The FDA Critical Path Initiative

Clinical Considerations for Demonstration of Dose-response for Inhaled Corticosteroids - Exhaled Nitric Oxide Model

Badrul A. Chowdhury, MD, PhD

Director

Division of Pulmonary and Allergy Products

US Food and Drug Administration, Rockville, MD

PQRI and INTFG Conference, Bethesda, Maryland, March 9-10, 2009

Disclaimer

- In this presentation I am relaying personal views and opinion. This presentation is not intended to convey official US FDA policy, and no official support or endorsement by the US FDA is provided or should be interred.
- I do not have any financial interest or conflict of interest with any pharmaceutical company
- The materials presented are available in the public domain

Outline of the Presentation

- Relevant regulatory framework
- Challenges in developing generic inhaled drugs, particularly inhaled corticosteroids
- Exhaled nitric oxide as a biomarker to show dose-response with inhaled corticosteroids

Drug Development

- NDA process: Sec. 505 (d) of FD&C Act
  - Adequate manufacturing and controls to ensure identity, strength, quality, and purity (QUALITY)
  - Safety under conditions of labeled use (SAFETY)
  - Substantial evidence of efficacy under conditions of labeled use (EFFICACY)
- ANDA process: Sec. 505 (j) of FD&C Act
  - Same active ingredients as listed drug
  - Same strength, route, and dosage form as listed drug
  - Bioequivalence to listed drug
  - Same labeling as listed drug
    - Exceptions for exclusivity claims

Drug Development

- Three types of drug development applications
  - 505(b)(1)
    - Contains full reports of investigations of safety and effectiveness
  - 505(b)(2)
    - Some of the information required for approval comes from studies not conducted by or for the applicant
  - 505(j)
    - Proposed product is identical to a previously approved product

Generic Drug Development

- Demonstration of bioequivalence (BE) to the reference listed drug is critical to the approval of a generic drug
- BE means “the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives become available at the site of drug action when administered at the same molar dose under similar conditions” [21 CFR 320.1(e)]

BE for Inhaled Respiratory Drugs

- Relevant diseases
  - Asthma
  - Chronic Obstructive Pulmonary Diseases (COPD)
- Relevant drugs classes
  - Bronchodilator drugs, such as albuterol
  - Controller drugs, such as inhaled corticosteroids (ICS)
  - Combination products, such as combination of a bronchodilator and an ICS

BE for Inhaled Respiratory Drugs

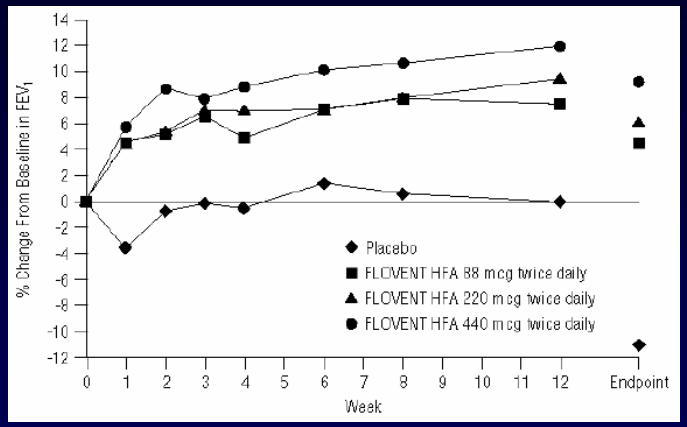
- Bronchodilator drugs, such as albuterol
  - There are prior precedence and generally accepted models for demonstrating BE [Creticos PS, Adams WP, Petty BG, Lewis LD, Singh GJP, et al., A methacholine challenge dose-response study for development of a pharmacodynamic bioequivalence methodology for albuterol metered-dose inhalers; J Allergy Clin Immunol 2002; 110:713-20]
- Controller drugs, such as ICS
  - There are no prior precedence and there are challenges to overcome

Challenges in Demonstrating BE for Inhaled Corticosteroids (ICS)

- For drugs that reach their site of action through the systemic circulation, BE is demonstrated by drug concentration in a relevant biologic fluid, such as blood
- For orally inhaled drugs intended for local action in the lung, the typical BE approach is not applicable, because delivery and action in the lung are not dependent on levels in the systemic circulation

Flovent HFA Inhalation Aerosol
(fluticasone propionate 44, 110, 220 mcg)

