Benefits and Risks of Long Acting Beta-2 Agonists (LABAs) for the Treatment of Asthma

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Long-Acting Beta-Agonist Advisory Committee, Meeting
December 10, 2008

PURPOSE

- Discuss risks of LABA use for the asthma indication.
- Discuss benefits of LABA use for the asthma indication.
- Pose questions of risk versus benefits of LABA use for the asthma indication.

Outline

- Background
- Summarize highlights FDA meta-analysis: risks
- Summarize pivotal studies: benefits
- Weigh risks and benefits of the LABA products.
- Conclusions
- Recommendations
- Questions

BACKGROUND: Long-Acting Beta Agonist Approvals in US for asthma indication

Product Name	Year of Approval	Long-Acting Beta-Agonist	Corticosteroid	Approved Age Range (yrs)
Symbicort	2006	Formoterol fumarate	Budesonide	≥12
Serevent Diskus	1997	Salmeterol xinofoate	None	≥12
Advair HFA	2006	Salmeterol xinofoate	Fluticasone	>12
Advair Diskus	2000	Salmeterol xinofoate	Fluticasone	≥4
Foradil Aerolizer	2001	Formoterol fumarate	None	≥5
Serevent MDI	1994	Salmeterol xinofoate	None	≥12
Foradil Certihaler	2006	Formoterol fumarate	None	≥5

Deaths from Asthma in Two Randomized Trials of Salmeterol Safety

Study	Population	Number salmeterol treated with outcome/ exposed	Number in control arm with outcome/ exposed	Relative Risk (95% CI)
SNS[1]	General practices in United Kingdom	12/16,787	2/8,393	3.0 (0.7-20)
SMART[2]	United States, multicenter	13/13,176	3/13,179	4.37 (1.25-15.34)

[1]Castle W, Fuller R, Hall J, Palmer J. BMJ, 1993;306: 1034-1037.
[2]Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM, Study Group. Chest, 2006;129:15-26.

Key Meta-Analyses* on Outcomes with LABA Use for Asthma

First author	Total N	LABA and comparator	Trial duration mean/median (months)	Odds Ratio (95% CI) Asthma exacerbation Adults;children
Cates et al.	8,032	formoterol and placebo or salbutamol	4	1.57 (1.05-2.37); 2.92 (1.26-6.74)
Salpeter et al.	33,826	salmeterol or formoterol and placebo	6	2.6 (1.6-4.3); 3.9 (1.7-8.8)
Bateman et al.	20,966	salmeterol+ICS and ICS	3	1.07 (0.66-1.73)

1CatesCJet al. Cochrane Database of Systematic Reviews 2008, Issue 4. Art. No.: CD006923. DOI:10.1002/14651858. CD006923.pub2.
2Salpeter SR et al. Meta-analysis: Ann Intern Med 2006;144:904-912.
3Bateman E et al. Ann Intern Med, 2008;149:33-42.
*Also see Table 4A OSE review

