Guidance for Industry

Orally Inhaled and Intranasal Corticosteroids: Evaluation of the Effects on Growth in Children

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Clinical/Medical

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Contains Nonbinding Recommendations

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I. INTRODUCTION

This guidance provides recommendations for sponsors of orally inhaled and intranasal corticosteroids regarding the design, conduct, and evaluation of clinical studies to assess the effects of these drug products on growth. The recommendations comprise study design and efficacy and safety issues for: 1) approved drug products whose treatment effect on prepubescent growth has not been adequately characterized, and 2) potential new drug products that could be used in the treatment of allergic rhinitis and/or asthma in children. Although the recommendations in this guidance specifically apply to intranasal and orally inhaled corticosteroids, many of the recommendations can be extended to include evaluation of possible growth effects with other therapies for asthma and allergic rhinitis.

This guidance does not address study designs for comparison of two different products containing the same active moiety. This guidance also does not address study designs for the effects of orally inhaled and intranasal corticosteroids on final adult height. The study design considerations suggested in this guidance are not intended to reproduce actual clinical practice. Rather, this guidance outlines characteristics of study designs that can reduce the variability and/or potential bias of the estimates of differences in growth velocity between treatment groups.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are

[1] This guidance has been prepared by the Division of Pulmonary and Allergy Products in consultation with the Division of Metabolism and Endocrinology Products and the Office of Biostatistics in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Information regarding the potential adverse effects of orally inhaled and intranasal corticosteroids on growth rates in children first became available in the mid-1990s. Studies submitted to the FDA with several different active corticosteroid moieties demonstrated reduced growth velocities over a 1-year time period of approximately 1 centimeter (cm) per year among active treatment groups exposed to orally inhaled or intranasal corticosteroids as compared to control groups (placebo or noncorticosteroid asthma treatments such as beta-agonists).

After the FDA received the results of several growth studies with intranasal and orally inhaled corticosteroids in 1996-7, the FDA convened a joint meeting between the Pulmonary Allergy Drugs Advisory Committee and the Endocrine and Metabolic Drugs Advisory Committee in 1998 to discuss the implications for the labeling of these drug products. Results from the available growth studies were presented. The joint Advisory Committee recommended the addition of labeling for orally inhaled and intranasal corticosteroids to the Precautions/General, Precautions/Pediatric Use, and Adverse Reactions sections. The recommended labeling presumes that all corticosteroids administered by all routes can potentially have systemic effects, including effects on growth. This finding is considered to be a class effect, the result of a presumed direct effect on bone osteoclast-osteoblast activity as well as indirect hormonal effects. Based on the joint Advisory Committee recommendation, the FDA sent a letter to the holders of new drug applications for all orally inhaled and intranasal corticosteroids on file as of November 1998, requesting the addition of standardized language to the labeling regarding the potential for effects on growth.[2] Labeling changes were implemented in 1998-9.

[2] The language shown below is what was requested in 1998, with currently recommended modifications. Some of the wording is no longer applicable, or has since been modified for clarity. Language in square brackets (e.g., [orally inhaled/intranasal]) is to be inserted as appropriate. The *product name* is to be inserted by the sponsor. Language in curly brackets {} can be omitted. Some labels have minor variations of the wording.

PRECAUTIONS, General: "[Orally inhaled/intranasal] corticosteroids may cause a reduction in growth velocity when administered to pediatric patients (see PRECAUTIONS, Pediatric Use section)."

PRECAUTIONS, Pediatric Use: "Controlled clinical studies have shown that [orally inhaled/intranasal] corticosteroids may cause a reduction in growth velocity in pediatric patients. {In these studies, the mean reduction in growth velocity was approximately one centimeter per year (range 0.3 to 1.8 cm per year) and appears to be related to dose and duration of exposure.} This effect has been observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with [orally inhaled/intranasal] corticosteroids, including the impact on final adult height, are unknown. The potential for "catch-up" growth following discontinuation of treatment with [orally inhaled/intranasal] corticosteroids has not been adequately studied. The growth of pediatric patients receiving [orally inhaled/intranasal] corticosteroids, including (*product name*), should be monitored routinely (e.g., via stadiometry). The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained and the risks/benefits of treatment alternatives. To minimize the systemic effects of [orally inhaled/intranasal] corticosteroids, including (*product name*), each patient should be titrated to {his/her lowest effective dose} [the lowest dose that effectively controls his or her symptoms]."