- Phase 3 program studied a range of doses in 12-week studies in patients 12 years of age and older with asthma
  - 1 study in patients previously maintained on bronchodilators alone
  - 1 study in patients previously maintained on inhaled corticosteroids
  - 1 study in patients previously maintained on oral corticosteroids



Previous Therapy	Recommended Starting Dosage	Highest Recommended Dosage
Adolescent and adult patients (≥12 years)		
Bronchodilators alone	88 mcg twice daily	440 mcg twice daily
Inhaled corticosteroids	88-220 mcg twice daily*	440 mcg twice daily
Oral corticosteroids†	440 mcg twice daily	880 mcg twice daily
Pediatric patients (4 to 11 years)‡	88 mcg twice daily	88 mcg twice daily

Ref: Product Label

Critical Path Opportunities for Generic Drugs – BE of Inhalation Products

- "The assessment of bioequivalence for locally acting and targeted delivery products has presented scientific challenges to the approval of generic products"
- "The current method of comparative clinical trials can be prohibitively expensive and is the least efficient way to detect difference in product performance"
- Critical path opportunities for new methods and approaches, such as novel pharmacodynamic study designs, and use of biomarkers

http:www.fda.gov/oc/initiatives/criticalpath/reports/generic.html

Determination of BE of ICS

Similar Drug Product Characteristics

- Formulations: qualitatively and quantitatively same
- Devices: similar shape, design, and operational characteristics

Similar In Vitro Performance

- Similar emitted dose per inhalation
- Same particle size distribution of emitted dose
- Similar device airflow resistance at different flow rates (for DPI)

Equivalent Systemic Exposure

- Based on PK (AUC, Cmax) data
- Based on PD endpoint, if plasma concentration of drug not measurable

Equivalent Local Action

- Based on relevant clinical or PD endpoint showing dose-response that can allow appropriate statistical comparison between products

Models for ICS Dose-Response

- Asthma Stability model
  - Pilot study results encouraging [Ahrens RC, Teresi ME, Han S-H, et al., Asthma Stability Model after Oral Prednisone. A Clinical Model for Comparing Inhaled Steroid Potency. Am J Respir Crit Care med 2001; 164: 1138-45]
  - FDA has funded a follow up study to University of Iowa
- Exhaled nitric oxide (ENO) model
  - Literature and published clinical studies very encouraging
  - FDA has funded a study to be conducted at National Jewish Medical and Research Center, Denver, Colorado

Suitability of Using Exhaled Nitric Oxide in ICS BE Studies

- Relevant marker of asthma
  - Biologically relevant
  - Increased in asthma
- Responsive to ICS
  - Decreased by ICS and antileukotriene agents
  - Dose-response within clinically relevant ICS doses
  - Not affected by bronchodilators
- Suitable for cross-over BE study
  - Reproducibility of effect
  - Reasonably fast onset and reversibility of effect
- Methodology for measurement standardized and harmonized

Exhaled Nitric Oxide in Airways

- NO in breath originates from the lower airway and nasal/sinus cavity
- Nitric oxide (NO) is synthesized by nitric oxide synthase (NOS) found in several cell types

J Allergy Clin Immunol 2003: 111:256-62; Physiol Rev 2004; 84:731-65;
Am J Resp Crit Care Med 2005; 912-30

Nitric Oxide Synthase in Airways

- Constitutive NOS (NOS 1 or neuronal NOS, NOS 3 or endothelial NOS)
  - Calcium and calmodulin dependent and released within seconds
  - Produce NO intermittently at femtomolar or picomolar concentration
  - nNOS expressed in airway nerves
  - eNOS expressed in endothelial cells, bronchial epithelial cells, and type II alveolar epithelial cells
- Inducible NOS (NOS 2)
  - Regulated at pretranslational level
  - Induced by pro-inflammatory cytokines, e.g., TNFα, INFγ, IL-1β
  - Produce NO at nanomolar concentrations several hours after exposure that may continue in a sustained manner
  - Expressed in variety of cells (e.g., type II alveolar airway epithelial cells, endothelial cells, airway and vascular smooth muscle cells, fibroblasts, chondrocytes, neutrophils, and mast cells)
  - Steroid sensitive