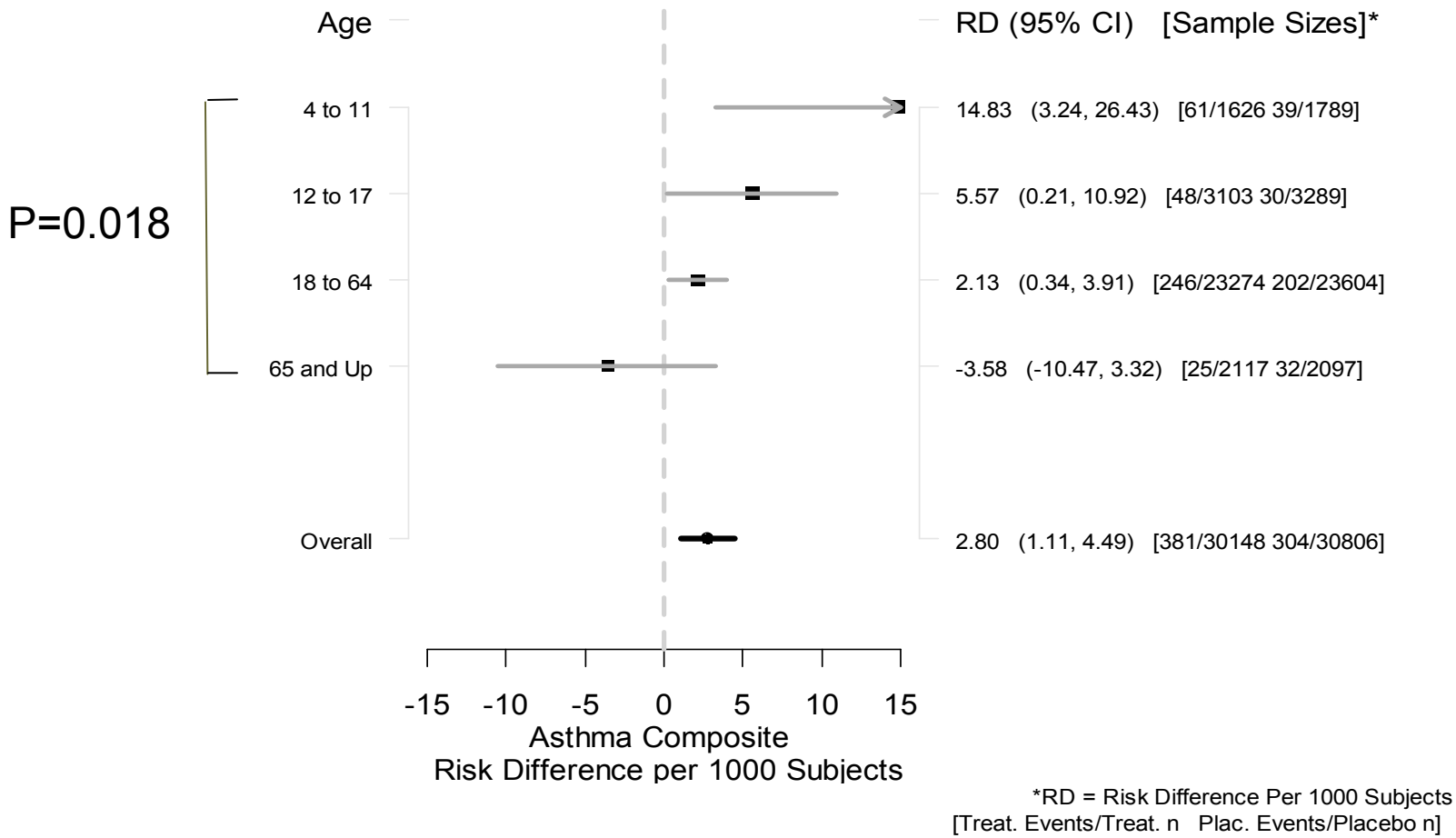
Highlights of FDA meta-analysis of the data related to risks of LABA use.

Characteristics of the Trials, Treatments, and Patients By Age in the FDA Meta-analysis

	N
Total	60,954
By LABA Treatment	
Received a LABA	30,148
Did not receive a LABA	30,806
By Trial Study Drug	
Serevent Trials	43,824
Advair Trials	13,212
Foradil Trials	3,765
Symbicort Trials	1,270
By Age (years)	
4-11	3,415
12-17	6,392
18-64	46,878
≥65	4,214

Adjusted Overall Risk Differences in Long-Acting Beta Agonists by Age

Asthma Composite Index*



*Asthma composite:
Asthma-related death, Asthma-related intubation, Asthma-related hospitalization

Adjusted Risk Differences in salmeterol-based Long-Acting Beta Agonists by Age

Asthma Composite Index

	Age Group	Risk Difference (RD) Per 1,000	95% CI RD	N LABA; N comparator
Serevent	4 to 11 years	16.97	-1.94-35.88	899;1,085
	12-17 years	5.88	-1.07-12.83	2,205;2,411
	18-64 years	3.27	0.94-5.6	16,492;17,696
	≥65 years	-6.38	-15.38-2.63	1,485;1,502
	Overall	3.49	1.27-5.71	21,108;22,716
Advair	4 to 11 years	ND	ND	409;401
	12-17 years	-0.53	-4.52-3.46	627;682
	18-64 years	-0.98	-3.22-1.25	5,189;5,043
	≥65 years	10.80	1.16-20.44	422;433
	Overall	-0.15	-2.01-1.70	6,648; 6,564

