CLINICAL STUDY RESULTS.ORG STUDY 051-357

Title of Study: A Study to Determine the Reliability of a Top Mount Actuation Indicator when used with Levalbuterol Tartrate HFA MDI in Adult and Pediatric Subjects with Asthma or Chronic Obstructive Pulmonary Disease	
Investigators and Study Center: 26 Investigators at 26 clinical sites in the United States.	
Study Period: 4 October 2005 – 29 March 2006	**Clinical Phase:** IIIb

Primary Objective: To investigate the reliability, ruggedness, and safety of the Top Mount Actuation Indicator (TMAI) when used as part of the integrated drug product with Levalbuterol HFA.

Secondary Objectives: The secondary objectives of the study were to assess:

- The device performance of the integrated drug product (Levalbuterol HFA plus TMAI)
- The safety of levalbuterol administered as needed (PRN) for up to 9 weeks using the integrated drug product

Methodology: This was an open-label, multicenter TMAI study with Levalbuterol HFA MDI in adult and pediatric subjects with asthma or chronic obstructive pulmonary disease (COPD). Period I: Subjects completed a 1 week, open-label, run-in period during which subjects must have had asthma or COPD symptoms requiring the use of PRN Levalbuterol HFA MDI (without TMAI) on at least 50% of the days [minimum of 2 doses (4 actuations) and no more than 6 doses (12 actuations) taken on a single day]. A subset of 50 subjects participated in spirometry testing only during Visits 1 and 2 to assess the MDI device performance with and without the TMAI. At Visit 1, these subjects were randomly assigned to 1 of 2 device sequences: with TMAI/without TMAI or without TMAI/with TMAI. The open-label devices assigned for spirometry testing were used in clinic for Visits 1 and 2 only. Period II: Nine week, open-label period during which subjects used the Levalbuterol HFA MDI with TMAI PRN. The total study duration for a subject was not to exceed 10 weeks.

No. of Subjects: Planned 200. Screened 248. Analyzed 174 [124 subjects with Asthma and 54 with COPD; 28 subjects 4-11 years, 116 subjects 12-64 years, and 30 subjects > 64 years].

Diagnosis and Main Criteria for Inclusion: Male and female subjects ≥4 years of age with a minimum 6-month documented asthma or COPD history or a new diagnosis of asthma for subjects 4-11 years of age. (Subjects with asthma had to have a pre-dose FEV_1 of ≥60% to ≤85% of predicted and subjects with COPD had to have a pre-dose FEV_1 of ≥40% to ≤85% of predicted at Visit 1.)

Test Product: Levalbuterol HFA MDI with TMAI
Reference Product: Levalbuterol HFA MDI without TMAI

Dosage: 90 μg of Levalbuterol Tartrate 2 actuations (45 μg each) prn

Mode of Administration: Metered Dose Inhaler

Meal Relationship: none

Duration of Treatment: 10 weeks (1 week placebo run-in, 9 weeks treatment)

Criteria for Evaluation

Efficacy: The primary efficacy assessment was the categorization (ie, undercount, same, overcount) of the difference between the number of actuations used according to the TMAI and the number of actuations estimated via canister weight for All End of Life Canisters.

The secondary device performance parameters were:

- Categorization of the difference between the number of actuations used according to the TMAI and the number of actuations estimated via canister weight for All Partially Used Canisters and All Canisters.
- The difference between the number of actuations used according to the TMAI and the number of actuations estimated via canister weight for All End of Life Canisters, All Partially Used Canisters, and All Canisters.
- Subject assessment of device performance.

