

cases in our analysis. Moreover, the inclusion criterion used for new asthma in our study means by definition that they used antiasthmatic (anti-inflammatory) medication on a regular basis. The current guideline⁴ states that when assessing disease severity FEV₁ (and its variability) should be used only in the initial phase before treatment. Thereafter, the classification of severity should be based on the clinical features present and the step of the daily medication regimen that the patient is currently on.

Repeated measurements of prebronchodilator FEV₁ have previously been used to determine loss of lung function over time in population-based studies.^{5,6} Certainly, if possible, postbronchodilator FEV₁ measurements should be selected for analysis when assessing remodeling. The importance of this choice is emphasized when studying patients with poor asthma control.

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Disclosure of potential conflict of interest: The authors have declared that they have no conflict of interest.

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Available online April 3, 2006.
doi:10.1016/j.jaci.2006.02.010

Ciclesonide inhalation aerosol for persistent asthma

To the Editor:

A recent issue of this Journal published a report of the combined analysis of 2 studies conducted by Aventis Pharmaceuticals to support marketing approval of ciclesonide inhalation aerosol for asthma in the United States. The authors conclude that ciclesonide at once-daily doses of 80 µg, 160 µg, and 320 µg is effective in the treatment of mild-to-moderate persistent asthma.¹ There are 2 major issues with this article worth noting. First, combining 2 studies *post hoc* as if they were 1 study and presenting data from the combined analyses is not appropriate. Such analyses, with increased sample size, may show statistical significance for small, potentially

clinically insignificant differences. Second, the article mentions 2 strata of eligibility for enrollment—patients previously not on inhaled corticosteroids (ICSs) and patients previously maintained on low-to-moderate ICS doses—but results from these 2 strata are not presented. It would have been more appropriate for the authors to present results of the 2 studies separately based on the original analysis plan, and also present the 2 strata of patients from each study separately. This would have allowed the readers to get a better sense of efficacy of once-daily ciclesonide from the studies, analyzed as planned.

Results of the primary and secondary efficacy variables show small effect sizes for ciclesonide, some reaching statistical significance, in all probability as a result of pooling of the 2 studies. Primary efficacy variable results are explored here to illustrate the point further. The primary efficacy variable in the studies was the difference between ciclesonide and placebo in change in predose FEV₁ from baseline to the end of the study (week 12). In this variable, the effect size for the 3 doses of ciclesonide ranged from 110 to 140 mL. There was no active comparator in the studies to place these numbers in perspective, but they appear small from cross-study comparisons to other drugs of this class marketed in the United States. For example, in studies conducted to support marketing approval of mometasone furoate inhalation powder, which has a once-daily dosing recommendation, the difference between mometasone and placebo in the change in predose FEV₁ from baseline to the end of the study (week 12) ranged from 250 to 350 mL.² These results are from patients previously maintained on inhaled bronchodilators and patients previously maintained on ICSs. These 2 strata are reflective of patients with mild-to-moderate persistent asthma, similar to the patients enrolled in the ciclesonide studies. For mometasone, the same nominal dose administered once daily and twice daily in the same study had comparable effect sizes.²

Although the Food and Drug Administration cannot comment on the details of its action on a drug that has not yet been approved, I would state that in my opinion, it is important that data from registration studies be presented in journal publications in a manner accurately reflective of how the studies were conducted and analyzed. If these results were published in that form, the conclusions from the efficacy data for ciclesonide might have been less definitive, if not quite different, from those reported in this article.

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Disclosure of potential conflict of interest: B. Chowdhury has declared that he has no conflict of interest.

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doi:10.1016/j.jaci.2006.02.041

Reply

To the Editor:

Dr Chowdhury¹ raises several issues. His first and main concern regards the appropriateness of combining studies *post hoc*. Although combining identical studies is not unique and can enhance the statistical power,²⁻⁶ we appreciate his concern that this could be potentially misleading. However, considering that the 2 protocols were identical and that of the method of the integrated analysis was the same as those described in the protocols, we determined that combining the 2 for publication as indicated in the introduction to our paper, rather than submitting each study with identical methodology, similar results, and virtually identical discussions to the same or different journals, would be more appropriate and informative. A comparison of the results of the combined analysis with the 2 studies separately was provided for the process of review of our publication. Table I summarizes efficacy endpoints similar to what was provided for the peer review: the 2 parent studies (321 and 322) and the integration.

