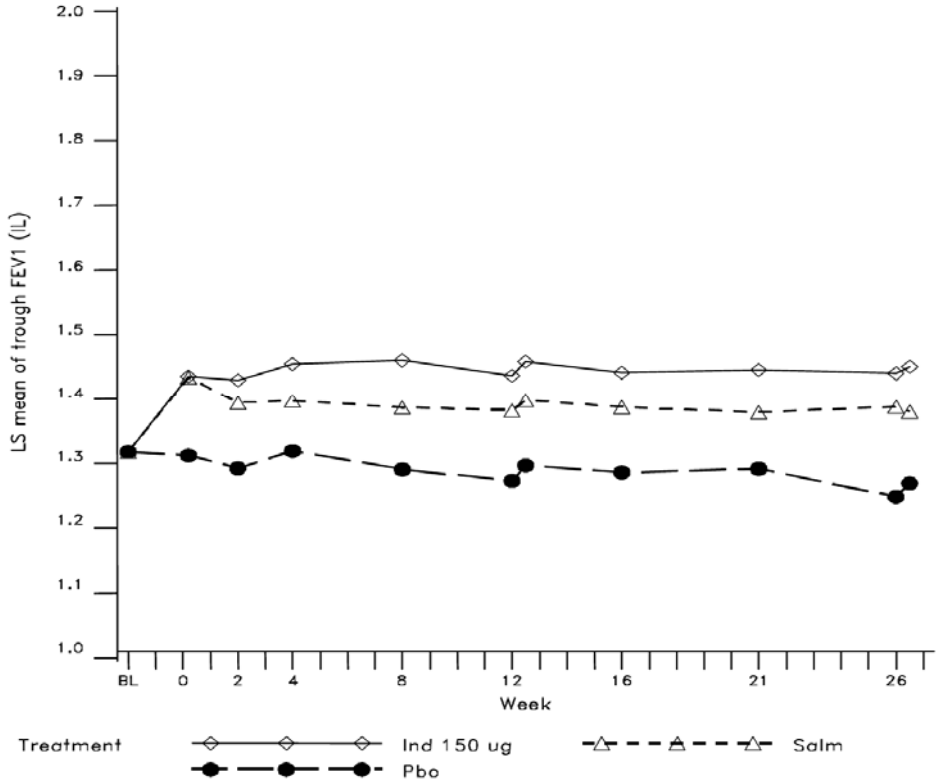


Source: Adapted from the review of Biostatistician, Dr Dongmei Liu

5.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

To evaluate the persistence of efficacy/tolerance claim proposed by the Applicant, examination of the FEV1 response over long term use of indacaterol is necessary. The figure below displays the trough FEV1 (L) over 26 weeks of treatment and shows that the trough FEV1 for indacaterol 150mcg is maintained over the 26 weeks of treatment.

Figure 22 Protocol B2336 Least squares means of trough FEV1 (L) over 26 weeks of treatment (ITT population)



Source: Figure 11-2 Study No. CQAB149 B2336 Clinical Study Report

5.1.10 Additional Efficacy Issues/Analyses

Onset of Action

The Applicant has proposed an onset of action claim, which is not unusual as many bronchodilators have onset of action claims. Serial spirometry data in Trials B2355 and B2354 is shown in the table below. at the 5 min time point on Day 1, the magnitude of the improvements in FEV1 between indacaterol 75 mcg and placebo was 0.10 L and was statistically significant ($p<0.001$) and represented 69% of the trough FEV1 on Day 85 refer to Figure 23 for details. In B2354, it was 0.09 L and also statistically significant ($p<0.001$).

Figure 23 Analysis of FEV1 (L) 75 mcg indacaterol vs. placebo at each time point, by visit (FAS)

Analysis of FEV1 (L) 75 mcg indacaterol vs. placebo at each time point, by visit (FAS)									
B2355					B2354				
Time point		Treatment difference (L)	95% CI	p-value	Time point	Treatment difference (L)	95% CI		p-value
Day 1	5 min	0.10	(0.08, 0.12)	< 0.001	Day 1	5 min	0.09	(0.07, 0.10)	< 0.001
	30 min	0.12	(0.10, 0.15)	< 0.001		30 min	0.12	(0.10, 0.14)	< 0.001
	1 hr	0.12	(0.09, 0.15)	< 0.001		1 hr	0.11	(0.09, 0.13)	< 0.001
	2 hr	0.12	(0.09, 0.15)	< 0.001		2 hr	0.13	(0.10, 0.15)	< 0.001
	4 hr	0.13	(0.09, 0.16)	< 0.001		4 hr	0.12	(0.10, 0.15)	< 0.001
Day 2	23 hr 10 min	0.08	(0.04, 0.11)	< 0.001	Day 2	23 hr 10 min	0.08	(0.05, 0.10)	< 0.001
	23 hr 45 min	0.07	(0.04, 0.11)	< 0.001		23 hr 45 min	0.08	(0.06, 0.11)	< 0.001
Day 84	5 min	0.16	(0.11, 0.20)	< 0.001	Day 84	5 min	0.18	(0.15, 0.22)	< 0.001
	30 min	0.19	(0.14, 0.23)	< 0.001		30 min	0.18	(0.14, 0.22)	< 0.001
	1 hr	0.18	(0.14, 0.23)	< 0.001		1 hr	0.18	(0.14, 0.21)	< 0.001
	2 hr	0.19	(0.15, 0.24)	< 0.001		2 hr	0.17	(0.14, 0.21)	< 0.001
	4 hr	0.17	(0.12, 0.21)	< 0.001		4 hr	0.15	(0.11, 0.19)	< 0.001
Day 85	23 hr 10 min	0.15	(0.10, 0.19)	< 0.001	Day 85	23 hr 10 min	0.11	(0.07, 0.15)	< 0.001
	23 hr 45 min	0.14	(0.10, 0.19)	< 0.001		23 hr 45 min	0.12	(0.07, 0.16)	< 0.001

6 Review of Safety

Safety Summary

The action letter dated October 16, 2009 for the original cycle specified a lack of substantial evidence of safety to support the originally proposed 150 and 300 mcg doses in COPD as one explanation for the complete response action. Key safety issues were unacceptable higher frequencies of cardiovascular and cerebrovascular adverse events (AEs) compared to placebo and to formoterol in patients with COPD and possible asthma related deaths compared to salmeterol in patients with asthma. While there is substantial evidence of adverse respiratory events associated with the use of LABAs in patients with asthma [13](SMART), it is unclear if this safety concern applies to COPD patients. Furthermore, since the Sponsor is requesting approval for 2 doses for the treatment of COPD, they are tasked in the current cycle to balance the safety data to show no unacceptable safety disadvantages with the higher dose.

Exposure to indacaterol 75 mcg was less than ideal. As described in the E1A-Guideline for Industry, The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life Threatening Conditions, March 1995, “The number of patients treated for 6 months at dosage levels intended for clinical use, should be adequate to characterize the pattern of ADEs over time. To achieve this objective the cohort of exposed subjects should be large enough to observe whether more frequently occurring events increase or decrease over time as well as to observe delayed events of reasonable frequency (e.g., in the general range of 0.5%-5%). Usually 300 to 600 patients should be adequate.” Furthermore, “100 patients exposed for a minimum of one-year is considered to be acceptable to include as part of the safety data base.” The mean exposure of 75 mcg indacaterol was 85.5 days and for 150 mcg indacaterol it was 120 days. Therefore the sponsor is relying on the extrapolation of the safety data for the 75 mcg dose to the 150 mcg dose. The safety datasets were categorized by 3-, 6-, and 12- month duration of exposure as well as a “COPD safety” population and a “COPD tiotropium combination safety” population. Evaluation of the demographics of the datasets revealed a mean age range of 63-65 years across the indacaterol treatment groups with the majority of patients being caucasian males. The median duration ranged from 4- 7 years across the safety populations and the degree of reversibility was balanced with the mean FEV1% predicted above 50%.

There were a total of 9441 patients in the 3 month COPD safety dataset, 4764 of whom received indacaterol in the following dose groups—75 mcg (N-449), 150 mcg (N=2611), 300 mcg (N=1157), and 600 mcg (N=547). Twelve month data is available for 2142 patients, 1152 of whom received indacaterol in the following dose groups—150 mcg (N=144), 300 mcg (N=583), and 600 mcg (N=425). The sponsor proposes to use long-term (12-month) safety data from the 150 mcg dose group to support safety for the 75 mcg group. The longest duration of exposure for the proposed 75 mcg once daily dose is 3 months.

The most common AEs in both the 3 and 12 month safety datasets were COPD exacerbation, nasopharyngitis, cough, headache, upper respiratory infection, and muscle spasms. Both cough and muscle spasms occurred more frequently in the indacaterol groups than in placebo or active comparator groups. Six Phase 3 studies proactively solicited information on post-inhalational cough that occurred at the study center after dosing. Based on this analysis, post-inhalational cough occurred in 23 to 31% of indacaterol treated patients compared to 3 to 6% of placebo treated patients. A small dose effect was seen, with 23% of patients coughing in the 75 mcg group compared to 31% in the 600 mcg group, with the odds ratio compared to placebo of 7.75 (95% CI 5.07, 11.86) and 17.62 (95% CI 13.57, 22.87), respectively. However, the cough was generally of very short duration (≤ 15 seconds), did not cause discontinuation from the trial, and did not cause a drop in FEV1.

[13] Nelson HS, Weiss ST, Bleecker ER, et al. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest, 2006 Jan; 129(1):15-26

In the original submission, there were more cardiac or cerebrovascular AEs and serious adverse events (SAEs) in the indacaterol treatment groups compared to placebo (3.4% indacaterol 300 mcg versus 0.9% placebo SAEs) in the 12 month safety evaluation. The 12 month safety data from the complete response, which includes data from the 26 week safety extension to the adaptive design study (Protocol B2335SE), shows that patients with SAEs in any organ system are balanced in the 150 mcg dose group compared to placebo (10.4% of patients in the indacaterol 150 mcg group compared to 11.0% in placebo). There were 0.69% of patients in the 150 mcg indacaterol group with cardiac or cerebrovascular SAEs compared to 1.4% in the placebo group.

The second safety concern raised by the original submission was asthma related death, with two deaths in the 268 patient 300 mcg dose group of a single 26 week asthma study. The Sponsor was asked to conduct a blinded adjudicated analysis comparing indacaterol treated patients to controls by evaluating AE of interest: all cause death, respiratory-related deaths, respiratory-related, respiratory related hospitalizations, pneumonia-related death and pneumonia-related intubation. Results of the meta-analysis are pending at the time of this review.

6.1 Methods

6.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety review includes a separate analysis of the asthma trials including those in the original submission. See Section 6.6 Additional Safety Evaluations. The data from the two week dose finding trials B2356, B2357 and the 2 week dose regimen trial, B2223 were not included in the Sponsor's pooled safety analyses. The Sponsor suggests that the different doses and dose regimens not used in other trials, the short duration of treatment time and the different population (asthmatics) would not add to the quality of the pooled safety evaluation. The safety results of these trials were reviewed in the individual trial sections and will also be summarized in Section 6.6 Additional Safety Evaluations.

- B2356, 2 weeks of treatment with indacaterol 18.75 mcg q.d., 37.5 mcg q.d., 75 mcg q.d,, 150 mcg q.d,, placebo, or salmeterol 50 mcg b.i.d in patients with moderate to severe COPD.
- B2357, 2 weeks of treatment with indacaterol 18.75 mcg q.d, 37.5 mcg q.d, 75 mcg q.d, 150 mcg q.d, placebo, or salmeterol 50 mcg b.i.d in patients with persistent asthma.
- B2223, 2 weeks of treatment with indacaterol 37.5 mcg b.i.d, 75 mcg q.d, 150 mcg q.o.d, or placebo, in patients with persistent asthma.

The pivotal COPD trials submitted during this cycle, B2354, B2355 and B2336 were the primary source of safety data that were reviewed.

- B2355, 12 weeks of treatment with indacaterol 75 mcg q.d, or placebo (double-blind)
- B2354, 12 weeks of treatment with indacaterol 75 mcg q.d, or placebo (double-blind)
- B2336, 26 weeks of treatment with indacaterol 150 mcg q.d, salmeterol 50 mcg bid or placebo (double-blind)

The Sponsor's pooled analyses included data from trials submitted during the first cycle as well as 10 supportive trials added during this cycle. Summaries of B2341 and B2351, the largest of the supportive trials, may be found at the end of the individual trial summaries.

- B2346, 12 weeks of treatment with indacaterol 150 mcg q.d, or placebo (double-blind)
- B2334, 52 weeks of treatment with indacaterol 300 mcg q.d, 600 mcg q.d, placebo (double-blind) or formoterol 12 mcg bid (double-blind) and providing long-term safety data
- B2335S, 26 weeks of treatment with indacaterol 150 mcg q.d, 300 mcg q.d, placebo (double-blind) or tiotropium 18 mcg q.d, (open-label)
- B1302, 12 weeks of treatment with indacaterol 150 mcg q.d, 300 mcg q.d or placebo (double-blind)
- B2333, 26 weeks of treatment with indacaterol 150 mcg q.d, 300 mcg q.d or placebo (double-blind)
- B2349, 12 weeks of treatment with indacaterol 150 mcg q.d, or salmeterol 50 mcg b.i.d (double-blind)
- B2350, 12 weeks of treatment with indacaterol 150 mcg q.d, or tiotropium 18 mcg q.d (double-blind)
- B2335SE, 52 weeks of treatment with indacaterol 150 mcg q.d, 300 mcg q.d, or placebo (double-blind) - patients were included only after completion of B2335S.
- B2311, 21 days of treatment in each period with indacaterol 300 mcg q.d, or placebo (double-blind).
- B2331, 14 days of treatment in each period with indacaterol 150 mcg q.d, 300 mcg q.d, or placebo double-blind); tiotropium 18 mcg q.d was used as a blinded active control (using third party blinding).
- B1303, 24 week interim analysis of a 52 week treatment with indacaterol 300 mcg q.d and salmeterol 50 mcg b.i.d.
- B2341, 12 weeks of treatment with indacaterol 150 mcg q.d via Concept1 device plus tiotropium 18 mcg q.d via Handihaler, vs. placebo via Concept1 device plus tiotropium 18 mcg q.d via Handihaler (double-blind)
- B2351, 12 weeks of treatment with indacaterol 150 mcg q.d via Concept1 device plus tiotropium 18 mcg q.d via Handihaler, vs. placebo via Concept1 device plus tiotropium 18 mcg q.d via Handihaler (double-blind)

Also included in the safety analysis were the PSUR-1 ranging from November, 2009 to May, 2010, additional postmarketing reports and the Mexico Patient Support Program. The metaanalysis of respiratory related adverse events particularly intubations, hospitalizations and deaths was pending at the time of this review.

6.1.2 Categorization of Adverse Events

Adverse events were captured into 2 data sets, the AE case report forms (CRF) and the COPD exacerbation-dedicated CRFs. The analysis of AEs involved coding of verbatim terms to preferred terms of the MedDRA medical dictionary system (version 13.0). Treatment emergent AEs (TEAEs) were defined by the Sponsor as the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after the first dose of study drug and up to 7 days after the last dose for non-serious AEs, or up to 30 days after the last dose for SAEs. An exception was for deaths occurring in the 30 days after the last dose in B2335S (these data were in the database for the ongoing extension study B2335SE) were described separately. Medical comorbidities present at baseline were considered AEs if they worsened after starting the study. Abnormal laboratory values or test results were recorded as AEs only if they induced clinical signs or symptoms, were considered clinically significant, or required therapy.

Coding of COPD exacerbations as well as the verbatim term “worsening of COPD” from an investigator were to the preferred term “chronic obstructive pulmonary disease”. The Sponsor also highlighted that if these “worsening of COPD” AEs did not meet the definition of COPD exacerbation, the AEs were not reported on the COPD exacerbation CRF.

All other events were coded based on preferred term. There was no grouping of similar terms for adverse events of interest, such as cardiovascular. For example, acute myocardial infarction and myocardial infarction were coded separately. Pneumonia was coded under the System Organ Class (SOC) of infections and infestations rather than in the respiratory category. Similar to MI, this under-counts the grouped AE of pneumonia because events for various types of pneumonia may be listed separately depending on the verbatim term listed by the investigator.

For the analysis of cardiac events, the sponsor prospectively grouped events by Standard MedDRa Queries (SMQs) based on published SMQ version 11.0 “narrow”, for the disorders “cardiac failure”, “ischemic heart disease”, and “cerebrovascular disorders” and “cardiac arrhythmias” (broad). The search did not include CV death, i.e. the preferred terms cardiac death, sudden cardiac death and sudden death.

The definition of COPD exacerbation changed during the development program. The original trials included a definition of:

- a new onset or worsening of more than one respiratory symptom (i.e. dyspnea, cough, sputum purulence or volume, or wheeze) present for more than 3 consecutive days,

plus at least one of the following:

- documented change or increase in COPD-related treatment due to worsening symptoms (e.g. steroids/antibiotics/oxygen),
- documented COPD-related hospitalizations or Emergency Room visits.

However, in the trials B2341, B2349, B2350 and B2351 conducted more recently, the definition of COPD exacerbation was updated:

worsening of 2 or more of the following major symptoms for at least 2 consecutive days:

- dyspnea
- sputum volume
- sputum purulence

or

worsening of any 1 major symptom together with any 1 of the following minor symptoms for at least 2 consecutive days:

- sore throat
- cold (nasal discharge and/or nasal congestion)
- fever without other cause
- increased cough
- increased wheeze

and

requiring treatment with systemic corticosteroids and/or antibiotic.

6.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The datasets evaluated by the Sponsor were categorized into the following populations for an integrated summary of safety:

- "COPD 3-month" safety population containing pooled 3-month data from phase III studies B2346, B2349, B2350, B2354, B2355, B1302 (all data), also studies B2333, B2334, B2335S, B2335SE, and B2336 (only the first 3 months).
- "COPD 6 month", the safety population containing pooled 6-month (26 week) data from phase III studies B2333, B2336, and B2335S, (all data), also studies B2335SE, and B2334 (each up to day 182).
- "COPD 12 month" safety population containing 52 week, pivotal, phase III studies B2334 and B2335SE.
- "COPD safety" populations containing all data from controlled studies in COPD patients of at least 3 months duration, these being B2333, B2334, B2335S, B2335SE, B2336, B2346, B2349, B2350, B2354, B2355, and B1302. The datasets included 449, 2611, 1157 and 547 patients who received treatment with indacaterol 75, 150, 300 and 600 mcg q.d, respectively.
- COPD Tiotropium combination safety population containing pooled data from two studies with indacaterol 150 mcg administered concurrently with open-labeled tiotropium, double-blind, controlled by tiotropium, parallel design, duration of total exposure to study drug of 3 months, studies B2341 and B2351.
- All treated subjects population containing pooled data from all completed COPD, asthma and healthy volunteer studies of indacaterol regardless of study design, excluding post-inhalation cough studies A2222 and D2301, pediatric study C2101, 3 ADME studies A2106, A2214 and A2223, device handling study B2353, formulation/delivery study B2222, special safety single dose study B2102, and studies B2356, B2357, and B2223.

These pooled data contain overlapping populations (i.e. the 3 month population includes patients who may also be included in the 6 month population). The COPD safety population included patients from all COPD trials with a treatment duration of at least 3 months. The COPD tiotropium combination safety population was analyzed because tiotropium is commonly used in the COPD indication, and it is of interest whether the safety profile of concurrently administered indacaterol and tiotropium is likely to differ from tiotropium alone. The dose finding trials, B2356, B2357 and B2223 were not included in the pooled safety analyses because of the doses and dose regimens investigated in these trials and not in others, the short duration and the different target population those with asthma in trials B2357 and B2223. Some special safety topics were identified due to particular concern. Subsets of the events in these special categories include the particularly focused on cardio- and cerebrovascular AEs.

6.2 Adequacy of Safety Assessments

6.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In the COPD safety population, this dataset included 4,764 patients who received indacaterol treatment: 449 received 75 mcg; 2,611 received 150 mcg; 1,157 received 300 mcg and 547 received 600 mcg. The number of patients with COPD and exposure to indacaterol at different doses is summarized in Table 75 below. Of note, the two week dose finding trials, B2357, B2356 and B2223 were not included in these analyses and the extent of exposure for these trials is described in the Safety Results section of the reviews for the individual trials. The largest numbers of patients were treated with the originally proposed doses of 150 mcg and 300 mcg.

Table 75 Exposure to indacaterol by safety population group

Safety population	Indacaterol treatment groups (N)			
	75 mcg	150 mcg	300 mcg	600 mcg
COPD 3- month	449	2611	1157	547
COPD 6- month	127	933	1041	547
COPD 12- month	---	144	583	425

Source: Section 1.2 CTD 2.7.4 Summary of Clinical Safety

Reviewer Comment:
For an acceptable safety assessment of a chronically administered drug for the treatment of a non-life threatening condition, ICH guidelines recommend evaluating a minimum of 300 patients for a 6 month duration and 100 for a 3 month duration, provided no concerning safety signals are identified. One-hundred-twenty-seven patients were exposed to the 75 mcg dose for 6 months and no patients were exposed for 12 months. However, 77 patients were exposed to indacaterol 150 mcg for ≥52 weeks and 57 were exposed for 44-52 weeks, giving over a hundred patients with nearly 12 months of data. Exposure numbers were much higher for the higher dose groups of 300 and 600 mcg. See Table 76.

The exposure of indacaterol amongst the total COPD safety population was heterogeneous across the different treatment groups. This was due to particularly to the variation of duration across the different trials. Data for one of the two proposed doses, 75 mcg group, for example, was drawn from the 3-month studies B2354 and B2355, and the dose-ranging Stage 1 of B2335S, whereas the data for the 150 and 300 mcg groups were drawn from a greater number of trials, with duration of up to 12 months. The Sponsor therefore adjusted the safety data for the COPD safety population for duration of exposure, for comparison across treatment group.

Table 76 Duration of exposure to study drug after randomization in the COPD safety population

	Indacaterol treatment groups				Control treatment groups			
	75 mcg	150mcg	300mcg	600mcg	For	Tio	Salm	Pbo
Exposure (days)	N=449	N=2611	N=1157	N=547	N=556	N=1214	N=895	N=2012
mean	85.5	120.3	232.7	263.4	260.3	107.7	112.2	167.7
sd	25.81	74.61	123.27	135.27	133.46	49.36	51.45	115.93
min- max	2 - 179	1 - 385	1 - 420	1 - 407	1 - 397	1 - 208	1 - 215	1 - 403
Patient-years	105.06	859.72	736.97	394.49	396.21	357.97	274.93	923.60
Exposure– n(%)								
≥ 3 months	90 (20.04)	257 (9.84)	132 (11.41)	87 (15.90)	101 (18.17)	161 (13.26)	83 (9.27)	204 (10.14)
≥ 6 months	0	583 (22.33)	539 (46.59)	191 (34.92)	190 (34.17)	240 (19.77)	230 (25.70)	687 (34.15)
≥ 12 months	0	77 (2.95)	256 (22.13)	167 (30.53)	168 (30.22)	0	0	240 (11.93)

Source: Adapted from Table 5-2 CTD 2.5 Clinical Overview

Demographics
Demographic information for the multiple indacaterol doses in the COPD 3- month, 6- month and 12- month safety population was analyzed. Conclusions about age, gender and race were common across all 3 populations. The mean age was similar across treatment groups, about 63- 65 years of age. Gender distribution was also skewed with the predominate gender being male across all groups with different

ratios between groups. The majority of patients were caucasian, with so few other races, no comment can be made regarding generalizability of trends based on race. See Table 77.

Table 77 Demographics in COPD 3- month and 6- month populations

	Indacaterol treatment groups				**Control treatment groups**			
	75 mcg n=449	150 mcg n=2611	300 mcg n=1157	600 mcg n=547	For n=556	Tio n=1214	Salm n=895	Pbo n=2012
COPD 3 month								
Age mean (years)	63.5	63.5	64.3	63.1	64	63.6	63.3	63.7
Gender- n (%)								
Male	248 (55.23)	1815 (69.51)	908 (78.48)	401 (73.31)	418 (75.18)	807 (66.47)	664 (74.19)	1436 (71.37)
Female	201 (44.77)	796 (30.49)	249 (21.52)	146 (26.69)	138 (24.82)	407 (33.53)	231 (25.81)	576 (28.63)
Race- n (%)								
Caucasian	414 (92.20)	2026 (77.59)	772 (66.72)	503 (91.96)	511 (91.91)	1110 (91.43)	736 (82.23)	1502 (74.65)
Black	19 (4.23)	56 (2.14)	13 (1.12)	6 (1.10)	3 (0.54)	18 (1.48)	11 (1.23)	38 (1.89)
Asian	11 (2.45)	462 (17.69)	348 (30.08)	15 (2.74)	13 (2.34)	52 (4.28)	120 (13.41)	415 (20.63)
Other	5 (1.11)	67 (2.57)	24 (2.07)	23 (4.20)	29 (5.22)	34 (2.80)	28 (3.13)	57 (2.83)
	75 mcg ---	150 mcg n=144	300 mcg n=583	600 mcg n=425	For n=434	Tio ---	Salm ---	Pbo n=556
COPD 12 month								
Age mean (years)	---	62.5	63.6	62.9	63.6	---	---	63.1
Gender- n (%)								
Male	---	87 (60.42)	437 (74.96)	327 (76.94)	348 (80.18)	---	---	433 (77.88)
Female	---	57 (39.58)	146 (25.04)	98 (23.06)	86 (19.82)	---	---	123 (22.12)
Race- n (%)								
Caucasian	---	120 (83.33)	526 (90.22)	393 (92.47)	400 (92.17)	---	---	502 (90.29)
Black	---	4 (2.78)	6 (1.03)	1 (0.24)	0 (0.00)	---	---	3 (0.54)
Asian	---	19 (13.19)	27 (4.63)	8 (1.88)	7 (1.61)	---	---	31 (5.58)
Other	---	1 (0.69)	24 (4.12)	23 (5.41)	27 (6.22)	---	---	20 (3.60)

Source: Adapted from Tables 1-18, 1-19 and 1-20

Disease Characteristics

Disease characteristics such as baseline duration, severity of COPD, smoking status, use of ICS, medical history, concomitant disease characteristics and use of concomitant medications were included for

subgroup analyses in the 3 safety populations. The patterns of distribution of baseline disease characteristics were similar across the 3 safety populations.

COPD 3- month safety population

Overall, disease characteristics were balanced across the treatment groups. The median duration of COPD ranged from 4.6 to 5.8 years with >94% of patients across treatment groups categorized as moderate to severe. The degree of reversibility was balanced with the mean FEV1% predicted (after SABA) above 53% in all treatment groups. The mean percent increase after SABA ranged from 10-19%. The mean percent increase ranged from 11% for salmeterol to 19% in the 75 mcg indacaterol group. The majority of patients were on ICS and were ex smokers. Mean lifetime number of pack years ranged from 40 to 57 years across all treatment groups. The presence of comorbidities such as CCV, hypertension or hyperlipidemia at baseline was proportionate across all groups.

COPD 6- month safety population

Disease characteristics were balanced across the safety populations. The median duration of COPD ranged from 4.8 to 5.7 years with >94% of patients across treatment groups categorized as moderate to severe. The degree of reversibility was balanced with the mean FEV1% predicted (after SABA) was above 50% in all treatment groups. The mean percent increase after SABA ranged from 12-17%. The mean percent increase ranged from 13% for formoterol to 15% between all treatment groups except indacaterol 75 mcg with the highest of 17%. ICS use ranged from 42% in 75 mcg group to 50% in formoterol group. Most patients were ex-smokers; the lowest percent was in 75 mcg (52%) and the highest in the 300 mcg (60.85%) treatment group. Mean lifetime usage was >40 pack years in all treatment groups with the highest mean usage found in the indacaterol 75 mcg q.d. group (54 pack years) and the lowest (43 pack years) in the salmeterol group. The presence of comorbidities such as CCV, hypertension or hyperlipidemia at baseline was proportionate across all groups.

COPD 12- month safety population

Similar to the 3- month and 6- month safety population, the disease characteristics were balanced across the treatment groups. The median duration of COPD ranged from 6.8 to 7.3 years with >93% of patients across treatment groups categorized as moderate to severe. The degree of reversibility was balanced with the mean FEV1% predicted (after SABA) above 52% in all treatment groups. The mean percent increase after SABA ranged from 12-18%. The mean percent increase ranged from 13% for formoterol to 15% between all treatment groups. ICS use ranged from the lowest of 34% in 75 mcg group to 53% in the indacaterol group. Most patients except the 75 mcg group were ex smokers. Mean lifetime usage was 48 to 54 pack years across all treatment groups. The presence of comorbidities such as CCV, hypertension or hyperlipidemia at baseline was proportionate across all groups.

6.2.2 Explorations for Dose Response

Four doses of indacaterol (75 mcg, 150 mcg, 300 mcg and 600 mcg once daily) were assessed in large Phase III clinical trials with the 150, 300 and 600 mcg doses studied for up to 12 months. The safety evaluation for the dose response trials are discussed in the individual sections (B2357, B2356, B2223)..

6.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro safety assessments were submitted as part of this application.

6.2.4 Routine Clinical Testing

Routine clinical testing conducted in the submitted trials was adequate to assess for systemic effects of indacaterol. Assessments included measurements of vital signs, clinical laboratory testing (with particular focus on potassium, glucose, and LFTs), and ECGs, notably during baseline, time of peak effect and at serial time points post dosing.

6.2.5 Metabolic, Clearance, and Interaction Workup

The metabolic, clearance and drug interaction assessments conducted were adequate. Please see the review by the Clinical Pharmacology reviewer, Dr. Ying Fan. Two trials (B2341 and B2351) were conducted investigating the bronchodilator effects of indacaterol when combined with an often prescribed bronchodilator for COPD, tiotropium. The two 12 week, randomized, controlled trials demonstrated that indacaterol provides additional bronchodilator benefit in patients receiving a long-acting anticholinergic.

6.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The known adverse events reported for LABAs include: anxiety, back pain, chest pain, muscle cramps and myalgia, diarrhea, dizziness, dyspnea, headache, insomnia, musculoskeletal pain, nasal congestion, nausea, peripheral edema, pruritis, rash, rhinitis, sinusitis, throat irritation, tremor, and upper respiratory tract infection. These as well as the established laboratory effects such as hypokalemia and hyperglycemia, effects of tachycardia and increased blood pressure as well as effects on QTc were adequately evaluated across the different indacaterol treatment groups.

6.3 Major Safety Results

6.3.1 Deaths

The fatal events included in the safety analysis conducted by the Sponsor were events which occurred after administration of the first dose of study drug up to and including the last dose [CTD 2.7.4 Summary of Clinical Safety Section 2.1.2.1.1]. Deaths occurring more than 30 days after the last dose or ≤ 30 days but not captured in the clinical database i.e. data submitted after database lock were not included in the clinical study database. Narratives for the subjects were reviewed. The deaths of only patients in an indacaterol treatment group are summarized below.

There were a total of 17 deaths of indacaterol treated patients reported, this number does not include 29 deaths from two ongoing trials. The COPD safety population included a total of 7 reported deaths in the indacaterol treatment group, 4 in the formoterol group, 4 in the tiotropium group, 1 in the salmeterol and 14 patients in the placebo group.

There were seven deaths in the indacaterol groups during the double-blind periods in the pivotal trials:

- Patient B2334-0165-00002 (indacaterol 600 mcg q.d.) was 66 year old male who developed gastric ulcer bleeding on Day 164 underwent surgical repair had a severe COPD exacerbation on Day 169 and died on Day 189 25 days after last dose.
- Patient B2334-0214-00004 (indacaterol 300 mcg q.d.) was a 57 year old male with a prior history of respiratory failure 5 months prior to death. The patient was taking concomitant budesonide when he developed a severe COPD exacerbation on Day 47 after a respiratory tract infection. On Day 84 he had a second COPD exacerbation with hyperinflation and 3 days after the last dose he had a cardiac arrest.
- Patient B2335S-0135-00006 (indacaterol 150 mcg q.d.) was a 52 year old male with a history of hypertension who developed cardiac failure on Day 113. He was treated with diclofenac and furosemide. Study medication was discontinued on Day 144 and the next day the patient was found dead at home.
- Patient B2335SE-0043-00046 (indacaterol 300 mcg q.d.) was a 66 year old male with a history of hypertension who on Day 232 developed sudden dyspnea and collapse en route to the hospital with unsuccessful CPR. The principal cause of death was identified as myocardial infarction.
- Patient B2336-0311-00037 (indacaterol 150 mcg q.d.) was a 67 year old male with a history of pedal edema since Day 28. He developed chest pain on Day 171 and was taken to the emergency department where he was declared dead due to sudden cardiac arrest.

- B2349-0403-00008 (indacaterol 150 mcg q.d.) was a 57 year old male with a history of 20 kg weight loss over the span of a few months. He was hospitalized on Day 38 for abdominal pain and was diagnosed with gastric cancer and thrombocytopenia. The patient died on Day 40 due to severe cardiopulmonary failure.
- B2349-0906-00004 (indacaterol 150 mcg q.d.) was a 74 year old male who developed a myocardial infarction on Day 16 and was found dead the following night 2 days after last dose.

Two deaths were reported in the indacaterol more than 30 days from last dose:

- Patient B2334-0376-00003 (indacaterol 600 mcg q.d.) was a 77 year old female who experienced a COPD exacerbation 85 days after the last dose.
- Patient B2334-0400-00027 (indacaterol 600 mcg q.d.) was a 65 year old male who was diagnosed with metastases lung & bone 51 days after the last dose

There were 2 deaths of patients on indacaterol and 1 patient on tiotropium reported after database lock:

- Patient B2205-0083-00005 (indacaterol 400 mcg q.d.) was a 64 year old female found dead at home on Day 40. An autopsy performed indicated that the patient died 29 days after last dose. The cause of death was labeled as pulmonary embolism
- Patient B2305-0031-00002 (indacaterol 300 mcg q.d.) was a 70 year old male with a history of hypertension and stroke who was discontinued due to a diagnosis of lung cancer with metastases to the brain. On Day 68 he was hospitalized with a stroke. On Day 132 (85 days after last dose) he died.

There were 2 deaths in the asthma study B2338 on indacaterol:

- Patient B2338-0549 -00003 (indacaterol 300 mcg q.d.) was a 75 year old female with a history of hypertension who suffered a cardiac arrest on Day 119, the day of her last dose. Cardiopulmonary resuscitation occurred, an ECG was compatible with infarction and life support was withdrawn on Day 129.
- Patient B2338-0099-00002 (indacaterol 300 mcg q.d.) was a 60 year old male with a past medical history of asthma who had a one day hospitalization for an acute asthma exacerbation 165 days into treatment. Four days later he developed an acute asthma exacerbation leading to death *en route* to the hospital.

The COPD tiotropium combination safety population had 7 fatal events reported, 4 for patients receiving indacaterol and tiotropium concurrently and 3 patients on tiotropium alone.

The 4 deaths of patients on the combination indacaterol 150 mcg plus open-label tiotropium HandiHaler, 18 mcg) were:

- Patient B2341-0104-00006 was a 67 year old male with a history of hypertension, CAD, CVA and myocardial infarction who was hospitalized on Day 33 due to a severe COPD exacerbation. The patient received the antibiotic ceftriaxone and 30 minutes later he developed tongue and facial edema, apnea and became pulseless CPR was not successful.
- Patient B2341-0305-00015 was a 58 year old male with a history of diabetes mellitus, hypertension and gastroesophageal reflux. Approximately 28 days after the patient's last study visit (Visit 9 = end of study) he was found dead in the bathroom.
- Patient B2341-0822-00018 was a 62 year old male who was found dead on Day 19, one day after the last dose. The death certificate identified acute myocardial infarction as the cause of death.
- Patient B2351-0509-00014 was a 74 year old female who was found dead on Day 73, one day after last dose. An autopsy identified atherosclerotic cardiovascular disease due to "natural causation (myocardial infarction)" as cause of death.

There were no deaths reported during the trial or within 30 days of last doses in the 2-week dose finding trials, B2356, B2357 and B2223. There was 1 death in the ongoing open label study B1303 and 28 deaths in ongoing study B2348 reported to Novartis as of July 28, 2010. Summaries are included in Table 78 below.

Table 78 Summaries of deaths reported in ongoing studies with indacaterol monotherapy arm

Study-center-patient	Age/ sex/ race	Treat-ment	Principal cause of death Description of event & medical history	Study day/ day after LD	Caus-ality †
B1303-0418-00002	77/M/As	Ind 300 µg	Sudden death	211/1	Susp
B2348-0001-00003	79/M/Ca	Blinded	Myocardial infarction	73	NS
B2348-0001-00005	64/M/Ca	Blinded	Completed suicide	184	NS
B2348-0001-00014	62/M/Ca	Blinded	Pneumonia	347	NS
B2348-0001-00032	57/M/Ca	Blinded	COPD	115	NS
B2348-0003-00005	67/M/Ca	Blinded	Pancreatic carcinoma metastatic	167/89	NS
B2348-0023-00031	73/M/Ot	Blinded	Sudden death	8	NS
B2348-0025-00006	74/F/Ot	Blinded	Death, dyspnea	48	NS
B2348-0087-00010	61/M/Ca	Blinded	Cardiac arrest	86	NS
B2348-0101-00001	78/M/Ca	Blinded	Multi-organ failure	99	NS
B2348-0150-00006	63/M/Ca	Blinded	Lung carcinoma cell type unspecified stage IV	6	NS
B2348-0176-00007	66/M/Ca	Blinded	Cardiac failure	Pre-dose	NS
B2348-0183-00006	55/M/Ot	Blinded	COPD	Unk	NS
B2348-0186-00008	62/M/As	Blinded	COPD	68	Susp
B2348-0187-00009	43/M/Ot	Blinded	Cardiopulmonary failure, COPD exacerbation, cardiomegaly, fibrosis, anemia	218	NS
B2348-0189-00004	73/M/Ot	Blinded	COPD exacerbation, lower RTI, fibrobronchiectasis lung, respiratory failure	NA	Susp
B2348-0189-00017	M/Unk/Ot	Blinded	Death	99	NS
B2348-0190-00035	60/M/Ot	Blinded	Death	141	NS
B2348-0190-00054	51/M/Ot	Blinded	Death	64	NS
B2348-0269-00002	69/F/Ca	Blinded	Pulmonary embolism	241	NS
B2348-0292-00021	63/M/Ca	Blinded	Cardiac arrest	144	NS
B2348-0294-00014	75/M/Ca	Blinded	COPD	530	NS
B2348-0315-00005	50/F/Ca	Blinded	Meningitis pneumococcal	40	NS
B2348-0424-00016	70/M/Ca	Blinded	Acute respiratory failure, COPD exacerbation, dyspnea, pneumonia	15	NS
B2348-0440-00015	Unk/M/Ca	Blinded	Aortic stenosis	346/7	NS
B2348-0455-00005	85/M/Ca	Blinded	Cardiac failure	80	NS
B2348-0635-00017	57/M/Ca	Blinded	Cardiac failure	150	NS
B2348-0642-00003	56/M/Ca	Blinded	N. recurrens paresis, disease progression	249	NS
B2348-0818-00008	72/M/Unk	NA	Sudden death	Screening	NS

Source: Table 2-35 CTD 2.7.4 Summary of Clinical Safety

Reviewer comment:
Protocol B2348 is a 3000 patient one year trial enrolling patients with severe COPD and a history of exacerbation. Since this trial includes sicker patients and has a longer duration than most of the trials included in the safety database, it is not unexpected that there would be a greater number of deaths in the trial. Since the data are still blinded, the treatment distribution of these deaths is unknown.

6.3.2 Nonfatal Serious Adverse Events

The SAEs reported in the safety analysis conducted by the Sponsor included events that occurred after administration of the first dose of study drug through to 30 days past the last dose [CTD 2.7.4 Summary of Clinical Safety Section 2.1.2.1.1]. Serious adverse events occurring more than 30 days after the last

dose or ≤ 30 days but not captured in the clinical database i.e. data submitted after database lock were not included. Narratives for the subjects were reviewed. The SAEs were categorized by the Sponsor into the same 3-, 6- and 12- month safety groups (not mutually exclusive) and summarized by SOC and preferred term below.

COPD- 3 month safety population

The frequency of SAEs in the COPD 3-month safety population was similar across the active treatment groups and placebo. The lowest rate was observed in the salmeterol group with 3% of patients reporting SAEs, the largest was 4.4% for placebo. Amongst the indacaterol doses, the rates of SAEs did not change with increasing doses: 3.3%, 3.8%, 3.3% and 3.1% for 75 mcg, 150 mcg, 300 mcg and 600 mcg. Across the different treatment regimens, the MedDRa System Organ Classes (SOCs) with the greatest rates include respiratory thoracic and mediastinal disorders and infections and infestations. The most commonly reported SAEs in the COPD 3-month group were COPD (which included disease progression as well as exacerbations) and pneumonias. Refer to Table 79 for details.

Table 79 SAEs affecting ≥ 2 patients in any treatment group by preferred term in COPD 3- month safety population

	Indacaterol treatment groups				Control treatment groups			
	75 µg N=449 n (%)	150 µg N=2611 n (%)	300 µg N=1157 n (%)	600 µg N=547 n (%)	For N=556 n (%)	Tio N=1214 n (%)	Sme N=895 n (%)	Pbo N=2012 n (%)
Patients with SAE(s)	15 (3.3)	98 (3.8)	38 (3.3)	17 (3.1)	21 (3.8)	51 (4.2)	27 (3.0)	89 (4.4)
Preferred term								
COPD †	4 (0.89)	30 (1.15)	8 (0.69)	4 (0.73)	9 (1.62)	12 (0.99)	11 (1.23)	32 (1.59)
Pneumonia	2 (0.45)	7 (0.27)	4 (0.35)	0	2 (0.36)	3 (0.25)	0	4 (0.20)
Angina pectoris	0	4 (0.15)	1 (0.09)	0	0	0	0	2 (0.10)
Acute myocardial infarction	0	3 (0.11)	1 (0.09)	0	0	0	1 (0.11)	0
Cholelithiasis	0	3 (0.11)	0	0	1 (0.18)	0	0	1 (0.05)
Coronary artery disease	0	3 (0.11)	1 (0.09)	1 (0.18)	0	1 (0.08)	1 (0.11)	0
Fall	0	3 (0.11)	0	0	0	1 (0.08)	0	1 (0.05)
Lower RTI	0	3 (0.11)	1 (0.09)	0	1 (0.18)	0	2 (0.22)	4 (0.20)
Myocardial infarction	0	3 (0.11)	1 (0.09)	1 (0.18)	0	0	1 (0.11)	4 (0.20)
Atrial fibrillation	0	2 (0.08)	0	0	0	3 (0.25)	1 (0.11)	1 (0.05)
Cellulitis	0	2 (0.08)	0	0	0	0	0	2 (0.10)
Cerebral infarction	0	2 (0.08)	0	0	0	0	0	0
Cerebrovascular accident	1 (0.22)	2 (0.08)	0	0	0	2 (0.16)	0	0
H1N1 influenza	0	2 (0.08)	0	0	0	0	0	0
Hemiparesis	0	2 (0.08)	0	0	0	0	1 (0.11)	0
Lung adenocarcinoma	0	2 (0.08)	0	0	0	1 (0.08)	0	0
Pancreatitis acute	0	2 (0.08)	0	0	0	0	0	0
Syncope	0	2 (0.08)	3 (0.26)	0	0	2 (0.16)	1 (0.11)	0
Upper RTI bacterial	1 (0.22)	2 (0.08)	0	0	1 (0.18)	0	2 (0.22)	4 (0.20)
Benign prostatic hyperplasia	0	1 (0.04)	0	1 (0.18)	0	0	0	2 (0.10)
Dyspnea	0	1 (0.04)	2 (0.17)	0	0	3 (0.25)	0	3 (0.15)
Foot fracture	0	1 (0.04)	1 (0.09)	2 (0.37)	0	0	0	0
Non-cardiac chest pain	2 (0.45)	1 (0.04)	0	1 (0.18)	0	1 (0.08)	0	1 (0.05)
Colonic polyp	0	0	0	0	0	0	0	2 (0.10)
Coronary artery occlusion	0	0	0	0	0	2 (0.16)	0	0
Diverticulitis	0	0	0	0	0	0	0	3 (0.15)
Inguinal hernia	0	0	0	0	0	0	0	2 (0.10)
Lobar pneumonia	0	0	0	0	0	2 (0.16)	0	0
Presyncope	0	0	2 (0.17)	0	0	0	0	0
Respiratory failure	0	0	1 (0.09)	0	1 (0.18)	1 (0.08)	2 (0.22)	1 (0.05)
Rib fracture	0	0	2 (0.17)	0	1 (0.18)	2 (0.16)	0	0
Road traffic accident	0	0	1 (0.09)	0	0	2 (0.16)	0	0
Volvulus	0	0	0	2 (0.37)	0	0	0	0

Source: Table 2.37, CTD2.7.4 Section 2.1.3.1 Summary of Clinical Safety

COPD- 6 month safety population

This dataset was derived from trials: B2333, B2335S, B2336 and up to 6 months of data from B2334 and B2335SE. The numbers of patients included in the evaluation were smallest for the indacaterol 75 mcg group (n= 127) and largest in the placebo group (n= 1,371). The SOCs with the largest percentage of SAEs include: respiratory, thoracic and mediastinal disorders; infections and infestations; cardiac disorders, nervous system disorders and gastrointestinal disorders. Many of the SAE rates observed in the active treatment groups were similar to placebo. See Table 80 for summary.

Table 80 SAEs (n (%) of patients) by primary system organ class in COPD 6- month safety population

	Indacaterol treatment groups				Control treatment groups			
	75 µg N=127 n (%)	150 µg N=933 n (%)	300 µg N=1041 n (%)	600 µg N=547 n (%)	For N=556 n (%)	Tio N=415 n (%)	Sme N=333 n (%)	Pbo N=1371 n (%)
Patients with SAE(s)	9 (7.1)	76 (8.2)	75 (7.2)	34 (6.2)	45 (8.1)	34 (8.2)	19 (5.7)	109 (8.0)
Primary system organ class								
Respir., thoracic and mediastinal disorders†	4 (3.2)	25 (2.7)	26 (2.5)	7 (1.3)	18 (3.2)	8 (1.9)	6 (1.8)	42 (3.1)
Infections and infestations	3 (2.4)	17 (1.8)	15 (1.4)	5 (0.9)	13 (2.3)	9 (2.2)	9 (2.7)	27 (2.0)
Cardiac disorders	2 (1.6)	14 (1.5)	9 (0.9)	7 (1.3)	4 (0.7)	8 (1.9)	5 (1.5)	14 (1.0)
Nervous system disorders	1 (0.8)	6 (0.6)	7 (0.7)	0	3 (0.5)	3 (0.7)	0	9 (0.7)
Gastrointestinal disorders	1 (0.8)	5 (0.5)	3 (0.3)	7 (1.3)	2 (0.4)	3 (0.7)	2 (0.6)	9 (0.7)

Adapted from Table 2-40 CTD2.7.4 Section 2.1.3.1 Summary of Clinical Safety

The frequency of SAEs in the COPD 6-month safety population, ranged from 5.7% in the salmeterol group to 8.2% in the indacaterol 150 mcg and tiotropium treatment groups as detailed in Table 81. A dose response relationship is not apparent with the SAEs reported. However, these safety analyses did not include the lower doses of indacaterol. The most frequent preferred terms reported in the COPD 6-month safety population were COPD, pneumonia, angina, atrial fibrillation, upper respiratory tract infection and acute myocardial infarction. The preferred term, COPD had similar rates compared to placebo however pneumonia and upper respiratory tract infection had higher rates in some of the active treatment groups (i.e., 75 mcg) than placebo. See Table 81 for further details. There were 2 acute myocardial infarctions in the 150 mcg group, 1 in the 300 mcg indacaterol group, 1 in salmeterol and none reported in the placebo group.

Table 81 SAEs affecting ≥ 2 patients in any treatment group by preferred term in COPD 6- month safety population

	Indacaterol treatment groups				Control treatment groups			
	75 µg N=127 n (%)	150 µg N=933 n (%)	300 µg N=1041 n (%)	600 µg N=547 n (%)	For N=556 n (%)	Tio N=415 n (%)	Sme N=333 n (%)	Pbo N=1371 n (%)
Patients with SAE(s)	9 (7.1)	76 (8.2)	75 (7.2)	34 (6.2)	45 (8.1)	34 (8.2)	19 (5.7)	109 (8.0)
Preferred term								
COPD †	3 (2.4)	25 (2.7)	24 (2.3)	7 (1.3)	17 (3.1)	7 (1.7)	4 (1.2)	39 (2.8)
Lower RTI	0	4 (0.4)	1 (0.1)	0	1 (0.2)	0	2 (0.6)	5 (0.4)
Angina pectoris	1 (0.8)	3 (0.3)	1 (0.1)	1 (0.2)	0	0	1 (0.3)	2 (0.2)
Atrial fibrillation	1 (0.8)	3 (0.3)	0	0	0	3 (0.7)	1 (0.3)	3 (0.2)
Pneumonia	1 (0.8)	3 (0.3)	4 (0.4)	1 (0.2)	3 (0.5)	4 (1.0)	3 (0.9)	4 (0.3)
Acute myocardial infarction	0	2 (0.2)	1 (0.1)	0	0	0	1 (0.3)	0
Cholelithiasis	0	2 (0.2)	1 (0.1)	0	1 (0.2)	0	0	1 (0.1)
Sinusitis	0	2 (0.2)	0	0	0	0	0	0
Upper RTI bacterial	1 (0.8)	2 (0.2)	4 (0.4)	0	1 (0.2)	0	2 (0.6)	5 (0.4)
Benign prostatic hyperplasia	0	1 (0.1)	0	1 (0.2)	0	0	0	2 (0.2)

	Indacaterol treatment groups				Control treatment groups			
	75 µg N=127 n (%)	150 µg N=933 n (%)	300 µg N=1041 n (%)	600 µg N=547 n (%)	For N=556 n (%)	Tio N=415 n (%)	Sme N=333 n (%)	Pbo N=1371 n (%)
Coronary artery disease	0	1 (0.1)	2 (0.2)	2 (0.4)	0	0	2 (0.6)	1 (0.1)
Myocardial infarction	0	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.2)	0	1 (0.3)	2 (0.2)
Sudden death	0	1 (0.1)	1 (0.1)	0	0	0	0	2 (0.2)
Cellulitis	0	1 (0.1)	0	0	0	0	0	2 (0.2)
Upper RTI	0	1 (0.1)	0	0	3 (0.5)	0	0	1 (0.1)
Syncope	0	1 (0.1)	3 (0.3)	0	0	2 (0.5)	0	0
Hypertension	0	1 (0.1)	0	0	0	0	1 (0.3)	2 (0.2)
Acute coronary syndrome	0	0	0	0	0	2 (0.5)	0	0
Angina unstable	1 (0.8)	0	2 (0.2)	1 (0.2)	0	0	0	1 (0.1)
Coronary artery occlusion	0	0	0	0	0	2 (0.5)	0	0
Cataract	1 (0.8)	0	2 (0.2)	0	1 (0.2)	0	0	1 (0.1)
Inguinal hernia	0	0	0	1 (0.2)	0	0	0	4 (0.3)
Bronchitis	1 (0.8)	0	2 (0.2)	0	0	1 (0.2)	0	4 (0.3)
Diverticulitis	0	0	0	0	0	0	0	3 (0.2)
Foot fracture	0	0	1 (0.1)	2 (0.4)	0	0	0	0
Rib fracture	0	0	3 (0.3)	0	1 (0.2)	1 (0.2)	0	0
Road traffic accident	0	0	2 (0.2)	0	0	2 (0.5)	0	0
Lung neoplasm malignant	0	0	1 (0.1)	2 (0.4)	1 (0.2)	0	0	0
Convulsion	0	0	0	0	2 (0.4)	0	0	0
Dyspnea	1 (0.8)	0	3 (0.3)	0	0	0	0	5 (0.4)
Respiratory failure	0	0	2 (0.2)	0	1 (0.2)	1 (0.2)	0	1 (0.1)
Hypertensive crisis	0	0	0	0	2 (0.4)	0	0	2 (0.2)
Volvulus	0	0	0	2 (0.4)	0	0	0	0
Loss of consciousness	0	0	0	0	0	1 (0.2)	0	2 (0.2)
Presyncope	0	0	2 (0.2)	0	0	0	0	0
Transient ischemic attack	1 (0.8)	0	0	0	0	0	0	2 (0.2)

Source: Table 2-41 CTD 2.7.4 Summary of Clinical Safety

Reviewer Comment:
Interpretation of the 75 mcg indacaterol 6 month safety data is difficult with the small number of patients included.

COPD- 12 month safety population
Two trials were included in the COPD 12- month safety dataset, B2334 and B2335SE. There were no data for the lower proposed 75 mcg dose of indacaterol included in this analysis. The incidence of SAEs was highest in the formoterol group, at 15.9%, and lowest in the indacaterol 150 mcg group, 10.4%. See Table 82. Consistent with the other safety populations, the SOCs with the highest SAE rates included infections and infestations and respiratory, thoracic and mediastinal disorders. The placebo group had comparable SAE rates (4.7%) for respiratory, thoracic and mediastinal disorders to indacaterol 300 mcg and 600 mcg doses (5% and 3.1% respectively) but smaller than formoterol (7.8%). Other SOCs with high incidence rates included: injury, poisoning and procedural complications; gastrointestinal disorders and vascular disorders, with indacaterol 150 mcg having higher rates except for gastrointestinal disorders where the rates were comparable with placebo.

Table 82 SAEs (n (%) of patients) by primary system organ class in COPD 12- month safety population

	Ind 150 µg N=144 n (%)	Ind 300 µg N=583 n (%)	Ind 600 µg N=425 n (%)	For N=434 n (%)	Pbo N=556 n (%)
Patients with SAE(s)	15 (10.4)	81 (13.9)	51 (12.0)	69 (15.9)	61 (11.0)
Primary system organ class:					
Infections and infestations	4 (2.8)	16 (2.7)	8 (1.9)	23 (5.3)	14 (2.5)
Respir., thoracic and mediastinal disorders†	4 (2.8)	29 (5.0)	13 (3.1)	34 (7.8)	26 (4.7)
Injury, poisoning and procedural complications	3 (2.1)	7 (1.2)	6 (1.4)	5 (1.2)	4 (0.7)
Gastrointestinal disorders	2 (1.4)	3 (0.5)	7 (1.7)	2 (0.5)	8 (1.4)
Vascular disorders	2 (1.4)	3 (0.5)	4 (0.9)	3 (0.7)	2 (0.4)
Cardiac disorders	1 (0.7)	15 (2.6)	8 (1.9)	6 (1.4)	10 (1.8)
Metabolism and nutrition disorders	1 (0.7)	0	1 (0.2)	1 (0.2)	0
Musculoskeletal and connective tissue disorders	1 (0.7)	3 (0.5)	1 (0.2)	2 (0.5)	4 (0.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.7)	9 (1.5)	7 (1.7)	7 (1.6)	7 (1.3)
Nervous system disorders	1 (0.7)	5 (0.9)	3 (0.7)	3 (0.7)	4 (0.7)
Blood and lymphatic system disorders	0	0	1 (0.2)	0	0
Congenital, familial and genetic disorders	0	0	0	0	1 (0.2)
Ear and labyrinth disorders	0	0	0	0	1 (0.2)
Eye disorders	0	3 (0.5)	0	5 (1.2)	1 (0.2)

Source: Adapted from Table 2-44 CTD 2.7.4 Summary of Clinical Safety

Consistent with the other 2 safety populations, the most frequent SAE observed for the COPD 12- month group was COPD with the rates highest for the placebo group (4.1%) but comparable to indacaterol 300 mcg (4.0%). Atrial fibrillation, syncope and upper respiratory tract infection all had rates ≤ 1%, but higher than placebo, refer to Table 83. Note that in the COPD 12-month safety population, there was one additional patient in the indacaterol 300 mcg treatment group with a non-fatal SAE of atrial fibrillation which occurred on Day 197.

Table 83 SAEs affecting ≥ 2 patients in any treatment group by preferred term in COPD 12- month safety population

	Ind 150 µg N=144 n (%)	Ind 300 µg N=583 n (%)	Ind 600 µg N=425 n (%)	For N=434 n (%)	Pbo N=556 n (%)
Patients with SAE(s)	15 (10.4)	81 (13.9)	51 (12.0)	69 (15.9)	61 (11.0)
Preferred term:					
COPD†	4 (2.8)	23 (4.0)	12 (2.8)	32 (7.4)	23 (4.1)
Atrial fibrillation	1 (0.7)	3 (0.5)	0	1 (0.2)	1 (0.2)
Syncope	1 (0.7)	2 (0.3)	0	0	0
Upper RTI	1 (0.7)	0	0	3 (0.7)	0
Angina pectoris	0	2 (0.3)	1 (0.2)	0	1 (0.2)
Aortic aneurysm	0	2 (0.3)	0	0	1 (0.2)
Benign prostatic hyperplasia	0	0	1 (0.2)	0	2 (0.4)
Cardiac arrest	0	0	0	0	2 (0.4)
Cardiac failure congestive	0	2 (0.3)	0	0	1 (0.2)

Source: Adapted from Table 2-45 CTD 2.7.4 Summary of Clinical Safety

Other population analyses
Below is a brief evaluation of SAEs for the COPD safety population adjusted for exposure. The rates described are episodes per patient years. The preferred terms with the highest rate for this safety population were COPD, pneumonia and angina with comparable rates between the indacaterol 300 mcg dose and placebo. However, angina was highest for all indacaterol doses: 0.01, 0.007, 0.003 and 0.003 episodes per patient year for 75 mcg, 150 mcg, 300 mcg and 600 mcg vs. placebo with 0.002 episodes per patient year. Acute myocardial infarction, atrial fibrillation, CVA, TIA and dyspnea are events that had higher rates observed during the first cycle also had higher rates over placebo in this analysis.

Reviewer comment:
Although there is a numerical increase in acute myocardial infarction, atrial fibrillation, CVA, TIA, and dyspnea, the difference is small and difficult to interpret. A dose effect is not observed.

Table 84 SAEs (fatal and nonfatal) occurring at > 0.005 episodes per patient year in any treatment group by preferred term adjusted for exposure (episodes per patient year) in COPD safety population

	Indacaterol treatment groups				Control treatment groups			
	75 µg N=449	150 µg N=2611	300 µg N=1157	600 µg N=547	For N=556	Tio N=1214	Sme N=895	Pbo N=2012
Exposure in patient years	105.06	859.72	736.97	394.49	396.21	357.97	274.93	923.60
SAE episodes: n / patient year	0.247	0.235	0.244	0.205	0.318	0.332	0.182	0.270
Preferred term								
COPD †	0.048	0.048	0.061	0.033	0.096	0.039	0.040	0.065
Pneumonia	0.019	0.008	0.011	0.005	0.015	0.017	0.011	0.010
Angina pectoris	0.010	0.007	0.003	0.003	0	0	0.004	0.002
Lower RTI	0	0.006	0.004	0.005	0.013	0	0.007	0.010
Acute myocardial infarction	0	0.005	0.001	0	0	0	0.004	0.001
Atrial fibrillation	0.010	0.005	0.005	0	0.003	0.011	0.004	0.005
Upper RTI bacterial	0.010	0.005	0.008	0	0.013	0	0.007	0.010
Coronary artery disease	0	0.003	0.003	0.008	0	0.003	0.011	0.001
Myocardial infarction	0	0.003	0.003	0.005	0.005	0	0.004	0.005
Cerebrovascular accident	0.010	0.002	0	0.003	0.003	0.006	0	0
Peripheral arterial occlusive disease	0	0.002	0	0	0	0.006	0	0
Transient ischemic attack	0.010	0.002	0	0	0	0	0	0.002
Acute coronary syndrome	0	0.001	0	0	0	0.006	0.004	0
Dyspnea	0.010	0.001	0.007	0	0.003	0.008	0	0.005
Non-cardiac chest pain	0.019	0.001	0	0.003	0	0.003	0	0.001
Small intestinal obstruction	0.010	0.001	0	0	0	0	0	0
Viral upper RTI	0	0.001	0.001	0	0.005	0.003	0	0

Source: Adapted from Table 2-48 CTD 2.7.4 Summary of Clinical Safety

Despite the lower numbers, different designs (controlled and uncontrolled) and disparate treatment populations (i.e., asthma, COPD, healthy subjects), the most frequent SAE reported in the 'short term safety population' was COPD.

The SAEs reported in the asthma safety trial B2338 demonstrated the most frequent was asthma (2 in 300 mcg and 3 in 600 mcg indacaterol and 0 in placebo). There was 1 atrial fibrillation, 1 splenic cyst, 1 cholangitis in the 600 mcg indacaterol group and none in placebo. There was 1 neck abscess and 1 upper respiratory tract infection (bacterial) and none in placebo.

The SAEs in the COPD tiotropium combination safety population were comparable across treatment groups however, consistent with other populations, COPD was the highest reported and similar across the two groups. Pneumonia, angina and upper and lower respiratory tract infections were more frequent in the indacaterol 150 mcg plus tiotropium, 18 mcg group vs. tiotropium 18 mcg group.

Subgroup analyses
For age, the 300 mcg indacaterol group compared to all other indacaterol treatment groups had the most varied percentages of patients with SAEs. For the 3- month COPD: < 65 (2.26%) and ≥ 65-<75 (3.92%) and ≥ 75 (5.3%). This was consistent across the 6- month and 12 month COPD safety groups. There were no apparent trends for gender and no comments of generalizability can be made regarding race due to the low numbers of representation of blacks, asians and other.

The severe population also had the largest numbers of respiratory, thoracic and mediastinal SOC rates across most treatment groups and across all safety populations. Across all safety populations ex-smokers in the placebo and formoterol groups had more frequent respiratory disorder SAEs versus current smokers. SAEs related to infections and infestations were more frequent in patients with severe or worse COPD across most treatment groups. However, many of these subgroup analyses have small numbers making any general statements difficult.

6.3.3 Dropouts and/or Discontinuations

In general, adverse events rates leading to discontinuation were comparable across treatment groups. As seen in other analyses, the most common AEs leading to discontinuation by SOC was respiratory, thoracic and mediastinal. The highest rates were seen in those on placebo (1.6%) vs. the indacaterol doses (ranging from 0.4-1.1%) in the 3 month safety group; placebo (3.4%) vs. indacaterol doses (ranging from 1.57-2.11) in the 6 month group and placebo (4.9%) vs. indacaterol doses (0.7-1.9%) in the 12 month safety group. The two most common AEs leading to discontinuation in preferred terms were COPD and dyspnea across the 3 safety populations. Others included cough, upper and lower respiratory tract infections, ventricular tachycardias and atrial fibrillation.

6.3.4 Submission Specific Primary Safety Concerns

Cardio- and cerebrovascular events
The safety evaluation during the first cycle highlighted a higher frequency of combined cardio- and cerebrovascular (CCV) events as well as two probable asthma deaths in the indacaterol 300 mcg treatment group (B2338). To further evaluate any potential respiratory related events resulting in intubation, hospitalization or death, the metaanalysis conducted by the Sponsor is intended to assess this safety concern. At the time of this review the results of the metaanalysis are pending.

Regarding the CCV events, the Sponsor utilized two approaches to explore the pooled Phase III safety databases for patients with events meeting the search criteria for: 1). Standard MedDRA queries (SMQs) for cardio- or cerebrovascular events, and 2). Analysis of events using [14]Antiplatelet Trialist' Collaboration (APTC) criteria. In a prospective manner, the Sponsor developed a list of pre-defined search criteria for preferred terms related to CCV disorder based on published SMQ version 11.0 "narrow", for the disorders: cardiac failure; ischemic heart disease; cerebrovascular disorders and "broad" for cardiac arrhythmias. Of note, sudden death or cardiac death was not included in the analysis. A summary of the number and percentage of patients with COPD in the 3-, 6- and 12- month safety populations with AEs or SAEs meeting the criteria is presented below.

[14] Collaborative overview of randomized trials of antiplatelet therapy, I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ 1994; 308:81-106.

CCV AEs in 3- month COPD safety population

The percentage of patients with ≥ 1 CCV AE was similar across the different treatment regimens with the highest rate observed in the indacaterol 300 mcg group with 3.11%. Placebo had a rate of 2.58%.See Table 85 below for details.

Of those events reported more than once, ventricular tachycardias, coronary artery disease, atrial flutter and cardiac failure congestive were higher in the indacaterol groups than placebo.

