

FDA Advisory Committee Meeting, March 8, 2011

**New Drug Application (NDA) from Novartis
for indacaterol inhalation powder for chronic
obstructive pulmonary disease (COPD)**

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Center for Drug Evaluation and Research

US Food and Drug Administration

Indacaterol

- New molecular entity
- Beta₂-adrenergic agonist
- Other beta₂-adrenergic agonists
 - Long-acting beta-adrenergic agonist (LABA)
 - Salmeterol
 - Formoterol
 - Short-acting beta-adrenergic agonist (SABA)
 - Albuterol

Indacaterol

- Indication and Usage
 - Indacaterol is a beta₂-adrenergic agonist indicated at a dose of 75 mcg or 150 mcg every day (once-daily), for the long term, maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema
- Dosage and Administration
 - The recommended dose is 75 mcg once-daily
 - The 150 mcg once-daily has been shown to provide additional benefit in patients with more severe bronchial obstruction

Clinical Program Summary

- Original NDA, submitted December 2008
 - Adaptive design trial: B2335
 - Efficacy and safety trials: B2334, and B2346
 - Safety trials in asthma patients: A2210, and B2338
 - *Proposed dose: 150 mcg or 300 mcg once-daily*

- Complete Response, submitted October 2010
 - Dose ranging and dosing regimen trials: B2357, B2356, and B2223
 - Efficacy and safety trials: B2336, B2354, and B2355
 - *Proposed dose: 75 mcg or 150 mcg once-daily*



Original NDA

- Efficacy and Safety Trials in COPD

Trial ID	Duration	Groups	N (ITT)	Primary efficacy variable	Countries/Regions
B2335	[2 wks] → 26 wks	Indacaterol 75 mcg QD Indacaterol 150 mcg QD Indacaterol 300 mcg QD Indacaterol 600 mcg QD Formoterol 12 mcg BID Tiotropium 18 mcg QD Placebo	[107] [105] → 416 [110] → 416 [102] [112] [112] → 415 [104] → 418	FEV1 trough at 24 hr at [wk 2] or wk 12	US, and International
B2334	52 wks	Indacaterol 300 mcg QD Indacaterol 600 mcg QD Formoterol 12 mcg BID Placebo	437 425 434 432	FEV1 trough at 24 hr at wk 12	International
B2346	12 wks	Indacaterol 150 mcg QD Placebo	211 205	FEV1 trough at 24 hr at wk 12	US, and International



Original NDA

- Safety Trials in Asthma

Trial ID (Patients)	Duration	Groups	N (ITT)	Primary efficacy variable	Countries/ Regions
A2210 (Asthma)	4 wks	Indacaterol 400 mcg QD Indacaterol 800 mcg QD Placebo	59 59 26	None (safety study)	International
B2338 (Asthma)	26 wks	Indacaterol 300 mcg QD Indacaterol 600 mcg QD Salmeterol 50 mcg BID	268 268 269	None (safety study)	US, and International

Original Submission Issues

- Doses proposed for marketing were high and not supported by efficacy and safety data
- Higher frequencies of cardiovascular and cerebrovascular adverse events with indacaterol compared to placebo and formoterol
- No demonstrated clinically meaningful advantage of the 300 mcg dose over the 150 mcg dose
- Possible asthma-related deaths with indacaterol



Complete Response

- Dose Ranging and Dose Regimen Trials

Trial ID [Patients]	Duration	Groups	N (ITT)	Primary efficacy variable	Countries and Regions
B2357 [Asthma]	2 wks	Indacaterol 18.75 mcg QD Indacaterol 37.5 mcg QD Indacaterol 75 mcg QD Indacaterol 150 mcg QD Salmeterol 50 mcg BID Placebo	84 81 84 85 84 84	FEV1 trough at 24 hr at day 15	US
B2356 [COPD]	2 wks	Indacaterol 18.75 mcg QD Indacaterol 37.5 mcg QD Indacaterol 75 mcg QD Indacaterol 150 mcg QD Salmeterol 50 mcg BID Placebo	89 90 94 92 91 91	FEV1 trough at 24 hr at day 15	US
B2223 [Asthma]	2 wks	Indacaterol 37.5 mcg BID Indacaterol 75 mcg QD Indacaterol 150 mcg QOD Placebo	48 48 48 47	FEV1 trough at 24 hr at wk 2	US, and International



Complete Response

- Efficacy and Safety Trials in COPD

Trial ID	Duration	Groups	N (ITT)	Primary efficacy variable	Countries and Regions
B2336	26 wks	Indacaterol 150 mcg QD Salmeterol 50 mcg BID Placebo	330 333 335	FEV1 trough at 24 hr at wk 12	International
B2354	12 wks	Indacaterol 75 mcg QD Placebo	163 160	FEV1 trough at 24 hr at wk 12	US
B2355	12 wks	Indacaterol 75 mcg QD Placebo	159 159	FEV1 trough at 24 hr at wk 12	US

Issues

- Whether the proposed doses of 75 mcg and 150 mcg and the once-daily dosing frequency are supported by submitted data
- Whether the second higher dose of 150 mcg is necessary and supported by submitted efficacy data and balancing safety data
- Whether the SGRQ benefit claim is supported, and whether the SGRQ data provide supportive evidence of efficacy for any of the doses
- Safety of the proposed dose and dosing regimen of indacaterol

Purpose of Proceedings Before an Advisory Committee (21 CFR 14.5)

- a) An advisory committee is utilized to conduct public hearing on matters of importance that come before FDA, to review the issues involved, and to provide advice and recommendations to the Commissioner
- b) The Commissioner has sole discretion concerning action to be taken and policy to be expressed on any matter considered by an advisory committee



Thank You!



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**New Drug Application (NDA) from Novartis
for indacaterol inhalation powder for chronic
obstructive pulmonary disease (COPD)**

Dongmei Liu, PhD

Mathematical Statistician, Division of Biometrics II

Center for Drug Evaluation and Research

US Food and Drug Administration

Outline

- Dose selection
 - In the original NDA
 - In the complete response
- Efficacy (comparison of 75 vs. 150 mcg)
 - Trough FEV₁
 - SGRQ (St. George's Respiratory Questionnaire)

Clinical Program Summary

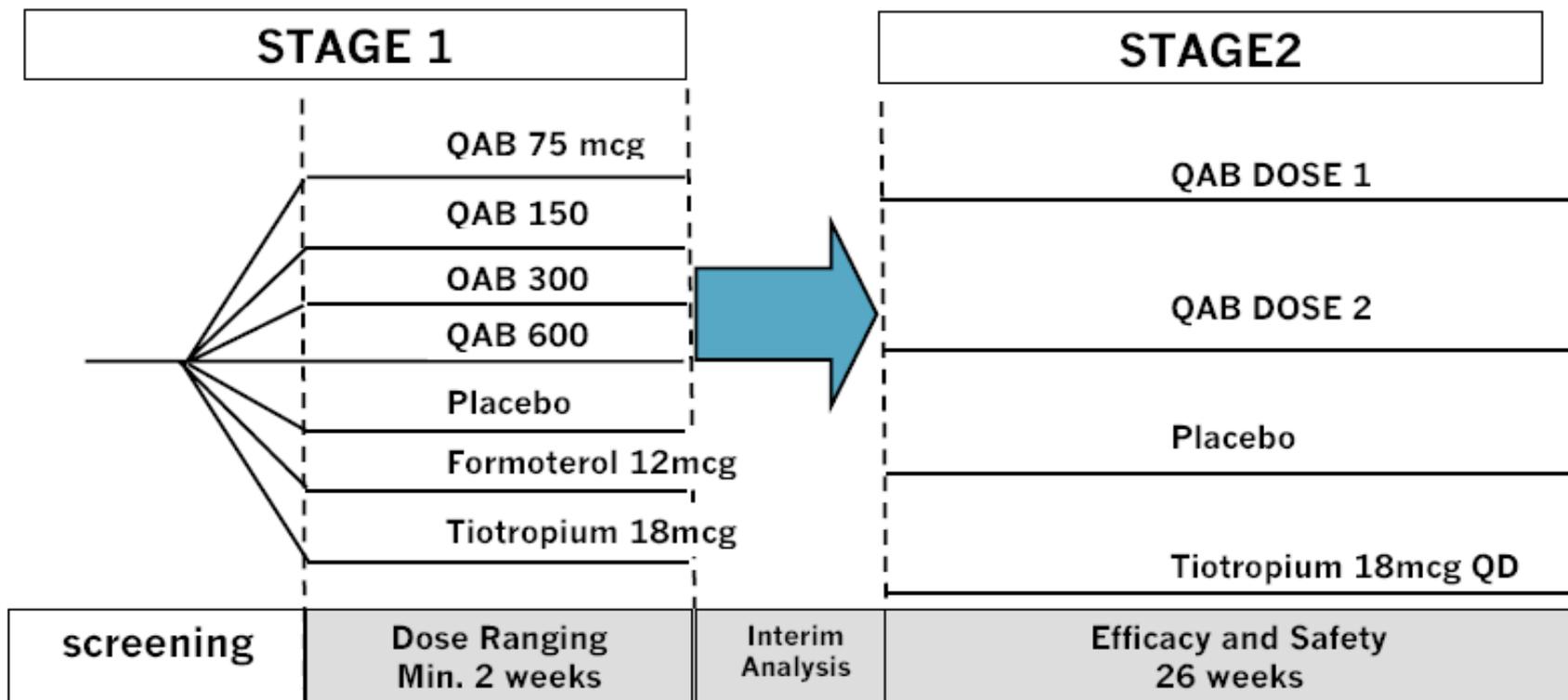
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 - *Proposed dose: 150 mcg or 300 mcg once-daily*
- Complete Response, submitted October 2010
 - Dose ranging and dosing regimen trials: B2357, B2356, and B2223
 - Efficacy and safety trials: B2336, B2354, and B2355
 - *Proposed dose: 75 mcg or 150 mcg once-daily*



Relevant Clinical Trials – Original NDA - COPD Patients

Trial ID	Duration	Groups	N (ITT)	Primary efficacy variable	Countries and Regions
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B2335s Trial Design



Dose Selection Rationale

(defined by the applicant)

- After 2 weeks treatment, the selected doses need to be
 - 120mL greater than placebo (minimal important difference – MID, defined by the applicant) in terms of trough FEV_1 and numerically higher than tiotropium and formoterol;
 - numerically higher than tiotropium and formoterol in terms of FEV_1 standardized $AUC_{(1-4h)}$.

Interim Analysis Results (quoted from B2335s CSR)

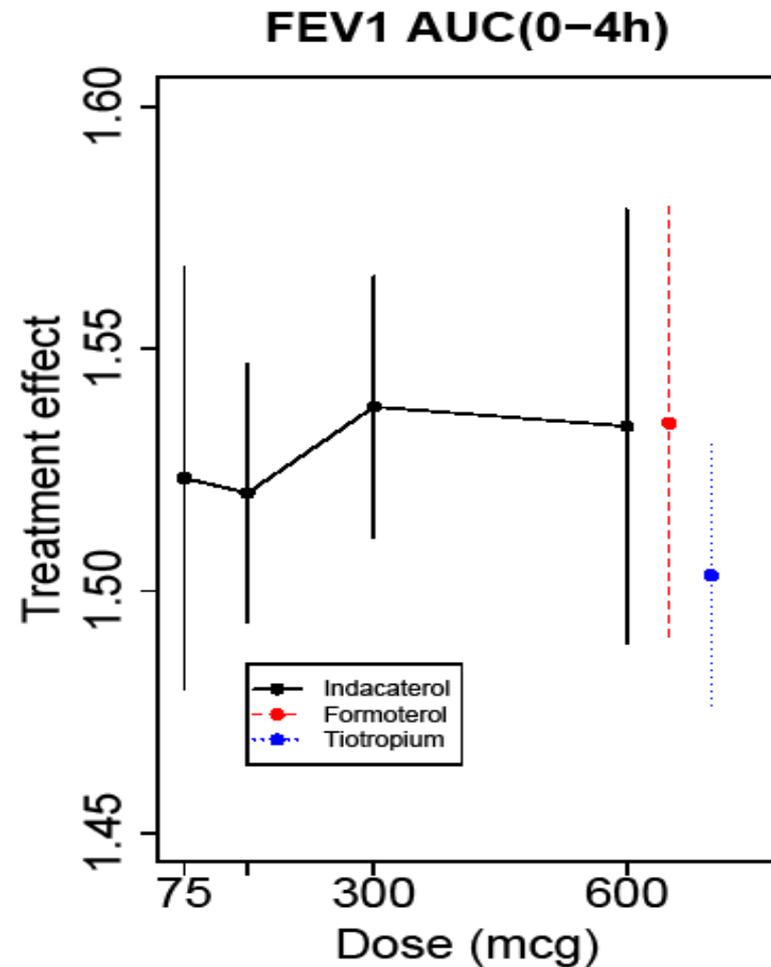
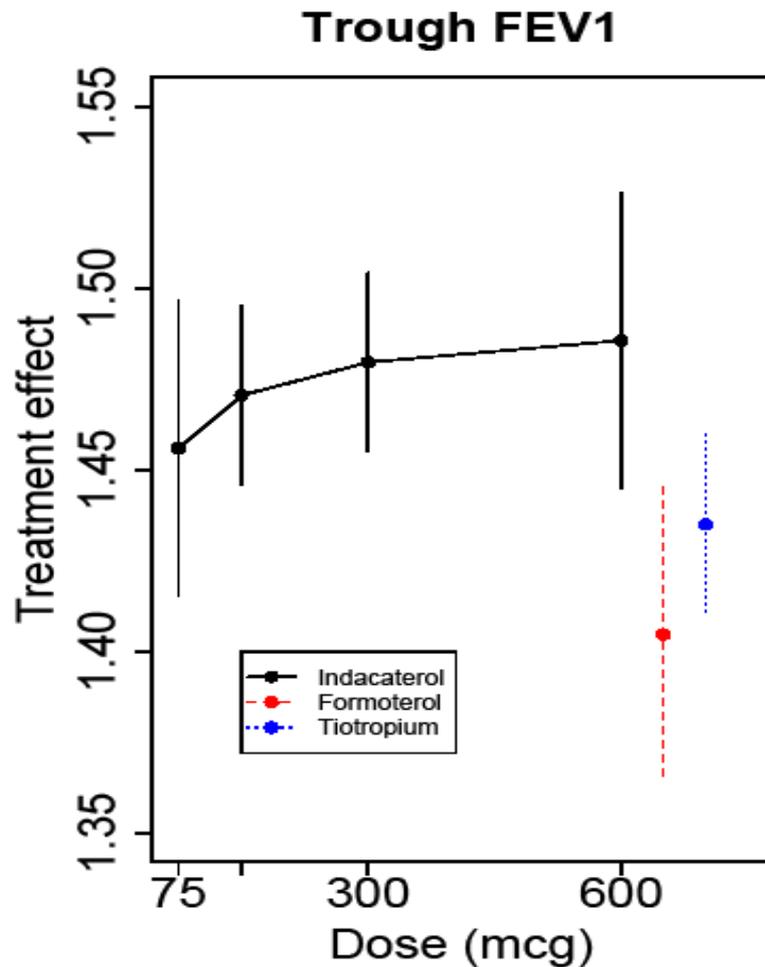
Table 3-21 Study B2335S Key interim analysis results at Day 15 (imputed with LOCF): treatment comparisons (interim ITT population)