ADVERSE REACTIONS: "Cases of growth suppression have been reported for [orally inhaled/intranasal] corticosteroids [including (*product name), if appropriate*] (see PRECAUTIONS, Pediatric Use section)."

III. OVERVIEW OF RECOMMENDATIONS FOR GROWTH STUDIES

Many long-term adverse consequences of the systemic activity of corticosteroids are difficult to measure. Our experience has been that growth studies have yielded positive results even when carefully performed hypothalamic-pituitary-adrenal axis studies have not. Therefore, we believe that well-conducted growth assessments represent one of the most sensitive indicators of systemic effects of corticosteroids, and should be considered an important sentinel of unmeasured systemic effects. For this reason, the FDA considers growth information important additional safety information for orally inhaled and intranasal corticosteroid drug products, and we encourage sponsors to perform growth studies as part of their development program. Sponsors should discuss with the review division the timing of submission of the results of a growth study with respect to their overall development program.

The growth studies that the FDA has reviewed have varied greatly in their designs. Although some studies focused on the question of potential differences in growth rates between treatment regimens that represent how children are actually treated in clinical practice, this approach has led to the introduction of confounders that limited the interpretation of the studies' results. Specifically, some studies allowed for one or more of the following practices: titration of corticosteroid dose, generous use of oral corticosteroids as rescue medication, and inclusion of older children who could potentially enter the pubertal growth spurt during the trial. Measurement error and missing data further complicated the analyses and results. The recommendations provided in this guidance are based on an in-depth review of the issues raised by these types of pediatric growth studies. Sponsors are strongly encouraged to discuss details of study design and specific issues relating to individual drug products with the review division before conducting clinical trials that estimate growth effects.

It should be noted that the recommendations for pediatric growth studies contained in this guidance reflect normative growth data gathered from healthy children in a U.S. population. Sponsors planning to conduct international studies should take this observation into consideration and are strongly encouraged to contact the Division of Pulmonary and Allergy Products for further guidance before the initiation of such trials.

The growth study recommendations described in this guidance do not fit into the usual framework of a superiority, inferiority, or equivalence study, and we discourage growth studies from being designed and interpreted in this manner. Rather, the objective of a growth study should be to characterize, as accurately as possible, the estimate of the difference in prepubescent growth velocities between treatment with an active moiety and a control group. The reasoning for not using an hypothesis testing design (e.g., superiority, inferiority, or equivalence study) is because systemically administered corticosteroids are known to affect growth. Since there is a presumption of a growth effect, the studies should be designed to characterize that effect as fully as feasible.

The goal of growth studies characterized in this guidance is, in many respects, pharmacodynamic in nature. The safety information from such studies is considered a stand-alone measure of the potential of a corticosteroid to cause systemic effect. To detect a deceleration in growth velocity over the approximate 1-year study course, the expected growth velocity should be relatively

constant. For this reason, we recommend that growth studies be conducted during a narrow window of age ranges during the so-called growth hormone dependent phase between the infant/toddler and pubescent growth periods, when the growth velocity is relatively linear. This age range is the only one with relatively constant background growth velocity, providing accurate measurement and a less confounded comparison of active and control treatments over time. Although the growth effect is measured in children, the pharmacodynamic effect is not age-limited and is applicable to patients of all ages.

The clinical relevance of the differences in prepubescent growth velocities on final adult height as estimated by 1-year trials is yet unknown. Several studies have evaluated effects on longer-term growth, but the growth studies recommended in this guidance are relatively short, and not designed to determine effects on longer-term growth. These studies are not designed to determine whether the changes are transient or permanent, or whether catch-up growth occurs with continued use. Because the clinical relevance of the differences in prepubescent growth velocities on final adult height is unknown, a *clinically meaningful difference* of 1-year growth velocities between treatment groups can be difficult to define. Therefore, the sample size of the study should be based on the desired precision (width of a 95 percent confidence interval) for the treatment effect and not on a clinically meaningful difference between treatments (see section V.F., Sample Size).