Table 85 Cardio- and cerebrovascular AEs by preferred term in COPD 3- month safety population

	Indacaterol treatment groups				Control treatment groups			
	75µg N=449 n (%)	150µg N=2611 n (%)	300µg N=1157 n (%)	600µg N=547 n (%)	For N=556 n (%)	Tio N=1214 n (%)	Sme N=895 n (%)	Pbo N=2012 n (%)
Patients with ≥1 CCV AE	9 (2.00)	62 (2.37)	36 (3.11)	11 (2.01)	11 (1.98)	27 (2.22)	21 (2.35)	52 (2.58)
CCV AEs:								
Electrocardiogram QT prolonged	0	8 (0.31)	4 (0.35)	5 (0.91)	3 (0.54)	4 (0.33)	3 (0.34)	11 (0.55)
Angina pectoris	0	7 (0.27)	6 (0.52)	0	1 (0.18)	2 (0.16)	3 (0.34)	4 (0.20)
Atrial fibrillation	0	6 (0.23)	5 (0.43)	2 (0.37)	0	5 (0.41)	4 (0.45)	5 (0.25)
Coronary artery disease	0	6 (0.23)	1 (0.09)	1 (0.18)	0	1 (0.08)	1 (0.11)	0
Ventricular extrasystoles	1 (0.22)	6 (0.23)	6 (0.52)	1 (0.18)	2 (0.36)	2 (0.16)	1 (0.11)	7 (0.35)
Ventricular tachycardia	2 (0.45)	5 (0.19)	0	0	0	2 (0.16)	0	0
Acute myocardial infarction	0	3 (0.11)	1 (0.09)	0	0	0	1 (0.11)	0
Atrioventricular block first degree	1 (0.22)	3 (0.11)	4 (0.35)	0	0	1 (0.08)	0	3 (0.15)
Cardiac failure congestive	0	3 (0.11)	1 (0.09)	0	0	2 (0.16)	0	0
Myocardial infarction	0	3 (0.11)	1 (0.09)	1 (0.18)	0	0	2 (0.22)	5 (0.25)
Atrial flutter	2 (0.45)	2 (0.08)	1 (0.09)	1 (0.18)	1 (0.18)	0	0	0
Bundle branch block left	0	2 (0.08)	0	0	0	0	1 (0.11)	0
Cerebral infaction	0	2 (0.08)	0	0	0	0	0	0
Cerebrovascular accident	1 (0.22)	2 (0.08)	0	0	0	2 (0.16)	0	0
Myocardial ischaemia	0	2 (0.08)	1 (0.09)	0	0	0	0	0
Acute coronary syndrome	0	1 (0.04)	0	0	0	1 (0.08)	1 (0.11)	0
Arrhythmia	0	1 (0.04)	0	0	0	2 (0.16)	1 (0.11)	1 (0.05)
Arrhythmia supraventricular	0	1 (0.04)	0	0	0	0	0	0
Bundle branch block right	0	1 (0.04)	1 (0.09)	0	0	0	0	2 (0.10)
Cardiopulmonary failure	0	1 (0.04)	0	0	0	0	0	0
Carotid artery stenosis	0	1 (0.04)	0	0	0	1 (0.08)	0	2 (0.10)
Cerebral ischaemia	0	1 (0.04)	0	0	0	0	0	1 (0.05)
Cerebrovascular insufficiency	0	1 (0.04)	0	0	0	0	0	0
Coronary artery occlusion	0	1 (0.04)	0	0	0	3 (0.25)	0	0
Coronary artery thrombosis	0	1 (0.04)	0	0	0	0	0	0

	Indacaterol treatment groups				Control treatment groups			
	75µg N=449 n (%)	150µg N=2611 n (%)	300µg N=1157 n (%)	600µg N=547 n (%)	For N=556 n (%)	Tio N=1214 n (%)	Sme N=895 n (%)	Pbo N=2012 n (%)
Lacunar infarction	0	1 (0.04)	0	0	0	0	0	0
Sick sinus syndrome	0	1 (0.04)	0	0	0	0	0	0
Tachyarrhythmia	0	1 (0.04)	0	0	0	0	0	0
Transient ischaemic attack	1 (0.22)	1 (0.04)	0	0	0	0	1 (0.11)	2 (0.10)
Troponin increased	0	1 (0.04)	0	0	0	0	0	0
Angina unstable	0	0	1 (0.09)	0	0	0	0	1 (0.05)
Atrioventricular block second degree	0	0	2 (0.17)	0	0	0	0	0
Cardiac failure	0	0	0	1 (0.18)	0	1 (0.08)	1 (0.11)	1 (0.05)
Carotid artery occlusion	0	0	1 (0.09)	0	0	0	0	0
Cerebellar infarction	0	0	0	0	0	0	0	1 (0.05)
Cerebral haematoma	0	0	0	0	0	1 (0.08)	0	0
Cerebral haemorrhage	0	0	1 (0.09)	0	0	0	0	0
Cor pulmonale	0	0	0	0	1 (0.18)	0	0	1 (0.05)
Cor pulmonale chronic	0	0	0	0	1 (0.18)	0	1 (0.11)	0
Coronary artery bypass	0	0	0	0	0	1 (0.08)	0	0
ECG PR prolongation	0	0	0	0	0	0	0	1 (0.05)
ECG repolarisation abnormality	0	0	0	0	0	1 (0.08)	0	0
Extrasystoles	0	0	0	0	1 (0.18)	0	0	2 (0.10)
Ischaemic cardiomyopathy	0	0	0	0	0	1 (0.08)	0	0
Ischaemic stroke	0	0	0	0	0	0	1 (0.11)	1 (0.05)
Left ventricular failure	0	0	0	0	0	0	1 (0.11)	0
Sinus bradycardia	0	0	3 (0.26)	1 (0.18)	1 (0.18)	0	0	1 (0.05)
Sinus tachycardia	0	0	0	0	0	0	0	1 (0.05)
Supraventricular extrasystoles	2 (0.45)	0	1 (0.09)	0	1 (0.18)	1 (0.08)	1 (0.11)	1 (0.05)
Supraventricular tachycardia	0	0	0	0	0	1 (0.08)	0	0
Vertebrobasilar insufficiency	0	0	1 (0.09)	0	0	0	0	1 (0.05)

Source: Table 2-81 CTD 2.7.4 Summary of Clinical Safety

There were 5 ventricular tachycardias (VT) in the 150 mcg dose and 2 in the 75 mcg indacaterol dose and none reported in the placebo group. The events were captured on Holter monitoring as nonsustained VT. For the 5 in the 150 mcg group, 3 were 3-10 beats and 2 were >10 beats. One event was reported as a SAE.

CCV SAEs in the 3- month COPD population ranged between 0.18% in formoterol group to 0.92% in indacaterol 150 mcg group. Acute myocardial infarction, coronary artery disease, cerebral infarction and cerebrovascular accident all occurred at higher rates in the indacaterol and specifically more in the 150 mcg dose than placebo, and all these events were numerically greater than one for the indacaterol groups. Refer to Table 86 for a summary.

Table 86 Cardio- and cerebrovascular SAEs (n(%) of patients) by preferred term in COPD 3-month safety population

	Indacaterol treatment groups				Control treatment groups			
	75 µg N=449 n (%)	150 µg N=2611 n (%)	300 µg N=1157 n (%)	600 µg N=547 n (%)	For N=556 n (%)	Tio N=1214 n (%)	Sme N=895 n (%)	Pbo N=2012 n (%)
Patients with ≥1 CCV SAE	2 (0.45)	24 (0.92)	8 (0.69)	3 (0.55)	1 (0.18)	11 (0.91)	6 (0.67)	13 (0.65)
CCV SAEs:								
Angina pectoris	0	4 (0.15)	1 (0.09)	0	0	0	0	2 (0.10)
Acute myocardial infarction	0	3 (0.11)	1 (0.09)	0	0	0	1 (0.11)	0
Coronary artery disease	0	3 (0.11)	1 (0.09)	1 (0.18)	0	1 (0.08)	1 (0.11)	0
Myocardial infarction	0	3 (0.11)	1 (0.09)	1 (0.18)	0	0	1 (0.11)	4 (0.20)
Atrial fibrillation	0	2 (0.08)	0	0	0	3 (0.25)	1 (0.11)	1 (0.05)
Cerebral infarction	0	2 (0.08)	0	0	0	0	0	0
Cerebrovascular accident	1 (0.22)	2 (0.08)	0	0	0	2 (0.16)	0	0
Acute coronary syndrome	0	1 (0.04)	0	0	0	1 (0.08)	1 (0.11)	0
Atrial flutter	0	1 (0.04)	0	1 (0.18)	0	0	0	0
Cardiac failure congestive	0	1 (0.04)	0	0	0	1 (0.08)	0	0
Cardiopulmonary failure	0	1 (0.04)	0	0	0	0	0	0
Cerebrovascular insufficiency	0	1 (0.04)	0	0	0	0	0	0
Lacunar infarction	0	1 (0.04)	0	0	0	0	0	0
Myocardial ischaemia	0	1 (0.04)	1 (0.09)	0	0	0	0	0
Sick sinus syndrome	0	1 (0.04)	0	0	0	0	0	0
Transient ischaemic attack	1 (0.22)	1 (0.04)	0	0	0	0	0	1 (0.05)
Troponin increased	0	1 (0.04)	0	0	0	0	0	0
Ventricular tachycardia	0	1 (0.04)	0	0	0	0	0	0
Angina unstable	0	0	1 (0.09)	0	0	0	0	1 (0.05)
Arrhythmia	0	0	0	0	0	2 (0.16)	0	0
Bundle branch block left	0	0	0	0	0	0	1 (0.11)	0
Cardiac failure	0	0	0	1 (0.18)	0	0	0	0
Carotid artery occlusion	0	0	1 (0.09)	0	0	0	0	0
Cerebellar infarction	0	0	0	0	0	0	0	1 (0.05)
Cerebral haematoma	0	0	0	0	0	1 (0.08)	0	0
Cerebral haemorrhage	0	0	1 (0.09)	0	0	0	0	0
Cor pulmonale	0	0	0	0	0	0	0	1 (0.05)
Coronary artery occlusion	0	0	0	0	0	2 (0.16)	0	0
Electrocardiogram QT prolonged	0	0	0	0	1 (0.18)	0	0	0
Ischaemic cardiomyopathy	0	0	0	0	0	1 (0.08)	0	0
Ischaemic stroke	0	0	0	0	0	0	1 (0.11)	1 (0.05)
Sinus bradycardia	0	0	0	0	1 (0.18)	0	0	0
Ventricular extrasystoles	0	0	0	0	0	0	0	1 (0.05)
Vertebrobasilar insufficiency	0	0	1 (0.09)	0	0	0	0	0

Source: Table 2-82 CTD 2.7.4 Summary of Clinical Safety

CCV AEs in 6- month COPD safety population

The frequency of CCV AEs in the 6- month population ranged from 3.3% (indacaterol 600 mcg) to 5.8% (tiotropium). Of interest, indacaterol 150 mcg had a rate of 5.6% and placebo, 4.0%. ECG QT prolonged, angina pectoris, atrial fibrillation, ventricular extrasystoles, ventricular tachycardia, coronary artery

disease, acute myocardial infarction, left and right bundle branch blocks and cardiac failure congestive all occurred at higher rates in the indacaterol groups and again, particularly the 150 mcg group than placebo. The rates were higher for the 75 mcg indacaterol group for than the 150 mcg group for ventricular extrasystoles, ventricular tachycardia and cardiac failure congestive. All these events had numerical values greater than one in the affected groups

The highest rates of CCV SAEs were in the indacaterol 75 mcg group (2.4%) the lowest were in the indacaterol 300 mcg group (1.2%) and placebo (1.2%) as shown in Table 87. The highest SAEs rates were in angina pectoris, atrial fibrillation, acute myocardial infarction all at higher rates in the indacaterol groups than placebo and all events occurring more than once.

Table 87 Cardio- and cerebrovascular SAEs by preferred term in COPD 6- month safety population

	Indacaterol treatments				Control treatment groups			
	75 µg N=127 n (%)	150 µg N=933 n (%)	300 µg N=1041 n (%)	600 µg N=547 n (%)	For N=556 n (%)	Tio N=415 n (%)	Sme N=333 n (%)	Pbo N=1371 n (%)
Patients with ≥1 CCV SAE	3 (2.36)	16 (1.71)	12 (1.15)	7 (1.28)	3 (0.54)	9 (2.17)	5 (1.50)	17 (1.24)
CCV SAEs:								
Angina pectoris	1 (0.79)	3 (0.32)	1 (0.10)	1 (0.18)	0	0	1 (0.30)	2 (0.15)
Atrial fibrillation	1 (0.79)	3 (0.32)	0	0	0	3 (0.72)	1 (0.30)	3 (0.22)
Acute myocardial infarction	0	2 (0.21)	1 (0.10)	0	0	0	1 (0.30)	0
Cerebral infarction	0	1 (0.11)	0	0	0	0	0	0
Cerebrovascular accident	0	1 (0.11)	0	0	0	0	0	0
Coronary artery disease	0	1 (0.11)	2 (0.19)	2 (0.37)	0	0	2 (0.60)	1 (0.07)
Lacunar infarction	0	1 (0.11)	0	0	0	0	0	0
Myocardial infarction	0	1 (0.11)	1 (0.10)	1 (0.18)	1 (0.18)	0	1 (0.30)	2 (0.15)
Sick sinus syndrome	0	1 (0.11)	1 (0.10)	0	0	0	0	0
Subdural haemorrhage	0	1 (0.11)	0	0	0	0	0	0
Ventricular tachycardia	0	1 (0.11)	0	0	0	0	0	1 (0.07)

Source: Table 2-84 CTD 2.7.4 Summary of Clinical Safety

CCV AEs in 12- month COPD safety population

The 75 mcg indacaterol dose was not included in this analysis. The CCV AE rates were highest for the indacaterol 150 mcg group (9.7%) and lowest in the placebo group (5.4%). The most common CCV AE preferred terms were atrial fibrillation, ECG QT prolongation, angina pectoris, myocardial ischemia, ventricular extrasystoles, cardiac failure, AV block 1st degree, AV block 2nd degree, bundle branch block left, cardiac failure congestive, sinus tachycardia and ventricular tachycardia (including an additional patient not originally captured) which occurred more frequently in the indacaterol groups than placebo. Refer to Table 88 for a summary. Note that these events are not corrected for patient exposure.

Table 88 Cardio- and cerebrovascular AEs by preferred term in COPD 12- month safety population

	Ind 150 µg N=144 n (%)	Ind 300 µg N=583 n (%)	Ind 600 µg N=425 n (%)	For N=434 n (%)	Pbo N=556 n (%)
Patients with ≥1 CCV AE	14 (9.72)	50 (8.58)	26 (6.12)	28 (6.45)	30 (5.40)
Preferred term:					
Atrial fibrillation	1 (0.69)	8 (1.37)	2 (0.47)	2 (0.46)	5 (0.90)
ECG QT prolonged	6 (4.17)	8 (1.37)	4 (0.94)	3 (0.69)	5 (0.90)
Angina pectoris	1 (0.69)	6 (1.03)	2 (0.47)	1 (0.23)	1 (0.18)
Myocardial ischaemia	0	4 (0.69)	0	1 (0.23)	0
Ventricular extrasystoles	0	4 (0.69)	2 (0.47)	2 (0.46)	1 (0.18)
Cardiac failure	0	3 (0.51)	4 (0.94)	6 (1.38)	1 (0.18)
AV block first degree	1 (0.69)	2 (0.34)	0	0	0
AV block second degree	0	2 (0.34)	0	0	0
Bundle branch block left	1 (0.69)	2 (0.34)	0	1 (0.23)	0
Cardiac failure congestive	1 (0.69)	2 (0.34)	0	0	2 (0.36)
Myocardial infarction	0	2 (0.34)	2 (0.47)	1 (0.23)	3 (0.54)
Sinus tachycardia	1 (0.69)	2 (0.34)	0	0	0
Acute myocardial infarction	0	1 (0.17)	0	0	1 (0.18)

Source: Adapted from Table 2-85 CTD 2.7.4 Summary of Clinical Safety

Of note, there was an additional ventricular tachycardia event in the 150 mcg indacaterol group not captured in the 12- month COPD safety group because it occurred12 days after the patient discontinued from the trial.

The CCV SAEs in the 12- month safety group had a similar pattern as above. The highest rates were seen in the indacaterol 300 mcg group (3%) and the lowest in the indacaterol 150 mcg group. Atrial fibrillation, angina pectoris and cardiac failure congestive all occurred at higher rates in the indacaterol group, particularly, the 300 mcg group than in the placebo group. Refer to Table 89.

Table 89 Cardio- and cerebrovascular SAEs by preferred term in COPD 12- month safety population

	Ind 150 µg N=144 n (%)	Ind 300 µg N=583 n (%)	Ind 600 µg N=425 n (%)	For N=434 n (%)	Pbo N=556 n (%)
Patients with ≥1 CCV Serious AE	1 (0.69)	18 (3.09)	11 (2.59)	6 (1.38)	8 (1.44)
Preferred term:					
Atrial fibrillation	1 (0.69)	3 (0.51)	0	1 (0.23)	1 (0.18)
Angina pectoris	0	2 (0.34)	1 (0.24)	0	1 (0.18)
Cardiac failure congestive	0	2 (0.34)	0	0	1 (0.18)
Myocardial infarction	0	2 (0.34)	2 (0.47)	1 (0.23)	2 (0.36)
Myocardial ischaemia	0	2 (0.34)	0	0	0

Source: Adapted from Table 2-86 CTD 2.7.4 Summary of Clinical Safety

CCV AEs in COPD Tiotropium combination safety population

The CCV AEs in the COPD tiotropium combination safety group were reported at similar rates between the two treatment groups: 2.0% in the Ind 150 mcg + tiotropium and 1.8% in the placebo + tiotropium group (1.77%). Likewise, CCV SAEs occurred at almost identical rates between the two groups, 0.79% in the ind + tio group and 0.80% in the tio alone group.

Class related toxicities such as tachycardia, palpitations, leg cramps, dizziness, nervousness, tremors, insomnia, nausea, arrhythmias, worsening hypertension as well as increase serum glucose, decrease in serum potassium, and QT prolongation are well known and were adequately assessed during the indacaterol development program. Overall, there were no unexpected class related toxicities for indacaterol.

Class effects

Class related toxicities such as tachycardia, palpitations, leg cramps, dizziness, nervousness, tremors, insomnia, nausea, arrhythmias, worsening hypertension as well as increase serum glucose, decrease in serum potassium, and QT prolongation are well known and were adequately assessed during the indacaterol development program. Overall, there were no unexpected class related toxicities for indacaterol.

6.4 Supportive Safety Results

6.4.1 Common Adverse Events

3- month COPD safety population

The frequencies of the common events occurring ≥1% are listed in Table 90. The highest rate was observed in the 75 mcg indacaterol group (51.5%) and the lowest in the salmeterol (33.4%). The rate for those on placebo was 43.1%. COPD was the preferred term with the highest rate but was comparable across different groups. Cough, headache and muscle spasms are key examples of common AE reported at higher rates in the indacaterol groups than placebo. Dyspnea was observed at higher rates in the placebo group than other treatment groups.

Table 90 Common AEs (>1.0% of patients in any group) by preferred term in COPD 3- month safety population

	Indacaterol treatment groups				Control treatment groups			
	75 µg N=449 n (%)	150 µg N=2611 n (%)	300 µg N=1157 n (%)	600 µg N=547 n (%)	For N=556 n (%)	Tio N=1214 n (%)	Sme N=895 n (%)	Pbo N=2012 n (%)
Patients with ≥1 AE	231 (51.5)	1067 (40.9)	556 (48.1)	252 (46.1)	246 (44.2)	526 (43.3)	299 (33.4)	867 (43.1)
Preferred term								
COPD †	38 (8.5)	239 (9.2)	136 (11.8)	56 (10.2)	71 (12.8)	120 (9.9)	65 (7.3)	269 (13.4)
Nasopharyngitis	24 (5.4)	114 (4.4)	67 (5.8)	43 (7.9)	31 (5.6)	67 (5.5)	29 (3.2)	89 (4.4)
Cough	29 (6.5)	104 (4.0)	60 (5.2)	27 (4.9)	15 (2.7)	43 (3.5)	20 (2.2)	72 (3.6)
Headache	23 (5.1)	80 (3.1)	26 (2.3)	16 (2.9)	16 (2.9)	42 (3.5)	22 (2.5)	44 (2.2)
Upper RTI	16 (3.6)	59 (2.3)	41 (3.5)	17 (3.1)	8 (1.4)	36 (3.0)	7 (0.8)	54 (2.7)
Muscle spasms	6 (1.3)	38 (1.5)	25 (2.2)	22 (4.0)	14 (2.5)	6 (0.5)	12 (1.3)	15 (0.8)
Dyspnea	8 (1.8)	37 (1.4)	19 (1.6)	13 (2.4)	7 (1.3)	26 (2.1)	13 (1.5)	53 (2.6)
Bronchitis	12 (2.7)	35 (1.3)	11 (1.0)	7 (1.3)	7 (1.3)	12 (1.0)	6 (0.7)	31 (1.5)
Influenza	2 (0.5)	32 (1.2)	14 (1.2)	10 (1.8)	3 (0.5)	19 (1.6)	5 (0.6)	14 (0.7)
Upper RTI bacterial	5 (1.1)	32 (1.2)	22 (1.9)	10 (1.8)	14 (2.5)	17 (1.4)	4 (0.5)	33 (1.6)
Back pain	6 (1.3)	31 (1.2)	12 (1.0)	8 (1.5)	9 (1.6)	17 (1.4)	10 (1.1)	25 (1.2)
Oropharyngeal pain	10 (2.2)	30 (1.2)	13 (1.1)	4 (0.7)	2 (0.4)	16 (1.3)	8 (0.9)	13 (0.7)
Lower RTI	1 (0.2)	28 (1.1)	24 (2.1)	5 (0.9)	8 (1.4)	18 (1.5)	17 (1.9)	36 (1.8)
Nausea	11 (2.5)	28 (1.1)	8 (0.7)	4 (0.7)	5 (0.9)	7 (0.6)	5 (0.6)	19 (0.9)
Diarrhea	7 (1.6)	27 (1.0)	14 (1.2)	5 (0.9)	8 (1.4)	13 (1.1)	9 (1.0)	24 (1.2)
Dizziness	4 (0.9)	25 (1.0)	16 (1.4)	5 (0.9)	3 (0.5)	5 (0.4)	5 (0.6)	24 (1.2)
Hypertension	6 (1.3)	24 (0.9)	10 (0.9)	5 (0.9)	0	12 (1.0)	7 (0.8)	32 (1.6)
Sinusitis	5 (1.1)	24 (0.9)	15 (1.3)	2 (0.4)	4 (0.7)	11 (0.9)	4 (0.5)	21 (1.0)
Arthralgia	8 (1.8)	23 (0.9)	10 (0.9)	6 (1.1)	2 (0.4)	7 (0.6)	4 (0.5)	11 (0.6)
Pyrexia	3 (0.7)	21 (0.8)	10 (0.9)	4 (0.7)	6 (1.1)	7 (0.6)	4 (0.5)	14 (0.7)
Viral upper RTI	5 (1.1)	21 (0.8)	20 (1.7)	2 (0.4)	5 (0.9)	8 (0.7)	4 (0.5)	22 (1.1)
Odema peripheral	4 (0.9)	19 (0.7)	8 (0.7)	7 (1.3)	6 (1.1)	7 (0.6)	2 (0.2)	9 (0.5)
Fatigue	8 (1.8)	16 (0.6)	5 (0.4)	6 (1.1)	4 (0.7)	6 (0.5)	2 (0.2)	16 (0.8)
Urinary tract infection	15 (3.3)	16 (0.6)	10 (0.9)	1 (0.2)	5 (0.9)	14 (1.2)	8 (0.9)	21 (1.0)
Dry mouth	4 (0.9)	14 (0.5)	4 (0.4)	1 (0.2)	1 (0.2)	27 (2.2)	3 (0.3)	10 (0.5)
Vomiting	6 (1.3)	12 (0.5)	10 (0.9)	3 (0.6)	2 (0.4)	7 (0.6)	2 (0.2)	11 (0.6)
Insomnia	2 (0.5)	11 (0.4)	5 (0.4)	5 (0.9)	3 (0.5)	6 (0.5)	9 (1.0)	14 (0.7)
Pneumonia	6 (1.3)	11 (0.4)	14 (1.2)	1 (0.2)	3 (0.5)	7 (0.6)	2 (0.2)	11 (0.6)
Rhinorrhea	3 (0.7)	10 (0.4)	13 (1.1)	1 (0.2)	1 (0.2)	6 (0.5)	2 (0.2)	4 (0.2)
Nasal congestion	6 (1.3)	9 (0.3)	4 (0.4)	3 (0.6)	1 (0.2)	10 (0.8)	3 (0.3)	6 (0.3)
Tremor	0	4 (0.2)	3 (0.3)	7 (1.3)	5 (0.9)	3 (0.3)	2 (0.2)	5 (0.3)

Source: Table 2-1 Table 2-86 CTD 2.7.4 Summary of Clinical Safety

6- month COPD safety population

The most common AEs occurring in the 6- month safety population are similar to the previous safety group. COPD is the most common and rates were comparable across treatment groups including placebo. Cough and headache were observed at higher rates for the indacaterol groups than the placebo groups. The most common SOC was infections and infestations and respiratory, thoracic and mediastinal disorders.

12- month COPD safety population
Overall, the highest rates of AE were observed in the 150 mcg group (76.4%) and the lowest in the placebo group (63.1%). The most common AEs in the 12- month COPD safety population was COPD and as observed before, the rates were comparable across all treatment groups. Cough, upper respiratory tract infection, headache, muscle spasms, oropharyngeal pain and sinusitis, ECG QT were seen at higher rates in the indacaterol groups than placebo. The top two SOCs identified were infection and infestations and respiratory, thoracic and mediastinal disorders.

Subgroup evaluations of AE
Overall, the rates of the reported AE were comparable across subgroups except women who had higher incidences of AE than males. Consistent with other safety analyses, no generalization can be made regarding races as the representative numbers were too low. There were no trends in AE based on age. For baseline disease status, rates of AE were comparable between those with moderate versus severe disease. As well, there were no differences across groups based on ICS use and smoking status.

6.4.2 Laboratory Findings

The two known beta2-adrenergic effects of hypokalemia and hyperglycemia were evaluated adequately by the Sponsor during the conduct of clinical trials. A review of the laboratory safety data will first focus on alterations in serum potassium and glucose in the COPD 3- month, 6- month and 12- month safety populations. Evaluation of other laboratory values will follow.

Potassium assessment
The mean changes in potassium values were similar across all treatment groups. Minimum post-baseline values for patients in the indacaterol groups ranged from 2.50 mmol/L (indacaterol 300 mcg q.d.) to 3.10 mmol/L (indacaterol 600 mcg q.d.). Acute changes in potassium were also assessed, from 25 minutes pre-dose to 1 hour post-dose time points. The largest mean change from 25 minutes pre-dose at any visit (-0.11 mmol/L) was seen in the indacaterol 600 mcg q.d. group at Day 1, 1 hour post-dose. Refer to for a summary of the acute changes in potassium across the different treatment groups.

Table 91 Acute changes in potassium (mmol/L): mean change from 25 min predose to 1 hr post dose by visit in COPD safety population

		Indacaterol treatment groups				Control treatment groups			
Visit / Time		**75 µg**	**150 µg**	**300 µg**	**600 µg**	**For**	**Tio**	**Sme**	**Pbo**
Day 1 *	n	435	989	884	526	533	401	329	1731
-25m	Pre-dose mean	4.47	4.50	4.45	4.45	4.42	4.48	4.54	4.46
1h	Mean change	-0.04	-0.04	-0.05	-0.11	-0.09	0	-0.00	0.01
Week 2 *	n	117	749	855	508	513	384	309	1116
-25m	Pre-dose mean	4.44	4.46	4.42	4.39	4.41	4.45	4.53	4.42
1h	Mean change	0.02	0.02	-0.00	-0.02	-0.04	0.05	0.03	0.05
Month 3 *	n	356	872	789	439	449	342	287	1415
-25m	Pre-dose mean	4.37	4.46	4.43	4.43	4.43	4.42	4.55	4.42
1h	Mean change	0.04	-0.01	-0.01	-0.02	-0.03	0	0	0.03
Month 6 †	n	0	593	686	341	345	316	279	848
-25m	Pre-dose mean	0	4.48	4.44	4.49	4.48	4.41	4.57	4.42
1h	Mean change	0	0.01	0.01	-0.03	-0.01	0	-0.04	0.01
Month 12 ††	n	0	122	446	307	298	0	0	381
-25m	Pre-dose mean	0	4.39	4.50	4.49	4.50	0	0	4.41
1h	Mean change	0	-0.02	-0.03	-0.04	-0.07	0	0	0.02

Source: Table 3-11 CTD 2.7.4 Summary of Clinical Safety

Reviewer comment:

These data do not suggest a clinically important affect on potassium at the doses evaluated.

Glucose assessment
The observed incidences of newly occurring or worsening notably high glucose values as predefined as >9.99 mmol/L in the indacaterol treatment groups were and 4.7-8.4% in the whole COPD safety population. Based on the different safety subgroups the incidence was 4.0-6.4% in the COPD 3-month safety population, 3.9-7.2% in the COPD 6-month safety population and 9.0- 11.1% in the COPD 12-month.The highest incidences of notable high glucose levels within the COPD 3- and 6- months safety populations was observed in the 600 mcg indacaterol group; however for the 12-month safety population, highest incidences were in the indacaterol 150 mcg q.d. group. Acute changes in glucose measured from 25 minutes pre-dose to 1 hour post-dose for all visits were comparable among treatment groups. The greatest mean change from 25 minutes pre-dose at any visit was seen in the indacaterol 600 mcg q.d. group at Day 1, 1 hour post-dose (0.35 mmol/L = 6.3 mg/dL).

COPD 3- month safety population
In the 3- month population there was one patient who developed idiopathic thrombocytopenia purpura in the indacaterol 150 mcg group that was reported as an SAE. Otherwise there were no clinically meaningful differences in hematology and chemistry laboratory data for the indacaterol or placebo treatment groups.

COPD 6- month safety population
There were no clinically meaningful differences in hematology and chemistry laboratory data for the indacaterol or placebo treatment groups. Notable differences from baseline were similar across treatment groups.

COPD 12 month safety population
There were no clinically important differences from placebo in hematocrit or BUN and creatinine.

Overall, there were 18 patients with reported notably low platelets, 10 were in the indacaterol treatment groups. One of these patients had low levels at screening who had the diagnosis of alcoholic hepatitis. A second patient with a history of non-Hodgkin's lymphoma also had low platelets at screening and was subsequently diagnosed with a recurrence of disease, started treatment and later discontinued from the trial with worsening thrombocytopenia while on chemotherapy. Two other patients had low platelets at screening which subsequently worsened by the final visit, one with a history of hepatopathy.

The percentage of patients with notable differences in GGT >3 x ULN ranged from 2.9%-3.6% in indacaterol 75 mcg to 300 mcg groups but higher in the indacaterol 600 mcg group, 5.9%. There were small numbers of patients with AST> 3x ULN and ALT >3x ULN that were generally comparable between treatment groups and placebo. There were incidences of AST > 5 x ULN ranging 0.17 – 0.22% in indacaterol groups vs. 0.1% in placebo. There was one episode of AST > 10x ULN in the 150 mcg group and one in the tiotropium group. There were 6 episodes of ALT > 10x ULN, one in the 75 mcg, one in the 150 mcg group, one in formoterol, two in tiotropium and one in the placebo groups.

6.4.3 Vital Signs

The same safety datasets were utilized in evaluation of the vitals across different treatment regimens.

3- month COPD safety population
As shown in Table 92, Table 93 and Table 94 a small dose response effect is apparent across the indacaterol treatment groups with the exception of the 75 mcg dose for elevations in blood pressure and pulse, consistent with the known beta-agonist effect of the drug. This may likely be due to the smaller numbers of patients in trials treated with 75 mcg meeting the duration criteria of 3- or 6 months to be included in the safety dataset; there were none included in the 12- month safety dataset.

Table 92 Vital signs: incidence of clinically notable values any time post baseline in COPD 3-month safety population

		Treatment groups (%)				
		Ind 75 mcg N=449	Ind 150 mcg N=2611	Ind 300 mcg N=1157	Ind 600 mcg N=547	Pbo N=2012
3 month-COPD safety population	SBP ≥ 200 mm Hg	0.45	0.61	0.87	2.01	1.14
	DBP ≥ 105 mm Hg	1.56	0.58	0.61	0.92	1.09
	Pulse ≥ 120 bpm	0.22	0.19	0.26	0.37	0.30

High SBP: >200 mm Hg or ≥ 180 mm Hg and increase baseline by >20 mm Hg
High DBP: > 115 mm Hg or ≥ 105 mm Hg and increase baseline by > 15 mm Hg
High pulse: >130 bpm or ≥120 bpm and increase from baseline by ≥15 bpm
Source: Adapted from Table 4-1 CTD 2.7.4 Summary of Clinical Safety

In the COPD 3- month safety population there were 4 cases of intervals for QTcF > 500 ms, 2 in the indacaterol 150 mcg group and 2 in the tiotropium group. For notable increases of QTcF by >60 msec the incidences were higher in the placebo group (6 patients, 0.30%) than in the indacaterol 150 mcg q.d. (3 patients, 0.12%), 300 mcg q.d. (1 patient, 0.09%) and 600 mcg q.d. (1 patient, 0.19%) groups. The frequency of events with a notable QTcF increase by 30-60 msec was higher on indacaterol 150 mcg q.d. (155 patients, 5.96%) than on placebo (105 patients, 5.27%).

6- month COPD safety population
Increasing doses of indacaterol between 150 mcg and 600 mcg show increasing rates of notable high SBP and DBP. Refer to Table 93.

Table 93 Vital signs: incidence of clinically notable values any time post baseline in COPD 6-month safety population

		Treatment groups (%)				
		Ind 75 mcg N=127	Ind 150 mcg N=933	Ind 300 mcg N=1041	Ind 600 mcg N=547	Pbo N=1371
6 month-COPD safety population	SBP ≥ 200 mm Hg	0	0.96	1.15	2.20	1.53
	DBP ≥ 105 mm Hg	0.79	0.64	0.96	1.28	1.24
	Pulse ≥ 120 bpm	0.79	0.21	0.38	0.37	0.44

Source: Adapted from Table 4-2 CTD 2.7.4 Summary of Clinical Safety

In the COPD 6- month safety population, there were 4 cases of intervals for QTcF > 500 ms, 2 in the indacaterol 150 mcg group, 1 case in the 300 mcg indacaterol group and 1 in the tiotropium group. For notable increases of QTcF by >60 msec the incidences were higher in the placebo group (7 patients, 0.50%) than in the indacaterol 150 mcg q.d. (3 patients, 0.30%), 300 mcg q.d. (3 patients, 0.30%) and 600 mcg q.d. (1 patient, 0.20%) groups. The frequency of events with notable increase of QTcF by 30- 60 msec was highest in the tiotropium and placebo group with 0.50% for both.

12- month COPD safety population
The rates for notable increases in SBP, SBP and pulse were highest in placebo. Refer to Table 94 below.

Table 94 Vital signs: incidence of clinically notable values any time post baseline in COPD 12-month safety population

		Treatment groups (%)			
		Ind 150 mcg N=144	Ind 300 mcg N=583	Ind 600 mcg N=425	Pbo N=556
12 month-COPD safety	SBP ≥ 200 mm Hg	0.69	2.06	3.54	3.06
	DBP ≥ 105 mm Hg	0.69	1.03	2.12	2.52
	Pulse ≥ 120 bpm	0	1.03	0.24	0.90

Source: Adapted from Table 4-2 CTD 2.7.4 Summary of Clinical Safety

In the COPD 12- month safety population there were no cases of intervals for QTcF > 500 msec. For notable increases of QTcF by >60 msec there were 6 cases reported: indacaterol 150 mcg q.d. (1 case); indacaterol 300 mcg q.d. (2 cases); indacaterol 600 mcg q.d. (1 case); formoterol (1 case) and placebo (1 case). The frequency of events with notable increase of QTcF by 30- 60 msec was highest in the indacaterol 150 mcg group, 0.70%. The placebo group had a rate of 0.20%.

A thorough QTc study was conducted, B2339 and reviewed by the Clinical Pharmacology team. The trial was a randomized, multiple-dose, placebo and positive-controlled parallel group study to evaluate the effects of indacaterol on cardiac safety in healthy subjects, using the Concept1 device. The primary objective was to characterize the maximum mean prolongation of QTc Fridericia (QTcF) following treatment with indacaterol 150 mcg, 300 mcg and 600 mcg q.d. for 14 days. A total of 404 subjects were randomized with 388 subjects completing the trial. There was no evidence of statistically significant QT prolongation for the 3 doses evaluated.

6.5 Other Safety Explorations

6.5.1 Dose Dependency for Adverse Events

See Section 6.6 Additional Safety Evaluations for evaluation of dose and post inhalational cough.

6.5.2 Time Dependency for Adverse Events

See Section 6.6 Additional Safety Evaluations for evaluation of time of onset and post inhalational cough.

6.5.3 Drug-Demographic Interactions

Evaluation of treatment by subgroup interaction for various demographic groups including age, gender and race for the bronchodilatory effect of indacaterol was conducted in the pivotal Phase III COPD trials.

3- month COPD safety population
There was no clear age by treatment group interaction with respect to SAEs. Although the majority of patients were males, females had higher rates of “all SOCs” across the indacaterol treatment groups (ranging 3.61-4.98) than males (2.02-3.58). The majority of patients were caucasian and therefore no conclusions can be drawn by race. Patients with severe disease had higher rates of “all SOCs” in the 75 mcg, 150 mcg and 300 mcg indacaterol groups. There was no clear relationship between smoking status and ICS use and SAEs across the indacaterol treatment groups.

6- month COPD safety population

In the 6- month COPD safety dataset, here was no clear age by treatment group interaction with respect to SAEs. Females had higher rates of "all SOCs" across the indacaterol treatment groups (ranging 6.9 - 11.8) than males (4.0 -7.4). No conclusions can be drawn by race due to the small numbers of blacks, asians and others. There was no clear relationship between disease severity and smoking status and SAEs, however, patients on ICS had higher frequency of SAEs than non-ICS users.

12- month COPD safety population
There were no clear relationships between the frequencies of SAEs and age and gender. As before, no conclusions can be drawn about race. Overall, there was no consistent pattern between subgroups of disease characteristics and SAEs.

6.5.4 Drug-Disease Interactions

Drug disease interaction analyses were conducted for patients with CCV conditions (see Section 6.3.4 Submission Specific Primary Safety Concerns), diabetes mellitus 2 and hypertension. Overall, there were no clinical important differences, however in the 12- month COPD population, AE rates in patients with diabetes mellitus 2 were higher for all active treatment groups (indacaterol 150 mcg with 2.08%, indacaterol 300 mcg with 2.06%, indacaterol 600 mcg with 1.41%) than placebo (0.72%).

6.5.5 Drug-Drug Interactions

In vitro data demonstrated two key enzymes responsible for metabolic clearance of indacaterol, UGT1A1 and CYP3A (refer to clinical pharmacology review by Dr. Sandra Saurez, August 25, 2009). Therefore, substrates, inhibitors or inducers of these enzymes may affect the PK of indacaterol and its metabolites. Concomitant administration of indacaterol 300 mcg with ketoconazole 200 mcg BID resulted in a 2-fold increase in the AUC and a 31% increase in Cmax. Concomitant administration of indacaterol 300 mcg with verapamil 80 mcg t.i.d for 4 days showed an increase in the AUC and Cmax of indacaterol of 200% and 50%, respectively. Concomitant administration of a single dose of indacaterol 300 mcg with erythromycin 400 mcg q.i.d for 7 days showed an increase in the indacaterol AUC and Cmax of 60% and 15%, respectively. The indacaterol Cmax and AUC increased by 12% and 41%, respectively following single dose administration of indacaterol 250 mcg via Twisthaler + mometasone furoate 200 mcg dry powder inhaler formulation administered via Twisthaler™ compared to that after indacaterol 250 mcg alone via Twisthaler. Indacaterol did not alter the systemic exposure of mometasone.

6.6 Additional Safety Evaluations

Post inhalational Cough
The incidence of post inhalational cough (PI) was assessed along with any post inhalation events at the clinic visits as observed by the staff. This was conducted prospectively in pivotal phase III trials, B2334, B2335S, B2346, B1302, B2336, and B2333. The data was collected at each clinic visit, where the investigator completed a CRF page including the time of onset following inhalation of trial medication and duration of PI cough. The percentage of visits with patients having PI cough and the percentage of patients with PI cough were summarized for the safety populations. A patient was identified with a PI cough if the number of visits with PI cough was >1 or the number of visits with PI cough was more than 20% of all attended post baseline visits.

3- month COPD safety population
The mean percentages of attended visits at which patients experienced PI cough were statistically significantly greater in the indacaterol treatment groups than in the placebo or other active comparator groups. The mean percentage of attended visit with PI cough were as follows: indacaterol 75 mcg, 14%; 150 mcg group, 15.1%; 300 mcg group, 17.5% and the 600 mcg group 16.6%; formoterol, 0.9%; tiotropium, 0.9%, salmeterol, 0.9% and placebo 2%. The percent of PI coughers were: 23.6, 27.9, 29.7,

30.8, 4.3, 2.2, 3.9 and 6.6% for 75 mcg, 150 mcg, 300 mcg, 600 mcg, formoterol, tiotropium, salmeterol and placebo respectively.

6- month COPD safety population
The mean percentages of attended visits at which patients experienced PI cough were statistically significantly greater in the indacaterol treatment groups (range 14.1 to 17.7%) than in the placebo (1.9%) or other active comparator groups (0.8 to 0.9%). The mean percentage of attended visit with PI cough were as follows: indacaterol 75 mcg, 23.6%; 150 mcg group, 24.3%; 300 mcg group, 28.0% and the 600 mcg group 29.1%; formoterol, 1.6%; tiotropium, 2.2%, salmeterol, 1.5% and placebo 3.6%. The percent of PI coughers were: 23.6, 24.3, 28.0, 29.1, 1.6, 2.2, 1.5 and 3.6% for 75 mcg, 150 mcg, 300 mcg, 600 mcg, formoterol, tiotropium, salmeterol and placebo respectively.

12- month COPD safety population
The mean percentages of attended visits at which patients experienced PI cough were statistically significantly greater in the indacaterol treatment groups (range 18.3 to 19.9%) than in the placebo (1.7%) or other active comparator group, formoterol (0.8 %). The mean percentage of attended visit with PI cough were as follows: indacaterol 150 mcg group, 18.3%; 300 mcg group, 19.9% and the 600 mcg group 18.9%; formoterol, 0.8% placebo 1.7%. The percent of PI coughers were: 28.5, 29, 29, 1.2, and 3.1% for 150 mcg, 300 mcg, 600 mcg, formoterol, and placebo respectively.

The time to onset of the PI cough for the majority of patients was within 15 seconds of inhalation and lasted ≤ 15 seconds. Subgroup analysis demonstrated that the percentage of patients with PI cough were similar across indacaterol groups. There were no consistent trends between PI cough and age, COPD severity or ICS use however, the percentage of patients with PI cough were higher for females and current smokers.

Asthma Safety Evaluation
Concern over the 2 asthma deaths in the 300 mcg indacaterol treatment group of trial B2338 in the first cycle prompted a further evaluation of available trials treating patients with asthma for deaths and SAEs at the onset of this cycle review. A summary is available in Table 95 below of deaths, SAEs and asthma exacerbations categorized as AEs leading to discontinuation.

A thorough evaluation of asthma exacerbations as relates to the trial inclusion criteria will be carried out using the Sponsor's metaanalysis of respiratory related intubations, hospitalizations and deaths, however, preliminary review of the asthma trials available reveal 1 asthma exacerbation in the 18.75 mcg group, 0 in the 75 mcg group and the highest numerical value was 10 captured in the 600 mcg indacaterol group. These numbers represent either asthma exacerbations or events labeled as bronchospasm associated with death, SAE or AE leading to discontinuation. Evaluation of these such asthma exacerbations show a range of 1 event occurring in the 18.75 mcg indacaterol group to 9 events in the 600 mcg indacaterol group.

Table 95 Deaths, SAEs and AEs leading to discontinuation in Asthma trials

ID Year*	**Study type**	**Study duration**	**N**	**Treatment groups**†	**Adverse Event**
Randomized, controlled trials					
A2201 [2003]	Safety Efficacy	5 x 1 dose	42	Ind HFA 50 mcg QD Ind HFA 100 mcg QD Ind HFA 200 mcg QD Ind HFA 400 mcg QD Placebo	0 Deaths, SAEs • Pbo (1: hypoglycemia) AE-> d/c: • Gilbert's syndrome
A2205 [2003]	Safety	4 weeks	156	Ind HFA 200 mcg QD Ind HFA 400 mcg QD	0 Deaths, SAEs AE-> d/c:

ID Year*	Study type	Study duration	N	Treatment groups[T]	Adverse Event
				Ind HFA 600 mcg QD Placebo	• Ind 400 mcg (1 cough) • Ind 600 mcg (1 asthma exac) • Pbo (1 asthma exac)
A2208 [2006]	Efficacy Safety	4 x 1week	115	Ind SDDPI 100 mcg QD Ind SDDPI 200 mcg QD Ind SDDPI 300 mcg QD Ind SDDPI 400 mcg QD Ind SDDPI 600 mcg QD Formoterol 12 mcg BID OL Pbo	0 Deaths SAEs • Pbo (1: pregnancy) AE-> d/c: • Ind 300 mcg (1 metrorrhagia) • Ind 100 mcg (1 insomnia, nervousness)
A2210 [2004]	Safety	4 weeks	144	Ind SDDPI 400 mcg QD Ind SDDPI 800 mcg QD Placebo	0 Deaths SAEs • Ind 400 mcg (1 bronchospasm, 1 hyperventilation) • Ind 800 mcg (1 bronchospasm, 1 asthma attack, 1 ectopic pregnancy) AE-> d/c: • Ind 800 mcg (1 cough, 1 asthma attack)
A2216 [2006]	Safety Efficacy	1 week	436	Ind MDDPI 50 mcg QD Ind MDDPI 100 mcg QD Ind MDDPI 200 mcg QD Ind MDDPI 400 mcg QD Ind SDDPI 400 mcg QD	0 Deaths SAEs • Pbo (1: ostectomy) AE -> d/c: • Ind 50 mcg (1 2nd degree AV block) • Ind 100 mcg (1 erythema, anxiety) • Ind 400 mcg (asthma exac, 1 headache, palpitations
A2218 [2005]	Efficacy Safety	2 weeks	25	Ind SDDPI 400 mcg QD Ind MDDPI 200 mcg QD	0 Deaths, SAEs, AE-> d/c
A2222 [2006]	Safety H20 effects on cough	2 weeks	87	Ind MDDPI 200 mcg QD Salmeterol 50 mcg	0 Deaths, SAEs, AE-> d/c
A2228 [2008]	Safety Efficacy	5 x 1 day each	45	Ind SDDPI 150 mcg QD Ind SDDPI 300 mcg QD Ind SDDPI 600 mcg QD Formoterol 12 mcg BID Pbo	0 Deaths SAEs • Pbo (1 appendicitis) • Ind 50 mcg (1 cellulitis R elbow) AE-> d/c • Pbo (1 asthma exac)
A1202 2008	Safety Efficacy	4 x 1 day each	41	Ind SDDPI 150 mcg QD Ind SDDPI 300 mcg QD Ind SDDPI 600 mcg QD Pbo	0 Deaths, SAEs, AE-> d/c
B2102 [2010]	Safety	4 x 1 day	98	Ind Maleate SDDPI 400 mcg QD Ind Xinafoate SDPPI 400 mcg QD Ind acetate SDDPI 400 mcg QD	0 Deaths, SAEs AE-> d/c • Ind Acetate 400 mcg (1 cold, fever) • Ind Acetate 400 mcg (1 fever, laryngitis)
B2223 [2010]	Safety Efficacy	2 weeks	189	Ind SDDPI 37.5 mcg BID Ind SDDPI 75 mcg QD Ind SDDPI 150 mcg	0 Deaths SAEs • 2 Prerandomization (anxiety attack, anemia) • Ind 150 mcg (1 asthma exac)

ID Year*	Study type	Study duration	N	Treatment groups†	Adverse Event
				QOD Pbo	AE -> d/c: • Pbo elevated transaminases
B2338 [2008]	Safety	26 weeks	805	Ind SDDPI 300 mcg QD Ind SDDPI 600 mcg QD Salmeterol 50 mcg BID Pbo	2 Deaths • Ind 300 mcg (asthma exac) • Ind 300 mcg (cardiac arrest/ asthma exac) SAEs • Ind 300 mcg (2 asthma exac, 1 biliary colic, 1 stress, 1 R neck mass, 1 bacterial URTI) • Ind 600 mcg (2 falls, 1 cholangitis, 3 asthma exac, 1 pneumonia, 1 atrial fibrillation, 1 foot fx, 1 splenic cyst, 1 food allergy • Salm (1 asthma exac, 1 cholelithiasis, 1 foot fx, 1 AMI, 1 facial paresis, 1 pneumonia, 1 allergic dermatitis, 1 angioedema) AE->d/c • Ind 300 mcg (2 asthma exac) • Ind 600 mcg (6 asthma exac,) • Salm (4 asthma exac)
B2357 [2010]	Efficacy Safety	2 weeks	502	Ind SDDPI 37.5 mcg QD Ind SDDPI 75 mcg QD Ind SDDPI 150 mcg QD Sal 50 mcg BID Pbo	0 Deaths SAEs • Substance abuse AE-> d/c • Ind 18.75 mcg (1 asthma exac) • Ind 37.5 mcg (1 ECG/Cardiac) • Salm (2 asthma exac)

* Year study subject enrollment ended
† Ind SDDPI = Indacaterol single dose dry powder inhaler, Arcapta Neohaler (Indacaterol single dose dry powder inhaler); Ind MDDPI = Indacaterol multiple dose dry powder inhaler; For = Foradil Aerolizer (formoterol fumarate inhalation powder); Tio = Spiriva Handilaler (tiotropium bromide inhalation powder); Salm = Serevent Diskus (salmeterol xinafoate inhalation powder); URTI = upper respiratory tract infection; asthma exac = asthma exacerbation
AE I-> d/c = AE leading to discontinuation, primarily asthma exac or serious cardiac events

6.6.1 Human Carcinogenicity

Human carcinogenicity studies have not been conducted with indacaterol. There were no apparent trends in cancer events and treatment with indacaterol observed in the safety datasets.

6.6.2 Human Reproduction and Pregnancy Data

There were no pregnancies reported in the indacaterol treatment groups for COPD patients. Therefore no clinical data is available to assess indacaterol use during pregnancy.

There were 7 pregnancies reported during the use of indacaterol in patients with asthma. These include 5 patients in the Phase III trial, B2338: 1 on 300 mcg; 3 on 600 mcg and 1 on salmeterol. In addition, there were 2 patients in the Phase II program: in A2210 there was 1 in the 800 mcg group and in A2208, there was 1 who completed the 5 way crossover. These pregnancies resulted in 3 normal babies, 2 abortions and one ectopic pregnancy with a successful surgical outcome.

6.6.3 Pediatrics and Assessment of Effects on Growth

A pediatric waiver was granted because COPD is a disease that does not occur in the pediatric patient population.

6.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The two trials of indacaterol 75 mcg versus placebo in patients with COPD over 12 weeks, B2355 and B2354 showed no evidence of tachyphylaxis over the duration of the trial. In the 26 week trial of indacaterol 150 mcg versus placebo, B2336 also revealed a lack of tachyphylaxis in the LS means of FEV1 over the 26 week trial duration. As well, higher doses of indacaterol revealed no appreciable evidence of acute toxicity with a single dose of 600 mcg. In Study B2202, not reviewed in this submission, single orally inhaled doses of 3000 mcg were reported to be associated with an increase in pulse rate, blood pressure and QTc interval which is consistent with the expected beta2 adrenergic effects of tachycardia, tremor, palpitations, headache, nausea, vomiting, drowsiness, ventricular arrhythmias, metabolic acidosis, hypokalemia and hyperglycemia. No formal trials of potential withdrawal and rebound effects of indacaterol have been conducted.

6.7 Additional Submissions / Safety Issues

The FDA requested information of an analysis to evaluate the incidence of respiratory-related death, intubation and hospitalization in indacaterol treated patients compared to control. At the time of this review the analysis is pending.

7 Postmarket Experience

Patient support program in Mexico

On January 24, 2011, Novartis submitted a summary of fatal cases from a branded patient support program ongoing in Mexico. Mexico approved indacaterol maleate SDDPI (Onbrize Breezhaler) at doses of 150 and 300 mcg once daily for the treatment of COPD on July 30, 2010. Novartis began a branded patient support program on September 26, 2010, with the last of 1316 patients enrolling in the 30 day program on January 4, 2011. In this program, participating physicians, primarily pulmonologists, are asked to enroll patients on starting indacaterol. Upon enrollment, patients are given a 10 day supply of indacaterol 150 mcg and complete a survey regarding COPD symptoms via a centralized call center. Upon completion of the initial survey, patients receive a free 30 day supply of indacaterol 150 mcg. The call center then contacts the patient for follow up surveys 2 weeks and 4 weeks after enrollment. Any adverse events reported in the surveys are transferred to Novartis pharmacovigilance.

Based on baseline survey data, the mean age of patients enrolled in the program was 66 years, and 52% of patients were female. The average symptom score was 6.6-7, on a Likert scale of 1-9, with 9 being the most severe. Based on a survey of participating physicians, the sponsor suggests that the majority of patients enrolled in the program had severe or very severe COPD.

As of January 19, Novartis reports a total of 16 deaths (1.2%) in the Mexican patient support registry. The most common cause of death was respiratory (3 pneumonia, 1 respiratory insufficiency, 1 COPD, and 1 PE), followed by cardiac (1 CHF, 2 cardiac arrest) and cancer (breast, lymphoma, GI). There were also 2 deaths of unknown cause, one GI bleed and one due to progression of Wegener's disease. Of the 16 patients who died, 11 were aged 75 years or older. The three patients who died of cardiac causes reportedly had pre-existing cardiac disease.

Reviewer comment:

While these deaths represent a much larger number than the rest of the post-marketing deaths from over 50 countries put together, it is difficult to determine the clinical meaningfulness of these events in the context of post-marketing reporting. The events in the Mexican patient support program were solicited as opposed to spontaneous reports in the rest of the database, which traditionally results in significant underreporting. In a severe COPD population enrolled in clinical trials, the expected mortality rate 3-5% over a one year period[15, 16]. The causes of death do not appear to be particularly unusual for a severe COPD patient population.

Spontaneous post-marketing reports

Novartis states that the estimated patient exposure to indacaterol based on worldwide sales is approximately 57,000 patient years. Excluding the deaths reported in the Mexican patient support program, there are 10 other fatal cases in post-marketing reports. These cases ranged in age from 44 to 96 years. The most common cause of death was respiratory: COPD exacerbation, status asthmaticus, respiratory failure, and pulmonary embolus. Three patients died of unknown causes, one of which was reported as sudden death. The other three patients died of circulatory collapse following diuresis, sepsis, and myocardial infarction.

In light of the known risk of asthma-related death with LABAs, the one concerning event was the patient who died of status asthmaticus. This was a 44 year old female with a history of asthma and COPD. Approximately 6 weeks prior to the fatal event, she developed a series of exacerbations requiring systemic corticosteroids. In addition, her maintenance regimen was changed from fluticasone plus tiotropium to indacaterol (unknown dose) plus tiotropium. An autopsy was not performed.

Reviewer comment:
While all of the details surrounding the case are unavailable, the single report of death from status asthmaticus raises the concern of LABA-related death. Unfortunately, it is not known whether the patient received a 150 mcg or 300 mcg indacaterol dose. Although her ICS was stopped, the patient was reportedly receiving concomitant oral corticosteroids.

[15] Calverley PMA, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 2007; 356:775-89.
[16] Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med 2008; 359:1543-54.

8 Appendices

8.1 Literature Review/References

Antiplatelet Trialist' Collaboration Collaborative overview of randomized trials of antiplatelet therapy, I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ 1994; 308:81-106.

Calverley PMA, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in Chronic Obstructive Pulmonary Disease. N Engl J Med 2007; 356: 775-789.

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Celli BR, Cote CG, Marin JM, et al., The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med 2004; 350:1005-12.

Chowdhury BA, Dal Pan G. FDA and safe use of long-acting beta-agonists in the treatment of asthma. N Engl J Med 2010; 362:1169-71.

Donahue JF. Minimal clinically important differences in COPD lung function. COPD: Journal of Chronic Obstructive Pulmonary Disease 2005; 2:111-124.

FDA Draft Guidance for Industry, Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment November, 2007, Available at the website http://www.fda.gov/cder/guidance/index.htm

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Jones PW. St. George's Respiratory Questionnaire: MCID. COPD: Journal of Chronic Obstructive Pulmonary Disease 2005; 2:75-79.

Mahler DA, Weinberg DH, Wells CK, Feinstein AR. The measurement of dyspnea. Chest 1984; 85:751-8.

Nelson HS, Weiss ST, Bleecker ER, et al. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest 2006; 129:15-26.

Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med 2008; 359:1543-54.

8.2 Labeling Recommendations

Review of the label is currently underway and will require substantial revision of the following but not limited to clinical sections: Boxed Warning, Contraindications, Warnings and Precautions; Adverse Reactions; Clinical Studies and the Patient Counseling Information. A completed label will be added as an addendum.

8.3 Advisory Committee Meeting

A Pulmonary, Allergy Drugs Advisory Committee (PADAC) meeting will be held on March 8, 2011. The purpose of the PADAC meeting is to discuss the adequacy of the efficacy and safety data submitted by Novartis to support the approval of indacaterol inhalation powder at a dose of 75 or 150 mcg for the long term, once-daily maintenance treatment of airflow obstruction in patients with COPD including chronic bronchitis and/or emphysema. The major issues for discussion are whether the 1). proposed doses of 75 mcg and 150 mcg and the once-daily dosing frequency are supported by submitted data, 2). second higher dose of 150 mcg is necessary and supported by submitted efficacy data and balancing safety data, 3). SGRQ benefit claim is supported and 4). SGRQ data provide supportive evidence of efficacy for any of the doses, and 5). safety of the proposed dose and dosing regimen of indacaterol.

Draft Questions

1. Discuss the efficacy data of indacaterol considering the following
    a) Dosing regimen or dosing frequency
    b) Total daily dose lower than 75 mcg
    c) Are there advantages of 150 mcg once-daily dose over 75 mcg once-daily dose
    d) Claim that 150 mcg once-daily dose improves SGRQ considering the totality of the SGRQ data

2. Discuss the overall safety profile of indacaterol considering the following
    a) Safety data from asthma studies
    b) Proposed indication specific to chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema
    c) Comparative safety assessment of 75 mcg and 150 mcg dose for balancing safety risk relative to efficacy

3. Considering the totality of the data, has indacaterol demonstrated substantial evidence of <u>efficacy</u> for the long term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema
    a) For the 75 mcg dose? **(Voting question)**
    b) For the 150 mcg dose over the 75mcg dose? **(Voting question)**
    c) If not, what further data should be obtained

4. Is the <u>safety</u> profile of indacaterol adequate for approval for the long term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema
    a) For the 75 mcg dose? **(Voting question)**
    b) For the 150 mcg dose? **(Voting question)**
    c) If not, what further data should be obtained

5. Does the totality of the data provide substantial evidence to support a claim that indacaterol improves health-related quality of life as measured using St. George's Respiratory Questionnaire (SGRQ)
    a) For the 75 mcg dose? **(Voting question)**
    b) For the 150 mcg dose? **(Voting question)**

6. Do the efficacy and safety data provide substantial evidence to support approval of indacaterol inhalation powder for the long term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema? **(Voting question)**
    a) If yes, should the dose be
        i. 75 mcg once-daily? **(Voting question)**
        ii. 150 mcg once-daily? **(Voting question)**
    b) If not, what further data should be obtained?

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/s/

ANYA C HARRY
02/14/2011

THERESA M MICHELE
02/15/2011

MEDICAL OFFICER REVIEW

Division of Pulmonary, Allergy, and Rheumatology Products (HFD-570)

Application #:	NDA 22-383	**Application Type:**	NDA – Response to FDA IR
Sponsor:	Novartis	**USAN Name:**	Arcapta Neohaler/Indacaterol
Category:	Long-acting beta-agonist	**Route of Administration:**	Inhalation
Reviewer:	Banu Karimi-Shah	**Date:**	April 12, 2011

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type	Comments
February 8, 2011	February 8, 2011	Response to IR	Meta-analysis of Respiratory Events (SDN 039)

REVIEW SUMMARY:

Arcapta Neohaler (indacaterol maleate inhalation powder) is a long-acting beta-agonist (LABA) proposed for the long-term, once daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. The Applicant seeks approval of two doses of indacaterol, 75 and 150 mcg. Due to concerns regarding asthma- and COPD-related deaths, hospitalizations, and intubations that were raised during the review of this application, the Agency asked that the Applicant conduct a blinded adjudicated analysis comparing indacaterol-treated patients to controls with respect to respiratory-related death, hospitalization, and intubation. This submission contains the results of this meta-analysis. The findings have been reviewed and presented to the Pulmonary-Allergy Drugs Advisory Committee on March 8, 2011.

This review focused on the All-treated COPD Safety Population I as this is the indication sought by the Applicant, and the majority of data included comes from a COPD patient population. Although the magnitude of the signal is not large, there does appear to be a numerical trend of increasing incidence of acute respiratory-related events, particularly those that were adjudicated as having been COPD-related, as the dose of indacaterol rises from 75 mcg to 300 mcg. This increase in the composite endpoint is driven primarily by an increase in acute-respiratory related hospitalizations. Although we realize the limitations of this type of an analysis, one can argue that the presence of a numerical trend towards an increase in a respiratory safety signal in a population expected to have respiratory benefit from the drug, is a concerning issue. Such a trend suggests that doses above 150 mcg may carry an increased risk of respiratory events compared to placebo, and further underscores the importance of selecting the lowest effective dose of a beta-agonist bronchodilator.

OUTSTANDING ISSUES: None

Medical Reviewer: Banu A. Karimi-Shah, MD
Medical Team Leader: Theresa Michele, MD

I. Introduction

Arcapta Neohaler (indacaterol maleate inhalation powder) is a long-acting beta-agonist (LABA) proposed for the long-term, once daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. The Applicant seeks approval of two doses of indacaterol, 75 and 150 mcg. The efficacy and overall safety of indacaterol have been discussed in detail in the reviews of Dr. Theresa Michelle and Dr. Anya Harry. The primary objective of this review is to discuss the respiratory safety of indacaterol, specifically the serious adverse events of respiratory-related death, hospitalization, and intubation in patients with COPD, and the possible impact these respiratory-related adverse events might have on which dose(s) should be approved, if any.

II. Background

The major safety concern with LABAs is the increase in asthma-related deaths, hospitalizations, and intubations. Although the mechanism by which inhaled beta-agonists cause these asthma-related serious adverse events has not been elucidated, historical and epidemiological data suggest that the use of less selective beta-agonists and use of higher doses may be risk factors.

Similar concerns have been raised within the indacaterol development program with two deaths in the 300 mcg treatment arm (n= 268 in arm, total study n = 805) of a single 26-week asthma study (Study B2338) while receiving concurrent ICS. Serious adverse events (SAEs) related to asthma exacerbation or respiratory events also seemed to be more common in patients treated with indacaterol in various asthma studies. The two deaths and incidence of SAEs are described in detail in the primary and CDTL reviews. The deaths raise concern for three reasons: 1) both the deaths occurred in patients treated with the 300 mcg dose, a dose not far removed from the 150 mcg dose currently proposed for marketing; 2) asthma-related deaths in LABA asthma development programs, even when LABAs were used alone without concomitant ICS, are rare to nonexistent; and 3) a post-marketing death occurred in a 44-year old COPD patient that was reported as being asthma-related.

Although the submitted application for indacaterol is for a COPD indication, and thus far a similar signal of worsening disease with LABA use does not appear to pertain to COPD, given the nature of the signal and the Applicant's large safety database, the Agency decided that further safety analysis was warranted.

To that effect, on December 16, 2010, the Agency asked Novartis to conduct a blinded adjudicated analysis comparing indacaterol-treated patients to controls with respect to respiratory-related death, hospitalization, and intubation. The Agency believed that such an analysis was necessary to provide balancing safety data to justify the proposed higher dose (150 mcg) of indacaterol. The absence of this balancing safety data showing that there was no unacceptable safety disadvantage with the higher dose was a deficiency noted during the first review cycle and communicated to the Applicant in the action letter. Also, based on historical knowledge that serious asthma-related adverse events (deaths, hospitalizations, and intubations) may be related to higher doses of beta-agonists, the Agency decided that it was important to evaluate whether such a signal might exist in COPD. An overview of the results of this meta-analysis, based on the Agency's review, will be presented here.

Reference ID: 2932046

III. Methodology

The Agency requested that the Applicant conduct an analysis to evaluate the incidence of respiratory-related death, intubation, and hospitalization related to asthma, COPD, or pneumonia in indacaterol-treated patients compared to control. The Agency requested that the Applicant implement an adjudication committee to provide an independent assessment of all serious adverse events (SAEs) occurring during the development of indacaterol, in both COPD and asthma. The committee was charged with categorizing which deaths, hospitalizations, and intubations were respiratory-related. They were further asked to classify events according to whether they were asthma-, COPD-, or pneumonia-related. Only events that occurred on-treatment were to be included in the meta-analysis. The Agency Information Request dated December 16, 2010 is attached at the end of this document.

Per FDA request, the Applicant included all blinded, parallel-arm, randomized, controlled trials of 7 or more days treatment duration in patients with both asthma and COPD, in which indacaterol maleate was delivered using the single dose dry powder inhaler Concept 1 (or similar) device, whether or not the trials were submitted as part of the NDA. Specifically, the meta-analysis included studies in which indacaterol was administered as a randomized treatment, either with or without a concomitant inhaled corticosteroid or other adjunctive therapy, and studies with indacaterol combination products that had a blinded indacaterol treatment arm.

The Applicant analyzed the data in six defined populations based on whether the studies included were in asthma or COPD patients, and whether they were active- or placebo-controlled. For the purposes of this review, we focus our discussion here on the All-treated COPD Safety Population I, which consisted of all patients who took at least one dose of study treatment in any COPD study, whether it was active- or placebo- controlled. This data is most relevant to the current application for two reasons: 1) indacaterol is being proposed for a COPD indication and 2) the preponderance of data presented in the meta-analysis comes from a COPD patient population. Following the discussion in COPD patients will be a brief summary of the findings in the smaller asthma population.