Treatment	N	Treatment		Comparison	Treatment difference		
		LS mean	SE		LS mean	SE	95% CI
Trough FEV₁ (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 FEV₁ (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				

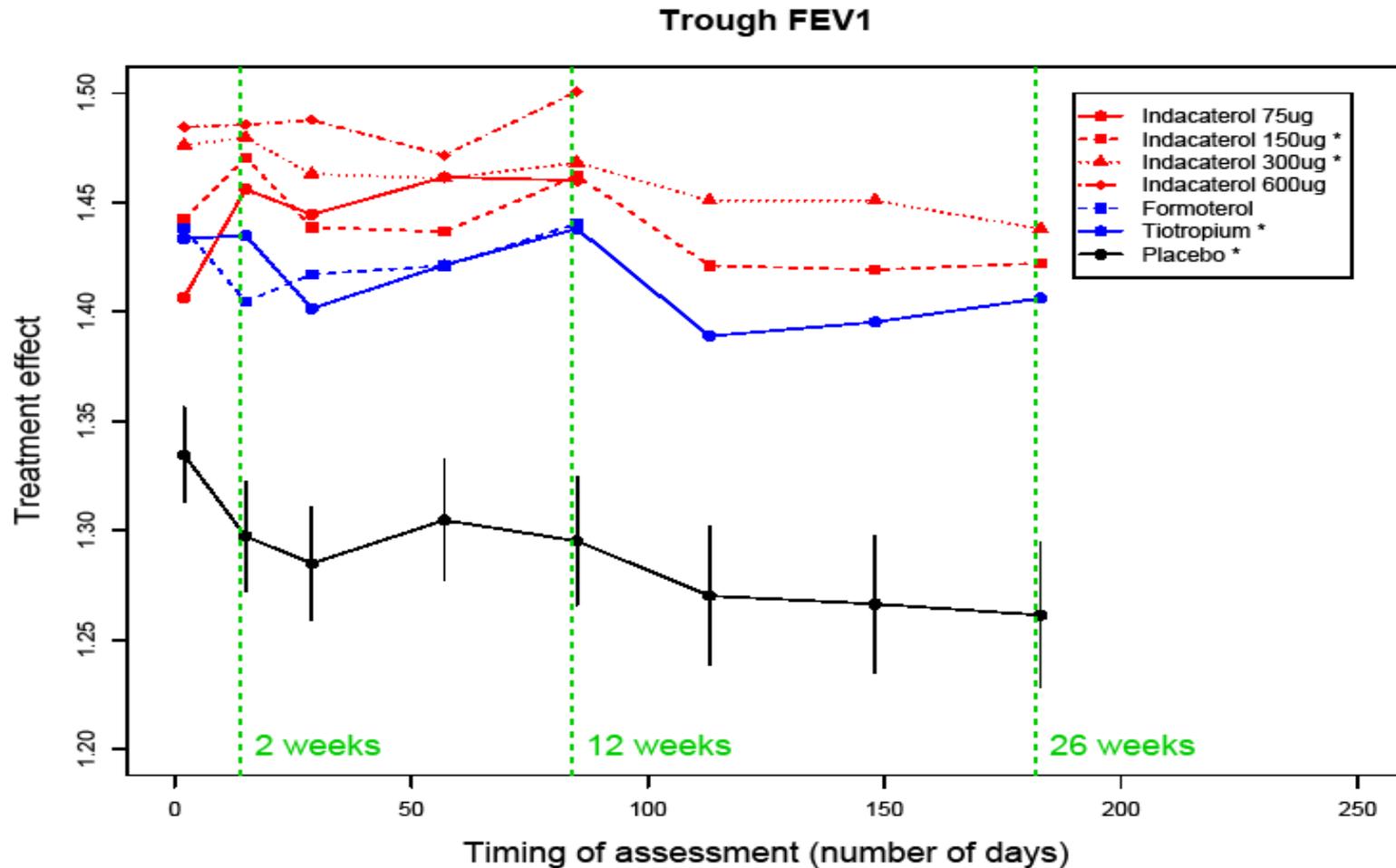
Applicant's Conclusions

- Based on analysis of FEV₁ standardized AUC_(1-4h), 75 mcg was seen to be inadequately effective on the first dose and after 2 weeks of treatment.
- 600 mcg offered no additional benefit.

Dose Response at Week 2



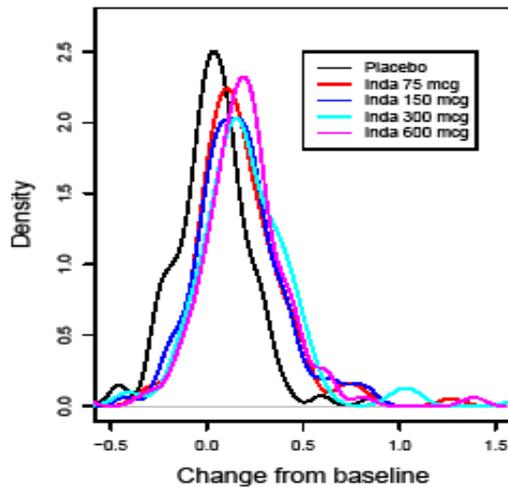
Trough FEV₁ over 26 Weeks



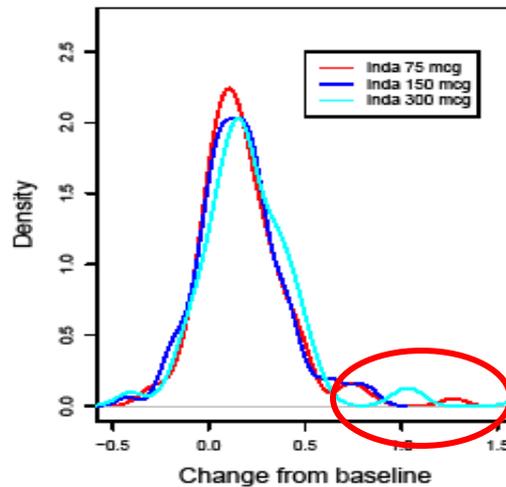
Treatment Effect in Patient Level

(Change from Baseline of Trough FEV₁ at Week 2)

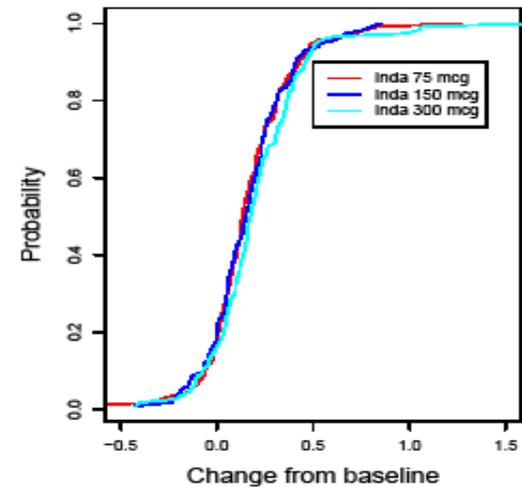
All treatment arms



Inda 75, 150, 300 mcg (PDF)



Inda 75, 150, 300 mcg (CDF)



Agency's Conclusions (Original Submission Issues)

- Doses proposed for marketing were high and not supported by efficacy and safety data
- Higher frequencies of cardiovascular and cerebrovascular adverse events with indacaterol compared to placebo and formoterol
- No demonstrated clinically meaningful advantage of the 300 mcg dose over the 150 mcg dose
- Possible asthma-related deaths with indacaterol

Outline

- **Dose selection**
 - In the original NDA
 - In the complete response
- Efficacy (comparison of 75 vs. 150 mcg)
 - Trough FEV₁
 - SGRQ

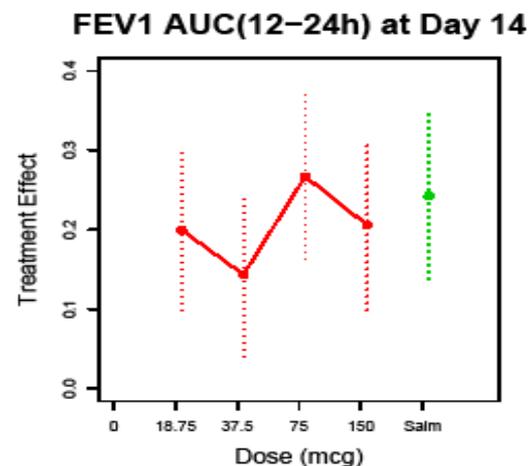
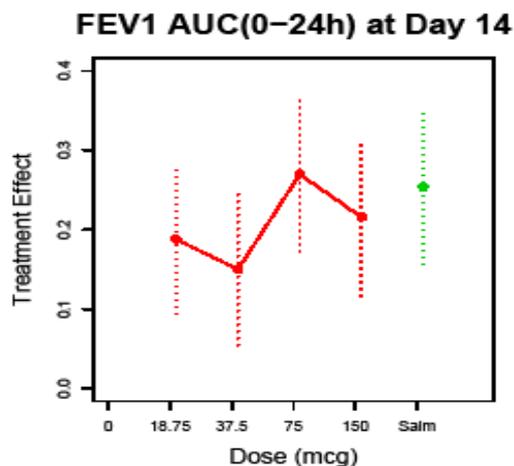
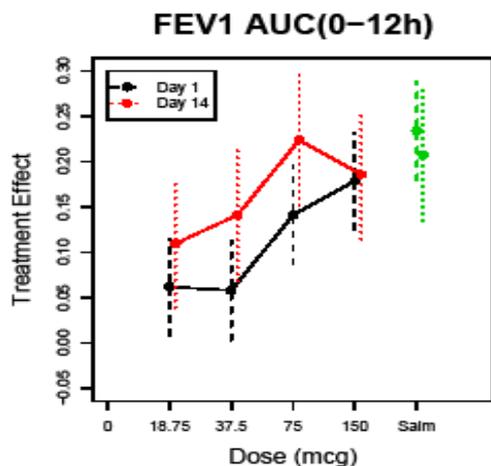
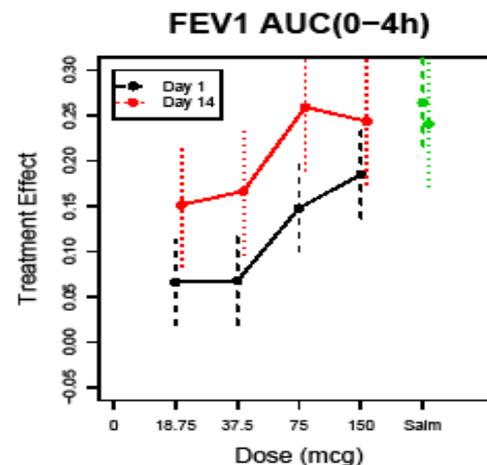
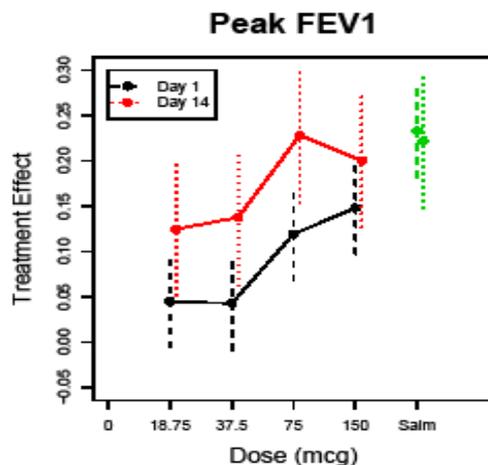
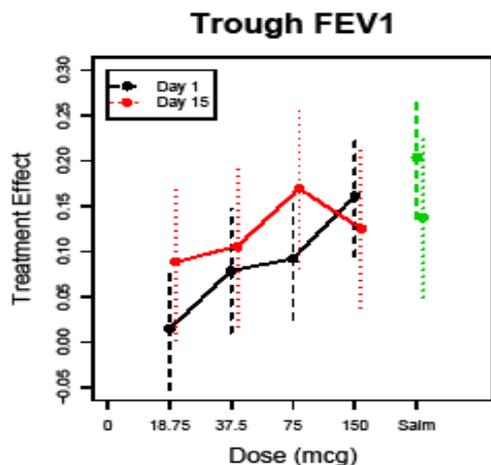


