

Aventis Pharmaceuticals



February 4, 2002

Via fax and UPS

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

3481 '02 FEB -6 A9:55

Re: Docket No. 01D-0432

Draft Guidance for Industry on the Evaluation of the Effects of Orally Inhaled and Intranasal Corticosteroids on Growth in Children [66FR 56109, November 6, 2001]

Dear Sir/Madam:

Aventis Pharmaceuticals Inc would like to thank you for the opportunity to comment on the above-referenced draft guidance entitled "Evaluation of the Effects of Orally Inhaled and Intranasal Corticosteroids on Growth in Children". The document provides general recommendations for the design and conduct of a growth study to assess the effects of nasally and orally inhaled corticosteroids on growth velocity in prepubertal children. We offer the following comments/clarification for your consideration.

III. GENERAL STUDY DESIGN RECOMMENDATIONS FOR GROWTH STUDIES

Lines 101 - 103

The duration of the baseline period should be at least 16 weeks, the treatment period should be at least 48 weeks, and the follow-up period should be at least 8 weeks.

Can an interim analysis be done when a substantial percentage of the patients have completed the study (e.g., 50 percent)?

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Lines 119 – 120

The sponsor should make every effort to obtain growth measurements as planned, irrespective of whether patients discontinue the study medication.

Is a minimum degree of adherence with the treatment required, and in this case how should the adherence be measured?

IV. PROTOCOL DESIGN

A. Inclusion Criteria

Lines 159 – 160

Patients should also have a documented percentage predicted FEV₁ ≥ 80 percent after withholding beta-agonist for ≥ 6 hours at both the screening and first baseline visits.

Is the requirement for FEV₁ ≥ 80 percent at two visits (e.g., screening and first baseline visits) necessary to confirm patients have mild, persistent asthma?
Due to inpatient variability in FEV₁, patients clinically considered to have mild, persistent asthma may be disqualified.

Lines 166 – 168

The patient population for the intranasal products should have a history of persistent allergic rhinitis for a minimum of 2 years prior to the study entry with expected symptoms during a majority of the treatment period.

With regard to the requirement of “*expected symptoms during a majority of the treatment period*”, how will this be determined prior to enrollment?
Should patients with seasonal allergic rhinitis only be excluded? Can patients with non-allergic rhinitis be entered in the study if the sponsor is developing the corticosteroid for allergic and non-allergic rhinitis (e.g., vasomotor rhinitis)?

D. Action Plan for Worsening Symptoms

Lines 213 – 214

For worsening allergic rhinitis, an oral decongestant or antihistamine can be considered.

There is mention that antihistamines can be considered for allergic rhinitis. Are these “in lieu” of placebo or to be used as needed?

H. Sample Size

Lines 255 – 262

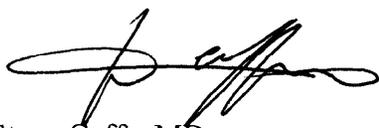
As stated above, a clinically meaningful difference of growth velocities between treatment groups is difficult to define. Therefore, the sample size of the study should be based on the desired precision (width of a 95% confidence interval) of the estimate of the difference in mean growth velocities between active and control treatments. Mean treatment effects seen in previous growth studies submitted to the Agency have been observed to be 0.5 cm per year and greater. It is desirable that the growth studies provide an estimate of treatment effect with high level of precision (e.g., total length of 95 percent confidence interval 0.5 cm).

The Agency's requirement that the length of 95 percent confidence interval for treatment effect be not more than 0.5 cm (i.e., half-width not more than 0.25 cm) seems to be quite restrictive, given that mean treatment effects seen in previous growth studies have been observed to be 0.5 cm per year and greater. Therefore, the draft guidance specifies the half-width of confidence interval to be half of the smallest observed treatment effect. Would it be reasonable to have the half-width equal to the smallest observed treatment effect, i.e. 0.5 cm?

Finally, with regard to the labeling, it is mentioned in the Federal Register Notice that growth study data can be included in product labeling. This statement should be reflected in the guidance document. It would be helpful to include in this guidance some recommendations on how to describe individual studies and how to present study data.

On behalf of Aventis Pharmaceuticals Inc we appreciate the opportunity to comment on the draft guidance for industry on the Evaluation of the Effects of Orally Inhaled and Intranasal Corticosteroids on Growth in Children, and thank you for your consideration.

Sincerely,



Steve Caffé, MD
Vice President, Head GRAMS – North America
Global Regulatory Approvals and Marketing Support

In This Space

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UPS Air Shipping Document

UPS Worldwide Waybill



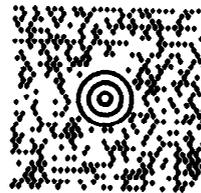
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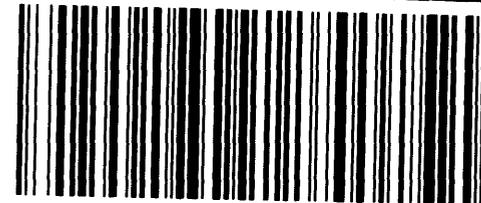
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