IV. Summary of Results

All-Treated COPD Safety Population I

The All-treated COPD Safety Population included a total of 11,755 patients in 23 studies. The majority of the studies were greater than 12 weeks in duration and were conducted with the to-be-marketed Concept1 (Neohaler®) device. Of the 11,755 COPD patients, 6863 were treated with indacaterol, 2482 with placebo, and 2408 with one of three active controls (formoterol n=556, tiotropium n = 842, and salmeterol n = 1010). These studies ordered by treatment duration are presented in Table 1.

Reference ID: 2932046

Table 1 COPD Studies Included in the Meta-Analysis

ID	Study type	N	Study duration	Indacaterol Dose (mcg)*	Control	Device
B2205	DR, DB, PG/XO	660	7 days	400	PBO	RS01
QVA A2204	DB, XO	140	7 days	300, 600	PBO	Concept1
B2305	DB, XO	78	14 days	300	PBO, SAL	Concept1
B2318	DB, XO	24	14 days	300	PBO	Concept1
B2331	DB, XO	148	14 days	150, 300	PBO, TIO	Concept1
B2340	DB, XO	54	14 days	300	PBO	Concept1
B2356	DR, DB, PG	576	14 days	18.75, 37.5, 75, 150	PBO, SAL	Concept1
QVA A2203	DB, PG	250	14 days	300	PBO	Concept1
B2311	DB, XO	83	21 days	300	PBO	Concept1
B2201	DB, PG	148	28 days	400, 800	PBO	RS01
B1302	DB, PG (Japan)	336	12 weeks	150, 300	PBO	Concept1
B2341	DB, PG	1126	12 weeks	150 + TIO	None**	Concept1
B2346	Pivotal, DB, PG	290	12 weeks	150	PBO	Concept1
B2349	DB, PG	1084	12 weeks	None**	SAL	Concept1
B2350	DB, PG	1568	12 weeks	150	TIO	Concept1
B2351	DB, PG	1126	12 weeks	150 + TIO	None**	Concept1
B2354	Pivotal, DB, PG	326	12 weeks	75	PBO	Concept1
B2355	Pivotal, DB, PG	326	12 weeks	75	PBO	Concept1
B2333	DB, PG (China)	558	26 weeks	150, 300	PBO	Concept1
B2335						
- S	DB, PG	1945	2-26 weeks	75, 150, 300, 600	PBO, FOR	Concept1
- SE	DB, PG	409	26 weeks	150, 300	PBO	
B2336	DB, PG	972	26 weeks	150	PBO, SAL	Concept1
B2334	DB, PG	1716	52 weeks	300, 600	PBO, FOR	Concept1

* Indacaterol dosing frequency is once-daily unless otherwise noted
* * Only blinded-treatment arms are listed; "None" indicates that treatment or control administration was not blinded, so that treatment arm was not included in the analysis
DR: dose ranging, DB: double-blind; XO: crossover; PG: parallel group; Dreg: dosing regimen; PBO: placebo; SAL: salmeterol; TIO: tiotropium; FOR: formoterol;

In the All-treated COPD-safety population I, a total of 239 of 11,755 patients were identified as having had a respiratory-related event. Of these 239 patients, there were 219 patients who had an acute respiratory-related hospitalization or intubation. There were no acute respiratory-related deaths in this population. The incidence of total and acute respiratory-related events is depicted in Table 2. "Total" refers to any respiratory related event (e.g. pulmonary embolus, lung cancer), while "acute" includes only those respiratory-related events which were adjudicated to be asthma-, COPD-, or pneumonia-related. Table 3 shows whether acute respiratory-related events were adjudicated as having been related to either COPD or pneumonia.

Reference ID: 2932046

Table 2: Total and Acute Respiratory-Related Events: All-treated COPD Safety Population I

	Indacaterol Treatment Groups (mcg)[a]						Active Comparators			
	75 n=543	150 n=2745	150 +Tio n=1142	300 n=1422	600 n=584	ALL[b] n=6863	For n=556	Tio n=842	Sal n=1010	PBO n=2484
Composite, n(%)										
Total	6 (1.1)	43 (1.6)	16 (1.4)	54 (3.8)	15 (2.6)	134 (2.0)	32 (5.8)	7 (0.8)	14 (1.4)	52 (2.1)
Acute	6 (1.1)	37 (1.3)	15 (1.3)	47 (3.3)	15 (2.6)	120 (1.8)	31 (5.6)	6 (0.7)	12 (1.2)	50 (2.0)
Hospitalizations, n(%)										
Total	6 (1.1)	43 (1.6)	16 (1.4)	53 (3.7)	15 (2.6)	133 (1.9)	32 (5.8)	7 (0.8)	14 (1.4)	52 (2.1)
Acute	6 (1.1)	37 (1.3)	15 (1.3)	46 (3.2)	15 (2.6)	119 (1.7)	31 (5.6)	6 (0.7)	12 (1.2)	50 (2.0)
Intubations, n(%)										
Total	0	1 (<0.1)	1 (<0.1)	2 (0.1)	0	4 (0.1)	4 (0.7)	0	0	1 (<0.1)
Acute	0	1 (<0.1)	0	1 (0.1)	0	2 (<0.1)	3 (0.5)	0	0	1 (<0.1)

a. Lower dose groups and dosing regimens for which no respiratory related events were reported are not included in this table [e.g. 18.75 mcg (n=173), 37.5 mcg QD/BID (n=219), 150 mcg QOD (n= 48), 400 mcg QD (n=7)]; all dosing regimens are QD unless otherwise noted

b. Includes patients that used other similar delivery device in addition to those patients who used the Concept1 device

Total: Includes those patients who had any respiratory related event

Acute: Includes those events that were deemed COPD/pneumonia related;

For: formoterol; Tio: tiotropium; Sal: salmeterol

Hospitalizations: admission or emergency room visit > 24 hours in duration (± corticosteroid treatment)

Intubations: endotracheal intubation for mechanical ventilation for the treatment of acute hypoxemic or hypercapneic respiratory failure

Source table: Response to FDA Information Request, February 18, 2011, re2.1c1 pages 478-483

Reference ID: 2932046

Table 3: Total and Acute Respiratory-Related Events: All-treated COPD Safety Population I

	Indacaterol Treatment Groups (mcg)[a]						Active Comparators			
	75 n=543	150 n=2745	150 +Tio n=1142	300 n=1422	600 n=584	ALL[b] n=6863	For n=556	Tio n=842	Sal n=1010	PBO n=2484
Composite, n(%)										
Acute	6 (1.1)	37 (1.3)	15 (1.3)	47 (3.3)	15 (2.6)	120 (1.8)	31 (5.6)	6 (0.7)	12 (1.2)	50 (2.0)
COPD-related	5 (0.9)	36 (1.3)	14 (1.2)	41 (2.9)	13 (2.2)	109 (1.6)	30 (5.4)	5 (0.6)	10 (1.0)	47 (1.9)
PNA-related	3 (0.6)	6 (0.2)	6 (0.5)	11 (0.8)	2 (0.3)	28 (0.4)	4 (0.7)	4 (0.5)	2 (0.2)	7 (0.3)
Hospitalizations, n(%)										
Acute	6 (1.1)	37 (1.3)	15 (1.3)	46 (3.2)	15 (2.6)	119 (1.7)	31 (5.6)	6 (0.7)	12 (1.2)	50 (2.0)
COPD-related	5 (0.9)	36 (1.3)	14 (1.2)	40 (2.8)	13 (2.2)	108 (1.6)	29 (5.2)	5 (0.6)	10 (1.0)	47 (1.9)
PNA-related	3 (0.6)	6 (0.2)	6 (0.5)	11 (0.8)	2 (0.3)	28 (0.4)	4 (0.7)	4 (0.5)	2 (0.2)	7 (0.3)
Intubations, n(%)										
Acute	0	1 (<0.1)	0	1 (0.1)	0	2 (<0.1)	3 (0.5)	0	0	1 (<0.1)
COPD-related	0	1 (<0.1)	0	1 (0.1)	0	2 (<0.1)	3 (0.5)	0	0	1 (<0.1)
PNA-related	0	1 (<0.1)	0	0	0	1 (<0.1)	1 (0.2)	0	0	0

a. Lower dose groups and dosing regimens for which no respiratory related events were reported are not included in this table [e.g. 18.75 mcg (n=173), 37.5 mcg QD/BID (n=219), 150 mcg QOD (n= 48), 400 mcg QD (n=7)]; all dosing regimens are QD unless otherwise noted
b. Includes patients that used other similar delivery device in addition to those patients who used the Concept1 device
For: formoterol; Tio: tiotropium; Sal: salmeterol; PNA: pneumonia
Source table: Response to FDA Information Request, Table re2.1c1, Pages: 478-483.

The incidence of acute respiratory related events as a composite endpoint, and then broken down by hospitalizations and intubations, is shown in Table 2. Of note, these incidences are not adjusted for exposure (*see Table 4 for exposure-adjusted values*). Deaths as described elsewhere in the safety reviews for this NDA, do not appear in this table because there were no on-treatment deaths adjudicated to be acutely respiratory-related in the COPD Safety Population

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I. Although the magnitude of the signal is not large, there does appear to be a numerical trend of increasing incidence of acute respiratory-related events, particularly those that were adjudicated as having been COPD-related (Table 3) as the dose of indacaterol rises from 75 mcg to 300 mcg. This increase in the composite endpoint is driven primarily by an increase in acute-respiratory related hospitalizations. When patients were analyzed by reversibility to bronchodilator (12% and 200 mL; yes or no) and duration on treatment (> 12 weeks or <12 weeks), the trend appeared consistent across these subgroups. In the All-Treated COPD Safety Population II, which excluded any studies that were not placebo-controlled, a similar numerical trend towards a dose-related safety signal was observed.

Reviewer's comment: The exposure-adjusted incidences of acute respiratory-related events were requested from the Applicant on February 24, 2011. The exposure-adjusted incidences are summarized in Table 4. These should be interpreted with caution, as the analysis assumes a constant event rate over time, which might not necessarily be the case.

Table 4: Total and Acute Respiratory-Related Events: All-Treated COPD Safety Population I - # of events per 1000 patient-years

	Indacaterol Treatment Groups (mcg)[a]						Active Comparators			
	75 n=543	150 n=2745	150 +Tio n=1142	300 n=1422	600 n=584	ALL[b] n=6863	For n=556	Tio n=842	Sal n=1010	PBO n=2484
Composite										
Total patient years	109	865	258	747	395	2394	396	179	280	941
Total	55	54	78	80	38	62	106	45	50	63
Acute	55	47	66	70	38	55	98	39	43	60
Hospitalizations										
Total	55	53	70	78	38	60	93	45	50	63
Acute	55	46	66	68	38	54	91	39	43	60
Intubations										
Total	0	1	4	3	0	2	10	0	0	1
Acute	0	1	0	1	0	1	8	0	0	1

Source: Table re2.1c1ei, Novartis Response to FDA Information Request, February 25, 2011.
a. Lower dose groups and dosing regimens for which no respiratory related events were reported are not included in this table
b. Includes patients that used other similar delivery device in addition to those patients who used the Concept1 device

Reference ID: 2932046

All-treated Asthma Safety Population I
The All-treated Asthma Safety Population I included a total of 1914 patients in 7 studies. Of the 1914 asthma patients, 1307 were treated with indacaterol, 254 with placebo, and 353 with a salmeterol active control. Theses studies ordered by treatment duration are presented in Table 5.

Table 5: Asthma Studies Included in the Meta-Analysis

ID	Study type	N	Study duration	Indacaterol Dose (mcg)*	Control	Device
A2208	DR, DB, XO	120	7 days	100, 200, 300, 400, 600	PBO	RS01
A2216	DB, PG	372	7 days	400	PBO	RS01
D2301	XO	32	7 days	400	PBO	Concept1
B2357	DR, DB, PG	558	14 days	18.75, 37.5, 75, 150	PBO, SAL	Concept1
B2223	DReg, DB, PG	192	16 days	37.5 BID, 75, 150 QOD	PBO	Concept1
A2210	DB, XO	148	28 days	400, 800	PBO	RS01
B2338	DB, PG, Safety	750	26 weeks	300, 600	SAL	Concept1

* Indacaterol dosing frequency is once-daily unless otherwise noted
* Only blinded-treatment arms are listed
DR: dose ranging, DB: double-blind; XO: crossover; PG: parallel group; Dreg: dosing regimen; PBO: placebo; SAL: salmeterol; TIO: tiotropium; FOR: formoterol.

The meta-analysis included far fewer patients with asthma when compared with the COPD patient population. It is notable, however, that even in this relatively small cohort of asthma patients, asthma-related serious adverse events occurred at a relatively high frequency. There was 1 death and 1 intubation in the 300 mcg indacaterol group (study B2338, n~268/arm, total n=805) versus none in the placebo group. Additionally, there were 3 hospitalizations each in the indacaterol 300 mcg and 600 mcg groups versus none in the placebo group, in patients who were taking concomitant ICS per protocol. The second death (described in detail in the reviews of others) was not included in this meta-analysis because the patient was taken off study drug when she entered the hospital for an acute-respiratory related event, and was therefore counted as off-treatment. It is notable, however, that this patient, though enrolled in an asthma-clinical trial, was adjudicated as having had a COPD-related death and intubation. Although the Applicant is not proposing to market indacaterol for an asthma indication, the adjudication of this death in an asthma patient as being COPD-related illustrates the clinical overlap that exists between these two disease entities and the possible safety implications that arise when considering the doses that are proposed for registration.

V. Conclusions

Arcapta Neohaler (indacaterol maleate inhalation powder) is a long-acting beta-agonist (LABA) proposed for the long-term, once daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. The Applicant seeks approval of two doses of indacaterol, 75 and 150 mcg. Due to concerns regarding asthma- and COPD-related deaths, hospitalizations, and intubations that were raised during the review of this application, the Agency asked that the Applicant conduct a blinded adjudicated analysis comparing indacaterol-treated patients to controls with respect to respiratory-related death, hospitalization, and intubation.

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This review focused on the All-treated COPD Safety Population I as this is the indication sought by the Applicant, and the majority of data included comes from a COPD patient population. Although the magnitude of the signal is not large, there does appear to be a numerical trend of increasing incidence of acute respiratory-related events, particularly those that were adjudicated as having been COPD-related, as the dose of indacaterol rises from 75 mcg to 300 mcg. This increase in the composite endpoint is driven primarily by an increase in acute-respiratory related hospitalizations. Although we realize the limitations of this type of an analysis, one can argue that the presence of a numerical trend towards an increase in a respiratory safety signal in a population expected to have respiratory benefit from the drug, is a concerning issue. Such a trend suggests that doses above 150 mcg may carry an increased risk of respiratory events compared to placebo, and further underscores the importance of selecting the lowest effective dose of a beta-agonist bronchodilator.

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VI. Attachment: Agency Information Request, December 16, 2010

NDA 22383 **INFORMATION REQUEST**

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Attention: Ann Shea
Director, Drug Regulatory Affairs

Dear Ms. Shea:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Arcapta Neohaler, (indacaterol maleate) inhalation powder, 75 and 150 mcg.

We also refer to your September 28, 2010 submission, received on October 1, 2010, containing your response to our Complete Response Letter dated, October 16, 2009.

In our action letter for your original submission, we stated the following:

> *To support approval of two doses of indacaterol in COPD patients, provide replicate data showing clinically meaningful advantage of a higher dose compared to a lower dose, and balancing safety data to show no unacceptable safety disadvantage with the higher dose.*

In addition to the risk benefit assessment of indacaterol in COPD patients, another important potential safety issue noted in the action letter is possible asthma-related death. Additional information is required to address these issues. To facilitate our safety review of your product, we have the following request for information.

Conduct an analysis evaluating the incidence of respiratory-related death, intubation, and hospitalization in indacaterol-treated patients compared to control. Use the following criteria to provide guidance in formulating your analysis.

1. Study inclusion criteria
   a. Include all blinded, parallel-arm, randomized, controlled trials of 7 or more days treatment duration that were conducted with indacaterol maleate delivered using the single dose dry powder inhaler Concept 1 device (to-be-marketed indacaterol product) for the treatment of COPD or asthma, whether or not the trials were submitted as part of the NDA.

   b. Include trials in which the to-be-marketed indacaterol product was administered as randomized treatment, either with or without a concomitant inhaled corticosteroid (ICS)

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or other adjunctive therapy. Include trials conducted with indacaterol combination products that have a treatment arm(s) using the to-be-marketed indacaterol product.

c. Include trials with any dose of the to-be-marketed indacaterol product.

d. Include both placebo- and active-controlled trials.

e. Include trials in which there was a randomized blinded phase followed by an open label extension phase. However, include only the blinded phase of the trial in your analysis.

f. Include randomized, double-blind crossover design trials. However, include only the first cross-over period of the trial.

g. Do not include trials in healthy volunteers, indications other than asthma or COPD, uncontrolled trials, or trials designed primarily to obtain clinical pharmacology data (e.g., Phase I trials).

h. Do not include trials in children less than 12 years of age.

i. Do not include trials conducted solely with devices other than the Concept 1 device or with other formulations of indacaterol, such as alternative salts.

2. <u>Identification and adjudication of events</u>
   a. Adverse events of interest to include:

      1. all-cause death,
      2. asthma-related death,
      3. asthma-related intubation,
      4. asthma-related hospitalization,
      5. COPD-related death,
      6. COPD-related intubation,
      7. COPD-related hospitalization,
      8. pneumonia-related death,
      9. pneumonia-related intubation, and
      10. pneumonia-related hospitalization.

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b. Review all serious adverse events reported in the trials, in a manner blind to treatment, to determine whether the event involved death, hospitalization, or intubation. For events involving one or more of these outcomes, determine whether the event occurred in the setting of an acute respiratory event or was otherwise respiratory-related. Base the determination of respiratory-relatedness on the clinical judgment of an independent adjudication committee. Do not rely upon the coded adverse event term to determine respiratory-relatedness, as the reliability and validity of the specific terms may be variable.

c. For the analysis of individual events, a patient may have more than one respiratory event related to a single experience. For example, a patient who had an asthma-related hospitalization, followed by an asthma-related intubation and died of an asthma-related cause should be considered as having each of four events. All four events are to be counted in the analysis, not just the most critical.

d. Count on-treatment events, not events that occurred after treatment. Include events regardless of determination of drug-relationship.

e. For each patient who died during the trial, provide cause of death as determined by an independent adjudication committee. Compare the adjudicated cause to the adverse event resulting in death as determined by the investigator.

f. Provide narrative summaries for each patient with an adverse event of interest.

3. <u>Statistical methods</u>

a. Analyze event rates based on exposure. Include time to event analyses and hazard ratios compared to placebo. Consider methods with statistical properties suited for the known incidence rates.

b. Consider composite endpoints of all COPD-related events, all asthma-related events, and all respiratory-related events. For composite endpoints, count only the first event if more than one event occurred for a single patient.

c. Include all available blinded, controlled data for a trial. Do not truncate based on an arbitrary cut off date.

d. Include at least the following analysis sets:

1. all included studies conducted using the to-be-marketed product,

2. placebo-controlled studies,

3. COPD only studies,

4. asthma only studies, and

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5. COPD only studies greater than 7 days duration.

b. Complete the analyses for each individual indacaterol dose. Also do an analysis with all indacaterol dosage groups combined.

c. For COPD only studies, conduct a subgroup analysis of patients with baseline bronchodilator responsiveness compared to non-bronchodilator responsive patients. Define bronchodilator responsiveness according to the American Thoracic Society criteria of FEV1 change of >200 ml and >12%. [Pellegrino R, Viegi G, Brusasco RO, et al. Interpretive strategies for lung function testing. *Eur Respir J* 2005; 26:948-68.]

d. Summarize non-completers by treatment group. Include reasons for non-completion, follow-up time after dropout, AEs of interest before dropout, and any known AEs of interest after dropout.

Please provide your proposed analysis plan and timeline for analysis completion by COB on January 2. Also provide in your timeline the planned date of submission of your Adjudication Committee charter. Include a detailed description of the procedures for adjudicating serious adverse events and cause of death in your Adjudication Committee charter.

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/s/

BANU A KARIMI SHAH
04/12/2011

THERESA M MICHELE
04/12/2011

SUMMARY REVIEW OF REGULATORY ACTION

Date:	October 16, 2009
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary and Allergy Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	22-383
Applicant Name:	Novartis Pharmaceuticals Corporation
Date of Submission:	December 15, 2008
PDUFA Goal Date:	October 18, 2009
Proprietary Name:	Arcapta Neohaler
Established Name:	Indacaterol maleate
Dosage form:	Dry powder for oral inhalation
Strength:	150 mcg and 300 mcg
Proposed Indications:	Chronic Obstructive Pulmonary Disease
Action:	Complete Response

1. Introduction

Novartis submitted this 505(b)(1) application for use of Arcapta Neohaler (indacatarol maleate 150 mcg and 300 mcg dry powder for oral inhalation) for once daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. The proposed dose is one inhalation of a 150 mcg capsule once daily; with a qualifier that administration of a 300 mcg capsule once daily has been shown to provide additional clinical benefit in some patients. The application is based on clinical efficacy and safety studies. This summary review will provide an overview of the application, with a focus on the clinical efficacy and safety studies. A major discussion point in this review is the safety of indacaterol, and the dose and dosing frequency proposed for marketing.

2. Background

There are several drug classes available for the relief of airflow obstruction in patients with COPD. These include beta-2 adrenergic agonists, anticholinergic agents, combination products containing beta-2 adrenergic agonists and anticholinergic agents, combination of long-acting beta-2 adrenergic agonists and corticosteroids, and methylxanthines.

Indacaterol is a new molecular entity that belongs to the class called beta-2 adrenergic agonists. Due to its possible longer duration of action, indacaterol belongs to the subclass called long-acting beta-2 adrenergic agonists (LABA). Inhaled LABAs are widely used in the United States and worldwide to treat bronchospasm in patients with asthma and COPD. LABAs currently marketed in the United States include salmeterol, formoterol, and R,R formoterol. These are marketed either as single ingredient products or as

combination products with inhaled corticosteroids and all are dosed twice daily. Indacaterol is proposed to be dosed once daily.

Inhaled beta-2 adrenergic agonists, particularly inhaled LABAs, have a safety concern of severe asthma exacerbations and asthma related deaths in patients who use these drugs to treat the symptoms asthma. Severe asthma exacerbations and asthma related deaths have been described with short-acting inhaled beta-2 adrenergic agonists for over the last 50 years.[1, 2, 3, 4] More recently, inhaled LABAs have also been linked to severe asthma exacerbations and asthma-related deaths,[5] and has been the subject of FDA Advisory Committee meetings.[6] The mechanisms by which inhaled beta-2 adrenergic agonists cause severe asthma exacerbations and asthma related deaths are not known. Controlled studies and epidemiological studies suggest that higher dose of inhaled beta-2 adrenergic agonists is a contributing factor. In the United States, a higher dose of inhaled formoterol was not approved because the higher dose caused more severe asthma exacerbation compared to an approved lower dose.[7] Unlike patients with asthma, patients with COPD do not appear to carry a similar signal of worsening disease. Nevertheless, the selection of appropriate and safe dose is an important consideration for development of all LABAs, including for indacaterol, which is being proposed to be marketed for COPD. The dose and dosing frequency for all beta-2 adrenergic agonists for asthma and COPD are the same, and most of these drug products have both the asthma and COPD indication.

Some regulatory history relevant to the current application is described below.

Novartis studied three different inhalation indacaterol products. These were the single-dose dry powder inhaler (IND 48, 649), an HFA propelled inhalation aerosol (IND 66,337), and a multi-dose dry powder inhaler using the Certihaler device (IND 69,754). IND 48,649 was submitted on February 13, 2004, and IND 69,754 was submitted on April 27, 2004, both to study persistent asthma. An end-of-phase 2 meeting was held on August 1, 2005, to discuss the development of indacaterol multi-dose dry powder product for asthma and COPD. Most of the questions and ensuing discussions were on the asthma program. Novartis later suspended the development of the HFA propelled inhalation aerosol product due to technical reasons. The multi-dose dry powder inhaler using the Certihaler device was also suspended because of a Certihaler device related problem regarding possible excessive delivery of dose. With the suspension of these preferred delivery devices, which would allow multiple dose products, the single-dose

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[1] Benson RL, Perlman F. Clinical effects of epinephrine by inhalation. J Allergy 1948; 19:129-140.
[2] Lowell FC, Curry JJ, Schiller IW. A clinical and experimental study of isoproteronol in spontaneous and induced asthma. N Eng J Med 1949; 240:45-51.
[3] Grainger J, Woodman K, Pearce N, Crane J, Burgess C, Keane A, et al. Prescribed fenoterol and death from asthma in New Zealand, 1981-1987: a further case-control study. Thorax 1991:46:105-111.
[4] Spitzer WD, Suissa S, Ernst P, Horwitz RI, Habbick BH, et al., The use of beta-agonist and the risk of death and near death from asthma. N Eng J Med 1992; 326:501-506.
[5] US Product Labels of salmeterol and formoterol containing products.
[6] Pulmonary-Allergy Drugs Advisory Committee Meeting, July 13, 2005; and, Pulmonary-Allergy Drugs, Drug Safety and Risk Management, and the Pediatric Advisory Committee Meeting, December 10-11, 2008.
[7] Mann M, Chowdhury B, Sullivan E, Nicklas R, Anthracite R, Meyer RJ. Serious asthma exacerbation in asthmatics treated with high-dose formoterol. Chest 2003; 124:7-74.

dry powder product was continued. A second end-of-phase 2 meeting was held on October 10, 2006, to discuss the development of indacaterol single-dose dry powder product for COPD. There was some discussion on asthma, but most of the questions and ensuing discussions were on COPD. The application proposed a COPD study (Study 2335, discussed further in section 7 below) with an adaptive design to build dose ranging assessment and determination into a pivotal efficacy and safety study. The Division cautioned that initiating such phase 3 studies was risky when using a single-dose dry powder product with limited prior information and Agency review of relevant data. On December 20, 2006, Novartis submitted the COPD study with adaptive design for Special Protocol Assessment (SPA). In a letter dated February 1, 2007, the Division expressed various concerns with the study, such as the role of the data monitoring committee (DMC), use of open-label tiotropium as an active comparator, selection of the non-inferiority margin to compare to tiotropium, definition of secondary endpoint of days of COPD exacerbation, and emphasis on trough FEV1 as dose selection criterion. On February 21, 2007, Novartis submitted questions in a Type A meeting request to seek clarification on the Division's response to SPA questions. On March 12, 2007, the Division sent responses to Novartis's clarification question in preparation for the meeting. Upon receiving the Division's response, Novartis cancelled the Type A meeting. While several discussions occurred between the Division and Novartis on the study, there were no formal SPA agreements. There were no agreements on dose selection criteria.

3. Chemistry, Manufacturing, and Controls

The product Arcapta Neohaler contains Arcapta (indacaterol maleate inhalation powder) Capsules packaged in aluminum blister cards, and a Neohaler Inhaler. Arcapta Capsules are of two strengths, (b) (4) The capsules will be packaged as five blister cards with 6 capsules each in a box of 30. Each capsule contains a dry powder blend of (b) (4) of indacaterol maleate with approximately 25 mg of lactose monohydrate. The Neohaler Inhaler is a plastic device to be used for inhaling Arcapta Capsules. Neohaler Inhaler consists of a white protective cap, a base with mouthpiece, capsule chamber, and two push buttons. To deliver a dose, the patient will place an Arcapta Capsule in the capsule chamber of the Neohaler Inhaler, press the push buttons to pierce the capsule on each end, and breathe in rapidly and steadily through the mouthpiece. Novartis has submitted adequate stability data to support expiry of (b) (4) months for the Arcapta Capsules.

The drug substance is manufactured by Novartis in their facilities in Ringaskiddy, Ireland and Basel, Pratteln, and Stein, Switzerland. The drug product dosage forms (capsules) are manufactured by Novartis at their facility in Stein, Switzerland, and the Neohaler Inhaler is manufactured by (b) (4). All manufacturing and testing facilities associated with this drug product have acceptable establishment evaluation status. All DMFs associated with this application were also found to be acceptable.

4. Nonclinical Pharmacology and Toxicology

Novartis submitted results from a full preclinical program with this submission. The program included studies in which animals were dosed with the drug via inhalation to evaluate local and systemic toxicities. Inhalation toxicity studies were conducted in rats for up to 26 weeks, and dogs for up to 39 weeks. The target organs of toxicity in the rats were the nasal cavity where the observed finding was degeneration of the olfactory epithelium, and the larynx where the observed finding was squamous metaplasia. The target organs of toxicity in the dogs were the cardiovascular system where the observed findings were increased heart rates, decreased blood pressure, and myocardial necrosis and fibrosis, and liver where the observed finding was periportal liver hepatocyte vacuolation due to glycogen deposition. The cardiovascular and liver findings are known class effects of beta-2 agonist drugs. For all the observed findings of concern, there were adequate margin of safety for the expected human exposure.

Studies addressing genotoxicity, reproductive toxicity, and carcinogenicity did not show any findings of concern. All genotoxicity studies were negative. The reproductive toxicity study in rats did not reveal adverse effects on male and female fertility and reproductive performance. Embryo-fetal development studies in rats and rabbits did not show any teratogenic effects. The pregnancy category was determined to be Class C, which is the same category for many other beta-2 adrenergic agonists. Carcinogenicity was assessed in a 26 week study in C6F1/TgrasH2 hemizygous mice, and in a 24 month study in Sprague-Dawley rats. These studies showed increased incidences of uterine and endometrial stromal polyps, and ovarian leiomyomas. These tumors have been observed with other beta-2 adrenergic agonists and are known to have no human consequence. These studies were judged to be negative by the Executive CAC.

5. Clinical Pharmacology and Biopharmaceutics

Novartis submitted results from a comprehensive clinical pharmacology program with this application. The program addressed the key pharmacokinetic issues, including in vitro studies to assess protein binding and metabolism, pharmacokinetics after single and multiple does, in vitro and in vivo metabolism, effect of hepatic impairment, QTc effect, and drug-drug interaction. Studies in renal impaired patients were not conducted since renal excretion of indacaterol is a minor route of elimination. Clinical pharmacology studies included inhalation, oral, and IV administration to fully characterize the pharmacokinetics of indacaterol maleate.

Inhaled indacaterol maleate has approximately 43% biovailability resulting from both pulmonary and intestinal absorption. Elimination is primarily through the fecal route where over 90% of the dose was recovered in a mass balance study. Approximately 54% of the drug was eliminated unchanged, and approximately 23% was excreted as a hydroxylated indacaterol metabolite. Urinary elimination is a minor route with less than 2% indacaterol excreted unchanged in the urine. Following inhalation of a single 150 mcg dose of indacaterol, Cmax values were generally reached 0.25 hours post-dose. Following multiple inhalations of 150 mcg doses, the elimination half life of indacaterol was 49.1 hours. In vitro studies showed that indacaterol is a substrate for CYP3A4, and UGT1A1 can metabolize indacaterol to the phenolic O-glucoronide. Indacaterol is a low

affinity substrate for the efflux pump P-gp. Population kinetic studies did not show any significant effect of age, race, gender, hepatic impairment, and presence or absence of COPD.

Novartis conducted a QT/QTc study with 150 mcg, 300 mcg, and 600 mcg once daily 2-week dosing with indacaterol, with a single dose of moxifloxacin active control. The mean prolongation of QTcF (QT corrected by Fridericia's method) with indacaterol was less than 5 msec with the upper limit of 90% confidence interval below 10 msec for all time-matched comparison to placebo. For moxifloxacin the lower bound of the 90% confidence interval was greater than 5 msec. The QT IRT team determined that the study did not demonstrate a significant effect of indacaterol maleate on the QTcF.

6. Clinical Microbiology

Not applicable.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

Some characteristics of the relevant clinical studies that form the basis of review and regulatory decision for this application are shown in Table 1. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in the following section.

Table 1. Relevant clinical studies with indacaterol maleate

ID	Study type	Study duration	Patient Age, yr	Treatment groups*	N (ITT)	Study Year#	Countries
Short-term dose ranging studies							
2201	Parallel arm	4 weeks		IN SDDPI 400 mcg QD IN SDDPI 800 mcg QD Placebo	68 67 28	2004	Europe
2205	Parallel arm	1 week		IN MDDPI 50 mcg QD IN MDDPI 100 mcg QD IN MDDPI 200 mcg QD IN MDDPI 400 mcg QD IN SDDPI 400 mcg QD Tio 18 mcg BID Placebo	103 105 105 110 105 107	2004	Europe, North America, South America
2212	Crossover	1 day treatment		IN SDDPI 150 mcg QD IN SDDPI 300 mcg QD IN SDDPI 600 mcg QD For 12 mcg BID Placebo	51	2007	Belgium
1202	Crossover	1 day treatment		IN SDDPI 150 mcg QD IN SDDPI 300 mcg QD IN SDDPI 600 mcg QD Placebo	50	2007	Japan
Pivotal COPD studies							
B2335	Adaptive design,	Initial 2 weeks,	≥ 40	*Initial 2 weeks:* IN SDDPI 75 mcg QD	107	2008	USA, Canada, W Europe,

ID	Study type	Study duration	Patient Age, yr	Treatment groups*	N (ITT)	Study Year#	Countries
	dose ranging, efficacy and safety	Continue for 26 weeks		IN SDDPI 150 mcg QD IN SDDPI 300 mcg QD IN SDDPI 600 mcg QD For 12 mcg BID Tio 18 mcg QD Placebo *Continue 6 months:* IN SDDPI 150 mcg QD IN SDDPI 300 mcg QD Tio 18 mcg QD Placebo	105 110 102 112 112 104 325 341 331 294		India, S Korea, Argentina, Turkey, Taiwan
B2334	Efficacy and safety	52 weeks	≥ 40	IN SDDPI 300 mcg QD IN SDDPI 600 mcg QD For 12 mcg BID Placebo	405 396 400 399	2008	W & E Europe, Russia, C/S America, Middle East, S Korea
B2346	Efficacy and safety	12 weeks	≥ 40	IN SDDPI 150 mcg QD Placebo	211 205	2008	USA, Australia, NZ, Belgium
Short-term crossover studies							
B2340	Efficacy and safety	2 weeks	≥ 40	IN SDDPI 300 mcg QD Sal 50 mcg BID Placebo	68	2008	USA, Belgium, Spain
B2305	Efficacy and safety	2 weeks	≥ 40	IN SDDPI 300 mcg QDAM IN SDDPI 300 mcg QDPM Sal 50 mcg BID Placebo	96	2008	France, Germany, Spain
B2307	Efficacy and safety	Single dose	≥ 40	IN SDDPI 150 mcg QD IN SDDPI 300 mcg QD Advair 50/500 mcg Albuterol 200 mcg Placebo	89	2008	USA, Belgium, Germany, Hungary
Asthma study							
B2338	Efficacy and safety	26 weeks	≥ 12	IN SDDPI 300 mcg QD IN SDDPI 600 mcg QD Salmeterol	268 268 269	2008	USA, Canada, Europe, South America

*IN SDDPI = Indacaterol single dose dry powder inhaler, Arcapta Neohaler (Indacaterol single dose dry powder inhaler); IN MDDPI = Indacaterol multiple dose dry powder inhaler; For = Foradil Aerolizer (formoterol fumarate inhalation powder); Tio = Spiriva Handilaler (tiotropium bromide inhalation powder); # Year study subject enrollment ended

As mentioned in section 2 above, Novartis studied three different inhalation indacaterol products – single dose dry powder inhaler, which is the subject of this application, multi dose dry powder inhaler, and an HFA propelled inhalation aerosol. Table 1 above lists relevant studies that used both the single dose dry powder inhaler and the multi dose dry powder inhaler. The clinical data generated with the multiple dose dry powder inhaler and the HFA propelled inhalation aerosol has limited value for the single dose dry powder inhaler because the in vitro delivery characteristics for the three products were substantially different.

b. Design and conduct of the studies

Short term dose ranging studies (2201, 2205, 2212, 1202):

These were the early studies conducted by Novartis to gather some dosing information for indacaterol. These studies used doses ranging from 50 mcg to 800 mcg and used different formulations and delivery devices. These studies did not provide useful dosing and dosing interval information because the studies were limited in duration, used different devices and formulations, and some had small sample sizes. Since dose selection information was limited, Novartis designed the first pivotal COPD study that had an adaptive design to build dose ranging information in a pivotal efficacy and safety study. In these short term dose ranging studies and in other studies dosing frequency other than once daily was not explored.

Pivotal COPD studies (B2335, B2334, B2346):

Study B2335, the adaptive design study, was randomized, double-blind (except for the tiotropium arm, which was open label), parallel-group, in design, conducted in patients with predominately moderate-to-severe COPD. Patients were required to be 40 years of age and older; have a clinical diagnosis of COPD, FEV1/FVC <70%, FEV1 ≤ 80% predicted; and be a current or previous smoker with a smoking history of ≥20 pack years. The study had a 2 week run-in period, followed by an initial 2 week double blind treatment period. There were seven treatment arms in this period as shown in Table 1. An independent DMC was chartered to review the 2 week interim data and make a decision on dose selection. [*The guideline given to DMC for dose selection was as follows: 1. The selected dose needed to be 0.12 L greater than placebo for trough FEV1, and should also have higher trough FEV1 than tiotropium and formoterol. 2. The dose needed to have higher FEV1 AUC 1-4 hours than tiotropium and formoterol. 3. The lowest dose that fulfill the above two criteria and the next highest dose are to be selected.*]. After the dose selection, patients continued on a double blind treatment period for a total of 26 weeks. There were four treatment arms in this period as shown in Table 1. The primary efficacy variable was 24-hour post-dose trough FEV1 after 12 weeks of treatment. The 24-hour post-dose trough FEV1 was defined as the average of two FEV1 measurements taken in the clinic after 23 hours 10 minutes and 23 hours 40 minutes after the previous dose. All patients had serial spirometry covering the first 1 hour after dosing (time points 5 minutes, 30 minutes, and 1 hour) and last 1 hour (time points 23 hours 10 minutes and 23 hours 40 minutes) after dosing at clinic visit days 2, 15, 85, and 183. In a subset (about 30 to 40 patients in each treatment arm) 12-hour serial spirometry (time points 2 hour, 4 hour, 6 hour, 8 hour, 10 hour, and 11 hour 45 minutes) were done on day 1, and after 2, 12, and 26 weeks of treatment. Other efficacy measures included days of poor control, COPD exacerbation, other variables from spirometry, peak expiratory flow measures, SGRQ, transitional dyspnea index (TDI) score, and BODE (body mass, airflow obstruction, dyspnea, and exercise capacity) index, MMRC dyspnea score, and 6 minute walk. Safety assessment included adverse event recording, vital signs, physical examination, clinical laboratory and hematology measures, and ECGs in all patients, and Holter monitoring in a subgroup of patients.

Studies B2334 and B2346 were randomized, double-blind, parallel group in design, conducted in patients with predominately moderate-to-severe COPD. The patient population, efficacy measures, and safety measures in these studies were similar to study B2335. The study duration and treatment arms were different as shown in Table 1. The intent of study B2234 was to gather efficacy and safety data on long term use, albeit for doses higher than the proposed 150 mcg starting dose. The intent of study B2346 was to gather efficacy and safety data for the proposed 150 mcg starting dose.

Short-term crossover studies (B2340, B2305, B2307):

Studies B2340, B2305, and B2307 were randomized, double-blind, crossover in design, conducted in patients with predominately moderate-to-severe COPD. Study B2340 was designed to collect data to construct a 24 our spirometry profile. Study B2305 was designed to compare the efficacy of morning and evening indacaterol dose. Study B2307 was designed to assess the onset of action of indacaterol.

Asthma study (B2338):

This study was randomized, double-blind, active control parallel group in design conducted in patients with moderate-to-severe persistent asthma. There was no placebo group in the study. The intent of the study was to evaluate the safety of indacaterol compared to salmeterol in patients with asthma using inhaled corticosteroids as background treatment.

c. Efficacy findings and conclusions

The clinical program shows that Arcapta Neohaler at 150 mcg and 300 mcg doses provide a statistically significant bronchodilator effect in patients with COPD with replicate findings with these two doses. But, the clinical program does not establish that these two doses are the appropriate doses for COPD patients, and also does not establish appropriate dosing frequency for indacaterol. Furthermore, there is no replicate finding to support the dosing recommendation statement that a 300 mcg dose provides additional clinical benefit in some patients over the 150 mcg dose.

In the pivotal adaptive design dose-ranging study, all active treatment arms provided a statistically significant bronchodilator effect as measured by trough FEV1 compared to placebo at the interim analysis time point of 2 weeks, with no significant differences among any of the Arcapta Neohaler doses (Table 2). Other measures of spirometry variables and other secondary measures went in the similar direction with trough FEV1 (data not shown in this review). Based on the DMC dose selection criteria using trough FEV1 and FEV1 AUC 1-4 hours (described in previous section), the 75 mcg dose was considered to be suboptimal and the 150 mcg and 300 mcg doses were carried forward for further assessment in the study. At the 2 week time point, the numerical differences between the 75 mcg dose and the higher Arcapta Neohaler doses were small. It appears that all doses were at the plateau of the dose-response curve. The data show that the

DMC dose selection criteria, which were geared towards selection of an Arcapta Neohaler dose that would provide numerically higher efficacy than the active comparators, may have led to the selection of doses higher than necessary.

Table 2. Study B2335, LS Mean for trough FEV1 (in L) at 2 weeks (interim analysis) and 12 weeks (primary efficacy time point)

Treatment	Baseline	Treatment comparison	Treatment Difference At 2 weeks LS Mean (95% CI)	Treatment Difference At 12 weeks LS Mean (95% CI)
IN 75 mcg	1.46	IN 75 - Placebo	0.15 (0.09, 0.20)	
IN 150 mcg	1.49	IN 150 - Placebo	0.18 (0.12, 0.24)	0.18 (0.15, 0.21)
IN 300 mcg	1.52	IN 300 - Placebo	0.21 (0.15, 0.27)	0.18 (0.15, 0.21)
IN 600 mcg	1.51	IN 600 - Placebo	0.20 (0.14, 0.25)	
For 12 mcg	1.42	For - Placebo	0.11 (0.06, 0.17)	
Tio 18 mcg	1.45	Tio - Placebo	0.14 (0.08, 0.19)	0.14 (0.11, 0.17)
Placebo	1.31			

IN = Indacaterol single dose dry powder inhaler, Arcapta Neohaler (Indacaterol single dose dry powder inhaler); For = Foradil Aerolizer (formoterol fumarate inhalation powder); Tio = Spiriva Handilaler (tiotropium bromide inhalation powder);

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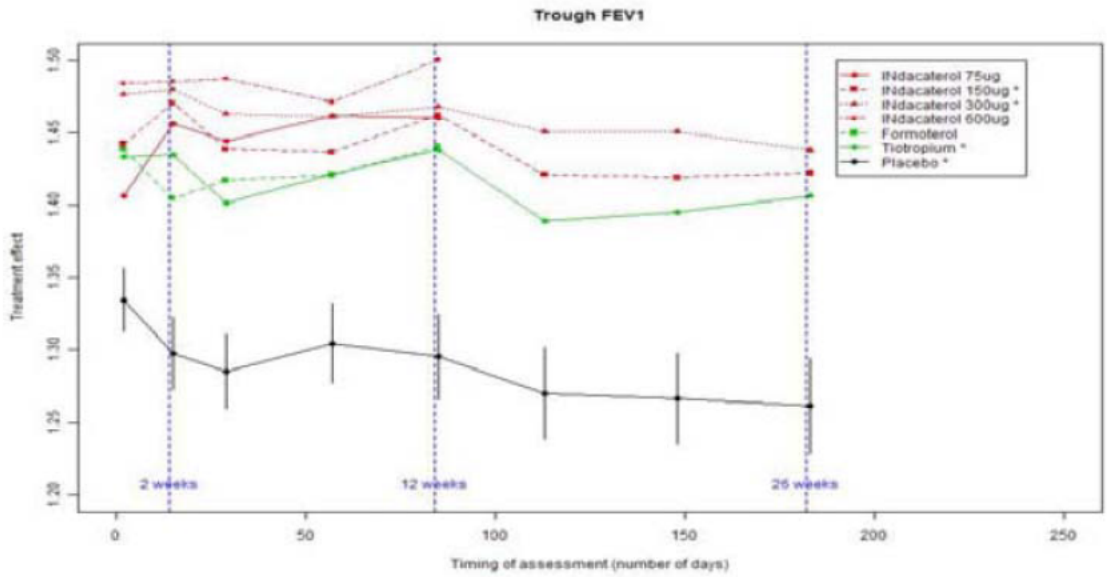

Figure 1. Study B2335, Summary of trough FEV1 in various treatment arms at different assessment times. Note: 2 weeks is interim analysis, 12 weeks is primary efficacy time point, and 26 weeks is end of the study

In the other two pivotal studies, Arcapta Neohaler 150 mcg, 300 mcg, and 600 mcg provided a statistically significant bronchodilator effect as measured by trough FEV1 compared to placebo (Table 3). Other measures of spirometry variables and other secondary measures went in a similar direction to trough FEV1 (data not shown in this review). Similar to the adaptive design study, in these studies separation between the

Arcapta Neohaler doses were minimal to none, but the separation between Arcapta Neohaler and Foradil Aerolizer 12 mcg were numerically large.

Table 3. Studies B2334 and B 2346, LS Mean for trough FEV1 (in L) at 12 weeks (primary efficacy time point)

Treatment	Baseline at week 12	Treatment comparison	Treatment Difference LS Mean (95% CI)
Study B2334			
IN 300 mcg	1.48	IN 300 - Placebo	0.17 (0.13, 0.20)
IN 600 mcg	1.48	IN 600 - Placebo	0.17 (0.13, 0.20)
For 12 mcg	1.38	For - Placebo	0.07 (0.04, 0.10)
Placebo	1.31		
Study B2346			
IN 150 mcg	1.49	IN 150 - Placebo	0.13 (0.09, 0.18)
Placebo	1.35		

IN = Indacaterol single dose dry powder inhaler, Arcapta Neohaler (Indacaterol single dose dry powder inhaler); For = Foradil Aerolizer (formoterol fumarate inhalation powder);

There are three efficacy questions that remain unanswered. These are dose selection, dosing frequency, and efficacy advantage of 300 mcg over 150 mcg.

The first question is whether the doses of Arcapta Neohaler proposed to be marketed are optimum, or whether a lower dose would be equally or similarly effective. Since Novartis did not test doses lower than 75 mcg once daily in the program, this question cannot be answered without a further dose exploration study. Based on the observation that all doses were at the plateau of the dose-response curve (Table 2, Figure 1, Table 3), it is possibly that a dose lower than 75 mcg once daily would be effective. Given the general safety concerns with LABAs, specifically the dose-related finding of severe asthma exacerbations and asthma-related deaths, exploration of lower doses will be necessary. The DMC dose selection criteria which were geared towards selection of an Arcapta Neohaler dose that would provide numerically higher efficacy than the active comparators is likely to result in selection of a high dose. The 150 mcg and 300 mcg doses selected seemed to provide numerically higher bronchodilator responses compared to formoterol, another LABA (Table 2, Figure 1, Table 3), but this may not be a safe strategy. It is worth noting that although a high dose of formoterol (Foradil Aerolizer 24 mcg) provided a numerically superior bronchodilator response compared to the approved dose of formoterol (Foradil Aerolizer 12 mcg) in patients with asthma,[8] the higher dose was not approved for marketing in the United States because of safety concerns noted in the formoterol NDA studies.[9] As with other beta-2 adrenergic agonists, the dose of formoterol for asthma and COPD are the same.

[8] US Product Label for Foradil Aerolizer (formterol fumarate inhalation powder).
[9] Mann M, Chowdhury B, Sullivan E, Nicklas R, Anthracite R, Meyer RJ. Serious asthma exacerbation in asthmatics treated with high-dose formoterol. Chest 2003; 124:7-74.

The second question is whether indacaterol is truly a once daily drug, or whether it is more appropriate to dose this product twice daily or more frequently. It is possible that similar efficacy can be achieved with twice daily or a more frequent dosing interval compared to a once daily dosing interval, with less total daily dose, hence with better safety. Since Novartis did not compare once daily dosing to a more frequent dosing interval in the program, this question cannot be answered without further dose frequency exploration study. At the other end of the dosing frequency spectrum, with the half-life of indacaterol being about 49 hours, it is a fair question to ask whether indacaterol should be dosed less frequently than once daily to prevent drug accumulation and alleviate drug accumulation related safety concerns. From efficacy data, it appears that indacaterol may not be effective at a dosing frequency less than once daily. In study B2340 where serial FEV1 measurements were done over 24 hour time period, the time FEV1 response curve for indacaterol seemed to run parallel to that for salmeterol for first 12 hours (Figure 2). Salmeterol is approved for administration twice daily. In this study the indacaterol dose used was 300 mcg, which is the higher than the recommended starting dose. Selection of dosing interval based solely on trough FEV1 is not appropriate because there is a normal physiologic increase in FEV1 in early morning hours (Figure 2).

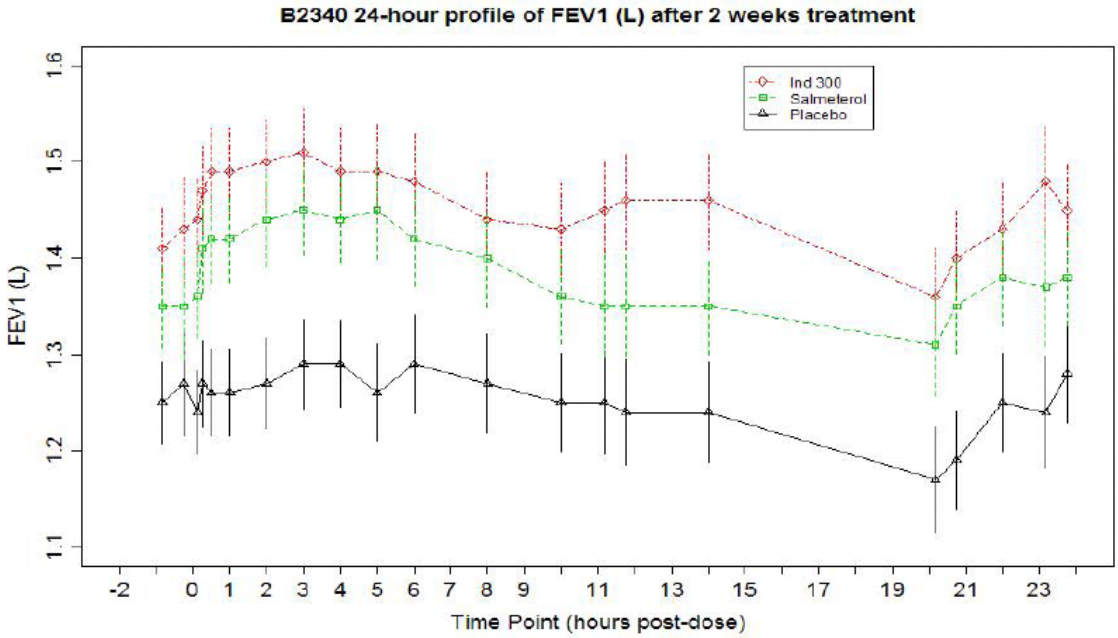

Figure 2. Study B2340, Serial FEV1 profile over 24 hours after 2 weeks of treatment

The Division's concerns with dose and dosing frequency were communicated to Novartis in the NDA filing letter (74-day letter). Shortly after receipt of the letter Novartis submitted an unsolicited pharmacodynamic modeling analysis to further justify the dose and dosing frequency. The report included meta-analysis of data from seven studies in COPD patients and four studies in asthma patients to support the dose, and analysis of peak-to-trough FEV1 ratios from three studies to justify the dosing interval. There are major flaws with such pharmacodynamic modeling analyses that limit the utility of the

findings. The modeling pooled all available FEV1 data from all time points from various studies. It is not appropriate to pool FEV1 data from various time points because it is known that the FEV1 response to beta-2 adrenergic agonists changes over time. It is also not appropriate to pool different studies for efficacy analysis because of varying demographic and baseline disease characteristics. The peak-to-trough analysis has problems because the trough FEV1 measure is influenced by the normal physiological increase in FEV1 that occurs in the early waking hours in addition to the drug effect. Nevertheless, even the pharmacodynamic modeling analysis did not provide persuasive support of the dose and the dosing frequency. The clinical data from the three pivotal studies, particularly the dose-ranging adaptive design study B2335, remains the more relevant data source to assess dose and dosing frequency.

The third question is whether the proposed labeling statement that the 300 mcg dose provide additional clinical benefit in some patients over the 150 mcg dose. The only study that compared 300 mcg and 150 mcg dose head-to-head is the adaptive design study B2335. In this study at the interim analysis time point of 2 weeks there was a numerical separation favoring the 300 mcg dose, but at the primary efficacy analysis time point of 12 weeks, there were no difference between the two doses (Table 1, Figure 2). Therefore, the proposed labeling statement is not supported. To support such a labeling statement, Novartis will need to provide replicate efficacy data showing clinically meaningful advantage of 300 mcg dose over 150 mcg, and provide balancing safety data showing no unacceptable safety disadvantages that could negate the efficacy advantage, if any.

8. Safety

a. Safety database

The safety assessment of Arcapta Neohaler for COPD patients is based on studies shown in Table 1. The primary safety database is the three pivotal COPD studies. The safety database is adequate and typical for other similar applications.

b. Safety findings and conclusion

The safety data do not raise any obvious safety concern in the COPD patients that would preclude approval by itself, but in the context of the dose and dosing frequency selected from efficacy standpoint, the safety data seem to suggest that a dose higher than necessary is proposed for marketing. Marketing an unnecessary and unreasonable high dose has safety concerns.

In the three pivotal COPD studies (Table 1) there were a total of 14 deaths. The deaths were balanced across all treatment arms and do not raise any unique safety concerns in COPD patients.

In the asthma study (Table 1) there were two deaths, both in indacaterol 300 mcg once daily arms. One death occurred in a 60 year old male with a seven year history of asthma with no other active medical problems. On day 165 of treatment the patient was hospitalized for one day with acute asthma exacerbation. Four days later he again

developed acute asthma exacerbation and died on his way to the hospital. This patient was on inhaled beclomethasone 500 mcg twice daily for approximately the first six months of the study, and then on inhaled budesonide 400 mcg twice daily for rest of the study till death. The second death occurred in a 70 year old woman with a two year history of asthma, allergic rhinitis, osteoporosis, and past history of respiratory arrest and anaphylactic reaction. On day 119 of treatment the patient experienced a cardiac arrest at home. The patient was resuscitated, intubated, and admitted to the hospital. On evaluation, significant findings were a small pneumothorax and pulmonary hyperinflation consistent with asthma. There were no findings consistent with myocardial infarction or other cardiovascular diseases. Life support was withdrawn on day 11 of hospitalization on family request and the patient expired. The patient was on inhaled mometasone 220 mcg once daily for the entire duration of the study.

Although the submitted application is for COPD, the two deaths related to Arcapta Neohaler in patients with asthma is concerning. The deaths are reminiscent of asthma related deaths seen with other LABAs. Both the deaths occurred in patients on the 300 mcg dose, which is one of the two doses proposed for COPD patients. Asthma related deaths in typical LABA programs for asthma, even when LABAs are used alone without concomitant inhaled corticosteroids, are very rare to nonexistent. In the indacaterol program two possible asthma-related deaths occurred in patients receiving indacaterol in a study where there was a salmeterol active comparator and in which the LABAs were administered concomitant with inhaled corticosteroids.

In the pivotal COPD studies, the adverse event profile was typical for COPD patients with respiratory disorder and cardiac disorders being most common. Adverse events leading to discontinuations, serious adverse events, and commonly reported adverse events did not raise any specific or unique safety concerns for Arcapta Neohaler in COPD patients.

To assess any potential effects of beta-2 adrenergic stimulation on the cardiovascular system, Novartis analyzed data pooled phase 3 COPD safety database adverse events for cardiac or cerebrovascular (CCV) events. Results of the analysis are shown in Table 4. In general, the tiotropium arm had the highest frequency, which is expected for an anti-cholinergic drug, and the placebo arm had the lowest frequency. Indacaterol arms had higher frequencies compared to formoterol. There was no dose ordering for the indacaterol doses and the number of patients with serious adverse events was small. The increased frequency of serious adverse events with indacaterol compared to placebo and to formoterol, particularly for later time points, is concerning (Table 4). This analysis suggests that indacaterol may have inherently more cardiac or cerebrovascular effects, or all the doses of indacaterol may be high relative to formoterol.

Table 4. Percentage of patients in various treatment groups from pooled COPD studies presenting with ≥1 cardiac or cerebrovascular (CCV) adverse events (AE) or serious adverse events (SAE)

	IN 150 mcg	IN 300 mcg	IN 600 mcg	For 12 mcg	Tio 18 mcg	Placebo
AE at 3 months	3.03	3.52	2.01	1.98	4.34	2.46
SAE at 3 months	0.96	0.94	0.55	0.18	1.45	0.66

	IN 150 mcg	IN 300 mcg	IN 600 mcg	For 12 mcg	Tio 18 mcg	Placebo
AE at 6 months	5.77	5.04	3.29	3.96	5.78	3.65
SAE at 6 months	2.16	1.41	1.28	0.54	2.17	1.06
AE at 12 months	-	6.6	6.1	6.5	-	3.90
SAE at 12 months	-	3.4	2.6	1.4	-	0.9
IN = Indacaterol single dose dry powder inhaler, Arcapta Neohaler (Indacaterol single dose dry powder inhaler); For = Foradil Aerolizer (formoterol fumarate inhalation powder); Tio = Spiriva Handilaler (tiotropium bromide inhalation powder);						
From Novartis submission: Summary of Clinical Safety, pages 187-195						

There were no unique or findings of concerns with indacaterol on analysis of clinical laboratory values, ECGs, and Holter monitoring.

c. REMS/RiskMAP

Not relevant because Arcapta Neohaler will not be approved in this cycle.

9. Advisory Committee Meeting

An advisory committee was not convened for this application. The efficacy and safety findings seen in the clinical program were fairly obvious. There were no issues that warrant discussion at an advisory committee meeting.

10. Pediatric

COPD is an adult disease, therefore, specific pediatric studies would not be required that relate to this action specific to COPD. Prior to the scheduled August 26, 2009, PeRC meeting, the Committee agreed that a full waiver should be granted because studies would be impossible or highly impracticable because the disease does not exist in pediatric patients. The program was not discussed at the PeRC meeting.

11. Other Relevant Regulatory Issues

a. DSI Audits

No DSI audit was conducted for this application. During review of this application the clinical team did not identify any irregularities that would raise concerns regarding data integrity. All studies were conducted in accordance with accepted ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. Three investigators had significant financial interest in Novartis. The number of subjects that these investigators enrolled was not large enough to alter the outcome of any study. Furthermore, the multi-center nature of the studies makes it unlikely that these financial interests could have influenced or biased the results of these studies.

c. Others

There are no outstanding issues with consults received from DDMAC, DMEPA, or from other groups in CDER.

12. Labeling

a. Proprietary Name

Novartis initially submitted Arcapta (b) (4) as the proposed proprietary name. The DMEPA rejected this proposed name (b) (4) Novartis subsequently submitted Arcapta Neohaler as the proposed proprietary name which was accepted by the DMEPA.

b. Physician Labeling

The labeling was not reviewed in detail and not discussed with Novartis during review of this application because the application will not be approved in this review cycle. There are efficacy and safety concerns that preclude meaningful labeling discussion.

c. Carton and Immediate Container Labels

The carton and immediate container labels were not reviewed in detail because the application will not be approved in this review cycle.

d. Patient Labeling and Medication Guide

The patient labeling and medication guide were not reviewed in detail because the application will not be approved in this review cycle.

13. Action and Risk Benefit Assessment

a. Regulatory Action

The applicant has not submitted adequate data to support approval of Arcapta Neohaler for the maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and emphysema. The action on this application will be Complete Response.

The comments below are for the Complete Response action letter.

1. The submitted data do not provide substantial evidence of safety to support use of Arcapta Neohaler at the proposed doses of 150 mcg and 300 mcg once daily in patients with chronic obstructive pulmonary disease (COPD). At the proposed doses there were unacceptable higher frequencies of cardiovascular and cerebrovascular adverse events compared to placebo and to formoterol in patients with COPD, and possible asthma related deaths compared to salmeterol in patients with asthma. The submitted studies do not show any meaningful efficacy difference between the 75 mcg once daily compared to the 150 mcg or 300 mcg once daily doses. Appropriate dosing frequency has also not been explored in clinical studies.

To support approval of indacaterol in COPD patients, conduct clinical studies to explore efficacy and establish safety of doses lower than the proposed 150 mcg dose, and study various dosing frequencies to support your proposed dosing frequency.

2. The submitted data do not provide substantial evidence to support use of two different doses in patients with COPD. The data submitted did not show a clinically meaningful advantage of 300 mcg dose over 150 mcg dose, especially in regards to potential safety disadvantages associated with the administration of a higher dose.

   To support approval of two doses of indacaterol in COPD patients, provide replicate data showing clinically meaningful advantage of a higher dose compared to a lower dose, and balancing safety data to show no unacceptable safety disadvantage with the higher dose.

b. Risk Benefit Assessment

The overall risk benefit assessment does not support approval of Arcapta Neohaler at the proposed doses of 150 mcg and 300 mcg once daily for maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including bronchitis and emphysema. The use of LABAs, while clinically useful at the correct dose in the appropriate patient population, has the potential to cause considerable dose-dependent morbidity and mortality in both the older medically fragile patients with COPD (especially those affecting the cardiovascular and central nervous systems) as well as in asthma patients where there is a increased risk of severe asthma exacerbations and asthma related deaths. Novartis has not submitted adequate data to support a dose or doses and dosing frequency of indacaterol that are both safe and efficacious. An effective dose or doses on the whole spectrum of the dose-response curve with an acceptable safety profile has not been sufficiently explored for indacaterol. There was little difference in FEV1 response at doses from 75 mcg to 300 mcg once daily for indacaterol. The dose selection criteria were geared towards selection of dose that would provide superior efficacy than approved active comparators. This resulted in selection of high doses. Safety data using the proposed and higher doses showed increased cardio- and cerebrovascular adverse events compared to both placebo and the active beta agonist control, formoterol, a known risk for the beta-2 agonist class of drugs. Safety data from the asthma patients also support the conclusion that the proposed doses are too high and, and doses 300 mg once daily and above unsafe for patients with asthma. Novartis has proposed 150 mcg and 300 mcg doses for marketing, but has not provided adequate replicate data showing clinically meaningful advantage of 300 mcg dose over 150 mcg, and provide balancing safety data showing no unacceptable safety disadvantages that could off balance efficacy advantage, if any.

c. Post-marketing Risk Management Activities

Not relevant because the application will not be approved in this review cycle.

d. Post-marketing Study Commitments

Not relevant because the application will not be approved in this review cycle.

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/s/

BADRUL A CHOWDHURY
10/16/2009

Summary Basis for Regulatory Action

Date	October 16, 2009
From	Curtis J Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA # Supp #	22-283
Applicant Name	Novartis
Proprietary / Established (USAN) Names	Arcapta Neohaler Indacaterol maleate
Dosage Forms / Strength	Inhalation Powder in hard gelatin capsules 150 and 300 mcg
Proposed Indication(s)	Long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.
Action:	*Complete Response*

1. Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding indacaterol and the reader should refer to the reviews in the action package for a more detailed discussion. Indacaterol is a new molecular entity belonging to the beta-2 adrenergic agonist class of drugs. Locally-acting beta-2 agonists, which cause dilation of bronchial smooth muscle upon inhalation, are commonly used in the treatment of patients with COPD, both as monotherapy or combined with other classes of inhaled medications such as corticosteroids. Formoterol and salmeterol, also beta-2 agonists, are currently approved domestically for this indication. The three aforementioned drugs are known as long-acting beta agonists (LABAs) due to their longer pharmacodynamic effect compared to shorter acting beta agonists such as albuterol (note: the terminal plasma half-life of albuterol is 4.6 hours which is similar to that of salmeterol at 5.5 hours and formoterol at 10 hours on average, so the pharmacodynamics effect may not be reflected in the pharmacokinetic profile). Indacaterol would be expected to have a similar mechanism of action and clinical effect as the other LABAs, but the sponsor anticipates that its longer half-life (systemic elimination half-life of 49 hours on average) would allow for daily dosing intervals instead of twice a day as it is with salmeterol and formoterol.