Relevant Clinical Trials – Complete Response

- Dose Ranging and Dose Regimen Trials

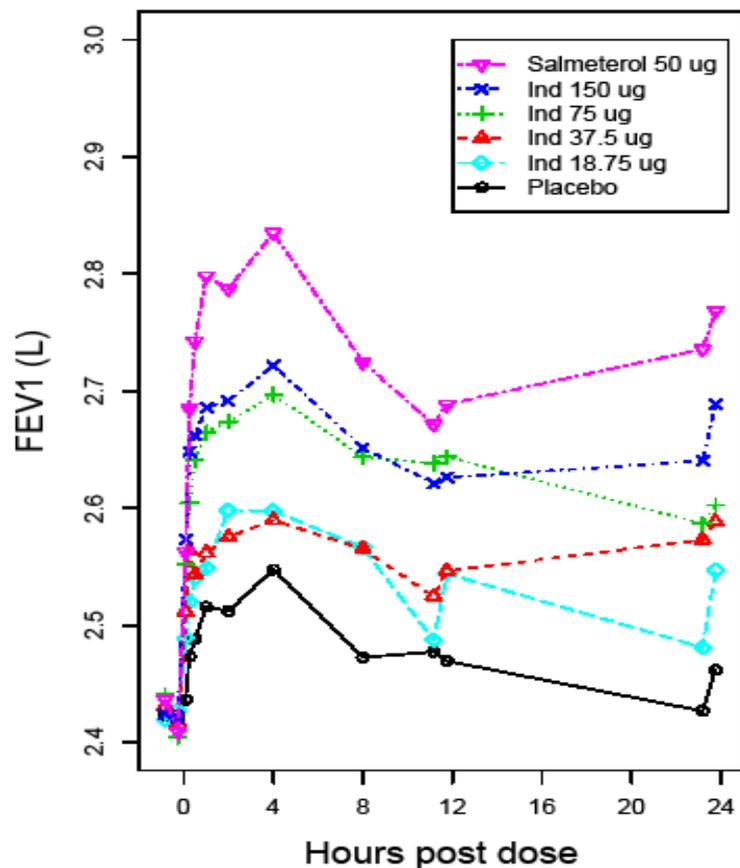
Trial ID [Patients]	Duration	Groups	N (ITT)	Primary efficacy variable	Countries and Regions
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B2356 [COPD]	2 wks	Indacaterol 18.75 mcg QD Indacaterol 37.5 mcg QD Indacaterol 75 mcg QD Indacaterol 150 mcg QD Salmeterol 50 mcg BID Placebo	89 90 94 92 91 91	FEV1 trough at 24 hr at day 15	US
B2223 [Asthma]	2 wks	Indacaterol 37.5 mcg BID Indacaterol 75 mcg QD Indacaterol 150 mcg QOD Placebo	48 48 48 47	FEV1 trough at 24 hr at wk 2	US, and International

B2357 Result Summary (Asthma dose ranging)

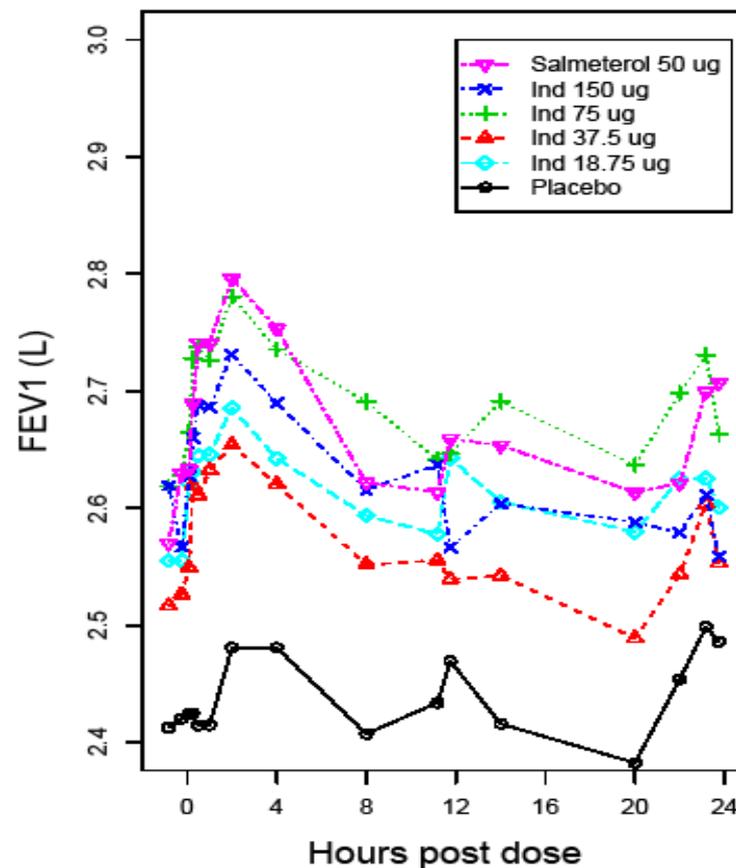


B2357 FEV₁ Profiles (Asthma dose ranging)

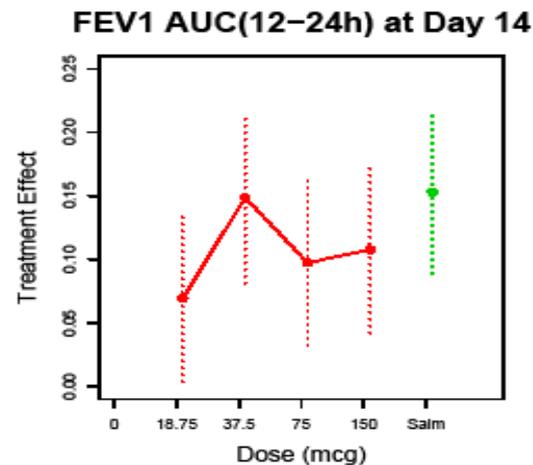
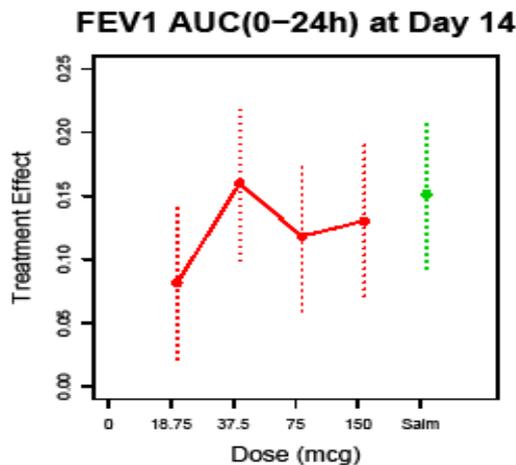
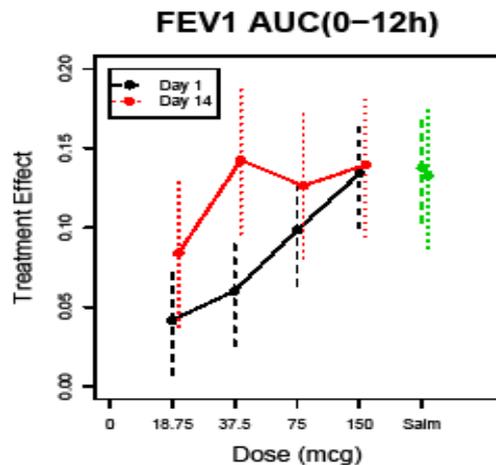
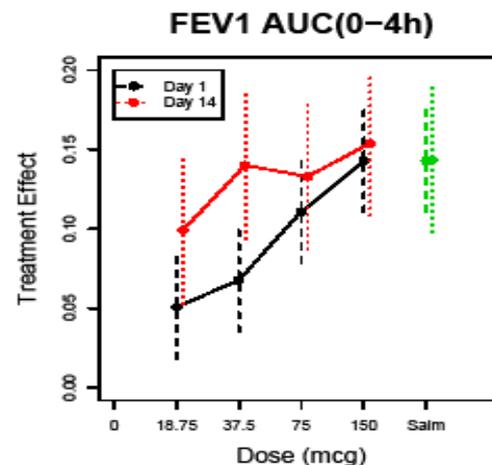
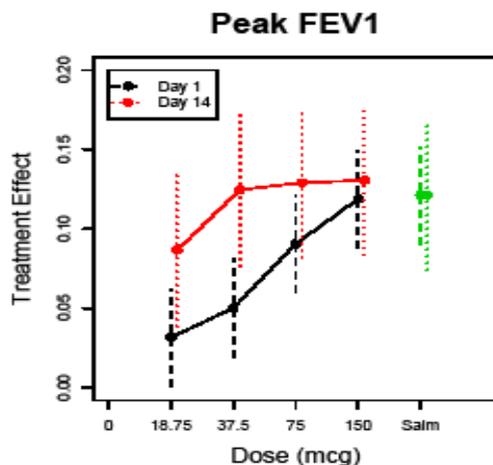
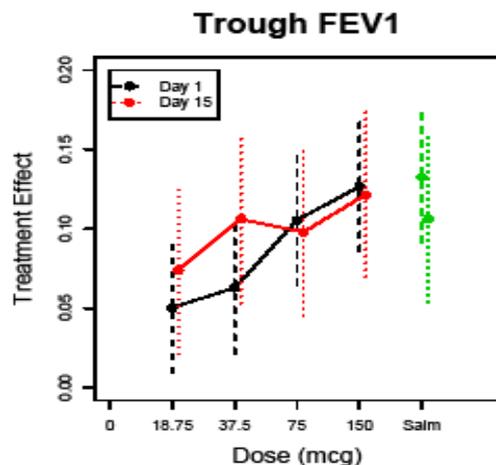
Day 1 (the first dose)



Week 2 (the last dose)

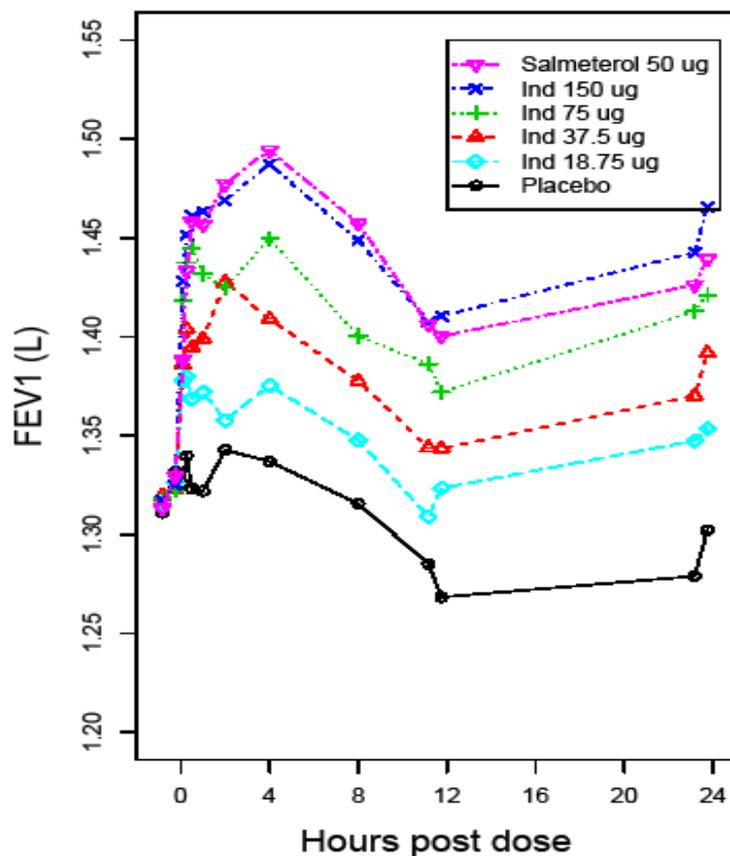


B2356 Result Summary (COPD dose ranging)

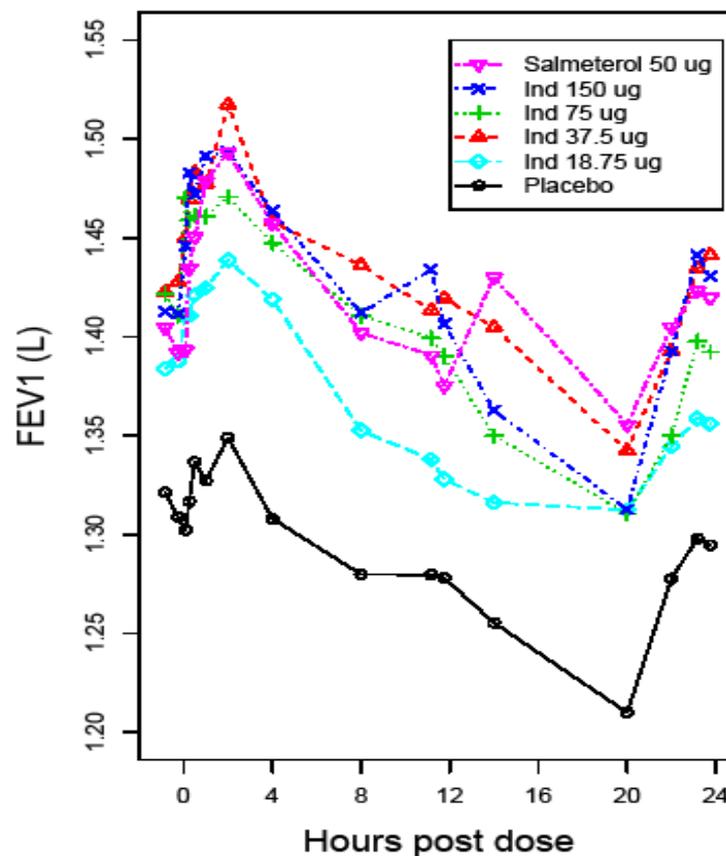


B2356 FEV₁ Profiles (COPD dose ranging)