Physiol Rev 2004; 84:731-65; J Allergy Clin Immunol 2003: 111:256-62

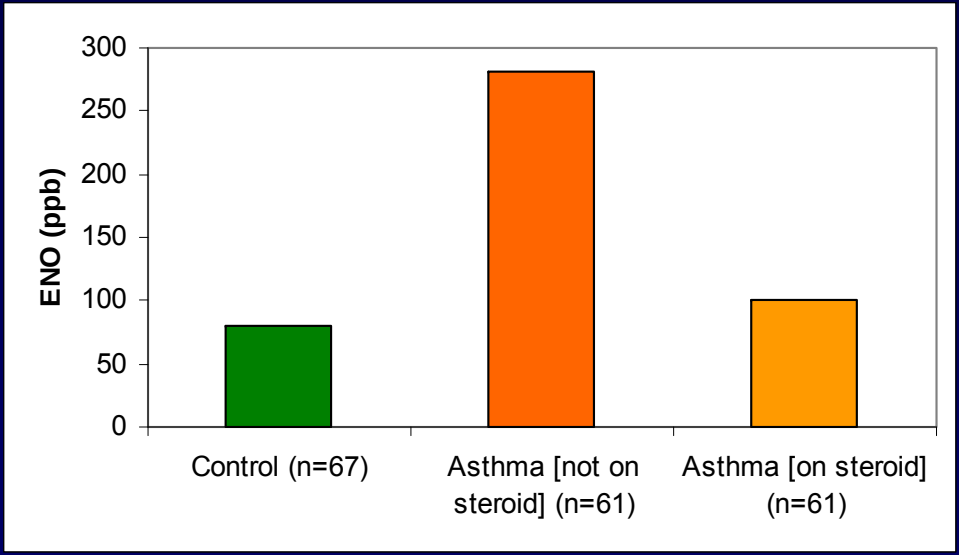
Exhaled NO in Respiratory Diseases

- **High levels of exhaled NO**
  - Asthma
  - Atopy with or without asthma
  - COPD in exacerbation
  - Acute lung allograft rejection
  - Post-transplant bronchiolitis obliterans
  - Bronchiectasis
  - Viral respiratory infections
  - Systemic lupus erythematosis
  - Liver cirrhosis
- **Low levels of exhaled NO**
  - Cystic fibrosis
  - HIV infection
  - Pulmonary hypertension

Am J Resp Crit Care Med 2005; 912-30

Effect of ICS on Exhaled NO Levels in Asthma

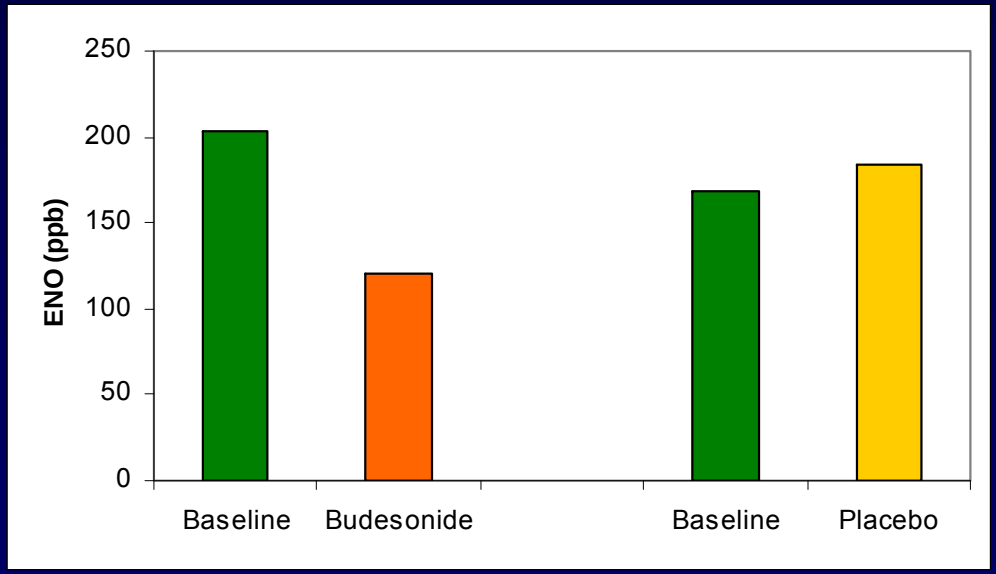
- Subjects : Healthy subjects and patients with asthma
- Cross-sectional observational study, no intervention