In general, an evaluation of growth should be performed separately for both orally inhaled and intranasal formulations containing the same active moiety of a corticosteroid where products given by both routes of administration are proposed for marketing. Separate evaluations are preferred because of substantial differences in the bioavailability of the two routes of administration for a corticosteroid and because of differences in the risk-to-benefit ratios for intranasal and orally inhaled indications. However, in certain circumstances, sponsors of both orally inhaled and intranasal corticosteroid products that contain the same active moiety can use pharmacokinetic data to bridge the growth findings associated with one formulation to a second formulation. Systemic exposure from an orally inhaled formulation may be adequate to support an intranasal formulation provided that the systemic exposure is higher with the orally inhaled formulation and a well-conducted growth study with the orally inhaled formulation shows no growth effect. Consultation with the review division is recommended before and during the design of a bridging program.

IV. GENERAL GROWTH STUDY DESIGN RECOMMENDATIONS

General recommendations for designing growth studies in children with asthma and/or allergic rhinitis are described in the following bulleted list. Adherence to these recommendations can help minimize variability in results and improve interpretability of findings.

- For both the orally inhaled and the intranasal corticosteroids, assessment of growth effects should be based on adequate and well-controlled phase 3 or phase 4, double-blind, randomized, parallel group clinical trials. There should be a single-blind (patient-blinded) baseline period to assess baseline growth velocity. There also should be a follow-up period (preferably using a single-blind placebo or noncorticosteroid

medication, as described earlier) to assess potential short-term *catch-up* growth and to assess Tanner stage. 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. Use of stadiometer data from office visits before randomization as baseline data in lieu of the baseline period may be appropriate under some circumstances. However, the sponsor is encouraged to consult with the review division concerning this approach because of the potential to introduce variability into baseline growth velocity estimates.

- Measurements should be made using stadiometry and recorded to the nearest 10th of a centimeter. If the stadiometer has not been calibrated in the previous 4 hours, it should be calibrated immediately before use. The stadiometric measurement protocol should be specific (e.g., no socks, shoes, or hats; three reproducible measurements; calibration frequency).

- The study design should incorporate practices that reduce measurement error. The investigators or examiners should be trained in stadiometry and calibration procedures. Ideally, the same person should measure the patients at every visit and should be blinded to the patients' status in the study (e.g., on-study, receiving double-blind treatment, discontinued, receiving open-label treatment). Visits should be scheduled so that measurements can be taken at approximately the same time of day throughout the study.

- The sponsor should make every effort to obtain growth measurements as planned, irrespective of whether patients discontinue the study medication. Although patients who discontinue study treatment may be administered other medications that affect growth, measurements obtained after discontinuation are useful for assessing the sensitivity of the analyses and results (see section VI.B., Secondary Analyses).

- The investigator, examiner, patient, caregiver, and study personnel should remain blinded to the study treatment for patients who discontinue, unless unblinding is important for safety or treatment decisions.

- To minimize the confounding effects of nonlinear growth rates and inaccuracies inherent in measurement of recumbent length, we recommend avoiding enrollment of children younger than 3 years of age. Likewise, we recommend not recruiting children near the time of puberty because of the rapid increase in growth velocity that can occur over a relatively brief period (Tanner and Davies 1985). Although information concerning growth suppression during the pubertal growth spurt has clinical relevance, the interpretation of resultant data is confounded when a child's growth velocity undergoes normal physiological acceleration associated with puberty. For this reason, prepubertal children are preferred, and the study design should minimize the likelihood of patients entering puberty during the study.

- Tanner staging at baseline and during the treatment and follow-up periods is intended to help identify patients entering puberty. However, such assessments may not identify all patients experiencing a pubertal growth spurt. The first measurable sign of puberty in girls can be the beginning of the growth spurt, and it can precede the onset of secondary

sexual characteristics by as much as 1 year (Kaplan and Love 2001; Kulin 1996). There are conflicting statements in the literature about the timing of the growth spurt in boys relative to the onset of secondary sexual characteristics.[3] Nevertheless, we recommend Tanner staging. In addition, stratified randomization based on age and sex is recommended to help balance the percentage of patients whose pubertal growth spurt may have already begun during the baseline period or will begin during the treatment period.