Adjusted Risk Differences in formoterol-based Long-Acting Beta Agonists by Age

Asthma Composite Index

	Age Group	Risk Difference (RD) Per 1,000	95% CI RD	N LABA; N comparator
Foradil	4 to 11 years	27.50	5.6-49.41	318;303
	12-17 years	12.75	-16.68-42.18	116;174
	18-64 years	-1.53	-5.16-2.09	1,027;1,457
	≥65 years	-11.91	-32.44-8.61	165;205
	Overall	3.80	-1.80-9.40	1,626;2,139
Symbicort	4 to 11 years	ND	ND	0;0
	12-17 years	23.36	-2.53-49.25	155;120
	18-64 years	3.55	-6.34-13.44	566;356
	≥65 years	ND	ND	45;28
	Overall	7.49	-1.47-16.44	766;504

Highlights of Efficacy Endpoints in Pivotal Trials of US-approved LABAs for Asthma Indication

Serevent Diskus studies 311 and 312 combined (≥12 years): baseline, absolute, and net change in efficacy measures

	Baseline	Absolute Δ (%)	Net Δ (%)
AM PEFR (L/min)	S 395 A 394	32 (8) 0 (0)	32 (8)
Rescue med use (puffs/24°)	S 4.3 A 4.3	-2.7 (-63) -2.1 (-49)	-0.6 (-14)
Symptom-free days (%)	S 13 A 12	20 9	11
Awakening-free nights (%)	S 63 A 68	22 3	19
Exacerbations (%)		S 15 A 16	

Serevent study SLD-390 (children 4-11 y.o.): baseline, absolute, and net efficacy measures.

	Baseline	Absolute mean Δ	Net Δ
Wk 12: % predicted FEV_1 12 hr post dose	S 75.3 P 78.9	7.8 4.5	3.3
Wk 12: % predicted PEF 12 hr post dose	S 86.6 P 85.5	17.6 12.2	5.4
% of pts with no nighttime awakenings/wk	S 85.8 P 84.3	9.1 4.1	5.0
Mean maximum asthma score (range 0-6)	S 1.2 P 1.1	-0.4 -0.1	-0.3
Mean Ventolin use/day	S 1.7 P 1.6	-0.8 -0.3	-0.3

Patients with out-of-clinic asthma exacerbations	Pbo (n=105)	Salmeterol (n=102)	Net Δ
During treatment	34 (32%)	25 (25%)	-7%
During 2 weeks post treatment	2 (2%)	12 (12%)	10%

Summary Points Regarding Serevent Efficacy from Pivotal Trials

Adults

- >11 years of age (salmeterol with albuterol), primary spirometric endpoints met
- Δ % nights with no symptoms and Δ % days with no symptoms favored salmeterol (by 10-20%)
- Δ % with asthma exacerbations favored albuterol

Children

- 4-11 years of age (salmeterol versus placebo) primary spirometric endpoints met
- Little difference in asthma symptom score

Advair Diskus study 3003 (≥12 years): baseline, absolute, and net change in efficacy measures

	Baseline	Absolute Δ (%)	Net Δ (%)
FEV_1	Ad 2.25 Fl 2.13	0.48 (21) 0.23 (11)	0.25 (10)
Asthma QOL (1-7)	Ad 4.90 Fl 5.04	1.0 (20) 0.55 (11)	0.45 (9)
Rescue-free days (%)	Ad 32.2 Fl 28.0	35.3 (110) 13.5 (48)	21.8 (62)
Symptom-free days (%)	Ad 27.8 Fl 22.6	31.7 (114) 15.7 (69)	16.0 (45)
Awakening-free nights (%)	Ad 91.1 Fl 90.8	6.3 (7) 2.3 (3)	4.0 (4)

Summary Points Regarding Advair Efficacy from Pivotal Trials

Adults

- > 11 years of age (Advair versus Fluticasone) all primary spirometric endpoints were met
- Δ 12° AUC FEV1 higher at 1 week than at 12 weeks
- Both Δ % symptom- free days and Δ % days without rescue medicine use approximately 20% increase

Children

- No efficacy trials for Advair in children

Foradil study 2302 (>12 years): baseline, absolute, and net change in efficacy measures

	Baseline	Absolute Δ (%)	Net Δ (%)
12° FEV_1 AUC	F 2.31 A 2.37	2.90 1.41	1.49*
Nocturnal asthma symptom score (0-4)	F 0.43 **P** 0.46	-0.08 (-19) -0.02 (-4)	-.06 (-15)
Rescue use (puffs/24°)	F 2.02 A 1.88	-0.73 (-36) -0.47 (-25)	-0.26 (-11)

*OND reviewing medical officer remarks:

”p-value (for F vs. P)
< 0.0001”

Foradil study DP/PD2 (5-12 years): baseline, absolute, and net change in efficacy measures