Day 1 (the first dose)

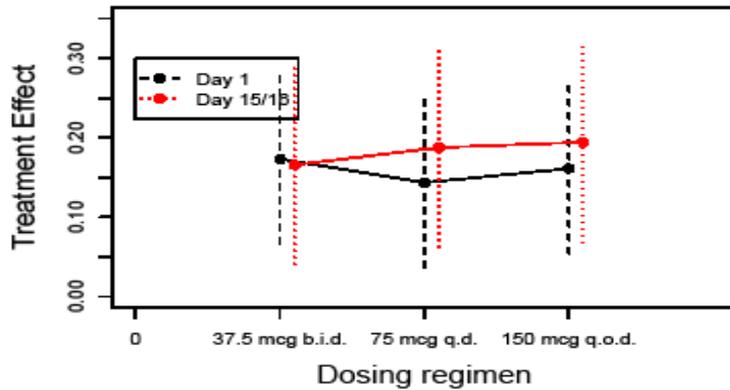


Week 2 (the last dose)

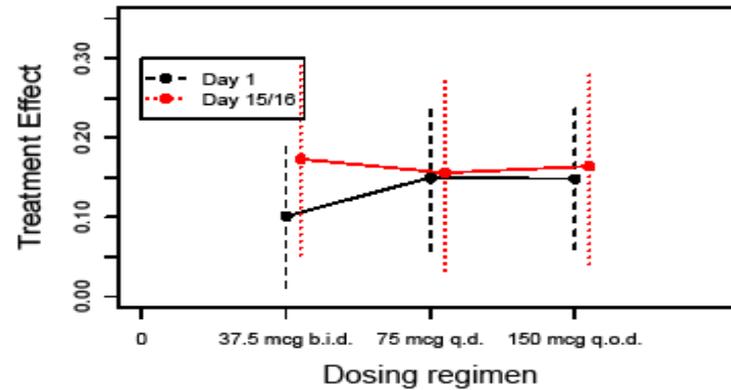


B2223 Result Summary (Asthma dosing frequency)

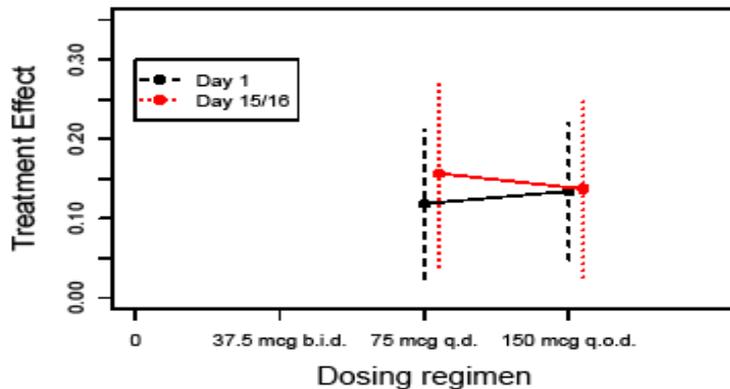
Trough FEV1



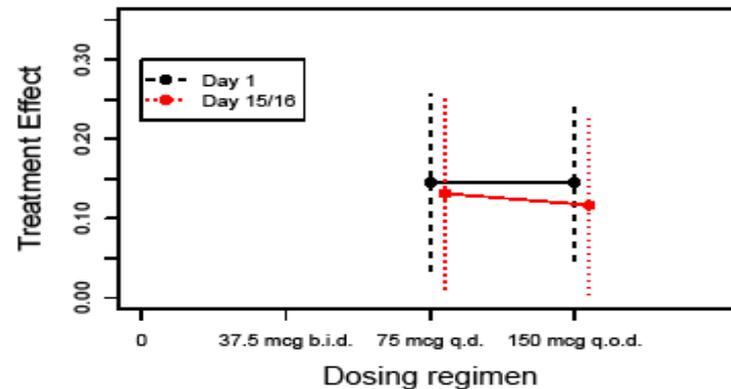
FEV1 AUC(0-24h)



FEV1 AUC(0-48h)

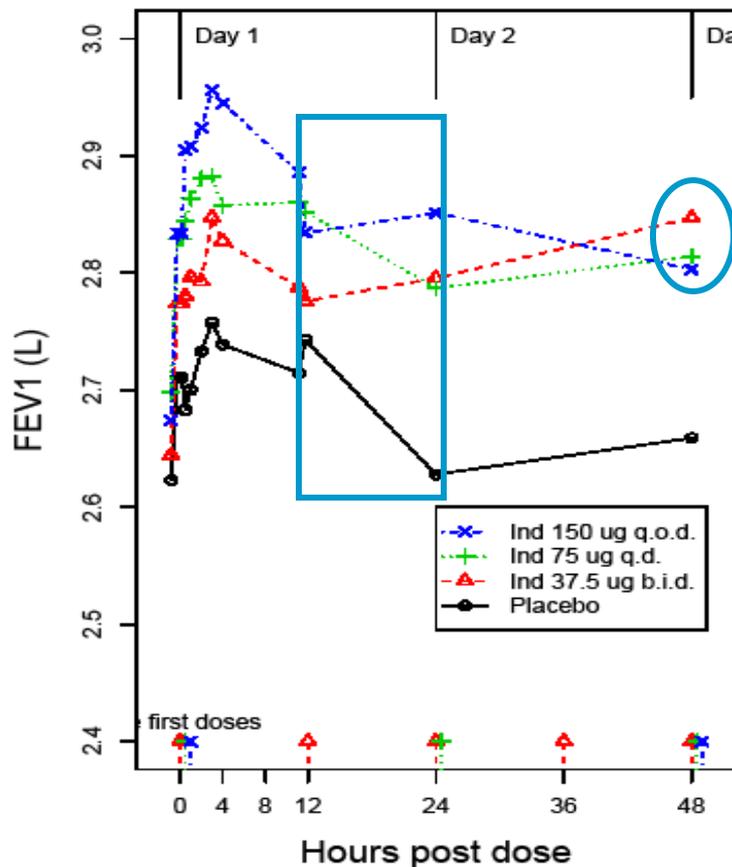


FEV1 AUC(24-48h)

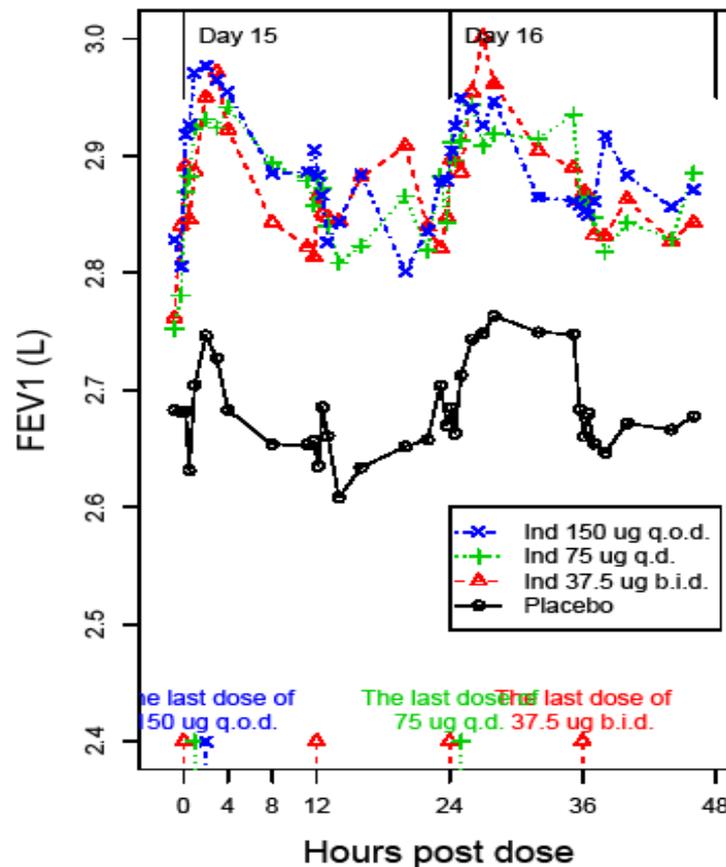


B2223 FEV₁ Profiles (Asthma dosing frequency)

Day 1 (the first dose)

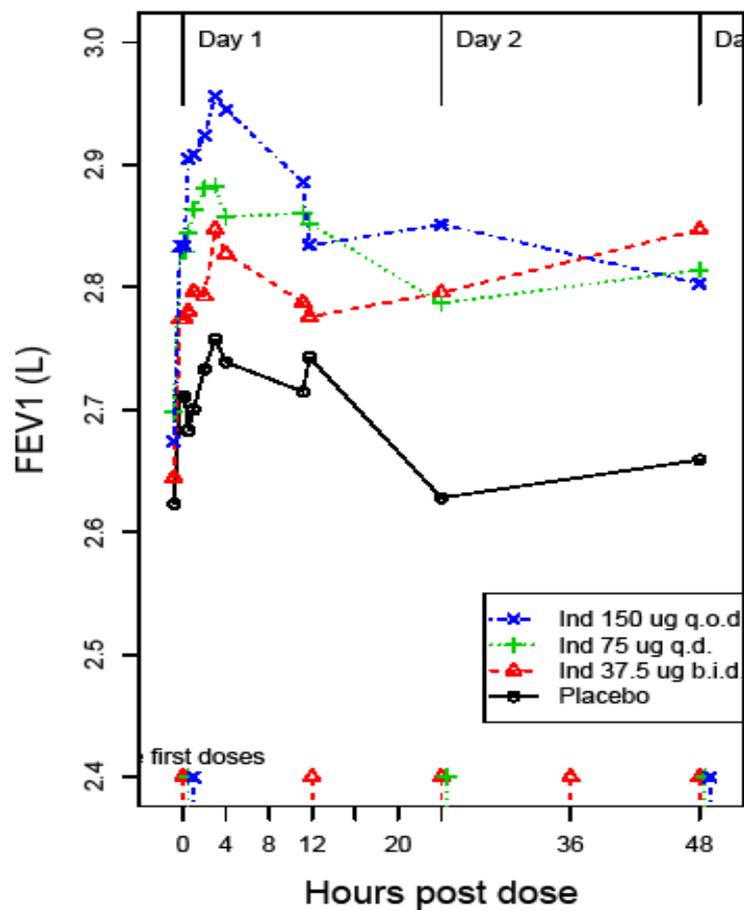


Day 15/16 (the last dose)

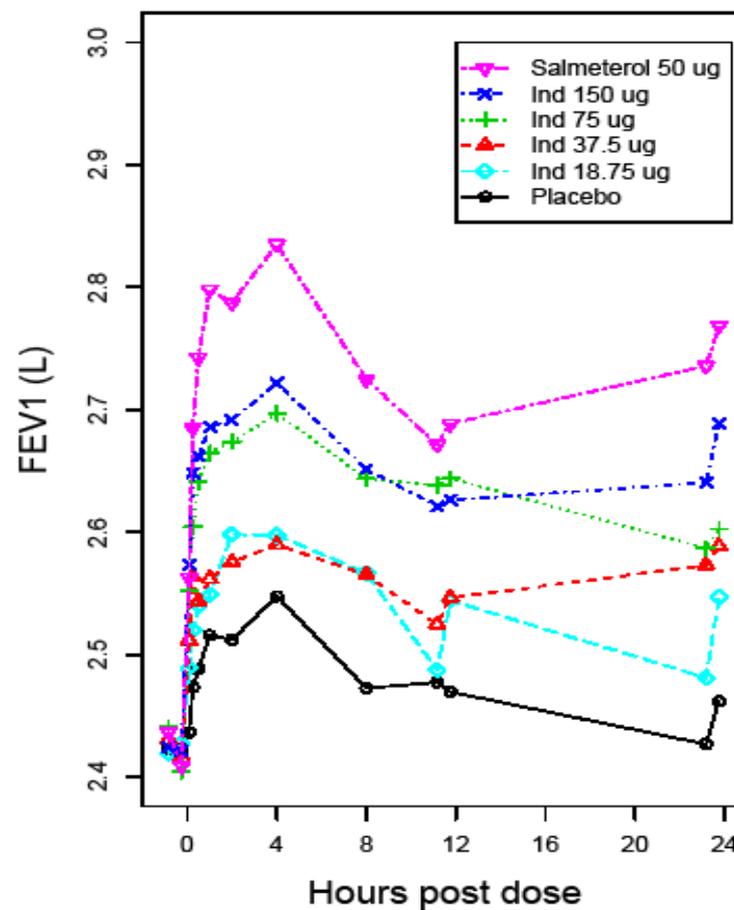


B2223 and B2357 Baseline FEV₁ Difference

B2223 Day 1 (the first dose)



B2357 Day 1 (the first dose)



Summary of Dose and Regimen Selection

- There was no clear separation among the doses and regimens studied.
- Multiple doses and regimens worked equally well in terms of efficacy.
- Which dose and regimen to approve is up for discussion at this meeting.

