CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022383Orig1s000

OFFICE DIRECTOR MEMO

Summary Basis for Regulatory Action

Date	July 1, 2011
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 75 and 150 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:	*Approval 75 mcg*

1. Introduction and Discussion

This is a brief high-level summary of my review of the Complete Response (CR) submitted by Novartis in regard to the CR action taken on October 16, 2009. I refer the reader to the reviews in the action package for a more detailed discussion. As noted above, the original application received a CR action and my conclusion at the time was:

> *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 noted at the time that the safety of the use of LABAs in therapy for asthma was under intense scrutiny. The SMART[1] trial demonstrated that a very small percentage of patients treated with long-acting B-agonist drug for asthma were at risk for a paradoxical increase in serious asthma exacerbations. Our own internal review of formoterol (and subsequent publication[2]) also demonstrated that for subjects with asthma there was a dose-related increase in serious asthma exacerbations as the dose increased from 12-mcg to 24-mcg given twice a day. The ramification of this result for formoterol was that only the 12-mcg dose was approved for

[1] Nelson HS, 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.
[2] Mann M, Chowdhury B, Sullivan E, et.al. Serious Asthma Exacerbations in Asthmatics Treated With High-Dose Formoterol. Chest, 2003; 124; 70-74

asthma. This dose was subsequently carried over and evaluated for subjects with COPD and ultimately approved. Therefore, B-agonist use in asthma is associated with a paradoxical increase in asthma related adverse events and should be considered dose-related for the class unless proven otherwise in a safety study for any one particular product. Such a concern however has not been demonstrated in COPD patients.

Much of the risk signal that we were concerned about with indacaterol was identified in an asthma population not in the database for COPD, where the B-agonist risks are not as clear. However, the typical regulatory approach for development of previous B-agonist agents is that a proper dose is determined for patients with asthma based on a risk:benefit assessment and then that dose is carried forward for the development of COPD indications. This is mainly because these agents are bronchodilators, and their effects are more readily demonstrated in a bronchoresponsive asthma population. There is a good scientific rational for limiting the dose for patients with COPD to what is considered the safe dose in patients with asthma. While patients with asthma are for the most part considered a different population (although there is probably some overlap) with a different disease pathophysiology than COPD patients, most COPD patients also have some degree of reversible bronchospasm that may not always be completely disassociated from asthma. Our experience has also been that the correct dose identified in the treatment of the asthma population has proven to also be efficacious and safe for the COPD population.

At the time of the first submission, the applicant based dose selection on the principal of demonstrating superior efficacy compared to active comparators including B-agonists. This was an unfortunate design plan for this class of drugs. Since we have significant concerns regarding safety and have considered B-agonist to have a narrow therapeutic index, an optimal risk:benefit ratio would dictate that maximal efficacy (or speed to onset of action) may need to be sacrificed in the interest of optimizing the safety profile. As such, to 'beat' an already established B-agonist (measured by FEV1), may also place the dose in a range of unacceptable toxicity. Such was the case for the first cycle of the indacaterol application as it appeared that there were higher frequencies of cardiovascular and cerebrovascular adverse events (as well as two possible asthma deaths) compared to placebo and salmeterol, which led to our demand to study lower doses (and different dosing intervals due to the long half-life of indacaterol).

For the first cycle, in order to 'beat' the comparator, the sponsor mainly studied a 150- and 300-mcg dose. However, there was some efficacy data available at the time indicated that the 75-mcg dose seemed indistinguishable from the 150-mcg dose at a 12-week endpoint (although the onset of action was somewhat delayed). As such, at the time I determined that the applicant had not done adequate dose exploration to maximize the risk: benefit ratio for indacaterol and recommend a CR action.

For the Complete Response, the sponsor has submitted several new studies evaluating efficacy and safety that include lower doses, dose ranging and various dosing frequencies. After completing several studies, the applicant is now requesting approval for indacaterol 75- or 150-mcg once daily. The applicant claims that 150-mcg is more effective than the 75-mcg dose based on pharmacodynamic modeling and the results of St George's Respiratory Questionnaire (SGRQ) evaluations.

Since the first review cycle, indacaterol has been approved for COPD in the European Union and many other countries for COPD at doses of 150- and 300-mcg a day.