The safety of the use of LABAs in therapy for asthma is currently under intense scrutiny. As Dr. Durmowicz notes, the SMART[1] study demonstrated that salmeterol use was associated with increased respiratory-related deaths and life-threatening experiences in patients with

[1] Nelson HS, Weiss ST, Bleecker ER, et al. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest, 2006 Jan; 129(1):15-26

asthma. Additionally, our own internal review of formoterol (and subsequent publication[2]) for use in asthma revealed a dose-related increase in serious asthma exacerbations as the dose increased from 12-mcg to 24-mcg given twice a day. This led us to approve only the 12-mcg dose, but has given caution that the safety signals associated with beta agonist use (or at least loss of asthma control/exacerbations) in patients with asthma is probably dose related and may have a narrow therapeutic index. Of course these findings were in a population with a different disease pathophysiology, asthma compared to COPD, than is the subject of this application, but most COPD patients also have some degree of reversible bronchospasm and in some patients COPD may not always be completely disassociated from asthma. As such, we have heightened concerns that sponsors exercise great care in finding a dose that optimizes the efficacy of LABA in regard to the known risk profile regardless of which disease is being treated. It should also be noted that typically, beta agonists are developed, and demonstrate an optimal risk:benefit ratio for asthma first and then that dose is carried over for trials in the COPD population. This application is different in that the sponsor is seeking a COPD indication first, although they have conducted large clinical trials in asthma patients. I also note, that while we have seen the adverse respiratory events associated with the use of salmeterol in patients with asthma as described above, this does not seem to be the case in a COPD population as described in the TORCH[3] study (note: while I did previously comment that most patients with COPD had some bronchospasm reversibility, inclusion criteria for the TORCH study limited FEV1 increase to with albuterol to less than 10% so the subjects had limited bronchospasm reversibility). The secondary endpoints presented in TORCH indicate that death from any cause or COPD-related death (as well as cardiovascular-related death) were similar in those patients receiving salmeterol or placebo.

The applicant based dose selection on the principal of demonstrating superior efficacy by point estimate compared to active comparators. In a narrow therapeutic window drug, this principal would predictably lead to choosing a dose, depending on the steepness of the safety profile slope, which may have increased efficacy at the expense of safety. This is an unfortunate dogma for the sponsor to have followed with this class of drugs, as we have significant concerns regarding safety such that an optimal risk:benefit ratio would dictate that maximal efficacy or speed to onset of action should be sacrificed in the interest of an optimal safety profile. It is particularly perplexing that the sponsor would follow this path in light of their previous experience with formoterol. As stated earlier, during the development of formoterol, the 24-mg dose clearly had adverse pulmonary SAEs compared to the 12-mg dose and led to the 24-mg dose not being approved. For this application they purposely chose a dose that had a higher FEV1 response compared to formoterol 12-mcg, which one could intuit may give a safety profile closer to the formoterol 24-mcg dose. This is perplexing as we didn't approve the 24-mg dose due to safety issues (even though this dose did seem to give approximately a 100cc increase in FEV1 compared to the lower dose). The choice of dosing to carry forward for phase 3 testing also seems perplexing in that the 75-mcg dose appears clinically indistinguishable (or the difference is so small as to be irrelevant) at the 15-day evaluation (study B2335s-to be discussed below) that was used as the decision point. Further data

[2] Mann M, Chowdhury B, Sullivan E, et.al. Serious Asthma Exacerbations in Asthmatics Treated With High-Dose Formoterol. Chest, 2003; 124; 70-74

[3] Peter MA, Calverley MD, Anderson JA. Et al. Salmeterol and fluticasone propionate and survival in Chronic Obstructive Pulmonary Disease. NEJM, 2007 Feb; 356(8): 775-789

evaluated by the team clearly demonstrate that at the 12-week primary evaluation point, the clinical effects of the 75-mcg dose continued to be virtually indistinguishable from those of the 150-mcg dose. Yet if formoterol taught us (and one would think the sponsor would understand this point since it is their drug) anything, it is that a doubling of the dose can carry dire consequences to the adverse event profile. However, to be fair, although we did voice our concern regarding dose selection at multiple meetings, we did not raise this issue in a direct fashion. Also, the December 2008 advisory committee meeting regarding the risks and benefits of LABAs in the treatment of adults and children demonstrates the continued evolution of thinking about risks of this class of drugs in the intervening years since the sponsor initiated their program.

In any event, as I will discuss further below, this application has not done adequate dose exploration to maximize the risk: benefit ratio for indacaterol. As such, I recommend a Complete Response for this application.

Efficacy

This has been thoroughly covered in Drs. Liu, Durmowicz and Chowdhury's reviews. There is not any dispute that the doses that the sponsor has chosen to bring forward are effective in increasing FEV1 compared to placebo in subjects with COPD. The following table from Dr. Liu's review (page 10) indicates the various studies submitted in support of efficacy.

Table 1 Design of pivotal studies.

Study ID (Period)	Location	Design and treatment duration	Number of Patients randomized	Treatment arms (Inda=Indacaterol) (For=Formoterol) (Tio=Tiotropium)
B2334 (Oct. 2006 - Jul. 2008)	West Europe, East Europe, South and Central America, Asia	52 weeks, Parallel-arm, Placebo and active controlled	405 396 399 400	Inda 300 mcg Inda 600 mcg Placebo (double dummy) For 12 mcg (b.i.d)
B2335s (Apr. 2007 - Aug. 2008)	USA, Canada, South America, West Europe, Asia	26 weeks, Parallel arm, Placebo and active controlled	107 105 / 325 † 110 / 341 † 102 104 / 294 † 112 112 / 331 †	Inda 75 mcg Inda 150 mcg * Inda 300 mcg * Inda 600 mcg Placebo (double dummy) * For 12 mcg (b.i.d) Tio 18 mcg * (open-label)
B2346 (Feb. 2008 - Jul. 2008)	USA, Belgium, New Zealand	12 weeks, Parallel-arm, Placebo controlled	211 205	Inda 150 mcg Placebo

- * Treatment arms that were continued into stage 2.
- † Sample size in stage 2.

These results of these studies for the primary endpoint are present in the table below from Dr. Liu's review.

Table 2 Summary of the primary efficacy endpoint (trough FEV_1 at week 12) in pivotal studies.

Study	Treatment	Mean (L)	SE (L)	Treatment difference	Mean (L)	SE (L)	95% CI (L)	P value
B2335s Stage 2	Placebo	1.28	0.015	---	---	---	---	---
	Tio 18 mcg	1.42	0.015	Tio18-placebo	0.14	0.016	(0.11, 0.17)	<0.001
	Inda 150 mcg	1.46	0.015	Ind150-placebo	0.18	0.016	(0.15, 0.21)	<0.001
	Inda 300 mcg	1.46	0.015	Ind300-placebo	0.18	0.016	(0.15, 0.21)	<0.001
B2334	Placebo	1.31	0.013	---	---	---	---	---
	For 12 mcg	1.38	0.013	For12-placebo	0.07	0.016	(0.04, 0.1)	<0.001
	Inda 300 mcg	1.48	0.012	Ind300-placebo	0.17	0.016	(0.13, 0.2)	<0.001
	Inda 600 mcg	1.48	0.013	Ind600-placebo	0.17	0.016	(0.13, 0.2)	<0.001
B2346	Placebo	1.35	0.019	---	---	---	---	---
	Inda 150 mcg	1.49	0.018	Ind150-placebo	0.13	0.024	(0.09, 0.18)	<0.001

As noted in Table 2 above, the 150 mcg and 300 mcg doses have demonstrated (nearly identical) efficacy. The larger consideration is in regard to dose selection. As discussed above, we have great concern regarding finding the 'optimal' dose that provides efficacy without sacrificing safety. Some drugs have a large 'safety' therapeutic index, such that we can tolerate what may be a larger dose than necessary for the average patient in order to expedite onset of action or to capture more of the population including those resistant to treatment. However, beta-agonists appear to have a fairly narrow therapeutic index as witnessed by the development program for formoterol where a simple doubling of the dose lead to subjects requiring intubations for destabilization of asthma control. As such, it is vital that the sponsor have adequate dose ranging.

Study B2335 was an adaptive trial that was used to determine the doses to study for potential marketing. As stated above, the typical beta-agonist program would have dose selection performed in subjects with asthma and those doses would be carried over to a COPD program, but that was not the case for this application. Regarding study B2335S, Drs. Liu and Durmowicz have described this protocol in detail in their reviews. In short, subjects were randomized to either indacaterol 75, 150, 300, or 600 mcg once daily or formoterol 12 mcg twice daily, tiotropium 18 mcg once daily, placebo for 2 weeks. At the end of two weeks, an

interim analysis of the efficacy was conducted using the following criteria to determine two doses of indacaterol to carry forward for the remainder of the trial with the two following stipulations:

- *The selected dose needed to be 120 mL greater than placebo (MCID) in terms of trough FEV_1 and numerically higher than tiotropium and formoterol.*
- *The selected dose needed to be numerically higher than tiotropium and formoterol in terms of weighted mean FEV_1 over 1-4 hours.*

The sponsor added in FEV1 AUC (0-4h) as another way of evaluating efficacy. As I discussed above, the doses were selected for higher FEV1 reversibility compared to existing products and would have made selection of the dose without any real consideration to safety. This is at odds to how we have viewed beta-agonists in the past and one could predict that these doses may be problematic because of safety concerns. Using these criteria would also predictably cause a situation in which we would not have lesser doses with which to compare safety such that if any signal arose compared to the comparators, we could not place this into the context of a lesser dose. One could speculate that increasing the dose of the other currently marketed LABA drugs would also result in increased bronchial dilation and a quicker onset of action, but would probably be resisted by us without a demonstration that this was not at the expense of safety (and we already know with formoterol that there are increased serious adverse events). Perhaps selection criteria to increase efficacy or onset of action compared to comparator drugs could be applied to a drug class with a more forgiving therapeutic index, where giving increased drug to try to find some clinical advantage over existing drugs may be appropriate as safety isn't so concerning, but not in a drug class with a narrower therapeutic index as we have in this instance. Again, to be fair, it does not seem from meeting minutes with the sponsor, that we ever explained this concern in a direct fashion and there has been continued evolution of scientific and societal thinking regarding these drugs over the last few years.

In any event, their decision to pick the 150 and 300 mcg dose over the 75 mcg dose seems to be based on a 20 mL (1.5L vs 1.52L) difference at the two week evaluation point. This is represented in the figure below from Dr. Liu's review where FEV1 evaluation was done at the two week interval.

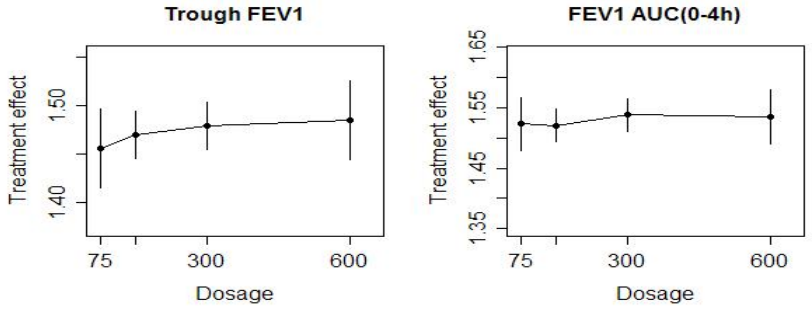
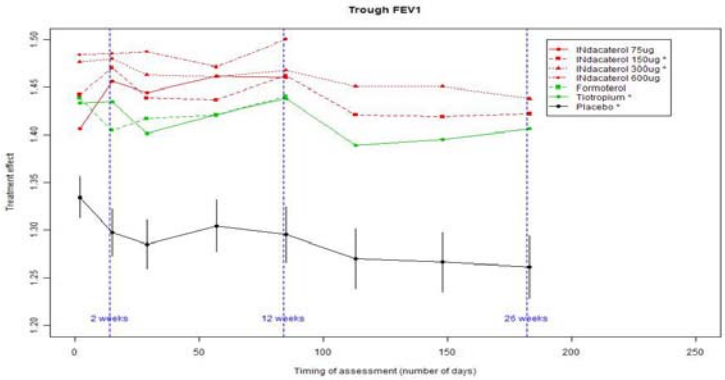


Figure 1. Dose responses by trough FEV_1 and weighted mean FEV_1 over 0-4 hours at Day 15 in B2335s.

Although one could argue that the trough FEV1 figure may indicate that the 75-mcg dose is nearing the slope-plateau point of the dose-response, the FEV1 AUC evaluation would seem to indicate that all the doses are on the plateau phase. There is further information that is informative regarding whether there are differences in FEV1 response of the different doses. Since subjects were enrolled into stage 1 at different times, more than half of the subjects had data available for 12 weeks of exposure. Figures 2 and 3 below from Dr. Liu and Durmowicz's reviews presents this data.



Best Available Copy

Figure 2. Summary of trough FEV_1 by treatment arms in B23335s at different assessment time.

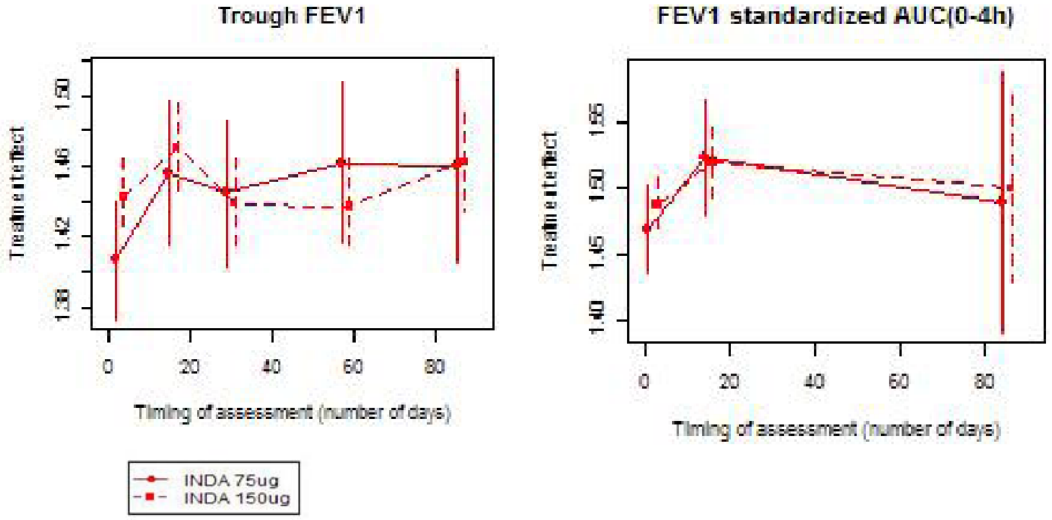
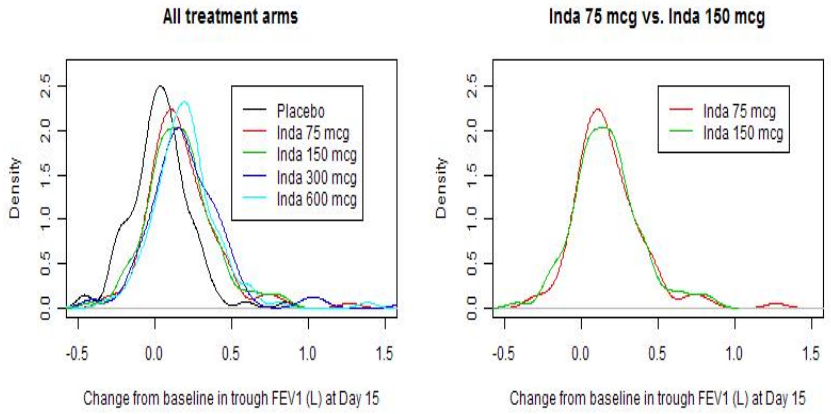


Figure 3. Comparison of Trough FEV1 and FEV1 AUC (0-4h) Treatment effects in study 2335s *(adapted fro Figure 11 from statistical review by Dr. Dongmei Liu)*

These figures indicate that there is no difference in bronchial dilation response measured by FEV1 between the 75 and 150 mcg doses when measured at the 12 week interval (timing of primary endpoint).

Dr. Liu also examined distribution changes from baseline in trough FEV1 after two weeks of treatment to see if there were shift that may be indicative of subpopulations receiving additional benefit. This is presented in the figure below.



Best Available Copy

Figure 1 Distribution of change from baseline in trough FEV_1 at Day 15 in study B2335s.

This figure would seem to indicate little if any difference in the efficacy of the 75-mcg dose compared to the 150-mcg dose. Yet, as stated before with formoterol, we have seen that a doubling of the dose can have significant safety implications.

While the sponsor has demonstrated efficacy of the 150-mcg and 300-mcg doses, this needs to be informed by the safety profile to define the risk:benefit relationship adequately.

<u>Safety</u>

The studies upon which the safety data are based are summarized below from Dr. Durmowicz's review (page 20).

- *Study B2334: 52 weeks of treatment with indacaterol 300 mcg, 600 mcg once daily, placebo (double-blind) or formoterol 12 mcg twice daily (double-blind) and providing long-term safety data.*
- *Study B2335S: 26 weeks of treatment with indacaterol 150 mcg once daily, 300 mcg once daily, placebo (double-blind) or tiotropium 18 mcg once daily (open-label).*
- *Study B2346: 12 weeks of treatment with indacaterol 150 mcg once daily or placebo (double-blind).*

In addition to the COPD patient data, because of its large size and length (6 months) the safety data from a trial of indacaterol 300 mcg and 600 mcg once daily for patients with asthma (study B2338) was also summarized.

As demonstrated above, there is not any safety data to 52-weeks for the proposed marketing dose of 150-mcg, only for the 300-mcg dose. Dr. Durmowicz notes that for the 12-month COPD safety population, cardiac disorders composed of atrial fibrillation, congestive heart failure, myocardial ischemia and coronary artery disease were increased in the 600 mcg (2.7%) and 300 mcg (1.9%) compared to formoterol and placebo (1.4% for each).

To assess any potential adverse effects of beta-adrenergic stimulation with indacaterol on the cardiovascular and cerebrovascular systems such as myocardial infarctions and stroke, the sponsor assessed combined cardio- and cerebrovascular adverse events and serious adverse events (CCV SAEs) in pooled Phase III safety databases. The data in Table 3 below indicate that indacaterol had a higher percentage of CCV SAEs than formoterol and placebo in COPD subjects and also indicates that doses less than 300-mcg have the same concern.

Table 3. Comparison of rates of CCV SAEs between 3 month, 6 month, and 12 month COPD safety population *(adapted from Table 37 from the clinical review by Dr. Lynne Wu)*

	Inda 150 mcg od	Inda 300 mcg od	Inda 600 mcg od	Formoterol 12 mcg bid	Tiotropium 18 mcg od	placebo
3 months	0.96%	0.94%	0.55%	0.18%	1.45%	0.66%
6 months	2.1%	1.4%	1.2%	0.5%	2.1%	1.0%
12 months	Not studied	3.4%	2.6%	1.4%	Not studied	0.9%

It is interesting to note that the in other data submitted by the sponsor, COPD SAEs such as exacerbations favored the sponsor's drug (4.1%-18/437; 2.8%-12/425; 7.4%-32/434; and 4.6%-20/432 for indacaterol 300, 600, formoterol and placebo groups respectively). However, all of these adverse events involve small numbers, and are very 'fragile' such that definitive conclusions cannot be made without a large safety study. As such, caution would dictate that our concern for the increase in CCV events noted in Table 3 above (which carries convincing biologic plausibility) would outweigh any possible advantage demonstrated by the cumulative data regarding COPD SAEs.

Also concerning (perhaps more so) is data from the study (B2338) in subjects with asthma. This study had two deaths, one of which seems clearly to be associated with an asthma exacerbation, and the second seems likely to be an asthma death. While there was not a placebo group for comparison, it is highly unusual to have an asthma related death in a development program. Even in the formoterol application where we were concerned about the 24-mcg dose, there no clear asthma related deaths, though there were two subjects requiring intubation (and one death, but this may have been from cardiovascular causes). Additionally, both of the subjects taking indacaterol were also taking inhaled corticosteroids (ICS), which some data indicates may negate some risk associated with LABA use, while those in the

formoterol study were not taking inhaled steroids. These deaths, in subjects taking ICS compared to previous experience where asthma deaths have not occurred even in subjects not taking ICS, gives us great concern that the sponsor has not found the correct dose and/or dosing interval. Safety data from this study is summarized in the table below from Dr. Durmowicz's review (page 25).

Table 5. Safety summary data from asthma study B2338 *(adapted from Table 30 from the clinical review by Dr. Lynne Wu)*

	Indacaterol 300 mcg N=268	Indacaterol 600 mcg N=268	Salmeterol 50 mcg bid N=268
Deaths	2	0	0
Asthma SAEs	0.7%	1.1%	0
Asthma AEs	11.6%	15.7%	14.9%
Muscle spasm AEs	1.9%	3.4%	1.5%
Tremor AEs	0.7%	3.7%	10.4%
Cardiac SAEs	0.4%	0.4%	0.4%

This table indicates that there is a dose related imbalance in asthma SAEs of indacaterol compared to salmeterol, which seems dose related. These results are quite concerning, and warrant further investigations of smaller doses and/or different dosing intervals.

The review team also has concerns whether the dosing interval is correct. I have not discussed this in my review at length and refer readers to the other reviews, but while indacaterol does have a long systemic half-life, I'm not aware that a correlation has been made between systemic half-life life of beta agonist drugs and local pulmonary effects as determined by assessing changes in lung function with spirometry. In fact, if the pharmacokinetics was linked to the pharmacodynamics, since this drug has a half-life of approximately two days, one could posit that it should be dosed every 48-hours instead of 24-hours (this was not evaluated by the sponsor). Also, the systemic half-life of albuterol is very similar to that of salmeterol, yet they have different dosing intervals. The sponsor has submitted pharmacokinetic modeling to justify their dosing interval that is somewhat compelling to our clinical pharmacology colleagues, at least as a hypothesis generating exercise. Considering the vital importance of getting the dose correct, and considering how it is possible and not overly burdensome to do a study comparing the same nominal dose given either once or twice a day (or even longer between doses), I do not feel I would ever be comfortable relying on modeling to make this

critical decision. We have had experience with ICS[4] where the same nominal dose given twice a day as opposed to once a day had twice the effects size. As such, the sponsor should demonstrate that their proposed dosing interval is indeed correct with a clinical study. This drug has demonstrated that it accumulates systemically, and given its half-life, I believe a full exploration of dosing interval should include increasing the dosing interval beyond 24-hours as well as dosing the same nominal dose given either once or twice a day.

Conclusions and Recommendations

The sponsor has demonstrated that the proposed doses of indacaterol do have efficacy, but they seem to have selected doses that are on the plateau of a dose response-response curve and have serious adverse events that are greater than comparator drugs. The adverse events include two deaths that are probably asthma related, which gives us great concern. The sponsor will need to examine lower doses and dosing intervals to optimize the risk:benefit ratio.

I recommend a Complete Response action for this cycle. The sponsor will need investigate lower doses of indacaterol.

[4] Purucker ME, Rosebraugh CJ, Zhou F, Meyer RJ, Inhaled fluticasone propionate by discus in the treatment of asthma: a comparison of the efficacy of the same nominal dose given either once or twice a day. Chest. 2003 Oct;124(4):1584-93

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22383	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	Arcapta Neohaler

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/s/

CURTIS J ROSEBRAUGH
10/16/2009

Cross-Discipline Team Leader Review

Date	September 29, 2009
From	Anthony G. Durmowicz, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	22-383
Applicant	Novartis
Date of Submission	December 15, 2008
PDUFA Goal Date	October 18, 2009
Proprietary Name / Established (USAN) names	Arcapta Neohaler/indacaterol maleate
Dosage forms / Strength	Inhalation powder/150 and 300 mcg hard gelatin capsules
Proposed Indication(s)	1. Long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.
Recommended:	Complete Response

1. Introduction

Novartis submitted a 505(b)(1) new drug application (NDA 22-383) on December 15, 2008, for the use of Arcapta Neohaler (indacaterol maleate dry powder for inhalation) as a once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. The proposed doses are 150 or 300 mcg (if symptoms are not adequately controlled with 150 mcg) administered once daily by inhalation. The PDUFA due date for this application is October 18, 2009. Indacaterol is not currently marketed anywhere in the world. Although large clinical studies have been performed in patients with asthma, Novartis is only seeking approval for indacaterol in COPD patients. This review will provide an overview of the application with a focus on issues that affect approvability; dose selection and long-term safety.

2. Background

Indacaterol is a new molecular entity that belongs to the class of beta-2 adrenergic agonists that are commonly used to treat bronchoconstriction in patients with COPD and asthma. COPD is characterized by air flow limitation that is not fully reversible, is usually progressive, and is associated with pathological changes in the lung, a combination of obstructive bronchiolitis and parenchymal destruction. COPD is a major public health problem and is currently the fourth leading cause of chronic morbidity and mortality in the USA. Inhaled beta2-agonists are widely used in the treatment of COPD. Currently, they are used as monotherapy or in combination with other classes of medication, such as anticholinergic bronchodilators or inhaled corticosteroids. In this application, indacaterol is proposed to be used as a monotherapy for COPD.

Indacaterol's USAN modified name is indacaterol maleate and the IUPAC nomenclature is (R)-5-[2- (5,6-Diethylindan-2-ylamino)-1- hydroxyethyl]-8-hydroxy-1H-quinolin-2-one maleate. Due to its possible longer duration of action it belongs to a subclass of beta-2 agonists termed long-acting beta agonists or LABAs that include the marketed drugs Foradil and Perforomist (formoterol), Brovana (R,R formoterol), and Serevent (salmeterol). The use of LABAs has come under scrutiny as a result of a safety signal of increased risk of severe exacerbations including death in patients with asthma. The increased risk was demonstrated in the Salmeterol Multicenter Asthma Research Trial (SMART) in 1996. The SMART was a randomized, double-blind study that enrolled patients with asthma not currently using LABAs to assess the safety of salmeterol (42 mcg twice daily for 28 weeks) compared to placebo when added to usual asthma therapy. The primary endpoint was the combined number of respiratory-related deaths or respiratory-related life-threatening experiences (intubation and mechanical ventilation). The study was prematurely terminated in January 2003 after a total of approximately 30,000 patients had been enrolled because a planned interim analysis suggested that salmeterol may be associated with an increased risk of severe asthma exacerbations including death.

As a result of the findings described above as well findings in smaller safety studies conducted with another LABA, formoterol, the safety of LABAs was the topic of discussion at a July 13, 2005, Pulmonary Allergy Drugs Advisory Committee Meeting. Subsequent to the meeting, in November, 2005, the FDA released a Public Health Advisory to alert healthcare professionals and patients that LABAs may increase the chance of severe asthma episodes and death. The existing product labels have been revised and now include a Boxed Warning and a Medication Guide for all marketed LABA products. While no such safety signal has been observed in patients with COPD, dose-related class effects of beta agonists, especially those affecting the cardiac and central nervous systems, can be deleterious to older patients with COPD, many of whom have increased cerebral and cardiovascular risk factors.

Novartis has studied three different indacaterol formulations for both COPD and asthma indications: Hydrofluoroalkane propellant (HFA; IND 66,337), single dose dry powder inhaler (SDDPI; IND 48, 649), and multi-dose dry powder inhaler (MDDPI; IND 69, 754). The HFA drug product development program was suspended by the applicant due to technical reasons. IND# 48,649 assigned to study indacaterol SDDPI was submitted on February 13, 2004 and IND# 69,754 to study indacaterol dosed via a MDDPI was submitted on April 27, 2004. On August 1, 2005, the Division met with the Applicant for an End-of-Phase-2 meeting to discuss the clinical development of indacaterol MDDPI. At that time, Novartis indicated that they planned to focus on the MDDPI formulation using the Certihaler delivery system, the system used with Foradil, another LABA. On February 2, 2006, the Novartis submitted a General Correspondence reporting difficulties with the formoterol-containing Certihaler MDDPI device which had been approved for use in Europe. Four cases of overdose were reported, attributed to excess powder release from the device. Subsequently, on May 22, 2006, the Novartis communicated plans to substitute a SDDPI device for the MDDPI for indacaterol program. The Division cautioned that Phase 3 studies using the SDDPI formulation without prior review were "extremely risky." Another End of Phase 2 meeting was held on October 10, 2006, to discuss the clinical development program on indacaterol SDDPI. The Applicant proposed the COPD study B2335s with an adaptive design. The study incorporated a full dose-ranging assessment within a pivotal safety and efficacy trial in which doses for the efficacy portion (Stage 2) were carried forward after selection from the dose-ranging portion of the study (Stage1). This approach carried more risk regarding dose selection, however, the previous multiple dose, dose-ranging study was unacceptable as it had been conducted with the MDDPI device which had significantly different dosing characteristics. The Division raised concerns regarding the data monitoring committee's (DMC) role, data blinding, dose-selection criteria, selection of appropriate efficacy endpoints, use of open-label tiotropium as an active comparator, and treatment of missing data.

On December 20, 2006, the Applicant submitted study B2335s to request a special protocol assessment (SPA). In comments conveyed to Novartis after reviewing the SPA, the Division emphasized again trough FEV1 (forced expiratory volume in one second) alone was not adequate dose-selection criteria and that other variables such as peak FEV1 and FEV1 AUC (area under the curve) would be considered in the review of dose selection. Specifically, when asked in the SPA submission "Does the Agency agree that the dose decision rules utilizing trough FEV1 only are adequate and that providing 12-hour serial FEV1 data from a subgroup of patients will be sufficient to address comments in relation to peak effect and AUC?" the

Division responded in correspondence related to the SPA dated February 1, 2007, "No, we do not agree with your proposal. As discussed in the End-of Phase 2 meeting, while it is your decision and your risk to base the DMC dose selection solely on trough FEV1, your application must include additional information on the FEV1 dose response for our review". We stated the Applicant should also collect 12 hour serial spirometry for all four indacaterol doses at steady state in Stage 1 to provide the necessary supplemental information. In addition, we noted that according to the DMC charter, if there are complexities in the data (e.g. no dose response), the DMC and selected Novartis personnel were to discuss the results to reach a decision regarding dose selection. We stated that if this is the case or if the DMC deviates from the dose selection guidelines, we may not agree to the criteria used for dose selection.

Novartis submitted additional questions on February 21, 2007 at the time they scheduled a post-SPA review Type A meeting to request clarification of the Division's February 1, 2007, responses to the SPA questions. Regarding dose selection, Novartis stated they intended to maintain trough FEV1 as the basis for the dose selection guidelines but on the basis of the Division's comments, they proposed to do additional serial spirometry out to 12 hours in a sub-group of patients in Stage 1 and in Stage 2 in order to further confirm the 24 hour dose profile. The Division acknowledged the proposal and responded in a communication dated March 12, 2007, that "while this may provide additional information for the DMC to select doses, it does not ensure that the Division will agree with the doses selected. This remains a potential risk with your proposed adaptive design study". After receiving the Divisions responses, the Applicant decided to cancel the Type A meeting. While several discussions noted above were had concerning the Applicant's SPA submission, no formal SPA agreement was made.

Other than the dose-selection criteria, the Division also raised concerns on the lack of well-accepted definitions on the key-secondary endpoints "days of poor control" and COPD exacerbations. Concerning a non-inferiority comparison of indacaterol and tiotropium, the Division made it clear in both the End of Phase 2 meeting on October 10, 2006 and the SPA review for study B2335s protocol that because of the open-label nature of the tiotropium arm, the Division would not consider any labeling claims based upon the non-inferiority comparison of indacaterol and tiotropium. In addition, the Division did not accept the proposed 55mL non-inferiority margin.

In April 2008, a pre-NDA meeting was held to discuss content and formulation for NDA submission. We reminded the Applicant that they would need to provide justification for the proposed once daily dosing frequency and that in addition to 24-hour FEV1 response curves and trough FEV1, we would also consider the efficacy results of indacaterol in comparison to the twice-daily active comparators included in study B2335s, salmeterol and formoterol. Since Novartis has not compared multiple dosing regimens of indacaterol within their clinical development program, the Division emphasized that, in addition to the endpoints mentioned, it will also use the comparison with the twice-daily LABAs to further evaluate the dosing frequency. The Division reminded Novartis that statistical significance in the pre-specified endpoints (e.g., trough FEV1) versus placebo would not necessarily be enough to justify the dosing interval.

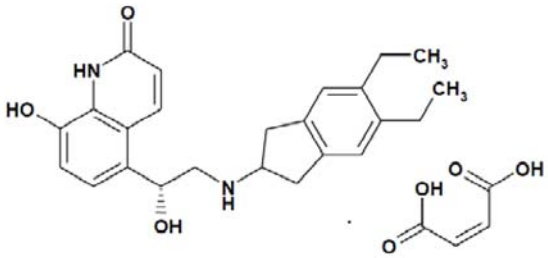
3. CMC/Device

The primary CMC review was conducted by Craig Bertha, Ph.D. His review has concluded that from a CMC perspective, the application is approvable pending acceptable cGMP recommendation from the Office of Compliance. All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.
In addition, the Applicant has agreed as a post-approval commitment to reassess and revise, as appropriate, the acceptance criteria for lactose impurities, once a sufficient number of batches (e.g., ten) are tested using the new reporting limit of (b) (4) and to propose acceptance criteria that are reflective of the data obtained.

Following is a brief summary of the chemistry and manufacture of indacaterol maleate and the drug product (Arcapta Neohaler).

The drug substance, indacaterol maleate, is a chemically synthesized chiral molecule. The USAN modified name is indacaterol maleate and the IUPAC nomenclature is (R)-5-[2-(5,6-Diethylindan-2-ylamino)-1- hydroxyethyl]-8-hydroxy-1H-quinolin-2-one maleate. The structure of the chiral drug substance is shown in Figure 1 below.

Figure 1. Molecular Structure of Indacaterol Maleate



Maleate salt: $C_{24}H_{28}N_2O_3 \bullet C_4H_4O_4$
Free base: $C_{24}H_{28}N_2O_3$
Maleate salt: 392.49 + 116.07 = 508.56
Free base: 392.49
Salt/base ratio: 1.296

The micronized drug substance is a white to very slightly grayish or very slightly yellowish powder. Solubility in water is limited to 0.23 mg/mL. The compound is slightly soluble in ethanol, methanol, propylene glycol, and polyethylene glycol 400, and freely soluble in N-methylpyrrolidone (NMP) and N,N-dimethylformamide (DMF). The drug substance is non-hygroscopic. One crystal form has been identified.

The proposed release specification for indacaterol maleate includes: appearance, color, clarity of solution, identity by IR and X-ray diffraction, assay by titration and high performance liquid chromatography (HPLC), impurity and enantiomer content by HPLC, heavy metals, residual solvents by gas chromatography (GC), particle size by laser light diffraction, moisture content by thermogravimetry, and sulphated ash (b) (4)

(b) (4) The drug substance is stored (b) (4) (b) (4) The re-test period of (b) (4) months is supported by stability data provided in the application for the micronized indacaterol maleate.

The drug product is Arcapta Neohaler (indacaterol) inhalation powder. It is a non-sterile dry powder inhaler drug product indicated for the treatment of chronic obstructive pulmonary disease. The inhalation powder product is pre-metered and the formulation is contained in hard gelatin capsules. Insertion of these capsules into the Neohaler device allows the contents to be accessed and inhaled. (b) (4)

(b) (4)

(b) (4)

4. Nonclinical Pharmacology/Toxicology

A full nonclinical pharmacology/toxicology program was conducted for indacaterol. No additional non clinical studies are recommended by the pharmacology/toxicology team.

Inhalation toxicity studies were conducted in rats (up to 26 weeks) and dogs (up to 39 weeks). The target organs of toxicity for indacaterol in the rat are nasal cavity, i.e. degeneration of the olfactory epithelium and larynx, i.e. squamous metaplasia. The target organs of toxicity in the dog are the cardiovascular system, i.e. increased heart rates, decreased blood pressure and myocardial fibrosis. These are known class effects of beta-2 agonist drugs. For these effects there is an adequate margin of safety of approximately 3-5 and 11 fold for the expected human exposure based on the AUCs at NOAELs determined in the 13-week and 39-week dog toxicity studies, respectively. The liver demonstrated periportal liver hepatocyte vacuolation due to glycogen deposition, another known class effect of beta-2 agonists.

Indacaterol was negative in a battery of genetic toxicology studies including Ames test, chromosome aberration test with V79 Chinese hamster cells and bone marrow micronucleus

test in rats. In reproduction studies in the rat, subcutaneous administration of indacaterol did not cause significant effects in males or females related to parameters of fertility, general reproductive performance or early embryonic development. In an embryo-fetal development study in rabbits, subcutaneous administration of QAB149 did not show teratogenic effects. When assessed for effects on pre-and postnatal development in rats subcutaneously administered indacaterol, there were increased stillborn pups for F0 and a statistically significant decrease in the number pregnant dams for F1 observed in the high dose group.

The carcinogenicity potential of QAB149 was assessed in a 26 week oral (gavage) carcinogenicity study with C6F1/TgrasH2 hemizygous mice and a 24 month inhalation oncogenicity study with Sprague-Dawley rats. While the studies were judged to be negative by the Executive CAC, here were increased incidences of uterine endometrial stromal polyps in the 26-week oral carcinogenicity study with female CB6F1/TgrasH2 hemizygous mice, and ovarian leiomyomas in the 24-month inhalation oncogenicity study with female Sprague-Dawley rats. These tumors have been observed with other β2-adrenergic agonists.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology program reviewed to support the indacaterol NDA included the results from 24 studies that contain pharmacokinetic information collected from healthy volunteers (14 studies), patients with COPD (10 studies). In these studies indacaterol was administered via the inhaled route using either single dose dry powder inhaler (SDDPI) devices, a pressurized metered dose inhaler (pMDI) device, or a multi dose dry powder inhaler (MDDPI) device. The development of the pMDI and the MDDPI was discontinued and the device used in the to-be marketed formulation is an SDDPI that was named the Concept1 during development. Studies included those to assess drug-drug interactions (DDI), hepatic impairment, effects of the UGT1A1 genotype, and ethnic differences between Japanese and Caucasian subjects. Information about the effect of covariates (such as age, gender, body weight, body mass index and race) on the PK of indacaterol was investigated using a population PK modeling approach with pooled pharmacokinetic data. Dose-response was evaluated in three single/multiple dose studies (Studies B1212, B2205, and B2335S). These data were extensively reviewed by several clinical pharmacology reviewer teams; general pharmacology, pharmacometrics, and/or pharmacogenomics, as appropriate. While the data originally submitted were judged robust enough to enable a full clinical pharmacology review, the pharmacometric review team also reviewed an unsolicited submission by the Applicant dated April 2, 2008 which contained pharmacometric modeling analyses of the dose response data in an attempt to support the dose selection and dosing interval. For a complete discussion of the clinical pharmacology program see the combined clinical pharmacology review dated August 25, 2009.

Pharmacokinetics

Following a single inhalation of indacaterol 150 mcg using the to-be-marketed product, measurable plasma concentrations of indacaterol were observed in the systemic circulation within 5 minutes post-dose. Mean Cmax and AUC0- 24hrs values were 253 ± 120 pg/mL and

1202 ±554 pg*hr/mL, respectively. Dose proportionality over the entire dose range of 150 to 600 mcg was demonstrated for peak exposure (Cmax). Following repeated administration, dose proportionality over the dose range of 150 to 600 mcg was also demonstrated for Cmax and AUC0-24hrs. Dose accumulation was noted at each dose level examined as mean trough concentrations increased approximately 5-fold between Day 2 and Day 14 following multiple dose administration of indacaterol. Steady state concentrations were achieved by Day 12 of dosing. The absolute bioavailability of indacaterol following inhalation was about 43%.

Indacaterol is highly protein bound as the plasma protein binding ranged is approximately 95%. The elimination half-life of indacaterol is also relatively long at approximately 49 hours after a 150 mcg inhalation. Elimination is predominantly via the GI tract (85%) with kidney elimination much lower at about 10%.

The principle enzymes responsible for metabolic clearance of indacaterol are UGT1A1 and CYP3A4. Indacaterol did not inhibit the major CYP450 enzymes.

The pharmacokinetic profile of indacaterol is similar across demographic groups. Dose adjustment based on age, sex, race, or weight is not felt to be necessary. Indacaterol AUC values across doses in COPD patients were about 16% to 20% lower than that observed in healthy volunteers. Dose adjustment is also not felt to be necessary in patients with mild to moderate liver impairment. The effect of severe hepatic impairment on the pharmacokinetics of indacaterol was not evaluated.

Drug-drug interactions were assessed with concomitant administration of indacaterol with ketoconazole, verapamil, erythromycin, and mometasone increased the systemic exposure of indacaterol by less than 2-fold. Indacaterol did not alter the PK of mometasone. Dose adjustment of the basis of concomitant administration with these drugs is not felt to be necessary.

The effect of indacaterol on the QT interval was evaluated in a double-blind, placebo controlled study following doses of indacaterol 150 mcg, 300 mcg or 600 mcg once-daily for 2 weeks, and a single oral dose of moxifloxacin 400 mg, in 404 healthy subjects (Study B2339). Fridericia's method for heart rate correction was employed to derive the corrected QT interval (QTcF). Results demonstrated the maximum mean prolongation of QTcF intervals were <5 ms with the upper limit of the 90% confidence interval below 10 ms (the threshold for regulatory concern as described in ICH E14 guidelines) for all time-matched comparisons versus placebo. The largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time was adequately demonstrated, indicating that assay sensitivity was established. Thus, no significant QT prolongation effect of indacaterol (150 mcg, 300 mcg and 600 mcg) was detected in the QT study.

Dose response

The clinical pharmacology team reviewed the results of 3 dose-ranging studies. Study B2212 was a single dose study in 60 (12 per arm) patients with COPD. Patients received a single dose of indacaterol 150, 300 or 600 mcg, formoterol 12 mcg or placebo via a SDDPI. The mean

difference to placebo in trough FEV1 was 0.14, 0.17, and, 0.18 L for the 150, 300, and 600 mcg, doses respectively. Study B2205 was a placebo-controlled, parallel group, multiple dose study in 660 patients (110 per arm). Patients were randomized to one of six treatments arms indacaterol 50, 100, 200, or 400 mcg once daily via a MDDPI, indacaterol 400 mcg via the SDDPI or placebo for 7 days. The interpretation of dose response for this study is not relevant for the current clinical program as indacaterol was administered via a multiple dose dry powder inhaler that had different dosing characteristics than the SDDPI proposed for marketing. Nevertheless, there were small dose-related differences in trough FEV1 compared to placebo ranging from 0.14 to 0.21 L for the 50 through 400 mcg doses. Study B2335S was the pivotal dose response and efficacy study in which 770 (115 per arm) patients with COPD were randomized to one of seven treatments groups (indacaterol 75, 150, 300, or 600 mcg given once a day via the SDDPI, formoterol 12 mcg twice daily, tiotropium 18 mcg once daily or placebo for 2 weeks (Stage 1). Following 2 weeks of treatment, an interim analysis of the efficacy and safety results from Stage 1 was conducted to determine the doses to be evaluated for efficacy in Stage 2. Dose selection was based on pre-defined criteria comparing the efficacy of indacaterol with placebo and the active controls, as well as safety data. The data evaluated at the end of Stage 1 after a 2-week dosing interval demonstrated small differences in trough FEV1 between the doses of indacaterol with mean differences from placebo in trough FEV1 of 0.15 L, 0.18 L, 0.21 L and 0.20 L for indacaterol 75, 150, 300, and 600 mcg, respectively. Based on the actual dose-response data reviewed, the clinical pharmacology team concluded that while there was a numeric trend for the higher doses tested to produce a bigger response in through FEV1, no clear dose-ordering response was observed following either single dose (150 to 600 mcg) or multiple dose (50 to 600 mcg) of once a day administration of indacaterol once daily. Further discussion of the dose-response and dose selection is found in Section 7, Clinical-Statistical.

Pharmacometric modeling analyses submitted to support dose selection:

Shortly after the receipt of the NDA filing letter in which the Division questioned if the correct doses and dosing frequency were selected, Novartis submitted a separate report to justify their dosing regimen. A Bayesian metanalysis that included data from 7 studies in COPD patients and 4 studies in asthma patients and a non-linear mixed effect modeling (hereafter NLME) analysis using the data from the Phase 3 dose-ranging and efficacy study, B2335S were performed in an attempt to support the dose selection (150-300 mcg) and an analysis of peak-to-trough FEV1 ratios from three clinical studies was included to try to justify the dosing interval. The Division did not solicit the metanalyses nor did it agree with the data included in them as it felt that the actual clinical data submitted with the original NDA package (predominantly from study B2335s, the Phase 3 combined dose-ranging and efficacy study) and supportive clinical data was adequate to fully assess whether the appropriate dose(s) and dosing interval had been selected.

Additionally, the use of pharmacometric modeling based on metanalyses of clinical trials for a locally acting bronchodilator is problematic on several fronts. First, the dose-response to an inhaled bronchodilator may change over time. Since the indication for COPD would be for long-term chronic daily use, the lung function responses that are most important are those after a substantial treatment period, at least 12 weeks for COPD studies. However, the metanalyses

performed took all available pulmonary function data from all time points not only the later 12 week time point as would be most appropriate. This is of particular importance for this submission as small differences observed between the FEV1 responses of the 75-300 mcg once daily doses measured early in treatment (2-weeks) further narrowed when data of patients dosed for 12 weeks at these doses was examined.

Another issue is the potential for differences between study COPD populations as there are differences in baseline pulmonary function, age, smoking status, geography, and bronchodilator reversibility that are unique to each study. In this case the data from each study would be best assessed separately in order to observe any differences in responses that could be based on study design and demographic differences. Finally, the Bayesian metanalysis included data from studies from both patients with COPD and asthma. As these are different disease with different pathophysiologies and responses to beta agonist bronchodilators, the inclusion of asthma data is inappropriate for COPD dose selection.

Despite the reservations concerning the validity of the pharmacometric modeling dose-response analyses submitted, the pharmacometric team reviewed the submission. Based on the meta-analysis of trough values performed by Novartis, the doses of 75, 150, 300, and 600mcg were predicted to correspond to the ED78, ED88, ED93, and ED97, respectively (ED=effective dose). Thus, the Applicant claimed that indacaterol 75mcg, dosed once daily, provided less complete bronchodilation in the typical patient compared with 150mcg or 300mcg doses. The analyses are depicted in tabular and graphic form in Table 1 and Figure 2.

Table 1. Parameter estimates from metanalysis and NLME analysis. The numbers in parentheses indicate the 90% CI.

	Meta-analysis			NLME analysis		
	Trough FEV1	Peak average (AUC0-4)	Observed Peak FEV1	Trough FEV1	Peak average (AUC0-4)	Observed Peak FEV1
Emax	0.18 (0.12-0.20)	0.27 (0.23-0.30)	0.26 (0.22-0.30)	0.18 (0.16-0.21)	0.23 (0.19-0.26)	0.22 (0.18-0.25)
ED50	22 (10-35)	25 (11-42)	35 (10-69)	22 (7-68)	14 (3-73)	12 (2-93)
%max effect at 75µg	78 (68-88)	76 (64-87)	70 (52-88)	78 (53-92)	84 (57-95)	86 (53-97)
%max effect at 150µg	88 (81-94)	86 (78-93)	82 (69-94)	87 (69-96)	91 (73-98)	93 (69-99)
%max effect at 300µg	93 (90-97)	92 (88-97)	90 (81-97)	93 (82-98)	95 (84-99)	96 (82-99)
%max effect at 600µg	97 (94-98)	96 (93-98)	95 (90-98)	97 (90-99)	98 (91-99)	98 (90-99)

Figure 2. Prediction of dose response for trough FEV1 at steady state. The data points and the corresponding vertical lines represent the least-squares means and standard errors as determined for each visit and treatment arm of the respective study. The solid line and the inner and outer shaded areas represent the mean dose response curve, its 95% confidence interval and 95% prediction interval, respectively *(from the Novartis' dose-response and regimen modeling report, page 27).*

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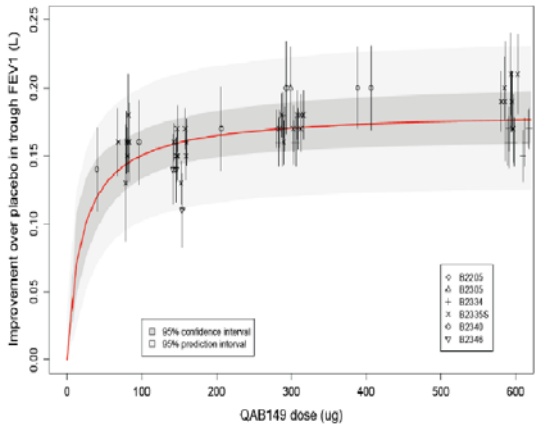


With regard to the analyses performed to support the once daily dosing interval, the Applicant provided data to show that once-daily administration of indacaterol was shown to have smaller peak-to-12 h trough FEV1 ratios than formoterol, a twice daily LABA. The sponsor claimed that this analysis confirmed the intrinsic difference between indacaterol and the twice daily bronchodilators in terms of their FEV1 profiles. While this analysis may show differences in peak and trough FEV1 ratios between indacaterol and formoterol, this type of analysis has not been shown to correlate to the dosing interval of locally active pulmonary drugs. Moreover, it is premature to finalize a dosing interval prior to properly assessing the dose-response curve and determining the appropriate likely clinical dose(s).

After review of the above data and conducting their own modeling of the data, the pharmacometric team concluded that the Applicant's metanalysis of lung function data does not fully justify a dose of 150 mcg once daily as an optimal dose for the following reasons:

- The Applicant's required minimal difference from placebo of 120 mL for dose selection is not justified.
- The Applicant's pharmacometric modeling method based on the publication, "Combining Multiple Comparisons and Modeling Techniques in Dose-Response Studies, F.Brets, J.C.Pinheiro and M.Branson. Biometrics, 2005, 61, p.738-748", for finding the minimum effective dose based on the lower bound of 95% confidence interval tends to overestimate the target dose.
- The Applicant's Emax model does not fit the observed data well, especially at lower doses due to the lack of data.
- The Applicant's ED50 estimates are not reliable due to the large uncertainty.
- The large uncertainty on ED50 estimates, especially for peak FEV1 response, makes it difficult to rule out the possibility of a BID regimen being the appropriate dosing regimen for indacaterol.

The overall recommendation by the clinical pharmacology teams was that the Applicant evaluate indacaterol at doses lower than those proposed (150 and 300 mcg) for the treatment of COPD.

6. Clinical Microbiology

This section is not applicable as indacaterol is not an antimicrobial product.

7. Clinical/Statistical- Efficacy

Overview of the clinical program:

The Applicant designated three pivotal and three additional clinical studies to provide support for the indacaterol COPD clinical program. Other clinical studies have been conducted for the COPD program, however their utility is limited as they studied different doses than those in the pivotal studies and utilized a multiple dose dry powder inhaler (MDDPI) that the Applicant subsequently abandoned in mid-development in favor of the single dose dry powder inhaler designated the Arcapta Neohaler. The pivotal clinical studies included an adaptive design dose-ranging and efficacy study (B2335) and two additional confirmatory efficacy and safety studies (studies B2334 and B2305) in which efficacy was determined at the 12-week time point. Studies B2334 and B2335 continued for 26 and 52 weeks, respectively, and supplied longer term safety data for the program. The supportive studies included study B2340 which the Applicant conducted in order to support a once daily dosing interval. Detailed reviews of these studies can be found in Dr. Lynne Wu's medical review, and Dr. Dongmei Liu's statistical review. The clinical and statistical teams have concluded that the submitted data do not support the safety and efficacy of indacaterol 150 or 300 mcg once daily in COPD patients.

The pivotal clinical studies mentioned above and study B2340 which assessed lung function over a 24 hour after a 300 mcg dose of indacaterol are briefly reviewed in the following sections. The design and conduct of these studies are briefly described first, followed by efficacy findings and conclusions.

Design and conduct of the studies:

Dose-ranging and efficacy study (B2335)

Study B2335 was an adaptive design 26 week multicenter, randomized, double blind, Double-dummy, placebo-controlled, parallel-group dose-ranging, safety, and efficacy study that assessed the safety and efficacy of two doses of indacaterol (from 75, 150, 300, and 600 mcg once daily) selected after a 2-week dose-ranging period in patients with COPD. Both blinded formoterol (12 mcg twice daily) and open label tiotropium (18 mcg once daily) acted as active controls. While a very similar conventionally designed 7-arm dose-ranging study with approximately 100 patients/arm had previously been conducted (study 2205), the necessity for repeating a full dose-ranging assessment in Phase 3 was due to the Applicant changing the inhaler device late in development from the originally planned multiple-dose dry powder inhaler (MDDPI) similar to the Foradil Certihaler device to a single dose dry powder inhaler device with significantly different drug delivery characteristics.

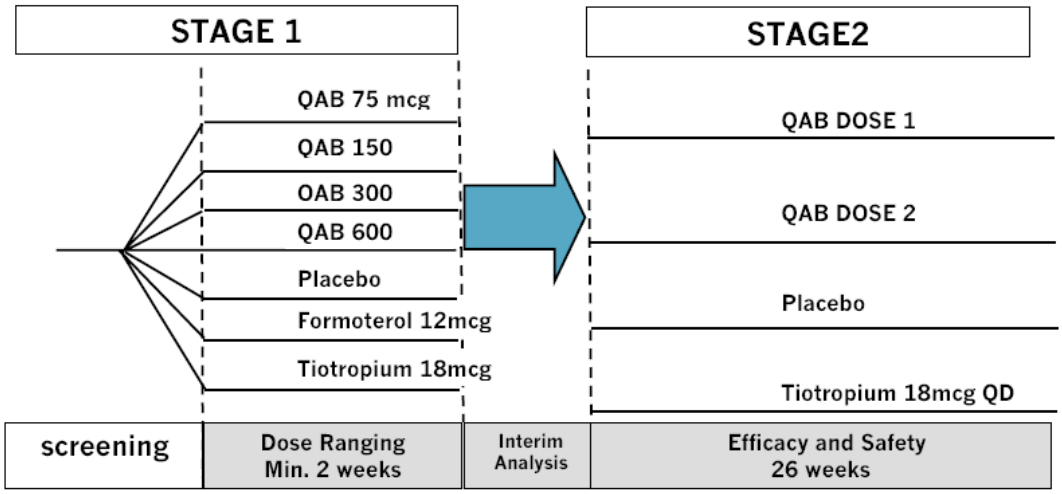
Study B2335s was conducted at 334 centers in 11 countries with about 60% of the centers located in the United States. A total of 2059 patients were randomized during the study, 376 of which were in one of the three treatment groups (75 and 600 mcg of indacaterol and formoterol) not continued into stage 2. The study was divided into two stages; stage 1 was two weeks in duration and consisted of the dose-ranging portion of the study while in stage 2, two indacaterol doses (150 and 300 mcg once daily) selected at the end of the 2-week dosing period for stage 1 were continued for a total of 26 weeks with efficacy determined at the end of a 12 week dosing period. Both blinded formoterol and tiotropium were included as active comparators during stage 1 while only open label tiotropium was carried forward during stage 2.

For stage 1, after a two week run-in period, eligible patients were randomized into one of the seven treatment arms (indacaterol 75 mcg, 150 mcg, 300 mcg, 600 mcg, placebo, formoterol 12 mcg, and tiotropium 18 mcg) in ratio of 1:1:1:1:1:1:1 with about 110 patients in each arm with stratification for smoking status. Twelve hour serial spirometry data were collected in a subset of about 30 to 40 patients in each arm.

When all patients in stage 1 had completed at least two weeks treatment, there was an interim analysis performed by an external independent data monitoring committee (DMC) to make decisions on dose selection. Based on the result of the interim analysis which will be discussed in detail below, two of the four indacaterol doses were continued into stage 2 with the placebo and open-label tiotropium arms. Patients, investigators, and the clinical trial team remained blinded to the specific treatments for any individual patient until the stage 2 database lock.

Patients randomized to the discontinued indacaterol dose arms or discontinued formoterol arm continued treatment until the completion visit. Thus, there is longer term data for the discontinued stage 1 patients that could range from 6 to 26 weeks. Patients randomized to the two selected indacaterol doses, placebo, and tiotropium continued on their assigned study treatments into stage 2 for a total of 26 weeks treatment. An additional 285 patients per treatment group were randomized until the total required number (400) of patients had been included. Each patient in stage 2 went through a total of 26 weeks treatment. Figure 3 below outlines the overall design of study B2335s.

Figure 3. Study B2335s Study Design



Inclusion and exclusion criteria were typical of lung function studies conducted in patients with COPD. Specifically, patients had to be aged ≥ 40 years, have a diagnosis of COPD according to the GOLD Guidelines (2005), have at least a smoking history of 20 pack years, and have a post-bronchodilator FEV1 < 80% and ≥ 30% of the predicted normal value and post-bronchodilator FEV1/FVC < 70%. Patients with a contraindication to receiving tiotropium were excluded. Inhaled corticosteroids were allowed.

The initial objective of the study was to select two doses of indacaterol in stage 1 to carry forward into stage 2. The primary efficacy endpoint was to demonstrate superiority in trough FEV1 (24 hour post dose) after 12 weeks of treatment for at least one of the indacaterol doses selected from stage 1. While the Applicant defined superiority as a difference in FEV1 from placebo of at least 120 mL, the Division has not formally recognized what change in FEV1 would be required to achieve "superiority". The Applicant chose non-inferiority in trough FEV1 (24 hour post dose) after 12 weeks of treatment of one of the indacaterol doses to tiotropium as a key secondary endpoint with non-inferiority defined as a difference in FEV1 not worse than -55 mL. However, the Division had previously commented that this endpoint was not acceptable for labeling purposes as the comparison to unblinded, open-label tiotropium was problematic. Moreover, the Division did not agree to the non-inferiority margin of 55 mL proposed. Additional secondary endpoints were superiority compared to placebo in the percentage of COPD "days of poor control" during 26 weeks of treatment of one of the indacaterol doses carried forward and superiority in trough FEV1 (24 hour post dose) after 12 weeks of treatment of one of the indacaterol doses to open-label tiotropium.

Efficacy studies B2334 and B2346

Study B2334 was a 52-week long, four parallel arm, placebo-controlled (indacaterol 300 mcg, 600 mcg, placebo, and formoterol 12 mcg) study, designed to collect further efficacy and safety data for the 300 mcg dose and support for long-term use. It did not study the proposed starting dose of 150 mcg of indacaterol once daily but did include a high dose of 600 mcg once daily in addition to the 300 mcg dose. The Division had previously commented at the EOP-2

meeting on September 5, 2006, that if Novartis decided to carry forward a dose other than 300 or 600mcg, then Study B2334 would not provide replicate efficacy and safety data. A decision was made by the Applicant to carry forward with a lower dose of 150 mcg as the starting dose. Replicate efficacy data were then to be provided by study B2346. However, this decision carried some additional risk since if any safety concerns were noted for the 300 or 600 mcg doses used to assess long-term safety, then the clinical program would lack long-term safety data for the 150 mcg dose. Study B2346 was a 12-week long, two parallel arms (indacaterol 150 mcg and placebo) study, designed to provide further efficacy data for indacaterol the 150 mcg dose.

Other than the obvious differences in study length and the inclusion of a formoterol arm as an active comparator for study B2334, the designs and patient populations of the studies, including the efficacy portion of study B2335s, were essentially the same. The primary endpoint was the same across all 3 pivotal studies, trough FEV1 (24 hour post dose) after 12 weeks of treatment. Study B2334 was conducted in 240 centers in 25 countries outside the United States, including Western Europe (141), Eastern Europe (38), Central and South America (21), the Middle East (18), Russia (15), and South Korea (7). The study randomized a total of 1732 patients equally across the four treatment groups for a total of approximately 400 patients per study group. Of note is that an audit of study sites in Egypt demonstrated noncompliance with GCP and collection of unreliable data so a modified ITT population excluded patients from these sites. This exclusion did not change any conclusions from the study. Study B2346 studied only the 150 mcg dose of indacaterol versus placebo. It was conducted at 103 centers, all but two in the United States (one in Australia and one in Belgium). In the study 416 patients were randomized equally to each of the two treatment groups.

Study efficacy findings:

Dose selection

Dose selection from the dose-ranging and efficacy study B2335s was made from data collected after 2 weeks of treatment with study drugs by an independent DMC which was given specific guidelines on which dose selection was to be made. These were:

- The selected dose needed to be 0.12 L greater than placebo for trough FEV1, it should also have higher trough FEV1 than tiotropium and formoterol
- The dose needed to have higher FEV1 AUC 1-4 h than tiotropium and formoterol.
- The lowest dose that fulfill the above two criteria and the next highest dose are to be selected.

According to the DMC charter, if there are complexities in the data (e.g. no dose response), the DMC and selected Novartis personnel were to discuss the results to reach a decision regarding dose selection.

The Division had discussed the issue of dose selection in study B2335s at length with Novartis as part of the dialogue after study B2335 was submitted for a special protocol assessment

(SPA) on December 20, 2006. Over the course of discussion and outlined in the Division's responses to questions submitted with the SPA submission dated February 1, 2007, the Division did not agree that dose selection should be based solely on trough FEV1 but the application must include additional information on the FEV1 dose response for review; serial spirometry was one additional assessment suggested. With regard to the issue of complexities with the data (no dose response) the Division stated that we may not agree to the criteria used by the DMC and select Novartis personnel for dose selection.

Novartis responded the Division's comments on dose selection on February 21, 2007 and stated that they intended to maintain trough FEV1 as the basis for the dose selection guidelines but proposed to do additional serial spirometry out to 12 hours in a sub-group of patients. The data would be used as supplemental information by the DMC as they deem necessary.
The Division noted Novartis' response but stated in responses dated "while the proposal may provide additional information for the DMC to select doses, it does not ensure that the Division will agree with the doses selected. This remains a potential risk with your proposed adaptive design study." Also of note regarding the dose selection criteria are the requirements that any dose of indacaterol selected should have both higher trough FEV1 and FEV1 AUC 1-4 h than either of the two marketed active comparator drugs, formoterol and tiotropium. This requirement may have lead the DMC to select higher doses (150 and 300 mcg) over the 75 mcg once daily dose. It also suggests that business/marketing principles were used, at least in part, for dose selection rather than scientific principles.

Based on the above criteria evaluated after a 2-week dosing period in stage 1 of study B2335s, the DMC selected the 150 and 300 mcg once daily doses of indacaterol as those to carry forward into stage 2 (efficacy and safety evaluation). The decision appeared to rest on the analysis of weighted mean FEV1 over 1-4 hours for which the Applicant/DMC considered the efficacy of indacaterol 75 mcg to be suboptimal because the point estimate of treatment effect of indacaterol 75 mcg was 20 mL lower than the point estimate of treatment effect of formoterol (1.50L vs 1.52L, see Table 2 below). Thus, the lowest dose that satisfied the dose selection criteria was 150 mcg.

Table 2. Summary of study B2335s interim analysis for dose selection *(from study B2335S study report, page 129)*

	Treatment				Treatment difference		
Treatment	**N**	**LS mean**	**SE**	**Comparison**	**LS mean**	**SE**	**95% CI**
Trough FEV_1 (L)							
Comparisons with placebo							
Ind 75 µg	104	1.46	0.024	Ind 75 µg - Placebo	0.15	0.029	(0.09, 0.20)
Ind 150 µg	105	1.49	0.024	Ind 150 µg - Placebo	0.18*	0.029	(0.12, 0.24)
Ind 300 µg	110	1.52	0.024	Ind 300 µg - Placebo	0.21*	0.029	(0.15, 0.27)
Ind 600 µg	108	1.51	0.024	Ind 600 µg - Placebo	0.20	0.029	(0.14, 0.25)
For	105	1.42	0.024	For - Placebo	0.11	0.029	(0.06, 0.17)
Tio	112	1.45	0.023	Tio - Placebo	**0.14**	0.028	(0.08, 0.19)
Placebo	104	1.31	0.024				
AUC 1h-4h FEV_1 (L)							
Comparisons with placebo							
Ind 75 µg	95	1.50	0.034	Ind 75 µg - Placebo	0.20	0.032	(0.14, 0.27)
Ind 150 µg	96	1.53	0.034	Ind 150 µg - Placebo	0.23*	0.032	(0.16, 0.29)
Ind 300 µg	99	1.58	0.034	Ind 300 µg - Placebo	0.28*	0.031	(0.22, 0.34)
Ind 600 µg	97	1.53	0.034	Ind 600 µg - Placebo	0.23	0.031	(0.17, 0.29)
For	93	1.52	0.035	For - Placebo	**0.22**	0.032	(0.16, 0.28)
Tio	99	1.49	0.034	Tio - Placebo	0.19	0.031	(0.13, 0.25)
Placebo	90	1.30	0.033				

The dose response data and dose selection are problematic in that a range of doses from which to be able to determine a full dose response was not studied. All doses studied appear to have reached a pulmonary function efficacy plateau as determined by both trough FEV1 and FEV1 AUC (0-4h) See Figure 4 below.