Issues for Discussion

- Whether the proposed doses of 75 mcg and 150 mcg and the once-daily dosing frequency are supported by the submitted data.
- Whether the second higher dose of 150 mcg is necessary and supported by the submitted efficacy data.

Outline

- Dose selection
 - In the original NDA
 - In the complete response
- Efficacy (comparison of 75 vs. 150 mcg)
 - Trough FEV₁
 - SGRQ



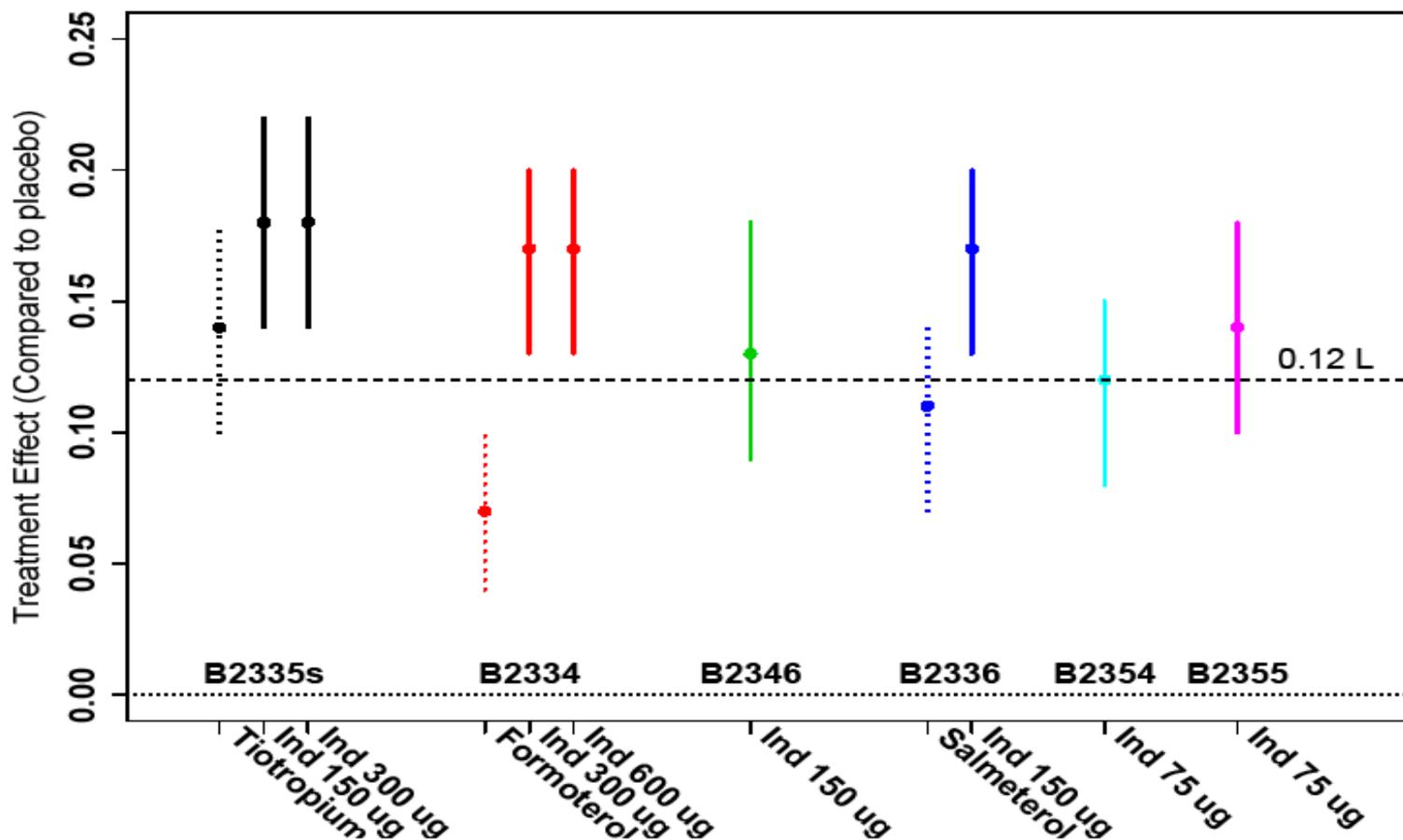
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Trough FEV₁ at Week 12 (ANCOVA)



COPD 3 Month Efficacy Population

- Consisted of double blind, placebo and/or active controlled trials of at least 12 weeks treatment in COPD patients
 - B2335S, B2346, B1302, B2333, B2336, B2349, B2350, B2354, B2355 and B2334.
 - Data are cut off at 3 months.
 - Focusing on the 75 mcg and 150 mcg doses of indacaterol.

Summary of Trough FEV₁ in COPD 3 Month Efficacy Population

Treatment	N	LS Mean (L)	SE (L)	Comparison	LS Mean (L)	95% CI (L)	P value
Placebo	1605	1.30	0.010	---	---	---	---
Ind 75 mcg	404	1.44	0.015	Ind 75 mcg – Placebo	0.15	(0.12, 0.17)	<0.001
Ind 150 mcg	1731	1.45	0.010	Ind 150 mcg - Placebo	0.16	(0.14,0.18)	<0.001
				Ind 150 mcg – Ind 75 mcg	0.01	(-0.02, 0.04)	0.375
Ind 300 mcg	864	1.47	0.012	Ind 300 mcg – Placebo	0.17	(0.15, 0.19)	<0.001
				Ind 300 mcg – Ind 75 mcg	0.03	(0.00, 0.16)	0.073
				Ind 300 mcg – Ind 150 mcg	0.01	(-0.01, 0.04)	0.162

Summary of Efficacy on Trough FEV₁

- All indacaterol treatment arms were superior to the placebo arms
 - with the mean estimate of treatment difference between indacaterol and placebo exceeds 120 mL in all six trials.
- There was no clinically meaningful efficacy difference between the 75 mcg once daily dose and the 150 mcg or 300 mcg once daily doses.

Issue for Discussion

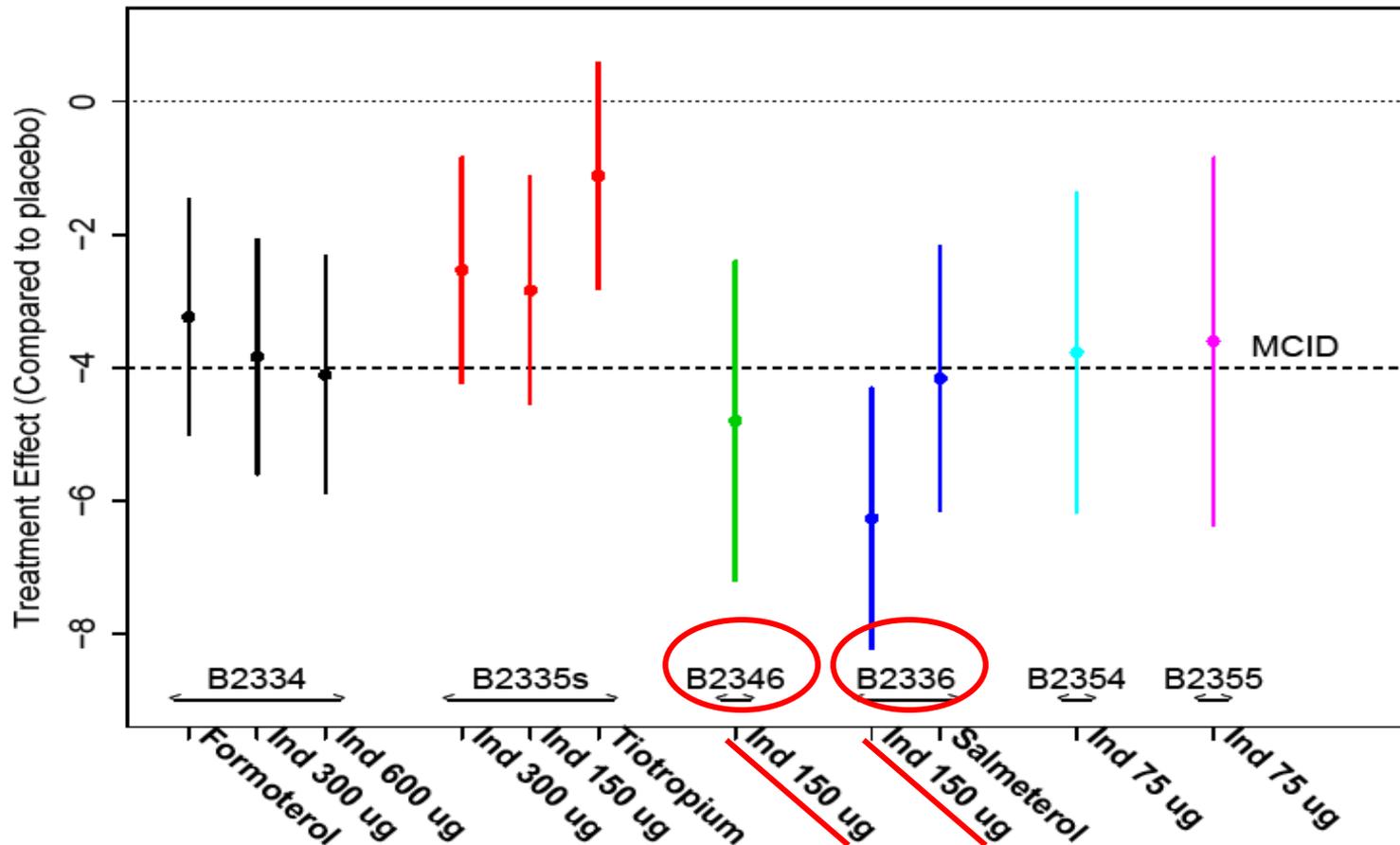
- Whether the second higher dose of 150 mcg is necessary and supported by the submitted efficacy data and balancing safety data

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 - SGRQ

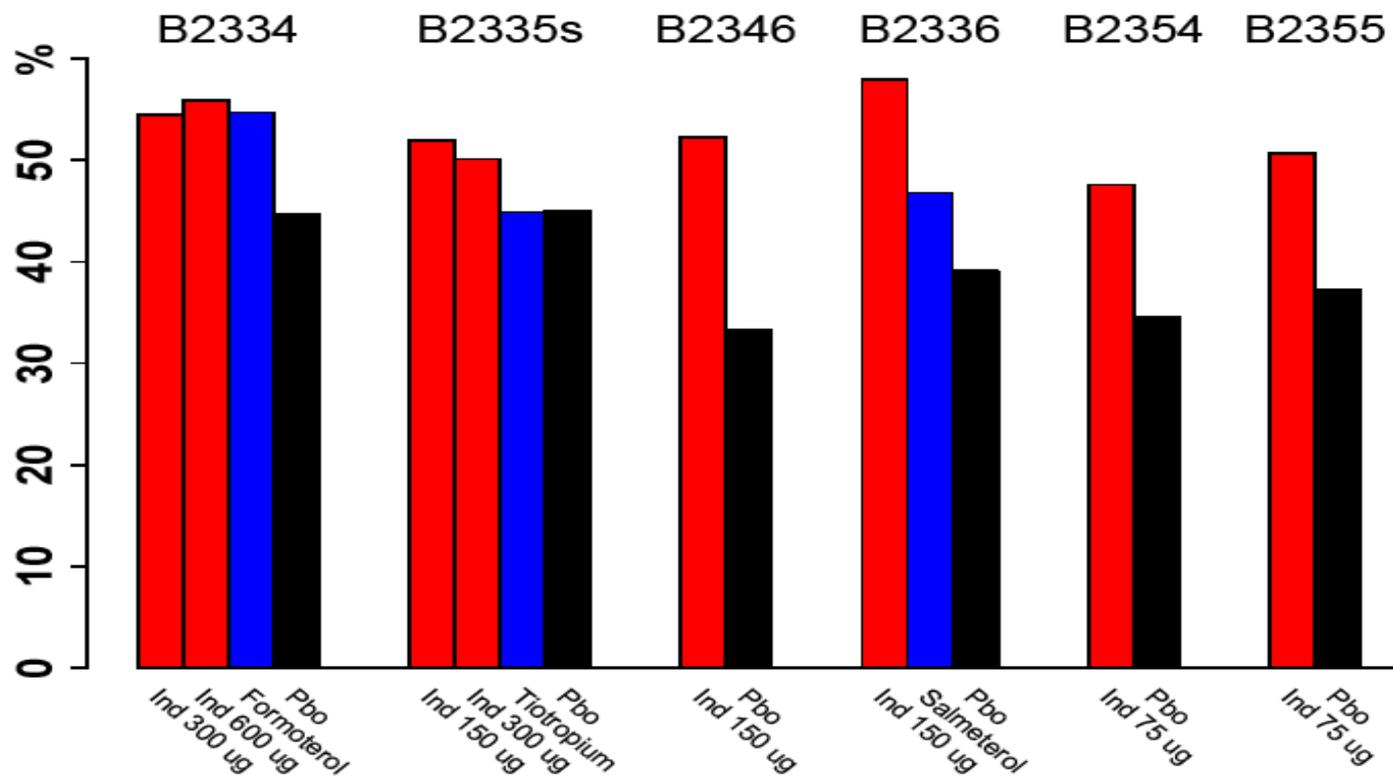
Summary of SGRQ Results

(ANCOVA analysis on total score at week 12)