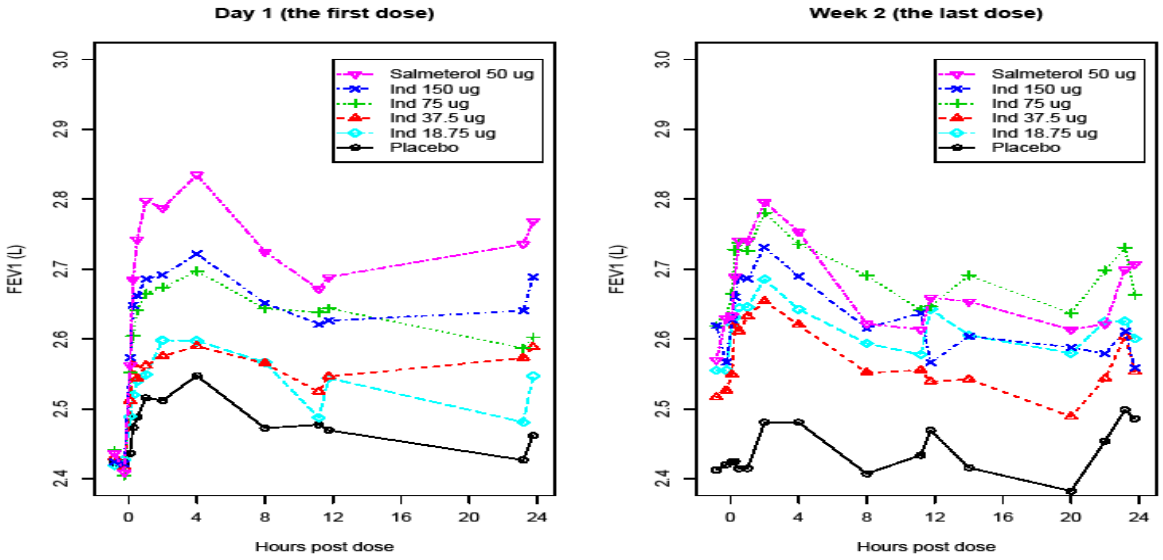
I believe that the sponsor has demonstrated that indacaterol 75-mcg a day has the appropriate risk:benefit balance that would allow domestic marketing for the purposed claim. I am not convinced that the 150-mcg dose offers any additional benefit over the 75-mcg dose. While it is also not evident to me that the 150-mcg dose does have additional safety concerns above the 75-mcg dose in the COPD population (although I think the 300-mcg dose does), since I do not see an advantage in the higher dose, and considering that safety data is at best a very imprecise estimate, and we know that higher doses can have adverse effects, I do not think it is prudent to approve the 150-mcg dose.

Efficacy

For the CR, the applicant has submitted six new pivotal trials. These include a dose ranging trial and dose regimen trial in bronchodilator-responsive asthma subjects, a dose ranging trial in COPD subjects, two replicated 12-week efficacy trials in COPD subjects with 75-mcg dosing and one 26-week confirmatory study in COPD subject with 150-mcg dosing. It is important to note that there is not an efficacy or safety trial that contains both the 75- and 150-mcg dose.

Efficacy has been thoroughly covered in Drs. Michele, Harry's, Liu and Chowdhury's reviews. As noted in their reviews, the sponsor claims that modeling data provides evidence that the 150-mcg dose is more effective than the 75-mcg dose. However, the modeling data is disputed by our clinical pharmacology team as being fragile and unreliable (see Dr. Michele and Chowdhury's review for a detailed discussion). It is interesting to note that the clinical pharmacology's modeling revealed opposing results to the sponsor's regarding what sub-populations may benefit from higher dosing. This all serves to demonstrate that modeling data is based on presumptions that may or may not be accurate, can be useful in providing guidance in dosing for further evaluation, but there are limitations and its use as a sole determinate for dose selection should always be done with great caution. For something as critical as dose selection in a narrow therapeutic drug class, while modeling can be very useful in generating hypothesis, I believe prudence dictates the requirement of a dose-ranging clinical trial. Therefore, we informed the sponsor we wanted to see the results of dose ranging of all potential doses within one trial (i.e. 'the rubber meets the road'). We also recommended that the greatest discriminatory effect would be manifest in a trial performed in a bronchoresponsive asthma population (B2357). The results of this trial are demonstrated in the Figure below from Dr. Liu's review (page 21).