Lancet 1994: 343:133-5

Effect of ICS on Exhaled NO Levels in Asthma

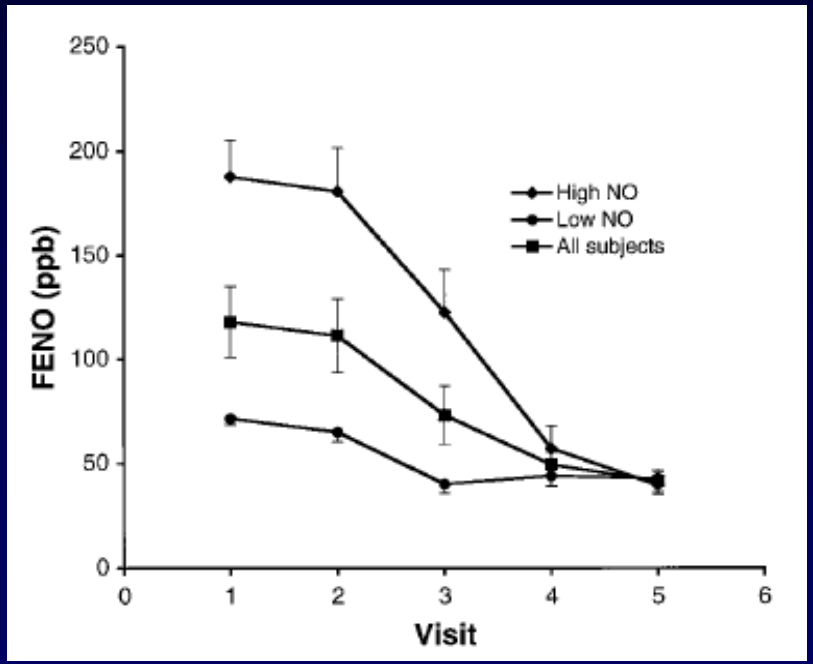
- Subjects : 11 patients 26 to 36 years of age with asthma
- Cross-over design
  - Budesonide 800 mcg BID for 3 weeks
  - Placebo for 3 weeks



Am J Resp Crit Care Med 1996; 153:454-7

Dose-Response with ICS

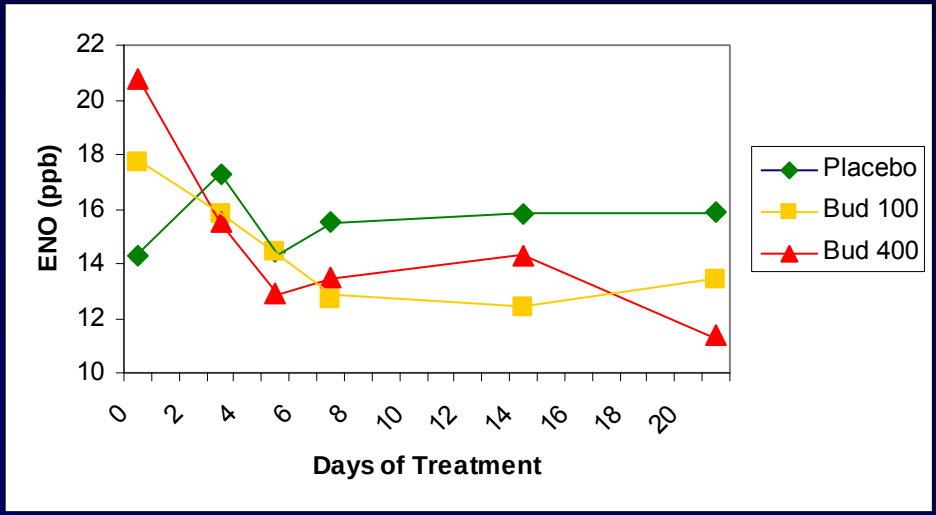
- Subjects
  - 15 patients 17 to 40 years of age with asthma
- Treatment: beclomethasone (BDP) for 1 week
- Sequential design
  - Visit 1: Baseline
  - Visit 2: Placebo
  - Visit 3: BDP 100 mcg/day
  - Visit 4: BDP 400 mcg/day
  - Visit 5: BDP 800 mcg/day