		Baseline	Absolute Δ (%)	Net Δ (%)
Δ AM PEFR (L/min)	F	258	31 (12)	14 (5)
	A	243	17 (7)	
Δ AM asthma score (0-3)	F	0.36	-0.17 (-47)	-0.12 (-42)
	A	0.26	-0.05 (-5)	
Δ PM asthma score (0-4)	F	0.27	-0.16 (-59)	-.07 (-24)
	A	0.26	-0.09 (-35)	
Δ sleep disturbance score	F	0.19	-0.12 (-63)	-0.01 (-13)
	A	0.22	-0.11 (-50)	
Δ AM rescue med use (puffs/d)	F	0.48	-0.19 (-40)	-0.14 (-21)
	A	0.26	-0.05 (-19)	
Δ PM rescue med use (puffs/night)	F	0.19	-0.10 (-53)	-0.08 (-39)
	A	0.14	-0.02 (-14)	

Summary Points Regarding Foradil Efficacy from Pivotal Trials

Adults

- >12 yrs → FEV1 significantly greater Foradil compared with Albuterol.
- % nights awakened and % nights using rescue medication ↓ in Foradil compared with Albuterol (10-20%)
- All other secondary endpoints, small changes in Foradil compared with Albuterol.

Children

- 5-12 years of age, the two spirometric primary endpoints were met.
- None of the secondary endpoints showed large change in the Foradil compared with either Albuterol or, where relevant, placebo.

Symbicort study 716 (≥12 years): baseline, absolute, and net change in efficacy measures

	Baseline	Absolute Δ (%)	Net Δ (%)
Mean 12° FEV_1 (L)	S 2.40 B 2.33	0.45 (19) 0.26 (11)	0.19 (8)
Δ Asthma score (0-3)	S 1.13 B 1.10	-0.43 (-38) -0.40 (36)	-0.03 (2)
AQOL (1-7)	S 5.24 B 5.09	0.78 (15) 0.62 (12)	0.16 (3)
Rescue use (per 24°)	S 2.75 B 2.99	-1.84 (-67) -1.49 (-50)	-0.35 (17)
Symptom-free days (%)	S 6.7 B 8.7	24.1 22.7	1.4
Awakening-free nights (%)	S 71 B 69.3	21.6 21.3	0.3
Rescue-free days (%)	S 30.7 B 27.7	41.2 30.4	10.8

Summary Points Regarding Symbicort Efficacy from Pivotal Trials

Adults

- In pivotal trials comparing Symbicort with Budesonide in patients >11 yrs, primary spirometric endpoints met
- Little difference between Symbicort and Budesonide in secondary endpoints including Δ % nocturnal awakening, but showed some improvement over budesonide in Δ % rescue-free days (+net 10%) and % asthma exacerbation (- net 14%).

Children

- No data reviewed in individuals <12 years of age

Overall Comments from Efficacy Endpoints for Pivotal Trials of US-Approved LABAs for Asthma

Adults

- Primary endpoints spirometric -consistently met
  - Prerequisite to trials response to a short-acting beta agonist
- Largest clinical differences were approximately 1.5 less puff(s) of rescue medicine per day or 15-20% more symptom-free days in the LABA versus comparator group.

Children

- Primary endpoints spirometric -consistently met
  - Prerequisite to trials response to a short-acting beta agonist
- Little improvement over comparator in the secondary endpoints for children <12 years of age
- Adolescents not assessed separately

Discussion: Risk/Benefit of LABAs and Age

Benefit considerations:

- Spirometric endpoints were consistently met in LABA pivotal trials
- Data reviewed do not suggest large benefits on secondary endpoints, especially in children <12 years of age
  - Efficacy trials not powered to study more "quality of life" endpoints.
  - Difficult to assess age-specific benefits: Small numbers in pediatric and elderly populations

Risk considerations:

- Age of the patient may have a large impact on risk/benefit ratio.
- Age trend in risk patterns in asthma-related hospitalization across drugs are concerning from FDA meta-analysis
- Drawing distinctions between LABA drugs not possible due at least in part to small sample sizes

CONCLUSIONS

- These data substantiate and quantify an increased risk overall in serious asthma-related events with the use of LABAs compared with non-LABA therapy for asthma.
- Children appear to be at greater risk of the adverse effects of LABAs than adults.
- LABAs have a consistent effect of improving spirometric outcomes.
- Data reviewed do not suggest large secondary benefits, especially in children <12 years of age.
- Correlation of spirometric endpoints with clinical benefits not clear.