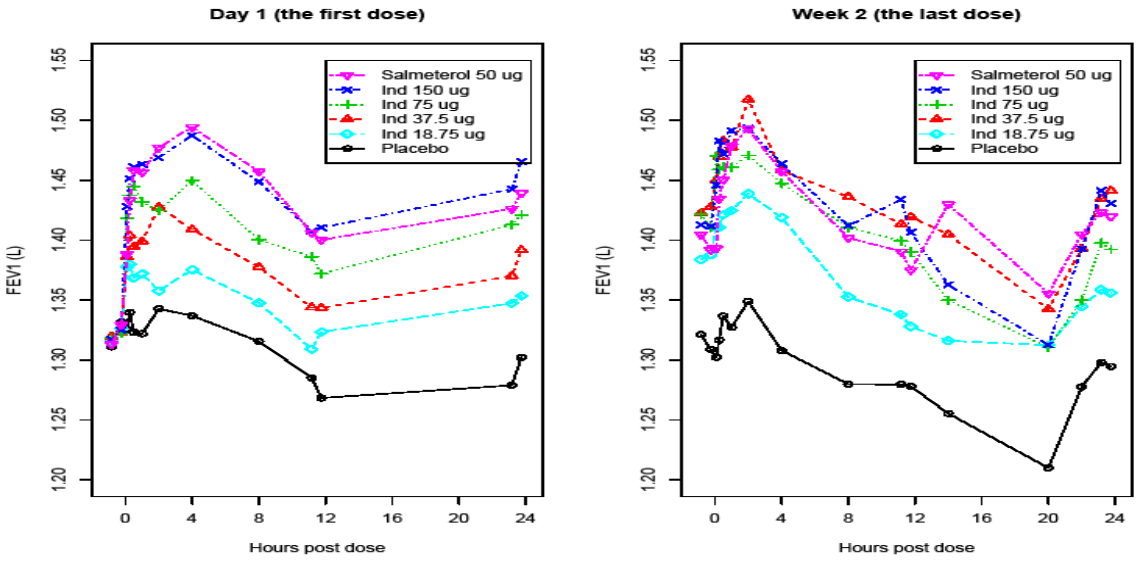
Figure 1 Study B2357 Summary of spirometric parameters at Day 1 and after 2 weeks treatment.



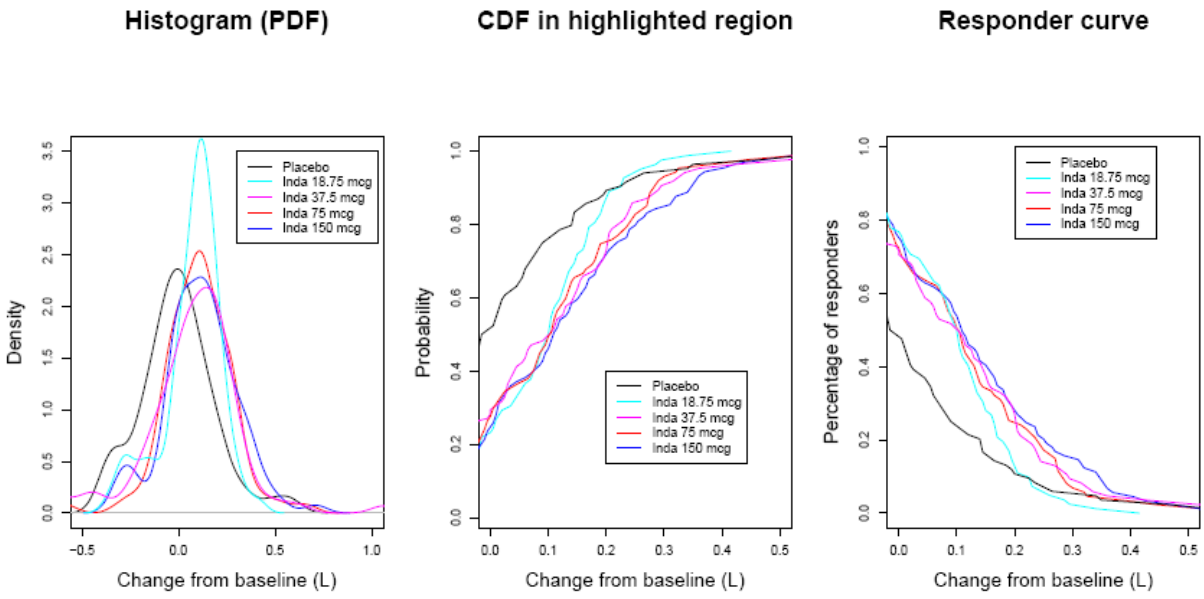
These results indicate that there may be some single dose separation of effect, but this response disappears after two weeks of dosing. The results above also do not validate the modeled predicted advantage that the sponsor had purported (although the dose-ranging above is in an asthma population and the modeling was based on a COPD population). Therefore, while modeling can provide some estimates of effect, the gold standard of an actual head-to-head dose ranging trial reveals that the 150-mcg dose is indistinguishable from the 75-mcg dose after a two week dosing period. The FEV1 time profile curves showed some numerical dose ordering after the first dose, but this difference disappears with the week 2 evaluations for all doses. So while higher doses may have a greater first dose effect, after 2 weeks, the doses for 75 mcg and 150 mcg are indistinguishable. It is also difficult to distinguish the advantage of any of the doses after two weeks, as while the 75-mcg seems to have the greatest effect of all the indacaterol doses, the 150-, 37.5 also appear indistinguishable.