Chest 2001; 119:1322-8

Dose-Response with ICS

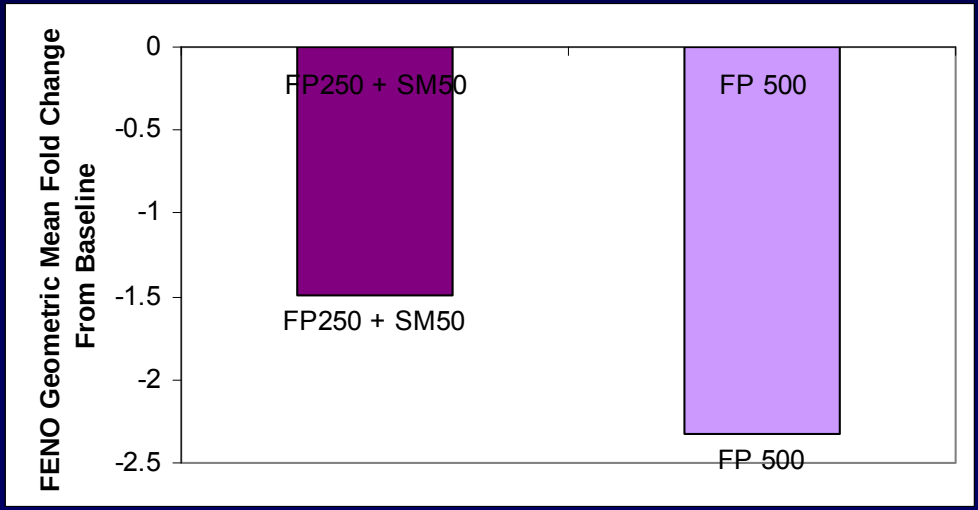
- Subjects : 28 patients with asthma, mean age 28 years
- Parallel group design
  - Placebo for 3 weeks
  - Budesonide 100 mcg QD for 3 weeks
  - Budesonide 400 mcg QD for 3 weeks



Thorax 2002; 57:889-96

Stability of Effect in Presence of Inhaled Beta-Agonist Bronchodilator

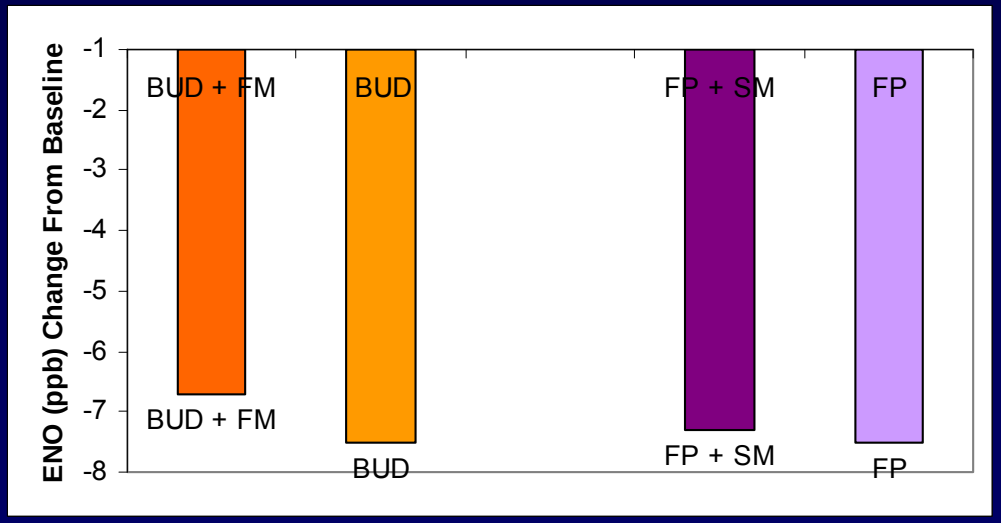
- Subjects : 15 patients with asthma, mean age 36 years
- Baseline ENO: 19 ppb
- Cross-over design
  - Fluticasone propionate 250 mcg + salmeterol 50 mcg BID for 2 weeks
  - Fluticasone propionate 500 mcg BID for 2 weeks