Figure 4. Dose responses by trough FEV_1 and FEV_1 AUC (0-4h) at day 15 in study B2335s *(adapted from Figure 2 from statistical review by Dr. Dongmei Liu)*

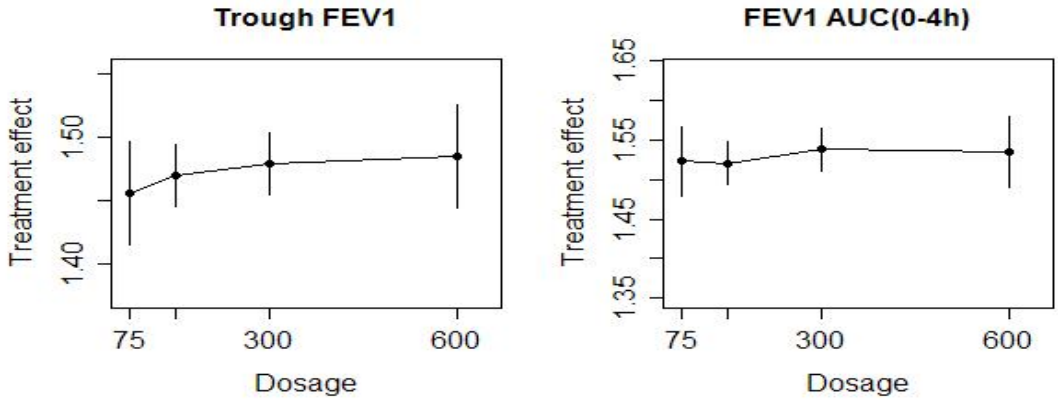
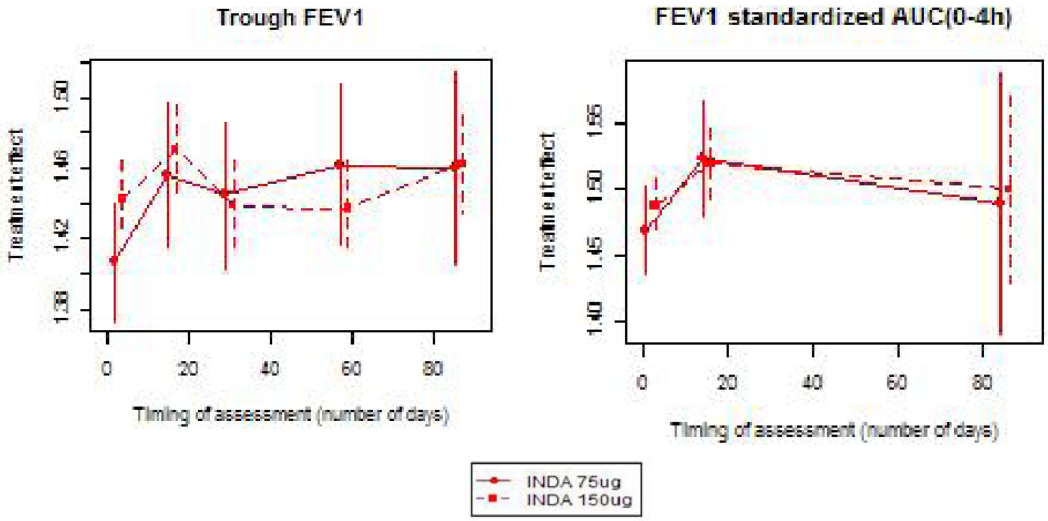


Figure 5 also demonstrates the almost identical trough FEV1 and FEV1 AUC (0-4h) values between the 75 and 150 mcg doses of indacaterol.

Figure 5. Comparison of Trough FEV1 and FEV1 AUC (0-4h) Treatment effects in study 2335s *(adapted fro Figure 11 from statistical review by Dr. Dongmei Liu)*



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The data presented above from the 2-week time point that demonstrate that he efficacy of 75 and 150 mcg of indacaterol are very similar were confirmed by data obtained at week 12 in patients enrolled in stage 1 in the 75 mcg dosing group who had already completed the 12 week dosing period at the time of the dose selection analysis (see Figure 3 from statistical review by Dr. Dongmei Liu). The data above do not allow an adequate evaluation of the dose-response curve for indacaterol as all doses selected for evaluation are at the top plateau of the dose response curve. Thus, a lowest effective dose could not be determined. In addition, the Applicant's dose selection rationale of requiring that indacaterol demonstrate better efficacy than the active comparators resulted in the selection of higher doses that stressed efficacy but with the risk on increased toxicities.

Dosing frequency

During the Division's discussion with the Applicant regarding dosing frequency at pre-NDA meeting in April 2008, the Division reminded Novartis that it would need to provide justification for the proposed dosing frequency. Since indacaterol has not been evaluated when administered at dosing frequencies other than once daily, the Division stressed that other data besides trough FEV1 would need to be submitted to justify the once daily dosing regimen. Novartis has submitted a supportive study B2340 that provides 24 hour serial FEV1 curves for indacaterol 300 mcg once daily and comparison with the active comparator, salmeterol 50 mcg twice daily. The study is problematic in that it assesses only the higher 300 mcg dose on indacaterol thus it cannot be used to support the lower primary dose selected of 150 mcg once daily. Going forward Novartis must establish a dose of indacaterol that is both safe and efficacious and justify the once daily dosing regimen with the dose selected. In addition to providing 24 hour serial FEV1 curves, justification should include a comparison of the selected dose when given at different frequencies (once vs twice daily) identifies the lowest efficacious dose for future submission, data will be needed to support the once daily dosing frequency at that dose.

Efficacy

The demographics of the patient populations were similar and well balanced across studies and treatment groups. Despite no requirement that patients show reversibility to short-acting beta-2 agonists or antimuscarinic agents, the study population had relatively high reversibility to both; 13-19% for short-acting beta-2 agonists and 13-18% for short-acting antimuscarinic agents. Approximately 65% of patients were male with a mean age of 65 years. Approximately 90% of patients in each study group could be characterized as moderate to severe COPD. About half the patients received inhaled corticosteroids and about 45-50% also remained current smokers. Pre-bronchodilator FEV1 was 1.3-1.4L.

The pre-specified primary endpoint for all three studies was to demonstrate superiority of indacaterol doses versus placebo with respect to 24 hour post-dose (trough) FEV1 after 12 weeks of treatment in patients with COPD. All doses of indacaterol studied (150, 300, and 600 mcg once daily) as well as the active comparators formoterol and tiotropium demonstrated statistical superiority to placebo in 12 week trough FEV1 (see Table 3 below). For study B2335s, treatment with indacaterol 150 µg and 300 µg resulted in a 12 week trough FEV1 improvement of 0.18 liter greater than placebo. For study B2334 the indacaterol 300 and 600 mcg groups both demonstrated a trough FEV1 advantage of 0.17 liters over placebo, and for study B2346, treatment with indacaterol 150 µg resulted in a trough FEV1 improvement of 0.13 liter greater than placebo.

Table 3. Summary of the primary efficacy endpoint (trough FEV1 at week 12) in pivotal studies.

Study	Treatment	Mean (L)	SE (L)	Treatment difference	Mean (L)	SE (L)	95% CI (L)	P value
B2335s	Placebo	1.28	0.015	---	---	---	---	---
Stage 2	Tio 18 mcg	1.42	0.015	Tio18-placebo	0.14	0.016	(0.11, 0.17)	<0.001
	Inda 150 mcg	1.46	0.015	Ind150-placebo	0.18	0.016	(0.15, 0.21)	<0.001
	Inda 300 mcg	1.46	0.015	Ind300-placebo	0.18	0.016	(0.15, 0.21)	<0.001
B2334	Placebo	1.31	0.013	---	---	---	---	---
	For 12 mcg	1.38	0.013	For12-placebo	0.07	0.016	(0.04, 0.1)	<0.001
	Inda 300 mcg	1.48	0.012	Ind300-placebo	0.17	0.016	(0.13, 0.2)	<0.001
	Inda 600 mcg	1.48	0.013	Ind600-placebo	0.17	0.016	(0.13, 0.2)	<0.001
B2346	Placebo	1.35	0.019	---	---	---	---	---
	Inda 150 mcg	1.49	0.018	Ind150-placebo	0.13	0.024	(0.09, 0.18)	<0.001

Support for the 300 mcg once daily dose

(b) (4)

In order to support the proposed 300 mcg once daily dosing regimen, clinical studies that demonstrate that administration of 300 mcg of indacaterol in the same patient who was receiving 150 mcg once daily without sufficient benefit added additional clinically meaningful improvement in lung function or other clinically meaningful measure without adding additional risk of adverse effects known to occur with beta-2 agonists including cardiovascular and central nervous system effects. Since no clinical studies of this

type have been conducted to support the higher 300 mcg dose, the proposal to allow an increase in dosing up to 300 mcg is unacceptable.

A main secondary endpoint was difference between treatment groups in days of poor control of COPD symptoms (DOPC). In study B2335s, the differences between the indacaterol and active comparator arms and the placebo arm were not significant. However, indacaterol and the active comparator formoterol were statistically superior to placebo in the other two pivotal studies (B2334 and B2346).

8. Safety

Data Base and Patient Demographics

The majority of safety data for this review comes from the pivotal phase 3 studies which are placebo and active- controlled, and includes exposure of indacaterol 150 mcg, 300 mcg, and 600 mcg that range from 3-12 months. They include:

- Study B2334: 52 weeks of treatment with indacaterol 300 mcg, 600 mcg once daily, placebo (double-blind) or formoterol 12 mcg twice daily (double-blind) and providing long-term safety data.
- Study B2335S: 26 weeks of treatment with indacaterol 150 mcg once daily, 300 mcg once daily, placebo (double-blind) or tiotropium 18 mcg once daily (open-label).
- Study B2346: 12 weeks of treatment with indacaterol 150 mcg once daily or placebo (double-blind).

In addition to the COPD patient data, because of its large size and length (6 months) the safety data from a trial of indacaterol 300 mcg and 600 mcg once daily for patients with asthma (study B2338) will also be summarized.

Of particular note in the safety data base is that the long-term (52 weeks) safety data for the program provided by study B2334 assessed doses higher than the proposed staring dose of 150 mcg. The risk in this approach by the Applicant is that if there are safety concerns with the higher doses of indacaterol studied there would be no long-term safety data to support the lower 150 mcg dose.

Using the above mentioned studies for the safety data base, 2154 COPD patients were exposed to indacaterol at doses ranging from 75-600 mcg for at least 3 months, 1943 patients exposed for at least 6 months, and a total of 862 patients, all from the long-term safety study B2334, were exposed to doses of 300 or 600 mcg for 12 months.

The patient demographics in the 3 month, 6 month, and 12 month safety populations have similar patterns. The mean and median ages are about 63- 64 years old. For most of the groups, the ratio of men to women range from 2:1 to 3:1. Between 83%- 93% of the patients are Caucasian with very few African Americans (essentially none in the 12 month safety data base). The mean BMI and median BMI range from 25- 27.

Patient disease characteristics were also similar across dosing groups. The mean duration of COPD was about 7 years, > 90% of patients had moderate and severe COPD defined by the GOLD criteria, 40%- 45% of the patients were current smokers with a mean pack-year range of 49-53, and 35%-50% of the patients used concomitant inhaled corticosteroids. Post-bronchodilator FEV1 was 51% -56%. Patients had a notable amount of reversibility after short-acting beta-agonist administration ranging from 13-19%.

Similar proportions of patients in the different groups had co-existing medical conditions that occur relatively frequently in the older COPD patient population: cardio- cerebrovascular (CCV) 20%, diabetes mellitus 7%-11%, hypertension 50%, hyperlipidemia 30%-35%. Of note is that fewer patients in the one year safety data base in the 300 mcg dosing group had a co-existing CCV condition (80) than in other groups (82-93) and more people in the placebo group (50) has diabetes mellitus than in other groups (33-37).

The clinical testing program for the indacaterol was typical of that for long-acting beta-2 agonists and was adequate to assess the systemic effects of beta-2 receptor stimulation by indacaterol. Assessments included measurements of vital signs, clinical laboratory testing (especially potassium, glucose, and LFTs), and ECGs, both at baseline and at several time points post dosing, including what would be considered the time of peak effect (one hour post-dose). Holter monitoring was also performed. In addition, the effect of indacaterol on the QT interval was evaluated in a double-blind, placebo controlled study following multiple doses of indacaterol 150 mcg, 300 mcg or 600 mcg once daily.

Deaths

A total of 14 patients died in the three pivotal studies B2334, B2335s, and B2346 that make up the COPD safety database. Seven patients who died were in the placebo group, three received formoterol, two received tiotropium, and two received indacaterol (one each for the 150 and 300 mcg dosing groups). The causes of death varied; for the indacaterol groups, in study B2334, a 57 year old male in the 300 mcg dosing arm died as a result of cardiac arrest. The patient had received his last dose of medication three days previously when he had been discontinued due to moderate dyspnea which was suspected by the investigator of being related to study drug. In study B2335s, a 52-year-old male in the indacaterol 150 µg dosing arm died suddenly on Day 145 of the study at home. The patient had heart failure from Day 113 of the study onwards, which had been treated with furosemide. An autopsy was not performed.

All three patients who died while being treated with formoterol were enrolled in study B2334. A 70 year old male died of multi-system organ failure following a series of adverse events, a 68 year old male died of respiratory failure, and a 77 year old male died suddenly during surgery to implant a pacemaker device. None of the deaths were assessed as being related to the study drug.

For tiotropium, a 63-year-old male died on Day 34 of the study at home, six days after his last dose of study medication, from an unspecified event secondary to worsening arteriosclerosis and a 78-year-old male died on Day 55 of the study from severe acute bronchopneumonia. The

patient had earlier experienced a non-serious upper respiratory tract infection which had resolved. In addition, at autopsy, the patient had acute congestion of the spleen and liver.

Serious Adverse Events/Adverse Events:

The most common SAEs in the 12 month COPD safety population were COPD-related respiratory disorders which were similar across treatment groups at 3.1-5.3 %. Cardiac disorders were notably increased in both indacaterol groups (2.7 and 1.9% for the 300 and 600 mcg groups, respectively) compared to formoterol or placebo (1.4% each). The specific SAEs of atrial fibrillation, congestive cardiac failure, myocardial ischemia, and coronary artery disease were the principle SAEs responsible for the imbalance. The pattern of SAEs was similar for the 3 and 6 month safety populations.

The patterns of general adverse events were generally consistent with what is expected with the beta-2 agonist class of drug. The most common AEs were COPD-related and occurred less in the active treatment groups (10-13%) compared to placebo (15%). Drug class related AEs observed included muscle spasms which showed a dose-related increase between the 300 and 600 mcg indacaterol doses (2.8 to 4%). Other common AEs were cough, which was higher in the indacaterol groups (4.9-5.3%) than either of the active treatment groups or placebo (2.7-4.3%), upper respiratory tract infection, headache, diarrhea dyspnea and back pain, and for the tiotropium group, dry mouth (4.1%).

Cardio- and cerebrovascular adverse events:

To assess any potential adverse effects of beta-adrenergic stimulation with indacaterol on the cardiovascular system, combined cardio- and cerebrovascular adverse events and serious adverse events were assessed in pooled Phase III safety databases. A list of pre-defined search criteria for preferred terms related to the CCV disorders “cardiac failure”, “ischemic heart disease”, and “cerebrovascular disorders” was determined prospectively. The number and percentage of patients in the COPD 3-, 6- and 12-month safety populations reporting AEs and/or SAEs meeting any of those definitions were then summarized.

COPD patients that were treated with indacaterol at the 300 and 600 mcg doses for 12 months were noted to have higher rates of cardio- cerebrovascular (CCV) SAEs than either placebo or the formoterol active comparator. The rates for the indacaterol 300 and 600 mcg groups were approximately 3.5 and 2.5 times the rate observed in the placebo group and 2.5 and 2 times that observed for formoterol, respectively (Table 4). The most frequent events in the indacaterol 300 mcg group were atrial fibrillation, heart failure and myocardial ischemia, and in the 600 mcg group these were coronary artery disease and myocardial infarction. In the placebo group there was no event reported in more than one single case.

Table 4. Comparison of rates of CCV SAEs between 3 month, 6 month, and 12 month COPD safety population *(adapted from Table 37 from the clinical review by Dr. Lynne Wu)*

	Inda 150 mcg od	Inda 300 mcg od	Inda 600 mcg od	Formoterol 12 mcg bid	Tiotropium 18 mcg od	placebo
3 months	0.96%	0.94%	0.55%	0.18%	1.45%	0.66%
6 months	2.1%	1.4%	1.2%	0.5%	2.1%	1.0%
12 months	Not studied	3.4%	2.6%	1.4%	Not studied	0.9%

As for CCV AEs at 6 months and 12 months, the indacaterol doses had similar or slightly higher rates as formoterol and higher than that of placebo (At 6 months, 2.1%, 1.4%, 1.2%, 0.5% and 1% for indacaterol 150 mcg, 300 mcg, 600 mcg, formoterol and placebo, respectively; at 12 months, 3.4%, 2.6%, 1.4%, and 0.9% for indacaterol 300 mcg, 600 mcg, formoterol, and placebo, respectively).

Vital Signs and Clinical Laboratory Assessments:

Vital signs were assessed in all studies throughout the clinical program. Treatment with indacaterol had little effect on heart rate. There were, however, dose-related increases in the numbers of patients who had high systolic blood pressure (>200 mm Hg) and both high and low diastolic blood pressure (>115 and < 40 mmHg, respectively).

Because the pharmacodynamic effects of beta agonists include increases in glucose and decreases in serum potassium, glucose and potassium values were assessed throughout the clinical program. Small dose related increases in glucose and decreases in potassium that would not be considered clinically significant were observed in the clinical trials. There were no differences in any of the other clinical laboratory assessments measured, including liver function tests.

The cardiac monitoring program throughout the indacaterol studies was adequate. In the phase III studies ECGs were performed 25 min pre-dose, 30 min post-dose, and 1 h post-dose at each visit. Continuous ECG recordings (Holter monitoring) were performed in a subset of patients in study B2335S at screening and after 2, 12 and 26 weeks of treatment in a subset of patients randomized to one of two indacaterol dose groups or placebo. A total of 522 randomized patients were included to ensure Holter monitoring data on at least 450 patients (150 patients in each group) were available for at least 12 weeks of treatment. Additionally, a thorough study reviewed by the IRT was conducted to characterize the maximum mean prolongation of QTc following multiple dose treatment with indacaterol 150 mcg, 300 mcg and 600 mcg once daily for 14 days. Review of the clinical ECG data did not find any meaningful differences between patients in the indacaterol groups versus placebo or active comparator. The IRT

concluded that treatment of indacaterol at doses up to 600 mcg for 14 days did not appreciably affect QTc.

Safety conclusion for the COPD population:

The data from the pivotal trials demonstrated that in COPD patients, indacaterol treatment at doses 300 and 600 mcg is associated with higher risk of cardio- cerebrovascular (CCV) SAEs as compared to placebo or formoterol. The data also indicated that the risk increased with longer time of indacaterol exposure. Other dose-related beta mediated adverse events were noted in the studies and began to occur between the 300 and 600 mcg doses. The long-term safety for the 150 mcg proposed starting dose was not evaluated.

Safety Summary of asthma study B2338:

In addition to the COPD patient data, because of its large size and length (6 months) a trial of indacaterol 300 mcg and 600 mcg once daily for patients with asthma (study B2338) was also reviewed to assess safety. The study was a 26-week treatment, randomized, multi-center, double blind, double dummy, parallel-group study to assess the safety of indacaterol (300 and 600 mcg once daily) in 805 patients with moderate to severe persistent asthma, using salmeterol (50 mcg twice daily) as an active control. The study contained no placebo group. In this 6 month study there were 2 deaths in asthma patients, one as a result of a severe asthma exacerbation and the other termed cardiac arrest, both in indacaterol 300 mcg once daily treated groups.

The asthma death was a 60 year Native American male with a 7 year history of asthma and no other active medical problems. Prior treatments for asthma included only the inhaled corticosteroids, beclomethasone and budesonide. He was a non-smoker. At baseline, the patient's ECG was normal and remained normal throughout the study period. At baseline, the patient's FEV1 was 2.45 L and FEV1/FVC was 72.92 % signifying relatively mild obstructive disease. On Day 165 (b) (6) 164 days after the first dose of the study medication, he presented with dyspnea and was hospitalized. He was diagnosed with an asthmatic crisis (exacerbation). No action was taken with the study medication. The patient was treated with prednisone and nebulization therapies. He recovered on the same day as its onset and was discharged home. Four days later, he again presented with dyspnea and died on his way to the hospital on (b) (6) The patient had received the last dose of the study medication on Day 169 (b) (6) The cause of death was determined to be an asthmatic crisis.

The cardiac death was 70 year old Caucasian woman had a 2 year history of asthma, allergic rhinitis, osteoporosis and a past medical history of respiratory arrest and anaphylactic reaction. Prior treatment for asthma included salbutamol and mometasone furoate. Active medications also included hydrochlorothiazide, potassium chloride and alendronate sodium. The patient's baseline FEV1 was 1.06 L and FEV1/FVC was 43.8 % signifying relatively severe obstructive disease. Her baseline EKG, hematology and chemistry laboratory values were normal. On Day 119 (b) (6), the patient experienced a cardiac arrest at home. The patient was reported to have become dyspneic and stopped talking and received cardio-pulmonary resuscitation. The patient was intubated and received epinephrine and atropine. Prior to hospitalization, the

patient's heart rate was 115, glucose was 90 mg/dL and blood pressure was 69/45 mmHg. The patient's last ECG was performed on Day 110 (b) (6) and was normal. At the hospital laboratory studies were not indicative of a myocardial infarction. A thoracic CT scan showed small pneumothorax and left lower hemithorax as well as pulmonary hyperinflation consistent with underlying asthma. An ECG performed showed normal sinus rhythm. She was treated with ceftriaxone sodium and levofloxacin for possible infection and lorazepam and phenytoin for the seizures and received Propofol for sedation. Life support was withdrawn at the request of her family on (b) (6) (Day 129), 11 days after the last dose of the study medication. An autopsy was not performed.

Additional safety data from asthma study B2338 are summarized in Table 5 below. In addition to the imbalance in deaths compared to the active marketed LABA control, salmeterol, more asthma patients in both the indacaterol 300 and 600 mcg groups had increased asthma SAEs and muscle spasm AEs compared to patients in the salmeterol group. The imbalances in deaths, asthma-related SAEs and muscle spasm AEs in asthma patients dosed with both 300 and 600 mcg of indacaterol once daily provides further support that those doses are too high and unsafe.

Table 5. Safety summary data from asthma study B2338 *(adapted from Table 30 from the clinical review by Dr. Lynne Wu)*

	Indacaterol 300 mcg N=268	Indacaterol 600 mcg N=268	Salmeterol 50 mcg bid N=268
Deaths	2	0	0
Asthma SAEs	0.7%	1.1%	0
Asthma AEs	11.6%	15.7%	14.9%
Muscle spasm AEs	1.9%	3.4%	1.5%
Tremor AEs	0.7%	3.7%	10.4%
Cardiac SAEs	0.4%	0.4%	0.4%

9. Advisory Committee Meeting

An advisory committee meeting will not be held for indacaterol during the current review cycle but will be scheduled when the Applicant has addressed the issues to be conveyed in the Complete Response.

10. Pediatrics

COPD is an adult disease, therefore, specific pediatric studies would not be required that relate to this action specific to COPD.

11. Other Relevant Regulatory Issues

- Financial Disclosures: Three investigators were noted to receive significant payments from the Applicant > $25,000 (Category 2), (b) (6) possessed a significant equity interest of > $50,000. (b) (6) enrolled patients in (b) (6) for study B2335s. (b) (6) enrolled patients in (b) (6) for study B2335s and in (b) (6) for study B2338. (b) (6) enrolled patients in (b) (6) for study B2335s. Lastly, (b) (6) enrolled patients in (b) (6) for study B2335s. Based on the large size and multi-center nature of the pivotal clinical studies, it is unlikely that financial interests could have influenced or biased the results of these studies.
- DSI audits of study sites were not conducted during the course of this review cycle.
- The Division of Risk Management was consulted to review proposed patient labeling and Risk Evaluation and Mitigation Strategy (REMS) the indacaterol NDA but comments were deferred on the Medication Guide and REMS until such time labeling is addressed.
- The Division of Medication Error Prevention and Analysis reviewed the proposed proprietary name Arcapta (b) (4) A subsequent proposed proprietary name "Arcapta Neohaler" was evaluated from a safety and promotional perspective and judged acceptable.

12. Labeling

A substantial labeling review was not performed for this submission as the Applicant has not demonstrated a dose or doses of indacaterol that is both safe and efficacious for the treatment of bronchospasm associated with COPD and the recommended regulatory action the dose is a Complete Response.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The data submitted in this NDA do not provide support for approval and the recommended regulatory action is a Complete Response. Although the proposed indacaterol maleate 150 mcg once daily delivered as single dose dry powder inhalation provided a statistically significant degree of bronchodilation over placebo in study subjects with chronic obstructive pulmonary

disease (COPD), the long-term safety of indacaterol at doses less than 300 µg has not been evaluated. The one year safety data submitted to support the application has demonstrated that patients with COPD who received indacaterol at doses of 300 and 600 mcg once daily had increased cardio- and cerebrovascular serious adverse events, a known risk for the beta-2 agonist class of drugs. Dose-response data and safety data reviewed for asthma patients also support the conclusion that the doses selected for Phase 3 trials were too high and, at least for doses of 300 mcg once daily dose and above, unsafe for both the COPD and asthma patient populations. Thus, the Applicant has not adequately demonstrated a dose or doses of indacaterol that is both safe and efficacious for the treatment of bronchospasm associated with COPD.

- Risk Benefit Assessment

The risk benefit assessment does not support approval of the long-acting beta-2 agonist (LABA) indacaterol 150 or 300 mcg once daily for the maintenance treatment of bronchospasm in patients with chronic obstructive pulmonary disease. The use of long-acting beta agonists, while clinically useful at the correct dose in the appropriate patient population, has the potential to cause considerable dose-dependent morbidity and mortality in both the older medically fragile population of patients with COPD (especially those affecting the cardiovascular and central nervous systems) as well as in asthma patients where there is a documented increased risk of severe exacerbations including death in patients using long-acting beta agonists. In this submission, the Applicant has not adequately demonstrated a dose or doses of indacaterol that is both safe and efficacious for the treatment of bronchospasm associated with COPD. An effective dose on the lower end of the dose-response with an acceptable safety profile has not been sufficiently explored for indacaterol. There is little difference in FEV1 response at doses of 75-300 mcg once daily and indacaterol at doses of 300 and 600 mcg once daily had increased cardio- and cerebrovascular serious adverse events compared to both placebo and the active beta agonist control, formoterol, a known risk for the beta-2 agonist class of drugs. Dose-response data and safety data reviewed for asthma patients also support the conclusion that the doses selected for Phase 3 trials were too high and, at least for doses of 300 mcg once daily dose and above, unsafe. The long-term safety of indacaterol at doses less than 300 mcg has not been evaluated.

- Recommendation for Postmarketing Risk Management Activities

While not approved during this review cycle, similar to all other LABA medications, a Medication Guide will be recommended as necessary for patients' safe and effective use of Arcapta Neohaler. Long-acting beta -2 agonists, the class of drug to which Arcapta Neohaler belongs, are known to increase the risk of asthma related death in patients with asthma. Therefore Arcapta Neohaler is a product that has serious risk(s) (relative to benefits) in patients with asthma of which all patients prescribed Arcapta Neohaler should be made aware.

- Recommendation for other Postmarketing Study Commitments

Not relevant because this application will not be approved in this review cycle.

- Recommended Comments to Applicant

1. You have not adequately demonstrated a dose or doses of indacaterol that is both safe and efficacious for the treatment of bronchospasm associated with COPD. While data from study B2335s suggest that indacaterol at doses of 75-300 mcg once daily elicit a similar FEV1 response compared to placebo, the long-term safety of indacaterol at the proposed doses of 150 and 300 mcg has not been determined. In the 12 month safety study (B2334), COPD patients who received indacaterol at doses of 300 and 600 mcg once daily had more combined cardiac and/or cerebrovascular (CCV) serious adverse events than those who received placebo or the marketed long-acting beta-2 agonist, formoterol (3.4%, 2.6%, 1.4%, and 0.9% for indacaterol 300 mcg, 600 mcg, formoterol and placebo, respectively). The long-term safety of indacaterol at doses less than 300 mcg has not been evaluated.

You will need to conduct future clinical studies to support the efficacy and dosing frequency of a dose or doses of indacaterol and demonstrate its safety in the population of patients with COPD.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22383	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	Arcapta Neohaler
NDA-22383	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	Arcapta Neohaler
NDA-22383	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	Arcapta Neohaler
NDA-22383	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	Arcapta Neohaler
NDA-22383	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	Arcapta Neohaler
NDA-22383	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	Arcapta Neohaler
NDA-22383	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	Arcapta Neohaler
NDA-22383	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	Arcapta Neohaler
NDA-22383	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	Arcapta Neohaler
NDA-22383	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	Arcapta Neohaler

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/s/

ANTHONY G DURMOWICZ
09/29/2009

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22-383
Priority or Standard	Standard
Submit Date(s)	December 15, 2008
Received Date(s)	December 15, 2008
PDUFA Goal Date	October 18, 2009
Division / Office	DPAP/ODE II
Reviewer Name(s)	Lynne H. Wu, M.D.
Review Completion Date	August 24, 2009
Established Name	Indacaterol
(Proposed) Trade Name	Arcapta Neohaler
Therapeutic Class	Long-acting Beta-2 Agonist
Applicant	Novartis Pharmaceuticals
Formulation(s)	Single dose dry powder inhaler
Dosing Regimen	Once daily
Indication(s)	Long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD).
Intended Population(s)	Patients with COPD

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical perspective, the data submitted in this NDA do not provide support for approval and the regulatory action will be a Complete Response. Although the proposed indacaterol maleate 150 µg once daily delivered as single dose dry powder inhalation provided a statistically significant degree of bronchodilation over placebo in study subjects with chronic obstructive pulmonary disease (COPD) the dose response data submitted are inadequate to support the 150 µg once daily dose as that which is both efficacious and provides an acceptable long term safety profile.

In this regard, there is little difference in FEV1 response at doses of 75-300 µg once daily, thus the dose which is efficacious, while giving the lowest systemic exposure has not been determined. This is especially important giving the known cardiovascular risks of LABAs and was demonstrated in 12 month safety studies in which COPD patients who received indacaterol 300 µg once daily had more cerebral/cardiovascular serious adverse events than those who received placebo and the active comparator LABA, formoterol.

1.2 Risk Benefit Assessment

The risk benefit assessment does not support approval of the long-acting beta-2 agonist (LABA) indacaterol 150 µg (proposed tradename Arcapta Neohaler) once daily for the maintenance treatment of bronchospasm in patients with chronic obstructive pulmonary disease. The use of long-acting beta agonists, while clinically useful at the correct dose in the appropriate patient population, has come under scrutiny as a result of a safety signal of increased risk of severe exacerbations including death in patients with asthma; a safety signal that appears to include indacaterol. While no such safety signal has been observed in patients with COPD, dose-related class effects of beta agonists, especially those affecting the cardiovascular and central nervous systems, dictate careful dose selection in this older patient population which tends to have increased cerebral and cardiovascular risk factors with a focus on selection of the lowest dose demonstrated to provide efficacy with an acceptable safety profile. In this regard the lowest effective dose with an acceptable safety profile has not been sufficiently explored for indacaterol. There is little difference in FEV1 response at doses of 75-300 µg once daily, thus the dose which is efficacious, while giving the lowest systemic exposure has not been determined. This is especially important giving the known cardiovascular risks of LABAs and was demonstrated in this program in the 12 month safety study in which COPD patients who received indacaterol 300 µg once daily had more combined cerebral and cardiovascular serious adverse events than those who received placebo or the marketed LABA, formoterol.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Since an appropriate dose of indacaterol was not supported by the data submitted and this submission will not be approved, postmarketing risk evaluation and mitigation strategies (REMS) was not reviewed. However, typical of drugs in the long-acting beta-2 agonist family, medication guide at a minimum will be required.

1.4 Recommendations for Postmarket Requirements and Commitments

This is not applicable since the submission will not be approved.

2 Introduction and Regulatory Background

2.1 Product Information

The applicant, Novartis Pharmaceuticals Corporation, submitted NDA 22-383 on December 15, 2008 for an inhalation powder containing indacaterol maleate, a long-acting beta-2 agonist (LABA) to be indicated for the long-term maintenance treatment of bronchospasm associated with COPD.

Indacaterol maleate is a new molecular entity. The dry powder is pre-metered and the formulation is contained in hard gelatin capsules. Insertion of these capsules into the single dose inhalation (also known as Concept1) device allows the contents to be accessed and inhaled.

The Applicant initially proposed the trade names Arcapta (b) (4) but due to recommendation from the Division of Medication Error Prevention and Analysis (DMEPA) that (b) (4) , Novartis changed the trade name to Arcapta Neohaler, which was acceptable to DMEPA and DPAP.

2.2 Tables of Currently Available Treatments for Proposed Indications

The following table lists drugs currently used for treatment of COPD. Note that the indication for short-acting beta-agonists is generally for treatment of acute bronchospasm, a condition present in many patients with COPD.

Table 1 Table of Currently Available Treatments for Proposed Indications

class		**medication**	
Beta agonists			
	Short-acting		
		Albuterol (Pro-air HFA, Ventolin HFA, Proventil HFA), Levalbuterol (Xopenex)	
		Pirbuterol (max-air)	
		Terbutaline (generic only)	
	Long-acting		
		Salmeterol (Serevent and as a component of Advair)	
		Formoterol (Foradil and as a component of Symbicort)	
		Arformoterol (Brovana)	
		Formoterol solution (Perforomist)	
Anti-cholinergics			
	Short-acting		
		Ipratropium bromide (Atrovent and as a component of Combivent)	
	Long-acting		
		Tiotropium bromide (Spiriva)	
Xanthines		theophylline	

2.3 Availability of Proposed Active Ingredient in the United States

Indacaterol is not marketed in the United States or any foreign country.

2.4 Important Safety Issues With Consideration to Related Drugs

The LABAs, salmeterol (Serevent®), racemic formoterol (Foradil®, performist, and R,R-formoterol [brovana]) are marketed world-wide for the relief of bronchospasm in both patients with COPD and (for serevent and foradil) those with asthma. The safety of chronic use of LABAs, especially for the control of asthma symptoms has been an issue of concern in recent years.

Salmeterol was first approved in the United States for use in patients with asthma in 1994. Shortly thereafter, reports in the literature suggested that chronic usage of salmeterol may make asthma worse. Due to accumulating concerns regarding the safety of chronic, regular use of salmeterol, the FDA worked with GlaxoSmithKline (GSK), the makers of Serevent® to have them conduct a large, controlled prospective safety study to address this issue.

As a result, GSK initiated the Salmeterol Multicenter Asthma Research Trial (SMART) in 1996. The SMART was a randomized, double-blind study that enrolled patients with asthma not

currently using LABAs to assess the safety of salmeterol (42 mcg twice daily for 28 weeks) compared to placebo when added to usual asthma therapy. The primary endpoint was the combined number of respiratory-related deaths or respiratory-related life-threatening experiences (intubation and mechanical ventilation). The study was prematurely terminated in January 2003 after a total of approximately 30,000 patients had been enrolled because a planned interim analysis suggested that salmeterol may be associated with an increased risk of severe asthma exacerbations including death, particularly in African Americans.

As a result of the findings described above, the safety of LABAs was the topic of discussion at a July 13, 2005, Pulmonary Allergy Drugs Advisory Committee Meeting. Subsequent to the meeting, in November, 2005, the FDA released a Public Health Advisory to alert healthcare professionals and patients that LABAs may increase the chance of severe asthma episodes, and death when those episodes occur, and that even though LABAs decrease the number of asthma episodes, they may increase the chances of a severe asthma episode when they do occur. The existing product labels have been revised and now include a Boxed Warning and a Medication Guide for both marketed LABA products.

The issue of safety of LABAs was again discussed at a subsequent another FDA advisory meeting. On December 2008, FDA convened a joint meeting of the Pediatric Advisory Committee, the Pulmonary-Allergy Drugs Advisory Committee, and the Drug Safety and Risk Management Advisory Committee to review the risks and benefits of LABAS for the treatment of asthma in adults and children.

The committee unanimously agreed that for single agent LABAs the benefits did not outweigh the risks in children 4-11 years of age. The committee members also agreed the same for adolescents and adults under the current label. However, many indicated that their concern could be addressed if labeling changes were made both to strengthen warnings against using LABAs as monotherapy and that LABAs should be added to corticosteroids only when corticosteroids alone proved inadequate for asthma control.

As for Advair and Symbicort, the committee voted that for adults and adolescents the benefits outweighed the risks, for a slim majority thought the same applied for children 4-11 years of age. At the date of this review, FDA has not decided on a course of action based on the results of this joint advisory meeting.
The safety studies described above pertain to the use of LABAs for treatment of asthma. However, the pharmaceutical company, GlaxoSmithKline, has funded a large clinical study (TORCH) which evaluated the effect of the LABA, salmeterol, and the inhaled corticosteroid, fluticasone, on all-cause mortality in 6,100 patients with COPD. No association with COPD exacerbation and mortality was seen.

All LABAs indicated for use in COPD and asthma contains a Boxed Warning and Medication Guide concerning the safety risks in asthma. The fact that indacaterol will be indicated for treatment of patients with COPD and not asthma raises some unique safety concerns. It is possible that indacaterol, even if approved for use in COPD only, may be used “off-label” in patients with asthma, the population in which the risk of severe exacerbations has been shown to be increased with the use of other LABAs.

FDA, as a result of the advisory meeting conducted in December 2008, is currently deliberating on the role of LABAs as maintenance therapy for asthma and COPD.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Novartis has studied three different indacaterol formulations: HFA (IND 66,337), single-dose dry powder inhaler (SDDPI; IND 48,649), and multi-dose dry powder inhaler (MDDPI; IND 69,754). The HFA drug product development program was suspended by the sponsor due to technical reasons. Following is a summary of early phase and later phase (EOP-2, pre-NDA) activity.

- On February 13, 2004, the sponsor submitted IND 48,649 to study indacaterol SDDPI in subjects with persistent asthma. An open-label, single-dose study was approved to proceed up to a 3000mcg dose in adult subjects ages 18 to 45. A higher dose of 4000mcg was not approved due to lack of preclinical support. Subjects older than age 45 were excluded due to concerns of increased cardiac toxicity in older animals in animal studies.

- On April 27, 2004, the sponsor submitted IND 69,754 to study indacaterol MDDPI in subjects with persistent asthma. The double-blind, placebo-controlled, 4-treatment cross-over study proposed doses of 50, 200, and 400mcg for 7 days was deemed safe to proceed.

- On August 1, 2005, the Division met with the sponsor for an end-of-Phase-II meeting to discuss the clinical development of indacaterol MDDPI. At that time, Novartis indicated that they planned to focus on the MDDPI formulation using the Certihaler delivery system, the system used with Foradil, another LABA.

- On October 26, 2005, the sponsor submitted Study B2329 for COPD, a 52-week, randomized, double-blind, placebo-controlled Phase III study to evaluate efficacy, safety, and tolerability of indacaterol MDDPI (200 or 400mcg daily) in patients with COPD.

- On December 5, 2005, the sponsor submitted Study A2301 for asthma, a 52-week randomized, double-blind, placebo-controlled Phase III study to evaluate efficacy, safety, and tolerability of indacaterol MDDPI (200 and 400mcg daily) in patients with persistent asthma.

- On February 2, 2006, the sponsor submitted a General Correspondence reporting difficulties with the Foradil Certihaler in Europe. Four cases of overdose were reported, attributed to excess powder release from the device. The foradil certihaler was voluntarily recalled in Germany and Switzerland.

- On May 22, 2006, the sponsor communicated via General Correspondence plans to substitute indacaterol SDDPI for indacaterol MDDPI (Certihaler) in Phase III studies. The applicant had previously planned to use the Certihaler delivery system (the system used with Foradil) for the MDDPI formulation. The Division cautioned that Phase III studies using the SDDPI formulation without prior review were “extremely risky.”

EOP2 meeting
On September 5, 2006, the applicant submitted proposals for three studies in preparation for an end of phase 2 meeting. The proposed studies included B2335s, the dose ranging adaptive design, B2334, one year study with indacaterol 300 µg and 600ug, and the 14 days QT prolongation study. Our comments included:

- The proposed plan for interim analysis and dose selection is reasonable. In addition to trough FEV1, the full FEV1 response curve will be a review issue. As part of the interim analysis, pre-specified evaluation of the full FEV1 response curve will further facilitate selection of appropriate doses.
- If you plan to carry forward the 300 or 600 µg doses of indacaterol, then B2335S could be 6 months duration. However, if you decide to carry forward a dose other than 300 or 600mcg, then Study B2334 will not provide replicate efficacy and safety data.
- The secondary endpoints for Study B2335S include non-inferiority and superiority comparisons between indacaterol and tiotropium. The proposed study using open-label tiotropium would not be adequate basis for any label claims.
- Address the potential for off-label use in asthma in your development program for indacaterol in the treatment of COPD.

Special protocol assessment
In February 2007, the adaptive design combined dose ranging and pivotal phase 3 protocol, B2335s, was submitted for review. We had the following comments.

- while it is your decision and your risk to base the DMC dose selection solely on trough FEV1, your application must include additional information on the FEV1 dose response for our review. Obtain serial spirometry on all four doses of indacaterol at baseline and at an appropriate follow up visit during Stage 1 to provide information on other key variables, such as peak FEV1 and FEV1 AUC.

Reviewer's comment: applicant selected 2 week treatment period as the point at which dose selection was made.

Pre-NDA meeting
In April 2008, a pre-NDA meeting was held to discuss content and formulation for NDA submission. Our comments included:

- Although COPD is not a disease of the pediatric population, as a once daily beta-agonist, QAB 149 has potential for off-label use in asthma patients, including pediatric patients. Due to the potential for off-label use in asthma, we expect studies to be conducted in patients with asthma, including pediatric patients.
- We remain concerned regarding the periportal hepatocellular vacuolation/ glycogen deposition that was seen in dog toxicity studies as this toxicity is not easily monitored in humans. The result of the serum glucose monitoring in your Phase 3 program and the issue of glycogen deposition will be a review issue.
- From a clinical perspective, the division did not feel that Novartis' approach to monitoring serum glucose was unreasonable; however, the Division did not necessarily agree that there was a correlation between serum glucose and hepatic glycogen deposition.

- We remind you that you will need to provide justification for your proposed once daily dosing frequency. In addition to 24-hour FEV1 response curve and trough FEV1, we will also consider the efficacy results of QAB 149 in comparison to the twice-daily active comparators, salmeterol and formoterol.
- Novartis requested clarification regarding the Division's request for justification of the once daily dosing frequency of QAB149. Novartis summarized the endpoints that will be reported, including trough FEV1 as the primary endpoint and 24 hour FEV1 profiling in two studies. Novartis also provided a table that summarized all the studies which included twice-daily beta agonists as active comparators to their product. Novartis requested the Division's input regarding additional information required to justify the dosing frequency. The Division stated that the intent of this comment was not to imply that additional studies should be conducted. Rather, the division wanted to remind Novartis that there are a numbers of way to justify dosing frequency. Since Novartis has not compared multiple dosing regimens of QAB 149 within their clinical development program, the Division emphasized that, in addition to the endpoints mentioned, it will also use the comparison with the twice-daily LABAs to further evaluate the dosing frequency. The Division reminded Novartis that statistical significance in the pre-specified endpoints (e.g. trough FEV1) versus placebo would not necessarily be enough to justify the dosing interval. Other supportive information will be taken into account.

2.6 Other Relevant Background Information

Indacaterol has not been marketed in any other country and there have not been any foreign regulatory actions on indacaterol.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Review of the data from the pivotal studies by the statistician Dr. Dongmei Liu did not show any evidence of treatment-by-site interaction at this time. DPAP did not request audits by the Division of Scientific Investigation. This decision is based on the fact that the review of this submission revealed that the optimal indacaterol dose has not been identified and that the submission will not be approved this cycle.

For study B2334, a total of 129 patients from centers in Egypt had serious GCP non-compliance and unreliability of data, so these patients were excluded from the ITT (intention-to-treat) population for efficacy analysis. [See study B2334, page 7] In addition, since study B2334 does not include the indicated dose, its study results mainly contribute to safety assessment and will not affect efficacy conclusions.

3.2 Compliance with Good Clinical Practices

The Applicant has indicated that all clinical trials were conducted in accordance with Good Clinical Practices [See CTD 2.5 Clinical Overview, page 9]

During the course of study B2334, 129 patients from centers in Egypt had serious GCP non-compliance and unreliability of data. This issue is discussed in study B2334 of this NDA, and is summarized above in Section 3.1 of this review.

3.3 Financial Disclosures

Section 1.3.4 of the NDA addresses the Applicant's compliance with the Final Rule on Financial Disclosure by Clinical Investigators. The Applicant certifies that it did not enter into financial arrangements with any investigator whereby the value of compensation could be affected by the outcome of the study (Category 1), that no investigator received significant payments (Category 2), that none of the investigators disclosed a proprietary interest in the product (Category 3), or possessed a significant equity interest in the Applicant (Category 4) as defined in 21 CFR 54 with the following exceptions.

Three investigators were noted to receive significant payments from the Applicant > $25,000 (Category 2), (b) (6) possessed a significant equity interest of > $50,000.

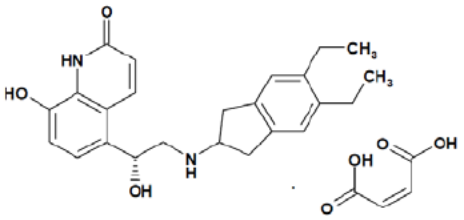
(b) (6) enrolled patients in (b) (6) for study B2335s. (b) (6) enrolled patients in (b) (6) for study B2335s and in (b) (6) for study B2338. (b) (6) enrolled patients in (b) (6) for study B2335s. Lastly, (b) (6) enrolled patients in (b) (6) for study B2335s. Based on the large size and multi-center nature of the pivotal clinical studies, it is unlikely that financial interests could have influenced or biased the results of these studies.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Indacaterol maleate inhalation powder is a non-sterile dry powder inhaler drug product. It is pre-metered and the formulation is contained in hard gelatin capsules. Insertion of these capsules into the (b) (4)/Neohaler (a.k.a., Concept1) device allows the contents to be accessed and inhaled. The patient uses the (b) (4)/Neohaler device to pierce the capsule simultaneously once on each end. Inhalation from the mouthpiece causes the capsule to spin and the formulation powder is entrained into the air stream and is emitted from the mouthpiece.

IUPAC name of indacaterol maleate is (R)-5-[2-(5,6-Diethylindan-2-ylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one maleate. The structure of the drug substance is as below.



Indacaterol maleate is a new molecular entity manufactured by Novartis Pharma. (b) (4)

The drug substance is white to of off-white which melts with decomposition in the temperature range of 195-202°C. The composition of QAB 150 µg inhalation powder hard capsule is as follows:

(b) (4)

At the time of finalization of this review, Dr. Craig Bertha, the Division's CMC reviewer, considered this application to be approvable. A draft letter of deficiency to the applicant includes issues such as clarification regarding drug substance synthesis, revision of drug substance quality control methods, clarification of the drug product quality control methods, revision to drug product, device, and lactose excipient specification acceptance criteria, request

for information regarding the placebo capsule and revision of label. For additional information, refer to Dr. Bertha's CMC review.

4.2 Clinical Microbiology

This section is not applicable for this NDA.

4.3 Preclinical Pharmacology/Toxicology

The target organ toxicity for Indacaterol (QAB149) was delineated in the rat and the dog. Typical of beta adrenergic agonists, the main target system is the cardiovascular system. In the rat nasal lesions and macrophages in the pulmonary tree, mostly in the lungs were also observed. The target organs in the dog are the cardiovascular system and the liver.

Carcinogenicity studies, 6 month in the mouse and two years in the dog do not indicate a tumorigenic potential for indacaterol other than a low incidence of leiomyomas in the ovaries of the rats which is thought to be a class effect of beta-agonists. Indacaterol was negative in a battery of genetic toxicology studies, e.g., Ames test, chromosome aberration test with V79 Chinese hamster cells and bone marrow micronucleus test in rats.

In reproduction studies in the rat, indacaterol decreased organ weights but did not cause significant effects in males or females related to parameters of fertility, general reproductive performance or early development. In embryofetal development studies in the rat and the rabbit, there was no embryo-fetal toxicity, gross malformations or teratogenicity. When assessed for effects on pre-and postnatal development, indacaterol increased slightly the duration of the gestation period but had no significant effect on neurobehavior or reproduction of the F1 pups or the gross appearance of the F2 pups.

For additional details in the preclinical program, see pharmacology/ toxicology review by Dr. Virgil Whitehurst.

4.4 Clinical Pharmacology

In support of this submission, the applicant included the results from 36 clinical studies that contain pharmacokinetic information collected from healthy volunteers (14 studies), patients with COPD (10 studies), and asthma patients (12 studies). The studies conducted in asthma patients (12 studies) were not reviewed for this submission because of their lack of relevance of the approval of this NDA for COPD.

4.4.1 Mechanism of Action

[From CTD 2.5 Clinical Overview, page 18]

Indacaterol is a long-acting β2-adrenergic agonist that acts locally in the lung as a bronchodilator. It is a nearly full agonist at the human β2- adrenergic receptor with nanomolar potency. In isolated human bronchus, indacaterol has a rapid onset of action and a long duration of action. The pharmacological effects of β2- adrenoceptor agonist drugs, including indacaterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels result in relaxation of bronchial smooth muscle.

4.4.2 Pharmacodynamics

[From CTD 2.5 Clinical Overview, page 18-19]

The bronchodilator effects of indacaterol were investigated in COPD patients up to doses of 3000 µg in single dose and 800 µg in repeated dose studies. Common endpoints were trough FEV1 to characterize the bronchodilator effect of indacaterol at the end of the 24 h dosing interval and peak FEV1. Two short term efficacy studies were undertaken in patients with COPD and characterized the bronchodilator effects of indacaterol over 24 h.

The full bronchodilator effect of indacaterol is achieved within 30 minutes of inhalation with bronchodilator effects within 5 minutes after inhalation. No difference in bronchodilator effect after morning or evening administration of indacaterol was observed.

For the precise characterization of the effects of indacaterol on the QT-interval a large thorough QT-study (Study CQAB149B2339) was conducted in 404 healthy subjects. The primary objective was to characterize the maximum mean QTcF prolongation following multiple doses of indacaterol for 14 days. With indacaterol treatment at multiple daily doses of 150, 300 and 600 µg maximum mean prolongations of QTcF intervals were below <5 ms (the regulatory threshold of concern) and the upper limit of the 90% confidence intervals was below 10 ms for all comparisons vs. placebo.

In Study CQAB149B2202 with single doses of indacaterol, there was a dose-dependent increase in heart rate up to 3000 µg indacaterol which produced a maximum heart rate change versus placebo of 12.4 bpm.

4.4.3 Pharmacokinetics

After oral inhalation from an SDDPI device such as Concept1, indacaterol was rapidly absorbed and achieved peak serum levels (Cmax) in the majority of subjects within the first 30 minutes after administration. Thereafter, indacaterol concentrations declined in a multi-phasic manner with an apparent terminal half-life that ranged from 45.5 to 126 h. From the multiple dose inhalation study (Study CQAB149B2339) the effective half-life accumulation was determined to be in the range of 40 to 52 hours which was consistent with the observation that steady state was achieved between 12 and 14 days of once daily dosing.

Absolute bioavailability of an inhaled dose was on average 43.2%. There was no clinically meaningful difference in systemic exposure when comparing dosing via Concept1 in the morning versus evening. Relative bioavailability of an oral dose compared to an inhaled dose was 46% (Study CQAB149A2106). The bioavailability data together suggest that systemic exposure to indacaterol after inhalation is a composite of pulmonary and intestinal absorption.

Indacaterol is highly bound to plasma and serum proteins. The in vitro human serum and plasma protein binding was high, ranging from 94.1 to 95.3 and 95.1 to 96.2% respectively. Renal clearance of serum indacaterol was on average between 0.5 and 1.2 L/h in healthy subjects and COPD patients. After inhaled administration of indacaterol, generally less than 2% of the inhaled dose was excreted into urine.

The primary metabolic pathways of indacaterol in humans involved monohydroxylation and N-glucuronidation, and both C- and N-dealkylation. After oral administration of indacaterol in the human ADME study [Study CQAB149A2223] unchanged indacaterol was the main circulating component in human serum, accounting for 32.5% of the total drug related AUC0-24h. The contribution of individual metabolites to the total drug related AUC0-24h in human serum ranged from 4.2% to 12% with the hydroxylated metabolite P26.9 being the most prominent.

Indacaterol showed no significant inhibition of the P450 enzymes. Data suggest that systemic clearance is influenced by modulation of both P-gp and CYP3A4 activities and that the 2-fold AUC increase caused by the strong dual inhibitor ketoconazole reflects the impact of maximal combined inhibition.

Indacaterol pharmacokinetics is not different amongst COPD patients of different ethnicities.

Population PK analysis indicated that within the COPD analysis population the systemic exposure increased with increasing age (41% increase in peak exposure and 23% increase in steady state AUC0-24h within the age range of 48 to 78 years). When body weight increased from 50 to 107 kg in the COPD analysis population, peak concentrations decreased by 25% and AUC0-24h decreased by 21%. Female COPD patients had on average 7%-11% higher systemic exposure than males.

Mild and moderate hepatic impairment does not alter indacaterol pharmacokinetics or protein binding.

For further detail of the clinical pharmacology program, see clinical pharmacology review by Dr. Sandra Suarez.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Tables 3 and 4 provide a summary of the pivotal and supportive clinical studies in this application.

Table 3 Pivotal Phase 3 Clinical Trials

Study Number (Report #)	Study Type	Treatment Groups	Location	Duration	Design	# of Subjects	Primary Endpoint
B2335s	Safety/ Efficacy	***Initial 2 weeks*** IND 75 µg qd IND 150 µg qd IND 300 µg qd IND 600 µg qd Placebo Formoterol 12 µg bid (blinded) Tiotropium (18 µg qd, open label) ***Continue for entire 6 months*** *IND 150 µg* *IND 300 µg* *Placebo* *Tiotropium*	334 centers 11 countries USA (185) W europ(78) Canada((24) Argentina (6) India (13) Korea (13) Turkey (8) Taiwan (7)	26 weeks	R, DB, PC, PG Double dummy, Adaptive, Seamless	1665 pts	Superiority of indacaterol to placebo for trough (24 hr post dose) FEV1 after 12 wk of treatment
B2334	Safety	IND 300 µg qd IND 600 µg qd Formoterol 12 µg bid Placebo	230 centers 25 countries W Eur (141) E. Europ (38) Russia (15) C/S Ameri(21) m. East (18) S. korea(7)	52 weeks	R, DB, DD, PC, PG	1728 pts	Superiority of indacaterol to placebo for trough (24 hr post dose) FEV1 after 12 wk of treatment
B2346	Safety/ Efficacy	IND 150 µg qd Placebo	103 centers USA (101) Austral (1) Belgium (1)	12 weeks	R, DB, PC, PG	416 pts	Superiority of indacaterol to placebo for trough (24 hr post dose) FEV1 after 12 wk of treatment

Table 4 Supportive Clinical Trials

Study #	Design	Treatments	Duration	# of Subjects	Population	Primary Endpoint	Relevance to Review
B2305	P III, R, DB, DD, PC treatment, 3 period incomplete crossover	INDA 300 µg qAM INDA 300 ug qPM Salmeterol 50 µg bid placebo	12 weeks	95	COPD	Efficacy and safety	
B2307	treatment, 3 period incomplete	IND 150 µg qd IND 300 µg qd Salmeterol/fluticasone 50/500 µg Salbutamol 200 µg Placebo	Single dose	89	COPD	Efficacy and safety	none

B2340	crossover	INDA 300 µg qd placebo Salmeterol 50 µg bid (open label)	14 days	68	COPD	24 hr lung function profile	Dose interval

Additionally, a large clinical trial of indacaterol in asthma patients was also reviewed to further examine the safety of indacaterol (Table 5). Although this NDA seeks an indication for COPD patients, safety for off-label use of indacaterol in asthma patients is a concern.

Table 5 Clinical Trial in Asthma

Study #	Design	Treatments	Duration	# of Subjects	Population	Primary Endpoint	Relevance to Review
B2338	P, R, DB, DD, PG	IND 300 µg qd INDA 600 ug qd Salmeterol 50 µg bid	26 weeks	800	asthma	safety	Off-label use in asthma

There are number of other clinical studies performed that are not listed. They are generally smaller studies of shorter duration that are phase I or phase II type studies.

5.2 Review Strategy

Two pivotal, phase 3 studies (B2335s and B2334) shown in the table above are the primary basis in this review to support the efficacy of indacaterol maleate inhalation powder. Each of the studies is reviewed individually in detail in section 5.3. In the Review of Efficacy (Section 6), the efficacy results for the studies are pooled.

The pivotal, phase 3 study B2334 examined the effect of indacaterol 300 µg and 600 µg, which are higher doses than the dose that the applicant is seeking an indication. Therefore, the results from B2334 are used primarily for safety evaluation.

The supportive clinical trial B2305 contributes to safety database but does not contribute much to efficacy evaluation since it examined the effects of indacaterol 300 µg, which is higher than 150 µg, the dose for the proposed indication. The supportive clinical trial B2307 contributed little to efficacy or safety evaluation since it examined the effect of a single dose of indacaterol. The supportive clinical trial B2342 measures 24 hour lung function profile for indacaterol 300 µg as compared to salmeterol. Its main goal is to support once daily dosing interval for indacaterol. Since it examines the results from 300 µg, therefore, it is of limited use to support once daily dosing interval for the 150 µg dose. Study B2338 in patients with asthma is a large 800 patient study of 6 months duration which allows a further examination of the safety of indacaterol in a different, generally more healthy, patient population.

5.3 Discussion of Individual Studies/Clinical Trials

- **Pivotal Study: B2335S**

Title of Study: A 26-week treatment, multicenter, randomized, double blind, double dummy, placebo-controlled, adaptive, seamless, parallel-group study to assess the efficacy, safety and tolerability of two doses of indacaterol [selected from 75, 150, 300 & 600 µg once daily (o.d.] in patients with chronic obstructive pulmonary disease using blinded formoterol (12 µg b.i.d) and open label tiotropium (18 µg o.d.) as active controls

Design
This 26 week study was a multicenter, double-blind, randomized, double-blind, double- dummy, placebo and active controlled, adaptive, parallel-group study design consisting of 2 stages. The first stage was for dose selection in which patients were randomly assigned to receive one of the following double-blind, double-dummy treatments (indacaterol 75 µg o.d., indacaterol 150 µg o.d., indacaterol 300 µg o.d., indacaterol 600 µg o.d., indacaterol placebo, formoterol 12 µg b.i.d) or open label tiotropium 18 µg o.d. using 1: 1: 1: 1: 1: 1: 1 ratio with stratification for smoking status and 12 hour serial spirometry. Two out of four indacaterol doses were selected following interim analysis, along with placebo and tiotropium, to continue into a second stage for comparisons of efficacy, safety and tolerability for up to 26 weeks total treatment.

Duration
Patients in treatment arms discontinued at the end of Stage 1 were to have a minimum of 2 weeks treatment. Patients in treatment arms continued into Stage 2 were to have a total of 26 weeks treatment. The study was performed during the period of April 23, 2007 to August 23, 2008. The final study report is dated November 3, 2008.

Study Centers
334 centers in 11 countries: Argentina (6), Canada (24), Germany (35), India (13), Italy (16), Korea (13), Spain (21), Sweden (6), Turkey (8), Taiwan (7), United States (185)

Population
4130 patients were screened, and 2059 patients were randomized during the study. 1683 patients were randomized to treatment in the four treatment arms continued into Stage 2 of the study, 1665 patients were analyzed and 1291 patients completed the study, 325 indacaterol 150 µg, 341 indacaterol 300 µg, 331 tiotropium, 294 placebo. On the other hand, 376 patients were randomized to the three treatment arms not continued into Stage 2.

For the four treatment groups continued into Stage 2, 76.7% of all patients completed the study as planned.

Materials
The treatment groups in stage 1 were as follows:

- Indacaterol 75 µg
- Indacaterol 150 µg
- Indacaterol 300 µg
- Indacaterol 600 µg
- Placebo

- Formoterol (12 µg) twice daily
- Tiotropium (18 µg) once daily

Indacaterol and matching placebo were provided as powder filled capsules with a single dose dry powder inhaler (SDDPI). Formoterol fumarate and matching placebo were provided as powder filled capsules for oral inhalation via Aerolizer® inhalation device. Tiotropium consisted of hard gelatin capsules containing a dry powder formulation, to be administered for once daily inhalation via the manufacturer's proprietary inhalation device (Handihaler®). As patients were provided with commercially available tiotropium and a Handihaler device supplied to each investigator by the pharmacy, the tiotropium treatment arm was open-label.

The investigational and reference therapies (excluding tiotropium therapy above) were supplied by Novartis Drug Supply Management in monthly medication packs in sufficient quantity to last each subject for the duration of the trial. Study medication including the inhalation devices was supplied in monthly medication packs.

Patients were instructed to take morning (between 08:00 and 10:00 h) and evening doses (12 hours later). The morning dose consisted of sequential inhalation of capsule contents from each of three devices (one formoterol/placebo Aerolizer® and two indacaterol/placebo SDDPI devices) in a double-dummy manner to maintain treatment blinding. The evening dose consisted of a capsule for inhalation from the formoterol/placebo Aerolizer® only.

Stage 2
The trial treatments were as follows:
• Indacaterol dose 1* delivered via SDDPI
• Indacaterol dose 2* delivered via SDDPI
• Placebo delivered via SDDPI device
• Tiotropium (18 µg) dry powder capsules delivered via manufacturer's proprietary inhalation device (Handihaler®)

*Indacaterol doses 1 & 2 (selected from 75, 150, 300 or 600 µg o.d.) for Stage 2 were determined by interim analysis performed on Stage 1 data.

Novartis supplied each study site with study drug organized in uniquely numbered 30 day medication pack.

Objectives

The primary objective was to demonstrate superiority of at least one dose of indacaterol (selected at study Stage 1 from 75, 150, 300 or 600 µg o.d. via SDDPI) to placebo with respect to 24 h post dose (trough) FEV1 after 12 weeks of treatment in patients with COPD.

The key secondary objective was to demonstrate non-inferiority of at least one dose of indacaterol (selected at study Stage 1 from 75, 150, 300 or 600 µg o.d. via SDDPI) to open label

tiotropium (18 µg o.d.) with respect to 24 h post dose (trough) FEV1 following 12 weeks of treatment.

Inclusion Criteria

- Male and female adults aged ≥ 40 years
- Diagnosis of COPD according to the GOLD Guidelines (2005)
- Smoking history of at least 20 pack years
- Post-bronchodilator FEV1 < 80% and ≥ 30% of the predicted normal value
- Post-bronchodilator FEV1/FVC < 70%.

Notable Exclusion Criteria

- Concomitant pulmonary disease, pulmonary tuberculosis (unless confirmed by chest x-ray to be no longer active) or clinically significant bronchiectasis
- Patients with a history of asthma (indicated by but not limited to)
- Blood eosinophil count > 400/mm3
- Onset of respiratory symptoms prior to age 40 years
- History of cancer except localized basal cell carcinoma.
- Use of long term oxygen therapy (> 15 h a day)
- Patients with contraindications for tiotropium treatment including symptomatic prostatic hypertrophy, bladder neck obstruction or narrow angle glaucoma
- Patients who do not maintain regular day/night, waking/sleeping cycles (e.g., night shift workers)
- Treatments for COPD and allied conditions: the following medications must not have been used prior to Visit 1 for at least the minimum washout period specified below or at any time during the study (see the list of prohibited medications, page 27)

Conduct

Following an initial 14 day screening phase, patients were randomized to treatments.

Stage 1: patients are randomized in a 1:1:1:1 ratio to one of 6 double-blind, double-dummy treatments (indacaterol 75 µg o.d., indacaterol 150 µg o.d., indacaterol 300 µg o.d., indacaterol 600 µg o.d., placebo, formoterol 12 µg b.i.d), or open label tiotropium 18 µg o.d. Stage 1 was double-dummy because formoterol was provided in a different device to indacaterol, and so all indacaterol dose arms and the indacaterol placebo arm received a placebo to formoterol to maintain blinding.

Interim analysis: After 801 patients were randomized and completed 2 weeks of treatment, interim analysis is performed and dose selection made. Enrollment and randomization was suspended until dose selection was made. However, all patients continued to receive study medication until dose selection had been made.

Reviewer's Comment: The continuation of dosing while dose selection was being made meant that patients receiving 75 and 600 µg of indacaterol were dosed for longer than 2 weeks period

and therefore pulmonary function data for these doses (albeit in many fewer patients) were available for review beyond the initial 2 week dosing period for Stage 1.

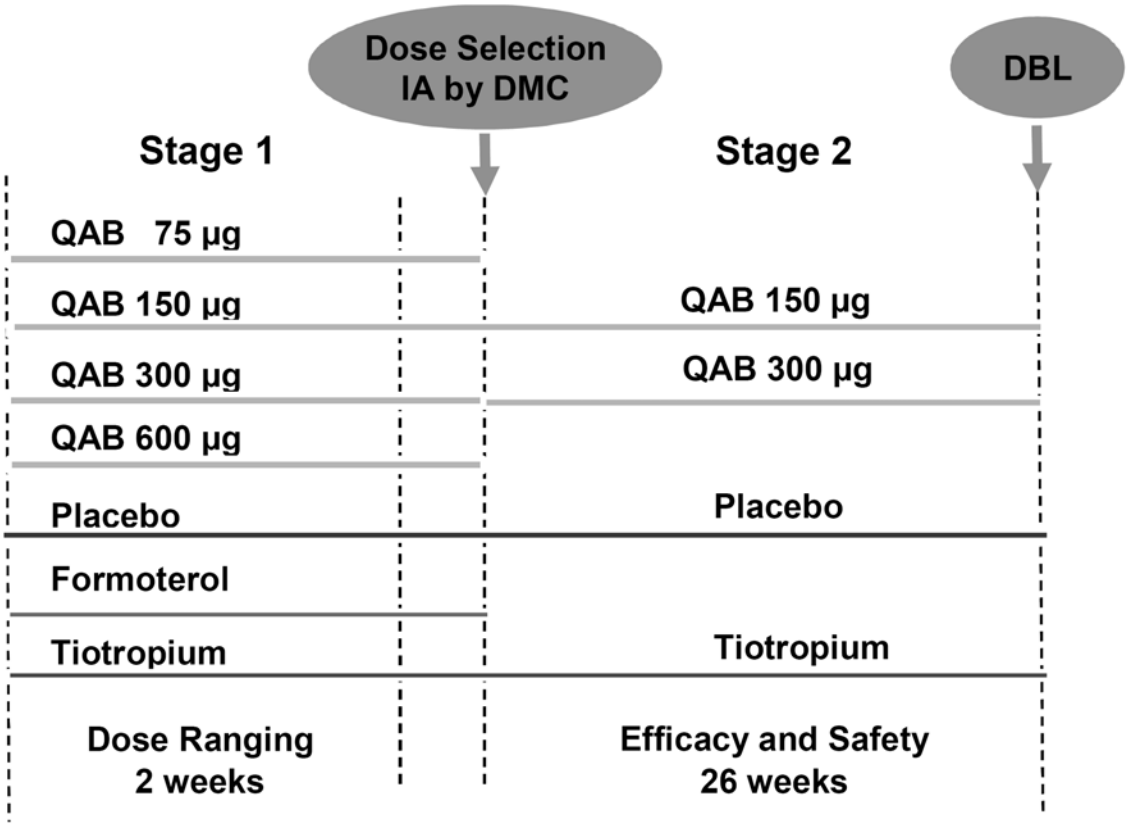
An external Data Monitoring Committee (DMC) independent of study conduct reviewed efficacy and safety data. Dose selection was primarily based on pre-defined criteria comparing the efficacy of indacaterol with placebo and the active controls, as well as safety data. Based on the results of this analysis two of the four indacaterol doses were continued into Stage 2 together with the tiotropium and placebo arms.