Figure 7 from Dr. Liu's (page 22-23) in COPD subjects, demonstrates a somewhat similar trend with perhaps better dose discrimination of the 18.75-mcg dose from the others at two weeks.

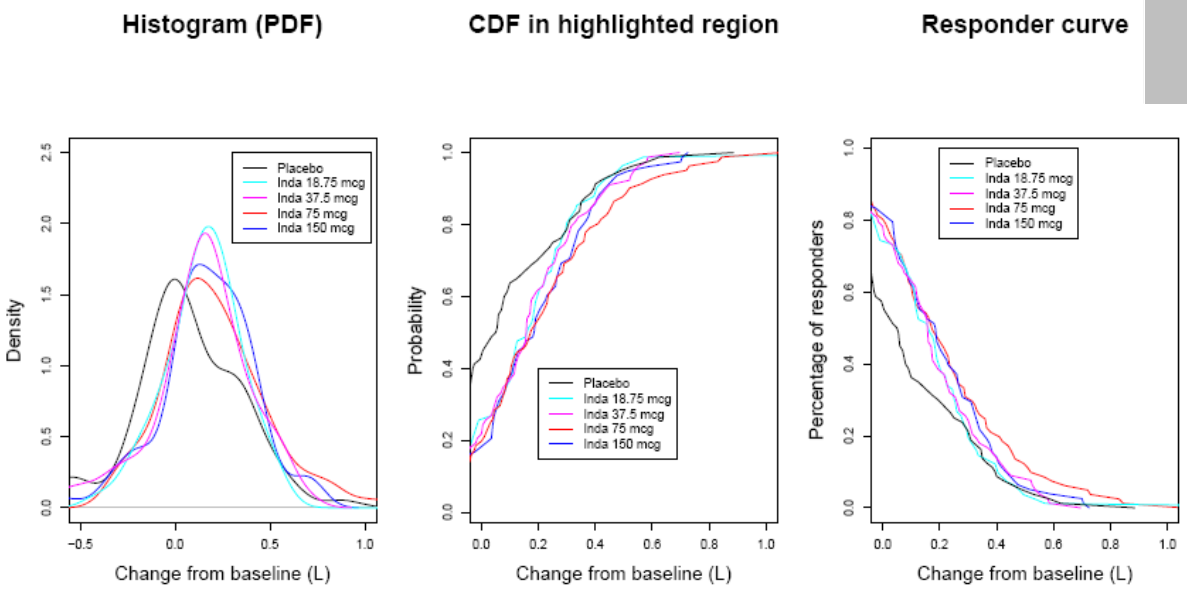
Figure 2 Study B2356 summary of spirometric parameters at Day 1 and after 2 weeks treatment.



This figure demonstrates that the 18.75-mcg dose clearly separates and is inferior to the other doses. The 37.5-, 75- and 150-mcg dose appear indistinguishable. Below are three additional plots that Dr. Liu has constructed for me for the dose ranging COPD trial.



I believe these graphs also demonstrate the inferiority of the 18.75-mcg dose. While one might imagine that the first graph demonstrates perhaps a slightly higher percentage of subjects with 0.5 L increase of the 150-mcg dose, one could also imagine that the 150-mcg dose has a higher percentage of subjects with -0.3 L change similar to the 18.75-mcg dose. This probably demonstrates the imprecision of FEV1 measurements. The same can be seen in additional plots that Dr. Liu has constructed for me for the dose ranging asthma trial.



These graphs confirm the inferiority of the 18.75-mcg dose, but would support that the 75-mcg dose is superior to all other doses. I believe this again points out that FEV1 by itself can be a somewhat insensitive predictor of efficacy and all the data needs to be considered.

The table below is from Dr. Michele's review (page 17) and summarizes the data that the above graphs are derived from.