Points of agreement in recommendations from OSE review

- There is a signal for asthma-associated morbidity and mortality in adults
  - That signal is largely from the SMART and SNS studies (single-entity LABA salmeterol)
- It is unclear what role inhaled corticosteroids play in mitigating LABA-associated risk
- There is an age effect, such that the risk of LABA-attributable asthma-associated hospitalization is increased in children.
- The extent of increased risk of LABA use for other demographic subsets among adults is less clear.
- Therefore, the team unanimously recommends:
  - Withdrawing the asthma indication from all LABAs for individuals <18 years of age.
  - Removing the asthma indication and contraindicating the use of the single entity LABAs (Serevent and Foradil) for all ages.

Point of disagreement among OSE reviewers on recommendations

- Whether to recommend removing the asthma indication for Advair and Symbicort for adults

ACKNOWLEDGEMENTS

Division of Biostatistics 6, OTS, CDER
Mark Levenson, PhD
Office of Surveillance and Epidemiology, CDER
Andrew Mosholder, MD, MPH
Shewit Bezabeh, MD, MPH
David Graham, MD, MPH
Gerald Dal Pan, MD, MS
Henry Francis, MD, MPH
Allen Brinker, MD, MPH
Sean Bradley, MPH

FDA's Questions for the Joint Advisory Committee on Long-Acting Beta-2 Agonists

December 10-11, 2008

We would like you to discuss and answer the questions below. We have structured Questions 1-4 by active LABA ingredient and by age group.
If there are issues that you believe are relevant for the entire LABA class, please state so in your discussion. Note that Questions 5-8, which concern individual LABA-containing products, require voting.

1. Discuss the benefits of using salmeterol for the treatment of asthma in patients not adequately controlled on other asthma-controller medications (eg, low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies, in each of the following age groups:

in adults [≥18 years of age]

in adolescents [12-17 years of age]

in children [4-11 years of age]

2. Discuss the benefits of using formoterol for the treatment of asthma in patients not adequately controlled on other asthma-controller medications (eg, low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies, in each of the following age groups:

in adults [≥18 years of age]

in adolescents [12-17 years of age]

in children [5-11 years of age]

3. Discuss the risks of using salmeterol for the treatment of asthma in patients not adequately controlled on other asthma-controller medications (eg, low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies, in each of the following age groups:

in adults [≥18 years of age]

in adolescents [12-17 years of age]

in children [4-11 years of age]

4. Discuss the risks of using formoterol for the treatment of asthma in patients not adequately controlled on other asthma-controller medications (eg, low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies, in each of the following age groups:

in adults [≥18 years of age]

in adolescents [12-17 years of age]

in children [5-11 years of age] (Note that Symbicort is not indicated in this age group.)

5. Do the benefits of Serevent (salmeterol xinafoate) outweigh its risks for the maintenance treatment of asthma in patients not adequately controlled on other asthma-controller medications (eg, low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies, in the following age groups:

in adults [≥18 years of age] (Voting question)

in adolescents [12-17 years of age] (Voting question)

in children [4-11 years of age] (Voting question)

6. Do the benefits of Foradil (formoterol fumarate) outweigh its risks for the maintenance treatment of asthma in patients not adequately controlled on other asthma-controller medications (eg, low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies, in the following age groups:

in adults [≥18 years of age] (Voting question)

in adolescents [12-17 years of age] (Voting question)

in children [5-11 years of age] (Voting question)

7. Do the benefits of Advair (fluticasone propionate; salmeterol xinafoate) outweigh its risks for the maintenance treatment of asthma in patients not adequately controlled on other asthma-controller medications (eg, low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies, in the following age groups:

in adults [≥18 years of age] (Voting question)

in adolescents [12-17 years of age] (Voting question)

in children [4-11 years of age] (Voting question)

8. Do the benefits of Symbicort (budesonide and formoterol fumarate dihydrate) outweigh its risks for the maintenance treatment of asthma in patients not adequately controlled on other asthma-controller medications (eg, low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies, in the following age groups:

in adults [≥18 years of age] (Voting question)

in adolescents [12-17 years of age] (Voting question)

9. Based on your discussion and votes above, are there further labeling changes or risk mitigation strategies for individual LABA products, or the class as a whole, that would be advisable?

10. What further studies, if any, would clarify important unanswered questions of safety and efficacy for individual LABA products or the class as a whole?