Stage 2: Study centers re-commenced recruitment for the two chosen indacaterol doses, placebo and tiotropium in a 1:1:1:1 ratio. An additional 285 patients per treatment group were randomized until the total required number of patients (400 per group) had been included. Each patient in Stage 2 was expected to receive study drug for a total of 26 weeks.

A subset of patients underwent 12 hour serial spirometry assessments, and another subset extended 24 hour serial spirometry assessments. A further subset of patients underwent 24 hour Holter monitoring.

Figure 1 Study design of B2335s [summary of clinical efficacy, page 18, figure 2.1]

IA= interim analysis, DMC= data monitoring committee



Efficacy endpoints

Primary

- Superiority in trough FEV1 (24 hour post dose) after 12 weeks of treatment of one of the indacaterol doses (150 and 300 µg o.d.) to placebo.
  [superiority was defined as a difference in FEV1 of at least 120 ml.]

Secondary

- Non-inferiority in trough FEV1 (24 hour post dose) after 12 weeks of treatment of one of the indacaterol doses (150 and 300 µg o.d.) to tiotropium.
  [Non-inferiority was defined as a difference in FEV1 not worse than -55 mL.]

- Superiority in the percentage of COPD 'days of poor control' during 26 weeks of treatment of one of the indacaterol doses (150 and 300 µg o.d.) to placebo.

- Superiority in trough FEV1 (24 hour post dose) after 12 weeks of treatment of one of the indacaterol doses (150 and 300 µg o.d.) to tiotropium.

Other secondary endpoints

Spirometry

- Trough FEV1 at Day 2 and after 2 and 26 weeks treatment
- Peak FEV1 during 4 h post morning dose
- FEV1: AUC (5 min – 4 h)
- FEV1: AUC (5 min – 11 h 45 min)
- FEV1 and FVC trough response over 26 weeks
- FEV1 and FVC early response over 26 weeks
- 24 hour serial spirometry

COPD exacerbations
Dyspnea
Symptoms
Rescue medications
PEF
Bode index
Health-related quality of life

Concomitant treatment

Adjustment to β2-agonists and fixed dose combinations prior to visit 1
Patients were required to stop the use of any long acting β2-agonist (LABA) prior to day 1 (visit 1,start of the run-in period) until the completion of the study. Patients using LABAs (e.g. formoterol or salmeterol) were switched to the 'as needed' use of the SABA salbutamol/albuterol at least 48 h prior to Visit 1. Patients taking fixed dose combination treatment with inhaled corticosteroid plus a LABA were taken off the combined medication and given equivalent monotherapy with an inhaled corticosteroid at the same dose and dosage regimen for the duration of the study, plus the inhaled short acting β2-agonist (SABA) salbutamol/albuterol (as needed), at least 48 h prior to Visit 1. Patients taking a fixed dose combination of an anti-cholinergic plus a SABA (e.g., Combivent®) must have been taken off the combination at least 8 h prior to Visit 1. Instead, salbutamol/albuterol only was to be used. In either case (above) where fixed dose combination products were discontinued, regular dosage regimens of salbutamol/ albuterol and/or use as rescue medication were permitted during the screening period. However, during the treatment period salbutamol/albuterol was to be taken for rescue ('when required') purposes only.

Prohibited medications

Patients are not allowed to take the following medications throughout the study period unless as part of the treatment for a COPD exacerbation. Withdrawal was required a pre-determined period of time prior to the initial screening visit (Visit 1) for some of the medications.

- The long acting anti-cholinergic agent tiotropium: 7 days
- Short acting anti-cholinergics: 8 h
- Fixed combinations of β2-agonists and inhaled corticosteroids: 48 h

- Fixed combinations of SABAs plus inhaled anticholinergics: 8 h
- LABAs: 48 h
- SABAs (other than those prescribed in the study): 6 h
- Theophylline and other xanthines: 1 week
- Parenteral or oral corticosteroids: 1 month
- Non-potassium sparing diuretics (unless administered as a fixed dose combination with a potassium conserving drug)
- Non-selective beta-blocking agents
- Cardiac anti-arrhythmics Class Ia, Class III. Terfenadine, astemizole, mizolastin and any other drug with potential to significantly prolong the QT interval.
- Tricyclic antidepressants and monoamino-oxidase inhibitors.

The following medications should not have been used unless they had been stabilized:

- Cromoglycate, nedocromil, ketotifen, inhaled or nasal corticosteroids and leukotriene antagonists – at least one month prior to Visit 1
- Antihistamines (excluding those listed above) – at least 5 days prior to Visit 1

COPD deterioration/exacerbation

It was the responsibility of the treating physician/investigator to initiate treatment for a COPD deterioration/exacerbation as best deemed appropriate. Such treatments may have included, but were not limited to:

- Courses of antibiotics
- Addition of oral steroids.

If the COPD exacerbation was treated with intra-muscular depot corticosteroids (e.g., Depo-Medrone®), the patient must have been withdrawn from the study.

Statistical plan

Sample size

Stage 1: The objective of Stage 1 was to investigate the risk-benefit profile of four doses of indacaterol and decide which two were to be taken forward into Stage 2. This decision was based on efficacy and safety data. The sample size of 110 evaluable patients per group in Stage 1 was considered sufficient to select the two doses to be continued in the second stage.

Stage 2: The primary objective was to demonstrate that at least one of the selected doses of indacaterol is superior to placebo in trough FEV1 following 12 weeks of treatment.

The sample size for the trial was based on the probability of selecting pairs of doses (75µg and 150 µg, 150 µg and 300 µg, or 300 µg and 600 µg) at the end of Stage 1 and the power for the key secondary endpoint after combining data from Stage 1 and Stage 2. In order to do this data from Study QAB149B2205 (dose ranging study using doses 50, 100, 200, and 400 µg o.d.) were used. It was assumed that the difference to placebo in FEV1 at 2 weeks for each of the 7 treatments would be similar to the results observed in Study QAB149B2205 after 1 week of

treatment. It was also assumed that the same difference would be seen at the 12 week time point for the primary efficacy endpoint. To determine the power for this study, a simulation with 100,000 repetitions was used incorporating the multiplicity adjustment and the decision rules as described in the DMC charter.

If the Stage 1 sample size was n1=110 per treatment arm and the stage 2 sample size was n2=230, then the chosen indacaterol treatment group would have 340 patients. With this number of patients, and the assumed dose response, the power for the primary endpoint was nearly 100%. Assuming 15% dropout for the evaluation of trough FEV1 after 12 weeks treatment a sample size of 340 evaluable patients for the 4 continued treatment arms did require 400 patients to be randomized per treatment.

Three populations were defined for the final analysis:

- The intention-to-treat (ITT) population, including all randomized patients who received at least one dose of study drug.
- The per-protocol (PP) population, including all patients of the ITT population without any major protocol deviations.
- The safety population, including all patients who received at least one dose of study drug.

Disposition of Subjects
A total of 4130 patients were screened and 2059 patients were randomized to treatment in 334 centers from 11 countries during the study. Of those, 1683 patients were randomized to the four treatment arms that continued into Stage 2 of the study, while 376 patients were randomized to the three treatment arms not continued into Stage 2.

For the four treatment groups continued into Stage 2, 76.7% of all patients completed the study as planned. Discontinuations from the study overall occurred more frequently for placebo patients than for the indacaterol or tiotropium treated patients (22.6%, 18.4%, 21.2%, and 30.8%, for the indacaterol 150 µg, indacaterol 300 µg, tiotropium, and placebo groups, respectively). The most common reasons for discontinuation were adverse events (6.9%, 6.2%, 4.0%, and 10.8% for indacaterol 150 µg, indacaterol 300 µg, tiotropium, and placebo, respectively), and withdrawal of consent (6.9%, 5.3%, 4.8%, 8.7%, respectively). In addition, more patients receiving placebo withdrew due to unsatisfactory therapeutic effect compared to the indacaterol and tiotropium treatment groups (1.0%, 2.2%, 2.1%, 4.0% for indacaterol 150 µg, indacaterol 300 µg, tiotropium, placebo, respectively).

Table 6 Patient disposition- for those that continued into stage 2 [study QAB149B2335S, page 123]

	Treatments continued into Stage 2				
	Ind150 µg n (%)	Ind 300 µg n (%)	Tio n (%)	Pbo n (%)	Total n (%)
Patients					
Randomized	420 (100)	418 (100)	420 (100)	425 (100)	1683 (100)
Exposed	416 (99.0)	416 (99.5)	415 (98.8)	418 (98.4)	1665 (98.9)
Completed	325 (77.4)	341 (81.6)	331 (78.8)	294 (69.2)	1291 (76.7)
Discontinued	95 (22.6)	77 (18.4)	89 (21.2)	131 (30.8)	392 (23.3)
Primary reason for premature discontinuation					
Adverse event(s)	29 (6.9)	26 (6.2)	17 (4.0)	46 (10.8)	118 (7.0)
Subject withdrew consent	29 (6.9)	22 (5.3)	20 (4.8)	37 (8.7)	108 (6.4)
Protocol deviation	13 (3.1)	9 (2.2)	14 (3.3)	11 (2.6)	47 (2.8)
Lost to follow-up	12 (2.9)	6 (1.4)	13 (3.1)	8 (1.9)	39 (2.3)
Administrative problems	5 (1.2)	3 (0.7)	6 (1.4)	9 (2.1)	23 (1.4)
Unsatisfactory therapeutic effect	4 (1.0)	9 (2.2)	9 (2.1)	17 (4.0)	39 (2.3)
Abnormal lab value(s)	1 (0.2)	1 (0.2)	2 (0.5)	1 (0.2)	5 (0.3)
Abnormal test procedure result(s)	1 (0.2)	1 (0.2)	6 (1.4)	2 (0.5)	10 (0.6)
Death	1 (0.2)	0 (0.0)	2 (0.5)	0 (0.0)	3 (0.2)

Reviewer's comments: It is reasonable that the placebo patients had a higher discontinuation rate due to unsatisfactory therapeutic effect and adverse events. The tiotropium group has lower rate of adverse events and subjects withdrawing consent than the indacaterol groups.

Only 76.7% of the randomized patients completed the protocol. This may be due to the length of the study.

Protocol deviations

Major protocol deviations (those which excluded ITT patients from the per-protocol during Stage 2 of the study) occurred slightly more frequently for the tiotropium group than for the indacaterol treatment groups. The most common major protocol deviation across all treatment groups was an eosinophil count above 400/mm3 at screening, which was reported for slightly fewer patients in the indacaterol 300 µg group (4.6%) than for the other treatment groups (7.0%, 7.5% and 7.2% for the indacaterol 150 µg, tiotropium and placebo groups, respectively). The proportion of patients with a screening HbA1c >8% of total hemoglobin was slightly higher for the three active treatment groups compared to placebo.

Reviewer's comment: It will be useful to consider whether there is a component of asthmatic pathology in patients with elevated eosinophil counts. Asthmatic patients typically have a larger response to beta agonists such as indacaterol.

Demographics and baseline characteristics

The mean age of patients in the study was 63.6 years, 62% of patients were male and 84% of the population was Caucasians. Just over half of patients were ex-smokers, with the remaining patients are still active smokers. The median duration of COPD was 5.1 years, slightly more than a third of patients were using ICS at baseline (37.5%). The majority of patients had moderate to severe COPD according to the GOLD 2005 guidelines (95%).

Table 7 Demographics [Adapted from study B2335S, page 127, table 11-3]

		Ind 150 µg N=416	Ind 300 µg N=416	Tio N=415	Pbo N=418	Total N=1665
Age (years)	**n**	416	416	415	418	1665
	Mean	63.4	63.3	64.0	63.6	63.6
	SD	9.40	9.32	8.77	8.92	9.10
	Median	64.0	63.0	64.0	64.0	64.0
	Min - Max	40 - 87	40 - 88	41 - 85	41 - 84	40 - 88
Age group - n (%)	**19-39 years**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	40-64 years	214 (51.4)	230 (55.3)	215 (51.8)	215 (51.4)	874 (52.5)
	≥ 65 years	202 (48.6)	186 (44.7)	200 (48.2)	203 (48.6)	791 (47.5)
Sex - n(%)	**Male**	259 (62.3)	263 (63.2)	269 (64.8)	255 (61.0)	1046 (62.8)
	Female	157 (37.7)	153 (36.8)	146 (35.2)	163 (39.0)	619 (37.2)
Race - n (%)	**Caucasian**	353 (84.9)	355 (85.3)	347 (83.6)	355 (84.9)	1410 (84.7)
	Black	14 (3.4)	12 (2.9)	10 (2.4)	7 (1.7)	43 (2.6)
	Asian	45 (10.8)	47 (11.3)	51 (12.3)	53 (12.7)	196 (11.8)
	Native American	0 (0.0)	0 (0.0)	3 (0.7)	2 (0.5)	5 (0.3)
	Pacific Islander	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	Other	3 (0.7)	2 (0.5)	4 (1.0)	1 (0.2)	10 (0.6)

Reviewer's comments:
Most of the patients are Caucasian, and 12% of patients are Asian. Therefore, there is some limitation in racial diversity.

Table 8 Disease characteristics [Adapted from study QAB149B2335S, page 126, table 11-3]

		Ind 150 µg N=416	Ind 300 µg N=416	Tio N=415	Pbo N=418	Total N=1665
Duration of COPD (years)	**n**	416	416	415	418	1665
	Mean	7.0	6.7	6.8	6.6	6.8
	SD	7.21	6.62	6.83	6.33	6.75
	Median	5.0	4.7	5.2	5.3	5.1
	Min - Max	<0.1-49.1	<0.1-45.1	<0.1-46.5	<0.1-67.6	<0.1-67.6
Duration of COPD - n (%)	**<1 year**	60 (14.4)	47 (11.3)	47 (11.3)	53 (12.7)	207 (12.4)
	1-5 yrs	148 (35.6)	167 (40.1)	152 (36.6)	148 (35.4)	615 (36.9)
	>5-10 yrs	104 (25.0)	115 (27.6)	130 (31.3)	134 (32.1)	483 (29.0)
	>10-15 yrs	55 (13.2)	42 (10.1)	51 (12.3)	47 (11.2)	195 (11.7)
	>15-20 yrs	22 (5.3)	20 (4.8)	14 (3.4)	23 (5.5)	79 (4.7)
	>20 yrs	27 (6.5)	25 (6.0)	21 (5.1)	13 (3.1)	86 (5.2)
Severity of COPD (GOLD 2005) - n (%)	**At risk**	0 (0.0)	0 (0.0)	3 (0.7)	0 (0.0)	3 (0.2)
	Mild	18 (4.3)	19 (4.6)	20 (4.8)	16 (3.8)	73 (4.4)
	Moderate	239 (57.5)	240 (57.7)	213 (51.3)	236 (56.5)	928 (55.7)
	Severe	157 (37.7)	156 (37.5)	176 (42.4)	165 (39.5)	654 (39.3)
	Very severe	2 (0.5)	1 (0.2)	3 (0.7)	1 (0.2)	7 (0.4)
ICS use - n (%)	**No**	257 (61.8)	261 (62.7)	270 (65.1)	253 (60.5)	1041 (62.5)
	Yes	159 (38.2)	155 (37.3)	145 (34.9)	165 (39.5)	624 (37.5)

Reviewer's comments: This is a population of COPD patients with relatively short duration of diagnosis. More than 10% of the patients have been diagnosed for less than one year. More of than half of the patients have been diagnosed for less than 5 years. More than 90% of the patients have moderate to severe COPD.

Table 9 Screening spirometry [study QAB149B2335S, page 127, table 11-4]

		Ind 150 µg N=416	Ind 300 µg N=416	Tio N=415	Pbo N=418	Total N=1665
Pre-bronchodilator (SABA) FEV1 at Visit 1 (L)	**n**	416	416	415	414	1661
	Mean	1.34	1.36	1.28	1.33	1.33
	SD	0.485	0.509	0.494	0.471	0.490
	Median	1.31	1.26	1.20	1.27	1.25
	Min - Max	0.53-3.19	0.43-2.95	0.41-2.94	0.44-2.90	0.41-3.19
Post bronchodilator (SABA) FEV1 at Visit 1 (L)	**n**	416	416	415	418	1665
	Mean	1.52	1.53	1.45	1.51	1.50
	SD	0.497	0.521	0.505	0.490	0.504
	Median	1.48	1.44	1.38	1.43	1.43
	Min - Max	0.62-3.45	0.57-3.14	0.48-3.00	0.53-2.98	0.48-3.45
Post bronchodilator (SABA) FEV1 at Visit 1 (% predicted)	**n**	416	416	415	418	1665
	Mean	56.1	56.3	53.9	56.1	55.6
	SD	14.47	14.50	15.56	14.27	14.73
	Median	56.0	55.5	52.9	55.1	54.7
	Min - Max	29.3-116.6	21.3-90.0	23.6-132.3	28.4-95.1	21.3-132.3
Post bronchodilator (SABA) FEV1/FVC at Visit 1 (%)	**n**	416	416	415	418	1665
	Mean	53.0	52.6	52.7	53.4	52.9
	SD	9.97	10.07	10.14	10.11	10.07
	Median	53.9	53.1	53.0	53.6	53.3
	Min - Max	24.4-69.7	25.7-69.5	24.7-72.6	24.0-69.9	24.0-72.6
FEV1 reversibility after SABA at Visit 1 (% increase)	**n**	416	416	415	414	1661
	Mean	15.6	15.2	15.6	15.5	15.5
	SD	15.43	15.44	17.64	18.03	16.66
	Median	13.2	13.3	12.8	12.8	13.0
	Min - Max	-22.5-88.2	-45.2-89.3	-35.4-81.1	-32.4-222.7	-45.2-222.7
FEV1 reversibility after anti-cholinergic at Visit 2 (% increase)	**n**	415	412	414	417	1658
	Mean	15.3	15.9	14.8	15.9	15.5
	SD	15.37	21.85	16.05	18.28	18.05
	Median	14.0	13.5	12.5	13.2	13.2
	Min - Max	-72.2-89.6	-35.1-342.9	-36.4-110.3	-59.5-178.3	-72.2-342.9

Post-bronchodilator FEV1/FVC and FEV1 reversibility at Visit 1 were measured 30 min after inhalation of 400 µg salbutamol/albuterol, a short-acting beta-agonist (SABA).
FEV1 reversibility at Visit 2 was measured 1 hour after inhalation of 42 µg ipratropium, an anticholinergic.

Reviewer's comment: The COPD patients in this study have a high degree of reversibility in FEV1 after short acting beta-agonist administration.

Interim analysis for dose selection
The interim analysis is performed after two weeks of treatment to select two of four doses to continue into Stage 2 of the study. The selection is made by the independent Data Monitoring committee. The guidelines for dose selection were based on the following:

- The selected dose needed to be 0.12 L greater than placebo for trough FEV_1, it should also have higher trough FEV_1 than tiotropium and formoterol
- The dose needed to have higher FEV_1 AUC $_{1\text{-}4\,h}$ than tiotropium and formoterol.
- The lowest dose that fulfill the above two criteria and the next highest dose are to be selected.

The reference value for trough FEV_1 was 0.14 L (tiotropium vs. placebo difference) and for FEV1 AUC $_{1\text{-}4\,h}$ was 0.22 L (formoterol vs. placebo). The lowest dose to surpass these reference values was the indacaterol 150 µg dose, with the next highest dose being the 300 µg.

Reviewer's Comment: The applicant decided that the dose selected must have a higher trough FEV1 and FRV1 AUC $_{1\text{-}4h}$ than formoterol and tiotropium, presumably to ensure future marketing potential. This was a risky decision as it may have resulted in inappropriately high doses to be carried forward.

Table 10 Interim analysis [study QAB149B2335S, page 129, table 11-5]

		Treatment			Treatment difference		
Treatment	**n**	**LS mean**	**SE**	**Comparison**	**LS mean**	**SE**	**95% CI**
Trough FEV1 (L)							
Comparisons with placebo							
Ind 75 µg	104	1.46	0.024	Ind 75 µg - Pbo	0.15	0.029	(0.09, 0.20)
Ind 150 µg	105	1.49	0.024	Ind 150 µg - Pbo	0.18*	0.029	(0.12, 0.24)
Ind 300 µg	110	1.52	0.024	Ind 300 µg - Pbo	0.21*	0.029	(0.15, 0.27)
Ind 600 µg	108	1.51	0.024	Ind 600 µg - Pbo	0.20	0.029	(0.14, 0.25)
For	105	1.42	0.024	For - Pbo	0.11	0.029	(0.06, 0.17)
Tio	112	1.45	0.023	Tio - Pbo	**0.14**	0.028	(0.08, 0.19)
Pbo	104	1.31	0.024				
AUC 1h-4h FEV1 (L)							
Comparisons with placebo							
Ind 75 µg	95	1.50	0.034	Ind 75 µg - Pbo	0.20	0.032	(0.14, 0.27)
Ind 150 µg	96	1.53	0.034	Ind 150 µg - Pbo	0.23*	0.032	(0.16, 0.29)
Ind 300 µg	99	1.58	0.034	Ind 300 µg - Pbo	0.28*	0.031	(0.22, 0.34)
Ind 600 µg	97	1.53	0.034	Ind 600 µg - Pbo	0.23	0.031	(0.17, 0.29)
For	93	1.52	0.035	For - Pbo	**0.22**	0.032	(0.16, 0.28)
Tio	99	1.49	0.034	Tio - Pbo	0.19	0.031	(0.13, 0.25)
Pbo	90	1.30	0.033				

LS mean = least squares mean, SE = standard error of the mean, CI = confidence interval.
Mixed model: Trough FEV1 = treatment + baseline FEV1 + FEV1 reversibility components + smoking status + country + center(country), with center(country) as a random effect.
Bold LS mean differences were those identified as reference values by dose selection criteria, * = selected doses

Reviewer's comment: The difference between 2 week trough FEV1 of indacaterol 75 µg and indacaterol 150 µg is not significant. This is also true of FEV1 AUC 1h- 4h. Sponsor chose dose selection criteria based on absolute value of trough FEV1 without considering the significance of the difference between the doses.

The difference in 2 week trough FEV1 between 75 µg, 150 µg, and 300 µg are small; besides 75 µg is superior to tiotropium which is known to have good trough FEV1 efficacy. In fact, Dr. Dongmei Liu, in her statistical analysis, examined the 75 µg patients who were treated for 12 weeks and found that 12 week trough FEV1 is the same between the 75 µg and 150 µg groups. Thus 75 µg should have been explored and even a lower dose should be studied. Due to the risk profile of long acting beta agonists, it is especially important to find the lowest effective dose of indacaterol. With this in mind, it would be good to locate the no effect dose in order to identify the lowest effective dose.

The sponsor did not discuss the specific dose selection criteria with the division. During the previous discussion about dose selection criteria in EOP2 meeting on date October 10, 2006, the division has emphasized some of the important principles that should be considered in dose selection criteria.

Efficacy results for treatments continued into Stage 2 of the study

Primary efficacy results

The least squares mean (LSM) estimate of the trough FEV1 at Week 12 was the same for both indacaterol 150 µg QD and 300 µg QD (LS mean 1.46 L, SE 0.015) and they are superior to placebo (LS mean 1.28 L, SE 0.015). The difference between either indacaterol 150 µg or indacaterol 300 µg and placebo is 0.18 L ($p < 0.001$). Results were similar for the per-protocol population.

Table 11 Trough FEV1 (L) at Week 12: treatment comparisons (ITT and per-protocol populations) [Study QAB149B2335S, page 131, table 11-6]

	Treatment				Treatment difference			
Treatment	**n**	**LS mean**	**SE**	**Comparison**	**LS mean**	**SE**	**98.75% CI**	**p-value**
ITT population								
Comparisons for superiority to placebo (1)								two-sided
Ind 150 µg	389	1.46	0.015	Ind 150 µg - Pbo	0.18	0.016	(0.14, 0.22)	<.001
Ind 300 µg	389	1.46	0.015	Ind 300 µg - Pbo	0.18	0.016	(0.14, 0.22)	<.001
Tio	393	1.42	0.015	Tio - Pbo	0.14	0.016	(0.10, 0.18)	<.001
Pbo	376	1.28	0.015					
Comparisons for non-inferiority to tiotropium (2)								one-sided
				Ind 150 µg - Tio	0.05	0.016	(0.01, 0.09)	<.001
				Ind 300 µg - Tio	0.04	0.016	(0.00, 0.08)	<.001
Other comparisons								two-sided
				Ind 300 µg - Ind 150 µg	-0.01	0.016	(-0.04, 0.03)	0.747
Comparisons for superiority to tiotropium							95% CI	two-sided
				Ind 150 µg - Tio	0.05	0.016	(0.02, 0.08)	0.004
				Ind 300 µg - Tio	0.04	0.016	(0.01, 0.07)	0.010
Per-protocol population								
Comparisons for superiority to placebo (1)							98.75%	two-sided
Ind 150 µg	348	1.45	0.015	Ind 150 µg - Pbo	0.17	0.017	(0.13, 0.21)	<.001
Ind 300 µg	350	1.45	0.015	Ind 300 µg - Pbo	0.17	0.017	(0.13, 0.21)	<.001
Tio	334	1.41	0.015	Tio - Pbo	0.13	0.017	(0.09, 0.17)	<.001
Pbo	326	1.28	0.015					
Comparisons for non-inferiority to tiotropium (2)								one-sided
				Ind 150 µg - Tio	0.04	0.017	(0.00, 0.08)	<.001
				Ind 300 µg - Tio	0.04	0.016	(0.00, 0.08)	<.001
Other comparisons								two-sided
				Ind 300 µg - Ind 150 µg	0.00	0.016	(-0.04, 0.04)	0.858
Comparisons for superiority to tiotropium							95% CI	two-sided
				Ind 150 µg - Tio	0.04	0.017	(0.01, 0.07)	0.010
				Ind 300 µg - Tio	0.04	0.016	(0.01, 0.07)	0.016

Reviewer's comment:
Indacaterol 150 µg and 300 µg, with the same week 12 trough FEV1, is superior to placebo and tiotropium. The difference between LS mean of both indacaterol doses and placebo is 170 ml (p < 0.001) which is a clinically significant change.

Efficacy Conclusions

Primary Endpoint of B2335s

Indacaterol 150 and 300 µg were superior to placebo on the 12 week trough FEV1, the primary endpoint. The two doses had the same result, which were 170 ml greater than placebo. This is a clinically significant improvement.

Secondary Endpoints B2335s

The key secondary endpoint: Indacaterol was statistically superior to tiotropium at 12 week trough FEV1. Both doses were 40 ml greater than tiotropium.

Other secondary endpoints: Indacaterol groups were statistically superior to placebo in most of the secondary endpoints including trough FEV1at multiple time points (day 2, day 15, week 26), peak FEV1 (4 hr post dose), AUC FEV1 (5 min- 4 hr, 5 min - 11 hr 45 min), 24 hour serial spirometry at week 26, rescue medication use, and peak expiratory flow. The one endpoint that indacaterol doses did not show an improvement over placebo was in the % of COPD "days of poor control." For number of days without rescue medication use, indacaterol doses had a 15% increase as compared to placebo, from 41% to 56%.

Descriptive analysis of symptoms and functional improvement assessed in the St. George's Respiratory Questionnaire, BODE index, and MMRC dyspnea score showed statistically significant improvement. However, for 6 minute walking distance, there was not a statistically significant difference between Indacaterol doses and placebo.

When compared to tiotropium, the Indacaterol groups had statistical superiority in week 12 trough FEV1, rescue medication use and peak expiratory flows.

There was no statistical difference between the two indacaterol groups on all measures.

Safety Review

The safety findings from this study, along with the safety data from the other placebo-controlled studies, will be reviewed in depth in the Integrated Review of Safety section of this review. Brief observations are described below.

Patient exposure

Median exposure for treatment groups continued into Stage 2 was the same for all treatment groups at 182 days. As for mean number days of exposure, the placebo had a lower number compared to Indacaterol doses and tiotropium: (156, 161, 158, and 144 days for Indacaterol 150 µg, Indacaterol 300ug, tiotropium, and placebo). The majority of patients were exposed to more than 24 weeks (of 26 weeks) of treatment (79%, 82%, 79%, and 70% for indacaterol 150ug, indacaterol 300ug, tiotropium, and placebo groups).

Treatment compliance was high (over 96% of planned doses were taken for the four treatment groups continued into stage 2). Compliance was also high (> 98% of doses) for those treatment groups discontinued at the end of Stage 1 of the study.

Reviewer's comment: Since the placebo had a higher rate of premature discontinuation at 69% as compared to 77% - 81% for the other three groups, it follows that the mean number days of exposure is also lower for the placebo group.

The proportion of patients with adverse events was comparable across the treatment groups (63%- 67%). COPD exacerbations are the most common, at 17% - 21% (placebo has the highest rate of 21%) and upper respiratory tract infections are next (7% - 8%). Other common adverse events include nasopharyngitis, cough, and headache (> 5% in any of the treatment groups).

Adverse events assessed as severe occurred with similar frequency across the treatment groups (10%, 7%, 10%, 9.8% for Indacaterol 150ug, 300ug, tiotropium, and placebo). One patient in the indacaterol 150 µg group, 2 patients in the tiotropium group died during the study, and one patient from the placebo group died during the 30 days post treatment followup period for SAEs. These deaths were not thought to be related to the study drugs.

Table 12 Adverse events occurring in ≥ 1.5 % of the subjects in any treatment group [study QAB149B2335S, page 164, table 12-3]

	Ind 150 µg N=416 n (%)	**Ind 300 µg N=416 n (%)**	**Tio N=415 n (%)**	**Pbo N=418 n (%)**
Patients with any AE(s)	277 (66.6)	273 (65.6)	279 (67.2)	266 (63.6)
Preferred term				
Chronic obstructive pulmonary disease	73 (17.5)	76 (18.3)	81 (19.5)	91 (21.8)
Upper respiratory tract infection	35 (8.4)	27 (6.5)	31 (7.5)	31 (7.4)
Nasopharyngitis	33 (7.9)	39 (9.4)	36 (8.7)	36 (8.6)
Cough	30 (7.2)	30 (7.2)	26 (6.3)	28 (6.7)
Headache	28 (6.7)	18 (4.3)	19 (4.6)	14 (3.3)
Viral upper respiratory tract infection	16 (3.8)	12 (2.9)	7 (1.7)	15 (3.6)
Lower respiratory tract infection	14 (3.4)	11 (2.6)	14 (3.4)	14 (3.3)
Diarrhoea	13 (3.1)	11 (2.6)	8 (1.9)	11 (2.6)
Muscle spasms	13 (3.1)	13 (3.1)	7 (1.7)	4 (1.0)
Back pain	12 (2.9)	7 (1.7)	8 (1.9)	10 (2.4)
Dyspnoea	12 (2.9)	11 (2.6)	11 (2.7)	19 (4.5)
Pharyngolaryngeal pain	12 (2.9)	12 (2.9)	10 (2.4)	4 (1.0)
Sinusitis	12 (2.9)	18 (4.3)	12 (2.9)	11 (2.6)
Influenza	11 (2.6)	12 (2.9)	4 (1.0)	7 (1.7)
Nausea	11 (2.6)	6 (1.4)	4 (1.0)	11 (2.6)
Urinary tract infection	11 (2.6)	11 (2.6)	10 (2.4)	8 (1.9)
Arthralgia	9 (2.2)	9 (2.2)	4 (1.0)	9 (2.2)
Dizziness	9 (2.2)	11 (2.6)	2 (0.5)	14 (3.3)
Myalgia	8 (1.9)	4 (1.0)	5 (1.2)	3 (0.7)
Bronchitis	7 (1.7)	19 (4.6)	13 (3.1)	26 (6.2)
Fatigue	7 (1.7)	4 (1.0)	4 (1.0)	6 (1.4)

Reviewer's comment: The indacaterol groups did not have increased number of patients with dizziness, QT prolongation, or hypertension as compared to placebo. Both indacaterol groups

had more patients with muscle spasm and pharyngolaryngeal pain than placebo. Interestingly, indacaterol 150 µg group had a higher % of patients than indacaterol 300 µg group with headache (6.7%, 4.3%,and 3.3% for indacaterol 150 µg, 300 µg, and placebo, respectively), ventricular tachycardia, atrial fibrillation, increased neck pain, myalgia, and anxiety. The Indacaterol 300 µg group had a higher % of patients than the indacaterol 150 µg group with pneumonia, sinusitis, rhinorrhea, and pain in extremity.

The indacaterol 150 µg group also had higher proportion of patients with hyperglycemia than the indacaterol 300 µg group. Neither of the indacaterol groups had increased proportion of patients with tachycardia or hypertension.

- **Pivotal study: B2334**

Reviewer's comment:
This study examines the effects of indacaterol 300 µg and 600 µg, which does not include 150 µg, the primary dose that the sponsor seeks an indication for. Therefore it is not supportive of efficacy but will be useful to assess the safety of indacaterol at higher than the proposed dose.

Title
A 52-week treatment, multicenter, randomized, double-blind, double dummy, placebo-controlled, parallel-group study to assess the efficacy, safety and tolerability of indacaterol (300 & 600 µg o.d.) in patients with chronic obstructive pulmonary disease, using formoterol (12 µg b.i.d.) as an active control

Study design
This 52 week study was a multicenter, double blind, double dummy, parallel group study of indacaterol in the treatment of subjects with chronic obstructive pulmonary disease. Patients were randomized 1:1:1:1 to either inhaled indacaterol 300 o.d., indacaterol 600 µg o.d., formoterol 12 µg b.i.d or placebo.

Population
1732 patients were randomized and the modified intention to treat population was 1600 patients, about 400 patients per group (modified ITT excluded patients from Egypt centers which had GCP noncompliance and unreliability of data issues.

Study duration and centers
The study was performed during the period of October 30, 2006 to July 21, 2008 and the report is dated October 20, 2008. The study was conducted in 230 centers in 25 countries; more than half of the centers were in Western Europe (141), the rest were in Eastern Europe (38), Russia (15), Center/ South America (21), Middle East (18) and south Korea (7).

Study objectives/ efficacy endpoints

The primary objective was to assess indacaterol (300 and 600 µg o.d.) superiority in patients with COPD as compared to placebo with respect to 24 h post dose (trough) FEV1 after 12 weeks of treatment.

The key secondary objective was to evaluate the effect of indacaterol (300 and 600 µg o.d.) on the percentage of 'days of poor control' reported over the 52 week randomized treatment period, as compared to placebo.

Other secondary objectives include evaluation of St. George's Respiratory Questionnaire, time to first COPD exacerbation, health related quality of life measures, COPD exacerbation rates, dyspnea index, peak flow, use of rescue medication.

Inclusion and Exclusion criteria
They are the same as the ones from study B2335s (see page 24 of this document) except that in this study, the definition of asthma was not specified.

Materials
Indacaterol and its placebo were provided as powder filled capsules with an SDDPI. Formoterol and its placebo were provided as dry powder capsule inhaled via Aerolizer® device.

Patients are instructed to inhale contents from 3 inhalers in the morning and content from one inhaler 12 hours later. Two of the three inhalers in the morning are for indacaterol (or placebo), and one inhaler in the morning is for formoterol (or placebo). The inhaler in the evening is for formoterol (or placebo). The capsules come in color coded blister packs that match the color of the inhaler.

Conduct
Following 14 days of screening, patients were randomized in 1:1:1:1 (with stratification to smoking status) to the four treatment groups. Patients had clinic visits on week 1, 3, 5, 9, 12, 13, 17, 21, 24, 29, 37, 45, 52, and 53 in which history, vitals, spirometry, EKG, symptom diary, and laboratory studies were evaluated. For subgroup of patients, 12 hour serial spirometry was performed.

Concomitant treatment
Same as in study B2335s (see page 27 of this document)

Disposition of subjects
The information about disposition of subjects is in the table below.

Table 13 disposition (Study QAB149B2334, page 116, table 10-1)

	Ind 300 µg n (%)	Ind 600 µg n (%)	For n (%)	Pbo n (%)	Total n (%)
Patients					
Screened	-	-	-	-	2446
Randomized	437 (100)	428 (100)	435 (100)	432 (100)	1732 (100)
Exposed	437 (100)	425 (99.3)	434 (99.8)	432 (100)	1728 (99.8)
Completed	338 (77.3)	326 (76.2)	323 (74.3)	295 (68.3)	1282 (74.0)
Discontinued	99 (22.7)	102 (23.8)	112 (25.7)	137 (31.7)	450 (26.0)
Primary reason for premature discontinuation					
Adverse event(s)	35 (8.0)	24 (5.6)	40 (9.2)	35 (8.1)	134 (7.7)
Subject withdrew consent	27 (6.2)	40 (9.3)	33 (7.6)	50 (11.6)	150 (8.7)
Unsatisfactory therapeutic effect	12 (2.7)	9 (2.1)	12 (2.8)	30 (6.9)	63 (3.6)
Protocol deviation	11 (2.5)	11 (2.6)	11 (2.5)	10 (2.3)	43 (2.5)
Administrative problems	7 (1.6)	8 (1.9)	5 (1.1)	2 (0.5)	22 (1.3)
Lost to follow-up	5 (1.1)	6 (1.4)	5 (1.1)	3 (0.7)	19 (1.1)
Abnormal lab value(s)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.1)
Death	1 (0.2)	1 (0.2)	5 (1.1)	5 (1.2)	12 (0.7)
Abnormal test procedure result(s)	0 (0.0)	1 (0.2)	1 (0.2)	2 (0.5)	4 (0.2)
Subject's condition no longer requires study drug	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)

Reviewer's comment: The placebo group had the lowest rate of completing the study. When compared to the other groups, it is noted for increased rates of unsatisfactory therapeutic effect and of subject withdrew consent. And also of note, indacaterol 600 µg has lower rate of adverse events than indacaterol 300 µg.

Protocol deviations

The most common protocol deviation is elevated eosinophil counts (6.7%, 4.3%, 5.0%, 2.3% for indacaterol 300 µg, indacaterol 600 µg, formoterol, and placebo). The next two most common ones are trough measurement timing not in window (0.7% - 1.8%) and study medication taken < 80% doses from baseline to primary endpoint (0.8 % - 1.8%).

Reviewer's comment: Elevated eosinophil counts were the most common protocol deviation for study QAB149B2335S also. Similar concerns about possible asthma pathology (with increased FEV1 reversibility post bronchodilator) should also be considered in this patient population.

Efficacy evaluation

Data set analyzed

The per protocol (PP) population included patients without major protocol deviations or any non-protocol deviation criteria. A total of 129 patients from centers in Egypt were excluded from the modified ITT (mITT) population and modified Safety population due to serious GCP non-

compliance and unreliability of data. The modified populations contained around 92% of randomized patients. The mITT population was used for the efficacy analysis.

Table 14 Analysis population (Study QAB149B2334, page 119, table 11-1)

Population	Ind 300 µg n (%)	Ind 600 µg n (%)	For n (%)	Pbo n (%)	Total n (%)
Randomized patients	437 (100.0)	428 (100.0)	435 (100.0)	432 (100.0)	1732 (100.0)
Safety population	437 (100.0)	425 (99.3)	434 (99.8)	432 (100.0)	1728 (99.8)
ITT population	437 (100.0)	425 (99.3)	434 (99.8)	431 (99.8)	1727 (99.7)
Modified Safety population	405 (92.7)	396 (92.5)	400 (92.0)	400 (92.6)	1601 (92.4)
Modified ITT population	405 (92.7)	396 (92.5)	400 (92.0)	399 (92.4)	1600 (92.4)
Per-protocol population	354 (81.0)	338 (79.0)	344 (79.1)	346 (80.1)	1382 (79.8)

In the safety population, patients were analyzed according to the treatment they received (if a patient incorrectly took more than one treatment, the patient was analyzed according to the treatment they were randomized to).
In the ITT population, patients were analyzed according to the treatment to which they were randomized.
In the modified safety and ITT populations, patients from centers in Egypt were excluded due to serious GCP non compliance and unreliability of data.
The per-protocol population includes patients of the modified ITT population without any major protocol deviations and any non-protocol deviation criteria.

Demographics and baseline characteristics
The demographic information is in the following table.

Table 15 Demographic summary (safety population) [Adapted from study QAB149B2334 report, page 120, table 11-2]

		Ind 300 µg N=437	Ind 600 µg N=425	For N=434	Pbo N=432	Total N=1728
Age (years)	n	437	425	434	432	1728
	Mean	63.9	62.9	63.6	63.2	63.4
	SD	8.57	8.74	8.49	8.28	8.52
	Median	64.0	63.0	64.0	63.0	64.0
	Min - Max	40 - 87	40 - 87	40 - 84	41 - 90	40 - 90
Age group - n (%)	19-39 years	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	40-64 years	220 (50.3)	232 (54.6)	226 (52.1)	239 (55.3)	917 (53.1)
	≥ 65 years	217 (49.7)	193 (45.4)	208 (47.9)	193 (44.7)	811 (46.9)
Sex – n (%)	Male	351 (80.3)	327 (76.9)	348 (80.2)	352 (81.5)	1378 (79.7)
	Female	86 (19.7)	98 (23.1)	86 (19.8)	80 (18.5)	350 (20.3)
Race - n (%)	Caucasian	407 (93.1)	393 (92.5)	400 (92.2)	404 (93.5)	1604 (92.8)
	Black	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	3 (0.2)
	Asian	7 (1.6)	8 (1.9)	7 (1.6)	7 (1.6)	29 (1.7)
	Native American	3 (0.7)	0 (0.0)	4 (0.9)	3 (0.7)	10 (0.6)
	Other	19 (4.3)	23 (5.4)	23 (5.3)	17 (3.9)	82 (4.7)

Reviewer's comments: About 93% of the patients are Caucasian, so there is lack of racial diversity. And most of the patients are male (80%).

Concomitant medication
Most of the patients took COPD-related concomitant medications (63%, 67%, 63%, and 68% for indacaterol 300 µg, 600 µg, formoterol, and placebo, respectively). The most commonly taken medications were corticosteroids (inhaled or oral), antibiotics and other (mainly aspirin).

Table 16 Baseline disease characteristics- safety population (Adapted from tudy QAB149B2335S, page 122, table 11-3)

		Ind 300 µg N=437	**Ind 600 µg** N=425	**For** N=434	**Pbo** N=432	**Total** N=1728
Duration of COPD (years)	n	437	425	434	431	1727
	Mean	7.4	6.8	7.3	7.0	7.1
	SD	7.10	5.79	6.18	6.14	6.32
	Median	5.5	5.2	5.9	5.3	5.6
	Min - Max	0.0-44.9	0.0-34.7	0.0-39.8	0.0-53.8	0.0-53.8
Duration of COPD - n (%)	< 1 year	53 (12.1)	43 (10.1)	53 (12.2)	43 (10.0)	192 (11.1)
	1-5 yrs	158 (36.2)	165 (38.8)	139 (32.0)	168 (38.9)	630 (36.5)
	> 5-10 yrs	117 (26.8)	120 (28.2)	132 (30.4)	123 (28.5)	492 (28.5)
	> 10-15 yrs	56 (12.8)	57 (13.4)	66 (15.2)	57 (13.2)	236 (13.7)
	> 15-20 yrs	28 (6.4)	28 (6.6)	25 (5.8)	26 (6.0)	107 (6.2)
	> 20 yrs	25 (5.7)	12 (2.8)	19 (4.4)	14 (3.2)	70 (4.1)
	Missing	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Severity of COPD (GOLD 2005) - n (%)	At risk	9 (2.1)	3 (0.7)	7 (1.6)	10 (2.3)	29 (1.7)
	Mild	2 (0.5)	6 (1.4)	7 (1.6)	10 (2.3)	25 (1.4)
	Moderate	226 (51.7)	212 (49.9)	226 (52.1)	216 (50.0)	880 (50.9)
	Severe	190 (43.5)	188 (44.2)	182 (41.9)	186 (43.1)	746 (43.2)
	Very severe	9 (2.1)	15 (3.5)	10 (2.3)	9 (2.1)	43 (2.5)
	Missing	1 (0.2)	1 (0.2)	2 (0.5)	1 (0.2)	5 (0.3)
ICS use - n (%)	No	194 (44.4)	199 (46.8)	213 (49.1)	208 (48.1)	814 (47.1)
	Yes	243 (55.6)	226 (53.2)	221 (50.9)	224 (51.9)	914 (52.9)

Reviewer's comment: This is a population of COPD patients with relatively short duration diagnosis. More than 45% of the patients have been diagnosed with COPD for < 5 years. More than 90% of patients have moderate to severe COPD.

Screening spirometry data demonstrated that the COPD patients in this study have a moderate degree of reversibility in FEV1 after short acting beta-agonist administration (11.7%- 13.7%). There is a slightly higher degree of reversibility in FEV1 after anti-cholinergic administration (13.6% - 15.0%). [Refer to study QAB149B2334 report, page 123, table 11-4]

Primary efficacy results
The primary efficacy variable of the study was the trough FEV1 at Week 12 comparing 300 and 600 µg indacaterol to placebo. The results of the analysis are shown in the following table.

Table 17 FEV1 (L) at week 12 [Study QAB149B2334, page 125, table 11-5]

	---- Treatment -----				---------- Treatment difference ----------			
Treatment	n	LS mean	SE	Comparison	LS mean	SE	95% CI	p-value
Modified ITT population								
Ind 300 µg	389	1.48	0.012	Ind 300 µg - Pbo	0.17	0.016	(0.13, 0.20)	<0.001*
				Ind 300 µg - For	0.10	0.016	(0.07, 0.13)	<0.001
Ind 600 µg	374	1.48	0.013	Ind 600 µg - Pbo	0.17	0.016	(0.13, 0.20)	<0.001*
				Ind 600 µg - For	0.10	0.016	(0.07, 0.13)	<0.001
				Ind 600 µg - Ind 300 µg	0.00	0.016	(-0.03, 0.03)	0.993
For	379	1.38	0.013	For - Pbo	0.07	0.016	(0.04, 0.10)	<0.001
Pbo	371	1.31	0.013					
Per protocol population								
Ind 300 µg	340	1.47	0.013	Ind 300 µg - Pbo	0.16	0.018	(0.13, 0.20)	<0.001
				Ind 300 µg - For	0.09	0.017	(0.06, 0.13)	<0.001
Ind 600 µg	324	1.48	0.014	Ind 600 µg - Pbo	0.17	0.018	(0.13, 0.20)	<0.001
				Ind 600 µg - For	0.10	0.018	(0.06, 0.13)	<0.001
				Ind 600 µg - Ind 300 µg	0.01	0.017	(-0.03, 0.04)	0.729
For	332	1.38	0.014	For - Pbo	0.07	0.018	(0.04, 0.10)	<0.001
Pbo	320	1.31	0.014					

LS mean = least squares mean, SE = standard error of the mean, CI = confidence interval.
Mixed model: Trough FEV_1 = treatment + baseline FEV_1 + FEV_1 reversibility components + smoking status + country + center (country), with center (country) as a random effect.
* denotes a statistically significant comparison according to the hierarchical testing procedure.

Reviewer's comment: Indacaterol 300 µg and 600 µg had the same least square mean trough FEV1 at 12 weeks and were statistically higher than formoterol and placebo. Both indacaterol doses showed 160 ml improvement over placebo, which is clinically significant. The 12 week trough FEV1 for indacaterol 300ug and 600 µg were just slightly higher than 12 week trough FEV1 from indacaterol 150 µg and 300 µg (1.48 L versus 1.46 L) from study QAB149B2335S. Overall, the results were similar to findings from study QAB149B2335S.

Efficacy Conclusions

Primary endpoint

Indacaterol 300 µg and 600 µg were superior to placebo on the 12 week trough FEV1, the primary endpoint. The two doses had the same result, which were 160 ml greater than placebo. This is a clinically significant improvement.

Secondary endpoints of B2334
The key secondary endpoint: both indacaterol doses had statistically lower percentage of days of "poor COPD control" than placebo (33%, 30%, 33%, and 38% for indacaterol 300ug, 600ug, formoterol, and placebo, respectively).

Other secondary objectives include evaluation of St. George's Respiratory Questionnaire, time to first COPD exacerbation, health related quality of life measures, COPD exacerbation rates, dyspnea index, peak flow, use of rescue medication.

Indacaterol groups showed statistical improvement over placebo in mean score of St. George's Respiratory Questionnaire at week 12, percentage of patients with COPD exacerbation, % of nights with no nighttime awakenings, mean daily number of puffs of rescue medication, and change from baseline in morning peak expiratory flow. For these endpoints, there is no difference between the two indactaerol groups.

Safety review

The safety findings from this study, along with the safety data from the other placebo-controlled studies, will be reviewed in depth in the Integrated Review of Safety section of this review. Brief observations are described below.

Patient exposure

The two indacaterol groups had similar mean number days of exposure, the formoterol group had fewer days, and the placebo group had the fewest days (311, 310, 304, and 285 for indacaterol 300 µg , 600 µg, formoterol, and placebo, respectively). The majority of patients were exposed to more than 44 weeks (of 52 weeks) of treatment (79%, 79%, 74%, and 71% for indacaterol 300 µg, 600 µg, formoterol, and placebo, respectively). Treatment compliance was greater than 98% in all groups.

Reviewer's comment: The placebo group had a higher rate of premature discontinuation and lower mean number of days of exposure.

Adverse events

Overall
The indacaterol 300 µg group had the highest rate of adverse events, and placebo had the lowest rate (70%, 64%, 65%, and 61% for indacaterol 300 µg, 600 µg, formoterol, and placebo respectively). COPD exacerbations are the most common at 27%- 34% (placebo has the highest rate of 34%) and nasopharyngitis are next (13%- 18%). Other common adverse events include cough, upper respiratory tract infection bacterial, lower respiratory tract infection, and muscle spasm.

AEs thought to be related to study drug

Adverse events suspected of being related to the study drug were higher the in indacaterol groups than in the formoterol or in the placebo group (11%, 12%, 8%, and 7% for indacaterol 300 µg, 600 µg, formoterol, and placebo, respectively). Cough and muscle spasm were the most commonly reported, and showed an increase for indacaterol 600 µg compared to 300 µg (for cough: 3.0%, 3.8%, 1.4%, and 0.7% ; for muscle spasm: 1.8%, 3.1%, 1.4%, and 0.2% for indacaterol 300 µg, 600 µg, formoterol, and placebo, respectively). Increased incidence of tremor was also seen as dose related (0.2%, 1.6%, 0.9%, and 0.2% for indacaterol 300 µg, 600 µg, formoterol and placebo, respectively). Increased incidence of headache was also seen, but is the same across the two indacaterol groups.

SAEs
Serious adverse events range from 11% to 16%, after adjusting for exposure the rate is similar across the groups, with a slightly higher rate in the formoterol group. COPD exacerbation and pneumonia are the most common and the indacaterol groups do not have higher rates than the placebo groups.

Reviewer's comment: In this study, increased muscle spasm and tremor was seen with the indacaterol groups, which is dose dependent. Increased headache was also seen, but was equal across the two indacaterol groups. In study QAB149B2335S, increased incidence of headache and muscle spasm was also seen with the indacaterol groups (no difference between the two doses).

Cardiac or cerebrovascular events (CCV)
The indacaterol groups had a higher rate of CCV related SAEs than placebo or formoterol (3.4%, 2.6%, 1.4%, and 0.9% for indacterol 300 µg, 600 µg, formoterol and placebo, respectively). The notable ones are atrial fibrillation and cardiac failure congestive, which had a few events in the indacaterol 300 µg group, but had no events with the 600 µg group. For CCV related AEs, the indacaterol groups had similar rates as formoterol, which is higher than that of placebo (6.6%, 6.1%, 6.5%, and 3.9% for indacaterol 300 µg, 600 µg, formoterol and placebo, respectively). The two categories with highest rates, atrial fibrillation and myocardial ischemia, the indacaterol 300 µg group had higher rates while the indacaterol 600 µg group had similar rates as placebo.

Reviewer's comment: The indacaterol groups had a higher rates of CCV related AEs than placebo, but similar to formoterol. However, for CCV related SAEs, the indacterol groups had higher rates than formoterol and placebo. Interestingly, indacaterol 300 µg had higher rates than indacaterol 600 µg for the most common types of CCV related AEs and SAEs.

Laboratory abnormalities
The indacaterol 300 µg (but not the 600 µg group) had a higher than normal % of patients with elevated WBC, elevated BUN, elevated potassium, and low potassium levels. Both indacaterol groups had slightly higher level of serum glucose.

Deaths
Nine patients died during the clinical trial (1, 0, 3, and 5 for indacaterol 300 µg, 600 µg, formoterol and placebo, respectively). Four patients died from sudden death, 2 from cardiac

arrest, 1 from respiratory failure, 1 from multi-organ failure, and 1 from multi-organ failure. These deaths will be discussed in detail in the Integrated Summary of Safety.

- **Pivotal study: B2346**

Title of study
A 12-week treatment, multi-center, randomized, double-blind, placebo-controlled, parallel-group study to assess the efficacy and safety of indacaterol (150 µg o.d.) in patients with chronic obstructive pulmonary disease

Design, population, and study centers
A 12 week multi-center, double-blind, placebo-controlled, parallel-group study evaluating safety and efficacy of indacaterol 150 µg versus placebo in patients with COPD.

416 patients were randomized 1:1 to the two groups. The study was performed during the period of 2/14/2008 to 7/22/2008 and the report is dated 10/13/2008. The study was conducted in 103 centers in 3 countries (101 centers in U.S., 1 center in Australia/ New Zealand, and 1 in Belgium).

Study objectives/ efficacy endpoints

Primary objective: To demonstrate superiority of indacaterol 150 µg versus placebo with respect to 24 hour post-dose (trough) FEV_1 after 12 weeks of treatment in patients with COPD.

Secondary objectives:
• To compare indacaterol (150 µg o.d.) to placebo on spirometry assessments in terms of:
  • Trough FEV1 measured on Day 2.
  • FEV1 measured at all time points, including approximate peak response (Day 1 and after 12 weeks of treatment) and trough response.
  • The standardized area under the curve (AUC) for FEV1 (5 min – 4 h), (5 min – 1 h) and (1 h – 4 h) on Day 1 and after 12 weeks of treatment.
• To assess the 12-week safety (particularly with regard to electrocardiograms (ECG), laboratory tests, blood pressure and adverse events (AEs)) of indacaterol (150 µg o.d.).

Inclusion and exclusion criteria

They are the same as the ones from study B2335s (see page 24 of this document) except that in this study, the following exclusion criteria are added: patients who are taking varenicline for smoking cessation or who have previous exposure to indacaterol are excluded.

Materials
Indacaterol and its placebo were provided as powder filled capsules with an SDDPI. Patient packs contained either active drug or placebo packaged in three x1 monthly visit packs (enough to last for the whole study) and labeled identically so to maintain the medication blind. Patients

were instructed to inhale the contents of one indacaterol/ placebo capsule from the SDDPI device in the morning (between 8 am to 11 am).

Conduct
Following 14 days of screening, patients were randomized to 1:1 to the two groups. Patients had clinic visits on week 1, 5, 9, 12, and 13 in which history, vitals, spirometry, EKG, symptom diary, and laboratory studies were evaluated.

Concomitant treatment
Same as in study B2335s (see page 27 of this document)

Disposition of subjects

Table 18 Patient disposition (study QAB149B2346 report, page 80, table 10-1)

	Ind 150 µg n (%)	Pbo n (%)	Total n (%)
Patients			
Screened			788
Randomized	211 (100)	205 (100)	416 (100)
Exposed	211 (100)	205 (100)	416 (100)
Completed	186 (88.2)	178 (86.8)	364 (87.5)
Discontinued	25 (11.8)	27 (13.2)	52 (12.5)
Primary reason for premature discontinuation			
Protocol deviation	7 (3.3)	9 (4.4)	16 (3.8)
Adverse event(s)	6 (2.8)	3 (1.5)	9 (2.2)
Subject withdrew consent	5 (2.4)	4 (2.0)	9 (2.2)
Lost to follow-up	3 (1.4)	2 (1.0)	5 (1.2)
Administrative problems	3 (1.4)	0 (0.0)	3 (0.7)
Unsatisfactory therapeutic effect	1 (0.5)	6 (2.9)	7 (1.7)
Not stated	0 (0.0)	1 (0.5)	1 (0.2)
Abnormal test procedure result(s)	0 (0.0)	1 (0.5)	1 (0.2)
Death	0 (0.0)	1 (0.5)	1 (0.2)

Reviewer's comment: The placebo group had a lower rate of completing the study and a higher rate of unsatisfactory therapeutic effect. The indacaterol group had a higher rate of adverse events.

Table 19 Top five major protocol deviations (Adapted from study QAB149B2346 report, page 81, table 10-2)

	Ind 150 µg N = 211 n (%)	Pbo N = 204 n (%)	Total N = 415 n (%)
Total number of ITT patients excluded from per-protocol population	12 (5.7)	22 (10.8)	34 (8.2)
Major protocol deviations			
Eosinophil count >400/mm^3 at Screening	3 (1.4)	6 (2.9)	9 (2.2)
Study medication taken <80% doses (from baseline to primary endpoint)	3 (1.4)	3 (1.5)	6 (1.4)
FDC or LABA/ICS use ≤ 48h prior to Screening	2 (0.9)	4 (2.0)	6 (1.4)
Not compliant with dosing schedule at key visits	2 (0.9)	2 (1.0)	4 (1.0)
Active cancer or cancer free for < 5 years	1 (0.5)	0 (0.0)	1 (0.2)

Demographics and baseline disease characteristics

Table 20 Demographics (Adapted from study QAB149B2346, page 83, table 11-2)

		Ind 150 µg N = 211	Pbo N = 205	Total N = 416
Age (years)	n	211	205	416
	Mean	62.9	63.2	63.0
	SD	9.89	9.62	9.75
	Median	63.0	63.0	63.0
	Min - Max	40.0 – 85.0	42.0 – 89.0	40.0 – 89.0
Age group – n (%)	40–64 years	117 (55.5)	119 (58.0)	236 (56.7)
	≥ 65 years	94 (44.5)	86 (42.0)	180 (43.3)
Sex – n (%)	Male	108 (51.2)	110 (53.7)	218 (52.4)
	Female	103 (48.8)	95 (46.3)	198 (47.6)
Race – n (%)	Caucasian	194 (91.9)	191 (93.2)	385 (92.5)
	Black	12 (5.7)	10 (4.9)	22 (5.3)
	Asian	1 (0.5)	1 (0.5)	2 (0.5)
	Native American	2 (0.9)	1 (0.5)	3 (0.7)
	Other	2 (0.9)	2 (1.0)	4 (1.0)

Table 21 Baseline disease characteristics (Adapted from study QAB149B2346, page 84, table 11-3)

		Ind 150 µg N = 211	Pbo N = 205	Total N = 416
Duration of COPD (years)	n	211	205	416
	Mean	6.6	7.3	6.9
	SD	6.86	5.64	6.29
	Median	4.7	5.8	5.7
	Min - Max	0.0 – 38.7	0.0 – 25.7	0.0 – 38.7
Duration of COPD – n (%)	<1 yr	38 (18.0)	18 (8.8)	56 (13.5)
	1–5 yrs	74 (35.1)	69 (33.7)	143 (34.4)
	>5–10 yrs	57 (27.0)	69 (33.7)	126 (30.3)
	>10–15 yrs	23 (10.9)	30 (14.6)	53 (12.7)
	>15–20 yrs	9 (4.3)	12 (5.9)	21 (5.0)
	>20 yrs	10 (4.7)	7 (3.4)	17 (4.1)
Severity of COPD (GOLD 2005) – n (%)	At risk	0 (0.0)	1 (0.5)	1 (0.2)
	Mild	7 (3.3)	10 (4.9)	17 (4.1)
	Moderate	119 (56.4)	117 (57.1)	236 (56.7)
	Severe	84 (39.8)	76 (37.1)	160 (38.5)
	Very severe	1 (0.5)	1 (0.5)	2 (0.5)
ICS use – n (%)	Yes	61 (28.9)	70 (34.1)	131 (31.5)
	No	150 (71.1)	135 (65.9)	285 (68.5)
Smoking history – n (%)	Ex-smoker	103 (48.8)	97 (47.3)	200 (48.1)
	Smoker	108 (51.2)	108 (52.7)	216 (51.9)

Table 22 Screening spirometry (Study QAB149B2346, page 84, table 11-4)

		Ind 150 µg N = 211	Pbo N = 205	Total N = 416
Pre-bronchodilator (SABA) FEV_1 at Visit 1 (L)	n	211	205	416
	Mean	1.3	1.4	1.3
	SD	0.52	0.52	0.52
	Median	1.2	1.3	1.3
	Min - Max	0.5-3.0	0.4-3.0	0.4-3.0
Post-bronchodilator (SABA) FEV_1 at Visit 1 (L)	n	211	205	416
	Mean	1.5	1.5	1.5
	SD	0.53	0.51	0.52
	Median	1.4	1.5	1.4
	Min - Max	0.6-3.5	0.6-3.0	0.6-3.5
Post-bronchodilator (SABA) FEV_1 at Visit 1 (% predicted)	n	211	205	416
	Mean	54.4	55.8	55.1
	SD	13.38	14.08	13.73
	Median	53.5	56.0	53.7
	Min - Max	28.1 – 84.1	27.6 – 91.9	27.6 – 91.9
Post-bronchodilator (SABA) FEV_1/FVC at Visit 1 (%)	n	211	205	416
	Mean	53.5	53.5	53.5
	SD	9.84	10.36	10.09
	Median	55.1	54.7	54.8
	Min - Max	28.6 – 69.8	28.0 – 70.0	28.0 – 70.0
FEV_1 reversibility after SABA at Visit 1 (% increase)	n	211	205	416
	Mean	16.4	16.6	16.5
	SD	17.31	19.44	18.37
	Median	14.0	12.4	13.6
	Min - Max	-34.8 – 80.9	-46.5 – 160.1	-46.5 – 160.1
FEV_1 reversibility after anti-cholinergic at Visit 2 (% increase)	n	210	205	415
	Mean	15.9	15.6	15.7
	SD	17.59	16.67	17.13
	Median	13.8	12.4	12.9
	Min - Max	-31.8 – 156.9	-26.9 - 85.9	-31.8 – 156.9

Post-bronchodilator FEV_1/FVC and FEV_1 reversibility at Visit 1 were measured 30 min after inhalation of 400 µg salbutamol or albuterol, a short-acting beta-agonist (SABA).

FEV_1 reversibility at Visit 2 was measured 1 hour after inhalation of 42 µg ipratropium, an anticholinergic.

Primary efficacy endpoint results

The least squares mean (LSM) estimate of the trough FEV1 at Week 12 was greater for indacaterol 150µg than for placebo (1.49 L vs. 1.35 L, respectively) ($p < 0.001$). The LSM difference was 130 mL.

Secondary efficacy endpoint results

Secondary efficacy analyses showed that relative to placebo, indacaterol 150 µg was associated with a statistically significant improvement in trough FEV1 at Day 2, in FEV1 at all post-baseline time points measured, including peak and trough response, in greater standardized

AUCs for FEV1 (between 5 minutes and 4 hours), (between 5 minutes and 1 hour) and (between 1 and 4 hours) at Day 1 and after 12 weeks of treatment.

Adverse events

The overall rate of AEs was similar for indacaterol 150 µg and placebo (49.3% and 46.8% for indacaterol and placebo, respectively). In the respiratory, thoracic, and mediastinal disorders category, the incidence of AEs was 19.0% in the indacaterol group and 21.0% in the placebo group. The overall difference between the treatment groups in this category was primarily due to higher incidences of the two most common adverse events: chronic obstructive pulmonary disease (8.5% indacaterol vs. 12.2% placebo) and cough (6.2% indacaterol vs. 7.3% placebo).

Muscle spasm and headache, two of the most common adverse events, occurred in similar proportions of patients in the indacaterol and placebo treatment groups (3.3% vs. 2.9% and 2.4% vs. 2.4%, respectively).

Death and serious adverse events
[Study B2346, page 107-108]

One patient, a 51-year-old female in the placebo group, died during the course of the study. The patient was found dead at home on Day 36. The cause of death was unknown at the time of the report.

A total of 7 (3.3%) patients in the indacaterol group and 5 (2.4%) in the placebo group experienced treatment-emergent SAEs, including COPD exacerbations which occurred in two patients on placebo.

Laboratory results, vitals, ECGs
[Study B2346 page 109-114]

No patient had clinically notable low potassium (< 3.0 mmol/L). Clinically notable hyperglycemia occurred in fewer indacaterol patients than placebo patients (3.3% vs. 6.3%, respectively).