Table 3: Studies B2357, B2223, and B2356, LS Mean for trough FEV1 (in L) at day 15 (primary efficacy time point)

Treatment	Trough FEV1 at week 2	Treatment comparison	Treatment Difference LS Mean (95% CI)
Study B2357 (asthma dose-ranging)			
IN 18.75 mcg	2.50	IN 18.75 - Placebo	0.09 (0.00, 0.17)
IN 37.5 mcg	2.52	IN 37.5 - Placebo	0.11 (0.02, 0.19)
IN 75 mcg	2.59	IN 75 - Placebo	0.17 (0.08, 0.26)
IN 150 mcg	2.54	IN 150 - Placebo	0.12 (0.04, 0.21)
Sal 50 mcg	2.54	Sal - Placebo	0.13 (0.04, 0.21)
Placebo	2.42		
Study B2356 (COPD dose-ranging)			
IN 18.75 mcg	1.35	IN 18.75 - Placebo	0.07 (0.02, 0.12)
IN 37.5 mcg	1.38	IN 37.5 - Placebo	0.10 (0.05, 0.16)
IN 75 mcg	1.38	IN 75 - Placebo	0.10 (0.04, 0.15)

Treatment	Trough FEV1 at week 2	Treatment comparison	Treatment Difference LS Mean (95% CI)
IN 150 mcg	1.40	IN 150 - Placebo	0.12 (0.07, 0.17)
Sal 50 mcg	1.39	Sal - Placebo	0.10 (0.05, 0.16)
Placebo	1.28		
Study B2223 (asthma dose-regimen)			
IN 37.5 BID		IN 37.5 BID - Placebo	0.16 (0.08, 0.23)
IN 75 QD		IN 75 QD - Placebo	0.20 (0.12, 0.27)
IN 150 QOD		IN 150 QOD - Placebo	0.20 (0.12, 0.27)
Placebo			
IN = Indacaterol single dose dry powder inhaler, Arcapta Neohaler (Indacaterol single dose dry powder inhaler); For = Foradil Aerolizer (formoterol fumarate inhalation powder); Sal = Serevent Diskus (salmeterol xinafoate inhalation powder)			

As demonstrated in the table above, equivalent doses given either bid, qd or qod had little differences in efficacy.

I believe the totality of the data and time profiles above indicate that the 18.75-mcg dose is inferior to the other doses studied. I would also interpret this that the 18.75-mcg dose is near, but not on, the plateau of B-agonist bronchial dilatory effect for indacaterol. The remaining doses are harder to distinguish as being different, but one could speculate that the confidence interval (or the standard deviation) of effect in the population surrounding the 37.5-mcg dose may be such that a significant proportion of patients could be receiving a dose that is still on the 'upward slope' of effect instead of on the plateau, whereas the confidence interval surrounding the 75-mcg dose should safely be above the slope of dose-response and was reasonable to carry forward in clinical trial.

Efficacy was evaluated in three trials new for the CR, the results summarized in the table below from Dr. Michele's review (page 20).

Table 1. Studies B2336, B2354, and B2355, LS Mean for trough FEV1 (in L) at 12 weeks (primary efficacy time point)

Treatment	Trough FEV1 at week 12	Treatment comparison	Treatment Difference LS Mean (95% CI)
Study B2336			
IN 150 mcg	1.45	IN 150 – Placebo	0.17 (0.13, 0.20)
		IN 150 – Sal 50	0.06 (0.02, 0.10)
Sal 50 mcg	1.39	Sal - Placebo	0.11 (0.07, 0.14)
Placebo	1.28		
Study B2354			
IN 75 mcg	1.38	IN 75 – Placebo	0.12 (0.08, 0.15)
Placebo	1.26		
Study B2355			
IN 75 mcg	1.49	IN 75 – Placebo	0.14 (0.10, 0.18)
Placebo	1.35		
IN = Indacaterol single dose dry powder inhaler, Arcapta Neohaler (Indacaterol single dose dry powder inhaler); Sal = Serevent Diskus (salmeterol xinafoate inhalation powder)			

It is clear that indacaterol 75-mcg is an effective dose based on the primary endpoint and all secondary endpoints support this conclusion. It is unfortunate that the applicant did not study the 75-mcg and 150-mcg in the same study, but based on the dose response trials I would expect little difference on the trough FEV1 parameter between these two doses.