V. PROTOCOL DESIGN

A. Inclusion Criteria

For reasons stated earlier, the lower age limit for enrollment should be patients 3 years of age. To minimize the potential for patients to reach the onset of puberty during the trial, the inclusion criteria should limit the maximal age of the male subjects to those who will be 10.5 years and the maximal age of the female subjects to those who will be 9.5 years at the end of the follow-up period. The sponsor is encouraged to set the upper age limit inclusion criteria as low as feasible to minimize the likelihood of recruiting pubertal children, based on prior recruitment experiences and available normative data for the population under study. The sponsor should choose an age range that is appropriate to the drug product, indication, and good clinical practices (i.e., stadiometry and FEV/Peak Flow measurements, ability to coordinate use of an inhaler).

The patient population for intranasal products should have a history of perennial allergic rhinitis with persistent symptoms for a minimum of 2 years before study entry.[4]

[3] *Adolescent Medicine,* 3rd Edition (1997), states that, "The growth spurt [in males] usually begins at stage 3, reaches a peak during stage 4 and is all but complete by stage 5" (p. 13). *Rudolph's Pediatrics,* 20th Edition (1996), section 22.9.1 states that, "the initiation of the adolescent growth spurt precedes the onset of secondary sex characteristics by approximately 1 year in boys and girls."

[4] For recommended inclusion and exclusion criteria for patients with perennial allergic rhinitis, see the draft guidance for industry *Allergic Rhinitis: Clinical Development Programs for Drug Products.* When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

For orally inhaled corticosteroids, patients with mild persistent asthma (National Heart, Lung, and Blood Institute 1997 and 2002) are the preferred population for a number of ethical and clinical design reasons.[5,6] The population of children with mild persistent asthma is likely to be less subject to confounding variables than populations encompassing more severe disease (e.g., need for oral corticosteroid bursts). This population should yield a more informative estimate of the growth effect compared to a more severely affected population, in whom both efficacy and growth effects can be confounded. Children with mild persistent asthma are unlikely to suffer serious consequences if randomized to noncorticosteroid maintenance therapy but are sufficiently ill to justify potential randomization to corticosteroid therapy that may suppress growth. Children with mild persistent asthma are expected to have limited, if any, need for oral corticosteroids during the 1-year treatment period; therefore, the effect of oral corticosteroid use on analyses of growth velocity will be minimized.

Patients should have a history of mild persistent asthma for a minimum of 6 months before study entry. Screening and first baseline visit qualification criteria should be set consistent with this diagnostic grouping. Qualification should be performed after withholding beta-agonists for 6 or more hours. Inclusion criteria can warrant modification if the sponsor is conducting a study of the growth effects of noncorticosteroid drug products to be used in the treatment of asthma.

Since the intent of such studies is to characterize the formulation and not the molecule's effect, we specifically discourage the use of a spacer for orally inhaled drug products. Use of a spacer device creates an extemporaneous formulation that can result in different local effects and systemic bioavailability than that achieved by the drug product without the spacer device. In vitro data show that a spacer used with certain orally inhaled corticosteroid metered dose inhalers can significantly reduce the amount of active drug inhaled if there is any delay between actuation and inhalation, potentially confounding the measurement of the growth effect of the drug product. For this reason, we encourage inclusion of patients who are able to adequately coordinate use of the device without the addition of a spacer.

B. Exclusion Criteria

Tanner staging should be performed at the end of each period (baseline, treatment, and follow-up) to help identify pubescent patients. Patients with Tanner stage greater than 1 during the baseline period should be excluded from entering the treatment period. (Note that if patients become pubescent during the treatment or follow-up periods, they should remain in the trial, performing all visit procedures.) Other exclusion criteria include:

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[5] Based on the consensus recommendations of the FDA Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee of November 15, 1999 (http://www.fda.gov/cder/pediatric/ethics-statement.htm), pediatric studies should be conducted in subjects who can benefit from participation in the trial. Usually this implies the subject has or is susceptible to the disease under study. The Advisory Subcommittee used a broad definition of potential benefit. Since patients with mild intermittent disease by definition might not benefit from daily controller therapy, a population of mild persistent asthmatics is the preferred population.