The incidence of patients who had a maximum post-baseline pulse rate >90 bpm, systolic blood pressure >140 bpm, diastolic blood pressure >90 bpm at any visit was lower in the indacaterol group compared with the placebo group.

There are no other clinically significant changes in laboratory, vital signs, or ECGs.

- **Pivotal study: B2338**

Reviewer's comment: A brief description of this clinical trial on asthma patients will be given here. The focus will be on safety evaluation for off-label use of indacaterol in asthma patients. Therefore, efficacy will not be discussed.

Title of study
A 26-week treatment, randomized, multi-center, double blind, double dummy, parallel-group study to assess the safety of indacaterol (300 and 600 µg q.d.) in patients with moderate to severe persistent asthma, using salmeterol (50 µg b.i.d.) as an active control.

Primary objective
To evaluate the safety of indacaterol 300 and 600 µg o.d over 26 weeks, in patients with moderate to severe persistent asthma who were receiving background therapy with inhaled corticosteroids.

Methodology
This phase III study was a multi-national, multi-center, double blind, double dummy, parallel group design, with stratification for asthma severity (randomization ratio 1:1:1, indacaterol 300 µg: indacaterol 600 µg: salmeterol 50 µg), with a 2 week run-in period, and a 26 week treatment period. The number of patients randomized into the study was 805 (268- 269 patients per group).

Notable inclusion criteria

- Male and female patients aged ≥ 12 years
- Patients with moderate to severe persistent asthma, diagnosed according to GINA guidelines (updated 2006) and who additionally met the following criteria:
    - Patients who had used treatment with a bronchodilator, either regularly or demand, and
        - who had used a daily dose of at least 100 µg BDP or equivalent dose of an alternative ICS for at least one month prior to Visit 1
    - Patients whose FEV1 was ≥50% of the predicted normal value for the patient

Notable exclusion criteria
- Diabetes Type I or those with uncontrolled diabetes Type II
- active cancer or a history of cancer with less than 5 years disease free survival time
- A history of long QT syndrome, or whose QTc interval (Bazett's formula) was prolonged to > 450 ms (males) or > 470 ms (females)

6 Review of Efficacy

Efficacy Summary

The applicant seeks an indication for indacaterol 150 µg as once daily maintenance treatment of bronchoconstriction in patients with COPD. The two pivotal trials that studied the 150 µg dose showed that indacaterol 150 µg once daily resulted in effective bronchodilation. Trough FEV1 (FEV1 at the end of dosing interval) after 12 weeks of treatment was chosen as the primary endpoint for the pivotal trials. The data showed that indacaterol at both doses studied (150 and 300 µg once daily produced statistically significant improvements in trough FEV1 130-170 ml improvement in 12 week trough FEV1 compared to placebo (an improvement of 9.6% - 14%).

While both the 150 and 300 µg doses met the primary endpoint, the data indicated that adequate dose ranging was not performed and that all doses (75 µg, 150 µg, 300 µg and 600 µg) studied in the dose ranging study, 2335s, had similar effects on FEV1 indicating that all doses were at the top of the dose response curve. Also, although the data appear supportive of a once daily dosing frequency for a dose of indacaterol higher than proposed (300 µg once daily), there is little data to support the proposed once daily dosing interval for the 150 µg dose. In the future submissions, data on once and twice-daily dosing of indacaterol should be required as it is the most direct method to determine dosing interval.

6.1 Indication

Many patients with COPD have an element of reversible bronchoconstriction that responds to Beta-2 agonist and anti-cholinergic bronchodilator agents and the use of these agents has been shown to improve symptoms of airway obstruction. The Applicant is thus seeking an indication for use of the LABA, indacaterol, as once daily maintenance treatment of bronchoconstriction in patients with COPD, including chronic bronchitis and emphysema. This is the standard indication that bronchodilator agents for the treatment of patients with COPD have been typically approved for.

6.1.1 Methods

Conclusions regarding the efficacy of indacaterol maleate inhalation powder (150 µg QD) were arrived at following detailed review of the efficacy findings of each of the two pivotal Phase 3 studies B2335s, and B2346. While study B2334 was subtitled as a “pivotal” study, the dose for which the applicant seeks an indication (150 µg QD) was not assessed. Therefore, because the study is useful predominately to support the safety of higher 300 µg and 600 µg QD dosing of indacaterol, the efficacy findings will not be discussed in detail in this section (see section 5.3 for a detailed review of study B2334).

Study B2335s is a 26-week treatment, multi-center, randomized, double-blind, double dummy, placebo-controlled, adaptive design dose-ranging and pivotal efficacy parallel group study involving 1665 patients to assess the efficacy, safety and tolerability of two doses of indacaterol

(selected from 75, 150, 300 & 600 µg QD) in patients with COPD using blinded formoterol (12 µg BID) and open label tiotropium (18 µg QD) as active controls.

Study B2346 is a 12-week, multi-center, randomized, double-blind, placebo-controlled, parallel-group study involving 416 patients to assess the efficacy and safety of indacaterol (150 µg QD) in patients with COPD.

Study B2334 is a 52-week treatment, multi-center, randomized, double-blind, double dummy, placebo-controlled, parallel-group study involving 1728 patients to assess the efficacy, safety and tolerability of indacaterol (300 & 600 µg QD) in patients with COPD using formoterol (12 µg BID) as an active control.

These studies are described in detail in section 5.3 of this document.

6.1.2 Demographics

The demographics of these three studies are similar with mean age around 65, 60%-70% of subjects are male, and > 85% of subjects is Caucasians. Thus, there is a lack of ethnic diversity. These subjects also have a relatively short duration of diagnosis of COPD with >50% diagnosed for < 5 years, and > 90% of subjects have moderate/ severe COPD. These patients have a high degree of FEV1 reversibility at baseline, with 12%- 15% improvement in FEV1 after short acting beta agonist administration during screening.

See B2335s demographics section, and B2346 demographics section (from section 5.3 of this document) for additional information.

6.1.3 Subject Disposition

The placebo groups of all three pivotal studies had a higher rate of discontinuation than the other groups due to unsatisfactory therapeutic results. B2335s, a 6 month study, had a study completion rate of 76%. B2346, a 3 month study, had a study completion rate of 87%.

See B2335s subject disposition section, and B2346 subject disposition section (from section 5.3 of this document) for additional information.

6.1.4 Analysis of Primary Endpoint(s)

The pre-specified primary endpoint for all three studies was to demonstrate superiority of indacaterol doses versus placebo with respect to 24 hour post-dose (trough) FEV1 after 12 weeks of treatment in patients with COPD.

All studies showed similar results that indacaterol at all doses studied was statistically superior to placebo in 12 week trough FEV1.

For study B2335s, treatment with indacaterol 150 µg and 300 µg resulted in a 12 week trough FEV1 improvement of 0.18 liter greater than placeb. For study B2346, treatment with indacaterol 150 µg resulted in a 12 week trough FEV1 improvement of 0.13 liter greater than placebo's 1.35 liters. This was a statistically significant improvement of 9%- 14% over the placebo values.

All indacaterol doses also had increased 12 week trough FEV1 results compared to formoterol and tiotropium. For study B2335s, treatment with indacaterol 150 µg and 300 µg resulted in a 12 week trough FEV1 improvement of 0.04 liter greater than tiotropium's. This is an improvement of 2% over the active comparator values.

6.1.5 Analysis of Secondary Endpoints(s)

All studies showed that the indacaterol groups achieved the key secondary endpoints and a number of other secondary endpoints. For most part, there is no meaningful difference between the results of the different indacaterol doses.

B2335s secondary endpoints
For B2335s, both indacaterol doses achieved the key secondary endpoint of statistical superiority to tiotropium at 12 week trough FEV1. Both doses were 0.04 liter greater than tiotropium's 1.42 liters. Indacaterol groups were also statistically superior to placebo in most of the secondary endpoints including other spirometry measures and assessment of COPD symptoms and functions. Indacaterol groups also demonstrated statistical superiority in few symptom measures when compared to tiotropium. There was no statistical difference between the two indacaterol groups on all measures.

Reviewer's Comment: The key secondary endpoint (superiority to tiotropium) should be considered invalid because dose selection for this study required that the doses selected needed to have a greater effect on FEV1 that tiotropium.

B2346 secondary endpoints
For B2346, indacaterol 150 µg achieved the secondary endpoints of statistical improvement over placebo in different spirometry measures (trough FEV1 on different days, FEV1 at different time points throughout 24 hours, and peak FEV1 and FEV1 AUC). Indacaterol 150 µg also showed statistical improvement over placebo in most of other endpoints of COPD symptom assessment and function.

The details of these study results are described in section 5.3 of this document.

6.1.6 Other Endpoints

Not applicable.

6.1.7 Subpopulations

Subgroup analyses for age, sex, race, COPD severity, smoking history, and ICS use at baseline, were performed for trough FEV1 after 12 weeks of treatment. Since the population for the studies was about 85- 90% Caucasian, it was difficult to make conclusions about the racial subgroups.

For both B2335s and B2346, males had higher trough FEV1 than females by 40-50 ml. For study B2346, inhaled corticosteroid users had higher trough FEV1 than non-users by 90 ml; difference in study B2335s 20 ml.

There was little difference in FEV1 response based on COPD severity (moderate/mild versus severe), age < 65 versus ≥ 65, and ex-smokers versus current smokers. See individual study reviews for B2335s page 132, table 11-7 and B2346 page 88, table 11-6 for additional information.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Dose selection
The dose for the COPD indication was chosen after the interim analysis of the initial dose-ranging portion of the adaptive design study B2335s, which was the first 2 weeks portion of the 6 month long study. The sponsor studied four doses (75 µg, 150 µg, 300 µg, and 600 µg), and chose 150 µg (and 300 µg as the next higher dose) based on the following criteria:

After 2 weeks treatment, the selected dose needed to be

- 120mL greater than placebo (minimal clinically important difference, MCID) in terms of trough FEV1 and numerically higher than tiotropium and formoterol;
- Numerically higher than tiotropium and formoterol in terms of FEV1 standardized AUC(1-4h).

General dose selection criteria were discussed with sponsor in EOP-2 meeting and SPA meeting. We were not informed or agreed to the sponsor's final choice of dose selection criteria.

Below is a history of our discussion with the sponsor regarding dose selection criteria.

"At the October 10, 2006 EOP-2 meeting and the December 20, 2006 SPA meeting and in subsequent discussions, Novartis had originally proposed trough FEV1 as an appropriate measure for dose selection. The division advised Novartis to provide the independent Data Monitoring Committee (DMC) with more information on the total FEV1 curve during the first 2 weeks of treatment as the Agency would consider other variables, such as peak FEV1 and FEV1 AUC as part of the assessment of dose selection. The intent was to help ensure that the selected doses were effective at other time points in addition to 24-hour trough, and to provide comparisons to the currently available once- and twice-daily bronchodilator treatments."

The results from the dose ranging portion of the trial are as follows:

Table 23 Interim analysis, after 2 weeks dosing of study B2335s [Study QAB149B2335S, page 129]

		Treatment			Treatment difference		
Treatment	**n**	**LS mean**	**SE**	**Comparison**	**LS mean**	**SE**	**95% CI**
Trough FEV1 (L)							
Comparisons with placebo							
Ind 75 µg	104	1.46	0.024	Ind 75 µg - Pbo	0.15	0.029	(0.09, 0.20)
Ind 150 µg	105	1.49	0.024	Ind 150 µg - Pbo	0.18*	0.029	(0.12, 0.24)
Ind 300 µg	110	1.52	0.024	Ind 300 µg - Pbo	0.21*	0.029	(0.15, 0.27)
Ind 600 µg	108	1.51	0.024	Ind 600 µg - Pbo	0.20	0.029	(0.14, 0.25)
For	105	1.42	0.024	For - Pbo	0.11	0.029	(0.06, 0.17)
Tio	112	1.45	0.023	Tio - Pbo	**0.14**	0.028	(0.08, 0.19)
Pbo	104	1.31	0.024				
AUC 1h-4h FEV1 (L)							
Comparisons with placebo							
Ind 75 µg	95	1.50	0.034	Ind 75 µg - Pbo	0.20	0.032	(0.14, 0.27)
Ind 150 µg	96	1.53	0.034	Ind 150 µg - Pbo	0.23*	0.032	(0.16, 0.29)
Ind 300 µg	99	1.58	0.034	Ind 300 µg - Pbo	0.28*	0.031	(0.22, 0.34)
Ind 600 µg	97	1.53	0.034	Ind 600 µg - Pbo	0.23	0.031	(0.17, 0.29)
For	93	1.52	0.035	For - Pbo	**0.22**	0.032	(0.16, 0.28)
Tio	99	1.49	0.034	Tio - Pbo	0.19	0.031	(0.13, 0.25)
Pbo	90	1.30	0.033				

LS mean = least squares mean, SE = standard error of the mean, CI = confidence interval.
Mixed model: Trough FEV1 = treatment + baseline FEV1 + FEV1 reversibility components + smoking status + country + center(country), with center(country) as a random effect.
Bold LS mean differences were those identified as reference values by dose selection criteria, * = selected doses

The difference between 2 week trough FEV1 of indacaterol 75 µg and indacaterol 150 µg is small, about 2%. This is also true of FEV1 AUC 1h- 4h. Sponsor chose dose selection criteria based on absolute value of trough FEV1 and the requirement that the doses selected must have a greater effect on FEV1 than either tiotropium or formoterolwithout considering the significance of the difference between the doses.

The difference in 2 week trough FEV1 between 75 µg, 150 µg, and 300 µg are small; besides 75 µg was superior to tiotropium which is known to have good trough FEV1 efficacy. In fact, Dr. Dongmei Liu, in her statistical analysis, examined the patients who received 75 µg QD who were treated for 12 weeks and found that 12 week trough FEV1 was the same between the 75 µg and 150 µg groups. The finding suggests our determination that the applicant has not adequately explored the dose ranging for indacaterol in order to be able to select the appropriate dose. That is, that all doses (75 µg, 150 µg, 300 µg, and 600 µg) selected for the dose response study have similar effects on trough FEV1 thus demonstrating that all these doses are at the top of the dose response curve. The other pivotal studies also support this conclusion. Thus 75 µg should have been explored further and even a lower dose should be studied. Due to the risk profile of long

acting beta agonists, it is especially important to find the lowest effective dose of indacaterol. With this in mind, it would be good to identify a non-efficacious dose in order to identify the lowest effective dose.

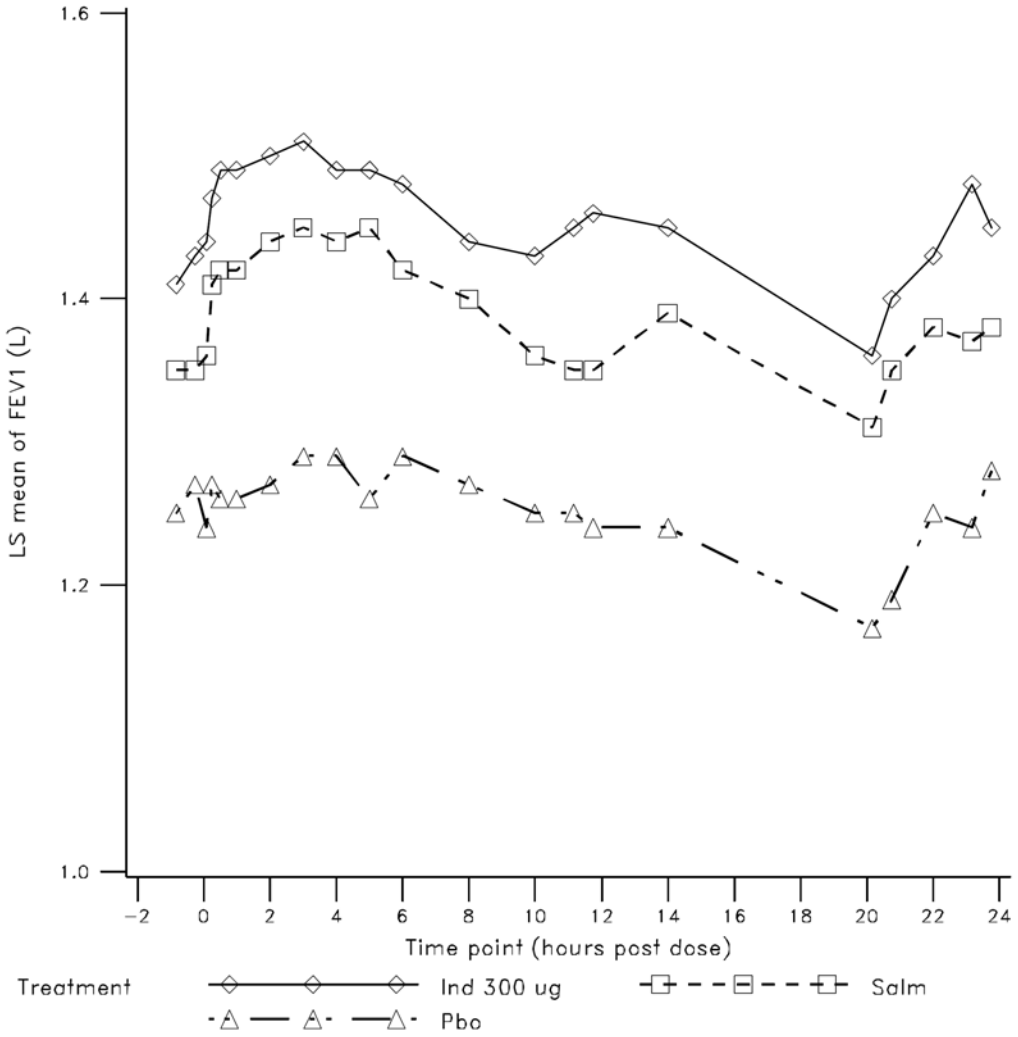
Dosing frequency
The applicant's proposed indication for indacaterol is 150 µg once daily. During the division's discussion with the applicant regarding dosing frequency at pre-NDA meeting in April 2008, it was stated "we remind you that you will need to provide justification for your dosing frequency. In addition to 24-hour FEV1 response curve and trough FEV1, we will also consider the efficacy results for QAB149 in comparison to twice-daily active comparators, salmeterol and formoterol."

The applicant has not conducted studies in which the same daily dose of indacaterol is administered at different dosing intervals (once daily vs. twice daily). While comparing to an active comparator with a known dosing interval may be helpful, comparing once and twice daily dosing of the same daily dose is the most precise way to assess dosing interval.

In this submission, the sponsor has supplied a supportive study B2340 that provided 24 hour FEV1 curve and comparison with twice-daily comparator, salmeterol. The results from that study did provide some level of support for once daily dosing frequency of indacaterol at that dose (see paragraph below). However, since the dose studied was 300 µg, it will not provide support dosing frequency for 150 µg or other lower doses. Once the applicant identifies the lowest efficacious dose for future submission, data will be needed to support the once daily dosing frequency at that dose. At that time the applicant should include data on once and twice-daily dosing of indacaterol to support the proposed dosing interval.

<u>Study B2340</u>
Study B2340 was a Phase III, randomized, double-blind, placebo controlled, 3-period, 14-day crossover study to determine the 24-h lung function profile of indacaterol (300 µg QD) in patients with moderate-to-severe COPD, using open-label salmeterol (50 µg BID) as an active control. As the figure below shows, the 24 hour curve of indacaterol 300 µg QD after 14 days of treatment has similar shape as that of salmeterol 50 µg BID.

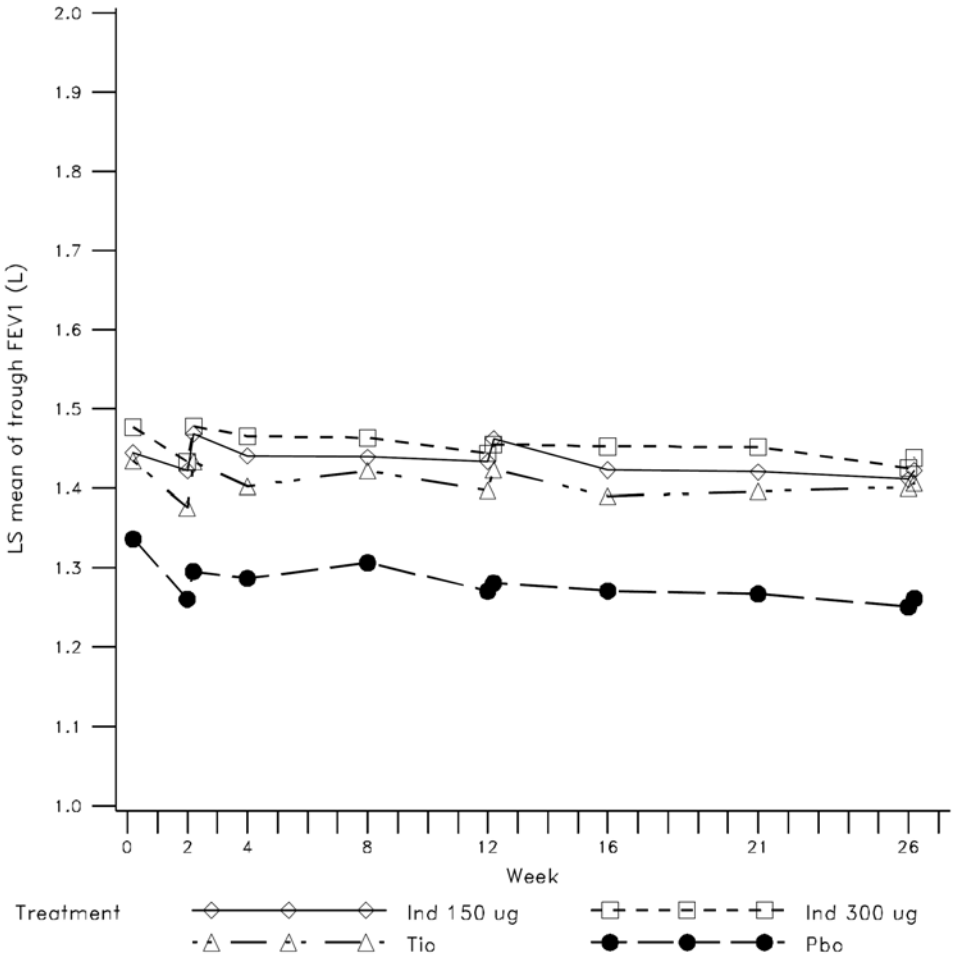
Figure 2 24-hour profile of least squares means of FEV1 (L) after 14 days treatment (Modified ITT population) [Study B2340, page 87, figure 11-3]



6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

For study B2335s, trough FEV1 was measured throughout the study. The improvement in FEV1 seen in subjects receiving indacaterol 150 µg persisted throughout the 26 weeks (ee figure 3 below). At day 2, the indacaterol 150 µg group had a 110 ml improvement over the placebo group; at day 15, it was 170 ml; at week 12, it was 180 ml, and at week 26, it was 160 ml.

Figure 3 Least squares means of trough FEV1 (L) over 26 weeks of treatment (ITT population) [study B2335s, page 136, figure 11-1]



6.1.10 Additional Efficacy Issues/Analyses

There are no additional efficacy issues.

7 Review of Safety

Safety Summary

The majority of safety data for this review comes from the pivotal phase 3 studies which are placebo and active- controlled, and includes exposure of indacaterol 150 µg, 300 µg, and 600 µg that range from 3-12 months. In addition, because of its large size and length (6 months) a trial of indacaterol 300 µg and 600 µg once daily for patients with asthma (study B2338) was also reviewed to assess safety.

Beta adrenergic agonists have been studied extensively and have the potential to produce certain adverse events related to beta adrenergic receptor stimulation, such as tachycardia, palpitations, leg cramps, dizziness, nervousness, tremors, insomnia, nausea, arrhythmias, and worsening hypertension. Dose-related beta mediated adverse events were noted in the studies and began to occur between the 300 and 600 µg doses. COPD exacerbations were less common in the 150 µg group than the placebo group, with other active treatment groups being similar to the indacaterol group. Hyperglycemia is also considered systemic beta adrenergic effects. Small changes in the mean concentrations of glucose were noted in the clinical studies.

However, more cerebro- cardiovascular (CCV) serious adverse events were seen for COPD patients treated with 300 µg and 600 µg of indacaterol for 12 months compared to the active comparator, formoterol and placebo. Data for patients treated with indacaterol 150 µg for 6 months also showed some increase in CCV serious adverse events compared to placebo.

Since potential off-label use of indacaterol in asthma patients is a concern, safety issues of indacaterol in asthma patients were also examined. The asthma study (B2338) showed that for subjects treated with indacaterol 300 µg and 600 µg for 6 months, there were increased deaths and asthma serious adverse events in the treatment groups as compared to placebo. Although long-acting beta-2 agonists are known in asthma patients to increase severe asthma episodes and asthma deaths, 6 months is a relatively short amount of time to observe such a serious safety signal.

For the future submissions, the long term safety of the lowest efficacious dose would need to be evaluated, especially regarding cerebro- cardiovascular events in COPD patients and asthma exacerbation and death in asthma patients.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The three pivotal phase III COPD trials were the primary source of safety data.

- Study B2334: 52 weeks of treatment with indacaterol 300 µg od, 600 µg once daily, placebo (double-blind) or formoterol 12 µg bid (double-blind) and providing long-term safety data.
- Study B2335S: 26 weeks of treatment with indacaterol 150 µg once daily, 300 µg once daily, placebo (double-blind) or tiotropium 18 µg od (open-label).
- Study B2346: 12 weeks of treatment with indacaterol 150 µg once daily or placebo (double-blind).

7.1.2 Categorization of Adverse Events

The MedRA medical dictionary system was used to categorize AEs by system, organ, and class.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Studies were pooled to provide an integrated safety profile. The populations were organized into the following datasets, according to the type of clinical trial, as follows:

- 3-month safety population (COPD) containing pooled 3-month data from pivotal, phase III studies B2346 (all data), B2334 (up to day 91) and B2335S (up to day 91)
- 6-month safety population (COPD) containing pooled 6-month (26 week) data from pivotal, phase III studies B2334 (up to day 182) and B2335S (all data)
- 12-month safety population (COPD) containing 52 week, pivotal, phase III study B2334
- COPD safety population containing all data from studies B2346, B2334 and B2335S
- Asthma safety population containing 26 week, phase III study B2338

Reviewer's comment: The three supportive studies have fewer patients and are short in duration. They were briefly reviewed and there was no new safety signal identified.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Exposure in the 3-month safety population
This dataset included 4180 patients, 2154 of whom received indacaterol treatment at doses of 75 µg once daily (N=127), 150 µg once daily (N=627), 300 µg once daily (N=853) or 600 µg once daily (N=547). The COPD 3-month safety population includes all the data from the 12-week study B2346, and only the first 3 months (91 days) of data from the 26-week study B2335S and the 52- week study B2334.

Table 24 Exposure in COPD 3 month safety population [CTD 2.7.4 Summary of Clinical Safety, page 41]

	Ind 75µg N=127	Ind 150µg N=627	Ind 300µg N=853	Ind 600µg N=547	For N=556	Tio N=415	Pbo N=1055
Exposure (days)							
mean	77.9	81.7	84.4	83.1	83.8	83.3	79.2
sd	20.77	20.62	20.08	20.86	19.57	21.42	24.77
median	91.0	91.0	91.0	91.0	91.0	91.0	91.0

Exposure in the 6 month population
This dataset included 3764 patients, 1943 of whom received indacaterol treatment at doses of 75 µg once daily (N=127), 150 µg once daily (N=416), 300 µg once daily (N=853) or 600 µg daily (N=547). They are the patients from the entire 26-week study B2335S and patients from the first 6 months of study B2334. [CTD 2.7.4 Summary of Clinical Safety, page 46]

Reviewer's comment: The formoterol and indacaterol 600 µg groups had lower mean number of exposure days since the dose ranging portion of study B149B2335S had these groups for a shorter duration of time. The indacaterol 75 µg group had much shorter duration of time since it is only included in the dose ranging part of study B149B2335S. The placebo group also had a relatively lower mean number of exposure days since there is a higher drop out rate in that group compared to the groups that received indacaterol or active comparator treatment.

Exposure in the 12 month population

The dataset contains 1728 patients, all of them from the 52-week study B2334 study. Higher proportions of patients in the indacaterol groups completed >44 weeks of treatment (79.4% and 79.1%) compared with formoterol (75.6%) and placebo (71.8%). [CTD 2.7.4 Summary of Clinical Safety, page 49]

Reviewer's comment: Because of placebo's lower rate of completing > 44 weeks of treatment, the mean number of days of exposure is also lower. In addition, because this long term study studied the 300 and 600 µg doses of indacaterol, there is no long term safety data (one year) for the proposed dose of 150 µg once daily. This is a major issue given what appears to be a safety signal (increased cerebro-cardiovascular SAEs in patients with COPD and increased death and asthma related SAEs) at the higher 300 and 600 µg doses.

Demographics

Demographics in the 3 month, 6 month, and 12 month safety populations have similar patterns. The mean and median ages are about 63- 64 years old. For most of the groups, the ratio of men to women range from 2:1 to 3:1. Between 83%- 93% of the patients are Caucasian. The African American population is usually less than 2%, few groups have as high as 4%. The mean BMI and median BMI range from 25- 27 (from CTD 2.7.4 Summary of Clinical Safety, page 58-62). Table 25 below shows summary demographic data from the 6-month safety population.

Table 25 Demographics in COPD 6 month safety population [adapted from CTD 2.7.4 Summary of Clinical Safety, page 61]

		Ind 150 µg N=416	Ind 300 µg N=853	Ind 600 µg N=547	For N=556	Tio N=415	Pbo N=850
Age (years)	n	416	853	547	556	415	850
	mean	63.4	63.6	63.1	64.0	64.0	63.4
	sd	9.40	8.94	8.83	8.53	8.77	8.60
	median	64.0	64.0	64.0	64.0	64.0	64.0
	min	40.0	40.0	40.0	40.0	41.0	41.0
	max	87.0	88.0	87.0	84.0	85.0	90.0
Age group - n(%)	< 65 years	214 (51.44)	450 (52.75)	292 (53.38)	282(50.72)	215(51.81)	454(53.41)
	≥ 65years	202 (48.56)	403 (47.25)	255 (46.62)	274(49.28)	200(48.19)	396 (46.59)
Sex – n (%)	male	259 (62.26)	614 (71.98)	401 (73.31)	418(75.18)	269(64.82)	607 (71.41)
	female	157 (37.74)	239 (28.02)	146 (26.69)	138(24.82)	146(35.18)	243 (28.59)
Race – n (%)	Caucasian	353 (84.86)	762 (89.33)	503 (91.96)	511(91.91)	347(83.61)	759 (89.29)
	Black	14 (3.37)	13 (1.52)	6 (1.10)	3 (0.54)	10 (2.41)	8 (0.94)
	Asian	45 (10.82)	54 (6.33)	15 (2.74)	13 (2.34)	51 (12.29)	60 (7.06)
	Other	4 (0.96)	24 (2.81)	23 (4.20)	29 (5.22)	7 (1.69)	23 (2.71)

Reviewer's comment: There is a lack of racial diversity. Most of the populations are Caucasians.

Disease Characteristics

Disease characteristic for the 3 month, 6 month, and 12 month safety populations are similar. Across the groups, the mean duration of COPD is around 7 years (median ~5 years), > 90% of patients have moderate and severe COPD, 40%- 45% of the patients are current smokers, the mean pack-year range from 49-53 (median 41-45), and 35%-50% of the patients use inhaled corticosteroids. Also, similar proportions of patients in the different groups have the following co-existing conditions: cardio- cerebrovascular 20%, diabetes mellitus 7%-11%, hypertension 50%, hyperlipidemia 30%-35%, and ≥ 3 cardiovascular risk factors 36%-47%. Additionally, the different groups have similar range of FEV1 (51% -56% of predicted) after administration of short-acting beta-agonist.

All three populations had a notable amount of reversibility after short-acting beta-agonist administration, with the 12 month group having the smallest amount of change. The 3 month group had a mean improvement of 12%- 16% (median of 10%-14%), the 6 month group had a mean improvement of 12%-16% (median of 12%- 16%), and the 12 month group had a mean of 11%- 14% (median of 10%- 11%) (from CTD 2.7.4 Summary of Clinical Safety, page 65-70).

7.2.2 Explorations for Dose Response

Three doses of indacaterol 150, 300, and 600 µg once daily were assessed in large Phase III clinical trials with the 300 and 600 doses studied for up to 12 months. This allowed assessment

of dose response to various pharmacodynamic and safety endpoints associated with administration of beta-2 agonists. These include effects on laboratory values (potassium, glucose), ECGs (QT interval), and AEs associated with beta-2 agonists such as tremor, muscle spasm, tachycardia, changes in blood pressure, as well as cardiovascular and cerebrovascular AES.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro safety assessments were conducted.

7.2.4 Routine Clinical Testing

Routine clinical testing was adequate to assess the systemic effects of beta-2 receptor stimulation by indacaterol. Assessments included measurements of vital signs, clinical laboratory testing (especially potassium, glucose, and LFTs), and ECGs, both at baseline and at several time points post dosing, including what would be considered the time of peak effect (one hour post-dose).

7.2.5 Metabolic, Clearance, and Interaction Workup

Appropriate metabolic, clearance, and drug interaction assessments were performed as part of the clinical program. See Section 4.4 Clinical Pharmacology above and the clinical pharmacology review by Dr. Sandra Suarez for complete details.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The marketed LABA, formoterol at the approved dose was used as an active comparator in the Phase III program including the year long safety and efficacy study, B2334. This allowed the safety profile of doses of indacaterol ranging from 150-600 μg to be compared with that of an approved LABA.

7.3 Major Safety Results

7.3.1 Deaths

A total of 14 patients died in the three pivotal studies B2334, B2335s, and B2346. Deaths that occur within 30 days after the individual's last dose is included. The indacaterol groups had fewer deaths than the placebo or the active comparator groups (see Table 26 below).

Table 26 Deaths in the three pivotal studies: B2334, B2335s, B2346

	Indacaterol 150 µg	Indacaterol 300 µg	Indacaterol 600 µg	Formoterol	Tiotropium	placebo
B2334		1	0	3		5
B2335s	1	0			2	1
B2346	0					1

Deaths in B2334

Table 27 Cause of death in study B2334 [Study QAB149B2334, pg 170]

	Ind 300 µg N=437 n (%)	**Ind 600 µg** N=425 n (%)	**For** N=434 n (%)	**Pbo** N=432 n (%)
Number (%) of deaths	**1 (0.2)**	**0 (0.0)**	**3 (0.7)**	**5 (1.2)**
Preferred term				
Cardiac arrest	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Aortic aneurysm rupture	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Multi-organ failure	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Respiratory failure	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Sudden death	0 (0.0)	0 (0.0)	1 (0.2)	3 (0.7)

One 57 year old male patient died in the 300 µg indacaterol treatment group, and this was as a result of cardiac arrest. The patient had received his last dose of medication three days previously when he had been discontinued due to moderate dyspnea (suspected by the investigator of being related to study drug and also recorded as an SAE).

In the formoterol treatment group, three patients died, each as a result of a different event. One male, 70 year old patient died of multi-system organ failure following a series of AEs, none of which were suspected by the investigator of being related to the study drug. A 68 year old male patient whose death was attributed to respiratory failure had a respiratory failure AE listed on the day of his death, which was not suspected by the investigator of being related to the study drug. Also, one 77 year old male experiencing sudden death died during surgery to implant a pacemaker device.

In the placebo group five patients died during the study, three of which were sudden death, all of whom were Caucasian males with the youngest aged 56 years.

Deaths in B2335s
[from study QAB149B2335S report, page 168]
One patient in the indacaterol 150 µg group, and two patients in the tiotropium group died during the study, and one placebo patient died during the 30 day post-treatment follow-up period for SAEs.

A 52-year-old male in the indacaterol 150 µg group died suddenly on Day 145 of the study at home. An autopsy was not performed. The patient had heart failure from Day 113 of the study onwards, which was treated with furosemide.

A 63-year-old male in the tiotropium group died on Day 34 of the study at home, six days after his last dose of study medication, from an unspecified event secondary to worsening arteriosclerosis. A 78-year-old male in the tiotropium group died on Day 55 of the study from severe acute bronchopneumonia. The patient had earlier experienced a non-serious upper respiratory tract infection which had resolved with treatment on Day 11. In addition, the patient had acute congestion of the spleen and liver due to ventricular dilation (revealed on autopsy).

A further patient, a 59-year-old male in the placebo group had an AE with a fatal outcome 15 days later: the patient had an accidental fall from height on Day 29 of the study and was discontinued from the study. The patient subsequently died from the fall on Day 44 of the study. The event was recorded on the AE eCRF as an SAE, but because this death occurred after study discontinuation, it was not captured in the listing of deaths.

Death in B2346
[from study B2335S report, page 107]
One patient died in the placebo group. A 51-year-old female with a history of diabetes mellitus, hyperlipidemia, anxiety, back pain, and peripheral neuropathy on multiple medications who, 7 days after receiving last dose of study medication, was found dead at home. Cause of death was unknown.

Deaths in B2338 asthma study
[from study B2338, page 102]
Two patients in the indacaterol 300 µg group died during the study.

Table 28 Deaths in B2338 asthma study

	Indacaterol 300 µg N= 268 n (%)	Indacaterol 600 µg N= 268 n (%)	Salmeterol N= 269 n (%)
death	2	0	0

<u>Death due to asthmatic crisis</u>
[From study B2338 report, page 1682]
This 60 year Native American male entered the study with an 7 years of asthma history of 7 years and otherwise no active or relevant past medical history. Prior treatment for asthma included beclometasone and budesonide. The patient was a non-smoker.

He received the first dose of the study medication on (b) (6) (Day 1). At baseline, the patient's ECG was normal and remained normal throughout the study period. At baseline, the patient's FEV1 was 2.45 L and FEV1/FVC was 72.92 %.

On Day 165 (b) (6) 164 days after the first dose of the study medication, the patient presented with dyspnea and was hospitalized. He was diagnosed with asthmatic crisis. No action was taken with the study medication. The patient was treated with prednisone and nebulization therapies. He recovered from the asthmatic crisis on the same day as its onset (b) (6) and was discharged home.

On Day 169 (b) (6) the patient again presented with dyspnea and died on his way to the hospital on (b) (6). The patient had received the last dose of the study medication on Day 169 (b) (6) The cause of death was determined to be asthmatic crisis. Prior to onset of dyspnea, the patient had used solutions with strong odors to fix furniture. An autopsy was not performed.

<u>Death due to cardiac arrest</u>
[from study B2338 report, page 1683]
This 70 year old Caucasian woman had a history of asthma (for 2 years), allergic rhinitis, osteoporosis and a past medical history of respiratory arrest and anaphylactic reaction (1995). Prior treatment for asthma included salbutamol and mometasone furoate. Active medications also included hydrochlorothiazide, potassium chloride and alendronate sodium.

Patient's baseline FEV_1 was 1.06 L and FEV_1/FVC was 43.8 %; her baseline EKG, hematology and chemistry laboratory values were normal. First dose of the study medication was given on (b) (6) (Day 1).

On Day 119 (b) (6) 118 days after the first dose of the study medication), the patient experienced a cardiac arrest at home. The patient was reported to have become dyspneic and stopped talking and received cardio-pulmonary resuscitation. The patient was intubated and received epinephrine and atropine. Prior to hospitalization, the patient's heart rate was 115, glucose was 90 mg/dL and blood pressure was 69/45 mmHg. The patient was hospitalized on the same day (b) (6)

The patient's last ECG was performed on Day 110 (b) (6) and was normal.

On the day of the cardiac arrest, the patient was also reported to have seizures, bandemia. Her CK was reported to be 244, CK-MB was 0.5 and troponin was 0.07, which indicated that she did not have a myocardial infarction. The patient received the last dose of the study medication on the Day 119 (b) (6) On an unspecified date, the patient underwent a brain CT scan which revealed cortical atrophy but no focal lesion, hemorrhage or midline shift. A thoracic CT scan showed small pneumothorax and left lower hemithorax. Pulmonary hyperinflation consistent with underlying asthma was also observed along with symmetric biapical pleural thickening. No evidence of pulmonary embolism or active pulmonary disease was seen. An ECG performed showed normal sinus rhythm.

She was treated with ceftriaxone sodium and levofloxacin for the bandemia and lorazepam and phenytoin for the seizures and received propofol for sedation. She was placed on life support which was withdrawn at the request of her family on (b) (6) (Day 129), 11 days after the last dose of the study medication. An autopsy was not performed.

7.3.2 Nonfatal Serious Adverse Events

[from CTD 2.7.4 Summary of clinical safety report, page 138-150]

COPD 3 month safety population
In the 3-month safety population, the overall frequency of SAEs was similar across the 6 treatment groups with 3.1 to 5.1%. Pulmonary, cardiac, infection type disorders were some of the more common types of SAEs (see Table 29 below).

Table 29 Six most common SAEs in COPD 3 month safety population [Adapted CTD 2.7.4 Summary of clinical safety report, page 140]

	Ind 150 µg N=627 n (%)	Ind 300 µg N=853 n (%)	Ind 600 µg N=547 n (%)	For N=556 n (%)	Tio N=415 n (%)	Pbo N=1055 n (%)
Patients with SAE(s)	30 (4.8)	33 (3.9)	17 (3.1)	21 (3.8)	21 (5.1)	47 (4.5)
Primary system organ class						
Respiratory, thoracic and mediastinal disorders †	8 (1.3)	6 (0.7)	4 (0.7)	10 (1.8)	7 (1.7)	18 (1.7)
Infections and infestations	7 (1.1)	5 (0.6)	1 (0.2)	7 (1.3)	4 (1.0)	10 (1.0)
Cardiac disorders	6 (1.0)	5 (0.6)	3 (0.6)	2 (0.4)	5 (1.2)	6 (0.6)
Gastrointestinal disorders	3 (0.5)	0	4 (0.7)	0	2 (0.5)	5 (0.5)
Injury, poisoning and procedural complications	2 (0.3)	5 (0.6)	3 (0.6)	2 (0.4)	2 (0.5)	5 (0.5)
Vascular disorders	2 (0.3)	0	0	2 (0.4)	3 (0.7)	0

COPD 6 month safety population

In COPD 6-month safety population, the overall frequency of SAEs was similar across the 6 treatment groups with 6.2% to 8.4%. COPD exacerbation, atrial fibrillation, and angina pectoris are some of the more common SAEs (seeCTD 2.7.4 Summary of clinical safety report, page 144 for additional information)

COPD 12 month safety population
In the COPD 12-month safety population, the overall frequency of SAEs was similar between the indacaterol 600 µg and the placebo groups, while the 300 µg and the formoterol groups had a higher overall frequency. COPD exacerbation, upper respiratory tract infection, and pneumonia

were some of the more common SAEs (seeCTD 2.7.4 Summary of clinical safety report, page 149).

SAEs in COPD safety population
In the COPD safety population there were overall 202 indacaterol treated patients who had SAEs: 9 patients on 75 µg, 42 patients on 150 µg, 95 patients on 300 µg, and 56 patients on 600 µg. There were 58 patients in the indacaterol groups with SAEs which led to permanent discontinuation from study drug: 3 on 75 µg, 14 on 150 µg, 27 on 300 µg, and 14 on 600 µg.

Reviewer's comment:
There may be a slight increased in syncope for the indacaterol 300 µg group in the 3 month and the 6 month safety population, but this is not seen in the 12 month safety population.

Additionally, more coronary artery disease type SAEs were seen in the 6 month population for the indacaterol 150 µg and 300 µg groups (indacaterol 150 µg group > 300 µg group), but this trend is not seen in the 12 month population. By organ class, there appears to be increased 12 month cardiac disorders in the indacaterol groups (not dose related), compared to placebo and formoterol.

SAEs in asthma safety study B2338
[adapted from CTD 2.7.4 Summary of clinical safety report, page 153-156]

In the asthma safety study B2338 the frequency of SAEs ranged from 1.9 to 4.1% of patients in the 3 treatment groups; the highest frequency was seen on indacaterol 600 µg (see table 30 below). Indacaterol 300 µg and 600 µg had higher rates of SAEs due to asthma than salmeterol (see table below)

Table 30 SAEs in respiratory and cardiac organ class in asthma safety study B2338 [adapted from CTD 2.7.4 Summary of clinical safety report, page 154, table 2-52]

	Ind 300 µg N=268 n(%)	Ind 600 µg N=268 n(%)	salmeterol N=269 n(%)
Patients with any SAEs	5 (1.9)	11 (4.1)	8 (3.0)
Respiratory, thoracic, mediastinal disorders	2 (0.7)	3 (1.1)	1 (0.4)
Asthma	2 (0.7)	3 (1.1)	0
Analgesic asthma syndrome	0	0	1 (0.4)
Cardiac disorders	1 (0.4)	1 (0.4)	1 (0.4)
Cardiac arrest	1 (0.4)	0	0
Atrial fibrillation	0	1 (0.4)	0
Myocardial infarction	0	0	1 (0.4)

In study B2338 there were 5 SAEs related to asthma exacerbation, all of which occurred on indacaterol, and all occurred in patients on concomitant inhaled corticosteroids. One of these cases was fatal. There is no increase in SAEs due to cardiac disorders in the indacaterol groups compared to salmeterol.

Reviewer's comment: There is a dose related increase in SAEs due to asthma exacerbation in the indacaterol groups compared to salmeterol.

7.3.3 Dropouts and/or Discontinuations

AEs leading to discontinuation in the 3 month safety population
[from CTD 2.7.4 Summary of Clinical Safety Report, page 172-175]

The indacaterol groups did not have a higher rate of patients with any AE(s) leading to discontinuation, as compared to the placebo group (See table 31 below).

The highest rates of AEs leading to discontinuation involved respiratory disorders, which was highest with placebo (1.4%, 2.0%, 0.7%, 1.8%, 0.7%, and 3.0% for indacaterol 150 µg, 300 µg, 600 µg, formoterol, tiotropium, and placebo, respectively). Indacaterol 150 µg had a higher rate of cardiac disorders leading to discontinuation, compared to indacaterol 300 µg, 600 µg, and other groups (1.6%, 0.8%, 0.7%, 0.4%, 1.0%, and 0.7% for indacaterol 150 µg, 300 µg, 600 µg, formoterol, tiotropium and placebo, respectively). The most frequently reported AE leading to discontinuation was COPD which occurred at a higher rate with placebo and formoterol, compared to the others (1.7%, 1.6%, 1.1%, 0.9%, 0.4%, and 0.2% for placebo, formoterol, indacaterol 150 µg, 300 µg, 600 µg, and tiotropium, respectively).

Table 31 Six most common AEs leading to discontinuation in COPD 3 month safety population [adapted from CTD 2.7.4 Summary of Clinical Safety Report, page 174, table 2-69]

	Ind 150 µg N=627 n (%)	Ind 300 µg N=853 n (%)	Ind 600 µg N=547 n (%)	For N=556 n (%)	Tio N=415 n (%)	Pbo N=1055 n (%)
Patients with AE(s) leading to discontinuation	31 (4.9)	42 (4.9)	15 (2.7)	22 (4.0)	14 (3.4)	59 (5.6)
Preferred term:						
COPD †	7 (1.1)	8 (0.9)	2 (0.4)	9 (1.6)	1 (0.2)	18 (1.7)
Ventricular tachycardia	4 (0.6)	0	0	0	1 (0.2)	0
Atrial fibrillation	2 (0.3)	1 (0.1)	1 (0.2)	0	1 (0.2)	2 (0.2)
Nausea	2 (0.3)	0	0	0	0	0
Dyspnea	2 (0.3)	8 (0.9)	1 (0.2)	0	1 (0.2)	8 (0.8)
Myocardial infarction	1 (0.2)	1 (0.1)	1 (0.2)	0	0	2 (0.2)

AEs leading to discontinuation in COPD 6 month safety population

[from CTD 2.7.4 Summary of Clinical Safety Report, page 175-178]

The proportion of patients with any AE leading to discontinuation was higher with placebo and indacaterol 150 µg compared to the other groups. The highest involved respiratory disorders which led to the highest proportion discontinuation in the placebo group (1.9%, 2.1%, 1.5%, 2.3%, 1.0%, 4.2% for indacaterol 150 µg, 300 µg, 600 µg, formoterol, tiotropium, and placebo, respectively). Similar to the 3 month safety data, the indacaterol 150 µg group had the highest rate of discontinuation due to cardiac disorders compared to the other groups (2.4%, 0.8%, 0.7%, 0.7%, 1.0%, 1.2% for indacaterol 150 µg, 300ug, 600 µg, formoterol, tiotropium, and placebo, respectively. COPD was the most commonly reported AE leading to discontinuation, with placebo having the highest rate (1.7%, 1.1%, 0.9%, 2.2%, 0.5%, and 2.6% for indacaterol 150 µg, 300 µg, 600 µg, formoterol, tiotropium, and placebo, respectively).

AEs leading to discontinuation in COPD 12 month safety population
[from CTD 2.7.4 Summary of Clinical Safety Report, pages 178-180]

The highest rates of AEs leading to discontinuation involved respiratory disorders which led to discontinuation more frequently with placebo and formoterol than with the indacaterol groups (2.5%, 1.9%, 4.6%, and 5.8% for indacaterol 300 µg, 600 µg, formoterol, and placebo, respectively). Cardiac disorders caused discontinuation occurred more often with indacaterol 300 µg than 600 µg, but discontinuation due to indacaterol 300 µg occur only slightly higher than that of formoterol and placebo (1.6%, 0.7%, 1.2%, and 1.2% for indacaterol 300 µg, 600 µg, formoterol, and placebo, respectively).

Consistent with the 3 and 6 month data, COPD is the most common adverse event causing discontinuation, and occurred more frequently in placebo and formoterol than in the indacaterol groups.

Reviewer's comment: The indacaterol groups had lower rates of discontinuation than the placebo group, and most of time also had lower rate of discontinuation than formoterol. The highest rates involved respiratory disorders which led to discontinuation more frequently with placebo. COPD is the most common adverse event causing discontinuation, and occurred more frequently in placebo and formoterol than in the indacaterol groups.

7.3.4 Significant Adverse Events

The data from the pivotal trials demonstrated that in COPD patients, indacaterol treatment at doses 150 µg, 300 µg, and 600 µg is associated with higher risk of cardio- cerebrovascular (CCV) SAEs as compared to placebo or formoterol. The data also indicated that the risk increased with longer time of indacaterol exposure.

After 6 months of treatment, the indacaterol 150 µg group had a 2.1 times higher risk of CCV SAEs than placebo. At this point, indacaterol 300 µg and 600 µg had lower incidences of CCV SAEs than 150 µg but still at least double that observed for the active comparator formoterol

(2.1%, 1.4%, 1.2%, 0.5%, and 1% for indacaterol 150 µg, 300 µg, 600 µg, formoterol, and placebo, respectively)

Significantly, after 12 months of exposure, indacaterol 300 µg and 600 µg groups had a 2 – 2.5 times higher risk of cardio- cerebrovascular (CCV) SAEs than formoterol and a 3 – 3.7 times higher risk than placebo (3.4%, 2.6%, 1.4%, and 0.9% for indacaterol 300 µg, 600 µg, formoterol and placebo, respectively). Indacaterol 150 µg was not studied for 12 months.

As for CCV AEs at 6 months and 12 months, the indacaterol doses had similar or slightly higher rates as formoterol, which is higher than that of placebo (At 6 months, 2.1%, 1.4%, 1.2%, 0.5% and 1% for indacaterol 150 µg, 300 µg, 600 µg, formoterol and placebo, respectively; at 12 months, 3.4%, 2.6%, 1.4%, and 0.9% for indacaterol 300 µg, 600 µg, formotorol, and placebo ,respectively).

Since potential off-label use of indacaterol in asthma patients is a concern, safety issues of indacaterol in asthma patients were also examined. The asthma study (B2338) showed that for subjects treated with indacaterol 300 µg and 600 µg for 6 months, there were increased deaths and asthma serious adverse events in the treatment groups as compared to placebo. It is not known if similar effects will be seen in lower doses of indacaterol.

7.3.5 Submission Specific Primary Safety Concerns

Beta adrenergic agonists have been studied extensively and as a class have the potential to produce certain adverse events related to beta adrenergic receptor stimulation, such as tachycardia, palpitations, leg cramps, dizziness, nervousness, tremors, insomnia, nausea, arrhythmias, and worsening hypertension. This class of medication can also increase serum level of glucose, decrease in serum level of potassium, and cause prolongation of QT interval. The COPD patient population tends to be older and many patients have either pre-existing cardiovascular and/or cerebrovascular conditions or have risk factors for increased cardiac and cerebrovascular adverse events which may be exacerbated by excessive cardiac and CNS stimulation from beta agonists. Thus, many of the safety concerns in the COPD patient population revolves around the assessment of cardiac and CNS related adverse events, especially serious adverse events.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Common adverse events in 3-month COPD safety population

Table 32 below shows the incidence and rate of adverse events for the 3 month COPD safety population. The incidence of common adverse events for different groups is in a similar range, from 44% to 55%. The 75 µg had the highest rate. The placebo group had the highest rate of

COPD exacerbations, 15% compared to 10% - 11% of the indacaterol groups, and 12-13% for formoterol and tiotropium. There is an increase in cough in the indacaterol groups compared to placebo (4.9% - 5.5% compared to 4.2% for placebo).

There is increased muscle spasm in the indacaterol groups compared to placebo and tiotropium. The rate of muscle spasm in the indacaterol may have a dose relationship, with the biggest increase seen between the 300 and 600 µg doses. As would be expected with an antimuscarinic, there is increased dry mouth with the tiotropium compared to the other groups.

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Table 32 Common AEs in 3 month COPD safety population

Preferred term	Ind 75 ug N=127 n (%)	Ind 150 ug N=627 n (%)	Ind 300 ug N=853 n (%)	Ind 600 ug N=547 n (%)	For N=556 n (%)	Tio N=415 n (%)	Pbo N=1055 n (%)
-Total	80(62.99)	324(51.67)	419(49.12)	252(46.07)	246(44.24)	229(55.18)	488(46.26)
Chronic obstructive pulmonary disease	10(7.87)	64(10.21)	101(11.84)	56(10.24)	71(12.77)	54(13.01)	159(15.07)
Cough	7(5.51)	33(5.26)	43(5.04)	27(4.94)	15(2.70)	16(3.86)	45(4.27)
Upper respiratory tract infection	8(6.30)	33(5.26)	30(3.52)	17(3.11)	8(1.44)	22(5.30)	27(2.56)
Nasopharyngitis	6(4.72)	30(4.78)	49(5.74)	43(7.86)	31(5.58)	30(7.23)	61(5.78)
Headache	9(7.09)	28(4.47)	24(2.81)	16(2.93)	16(2.88)	18(4.34)	27(2.56)
Muscle spasms	1(0.79)	18(2.87)	24(2.81)	22(4.02)	14(2.52)	6(1.45)	12(1.14)
Diarrhoea	3(2.36)	15(2.39)	12(1.41)	5(0.91)	8(1.44)	5(1.20)	16(1.52)
Dyspnoea	2(1.57)	14(2.23)	19(2.23)	13(2.38)	7(1.26)	11(2.65)	28(2.65)
Back pain	3(2.36)	13(2.07)	11(1.29)	8(1.46)	9(1.62)	6(1.45)	18(1.71)
Bronchitis	2(1.57)	13(2.07)	11(1.29)	7(1.28)	7(1.26)	5(1.20)	25(2.37)
Dizziness	4(3.15)	12(1.91)	14(1.64)	5(0.91)	3(0.54)	2(0.48)	17(1.61)
Nausea	6(4.72)	12(1.91)	6(0.70)	4(0.73)	5(0.90)	2(0.48)	15(1.42)
Lower respiratory tract infection	0(0.00)	11(1.75)	19(2.23)	5(0.91)	8(1.44)	11(2.65)	23(2.18)
Pharyngolaryngeal pain	2(1.57)	11(1.75)	9(1.06)	4(0.73)	2(0.36)	6(1.45)	8(0.76)
Sinusitis	0(0.00)	11(1.75)	15(1.76)	2(0.37)	4(0.72)	9(2.17)	8(0.76)
Urinary tract infection	5(3.94)	11(1.75)	9(1.06)	1(0.18)	5(0.90)	10(2.41)	13(1.23)
Viral upper respiratory tract infection	1(0.79)	10(1.59)	16(1.88)	2(0.37)	5(0.90)	3(0.72)	16(1.52)
Arthralgia	2(1.57)	8(1.28)	8(0.94)	6(1.10)	2(0.36)	2(0.48)	7(0.66)
Influenza	2(1.57)	8(1.28)	13(1.52)	10(1.83)	3(0.54)	3(0.72)	8(0.76)
Oedema peripheral	1(0.79)	7(1.12)	7(0.82)	7(1.28)	6(1.08)	4(0.96)	4(0.38)

Common adverse events in 6-month COPD safety population

Table 32 below shows the incidence and rate of adverse events for the 3 month COPD safety population. The trend in AEs for the 6 month safety population is similar to that for the 3 month safety population. The placebo group again had higher rates of COPD exacerbation. The indacaterol groups had an increase in rate of cough and muscle spasm compared to the placebo and the tiotropium groups. It is not clear if there is a dose relationship in muscle spasm. The formoterol group had a relatively higher rate of muscle spasm than placebo or tiotropium, but a lower rate than the indacaterol groups. Again, tiotropium had a higher rate of dry mouth.

Table 33 Common AEs (>=2.0% of patients in any group) adjusted for exposure (episodes per patient year) in 6-month safety population

	Ind 150 µg N=416	Ind 300 µg N=853	Ind 600 µg N=547	For N=556	Tio N=415	Pbo N=850
Exposure in patient years	178.552	379.811	222.519	227.488	180.227	345.188
AE episodes/patient year	5.438	4.392	4.422	3.556	5.249	4.467
Preferred term	AE episodes: n per patient year					
COPD †	0.510	0.529	0.562	0.593	0.544	0.716
Upper RTI	0.235	0.126	0.103	0.088	0.189	0.145
Nasopharyngitis	0.246	0.274	0.382	0.233	0.255	0.238
Cough	0.213	0.208	0.162	0.097	0.155	0.136
Headache	0.218	0.103	0.153	0.114	0.150	0.116
Viral upper RTI	0.101	0.074	0.013	0.035	0.039	0.067
Lower RTI	0.106	0.076	0.076	0.057	0.089	0.116
Muscle spasms	0.162	0.105	0.180	0.088	0.044	0.029
Diarrhea	0.073	0.047	0.040	0.053	0.044	0.046
Sinusitis	0.073	0.063	0.018	0.035	0.072	0.035
Dyspnea	0.067	0.063	0.085	0.048	0.061	0.084
Back pain	0.078	0.045	0.063	0.092	0.044	0.070
Pharyngolaryngeal pain	0.073	0.039	0.036	0.022	0.089	0.032
Influenza	0.067	0.068	0.063	0.031	0.022	0.035
Urinary tract infection	0.067	0.047	0.004	0.035	0.072	0.038
Nausea	0.078	0.018	0.018	0.035	0.022	0.055
Dizziness	0.062	0.055	0.040	0.022	0.011	0.058
Arthralgia	0.073	0.034	0.040	0.013	0.022	0.038

Common adverse events in 12-month COPD safety population

The rate of adverse events for the 12 month population is similar across the groups (see Table 34 below). The following similar trend again holds for the 12 month population as for the 6 month and the month population. The placebo group has the highest rate of COPD exacerbation. The indacaterol groups had a slight increase in cough. The indacaterol groups had a larger increase in muscle spasm compared to the placebo and the formoterol group. While this increase does not appear to be dose related, it should be noted that there is increased rate of an AE similar to muscle spasm (tremor) in the indacaterol 600 µg group compared to the indacaterol 300 µg, placebo, and formoterol groups.

Table 34 Common AEs (>=2.0% of patients in any group) adjusted for exposure (episodes per patient year) in 12-month safety population

	Ind 300 µg N=437	Ind 600 µg N=425	For N=434	Pbo N=432
Exposure in patient years	372.2	361.6	361.4	338.0
AE episodes: n (n per patient year)	1254 (3.369)	1201 (3.322)	1017 (2.814)	1076 (3.183)
Preferred term:	AE episodes: n (n per patient year)			
Chronic obstructive pulmonary disease †	221 (0.594)	195 (0.539)	206 (0.570)	251 (0.743)
Nasopharyngitis	112 (0.301)	117 (0.324)	84 (0.232)	80 (0.237)
Cough	46 (0.124)	39 (0.108)	23 (0.064)	24 (0.071)
Upper respiratory tract infection bacterial	37 (0.099)	32 (0.089)	29 (0.080)	49 (0.145)
Lower respiratory tract infection	33 (0.089)	35 (0.097)	30 (0.083)	36 (0.106)
Muscle spasms	35 (0.094)	29 (0.080)	16 (0.044)	6 (0.018)
Upper respiratory tract infection	33 (0.089)	25 (0.069)	25 (0.069)	17 (0.050)
Headache	24 (0.064)	34 (0.094)	22 (0.061)	32 (0.095)
Influenza	23 (0.062)	25 (0.069)	14 (0.039)	16 (0.047)
Viral upper respiratory tract infection	22 (0.059)	10 (0.028)	14 (0.039)	10 (0.030)
Dyspnea	19 (0.051)	24 (0.066)	13 (0.036)	12 (0.035)
Back pain	17 (0.046)	18 (0.050)	16 (0.044)	19 (0.056)
Bronchitis	19 (0.051)	19 (0.053)	14 (0.039)	17 (0.050)
Pneumonia	11 (0.030)	6 (0.017)	9 (0.025)	7 (0.021)
Productive cough	10 (0.027)	6 (0.017)	9 (0.025)	7 (0.021)
Arthralgia	9 (0.024)	11 (0.030)	7 (0.019)	8 (0.024)
Dizziness	9 (0.024)	9 (0.025)	3 (0.008)	6 (0.018)
Dyspepsia	10 (0.027)	5 (0.014)	1 (0.003)	3 (0.009)
Urinary tract infection	9 (0.024)	2 (0.006)	6 (0.017)	6 (0.018)
Diarrhea	10 (0.027)	12 (0.033)	17 (0.047)	8 (0.024)
Hypertension	8 (0.021)	9 (0.025)	7 (0.019)	12 (0.035)
Pharyngolaryngeal pain	9 (0.024)	6 (0.017)	5 (0.014)	12 (0.035)
Pyrexia	9 (0.024)	3 (0.008)	8 (0.022)	10 (0.030)
Chest pain	8 (0.021)	7 (0.019)	4 (0.011)	7 (0.021)
Sinusitis	8 (0.021)	6 (0.017)	6 (0.017)	6 (0.018)
Abdominal pain	9 (0.024)	6 (0.017)	4 (0.011)	7 (0.021)
Pain in extremity	7 (0.019)	2 (0.006)	3 (0.008)	3 (0.009)
Rhinitis	7 (0.019)	3 (0.008)	0	3 (0.009)
Edema peripheral	8 (0.021)	11 (0.030)	6 (0.017)	1 (0.003)
Tremor	1 (0.003)	10 (0.028)	6 (0.017)	2 (0.006)
Nausea	1 (0.003)	4 (0.011)	9 (0.025)	8 (0.024)

Reviewer's comment: For the COPD population, there appears to be an increase in muscle spasm in the indacaterol groups compared to the placebo and the active comparator groups in the 3 month, 6 month, and 12 month safety populations. However, it is unclear if this increase in muscle spasm is dose related. Additionally at the highest dose of indacaterol (600ug), there appears to be a marked increase in tremor, which is an expected beta-agonist side effect. Otherwise, there is not an increase in the cardiac, vascular, or nervous system type adverse

events in the COPD indacaterol groups compared to the placebo group or the active comparator group.

Adverse events for asthma study B2338
(from study B2338 report, page 98-102)

For the B2338 asthma study, there is a dose related increase in asthma, upper respiratory infection, headache, oropharyngeal pain, muscle spasm, and tremor in the indacaterol groups. There was an increased incidence of cough in both of the indacaterol groups compared to salmeterol. Indacaterol 600 µg had a higher rate than salmeterol for asthma, upper respiratory infection, oropharyngeal pain, muscle spasm, and tremor (see Table 25 below).

Table 35 most frequent AEs in B2338 asthma study (Adapted from study B2338 page 100, table 12-3)

	Ind 300 ug N=268 n (%)	Ind 600 ug N=268 n (%)	Salm N=269 n (%)
Patients with any AE(s)	147 (54.9)	178 (66.4)	181 (67.3)
Preferred term			
Asthma	31 (11.6)	42 (15.7)	40 (14.9)
Cough	28 (10.4)	29 (10.8)	14 (5.2)
Nasopharyngitis	20 (7.5)	22 (8.2)	26 (9.7)
Upper respiratory tract infection	17 (6.3)	27 (10.1)	18 (6.7)
Headache	14 (5.2)	18 (6.7)	20 (7.4)
Bronchitis	10 (3.7)	13 (4.9)	16 (5.9)
Diarrhoea	9 (3.4)	0 (0.0)	4 (1.5)
Influenza like illness	9 (3.4)	6 (2.2)	8 (3.0)
Pharyngitis	7 (2.6)	7 (2.6)	9 (3.3)
Viral upper respiratory tract infection	7 (2.6)	6 (2.2)	9 (3.3)
Oropharyngeal pain	6 (2.2)	11 (4.1)	6 (2.2)
Sinusitis	6 (2.2)	8 (3.0)	11 (4.1)
Muscle spasms	5 (1.9)	9 (3.4)	4 (1.5)
Nausea	5 (1.9)	6 (2.2)	5 (1.9)
Rhinitis allergic	5 (1.9)	9 (3.4)	6 (2.2)
Back pain	4 (1.5)	7 (2.6)	7 (2.6)
Rhinitis	4 (1.5)	7 (2.6)	10 (3.7)
Upper respiratory tract infection bacterial	3 (1.1)	5 (1.9)	7 (2.6)
Viral infection	3 (1.1)	2 (0.7)	6 (2.2)
Pain in extremity	2 (0.7)	3 (1.1)	6 (2.2)
Tremor	2 (0.7)	10 (3.7)	1 (0.4)

Cardio- and cerebrovascular events (CCV)
[from CTD 2.7.4 Summary of Clinical Safety Report, pages 187- 195]

The rate of CCV AEs for 12 month COPD safety population was similar between the indacaterol 300 µg, 600 µg, and formoterol populations and higher than seen in placebo (see Table 36 below).

