Budesonide/formoterol vs budesonide in asthmatic children (6-<12 years) (CHASE 3): Randomized, Double-Blind, Safety and Efficacy Study

BACKGROUND:

- The Childhood Asthma Safety and Efficacy (CHASE) program: efficacy & safety in 6 - 11 yrs
- CHASE 1: (dose confirming) budesonide(ICS) pMDI 160 μg BID vs placebo
- CHASE 2: (dose finding) higher dosages of formoterol (LABA) superior to lowest dose

OBJECTIVE:

- To evaluate efficacy of 2 formoterol doses with budesonide combinations (160/9 μg or 160/4.5 μg) as opposed to budesonide alone in children 6 to < 12 years with asthma

METHODS:

- Funding (AstraZeneca) → 2 authors employees and 2 received research funding
- **Design**: Phase 3, randomized, double-blinded, parallel-group, multicenter study - 88 site in the US, Mexico, Panama, and Slovakia
- **Inclusion criteria**:
  - Age: 6 to 11 years with ability to use a dry powder and meter dose inhaler
  - Documented clinical diagnosis of asthma for at least 6 months
  - FEV1 reversibility of at least 12% of pre-bronchodilator levels with albuterol
  - FEV1 60 – 100% of normal
  - Medium-dose ICS or fixed-dose ICS plus LABA for at least 4 weeks
- **Exclusion criteria**:
  - Hospitalization/emergency treatment for asthma within 6 months of enrollment
  - Treatment with systemic corticosteroids, a B-blocker (including eye drops), omalizumab, or other MoAb therapy within 6 months prior to run-in visit
  - Patients with significant disease besides asthma
- **Primary outcome measure**: demonstrate the efficacy of each budesonide/formoterol combination dose compared with budesonide alone in children 6 to 11 years with asthma
  - Primary efficacy variable: change from baseline of FEV1
- **Secondary outcome measures**:
  - Compare the efficacy between the 2 doses of budesonide/formoterol
  - Additional changes in clinic lung function parameters
  - Pediatric Asthma Quality of Life Questionnaire with Standardized Activities
  - Electronic diary (eDiary) variables – had to log in twice daily
  - Time to: occurrence of 1st asthma exacerbation & discontinuation of study drug
  - Safety of budesonide/formoterol vs. budesonide (AEs and discontinuations)
- 279 patients stratified via randomized interactive web response to ensure even distribution by age group (mean 9) to treatment groups for a total of 12 weeks
  - All patients: 7-28-day run-in on budesonide 160 micrograms divided BID
    - Total asthma score of ≥1 or rescue use at least 4 of 7 consecutive days
  - 92 patients: budesonide/formoterol 160/9 micrograms total – divided BID
  - 95 patients: budesonide/formoterol 160/4.5 μg total – divided BID
  - 92 patients: budesonide 160 μg total – divided BID
- Power 90% with an alpha level of 0.05 to detect a difference of 0.12 L in 1-hour post-dose FEV1 at the 5% significance level → calculated for 93 people per group
- Data handling method was intent-to-treat
- Primary and secondary measures analyzed by a mixed model for repeated measures
- PAQLQ(S) total and domain scores were analyzed by Cochran-Mantel-Haenszel test

RESULTS:

- 253 patients (90.7%) completed study, Patients not included:
  - 2 patients in each group did not receive any treatment
  - 7 in bud./formoterol 160/9: 4 subject decision, 1 lost to follow-up, 2 other → n= 85
  - 11 in bud./formoterol 160/4.5: 8 subject decision, 3 other → n = 84
  - 8 in budesonide 160: 2 adverse events, 3 subject decision, 3 other → n = 84
- **Primary outcome measure**: Budesonide/formoterol 160/9 μg resulted in a statistically significantly greater change from baseline FEV1 to the 1-hour post-dose FEV1 at week 12 vs budesonide 160 μg BID (treatment difference 0.12 L, 95% confidence interval [CI] 0.03 - 0.20, P = 0.006) (*other comparisons were not statistically significant differences)*
- **Secondary outcome measures**:
  - Numerical difference between 2 budesonide/formoterol groups (treatment difference 0.04 L, 95% CI 0.05 to 0.12, P = 0.373), were not statistically significant
  - $FEF_{25\%-75\%}$ at week 12 was statistically significantly higher with both budesonide/formoterol combinations compared with budesonide alone (P = 0.005)
  - PEF statistically significantly improvement for budesonide/formoterol 160/9 μg vs. budesonide (est. difference 25.47 L/min, 95% CI 10.94 - 40.00, P = 0.001)
  - Most common AEs in budesonide/formoterol compared with budesonide alone: URTI, pharyngitis, headache, and vomiting (All AEs can be found in Table 5)
  - No statistically significant differences for change in HRQoL, time to first asthma exacerbation, or time to discontinuation of drug between any treatment group
- **Author's conclusion:** Findings from the CHASE 1, 2, and 3 studies support appropriateness of adding LABA in children 6 - 11 years with asthma who are symptomatic on ICS alone

STRENGTHS:

- Phase 3, double blind, parallel, and performed at 88 centers
- Counseled patients and parents on how to use both types of inhalers
- eDiary to capture PEF, FEV1, rescue use, symptom scores, and nighttime awakenings
- Random assignment of patients separately by age group to ensure even distribution

LIMITATIONS:

- Excluded patients who were hospitalized for asthma or treated with a beta blocker eye drop
- FEV1 range for inclusion, 60 – 100%, is a very large range for debility or lack thereof in patients and asthmatic stage of patients was not included to clarify this
- Only 12-week duration of follow up and not stated if adherence was accounted for in eDiary
- Wording of dosing (inhalations, frequency) could be difficult to follow
- Not powered to detect a difference between the 2 budesonide/ formoterol doses which increases risk of type II error
- Statistically significant, but unclear if clinically significant due to no change in quality of life, exacerbations, or medication discontinuations between any group in the study

CONCLUSION:

- All formulations appear equally safe for use in children with asthma ages 6 to < 12 years
- Based on results of this trial, budesonide/formoterol 160/9 μg for pediatric patients who are currently on a medium-dose ICS or fixed-dose ICS plus LABA who remain uncontrolled on this regimen is appropriate and efficacious
- Future research: safety and efficacy of additional + budesonide or other ICS + LABA combinations in this age group would be beneficial, in order to increase medication options available for patients

Reference:
Pearlman DS, Eckerwall G, McLaren J, et al. Efficacy and safety of budesonide/formoterol pMDI vs budesonide pMDI in asthmatic children (6-<12 years). Ann Allergy Asthma Immunol. 2017 Apr;118(4):489-499.