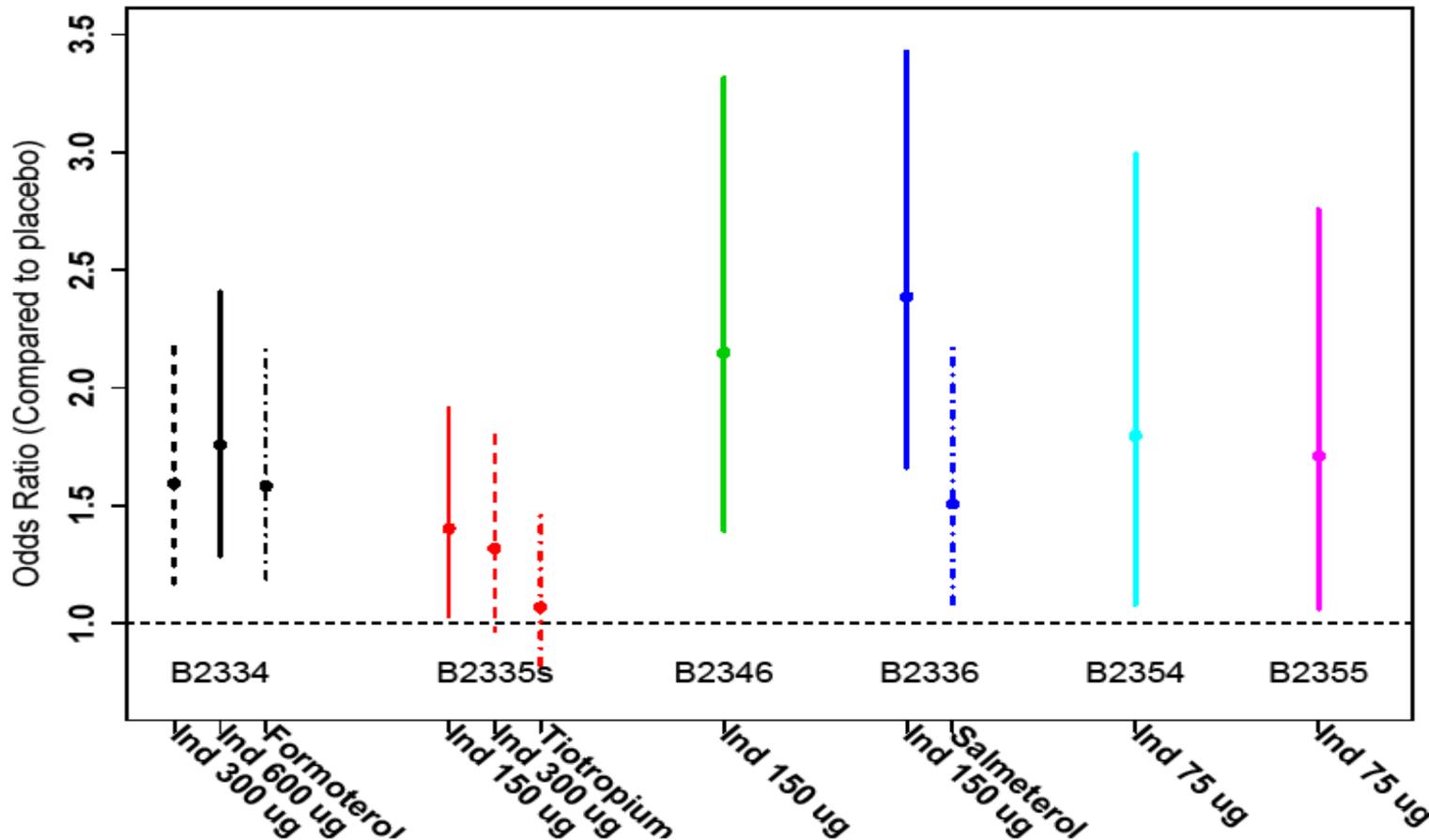


SGRQ Responder Analysis

(percentage of responders at week 12)



SGRQ Responder Analysis (odds ratio at week 12)



SGRQ Summary in COPD 3 Month Efficacy Population (ANCOVA analysis on total score)

Treatment	N	LS Mean (L)	SE	Comparison	LS Mean (L)	95% CI	P value
Placebo	1562	41.6	0.6	---	---	---	---
Ind 75 mcg	407	37.9	0.8	Ind 75 mcg – Placebo	-3.8	(-5.3, -2.3)	<0.001
Ind 150 mcg	1727	37.1	0.5	Ind 150 mcg - Placebo	-4.6	(-5.5, -3.6)	<0.001
				Ind 150 mcg – Ind 75 mcg	-0.8	(-2.4, 0.9)	0.358
Ind 300 mcg	853	37.8	0.6	Ind 300 mcg – Placebo	-3.8	(-4.9, -2.8)	<0.001
				Ind 300 mcg – Ind 75 mcg	0.0	(-1.8, 1.7)	0.956
				Ind 300 mcg – Ind 150 mcg	0.7	(-0.4, 1.9)	0.224

SGRQ Summary in COPD 3 Month Efficacy Population (Responder analysis)

Treatment	n/N	%	Comparison	Odds ratio	95% CI	P value
Placebo	617 / 1562	40	---	---	---	---
Ind 75 mcg	200 / 407	49	Ind 75 mcg / Placebo	1.7	(1.3, 2.2)	<0.001
Ind 150 mcg	904 / 1727	52	Ind 150 mcg / Placebo	1.8	(1.5, 2.2)	<0.001
			Ind 150 mcg / Ind 75 mcg	0.9	(0.7, 1.3)	0.674
Ind 300 mcg	440 / 853	52	Ind 300 mcg / Placebo	1.6	(1.3, 2.0)	<0.001
			Ind 300 mcg / Ind 75 mcg	1.1	(0.8, 1.4)	0.718
			Ind 300 mcg / Ind 150 mcg	1.1	(0.9, 1.4)	0.260

Summary of Efficacy on SGRQ

- The superiority of indacaterol over placebo in SGRQ scores was confirmed in all doses.
- The differences among indacaterol doses were small.
- Whether the improvement in SGRQ scores could be claimed as an advantage for the dose of 150 mcg is questionable.

Issue for Discussion

- Whether the SGRQ benefit claim is supported, and whether the SGRQ data provide supportive evidence of efficacy for any of the doses



FDA Advisory Committee Meeting, March 8, 2011

New Drug Application (NDA) from Novartis for indacaterol inhalation powder for chronic obstructive pulmonary disease (COPD)

Anya C. Harry, MD, PhD

Division of Pulmonary, Allergy, and Rheumatology Products

Office of New Drugs

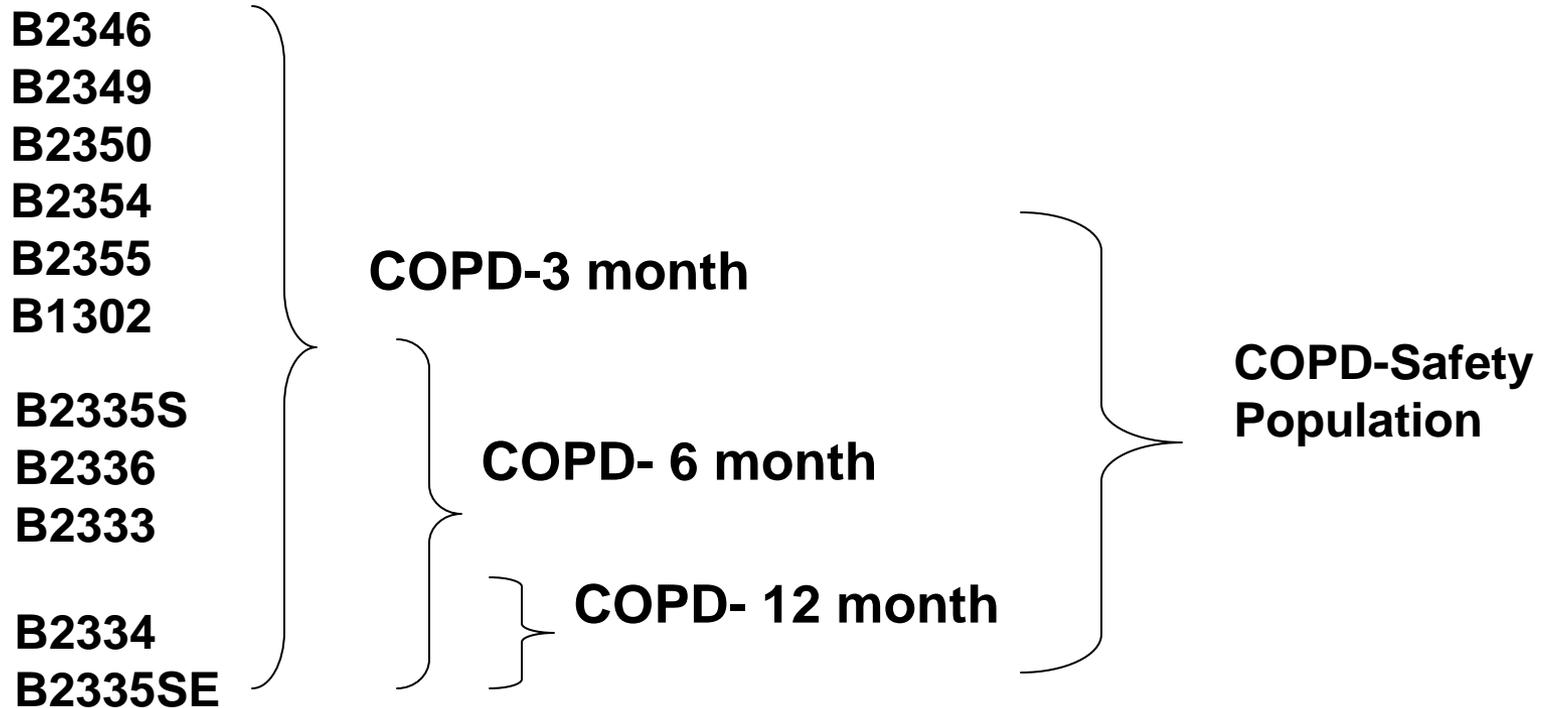
Center for Drug Evaluation and Research

US Food and Drug Administration

Safety Overview

- Summary of clinical safety in COPD
- Summary of clinical safety in Asthma
- Postmarketing

COPD Safety Dataset





Exposure

Indacaterol treatment groups					Control treatment groups			
	75 mcg	150 mcg	300 mcg	600 mcg	For	Tio	Sal	Pbo
COPD Safety Population								
Exposure (days)	N=449	N=2611	N=1157	N=547	N=556	N=1214	N=895	N=2012
<i>Mean</i>	86	120	233	263	260	108	112	168
<i>sd</i>	26	75	123	135	133	49	51	116
<i>min- max</i>	2 - 179	1 - 385	1 - 420	1 - 407	1 - 397	1 - 208	1 - 215	1 - 403

Demographics

	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 safety population								
Age mean (years)	64	64	64	63	64	64	63	64
Gender- %								
Male	55	70	78	73	75	66	74	71
Female	45	30	22	27	25	34	26	29
Race- %								
Caucasian	92	78	67	92	92	91	82	75
Black	4	2	1	1	0.5	1	1	2
Asian	2	18	30	3	2	4	13	21
Other	1	3	2	4	5	3	3	3



Disease Characteristics

	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 safety population								
Duration mean (yrs)	7	7	6	7	7	7	7	7
Severity-%								
<i>Moderate</i>	62	57	53	53	52	58	53	52
<i>Severe</i>	36	40	43	41	42	39	44	43
Mean % reversibility after albuterol	17	14	14	14	13	14	13	15
Baseline ICS use- (%)	42	44	42	50	50	49	46	41
Current smoker- %	48	44	39	41	41	44	45	43



Deaths

COPD safety dataset

Indacaterol treatment group				Control treatment group			
Cause of death Preferred term	Ind 150 mcg N=2611	Ind 300 mcg N=1157	Ind 600 mcg N=547	For N=556	Tio N=1214	Sal N=895	Pbo N=2012
Myocard. infarction	1	1					3
Cardiac arrest	2	1			1		2
Sudden death	1			1			3
Respiratory			1	1		1	1
Pneumonia					1		
Other				2	2		5

Serious adverse events COPD safety dataset

COPD 3- month safety	75 mcg N=449	150 mcg N=2611	300 mcg N=1157	Pbo N=2012
Patients with SAEs (%)	3.3	3.8	3.3	4.4
Respiratory, thoracic and mediastinal				
COPD	0.9	1.2	0.7	1.6
Infection and infestations				
Pneumonia	0.5	0.3	0.4	0.2
COPD 12- month safety	75 mcg ---	150 mcg N=144	300 mcg N=583	Pbo N=556
Patients with SAEs (%)	---	10.4	13.9	11
Respiratory, thoracic and mediastinal				
COPD	---	2.8	4	4.1
Cardiac				
Atrial fibrillation	---	0.7	0.5	0.2



Adverse events

COPD 3-month safety population

COPD 3-month safety	75 mcg N=449	150 mcg N=2611	300 mcg N=1157	Pbo N=2012
Patients with ≥ 1 AE (%)	52	41	48	43
Respiratory, thoracic and mediastinal disorders				
COPD	8.5	9.2	11.8	13.4
Nasopharyngitis	5.4	4.4	5.8	4.4
Cough	6.5	4.0	5.2	3.6
Oropharyngeal pain	2.2	1.2	1.1	0.7
Nervous system disorders				
Headache	5.1	3.1	2.3	2.2
Muscle Spasms	1.3	1.5	2.2	0.8
Gastrointestinal				
Nausea	2.5	1.1	0.7	0.9