Eur J Clin Pharmacol 2003: 59:11-5

Stability of Effect in Presence of Inhaled Beta-Agonist Bronchodilator

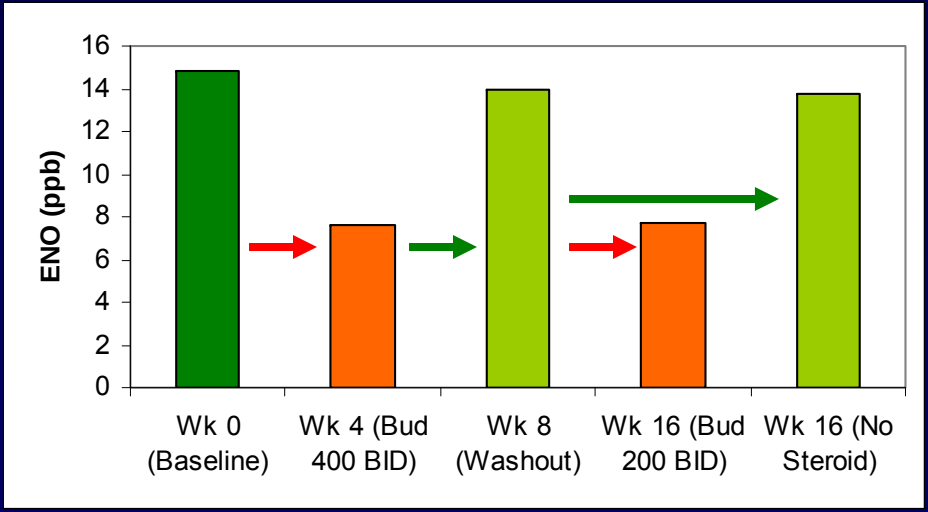
- Subjects : 29 patients with asthma, mean age 46 years
- Baseline ENO: 12.5 ppb
- Cross-over design
  - Budesonide 400 mcg + formoterol 12 mcg BID for 4 weeks (BUD+FM), followed by budesonide 400 mcg BID for 1 week (BUD)
  - Fluticasone propionate 250 mcg + salmeterol 50 mcg BID for 4 weeks (FP+SM), followed by fluticasone propionate 250 mcg BID for 1 week (FP)



Brit J Clin Pharmacol 2003: 56:494-500

Reproducibility of Effect with ICS

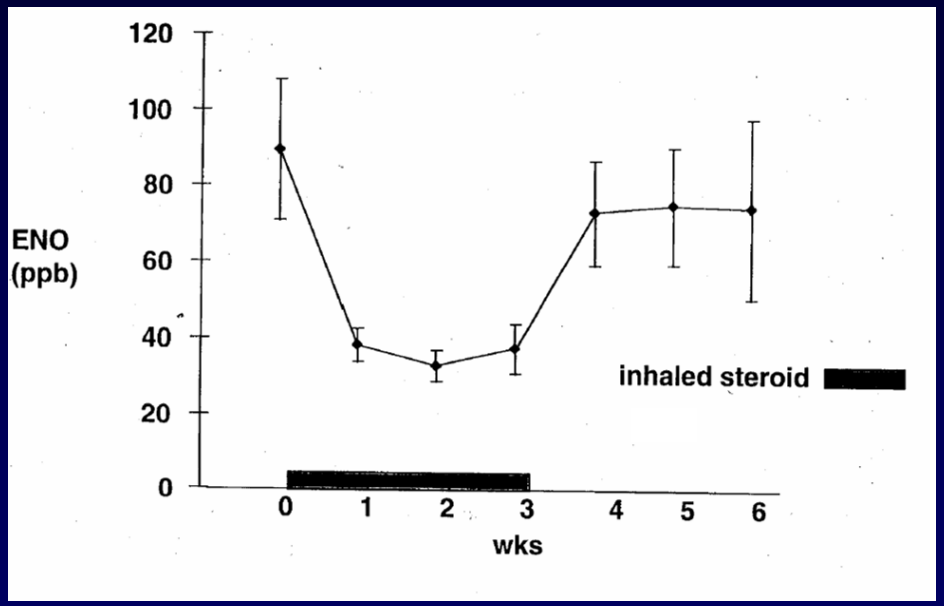
- Subjects : 54 patients 6-16 years of age with asthma
- Parallel design
  - 4 wk run-in : Budesonide (BUD) 400 mcg BID
  - 4 wk washout
  - 8 wk randomized treatment : BUD 200 mcg BID or Placebo