However, for 12 month CCV SAEs (Table 37 below), the indacaterol 300 and 600 µg doses both had a higher rates of CCV SAEs either that for formoterol or placebo groups (approximately 2.5 times that for formoterol and up to 4 times that seen in placebo). Overall, the risk of CCV SAEs increased for the indacaterol groups and formoterol going from 6 months safety population to 12 months safety population (see Tables 36, 37 below).

Table 36 Comparison of rates of CCV AEs between 3 month, 6 month, and 12 month COPD safety population

	Inda 150 ug	Inda 300 ug	Inda 600 ug	formoterol	tiotropium	placebo
3 months	3.0%	3.5%	2.0%	2.0%	4.3%	2.4%
6 months	5.7%	5%	3.2%	3.9%	5.7%	3.6%
12 months	Not studied	6.6%	6.1%	6.5%	Not studied	3.9%

Table 37 Comparison of rates of CCV SAEs between 3 month, 6 month, and 12 month COPD safety population

	Inda 150 ug	Inda 300 ug	Inda 600 ug	formoterol	tiotropium	placebo
3 months	0.96%	0.94%	0.55%	0.18%	1.45%	0.66%
6 months	2.1%	1.4%	1.2%	0.5%	2.1%	1.0%
12 months	Not studied	3.4%	2.6%	1.4%	Not studied	0.9%

Reviewer's comment: The indacaterol 300 µg and 600 µg population has a 2 – 2.5 times higher risk of cardio- cerebrovascular (CCV) SAEs than formoterol after 12 months of treatment and 3 – 3.7 times higher risk than placebo.

The indacaterol groups had a higher risk of CCV than placebo after 6 months of treatment; the indacaterol 150 µg group had 2.1 times higher risk of CCV SAEs than placebo and indacaterol 300 µg and 600 µg had lower risk than 150 µg. At this point, the formoterol has a lower risk of CCV SAEs than placebo.

Diabetes mellitus related adverse events
[from CTD 2.7.4 Summary of Clinical Safety Report, pages 201-203]

In the 12 month COPD safety population, the diabetes mellitus related AEs are similar between the indacaterol 300 µg and 600 µg groups, which are slightly lower than that of formoterol. The placebo group had a lower rate than the indacaterol groups (1.8%, 1.4%, 2.3%, and 0.7% for indacaterol 300 µg, 600 µg, formoterol, and placebo, respectively). With the exception of one patient with hyperglycemia on indacaterol 600 µg group, none of these events were classified as serious.

Post-inhalation cough (PI cough)

Because subjects enrolled in earlier studies for indacaterol tended to cough post-inhalation, in the Phase III program, the pivotal studies B2334, B2335S, and B2346 were designed to proactively solicit information about any post-inhalation (PI) events that occurred at the clinic visits after dosing, as observed by the study staff. The post-inhalation cough events were not recorded as adverse events.

The incidence of PI cough is summarized for the COPD safety populations in terms of the percentage of attended visits at which patients experienced PI cough and the percentage of patients with PI cough, by visit.

A patient was said to be a PI-cougher if the number of visits with PI cough was at least 1 or R (whichever is greater), where R was defined as 20% of all the attended (post-baseline) visits, rounded to the nearest integer.

The characteristics of PI cough are described in terms of the association of PI coughers with:
• Age, sex, COPD severity, smoking history, ICS use, duration of COPD
• ≥20% FEV1 decrease from pre-dose to post-dose, by visit
• COPD exacerbation and bronchospasm AE
• Use of ACE-inhibitors and use of anti-cough medication
• Patient participation and withdrawals
• AEs leading to discontinuation from the study

Post-inhalation cough in COPD safety population
[from CTD 2.7.4 Summary of Clinical Safety Report, pages 291-292]

In the COPD 12-month safety population, the mean percentages of attended visits at which patients experienced PI cough in the indacaterol 300 µg (18.3%) and 600 µg (18.5%) groups were statistically significantly greater than in the placebo (1.6%) and formoterol (0.8%) groups:

• Indacaterol 300 µg od vs placebo: odds ratio 19.56, 95% CI 12.83 - 29.80 (p<0.001)
• Indacaterol 600 µg od vs placebo: odds ratio 18.66, 95% CI 12.26 - 28.40 (p<0.001)

Episodes wre not dose related as there was no significant difference between the indacaterol 600 and 300 µg groups in the percentage of attended visits at which patients had PI cough (odds ratio 0.95, 95% CI 0.77-1.18, p=0.667) (see Table 28 below).

Table 38 Post-inhalation cough: percentage of attended visits with PI cough and frequency of PI coughers in COPD safety population [from CTD 2.7.4 Summary of Clinical Safety Report, page 291, table 4-41]

	Ind 150 µg N=627	Ind 300 µg N=853	Ind 600 µg N=547	For N=556	Tio N=415	Pbo N=1055
Percentage of attended visits with PI-cough (%)						
n	627	853	546	556	415	1054
mean	17.0	19.9	18.4	0.9	0.8	2.2
sd	29.8	32.4	31.0	4.1	3.6	9.4
minimum	0	0	0	0	0	0
Q25	0	0	0	0	0	0
median	0	0	0	0	0	0
Q75	20.0	33.3	25.0	0	0	0
maximum	100.0	100.0	100.0	50.0	27.3	100.0
PI coughers - n (%)	185 (29.5)	253 (29.7)	156 (28.6)	10 (1.8)	9 (2.2)	51 (4.8)

Reviewer's comments: PI cough typically occurred within 15 seconds of inhalation and last for less than 15 seconds. The phenomenon of PI cough is not seen with other inhaled beta-agonists. The indacaterol groups have significantly higher rates of clinic visits with post-inhalation cough than placebo or active comparators. Indacaterol 300 µg has a higher rate of clinic visits with PI cough than indacaterol 150 µg. But there is no difference when going from indacaterol 300 µg to 600 µg. Although PI cough was not necessarily reported as an AE, there were more AEs of cough in indacaterol groups that placebo or active comparator groups. Despite that, PI coughers do not appear to have an increased rate of COPD exacerbation or bronchospasm.

Miscellaneous information about PI coughers

For majority of patients, the PI cough started within 15 seconds of inhalation and lasted for ≤ 15 seconds. There was no association of PI cough with a decrease in FEV1 ≥ 20 % post inhalation.

Women were 1.5 – 2 times more likely than men to be PI coughers. Patients who are current smokers and who use inhaled corticosteroid are slightly more likely to be PI coughers. Severity and duration of COPD, and age were not notable factors.

7.4.2 Laboratory Findings

[from CTD 2.7.4 Summary of Clinical Safety Report, page 212-]

Overview
Laboratory findings will focus mainly on those obtained from the three pivotal studies, B2335s, B2334, and B2346. The three supportive studies, with fewer patients and shorter duration, were briefly reviewed with no new safety signal identified. In the pivotal studies, laboratory evaluations were performed at baseline and at each of the subsequent study visits. Because of the known effects of Beta-2 agonists on potassium and glucose levels, these parameters were measured pre-dose and at 30 minutes and 1 hours post-dose to measure for any acute changes.

Hematology
COPD safety population
The rate of notable hemoglobin and hematocrit values are in a similar range for all the groups. For abnormal platelet values, indacaterol 300 µg had a slightly higher rate of patients with lower platelet counts (0%, 0.4%, 0.2%, 0%, 0.2%, and 0.2% for indacaterol 150 µg, 300 µg, 600 µg, formoterol, tiotropium, and placebo, respectively). The rate of elevated WBC are higher in the formoterol and placebo groups (0.8%, 1.1%, 0.4%, 2.2%, 0.7%, and 1.6% for indacaterol 150 µg, 300 µg, 600 µg, formoterol, tiotropium, and placebo, respectively).
Reviewer's comment: There are no significant hematology abnormalities in the COPD safety population.

Glucose- Acute changes: COPD safety population
Acute changes of glucose from 25 minutes pre-dose to 1 hour post-dose time points by visit in COPD safety population is summarized in the Table 39 below. There was a trend towards higher mean changes from baseline with increasing dose of indacaterol. There is also some increase seen with formoterol, but little change or negative change was seen in tiotropium or placebo. The pre-dose glucose mean for different groups was in the similar range.

Table 39 Acute changes in glucose (mmol/L): mean change from 25 min predoseto 1 h post-dose by visit in COPD safety population [from CTD 2.7.4 Summary of Clinical Safety Report, page 228, table 3-10]

Visit / Time		Ind 150 µg	Ind 300 µg	Ind 600 µg	For	Tio	Pbo
Day 1 *	n	615	831	534	537	405	1033
-25m	Pre-dose mean	5.30	5.41	5.58	5.55	5.47	5.52
1h	Mean change	0.16	0.27	0.35	0.21	0.07	-0.01
Week 2 *	n	381	799	507	517	381	758
-25m	Pre-dose mean	5.56	5.54	5.68	5.65	5.58	5.62
1h	Mean change	-0.04	0.10	0.14	0.07	-0.14	-0.12
Month 3 *	n	522	737	437	451	344	833
-25m	Pre-dose mean	5.50	5.50	5.70	5.56	5.40	5.55
1h	Mean change	0.03	0.09	0.22	0.14	0.05	-0.03
Month 6 †	n	311	690	344	346	318	604
-25m	Pre-dose mean	5.49	5.50	5.69	5.71	5.53	5.70
1h	Mean change	0.09	0.09	0.13	-0.00	-0.00	-0.20
Month 12 ††	n	-	318	307	303	-	282
-25m	Pre-dose mean	-	5.77	5.77	5.59	-	5.95
1h	Mean change	-	-0.08	0.13	0.15	-	-0.23

Includes studies B2334, B2335S and B2346.

Glucose- chronic changes: COPD safety population
For the summary of chronic changes from baseline to post-baseline time points, the mean changes from baseline for glucose were small among the indacaterol treatment groups. With few exceptions, mean changes were slightly greater in magnitude than those observed for placebo. [from Summary of Clinical Safety- Appendix 1- Table 3.4-1, pages 6505-6463].

Glucose- frequency of notable values
For elevated glucose values, there appears to be a mild dose related increase for the indacaterol groups compared to placebo (7.5%, 7.8%, 8.4%, 5.8%, 7.5%, and 6.7% for indacaterol 150 µg, 300 µg, 600 µg, formoterol, tiotropium, and placebo, respectively).

Reviewer's comment:

- *The indacaterol groups appear to have a mild chronic increase in glucose values as compared to placebo. When looking at acute change one hour post administration, the indacaterol groups show a mild dose related increase. Formoterol demonstrates similar mild degree of change, indicating a class effect.*
- *For evaluation of acute changes in glucose, only 30 minute and one hour post administration was measured. More time points would have provided useful information.*

Potassium
Potassium- Acute changes: COPD safety population
There were small dose related decreases in mean potassium from 25 minutes pre-dose to 1 hour post-dose for all visit groups that are not likely clinicall significant. The largest decrease

occurred on day 1, with a decrease of 0.11 mmol/L in the indacaterol 600 µg group (see Table 40 below). A decrease is also seen with formoterol, but not with tiotropium or placebo.

Table 40 Acute changes in potassium (mmol/L): mean change from 25 min predose to 1 h post-dose by visit in COPD safety population [from CTD 2.7.4 Summary of Clinical Safety Report, page 230, table 3-11]

Visit / Time		Ind 150 µg	Ind 300 µg	Ind 600 µg	For	Tio	Pbo
Day 1 *	n	610	826	526	533	401	1028
-25m	Pre-dose mean	4.48	4.45	4.45	4.42	4.48	4.45
1h	Mean change	-0.05	-0.06	-0.11	-0.09	0.00	-0.00
Week 2 *	n	377	793	508	513	384	754
-25m	Pre-dose mean	4.42	4.42	4.39	4.41	4.45	4.40
1h	Mean change	0.03	0.00	-0.02	-0.04	0.05	0.05
Month 3 *	n	520	730	439	449	342	834
-25m	Pre-dose mean	4.41	4.43	4.43	4.43	4.42	4.39
1h	Mean change	-0.01	-0.01	-0.02	-0.03	0.00	0.04
Month 6 †	n	309	686	341	345	316	592
-25m	Pre-dose mean	4.40	4.44	4.49	4.48	4.41	4.39
1h	Mean change	0.03	0.01	-0.03	-0.01	0.00	0.03
Month 12 ††	n	-	315	307	298	-	279
-25m	Pre-dose mean	-	4.50	4.49	4.50	-	4.43
1h	Mean change	-	-0.02	-0.04	-0.07	-	0.03

Includes studies B2334, B2335S and B2346.

Potassium- chronic changes: COPD safety population
Most of changes from baseline were small. Maximum and minimum changes from baseline were comparable among groups at all visits. [from Summary of Clinical Safety- Appendix 1- Table 3.4-1, pages 6505-6463]. The maximum amount of change was a decrease of 1.8 at 6 months, occurring in the fomoterol group. In general, changes from baseline were comparable among treatment groups regardless of age, race (Caucasians, other race subgroups were too small for evaluation), smoking history, and ICS use.

Potassium- frequency of notable values
For low potassium values, all the groups have a similar range (0.2%, 0.5%, 0%, 0%, 0.2%, and 0.4% for indacaterol 150 µg, 300 µg, 600 µg, formoterol, tiotropium, and placebo, respectively). For high potassium values, tiotropium has the highest rate, while indacaterol 600 ug has the lowest rate (1.3%, 1.5%, 0.4%, 0.5%, 2.2%, and 1.3% for indacaterol 150 µg, 300 µg, 600 µg, formoterol, tiotroipum, and placebo, respectively).

Reviewer's comment:

- *The indacaterol groups appear to have a mild acute change one hour post administration, the indacaterol groups show a small dose related reduction that is not likely to be clinically significant. Formoterol also demonstrates similar small degree of acute change, indicating a class effect. There is no notable chronic change in potassium.*
- *For evaluation of acute changes in potassium, only 30 minutes and one hour post-administration was measured. More time points would have provided useful information.*

Chemistry

COPD safety population

[from CTD 2.7.4 Summary of Clinical Safety Report, page 226]

The ranges of abnormal chemistry values are similar between the groups except for a few items. For GGT, indacaterol 600 µg had the highest rate (3.8%, 4.2%, 5.9%, 3.4%, 2.4%, and 4.3% for indacaterol 150 µg, 300 µg, 600 µg, formoterol, tiotropium, and placebo, respectively). For elevated BUN, indacaterol 300 µg had the highest rate (5.3%, 7.8%, 4.9%, 5.8%, 6.5%, and 6.2% for indacaterol 150 µg, 300 µg, 600 µg, formoterol, tiotropium, and placebo, respectively).

Reviewer's comment: Outside of glucose, there are no other notable trends in the chemistry abnormalities.

Liver safety
COPD safety population
[from CTD 2.7.4 Summary of Clinical Safety Report, page 242-3]

The percentages of patients from the indacaterol 300 µg and 600 µg groups with ≥1 elevation of liver chemistries are slightly higher than that of placebo and lower than that of formoterol. Patients from indacaterol 150 µg had slightly lower percentage than that of placebo (see Table 41 below). For individual liver chemistries, the indacaterol groups are for the most part slightly higher than placebo and lower than formoterol. There was no dose-related increase.

Table 41 Liver chemistries: incidence of newly occurring or worsening values any time post-baseline in COPD safety population [from CTD 2.7.4 Summary of Clinical Safety Report, page 243, table 3-18]

Liver chemistries Abnormality criteria	Ind 150µg N=627 n (%)	Ind 300µg N=853 n (%)	Ind 600µg N=547 n (%)	For N=556 n (%)	Tio N=415 n (%)	Pbo N=1055 n (%)
Total	626	850	546	554	415	1052
Patients with ≥1 elevation of liver chemistries	22 (3.51)	41 (4.82)	28 (5.13)	33 (5.96)	20 (4.82)	42 (3.99)
ALT (SGPT)						
>3 x ULN	6 (0.96)	11 (1.29)	3 (0.55)	7 (1.26)	5 (1.20)	9 (0.86)
>5 x ULN	2 (0.32)	2 (0.24)	0	1 (0.18)	4 (0.96)	2 (0.19)
>10 x ULN	0	0	0	1 (0.18)	2 (0.48)	1 (0.10)
>20 x ULN	0	0	0	0	0	0
AST (SGOT)						
>3 x ULN	8 (1.28)	13 (1.53)	9 (1.65)	14 (2.53)	5 (1.20)	11 (1.05)
>5 x ULN	2 (0.32)	3 (0.35)	1 (0.18)	3 (0.54)	3 (0.72)	2 (0.19)
>10 x ULN	0	1 (0.12)	0	0	1 (0.24)	0
>20 x ULN	0	0	0	0	0	0
ALT and/or AST						
>3 x ULN	11 (1.76)	19 (2.24)	10 (1.83)	16 (2.89)	6 (1.45)	16 (1.52)
>5 x ULN	3 (0.48)	4 (0.47)	1 (0.18)	4 (0.72)	5 (1.20)	4 (0.38)
>10 x ULN	0	1 (0.12)	0	1 (0.18)	2 (0.48)	1 (0.10)
>20 x ULN	0	0	0	0	0	0
Bilirubin						
>1.5 x ULN	0	12 (1.41)	4 (0.73)	9 (1.62)	5 (1.20)	10 (0.95)
>2 x ULN	0	4 (0.47)	0	3 (0.54)	1 (0.24)	5 (0.48)
Alkaline phosphatase						
>1.5 x ULN	12 (1.92)	19 (2.24)	14 (2.56)	12 (2.17)	9 (2.17)	21 (2.00)
(Bilirubin >1.5xULN) and (ALT and/or AST >3xULN)						
	0	3 (0.35)	0	1 (0.18)	0	2 (0.19)
(Bilirubin >2xULN) and (ALT and/or AST >3xULN)						
	0	2 (0.24)	0	1 (.18)	0	1 (0.10)
(ALP >2xULN) and (bilirubin >=2xULN) and (ALT and/or AST >3xULN)						
	0	2 (0.24)	0	0	0	0
Lab criterion for Hy's Law: (ALP <2xULN) and (bilirubin >=2xULN) and (ALT and/or AST >3xULN)						
	0	2 (0.24)	0	1 (0.18)	0	1 (0.10)

Includes studies B2334, B2335S and B2346.

Reviewer's Comment: in COPD patients, there was no indication of a hepatic safety signal.

7.4.3 Vital Signs

Notable vital signs in COPD safety population
The frequencies of patients with notable values any time post-baseline in the COPD safety population are shown in Table 42.

The percentage of patients with low clinically notable systolic blood pressure (SBP) values was similar and about 2% in all treatment groups except indacaterol 150 µg in which it was lower (0.5%) and formoterol where it was slightly higher (2.7%) [see Table 42].

There appears to be a dose related increase for high SBP in the indacaterol group (0.8%, 1.76%, 3.3% for indacterol 150 µg, 300 µg, and 600 µg, respectively). Indacaterol 300 µg has rate of high SBP (1.76%) in a similar range as formoterol (1.8%) whereas placebo (2.18%) has higher rate than formoterol, and indacaterol 600 µg has the highest rate (3.3%). The differences in mean data are not likely clinically significant.

There also appears to be a dose related increase for rate of low diastoloc blood pressure (DBP) in the indacaterol groups. Indacaterol 300 µg (1.53%) has higher rate than formoterol (1.44%) and placebo (1.23%). Indacaterol 600 µg has the highest rate (2.0%) [see table 42].

There is also a dose related increase for rate of high DBP in the indacaterol groups (0.96%, 1.06%, 1.8% for Indacaterol 150 µg, 300 µg, and 600 µg, respectively). Indacaterol 150 µg is similar to formoterol (0.9%), and indacaterol 600 µg and placebo had the highest rate (1.8%).

Reviewer's comment: There appears to be a mild dose related increase in proportion of patients with low and high diastolic pressure in the indacaterol groups but in general the data are similar to placebo.

Table 42 Vital signs: incidence of clinically notable values any time post baseline by parameter in COPD safety population [CTD 2.7.4 Summary of Clinical Safety Report, page 254, table 4-7]

Vital signs parameters Notable criteria	Ind 150 µg N=627 n (%)	Ind 300 µg N=853 n (%)	Ind 600 µg N=547 n (%)	For N=556 n (%)	Tio N=415 n (%)	Pbo N=1055 n (%)
Systolic BP						
Total	626	851	546	556	415	1054
Low: (<75 mmHg *) or (<=90 mmHg & decrease from BL by >=20 mmHg)	3 (0.48)	18 (2.12)	11 (2.01)	15 (2.70)	9 (2.17)	20 (1.90)
High: (>=180 mmHg & increase from BL by >=20 mmHg) or (>200 mmHg *)	5 (0.80)	15 (1.76)	18 (3.30)	10 (1.80)	7 (1.69)	23 (2.18)
Both **Low and High** criteria	0	0	0	0	0	1 (0.09)
Diastolic BP						
Total	626	851	546	556	415	1054
Low: (<40 mmHg *) or (<=50 mmHg & decrease from BL by >=15 mmHg)	5 (0.80)	13 (1.53)	11 (2.00)	8 (1.44)	4 (0.96)	13 (1.23)
High: (>=105 mmHg & increase from BL by >=15 mmHg) or (>115 mmHg *)	6 (0.96)	9 (1.06)	10 (1.80)	5 (0.90)	6 (1.45)	19 (1.80)
Both **Low and High** criteria	0	0	0	0	0	0
Pulse rate						
Total	626	852	546	556	415	1053
Low: (<40 bpm *) or (<=50 bpm & decrease from BL by >=15 bpm)	4 (0.64)	11 (1.29)	1 (0.18)	6 (1.08)	8 (1.93)	19 (1.80)
High: (>=120 bpm & increase from BL by >=15 bpm) or (>130 bpm *)	0	6 (0.70)	2 (0.37)	5 (0.90)	1 (0.24)	6 (0.57)
Both **Low and High** criteria	0	1 (0.12)	0	0	0	0

Includes Study B2334, Study B2335S and Study B2346.

7.4.4 Electrocardiograms (ECGs)

[from CTD 2.7.4 Summary of Clinical Safety Report, page 255]

Study methods of ECG and Holter Monitoring
In the phase III, pivotal studies B2334, B2335S and B2346, ECGs were performed 25 min pre-dose, 30 min post-dose, and 1 h post-dose at each visit as well as at screening and at the end of the study. ECGs were to include all 12 standard leads and a Lead II rhythm strip of at least 10-second duration.

Additionally, study B2339 was a single-center, randomized, multiple-dose, placebo-controlled and positive-controlled parallel group study to evaluate the effects of indacaterol (150, 300 and 600 µg) on cardiac safety in healthy subjects. The primary objective was to characterize the maximum mean prolongation of QTc Fridericia (QTcF) following multiple dose treatment with indacaterol 150 µg, 300 µg and 600 µg once daily for 14 days.

Continuous 24 hour ECG recordings (Holter monitoring) were performed in a subset of patients in COPD study B2335S and asthma safety study B2338. In COPD study B2335S, Holter

monitoring was undertaken at screening and after 2, 12 and 26 weeks of treatment in a subset of patients randomized to one of two indacaterol dose groups or placebo. In total 522 randomized patients were to be included to ensure Holter monitoring data on at least 450 patients (150 patients in each group) were available for at least 12 weeks of treatment.

ECGs were centrally reviewed by a cardiologist; the assessments included standard comments on normal/abnormal, rhythm, arrhythmia, conduction, morphology, myocardial infarction, ST segment, T wave and U wave observations.

Clinically notable QTc values were defined as >450 ms for males, >470 ms for females and >500 ms for both males and females. Notable changes in QTc were defined as 30 - 60 ms and > 60 ms increases from baseline or from pre-dose time points.

Measured ECG intervals (RR, PR, QRS, QT) and heart rate
In the COPD safety population baseline PR intervals at corresponding time points were similar between treatment groups with mean values between 159.0 and 161.5 ms. Post baseline there was an increase from baseline by approx. 1.5 ms over time irrespective of the treatment group. [from CTD 2.7.4 Summary of Clinical Safety Report, pages 257-8, table 4-8]

The duration of the baseline QRS interval at corresponding time points was similar between treatment groups with mean values between 90.6 and 91.9 ms. Post-baseline there was an increase over time irrespective of the treatment group. By the end of the 12 months, increase from baseline has ranged from 1.3 to 2.5 msec higher than the difference from on day 1. [from CTD 2.7.4 Summary of Clinical Safety Report, pages 258-259, table 4-9]

The baseline ventricular rate at corresponding time points was similar between treatment groups with mean values of between 71.0 and 73.2 beats/min. Post baseline there was a decrease in the ventricular rate of up to 2 beats/min for all treatments, which generally increased over time. [from CTD 2.7.4 Summary of Clinical Safety Report, page 259-260, table 4-10]

QTc central Trend
COPD safety population
The mean QTcF values at baseline were similar across treatments ranging from 404.1 to 407.1 ms. The mean difference from baseline across all time points and doses ranged from -0.7 to 4.6 ms. For each indacaterol dose there was an increase in the QTcF duration over time, which was generally the largest at the last time point, without a dose response relationship. There is less of an increase in the placebo group, the largest amount of change is 1.5 ms. [from CTD 2.7.4 Summary of Clinical Safety Report, pages 262-263, table 4-14].

There was a statistically significant prolongation of QTcF for indacaterol doses of 300 and 600 μg once daily versus placebo at Day 1, 1 hour post-dose which was sustained during most of the subsequent visits up to one year (see Table 43). In comparison to placebo the magnitude of the effect was between 1.1 and 2.9 ms (300 μg) and 1.3 and 3.5 ms (600 μg). [from CTD 2.7.4 Summary of Clinical Safety Report, page 263-264, table 4-15].

Table 43 Summary statistics of QTc Fridericia (ms) by visit and time point in COPD safety population. [CTD 2.7.4 Summary of Clinical Safety Report, page 263, table 4-14].

				Baseline	Endpoint	Change from baseline	
Treatment	Visit	Time point	N	Mean (ms)	Mean (ms)	Mean (ms)	SD (ms)
Ind 150 µg	Day 1	30 min	408	406.1	406.9	0.9	9.92
		1 hour	622	407.1	408.2	1.1	10.28
	Week 2	1 hour	387	406.0	406.2	0.2	13.29
	Month 3	1 hour	533	406.5	411.2	4.6	14.26
	Month 6	1 hour	321	405.4	408.7	3.3	14.30
Ind 300 µg	Day 1	30 min	831	406.7	408.0	1.3	10.36
		1 hour	830	406.6	407.7	1.1	10.46
	Week 2	1 hour	800	406.6	407.4	0.8	13.51
	Month 3	1 hour	736	406.4	408.3	1.9	13.65
	Month 6	1 hour	688	406.5	409.0	2.5	14.33
	Month 12	1 hour	320	406.2	409.3	3.1	14.08
Ind 600 µg	Day 1	30 min	531	405.1	407.6	2.4	10.20
		1 hour	528	405.2	408.3	3.1	11.14
	Week 2	1 hour	508	404.9	406.1	1.2	13.10
	Month 3	1 hour	434	404.6	406.0	1.4	14.42
	Month 6	1 hour	339	404.1	405.9	1.9	13.21
	Month 12	1 hour	311	404.2	408.3	4.2	14.65
Placebo	Day 1	30 min	826	406.0	405.3	-0.7	10.17
		1 hour	1030	406.8	406.9	0.1	10.25
	Week 2	1 hour	764	405.5	405.3	-0.3	13.31
	Month 3	1 hour	838	406.6	407.1	0.4	13.84
	Month 6	1 hour	604	405.2	406.7	1.5	14.77
	Month 12	1 hour	280	404.7	405.3	0.6	14.71

Baseline defined as the averaged values at 25 min pre-dose of baseline visit

Acute effect on QTcF
In the COPD safety population, the acute effect on the QTcF interval comparing 25 min before versus 1 hour after study drug administration was larger at each visit on each of the active treatments compared to placebo. There was no dose relationship or time effect. [From CTD 2.7.4 Summary of Clinical Safety Report, page 265, table 4-16].

There were no QTcF increases by >60 msec in patients receiving indacaterol .Acute prolongations by 30-60 msec were seen in 0.1 to 1.5% of patients on indacaterol, and in 0.4 to 0.8% on placebo. Indacaterol data for QTcF increases of 30-60 msec pre-dose to 1 hour post-dose at Day 1 and Month 3 demonstrated a positive dose-response relationship.
[from CTD 2.7.4 Summary of Clinical Safety Report, page 267, table 4-20].

Results of thorough QTc study B2339Holter monitoring (Applicant's Conclusion)
[from CTD 2.7.4 Summary of Clinical Safety Report, page 278].

Multiple daily doses of indacaterol (150, 300 and 600 µg) resulted in mean maximum time matched differences versus placebo that were lower than 5 ms for delta QTcF vs. baseline.

The upper limit of the 90% CIs were below 10 ms for all time matched comparisons. Treatment comparisons are summarized in Table 44. Of note is that the review of the QT study by the clinical pharmacology team is pending at the time of this review.

Table 44 Thorough QTc Study B2339: Mean (90% confidence interval) of difference in change from baseline in QTcF (ms) versus placebo on Day 14 by post-dose time [from CTD 2.7.4 Summary of Clinical Safety Report, page 278, table 4-31].

Hours post-dose	Ind 150 µg vs. pbo	Ind 300 µg vs. pbo	Ind 600 µg vs. pbo	Placebo/moxifloxacin 400 mg vs. pbo
0.167	1.62 (-0.34, 3.57)	1.26 (-0.64, 3.16)	1.56 (-0.83, 3.94)	1.84 (-1.32, 5.01)
0.333	2.23 (0.34, 4.12)	2.24 (0.45, 4.03)	2.84 (0.72, 4.95)	3.74 (0.97, 6.51)
0.667	2.12 (0.21, 4.03)	1.54 (-0.41, 3.49)	1.40 (-0.96, 3.76)	8.25 (5.04,11.47)
1.000	0.89 (-1.12, 2.89)	1.05 (-0.99, 3.09)	0.70 (-1.72, 3.12)	10.76 (7.60,13.93)
2.000	2.66 (0.55, 4.77)	2.98 (1.02, 4.93)	2.18 (-0.25, 4.61)	13.90 (10.58,17.22)
3.000	0.48 (-1.53, 2.50)	1.06 (-0.91, 3.03)	2.14 (-0.19, 4.48)	11.12 (8.08,14.15)
4.000	0.36 (-1.82, 2.53)	0.29 (-1.76, 2.33)	1.17 (-1.26, 3.59)	11.91 (8.57,15.24)
6.000	0.46 (-1.70, 2.62)	1.21 (-0.64, 3.05)	3.34 (0.86, 5.82)	9.25 (5.93,12.57)
12.000	0.44 (-1.69, 2.57)	-1.24 (-3.26, 0.79)	-1.62 (-4.23, 0.98)	4.24 (0.82, 7.67)
24.000	1.88 (0.12, 3.64)	0.67 (-1.15, 2.49)	-0.08 (-2.27, 2.11)	7.77 (4.73,10.82)

24 hour Holter monitoring studies
[from CTD 2.7.4 Summary of Clinical Safety Report, page 279-284].

In Study B2335S and Study B2338 a subset of COPD and asthma patients, respectively, underwent continuous 24-hour ECG recording to provide further information on cardiac function and to monitor for occurrences of short lived arrhythmias.

For B2335, monitoring was done for week 2, week 12, and week 26. [Study B2335S Supplementary Report 1, table 14.3-6.3 and table 14.3-6.4].

For B2338, No evidence of a significant difference between indacaterol 300 or 600 µg and salmeterol 50 µg in the development of arrhythmic events was found in the subset of asthma patients that underwent Holter monitoring.

7.4.5 Special Safety Studies/Clinical Trials

The safety and adverse event profile of Beta-2 agonists, including LABAs such as indacaterol, have been well described and include cardiovascular effects such as tachycardia and QT prolongation, nervous system effects such as anxiety, nervousness, and tremor, and metabolic effects including hypokalemia and hyperglycemia. As such, these Beta-2 agonist class effect safety parameters were incorporated into the clinical studies performed to support the NDA. The review of these potential safety concerns is, therefore, incorporated into the appropriate section of the NDA safety section, e.g., Adverse Events, Vital Signs, Laboratory, etc.

One specific study deserves mention; study B2339, single-center, randomized, multiple-dose, placebo-controlled and positive-controlled parallel group study to evaluate the effects of indacaterol (150, 300 and 600 µg) on cardiac safety in healthy subjects. The primary objective was to characterize the maximum mean prolongation of QTc Fridericia (QTcF) following multiple dose treatment with indacaterol 150 µg, 300 µg and 600 µg once daily for 14 days. A total of 404 subjects were randomized to the study. The results of study B2339 pertaining to cardiovascular safety are incorporated into Section 7.4.4 (ECGs).

7.4.6 Immunogenicity

There were no notable issues regarding hypersensitivity reactions for indacaterol. One patient in the formoterol group experienced an SAE reported as severe shock, and one placebo patient had swollen tongue reported as an SAE [Summary of Clinical Safety Report -Appendix 1-Listing 2.1-2b].

7.5 Other Safety Explorations

There are no other safety explorations.

7.5.1 Dose Dependency for Adverse Events

For the 12 month COPD safety group, there is a dose related increase in rate of tremor for the indacaterol groups, although the incidence is low (0.003%, 0.028%, 0.017%. and 0.006% for indacaterol 300 µg, 600 µg, formoterol, and placebo, respectively). [From Summary of Clinical Safety Report, page 87].

In B2338 asthma study, there is a dose related increase in asthma SAEs for the indacaterol groups (0.7%, 1.1%, 0% for indacaterol 300 µg qd, 600 µg qd, and salmeterol, respectively). There is also a dose related increase in all SAEs for the indacaterol groups (1.9%, 4.1%, and 3.0% for indacaterol 300 µg qd, 600 µg, and salmeterol, respectively). [Study B2338 page 102]

Moreover, for B2338 asthma study, there is a dose related increase in asthma AEs for indacaterol groups (11.6%, 15.7%, and 14.9% for indacaterol 300 µg, 600 µg, and salmeterol, respectively). There is also a dose related increase in muscle spasm, tremor, upper respiratory infection, and oropharyngeal pain type adverse events. In general, there is a dose related increase in all AEs for the indacaterol groups. [Study B2338, page 98]

7.5.2 Time Dependency for Adverse Events

The analysis of adverse events after 6 months of exposure showed that the incidence of adverse events with onset in the first 13 weeks of treatment was greater than the incidence for those with onset >13 weeks after the first dose for all treatment groups. It appears that most of cough and ventricular tachycardia adverse events occurred in the first 4 weeks of treatment. Most of muscle

spasm adverse events occurred in the 4-13 week treatment period. [From Summary of Clinical Safety Report, pages 124- 126].

In addition, increase in cardio- cerebrovascular (CCV) AEs and SAEs in the indacaterol treatment groups and formoterol as compared to placebo are not seen until after 6 – 12 months of exposure.

7.5.3 Drug-Demographic Interactions

Analysis of data from the three pivotal studies (B2335s, B2334, and B2346) showed that at 3 months, there is little difference in adverse events between the subgroups of age, gender, COPD severity, inhaled corticosteroid (ICS) users, smoking status in different treatment groups. The only exception is that woman reported higher rates of adverse events (54%- 60% for women and 40%- 54% for men).

However, at 6 months and 12 months, the rates are different for some subgroups across the treatment groups. Women, age ≥ 65, ICS users, ex-smokers in general had higher rates of adverse events than men, age < 65, non-ICS users, and current smokers. [From Summary of Clinical Safety Report, pages 111-122].

7.5.4 Drug-Disease Interactions

In the COPD 6-month safety population the overall frequency of diabetes related events was approximately twice as high in the indacaterol groups compared to the placebo group (1.20%, 1.29%, 1.46%, 0.90%, and 0.59% for indacaterol 150 µg, 300 µg, 600 µg, formoterol, and placebo, respectively) [From summary of clinical safety, page 202].

In the 6-months safety population the frequency of hypertension related events was lower in the indacaterol groups than in the placebo group (1.2%, 1.6%, 1.1%, 1.4%, and 2.4% for indacaterol 150 µg, 300 µg, 600 µg, formoterol, and placebo, respectively).

In the 6- month safety population, cardio- cerebrovascular (CCV) AEs and SAEs occurred at a higher rate with the indacaterol treatment groups than placebo. On indacaterol 150 and 300 µg, CCV AEs were only reported in patients with at least one CV risk factor, while patients without CV risk factors did not report any CCV events. On those doses, the frequency of CCV events was dependent on the number of CV risk factors; e.g. on 150 µg od the number of CCV events was 0%, 3.0%, 5.6% and 8.2% with 0, 1, 2 and ≥3 CV risk factors. On indacaterol 600 µg and placebo the frequency of CCV events was independent of the number of pre-existing CV risk factors.

7.5.5 Drug-Drug Interactions

Drug interaction studies were carried out using potent and specific inhibitors of CYP3A4 and P-gp (i.e. ketoconazole [Study A2311], erythromycin [Study B2220] and verapamil [Study

B2216]). Verapamil was used as the prototypic inhibitor of P-gp and resulted in 1.4- to 2-fold increase in AUC and 1.5-fold increase in Cmax. Co-administration of erythromycin resulted in an increase of 1.4- to 1.6-fold for AUC and 1.2-fold for Cmax. Combined inhibition of P-gp and CYP3A4 by the very strong dual inhibitor ketoconazole caused a 2-fold and 1.4-fold increase in AUC and Cmax respectively. Taken together the data suggest that systemic clearance is influenced by modulation of both P-gp and CYP3A4 activities and that the 2-fold AUC increase caused by the strong dual inhibitor ketoconazole reflects the impact of maximal combined inhibition.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

This section is not applicable as human carcinogenicity studies have not been performed with indacaterol and cancers reported during relatively short clinical trials (pivotal trials 12-24 weeks, safety study 1 year) were few and likely related to co-morbid conditions/risk factors such as cigarette smoking.

7.6.2 Human Reproduction and Pregnancy Data

[From CTD 2.7.4 Summary of Clinical Safety Report, page 305-306].

There were no pregnancies reported in COPD patients in the indacaterol studies, therefore no clinical data on exposed pregnancies in COPD patients are available.

Seven pregnancies have been reported during the indacaterol studies in asthmatics, one in a patient on indacaterol 800 µg once daily in the phase II [Study A2210], one in a patient who completed the 5-way crossover phase II [Study A2208] and 5 in patients in the phase III [Study B2338]: 1 patient on indacaterol 300 µg once daily, 3 patients on indacaterol 600 µg once daily, and one patient on salmeterol 50 µg bid. These pregnancies resulted in delivery of three normal babies. Two underwent abortions, one involved an ectopic pregnancy that was successfully operated upon. One was lost to follow up.

7.6.3 Pediatrics and Assessment of Effects on Growth

All clinical trials were conducted in adults. There were no growth assessments made.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

In COPD patients, single doses of 3000 µg were associated with a moderate increase in pulse rate, systolic blood pressure increase and QTc interval [Study B2202]. An overdose of indacaterol is likely to lead to exaggerated effects typical of β2-adrenergic stimulants i.e.

tachycardia, tremor, palpitations, headache, nausea, vomiting, drowsiness, ventricular arrhythmias, metabolic acidosis, hypokalemia and hyperglycemia.

Indacaterol has no abuse potential. No specific studies of the withdrawal and rebound effects of indacaterol have been performed.

7.7 Additional Submissions / Safety Issues

There are no additional submission/ safety issues.

8 Postmarket Experience

To date, indacaterol has not been approved for treatment of any medical condition. There is no postmarketing experience.

9 Appendices

9.1 Literature Review/References

No literature was reviewed for this application.

9.2 Labeling Recommendations

A labeling review was not performed for this submission as it was determined that the dose ranging program was inadequate and the regulatory action is to not approve during this review cycle (Complete Response).

9.3 Advisory Committee Meeting

This application was not discussed at an advisory committee meeting as the regulatory action was to not approve the application (Complete Response) due to inadequate dose selection and the presence of a cerebro-cardiovascular safety signal.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22383	ORIG 1	NOVARTIS PHARMACEUTICALS CORP	INDACATEROL

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

/s/

LYNNE H WU
08/25/2009

ANTHONY G DURMOWICZ
08/25/2009

MEDICAL OFFICER REVIEW

Division of Pulmonary and Allergy Products (HFD-570)

Application #:	NDA 22,383	**Application Type:**	NDA
Sponsor:	Novartis	**Proprietary Name:**	Arcapta Neohaler
Category:	Long acting beta agonist	**USAN Name:**	indacaterol
Reviewer:	Lynne H. Wu, M.D.	**Route of Administration:**	inhalation
Medical Team Leader:	Anthony Durmowicz, M.D.	**Review Date:**	September 24, 2009

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type	Comments
April 14, 2009	April 16, 2009	120 day safety update	

NDA 22-383 REVIEW ADDENDUM: This is a 120 day safety update review for NDA 22,383. Indacaterol maleate 150 µg given once daily for treatment of bronchospasm associated with COPD, delivered via single dose dry powder inhaler, was submitted for NDA review on December 17, 2009.

Description of the studies

The cut-off date for SAEs included in the original submission was Oct 1, 2008. The 120 day safety update report includes SAEs and deaths reported between October 2, 2008 and February 1, 2009. There were no new clinical studies completed during the reporting period, therefore, the new safety data comes from 12 ongoing clinical studies (see table 1 for the description of the studies).

Five of the 12 ongoing studies reached database lock by February 1, 2009 and therefore in SAE listings, treatment is unblinded for the patients in studies. These studies were generally of short duration (1-14 days). Following is a brief description of the study design and safety assessment for the unblinded data.

QAB149 B2331: This was a R, DB, DD, placebo-controlled, 3-period incomplete block, multidose crossover study to determine the effect on lung function of indacaterol (150 µg and 300 µg od) in 148 patients with moderate to severe COPD using tiotropium (18 µg od) as an active control. Each arm consisted of 2 weeks of treatment with 2 weeks of washout period in between.

There were 6 SAEs reported, including 1 death secondary to MI, 4 COPD exacerbations and 1 CVA. Due to the crossover nature of the study, some of the patients have received more than one treatment prior to the onset of SAE.

The followings are descriptions of the events. 1) One 65 year old male who received all three arms of treatment died of acute myocardial infarction (symptom onset occurred two days after completion of treatments). 2) One 79 year old male who received the indacaterol arm was then hospitalized with pneumonia and COPD exacerbation. 3) One 74 years old male who received the tiotropium arm was then was hospitalized with COPD exacerbation. 4) One 77 years old male who received the tiotropium arm and placebo arm was then was hospitalized with COPD exacerbation. 5) One 74

years old male who received the indacaterol arm was then was hospitalized with COPD exacerbation. 6) One 77 years old male who received the indacaterol arm and the tiotropium arm was then hospitalized with CVA.

QAB149 B2102: A randomized, double-blind, 3-way crossover study to compare the systemic exposure of multiple inhaled doses of mometasone furoate and indacaterol when administered alone or in fixed dose combination via MDDPI Twisthaler™ device in 60 healthy subjects. No cases of SAEs were reported

QVA149 A2203: A randomized, double-blind, 3-way crossover study to compare the systemic exposure of multiple inhaled doses of mometasone furoate and indacaterol when administered alone or in fixed dose combination via MDDPI Twisthaler™ device in 60 healthy subjects. There were 3 types of treatments with14 days per treatment. No case of SAEs were reported

QVA149 A2204: A randomized, double-blind, 3-way crossover study to compare the systemic exposure of multiple inhaled doses of mometasone furoate and indacaterol when administered alone or in fixed dose combination via MDDPI Twisthaler™ device in 140 healthy subjects. There were 4 types of treatments with 7 days per treatment. There was one SAE report of a 71 years old woman who had humeral bone fracture following a fall.

QMF149 A2102: A randomized, double-blind, 3-way crossover study to compare the systemic exposure of multiple inhaled doses of mometasone furoate and indacaterol when administered alone or in fixed dose combination via MDDPI Twisthaler™ device in 60 healthy subjects. No cases of SAEs were reported

The safety data from the unblinded studies are of limited usefulness due to the short treatment duration, small patient population, and the crossover study design. Study QAB149 B2331 had the most number of SAEs due to the older COPD population with co- morbid diseases. Overall, the safety data did not point to new safety signals.

For the other 7 ongoing studies, treatment remains blinded at the cut-off date.

The studies included here from the QVA149A and QMF149A programs are evaluating combination therapies of indacaterol with glycopyrronium bromide (NVA237) and mometasone furoate, respectively. However, they have indacaterol monotherapy arms which contribute relevant safety data to the QAB149B program.

Ongoing studies QAB149B2335SE and QAB149B2336 are large, multinational, multicenter, double-blind, placebo-controlled, parallel group studies of similar design to the completed pivotal studies QAB149B2334, QAB149B2335S and QAB149B2346 in the original submission. Study QAB149B2335SE is a 26-week, placebo controlled, extension study to the completed core study QAB149B2335S in patients with moderate to severe COPD. Patients who had previously been randomized to indacaterol 150 µg, indacaterol 300 µg or placebo arms in Stage 2 of the core study, and who completed 26 weeks treatment continue to receive the same treatment (in a double-blind fashion) for an additional 26 weeks during the extension phase. The active control arms (formoterol and tiotropium) in the core study are not carried forward into the extension study.

Study QAB149B2336 is a 26-week, multicenter, double-blind, double-dummy, placebo controlled, parallel group study to assess the efficacy and safety of indacaterol (150 µg o.d.) in patients with COPD, using salmeterol (50 µg b.i.d.) as an active control.

Additional safety data

There were two deaths which occurred in this interval of patients in ongoing study QAB149B2336: 1) a 68 year old male died of sudden cardiac arrest on study day 171 and 2) an 80 year old male hospitalized with acute respiratory failure, pulmonary edema and chronic renal failure on study day 159 and died 22 days later of multi-organ failure. In addition, there was one death in ongoing study QAB149B2335SE which occurred 3 days before the beginning of the reporting interval for this safety update. However, it was not included in the original submission, therefore it is included here. It concerned a 76 year old male, who died of a possible myocardial infarction on study day 63. For each of these deaths, the treatment was not unblinded so it is not known to which study group these patients belonged.

There were 48 new non-fatal SAE cases reported in ongoing blinded studies. There were 5 in study QAB149B1302, 3 in study QAB149B2311, 4 in study QAB149B2331, 12 in study QAB149B2335SE and 24 in study QAB149B2336. For most of these events, the treatment was remained blinded. The SAEs are consistent with an older population with medical co-morbidities and included events such as multiple COPD exacerbations, some pneumonias, few myocardial infarction, tonsillitis, digoxin induced bradycardia, bone fracture, and others.

Conclusion

Overall, review of these new safety data does not change the conclusions made after reviewing the safety data from the original submission.

Table 1 Ongoing clinical studies

Indication Study	Study design and objectives	Planned no. of subjects	Treatment duration ‡	Investigational drug and dose	Control, type and dose
COPD: moderate to severe according to GOLD guidelines using SDDPI (Concept1 device)					
QAB149 B1302	MD, DB, PG, E&S for registration in Japan	336 (112/group)	12 weeks	Ind 150 µg od Ind 300 µg od	placebo
QAB149 B2311	MD, DB, DD, 2 period complete block crossover, exercise endurance profiling, E&S	83	21 days *	Ind 300 µg od	placebo
QAB149 B2331 (unblinded)	MD, DB, DD, 3 period incomplete block crossover, lung function profiling, E&S, PK	148	14 days *	Ind 150 µg od Ind 300 µg od	placebo tiotropium 18 µg od
QAB149 B2333	MD, DB, PG, E&S in mainly Chinese patients	558 (186/group)	26 weeks	Ind 150 µg od Ind 300 µg od	placebo

Indication Study	Study design and objectives	Planned no. of subjects	Treatment duration ‡	Investigational drug and dose	Control, type and dose
QAB149 B2335SE	MD, DB, DD, PG, E&S Extension study	eligible patients from core study B2335S (415 enrolled as of 01-Feb-2009)	26 weeks	Ind 150 µg od Ind 300 µg od	placebo
QAB149 B2336	MD, DB, DD, PG, pivotal E&S	972 (324/group)	26 weeks	Ind 150 µg od	placebo salmeterol 50 µg bid
QAB149 B2349	MD, DB, DD, PG, pivotal E&S	1084 (542/group)	12 weeks	Ind 150 µg od	salmeterol 50 µg bid
Asthma					
QAB149 B2102 (unblinded)	SD, DB, crossover, S&T, indacaterol salt (maleate, xinafoate and acetate) dependence of cough in patients with mild to moderate persistent asthma using SDDPI (Aerolizer®)	100	1 day *	Indacaterol maleate 400 µg Indacaterol xinafoate 400 µg Indacaterol acetate 400 µg	placebo
COPD or healthy subjects: Combination therapy studies with indacaterol monotherapy arm					
QVA149 A2203 (unblinded)	DB, PG, high dose safety and PK evaluation in COPD using SDDPI	250	14 days	Ind 300 µg od Ind 150, 300 and 600µg+Gly 100µg od (3 FDC arms)	placebo
QVA149 A2204 (unblinded)	DB, 4 period complete block crossover, medium dose E&S evaluation and PK in COPD using SDDPI	140	7 days *	Ind 300 µg od Ind 600 µg od Ind 300 µg+Gly 50 µg od (FDC)	placebo
QVA149 A2103	OL, 3 period crossover evaluation of systemic exposure of Gly and Ind alone or in FDC in healthy subjects using SDDPI	42	14 days *	Ind 150 µg od Gly 50 µg od Ind 110 µg+Gly 50 µg od (FDC)	none
QMF149 A2102 (unblinded)	DB, 3 period crossover, evaluation of systemic exposure of Mom and Ind alone or in FDC in healthy subjects using MDDPI (Twisthaler®)	60	14 days *	Ind 500 µg od Mom 800 µg od Ind 500 µg+Mom 800 µg od (FDC)	none

‡ Treatment duration is the planned follow-up period while on study drug.
For crossover studies: * duration of each treatment excluding washout period
Ind = indacaterol maleate, Gly = glycopyrronium bromide (NVA237), Mom = mometasone furoate
SDDPI = single dose dry powder inhaler, MDDPI = multiple dose dry powder inhaler, SD = single dose, MD =

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22383	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	Arcapta Neohaler

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/s/

LYNNE H WU
09/25/2009

ANTHONY G DURMOWICZ
09/25/2009

MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION #:	22-383	**APPLICATION TYPE:**	NDA
SPONS0R:	Novartis	**PROPRIETARY NAME:**	Arcapta™ (b) (4)
INVESTIGATOR:	Multiple	**USAN NAME:**	Indacaterol maleate
CATEGORY:	Long acting beta agonist	**ROUTE:**	Oral Inhalation
MEDICAL OFFICER:	Lynne H. Wu, MD	**REVIEW DATE:**	2009

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type	Comments
December 15, 2008	December 18, 2008	NDA	

RELATED APPLICATIONS

Document Date	Application Type	Comments

REVIEW SUMMARY:

This is a 45-day Filing Review of NDA 22-383. This NDA is submitted in support of the use of the bronchodilator, indacaterol maleate inhalation powder, 150 µg or 300 µg, once daily for the long term maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. Indacaterol maleate is a long-acting beta-2 agonist (LABA). The Sponsor has identified three pivotal clinical trials and three supportive profiling studies. The submission appears complete enough to allow for a further more complete review, and is therefore considered "fileable." Upon review of the efficacy, safety, dose and dosing interval data this submission, the Division will decide whether to present this NDA to the Pulmonary-Allergy Drugs Advisory Committee. Audits of clinical centers will be requested of the Division of Scientific Investigations.

OUTSTANDING ISSUES:

None.

RECOMMENDED REGULATORY ACTION

___X__ **FILEABLE** _____ **NOT FILEABLE**

REVIEWERS

Medical Reviewer: Lynne H. Wu, MD

Team Leader: Anthony G. Durmowicz, MD

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I. General Information

Drug Substance

Trade Name:	Arcapta™ (b) (4)
US Adopted Name:	Indacaterol maleate
International Non-proprietary Name:	Indacaterol maleate
Molecular Formula:	$C_{24}H_{28}N_2O_3 \cdot C_4H_4O_4$
Molecular Weight:	508.56
Manufacturer:	Novartis Pharma SteinAG Schaffhauserstrasse 4332-Stein Switzerland

This NDA is submitted in support of the use of indacaterol maleate inhalation powder, 150µg or 300µg, once daily for the long-term maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. Indacaterol maleate is a long-acting beta-2 agonist (LABA), which binds to beta-adrenergic receptors in the lung resulting in smooth muscle relaxation with resultant bronchodilation.

As of the NDA cutoff date, a total of 45 clinical trials have been completed, and five trials are ongoing. Three of the trials are proposed as being “pivotal”, and three are described as supportive “profiling” studies.

II. Background and Rationale

Indacaterol maleate is a novel, long-acting β2-agonist single dose dry powder inhaler intending to provide once daily dosing which would have an advantage over the currently available twice daily dosing long acting beta agonist, salmeterol and formoterol. It may have efficacy superior to the current standard bronchodilators. Thus, it may offer a new option besides other LABAs and anticholinergics for the treatment of COPD.

III. Regulatory and Foreign Marketing History

A. Regulatory History

Indacaterol maleate is a single dose dry powder inhaler developed under IND 48,649 which was submitted on February 13, 2004. Initially, the drug was being studied for asthma. However, in accordance with current Global Initiative for Asthma (GINA) guidelines that recommend the use of a LABA only in combination with an inhaled glucocorticosteroid, indacaterol as a monotherapy is not being developed as a stand-alone product for asthma.

Reviewer's Comment: The decision not to file the NDA for the asthma indication may have been influenced by the discussion at the combined pulmonary/allergy, pediatric, and surveillance/epidemiology advisory committee meeting held in December 2008 during which time the safety of LABA use in children and adults with asthma was extensively discussed.

The sponsor also initially developed indacaterol in a multiple dose dry powder inhaler format, initially using the Certihaler delivery system, the system developed for use with another LABA, Foradil. However, on February 2, 2006, the sponsor submitted a General Correspondence reporting difficulties with the Foradil Certihaler in Europe. The Foradil Certihaler was voluntarily recalled in Germany and Switzerland due to problems with excess powder release from device leading to overdose. The sponsor decided not to pursue the multiple dose format and transferred all of their DPI programs to the single dose format.

An End-of-Phase-2 meeting was held on October 10, 2006. A special protocol assessment was done on February 2, 2007. Pre-NDA meeting was held on March 7, 2008.

B. Foreign Marketing History

As of March 2009, indacaterol maleate is not being marketed in any country.

IV. Items Required for Filing and Reviewer Comments

A. Necessary Elements (21 CFR 314.50)

The following is the list of the necessary elements for an NDA and their location within the electronic submission.

- application form (FDA 356h) -- present -- located in m1\ us\ 356h.pdf
- Investigator debarment certificate -- present -- located in m1\ us\ debar.pdf
- Financial disclosure -- present -- located in m1\ us\ financial-cert.pdf
- Statement of good clinical practice – present -- located in module 2\ 2.5\ clinical overview.pdf
- Environmental assessment -- present -- located in m1\ 1.12.14
- Proposed label -- present -- located in m1\ 1.12.14
- Integrated summary of efficacy -- present -- located in m2\ 27-clin-sum\ summary-of-clinical-efficacy.pdf
- Integrated summary of safety -- present -- located in m2\ 27-clin-sum\ summary-of-clinical-Safety.pdf
- Statement that all clinical studies -- present -- located in individual study reports were conducted in accordance to IRB and informed consent procedure
- Statistical analysis -- present -- N21912\ clinstat\ clintoc.pdf
- Pediatric use section -- waived -- us\ pedwaiver.pdf
- Case report tabulation -- present -- N21912\ crftoc.pdf
- Case report forms -- present -- N21912\ crftoc.pdf (for patients who died or did not complete study)
- Patient information -- present -- m1\ us\ pat-info.pdfN21912\ other\ patcert.pdf

B. Decision

The submission appears adequate from a clinical standpoint to allow for further review, and is therefore fileable.

V. Preliminary Review of Package Insert

(b) (4)

The label also states that indacaterol maleate is not for acute relief of bronchospasm in COPD. It is not for asthma. Black box warning for asthma is given. Emphasis of not swallowing the capsule is also given.

Reviewer's comment: Division of Medication Error Prevention and Analysis (DMEPA) from office of surveillance and epidemiology has voiced concerns that that the name "Arcapta (b) (4) (b) (4)

VI. Clinical Studies

This clinical program contains 3 pivotal studies and 3 supportive profiling studies. There are also 44 other smaller studies evaluating pharmacokinetic, pharmacodynamic, efficacy and safety issues. Fourteen of smaller studies are conducted in asthma patients; however, in accordance with current Global Initiative for Asthma (GINA) guidelines that recommend the use of a LABA only in combination with an inhaled glucocorticosteroid, indacaterol as a monotherapy is not being developed as a stand-alone product for asthma.

A. Pivotal Studies

As discussed above, 3 "pivotal" studies are submitted (see summary table below). These include a dose ranging and efficacy study of 26 weeks duration (B2335s), a 52 week study in which indacaterol at doses of 300 and 600 µg were compared to placebo and formoterol administered teice daily as an active comparator (B2334), and a 12 week study in which indacaterol at a dose of 150 µg was compared to placebo only (B2346).

Study B2335s, the combined dose ranging and efficacy study was a randomized, double blind, double dummy, placebo controlled, adaptive, seamless, parallel group study of 1665 patients in 334 centers in 11 countries. During the first two weeks, 6 parallel groups consisting of indacaterol 75 µg, indacaterol 150 µg, indacaterol 300 µg, indacaterol 600 µg, placebo, fomoterol, and open labeled tiotropium were studied. Based on the results, indacaterol 150 µg and indacaterol 300 µg, placebo, and open labeled tiotropium were carried forth for 24 more weeks.

The same inclusion/exclusion criteria were used for the 3 pivotal studies.

- ≥ 40 years old, Smoking history of >20 pack-years
- Post-bronchodilator FEV1 <80% and ≥30% of normal predicted value, and an FEV1/FVC of < 70%.
- Subjects with a history of asthma or any chronic respiratory disease other than COPD, including the need for continuous oxygen therapy.
- Poorly controlled diabetes, type I or II
- Significant medical condition: e.g. unstable angina, arrhythmia, etc.

The primary endpoint for all studies was superiority of indacaterol versus placebo in trough FEV1 after 12 weeks of treatment. Secondary endpoints included comparing indacaterol versus placebo in trough FEV1 on day 2, FEV1 measured at all time points, including approximate peak response (day 1 & post 12 wk treatment) and trough response. Standardized AUC for FEV1 (5 min- 1 hr) and (1 hr – 4 hr) on day 1 and post 12 wk treatment hours, peak percent predicted FEV1, time-normalized area under the percent change in FEV1 from study baseline, time to peak change in FEV1, etc. Symptom and

patient functioning endpoints included supplemental ipratropium bromide use, rescue albuterol use, COPD exacerbations, SGRQ, distance walked in 6 minutes, and baseline and transitional dyspnea index.

Reviewer's Comment: During the development of indacaterol, contrary to the recommendation of the Division, Novartis did not compare different dosing intervals, i.e., once versus twice daily administration. As a substitute, tiotropium and formoterol were added as active comparators in two trials.

Summary of Applicant's Proposed Pivotal Studies

Study ID	Treatment Groups	Locations	Duration	Design	# of pts	Primary Endpoint
2335S	**2 doses, chosen from:** IND 75 µg qd IND 150 µg qd IND 300 µg qd IND 600 µg qd Placebo Formoterol 12 µg bid (blinded) Tiotropium (18 µg qd OL)	**334 centers** **11 countries** **USA (185)** W europ(78) Canada((24) Argentina (6) India (13) Korea (13) Turkey (8) Taiwan (7)	26 wk	R, DB, DD, PC, A, S, PG	1665 pts 1410 w 43 b 196 a 16 o	Superiority of INDA (at least 1 of 2 doses) to placebo for 24 hr post dose FEV1 after 12 wk of treatment
2334	IND 300 µg qd IND 600 µg qd Formoterol 12 µg bid Placebo	**230 centers** **25 countries** **W Eur (141)** E. Europ (38) Russia (15) C/S Ameri(21) m. East (18) S. korea(7)	52 wk	R, DB, DD, PC, PG	1728 pts 1604 w 3 b 29 a 92 o	Superiority of INDA to placebo for 24 hr post dose FEV1 after 12 wk of treatment
2346	IND 150 µg qd Placebo	103 centers **USA (101)** Austral (1) Belgium (1)	12 wk	R, DB, PC, PG	416 pts	Superiority of INDA to placebo for 24 hr post dose FEV1 after 12 wk of treatment

B. Supporting Studies

In addition to the 3 proposed "pivotal" studies, the sponsor states that the clinical program in support of efficacy consists of 3 studies examining the effect of time of dosing (study B2305), onset of treatment effect (B2307), and 24 hour profiling of lung function (B2340). The table below summarizes the features of these 3 studies.

Summary of Supportive Studies

Study #	Design	Treatments	Duration	# of pts	Primary Endpoint
2305	P III, R, DB, DD, PC treatment, 3- period incomplete crossover	INDA 300 µg qAM INDA 300 ug qPM Salmeterol 50 µg bid placebo	12 w	95	Efficacy and safety
2307	P III, R, DB, TD, PC 5 period, single-dose complete block crossover	IND 150 µg qd IND 300 µg qd Salmeterol/fluticasone 50/500 µg Salbutamol 200 µg placebo	Single dose	89	Efficacy and safety
2340	P III, R, DB, PC 3 period, 14 day crossover	INDA 300 µg qd placebo Salmeterol 50 µg bid (open label)	14 d	68	24 hr lung function profile

C. Other Studies

In addition to those that are mentioned in Sections A and B above, other clinical studies have been conducted with indacaterol. These include:

- 36 pharmacokinetic studies
  - Healthy volunteers (14)
  - COPD pts (9)
  - Asthma pts (13)
- 4 pharmacodynamic studies
  - Cardiac safety (1)
  - Asthmatic pts (1)
  - COPD pts (2)
  - Exercise testing on COPD pts taking indacaterol (1)
- 4 Efficacy & safety studies
  - Japanese COPD pts (1)
  - 28 day, in COPD (1)
  - 7 day DR in COPD (1)
  - SD, DR in COPD (1)

Reviewer's comments: The results from these studies need to justify the recommended dose and dosing interval for indacaterol in the COPD population. It will be important also to consider the effect of the chosen dose and dosing interval on the asthma patients since off-label use may occur.

VII. Advisory Committee Meeting

Since this is a new molecular entity, if sufficient evidence exists this cycle that Approval is being considered, it will be presented before the Pulmonary Allergy Drugs Advisory Committee.

VIII. DSI Review / Audit

Since this is a new molecular entity, the Division of Scientific Investigation will plan to request audits.

IX. Summary

This NDA is submitted in support of the use of the once daily long-acting-beta-agonist single dose dry powder inhaler for the long term maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. The Sponsor has identified 3 pivotal clinical trials. There are three other supporting profiling studies. The submission appears complete enough to allow for a further, more complete review, and is therefore considered "fileable." Since this is a new molecular entity, if sufficient evidence exists this cycle that Approval is being considered, it will be presented before the Pulmonary Allergy Drugs Advisory Committee. Audits of clinical centers will be requested of the Division of Scientific Investigations.

Comments to Sponsor for the 74 Day Letter

During our filing review of your application, we have identified the following potential review issues:

1. After preliminary assessment of the dose-ranging and dosing interval data submitted it is unclear whether the appropriate dose and dosing interval of indacaterol for the treatment of bronchospasm associated with chronic obstructive lung disease have been chosen.

2. We are concerned that the name "Arcapta (b) (4) (b) (4)

We also request that you submit the following information:

1. Submit summary dose response and dosing frequency data for indacaterol that you have collected from studies conducted to support its clinical development for patients with asthma. Include trough FEV1, 12 and 24 hour FEV1 time curves, data on once and twice daily dosing of indacaterol (if assessed), and data for active comparators that were given concurrently in clinical trial.

X. Timeline for Review

Timeline for Review

Milestone	Target Date for Completion
Study 2335S	Mid March, 2009
Team Meeting	April 10, 2009
Pivotal Studies Reviewed	May 5, 2009
MCR Mtg	May 12, 2009
Label reviewed	August 4, 2009
WU Mtg/Draft Primary Review	August 18,2009
Primary Review Due	August 25, 2009
Labeling Tcon	September 14, 2009
PDUFA Due Date	10/18/2009

Reviewed by:

Lynne H. Wu, MD
Medical Officer, DPAP

Anthony G. Durmowicz, MD
Clinical Team Leader, DPAP

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

/s/

Lynne Wu
2/27/2009 12:05:42 PM
MEDICAL OFFICER

Anthony Durmowicz
2/27/2009 12:11:43 PM
MEDICAL OFFICER