Cardio- and cerebrovascular SAEs COPD safety dataset

Treatment Groups					
Safety Dataset	75 mcg	150 mcg	300 mcg	For	Pbo
COPD 3- month safety					
<i>N</i>	449	2611	1157	556	2012
<i>SAE (%)</i>	0.45	0.92	0.69	0.18	0.65
COPD 12- month safety					
<i>N</i>	---	144	583	434	556
<i>SAE (%)</i>	---	0.69	3.09	1.38	1.44

Adverse events of interest COPD safety dataset

- Post inhalational cough
 - Indacaterol treated 23-31%
 - Placebo 3-6%
 - Short duration ≤ 15 sec
 - No decrease in FEV1

Safety Overview

- Summary of clinical safety in COPD
- **Summary of clinical safety in Asthma**
- Postmarketing

Asthma safety dataset

- 13 trials
- 8 trials with 1- 4 weeks duration, most small population size of 40-150
- Doses 18.75 mcg to 800 mcg
- B2338: 26 weeks, 800 patients enrolled, evaluated safety of indacaterol 300 mcg and 600 mcg

Deaths: Asthma trials

- Two deaths in Trial B2338
- 60 y.o. male PMH of asthma x 7 years
 - Respiratory medications: budesonide 400 mcg BID
 - Day 165 hospitalization x 1day with “asthmatic crisis”
 - Day 169 recurrent acute asthma exacerbation → Died *en route* to the hospital
- 75-y.o. woman PMH asthma x 2 years
 - Respiratory medications: mometasone 220 mcg QD
 - Day 119 cardiac arrest at home → Resuscitated
 - Small pneumothorax and pulmonary hyperinflation
 - Life support withdrawn on Day 11 of hospitalization

Respiratory-related SAEs

Asthma trials

	Ind 150 mcg N=168	Ind 300 mcg N=426	Ind 400 mcg N=459	Ind 600 mcg N=460	Ind 800 mcg N=59	Sal N=377
Asthma exacerbation	1	2		3	1	1
Bronchospasm			1		1	
Hyperventilation			1			
Total	1	2	2	3	2	1

Respiratory-related AE leading to discontinuation in asthma trials

	Ind 18.75 mcg N=84	Ind 300 mcg N=426	Ind 400 mcg N=459	Ind 600 mcg N=460	Ind 800 mcg N=59	Sal N=377	Pbo N=422
Asthma exacerbation	1	4	1	6	1	4	2
Bronchospasm					1		
Hyperventilation							
Cough			1	2	1	1	
Total	1	4	2	8	3	5	2

Postmarketing: Mexico Patient Support Program

- September 26, 2010- January 4, 2011
- 1316 patients most with severe COPD
- Solicited events and spontaneous reports
- 16 deaths reported (1.2%)
 - Respiratory (3 pneumonias, 1 respiratory insufficiency, 1 COPD, and 1 pulmonary embolism)
 - Cardiac (1 CHF, 2 cardiac arrests)
 - Cancer (breast, lymphoma, GI)
 - 2 deaths unknown cause, 1 GI bleed, 1 progression of Wegener's disease
- 11 out of 16 deaths were in patients ≥ 75 years of age

Issues

- Whether the proposed doses of 75 mcg and 150 mcg and the once-daily dosing frequency is supported by submitted data
- Whether the second higher dose of 150 mcg is necessary and supported by submitted efficacy data and balancing safety data
- Whether the SGRQ benefit claim is supported, and whether the SGRQ data provide supportive evidence of efficacy for any of the doses
- **Safety of the proposed dose and dosing regimen of indacaterol**

Safety Summary

- SAEs overall were comparable across treatment groups
- CCV events occurred at higher rates with the 300 mcg dose, no apparent consistent signal at 75 mcg and 150 mcg Ind treatment groups
- More asthma related events appeared at higher doses, notably 300 and 600 mcg doses
- Most common AEs
 - Nasopharyngitis, cough, headache, upper respiratory tract infection and muscle spasms
 - Post inhalational cough



FDA Advisory Committee Meeting, March 8, 2011

**New Drug Application (NDA) from Novartis
for indacaterol inhalation powder for chronic
obstructive pulmonary disease (COPD)**

Banu A. Karimi-Shah, MD

Medical Officer, Division of Pulmonary, Allergy, and
Rheumatology Products

Center for Drug Evaluation and Research

US Food and Drug Administration

Objective

- To discuss serious respiratory adverse events in COPD patients
 - Death
 - Hospitalizations
 - Intubations

Rationale for Meta-analysis

- Known asthma safety signal with other LABAs
- Possible asthma-related deaths in indacaterol development program
 - Both deaths occurred in 300 mcg dose group (Trial B2338)
- Rare events occurred in a relatively small number of patients
- Post-marketing asthma-related death
- Need for balancing safety data to justify the proposed higher dose (150 mcg) of indacaterol. ³

Information Request to Novartis: Dec. 16, 2010

- Conduct an analysis evaluating the incidence of respiratory-related death, intubation, and hospitalization in indacaterol-treated patients compared to control.
- Implement an adjudication committee to review all SAEs in blinded fashion to determine which of these events were respiratory related; classify events as asthma-, COPD-, or pneumonia-related.

Trials included in the meta-analysis

- All blinded trials (PC and AC) in asthma and COPD patients of >7 days duration using the to-be-marketed or similar device (even if not submitted to the NDA)
- Indacaterol administered as a randomized treatment with or without ICS
- Combination programs that had an indacaterol only treatment arm

Analysis Populations

All-treated safety population I	Any trial, AC/PC, COPD or asthma
All-treated safety population II	Similar to ALL1 but PC trials only
All-treated COPD safety population I	Any trials, AC/PC in COPD
All-treated COPD safety population II	Similar to COPD1, but PC trials only
All-treated asthma safety population I	Any trials, AC/PC in asthma
All-treated asthma safety population II	Similar to Asthma1, but PC trials only

Endpoints of Interest

- Hospitalizations, Intubations, and Deaths On-Treatment
 - 1. Asthma-related
 - 2. COPD-related
 - 3. Pneumonia-related
 - 4. Other respiratory-related (pulmonary embolus, lung cancer)
 - 5. Non respiratory-related
- Acute Respiratory-Related**
- Total Respiratory-Related**

COPD Safety Population I

- 23 trials
- Total N = 11,755
 - Indacaterol-treated = 6,863 patients
 - Placebo-treated = 2,482 patients
 - Active control-treated = 2,408
- Majority of the trials: > 12 weeks in duration
- Acute Respiratory-Related Event: 219 patients



Total and Acute Respiratory-Related Events: All-treated COPD Safety Population I

	Indacaterol Treatment Groups (mcg)						Active Comparators			PBO n=2484
	75 n=543	150 n=2745	150 +Tio n=1142	300 n=1422	600 n=584	ALL n=6863	For n=556	Tio n=842	Sal n=1010	
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)

Asthma Safety Population I

- Contributed fewer patients to meta-analysis
- 3 hospitalizations each in 300 mcg and 600 mcg groups vs. none in the placebo group
- 1 death (asthma-related) and 1 intubation in 300 mcg indacaterol group (Trial B2338)
 - Second death occurred off-treatment
 - Notable that it was classified as “COPD-related”

Conclusions

- Numerical trend of increasing incidence of acute respiratory-related events in COPD patients
 - Driven primarily by an increase in hospitalizations
- Potential existence of signal in COPD warrants further discussion and underscores the importance of selecting the lowest effective dose of a beta-agonist bronchodilator



FDA Advisory Committee Meeting

March 8, 2011

New Drug Application (NDA) from Novartis
seeking approval of indacaterol for
Chronic Obstructive Pulmonary Disease
(COPD)

Theresa M. Michele, MD

Clinical Team Leader, Division of Pulmonary, Allergy,
and Rheumatology Products

Center for Drug Evaluation and Research

US Food and Drug Administration

Issues

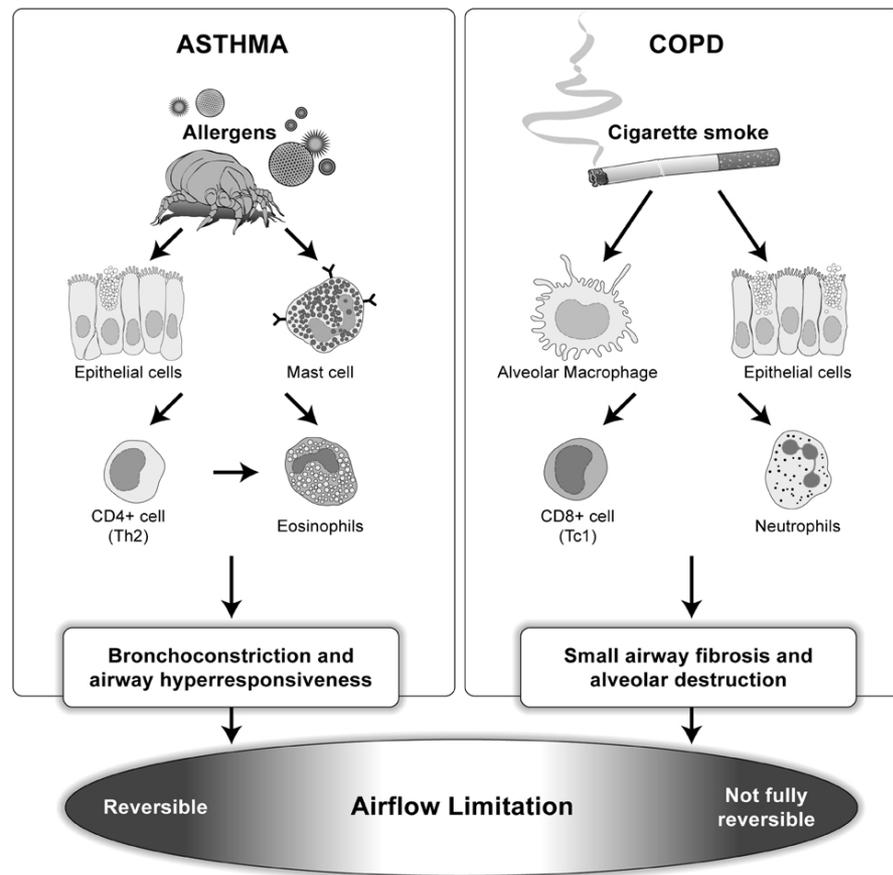
- Whether the proposed doses of 75 mcg and 150 mcg and the once-daily dosing frequency are supported by submitted data **Dose**
- Whether the second higher dose of 150 mcg is necessary and supported by submitted efficacy data and balancing safety data **150 mcg**
- Whether the SGRQ benefit claim is supported, and whether the SGRQ data provide supportive evidence of efficacy for any of the doses **SGRQ**
- Safety of the proposed dose and dosing regimen of indacaterol **Safety**

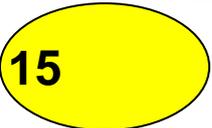
Dose

Safety

Rationale for Asthma Studies

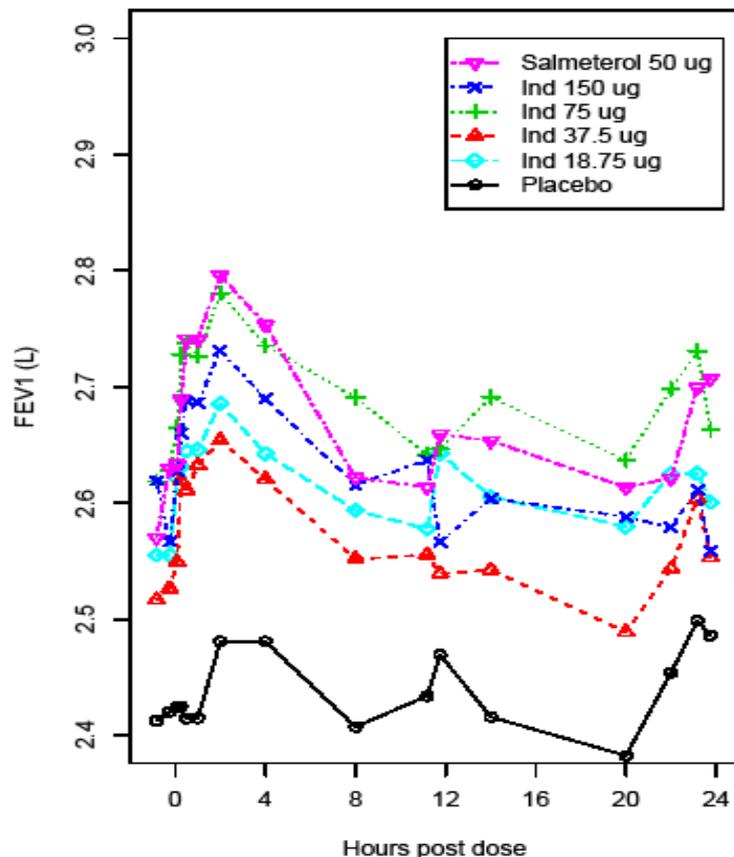
- Both COPD and asthma have airflow limitation; disease overlap
- Airflow limitation is on a spectrum
- Dose separation is more likely if there is a greater variation possible
- Asthma safety is potential concern for COPD





Efficacy: Bronchodilator Effect

Week 2 (the last dose)