Dr Chowdhury¹ also requests information on the 2 eligibility substrata of patients who entered on controller medications, mainly low to moderate maintenance doses

of inhaled corticosteroids (ICSs), versus patients entering on β_2 adrenergic agents only. Analysis performed on these 2 patient substrata in the combined analysis revealed statistically significant FEV₁ improvement in the subgroup that entered on ICSs, but not in the other subgroup. Since the studies were not sufficiently powered for analysis of both substrata, the subanalysis was considered inconclusive and not further considered in this paper. However, 2 separate ongoing studies with alternative entry criteria (one entry on ICS maintenance, the other entry on β_2 adrenergic agents only) will address any issues of differential response.

Dr Chowdhury¹ goes on to express concerns that efficacy variables such as FEV₁ show small effect size. He suggests that cross-study comparisons with other ICSs may indicate larger effect sizes of others in this class, and offers a comparator illustration of mometasone listed in the *Physicians' Desk Reference*. It is difficult to compare treatment effects between different studies performed with nonidentical protocols, variable patient populations, and various statistical plans for analysis, however. For example, the current ciclesonide studies dosed medications once daily in the morning, measured am FEV₁ at trough (24-hour postdose), and did not exclude from analysis certain efficacy measurements (eg, FEV₁ data) obtained after use of disallowed medications such as prednisone. In contrast, the cited *Physicians' Desk Reference* studies dosed study medications at night or twice daily, measured am FEV₁ only 12 hours after dosing, and published efficacy

TABLE I. Ciclesonide once daily versus placebo efficacy data, separate analyses (321 and 322 protocols) and combined analysis

Variable	Placebo			Ciclesonide 80 μ g			Ciclesonide 160 μ g			Ciclesonide 320 μ g		
	321	322	Combined	321	322	Combined	321	322	Combined	321	322	Combined
FEV ₁ (L)	0.2	0.13	0.17	0.32	0.25	0.28	0.26	0.32	0.29	0.35	0.25	0.31
P value*	—	—	—	.0123	.0224	.0007	.1645	.0003	.0004	.0014	.0173	<.0001
FEV ₁ Predicted (%)	5.39	3.45	4.47	8.83	7.31	8.07	7.66	8.84	8.24	9.70	7.07	8.45
P value*	—	—	—	.0081	.0059	.0002	.0844	.0001	<.0001	.0010	.0096	<.0001
Morning PEF (L/min)	-2.18	-1.12	-1.70	13.39	8.15	10.93	16.75	25.72	21.06	22.35	11.77	17.22
P value*	—	—	—	.0032	.0871	.0008	.0004	.0001	<.0001	.0001	.0171	<.0001
Evening PEF (L/min)	2.27	0.75	1.48	12.88	6.57	9.89	17.62	18.26	18.06	17.60	11.56	14.59
P value*	—	—	—	.0359	.2286	.0162	.0028	.0003	<.0001	.0027	.0250	.0002
24-h asthma symptom score	-0.14	-0.16	-0.15	-0.52	-0.62	-0.58	-0.69	-0.68	-0.70	-0.82	-0.41	-0.61
P value*	—	—	—	.0146	.0060	.0002	.0006	.0020	<.0001	.0001	.1346	<.0001
Albuterol use (puffs per day)	0.60	0.23	0.42	-0.91	-0.80	-0.86	-0.99	-1.02	-1.02	-1.27	-0.79	-1.04
P value*	—	—	—	.0001	.0002	<.0001	.0001	.0001	<.0001	.0001	.0002	<.0001
Nighttime awakenings (n/night)	0.04	0.10	0.07	-0.07	-0.08	-0.08	-0.19	-0.12	-0.16	-0.14	-0.12	-0.13
P value*	—	—	—	.0463	.0007	.0001	.0001	.0001	<.0001	.0014	.0001	<.0001
AQLQ score (overall)	0.15	0.14	0.14	0.46	0.54	0.50	0.59	0.63	0.61	0.81	0.57	0.69
P value*	—	—	—	.0078	.0010	<.0001	.0002	.0001	<.0001	.0001	.0004	<.0001

*Values are presented as least-squares mean: change from baseline in active groups compared with placebo group.