One secondary endpoint, which the applicant is using as a justification for marketing of the 150-mcg dose, is the St. George Respiratory Questionnaire (SGRQ). The SGRQ is an older health-related quality of life measure that has been firmly established in clinical care. The sponsor has contended that the 150-mcg dose demonstrated an improved mean total SGRQ score compared to the 75-mcg dose. As noted above however, these two doses were not compared in the same trial, so any comparison of numerical differences would be across different trials. This is not acceptable in terms of making critical dose selection decisions in a narrow therapeutic index drug. Dr. Michele has a very nice discussion of the results of SGRQ in her review, but the high level results are that the SGRQ is not a robust measure of effect, different doses are being compared across studies and offer inconsistent results (300-mcg appears less effective than 150-mcg). So the results of the SGRQ do not support the applicant's claims of differences in efficacy between the doses evaluated. Below are graphic representations of the results from Dr. Liu's review (page 26-27).

Figure 10: ANCOVA results of SGRQ total scores (imputed with LOCF) in key controlled efficacy studies.

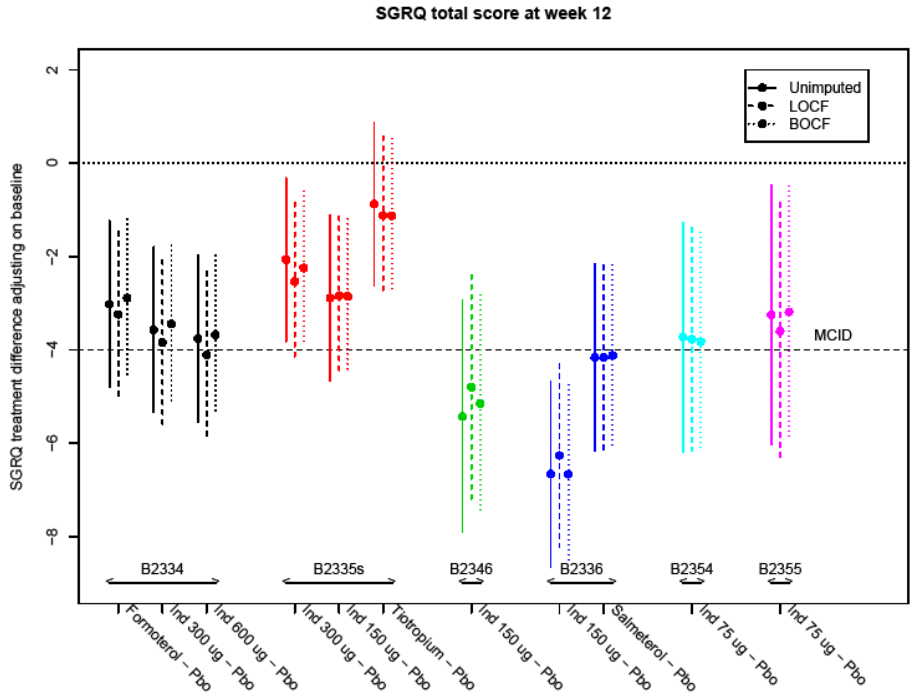
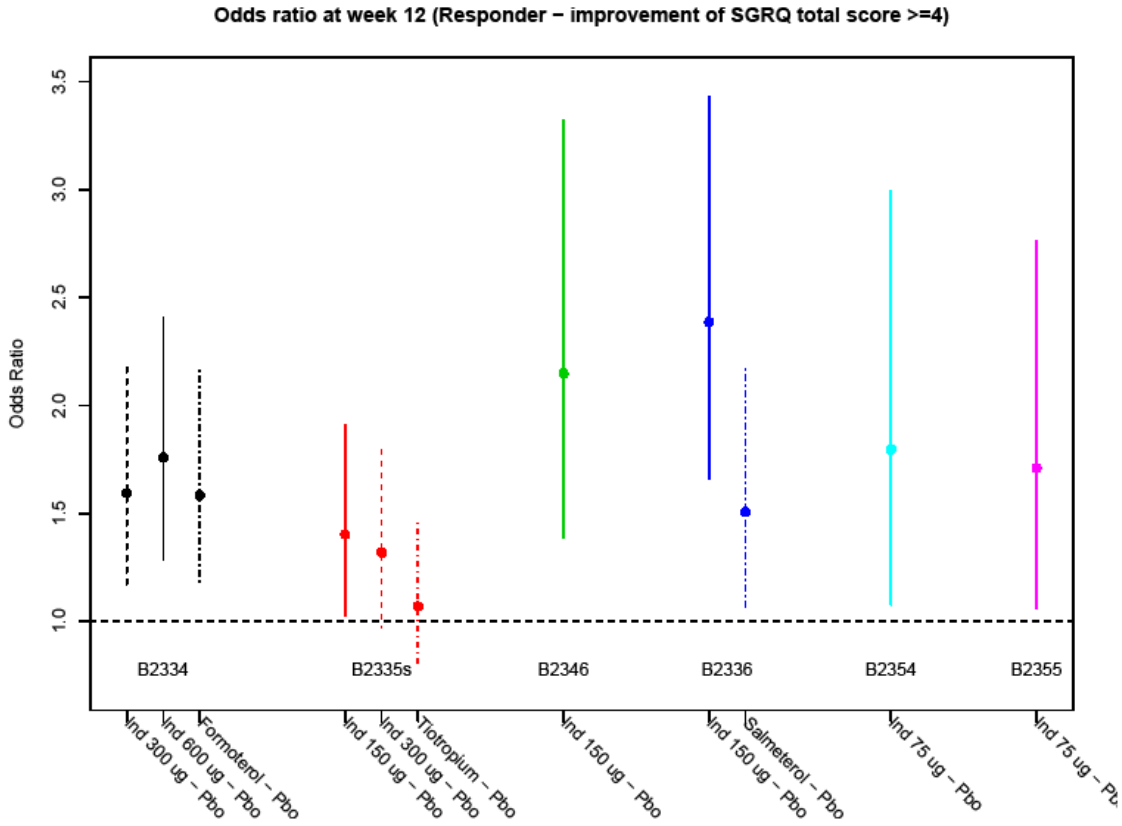