Criteria for Evaluation Continued:

In the subset of subjects undergoing spirometry testing at Visit 1 and Visit 2:

- Percent Change in FEV_1 from Visit Pre-Dose
- Change in FEV_1 from Visit Pre-Dose
- Percent of Predicted FEV_1
- Peak Percent Change from Visit Pre-Dose in FEV_1
- Peak Percent of Predicted FEV_1
- Area Under the Percent Change in FEV_1 from Visit Pre-Dose Curve (AUC_{0-6})
- Time to Onset of Response
- Forced Vital Capacity (FVC)

Safety: The following safety assessments were completed:

- Physical examinations
- Vital signs (HR, RR, BP, and temperature)
- Standard 12 lead ECGs, including ventricular heart rate, and RR, PR, QRS, QT, and QTc intervals

- Peak expiratory flow rates
- Clinical laboratory evaluations (hematology, serum chemistry, and urinalysis)
- Female subjects were tested for pregnancy at Visit 1 (predose), Visit 3, and Visit
- 5
- Monitoring of adverse events
- Concomitant medication use

Statistical Methods

Efficacy: For continuous variables, statistical summaries included means, medians, standard deviations, maxima, and minima. For categorical variables, statistical summaries included counts and percentages.

All significance testing was performed at an $\alpha=0.05$ level of significance, using two-sided tests, unless otherwise stated.

Device performance summaries were performed using the ITT population for All End of Life Canisters as well as All Partially Used Canisters and All Canisters. FEV_1 endpoints were summarized for the FEV_1 assessment subgroup (spirometry crossover subjects). All safety parameters except AEs during the run-in period were summarized for the ITT population. AEs during the run-in period were summarized for all subjects enrolled and for the spirometry crossover cohort. In addition, summaries of demographic information (age, gender, race, height, and weight), screening FEV_1, screening percent of predicted FEV_1, accuracy of TMAI device, device performance, FEV_1 endpoints, AEs, and concomitant medications were presented separately for each age group (4-11, 12-64, and ≥65 years), by diagnosis (with or without COPD), and for the spirometry crossover cohort. Medical history, asthma history, COPD history, and tobacco use history were presented separately for the spirometry crossover cohort.

RESULTS

EFFICACY:

- Based on an acceptable discrepancy of -5 to 5 actuations, the TMAI actuation counter device was accurate 34.5% of the time. Overcount occurred with greater frequency than undercount. TMAI accuracy was not affected by age.

- Based on a performance questionnaire, most subjects found that the TMAI canister was easy to use, reporting it either "easy" or "very easy" to push down the canister to receive a puff of medicine; only three subjects felt it was "hard" to push the canister down. As far as receiving study medication through the TMAI device, the vast majority of subjects felt it was either "easy" or "very easy" to inhale the medicine through the TMAI device. No subject felt it was "hard" to breathe in the medicine through the inhaler.

- The efficacy of levalbuterol administered through both the TMAI device and without it, was clearly demonstrated in all age groups and in both the COPD and non-COPD populations. There was ~ 15% peak increase from visit predose, with a 0.25L increase in absolute FEV_1, and an ~ 8% increase in percent of predicted FEV_1. Overall, of those subjects who achieved a 15% response, most did so by 15 minutes post dose, while nearly all did so by 30 minutes post dose.

RESULTS
SAFETY:

- There were no deaths or serious adverse events.

- The use of TMAI device had no affect on the safety profile of levalbuterol.

- Seven subjects discontinued the study due to adverse events of asthma, 6 of which were considered related to study treatment. All resolved with treatment, and the majority were assessed as mild or moderate; two events were considered severe.

- During the Run-in Period the rate of adverse events was low. Roughly half of the ITT subjects experienced adverse events. During Period 2 the overall rate of adverse events was not affected by age or COPD diagnosis. The respiratory system had the highest frequency of adverse events, driven primarily by asthma exacerbations in subjects with asthma.

- The incidence of β-mediated adverse events was low in the ITT population; one subject experienced non-cardiac chest pain and another experienced dizziness.

- Levalbuterol had little or no effect on vital signs or electrocardiograms. There was a slight increase in the number of subjects who had potentially clinically significant low measurements of potassium and glucose at the End of Study.

- Administration of levalbuterol was safe and well tolerated.