[6] Investigational Review Board duties and criteria for pediatric studies fall under the jurisdiction of 21 CFR part 50, subpart D, Additional Safeguards for Children in Clinical Investigations.

- Baseline growth velocity less than the 3rd or greater than the 97th percentile.[7]

- Weight and body mass index less than the 3rd or greater than the 97th percentiles.[8]

- Bone age greater than 1 year different from the patient's chronological age. It is strongly recommended that the bone age be determined by a central reader for all study patients.[9]

- Use of inhaled, intranasal, or high potency topical corticosteroids within 6 weeks and systemic corticosteroids within 3 months of the first baseline visit.

- Use of corticosteroids by any route of administration likely to have a systemic effect during the baseline period.

- Treatment at any time before screening that might influence growth, including, but not limited to, methylphenidate hydrochloride, thyroid hormone, growth hormone, anabolic steroids, calcitonin, estrogens, progestins, biphosphonates, anticonvulsants, or phosphate-binding antacids.

C. Dose and Dosage Regimens

For intranasal corticosteroids, sponsors are encouraged to study the highest dose proposed for the pediatric age range. For orally inhaled corticosteroids, sponsors are encouraged to study the highest dose proposed for the pediatric age range, although a sponsor can consider a lower dose or range of doses in consultation with the division.

D. Action Plan for Worsening Symptoms

The study protocol should specify the course of action to be taken in the event of worsening asthma or allergic rhinitis and should include the types and doses of allowed rescue medication.

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[7] The purpose of this criterion is to exclude patients with growth disorders from studies in which they may receive a growth-inhibiting drug. Historical data can be used to determine historical growth velocity as an exclusionary criterion.

[8] If the study is to be performed in the United States, current standard growth charts for height, weight, and body mass index percentiles for age from the Centers for Disease Control and Prevention should be used (http://www.cdc.gov/growthcharts).

[9] Children whose bone age is greater than or equal to 2 years different from their chronological age are considered to be outside of the normal range for this parameter. On this basis, it can be argued that a 1-year upper limit is unduly restrictive and that an upper limit of less than 2 years would be more appropriate. Sponsors considering modification of their protocols based on this exclusion criterion are strongly urged to contact the review division for advice. In particular, the importance of a 2-year difference between bone age and chronological age increases at the extremes of the prepubertal age range. A 4-year-old child who has the bone age of a 2-year old is of greater concern than an 8-year old with a bone age of 6 years and is more likely to have baseline growth abnormalities. Similarly, a 9-year-old child with a bone age of 11 years may be close to entering his or her pubertal growth spurt and ideally should not be recruited into a growth study. The importance of a close correlation between bone age and chronological age also increases if a non-U.S. study is contemplated, since normative data based on U.S. children may not apply (see section III, Overview of Recommendations for Growth Studies).

For worsening allergic rhinitis, an oral decongestant or antihistamine can be considered. For safety reasons, standard-of-care guidelines should be followed in the management of all acute asthma exacerbations. Asthma management can include repeat doses of beta-agonists and systemic corticosteroids, administered orally or parenterally, at the discretion of the primary investigator. Worsening asthma control that is asymptomatic (e.g., when a patient is found to have a decline from baseline in peak expiratory flow rate or FEV_1) can be managed less intensively. Continued observation with no immediate change in therapy or the addition of (or increase in) an inhaled corticosteroid can be considered reasonable options. In each of these cases, patients should be continued in the study, and the protocol should specify how rescue medication use will be analyzed between the treatment groups. Analyses of outcomes under the various conditions of rescue medication use (dose and duration) should be provided in the clinical trial report (see section VI.B., Secondary Analyses).

E. Methodology to Ensure Adequacy of Interpretability

In addition to the aforementioned general and specific recommendations regarding conduct of growth studies, the following recommendations can help ensure adequacy of interpretability of the findings.

