

The following case description uses published information to construct a generic description of a typical clinical investigation that is not unique or specific to any particular product.

Hypothetical Case Description: Clinical Trial of an Inhaled Corticosteroid in Children with Mild Persistent Asthma

A sponsor has developed a new inhaled corticosteroid (ICS) that may have a decreased steroid-induced effect on bone growth based on results from cell culture and animal models. The investigational (study) ICS has been shown to be safe and effective for the treatment of adolescents and adults (12 years of age and older) with asthma. The sponsor now wants to demonstrate that the study ICS is both safe and effective for the treatment of children with asthma and minimizes the adverse effect on growth (as measured by prepubescent growth velocity). As part of the pediatric clinical program, the sponsor is proposing a year-long growth study. The proposed study is a randomized, double-blind, double-dummy, parallel group, placebo-controlled, 56-week study to evaluate the safety and efficacy of two different doses of the study ICS when administered via metered-dose inhaler (MDI) to children between 5 to 8 years of age with mild persistent asthma. To assure assay sensitivity, the study design also includes an approved ICS with known effects on linear growth as a positive control group.

After a placebo run-in period, children with a history of mild persistent asthma for a minimum of six months will be randomized in equal ratios to one of four treatment arms: 100 µg BID of study ICS (one MDI puff), 200 µg BID of study ICS (two MDI puffs), 200 µg BID of the comparator ICS or matching-image placebo for each drug. The doses of the study ICS are chosen not to exceed the lowest dose found to be safe and effective in adolescents. In addition to meeting the 2007 National Asthma Education and Prevention Program (NAEPP) criteria for mild persistent asthma (e.g., FEV₁ > 80%), enrolled patients are required to be in Tanner stage I and with heights and weights in the 5th to 95th percentile range for age. In addition, bone age as measured by wrist radiograph should be less than 1 year different from the patient's chronological age. Children who used an ICS within 6 weeks and systemic corticosteroids within 3 months of the first baseline visit and during the placebo run-in period will be excluded. Subjects are permitted to receive an approved leukotriene modifier whose effect on linear growth has already been well characterized, if (1) the treatment was prescribed at least four weeks prior to the study, and (2) the dosing regimen remains constant following randomization. All subjects will be allowed to use β-agonists as needed throughout the study. The primary safety end point is linear growth velocity, measured using a stadiometer. The primary efficacy variable is the forced expiratory volume at 1 second (FEV₁). For safety reasons, standard-of-care guidelines based on the NAEPP guidelines will be followed in the management of all acute asthma exacerbations. Subjects are allowed up to four rescue treatments with oral corticosteroids during the trial before being converted to open-label ICS. In addition, any subject experiencing one episode of life-threatening asthma will also be converted to open-label ICS. These subjects will remain in the study for the purpose of the primary safety endpoint, and be considered a treatment failure for the primary efficacy variable.

Questions:

- (1) Please discuss the assessment of the potential benefits of this clinical investigation for the enrolled children. Issues you may want to consider include: (a) whether the potential benefits would apply equally to both the intervention and control groups; (b) the distinction between benefits that may occur as a direct result of the experimental intervention versus those that may occur from inclusion in the clinical trial independent of the experimental intervention (i.e., the so-called "inclusion" benefit); and (c) whether any additional monitoring

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procedures required by the administration of the experimental product would be considered a direct benefit or evaluated as a risk that must be balanced by the potential direct benefit of the experimental product.

- (2) Please discuss the assessment of the risks of this clinical investigation for the enrolled children. Issues you may want to consider include: (a) the risks of withholding the known effective ICS comparator from the two experimental ICS arms and the negative (i.e., placebo) control arm; (b) the impact of the selection of subject population on those risks (e.g., mild or moderate persistent asthma); (c) the role of other study modifications such as the use of other rescue and/or controller medications; and (d) the risks of any monitoring procedures made necessary by the experimental intervention.
- (3) Please discuss the analysis of this proposed trial under Subpart D. In your discussion, please address whether the different study arms should be evaluated together (i.e., as one cohort before randomization) or separately (i.e., as separate cohorts after randomization). Issues you may want to consider include: (a) the distinction between prospect of direct benefit for each arm of the clinical study and efficacy as the primary objective of the clinical study.

Background Literature:

Becker, A. B., O. Kuznetsova, et al. (2006). "Linear growth in prepubertal asthmatic children treated with montelukast, beclomethasone, or placebo: a 56-week randomized double-blind study." *Ann Allergy Asthma Immunol* 96(6): 800-7.

Ferguson, A. C., H. P. Van Bever, et al. (2007). "A comparison of the relative growth velocities with budesonide and fluticasone propionate in children with asthma." *Respir Med* 101(1): 118-29.

National Asthma Education and Prevention Program Expert Panel Report 3. Guidelines for the Diagnosis and Management of Asthma – Summary Report 2007. NIH Publication Number 08-5846. October 2007. Available at <http://www.nhlbi.nih.gov/guidelines/asthma/asthsumm.pdf>.

Strunk, R. C. for the Childhood Asthma Management Program (CAMP) Research Group (2007). "Childhood Asthma Management Program: Lessons Learned." *J Allergy Clin Immunol* 119(1): 36-42

The Childhood Asthma Management Program (CAMP) Research Group (2000). "Long-Term Effects of Budesonide or Nedocromil in Children with Asthma." *N Engl J Med* 343(15): 1054-63.

U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for Industry: Orally Inhaled and Intranasal Corticosteroids: Evaluation of the Effects on Growth in Children. March 2007. Available at <http://www.fda.gov/cder/guidance/5514fnl.pdf>.