Eur Res J 2002: 19:1015-19

Onset and Reversibility of ICS Effect

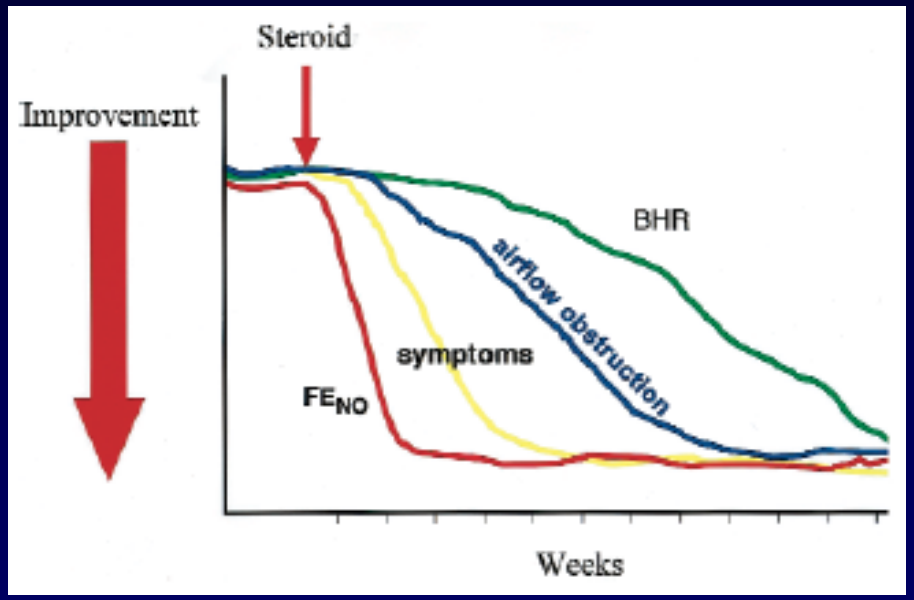
- Subjects
  - 10 patients 16-50 years of age with asthma
- Cross-over design
  - each patient tested on and off treatment
- Treatment
  - beclomethasone 1000 mcg/day for 3 weeks



J Asthma 1998: 35:473-9

Time Course of Asthma Outcome Measures

- Exhaled NO is a fast responding marker
- Exhaled NO does not correlate with pulmonary function parameters
- Correlations with sputum eosinophil and bronchial hyperreactivity are modest and not consistent



J Allergy Clin Immunol 2003: 111:256-62

Measurement of Exhaled NO

- Methodology for measurement of fractional concentrations of orally exhaled NO is standardized and harmonized
  - European Respiratory Society (ERS) published recommendation in 1997
  - American Thoracic Society (ATS) published statement in 1999
  - ATS/ERS published recommendation in 2005

Am J Resp Crit Care Med 2005; 912-930; Am J Resp Crit Care Med 2006: 173:811-13

Suitability of Using Exhaled Nitric Oxide in ICS BE Studies

- Relevant marker of asthma
  - Biologically relevant
  - Increased in asthma
- Responsive to ICS
  - Decreased by ICS and antileukotriene agents
  - Dose-response within clinically relevant ICS doses
  - Not affected by bronchodilators
- Suitable for cross-over BE study
  - Reproducibility of effect
  - Reasonably fast onset and reversibility of effect
- Methodology for measurement standardized and harmonized