1. Treatment Controls

The choice of the comparator or control group selected for allergic rhinitis and asthma indications is critical to interpretability. In addition, use of placebo control in studies involving children invokes ethical concerns. The combination of both ethical and methodological issues makes careful selection of control and population studied essential to the adequate performance and evaluation of such studies.

It is generally accepted that placebo-controlled studies can be ethically performed for the indication of allergic rhinitis.[10] For these studies, use of a placebo is recommended because the risk-to-benefit ratio precludes use of a positive control.

Choice of the control arm or arms is more complex in asthma studies. We have found that placebo-controlled studies in pediatric patients with asthma can be performed ethically as long as the study population (mild persistent asthma) and action plans for worsening symptoms are clearly and specifically defined, as previously outlined (see section V.A., Inclusion Criteria, and section V.D., Action Plan for Worsening Symptoms). One alternative methodology has been to include as a control arm a clinically appropriate, noncorticosteroid medication consistent with published guidelines (National Heart, Lung, and Blood Institute 1997 and 2002). This methodology is acceptable, as long as the on-treatment growth effect for that drug product has already been well characterized. One issue with the use of a placebo or an active comparator that is not expected to cause a growth effect is that if the study results show no growth effect for both the test treatment and the comparator, issues of interpretability may arise (e.g., low

[10] See the consensus recommendations of the FDA Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee of September 11, 2000 (http://www.fda.gov/cder/pediatric/ethics-statement-2000.htm) for a discussion of the use of a placebo control group in pediatric studies.

adherence may have impaired an ability to show a growth effect in the test treatment). For this reason, an ideal design might include three treatment arms: 1) test drug product; 2) a placebo or active comparator with a known lack of growth effects; and 3) use of an active control arm with a known growth effect (i.e., a positive control). The positive control group would allow for an assessment of the study's ability to show a growth effect of the test drug product, were one to exist. Since the choice of a comparator raises complex issues, the choice of the comparator or comparators for growth studies in asthma should be discussed with the review division.

2. Assessment of Patient Adherence

Since lack of compliance with use of study drugs is a potential major source of false-negative findings in long-term studies, every effort should be made to maximize and document patient adherence to use of study drug. The study protocol should specify how adherence to medication use will be determined and documented throughout the trial. Possibilities include but are not limited to the use of patient diaries, weighing (for inhalers) or counting (for tablets) returned study drug, and efficacy assessments (see section VI.D., Efficacy Endpoints and Analyses).

3. Assessment of Data Points

The protocol or prospective statistical analysis plan should specify the manner in which physiologically improbable data points or sequences of data points will be assessed (i.e., data points that demonstrate a large increase or decrease in height between visits, or a sequence of data points that show a pattern of linear growth for a time, then a sharp increase in height, followed by a decrease and the original linear pattern).

F. Sample Size

As discussed in section III, Overview of Recommendations for Growth Studies, the growth effect seen in such a trial should be regarded as a pharmacodynamic surrogate of the potential for a corticosteroid drug to cause systemic effects. Although there is general agreement that a decrement in growth velocity over a 1-year period can have clinical relevance, there remains some disagreement about how much change is clinically relevant. Since a *clinically meaningful difference* in growth velocities between treatment groups has not been determined and can be difficult to accurately define, interpreting inferential statistical testing also can be difficult. Therefore, a stand-alone approach is highly recommended, with the objective of the study to yield an estimation of the growth rate and the surrounding confidence interval with a high level of precision. If the sponsor plans to perform statistical tests comparing treatments, the study protocol or prospective statistical analysis plan should specify provisions for the statistical analyses and adjustments for multiple comparisons.

Since the objective of a growth study is to quantify any effect on growth as a measure of the potential to cause systemic effects, powering need not rely on an estimation of a clinically meaningful difference in growth velocities between treatment groups. Therefore, sample size estimations should be based on the desired precision (width of a 95 percent confidence interval) of the estimate of the difference in mean growth velocities between active and control treatments. A high level of precision should be obtainable with a carefully controlled study (e.g.,

few dropouts, complete follow-up on all patients, small measurement error), and a sample size of approximately 150 to 200 patients per arm. Sponsors should perform their own sample size calculations based on the expected standard deviation using their planned study design, patient population, and active moiety. Studies with 95 percent confidence intervals considerably wider than 0.5 cm likely will not be interpretable because of the lack of precision in the estimate of treatment effect. Similarly, studies with high numbers of dropouts, incomplete data on many patients, or obvious problems with measurement error might not be reliable enough to be interpreted.