Figure 12: Summary of SGRQ (imputed with LOCF) responder analysis results in key controlled efficacy studies



These graphs demonstrate considerable overlap of the CI in all the drugs evaluated. The bottom graph is a responder analysis based on logistic regression of the likelihood (point estimate and 95% CI) of achieving at least a 4 unit improvement in SGRQ compared to placebo. These graphs demonstrate that all active treatments except for tiotropium and indacaterol 300-mcg were greater statistically greater than placebo, with overlap of the CI of most active therapies. It is difficult to draw any conclusions without having different doses in the same trial, and it should be noted that indacaterol 300-mcg has some of the lower SGRQ scores, which is inconsistent with the postulate theory of the sponsor that higher doses are more effective. I believe this points out the pitfalls of cross-study comparisons and probably is also an indication of the lack of precision (and perhaps accuracy) of the SGRQ for this type of determination.

The efficacy data support a conclusion that both the 75- and 150-mcg doses are effective. They do not support a conclusion that these two doses can be distinguished from each other. As I discussed early, the 37.5-mcg dose was not evaluated. One might expect that it would demonstrate efficacy as well, but based on the dose-ranging data, I would expect that responder analysis would demonstrate that this dose is close enough to the break point on a

FEV1 response curve that the confidence interval would include the slope and may be inferior therapy for some COPD patients.

Safety

For this cycle review, we requested that the applicant conduct a meta-analysis to include blinded adjudicated (by external committee) comparing indacaterol-treated patients to controls with respect to respiratory-related death, hospitalization, and intubation in both the asthma and COPD populations. The meta-analysis included all blinded, parallel-arm, randomized, controlled trials of seven or more days treatment duration using the Concept 1 (or similar) device. The trials included are in Table 1 below from Dr. Karimi-Shah's review (page 4).

Table 2 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;

This forms the basis of the safety evaluation. The All-treated COPD Safety Population included a total of 11,755 patients in 23 studies. This included 6863 subjects treated with indacaterol, 2482 with placebo, and 2408 with one of three active controls (formoterol n=556, tiotropium n = 842, and salmeterol n = 1010). The results are in Table 6 below from Dr. Karimi-Shah's review (page 5). In this table "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: 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)	50 (2.0)
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)	47 (1.9)
Intubations, n(%)										
Total	0	1 (<0.1)	1 (<0.1)	2 (0.1)	0	4 (0.1)	3 (0.5)	0	1 (<0.1)	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: re2.1c1 pages 478-483

There does appear to be a dose related increase in the composite and hospitalization rates for the indacaterol treatment groups based on overall percentages, with the break point beginning at the 300-mcg dose. I think this should be viewed cautiously as there are few events, and this table is not exposure-adjusted. While it might be comforting to noted that the rates overall are similar, and in some cases lower, than comparator drugs that are currently approved, this conclusion should be viewed cautiously. While one could try to draw conclusions about the incidence of events above compared to the active comparators, these results could be biased due to the unknown state of rate consistency. As an example, none of the trials less than 26 weeks had formoterol as a comparator. As such, if the rate of events over time isn't constant, but increases over time, then formoterol would not 'benefit' of having shorter studies to

'dilute' any signal as indacaterol, salmeterol and tiotropium does. On the other hand, only one study has salmeterol as a comparator for 26 weeks, therefore limiting its use to shorter trials. I believe the above data is reassuring that the 75-mcg dose, in the COPD population, has an appropriate safety profile. Below is the same data as above, taken from Dr. Karimi-Shah (page 7) above except adjusted for exposure time.