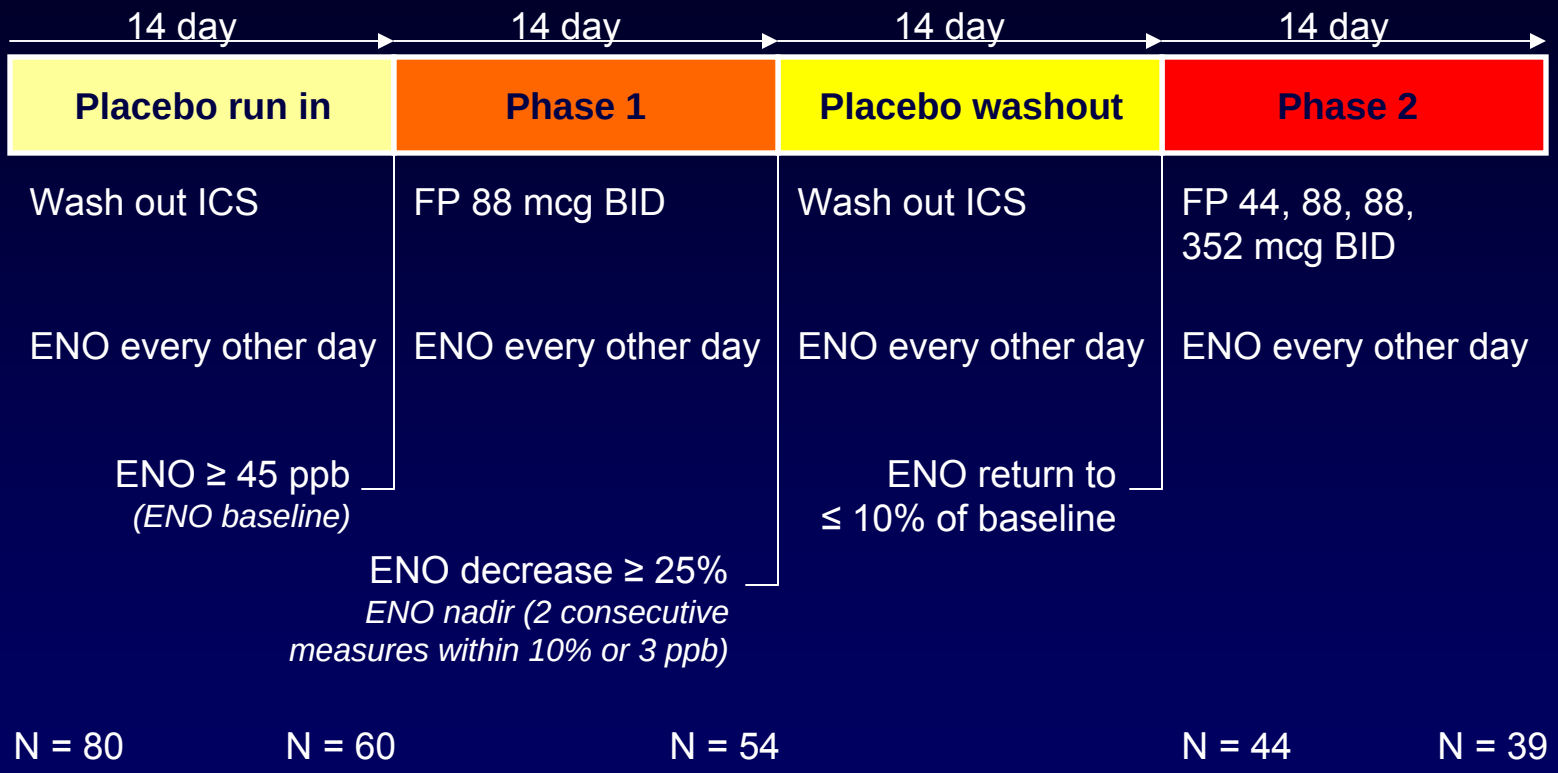
Study Using Exhaled NO to Show ICS Dose-Response

- Concept conceived by FDA
- Funded by FDA
- Objective
  - Evaluate the time course of various doses of fluticasone propionate inhalation aerosol (Flovent HFA) on exhaled NO
  - Evaluate exhaled NO as a marker for demonstrating ICS dose-response
- Contracted to National Jewish Health, Denver, Colorado

Design and Conduct of the Study

- Patients
  - Asthma diagnosed by history and ATS defined reversibility criteria
  - Mild-to-moderate persistent asthma based on NAEPP guideline
  - Ages 18 to 65 years
  - Exhaled NO ≥ 45 ppb
- Study periods
  - 14 day placebo run-in
  - 14 day phase 1
    - Treat with fluticasone propionate 88 mcg BID
  - 14 day placebo washout
  - 14 day phase 2
    - 4 way 12 sequence crossover separated by 14 days washout
    - Treat with fluticasone propionate 44 mcg, 88 mcg, and 352 mcg BID

Design and Conduct of the Study



Measures: 1. ENO by NIOX instrument
2. Spirometry using ATS standard guideline
3. Methacholine test using standard procedure

Concluding Remarks

- Development of a generic ICS is challenging because the standard BE approach based on drug concentration in a relevant biologic fluid, such as blood, is not applicable
- Pharmacodynamic studies or clinical endpoint studies to document equivalence of action at the local site is difficult because ICS have relatively flat dose-response curves on clinical endpoints
- Exhaled NO is a biologically relevant marker for asthma that has potential to show ICS dose-response