VI. DATA ANALYSIS

A. Primary Analysis

The preferred measure of growth effects is the difference in growth velocity during the treatment period between active and placebo (or other noncorticosteroid) treatments. Individual patient growth velocities during the baseline, treatment, and follow-up periods should be calculated.[11] A linear regression model is the preferred methodology to estimate growth velocity, since it takes into account all height measurements during the treatment period, whereas change from baseline in height does not. An ANCOVA model involving all randomized patients with at least three recorded height measurements during the double-blind treatment period is recommended to estimate the mean difference between treatment groups in growth velocity over the treatment period. Appropriate predefined factors and covariates should be used in the model as explanatory variables. Factors that should be considered include baseline height, age, and sex. A 95 percent confidence interval around the mean difference in growth velocities between the control group and the active treatment group should be constructed. No interim analyses should be performed.

B. Secondary Analyses

The sponsor should perform the following secondary analyses:

- Subset analyses excluding:
  - Any patient who exhibits greater than or equal to Tanner Stage 2 characteristics at any point during the treatment or follow-up period
  - Questionable height measurements
  - Measurements taken after children received *rescue* systemic corticosteroids during the double-blind treatment period

[11] The last day of the baseline period is usually the first day of the treatment period. The measurement on that day should be used in both the baseline growth velocity calculation and the treatment period growth velocity calculation.

- Analysis of the percent of children who are below a certain percentile of growth velocity (e.g., 3rd, 10th, 25th percentile) or percent of children whose percentile for height decreases during the treatment period

- Categorical or *shift* analysis showing change in growth velocity percentile for each child from baseline to endpoint (e.g., by quartiles)

- Analysis of the first 3 months of data

- Summary of growth velocities during the pretreatment and follow-up periods

- Descriptive comparison of the growth velocities based on sex and ethnicity

The sponsor also should consider performing the following secondary analyses:

- Analysis of efficacy (see section VI.D., Efficacy Endpoints and Analyses)

- Analysis of standard deviation scores, using currently published standards[12]

- Random coefficients analysis

C. Other Safety Endpoints and Analyses

All routine laboratory tests (chemistry, hematology, liver function, and urinalysis) should be obtained in study patients at least four times: at screening and at the last visit of each phase of the study (baseline, treatment, and follow-up). Also, assessment of adrenal response using a sensitive test (e.g., through 24-hour urinary-free cortisol level measurements or 24-hour plasma cortisol area under the curve, at pretreatment, study endpoint, and 6 weeks post-study) should be conducted in studies of corticosteroids. The sponsor can choose to include evaluations of other safety endpoints. The sponsor should summarize these data for each phase of the study (baseline, treatment, and follow-up periods) for each treatment group, as appropriate.

D. Efficacy Endpoints and Analyses

Assessment of efficacy endpoints in these studies can help identify nonadherence and/or poorly controlled asthma or allergic rhinitis. Therefore, for the asthma studies, pulmonary function tests should be performed at every office visit (FEV_1 in patients who are able to perform this test, or peak flow rates in patients who are unable to perform an FEV_1 maneuver because of age). Peak flow rates, asthma symptom scores, and use of rescue medication should be recorded in daily diaries. For allergic rhinitis studies, efficacy assessments should include nasal symptom scores

[12] The current equation used for calculation of standard deviation scores is:

$$\frac{\text{(Observed height)-(NCHS Std Median HT for age at baseline)}}{\dfrac{\text{(NCHS Standard 95 percentile HT – 5 percentile HT)}}{2 \times 1.645}}$$

and use of rescue medication recorded in patient diaries.[13] The sponsor should summarize these data for each study phase (baseline, treatment, and follow-up periods) for each treatment group.

[13] We suggest evaluation of the following instantaneous and/or reflective symptom scores: rhinorrhea, nasal congestion, nasal itching, and sneezing, rated on a 0-3 scale of severity before dosing.

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