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

There continues to be a trend, although perhaps not as pronounced as in the first table. This should be viewed with caution however. In order for time-exposure adverse events to carry more weight than just total number percentages, one must assume that the event rate is consistent over time. Usually we do not have enough information to make this type of determination, and it is doubtful if there is a consistent rate over time. Therefore, much like the story of the blind-folded people evaluating an elephant for truths and fallacies, it is appropriate to examine both types of data in order to try to form a complete picture upon which to draw conclusions.

The meta-analysis for subjects with asthma included far fewer patients. There were 1914 asthma patients, 1307 were treated with indacaterol, 254 with placebo, and 353 with a salmeterol active control. In this small cohort of asthma patients, there was one death and one intubation in the 300- mcg indacaterol group versus none in the placebo group with similar time-exposures. There were 3 hospitalizations each in the indacaterol 300 mcg and 600 mcg groups versus none in the placebo group, despite subjects taking concomitant ICS. The second

potential asthma-related death that I noted early apparently was not included in this meta-analysis because the patient was taken off study drug when she entered the hospital, although as Dr. Michele notes it is arguable whether this subject's results should have been omitted or not.

I believe this meta-analysis demonstrates the safety of the 75-mcg dose. One may be tempted to also think that the 150-mcg dose has little demonstration of a safety effect, but again this dose is closer to the 300-mcg dose, where I believe there is a clear demarcation of safety effects, and offers no demonstrative benefit over the 75-mcg dose.

Advisory Committee Meeting

A Pulmonary Allergy Drugs Advisory Committee Meeting (PDAC) was held on March 8, 2011. Regarding whether the efficacy and safety data supported approval of the 75-mcg indacaterol dose, the committee members voted 13-yes, and 4-no. Regarding the 150-mcg dose, the members voted 5-yes, 12-no. There was some discussion regarding whether the applicant had identified the lowest possible safe dose, but most commented that they felt the 75-mcg dose provide the optimal safety:efficacy ratio for moderate to severe COPD patients.

At the PDAC, during the open public forum, public citizen made comments regarding whether four studies were ethical or not. In addition, they have sent a letters to Dr. Woodcock, Dr. Menikoff and Secretary Sebelius requesting further investigation regarding whether Novartis conducted an unethical clinical trials. This has been looked into in conjunction with the Office of Good Clinical Practice at the Office of the Commissioner. The overall conclusion was that the conduct of the trials, with short-acting beta-agonist 'add-on' as well as the risk minimization strategies employed, were ethically acceptable. The observations were that patients in the placebo arm were not untreated and were allowed use of short-acting beta-agonists as needed which is acceptable therapy. Also, all trials in question were conducted with appropriate escape criteria for inadequate therapy. This is discussed in Dr. Michele and Chowdhury's reviews and I agree with their and the ethic's consultants conclusions.

Conclusions and Recommendations

The applicant has demonstrated that 75-mcg and 150-mcg of indacaterol have the effect purported for the requested indication. There are two things that must be decided for this application: 1) does the 150-mcg dose offer any efficacy above and beyond the 75-mcg dose and 2) does the safety of either, viewed in the context of their efficacy, allow marketing. I do not believe that the sponsor has demonstrated a difference between efficacy of the 75-mcg and 150-mcg dose. Therefore, considering that we view B-agonist under the prism of a narrow therapeutic window drug, only the 75-mcg dose should be considered for marketing.

I believe that the safety meta-analysis performed by the sponsor at our request should give us comfort that the safety of the 75-mcg dose is appropriate for this class of agent to allow marketing. In the future, should the sponsor seek marketing of the 150-mcg dose, we need to be cognizant that they should demonstrate increased clinically meaningful efficacy without sacrificing safety. Such considerations would likely require studying the 75- and 150-mcg

dose in the same study that evaluates safety and efficacy. 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. Therefore, providing justification for a 150-mcg dose may prove difficult.

I agree that indacaterol should have the class labeling and REMS requirements and I recommend approval of the 75-mcg dose.

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/s/

CURTIS J ROSEBRAUGH
07/01/2011