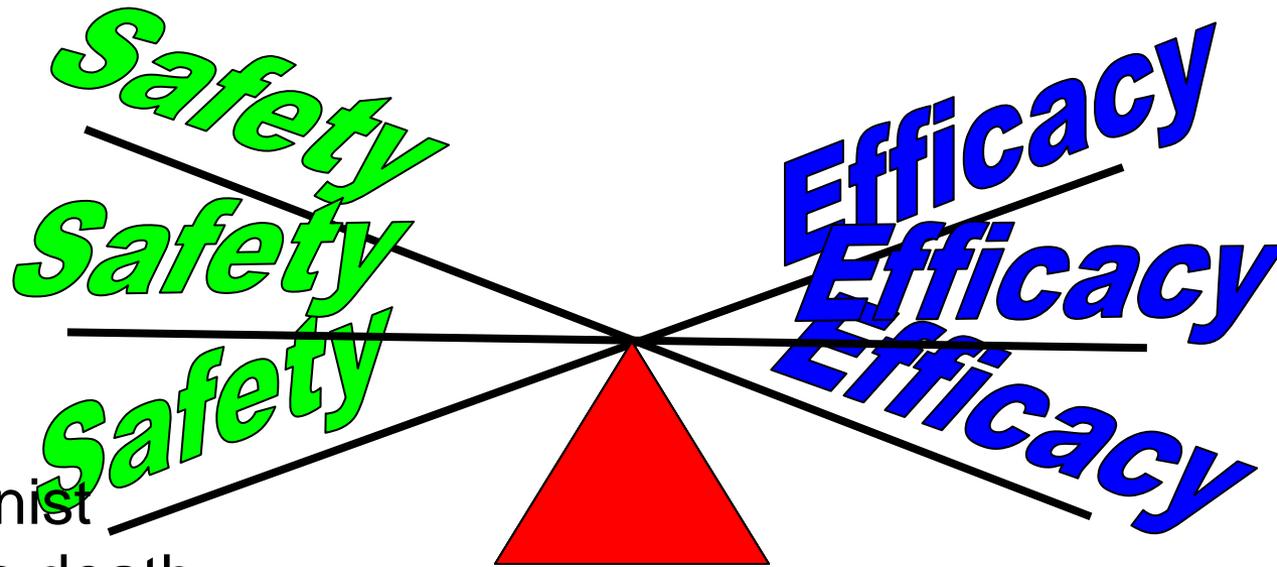


Trial B2357: asthma

- All doses have bronchodilator effect
- Larger separation at Day 1, but indacaterol is a chronic drug
- Slightly different profile in COPD
 - 37.5=75=150
- Frequency data
 - BID=QD=QOD

150 mcg

Support for Higher Dose??



- β -agonist
- Asthma death
- COPD events
- Cardiovascular
- Cough

- Bronchodilator
- FEV1
- SGRQ

150 mcg

SGRQ

Higher dose = Greater Efficacy?

- New paradigm; no bronchodilator with two different doses in adult population
- Modeling data
 - Sponsor claims additional benefit for more severe patients
 - Emax model sensitive to data → not a robust finding
- SGRQ: 3-month efficacy

	75 mcg	150 mcg	300 mcg	Placebo
Mean score difference (95% CI)	-3.8 (-5.3, -2.3)	-4.6 (-5.5, -3.6)	-3.8 (-4.9, -2.8)	--
% Responders	49	52	52	40

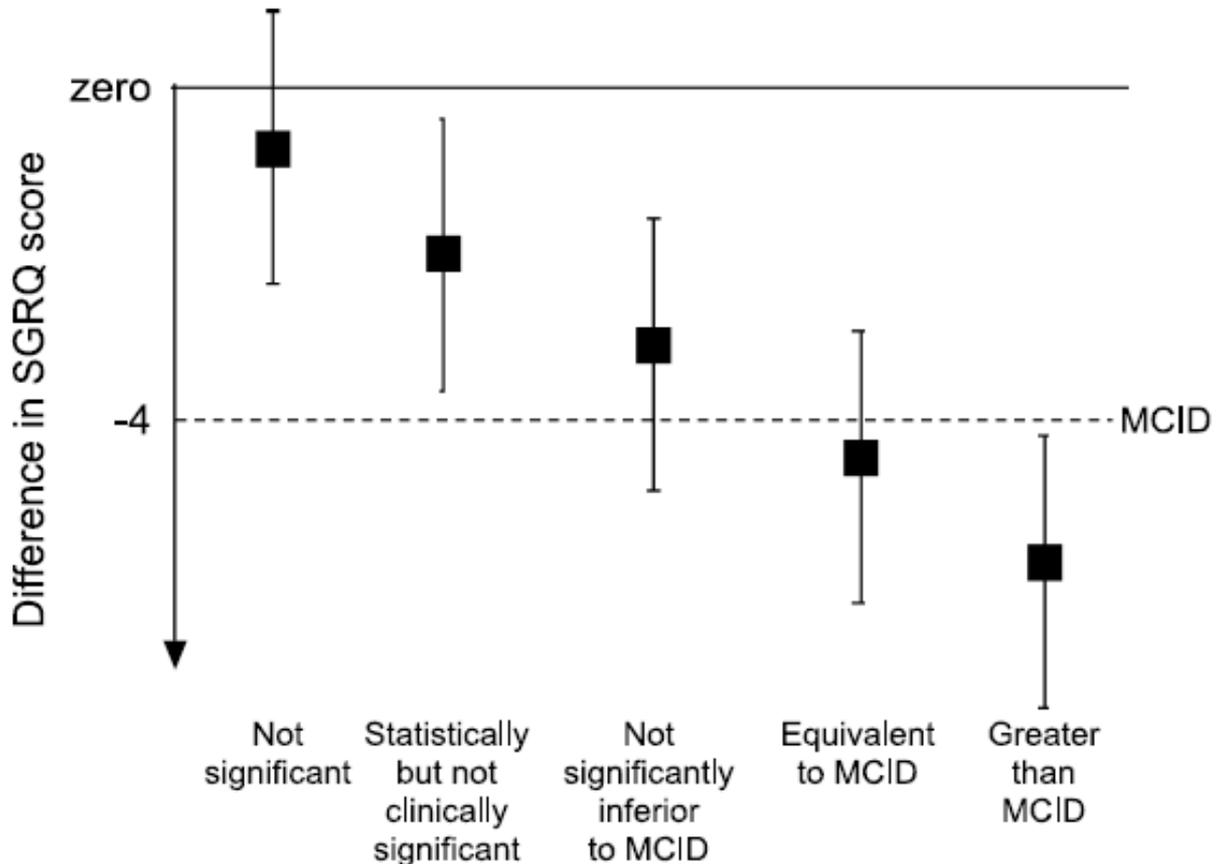
SGRQ

St. George's Respiratory Questionnaire

- Health related quality of life measurement first developed by Jones 1991
- Estimating the Minimum Clinically Important Difference (MCID)
 - Expert preference
 - Patient preference
 - Anchor based
 - Distribution based
 - Clinical trial results as anchors
- How does MCID apply to clinical trial results?

SGRQ

SGRQ Minimum Clinically Important Difference



SGRQ

150 mcg

SGRQ Summary

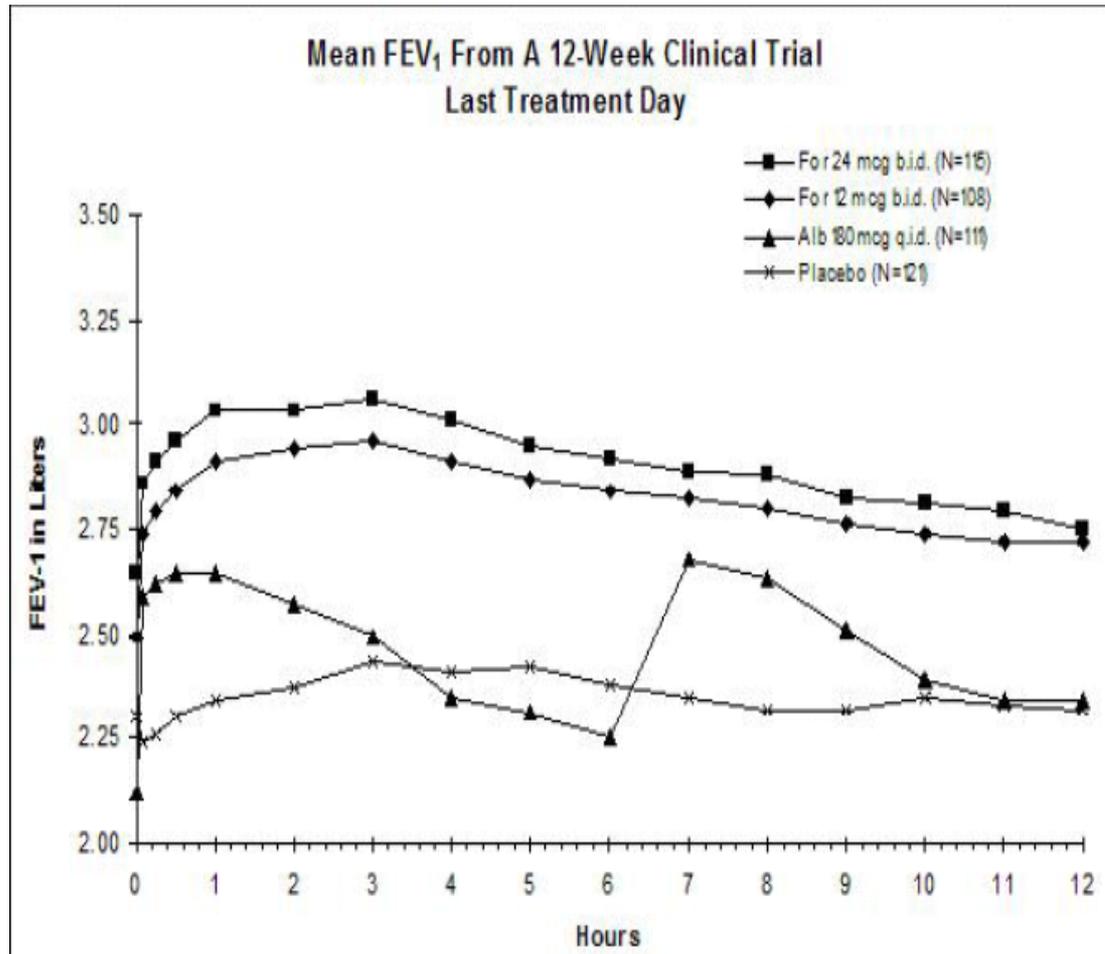
- SGRQ meets MCID of -4 for 150 mcg dose in two trials, but not in one other
- 75 mcg and 300 mcg doses do not meet MCID → U-shaped dose-response curve??
- Confidence intervals for 75 and 150 mcg widely overlapping
- 75 mcg and 150 mcg not tested together in same trial

Safety

Higher Dose Safety?

Example: Foradil Aerolizer

150 mcg



SafetyDose

Safety

- Intrinsically linked to dose selection
- Asthma-related exacerbations/death
 - Deaths on concurrent ICS in Trial B2338
 - Trend towards dose-related increase in COPD-related events in meta-analysis
 - Numerically more asthma-related events in indacaterol groups

Issues

- Whether the proposed doses of 75 mcg and 150 mcg and the once-daily dosing frequency are supported by submitted data
- Whether the second higher dose of 150 mcg is necessary and supported by submitted efficacy data and balancing safety data
- Whether the SGRQ benefit claim is supported, and whether the SGRQ data provide supportive evidence of efficacy for any of the doses
- Safety of the proposed dose and dosing regimen of indacaterol

Dose

150 mcg

SGRQ

Safety



Thank You!



FDA Advisory Committee Meeting

March 8, 2011

New Drug Application (NDA) from Novartis
seeking approval of indacaterol for
Chronic Obstructive Pulmonary Disease
(COPD)

Theresa M. Michele, MD

Clinical Team Leader, Division of Pulmonary, Allergy,
and Rheumatology Products

Center for Drug Evaluation and Research

US Food and Drug Administration

Issues

- Whether the proposed doses of 75 mcg and 150 mcg and the once-daily dosing frequency are supported by submitted data
- Whether the second higher dose of 150 mcg is necessary and supported by submitted efficacy data and balancing safety data
- Whether the SGRQ benefit claim is supported, and whether the SGRQ data provide supportive evidence of efficacy for any of the doses
- Safety of the proposed dose and dosing regimen of indacaterol

Dose

150 mcg

SGRQ

Safety

Approval of an Application - 21 CFR 314.105 (c)

“ FDA will approve an application after it determines that the drug meets the statutory standards for safety and effectiveness, manufacturing and controls, and labeling”

Efficacy Standard

- 21 CFR 314.125 Refusal to Approve an Application

(b) (5) “... substantial evidence consisting of adequate and well-controlled investigations ... that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.”

Safety Standard

- 21 CFR 314.125 Refusal to Approve an Application

(b) (2) "... do not include adequate tests by all methods reasonably applicable to show whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling."

(b) (3) "The results of the test show that the drug is unsafe for use under the conditions prescribed, recommended, or suggested in its proposed labeling or the results do not show that the drug product is safe for use under those conditions."

(b) (4) "There is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling."

Dose

SGRQ

150 mcg

Question 1

Discussion

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

150 mcg**Safety**

Question 2

Discussion

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

Dose

150 mcg

Question 3

SGRQ

Voting and Discussion

Considering the totality of the data, has indacaterol demonstrated substantial evidence of efficacy 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 (Discuss)

150 mcg

Safety

Question 4

Voting and Discussion

Is the safety 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 (Discuss)

150 mcg

SGRQ

Question 5

Voting

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)**

Dose

Safety

150 mcg

SGRQ

Question 6

Voting and Discussion

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)**

If yes, should the dose be

- a) 75 mcg once-daily? **(Voting question)**
- b) 150 mcg once-daily? **(Voting question)**
- c) If not, what further data should be obtained? (Discuss)