Long-term safety and efficacy of formoterol fumarate inhalation solution in patients with moderate-to-severe COPD

BACKGROUND:

COPD is a disease that is prevalent in the United States and is associated with significant morbidity and mortality. Long-acting B2 agonist (LABA) medications play an important role in the treatment of COPD. Some studies have shown long-term use of LABAs is safe while others suggest long term LABA use may increase the risk of a cardiovascular event. The FDA has requested further research to determine the safety of long-term LABA use.

OBJECTIVE

To determine the safety of long term use of formoterol fumarate inhalation solution in patients with moderate to severe COPD.

METHODS

- Design: Multicenter, randomized, double-blind, placebo-controlled, parallel-group noninferiority study; 106 sites; Duration: 52 weeks
- Inclusion criteria: Patients 40 years or older with a medical diagnosis of COPD, had 1 or more COPD exacerbations within the past year, had a current or former smoking history of >10 pack years, demonstrate a post-bronchodilator (albuterol) FEV1/FVC ratio of <0.7 and an FEV1 of 30%–70% of the predicted normal value after withholding LABA-containing medications for ≥48 hours.
- Exclusion criteria: Concomitant use of LABA, LABA-containing combination products, combination products containing short-acting β2-agonists and anticholinergics, nebulized and oral β2-agonists, orally inhaled nedocromil or cromolyn sodium, and theophylline background medications were all prohibited
- Concomitant Medications allowed: Inhaled short- or long-acting anticholinergics, inhaled corticosteroids (monotherapy only) leukotriene modifiers, oral phosphodiesterase-4 inhibitors and albuterol as needed
- Primary outcome measure: combined incidence of respiratory death, first COPD-related ER visit, or first COPD exacerbation-related hospitalization
- Secondary outcome measures: The primary endpoints were assessed individually.
- Secondary efficacy outcome measures: Spirometry end points (FEV1, FVC, % predicted FEV1, and inspiratory capacity), total SGRQ, and focal TDI scores were analyzed at each scheduled visit (baseline, 3, 6, 9, and 12 months).
- 1,071 patients were randomized
    - 541 patients received 20µg of Formoterol fumarate inhalation solution
      OR
    - 530 matching placebo
- Power was not stated in the study, but was stated it was adequate enough to observe an event rate of 15% in the placebo group

RESULTS

- 551 patients discontinued the study (FFIS, n=247 [45.7%]; placebo n=304 [57.4%])
- Primary outcome measure: 121 had ≥1 primary end point events (FFIS n=64; placebo n=57). HR of FFIS to placebo of 0.965 (90% CI: 0.711 - 1.308), demonstrating FFIS was noninferior to placebo
- Secondary outcome measures: Only 1 respiratory-related death occurred which was in the placebo group, COPD-related ER visit had a HR of FFIS to placebo of 0.834 (90% CI: 0.589 -

1.180), and COPD exacerbation-related hospitalization had a HR of FFIS to placebo of 0.772 (90% CI: 0.533 - 1.118) demonstrating FFIS is noninferior to placebo.

- Secondary efficacy outcome measures: FEV1 (3- and 6-month visits; P<0.05), FVC (all visits; P<0.005), and % predicted FEV1 (3-, 6-, and 9-month visits; P<0.05) were all statistically significant. The inspiratory capacity results were not statistically significant. The estimated mean (standard error) decrease from baseline in SGRQ total score at month 3 was -3.25 (0.55) for the FFIS group compared with -2.03 (0.57) for the placebo group (-1.226 (95% CI: -2.674 - 0.223) P=0.097) was not statistically significant. The estimated mean (SE) increase from baseline in focal TDI scores at month 3 was 0.7 (0.11) for the FFIS group compared with 0.0 (0.12) for the placebo group, and this difference (0.7 [95% CI: 0.4, 1.0]) was statistically significant (P<0.001).
- Adverse Effects: The most common medication-related AE were COPD (worsening and exacerbations; FFIS: 30.3%; placebo: 27.4%), dyspnea (FFIS: 6.5%; placebo: 7.5%), and cough (FFIS: 7.2%; placebo: 4.5%).
- Author's conclusion: Formoterol given twice daily did not increase the combined incidence of respiratory death, COPD related ER visits, or COPD exacerbation related hospitalizations. FFIS group showed fewer treatment withdrawals and improved lung function. These results show the safety of long term LABA use in COPD patients.

STRENGTHS

- Large sample size
- >80% adherence between both groups
- Concomitant therapy washout periods prior to spirometry
- Use of an independent mortality adjudication board

LIMITATIONS

- High dropout rates
- Lower than expected event rates
- Large noninferiority margin (≤50%)
- No power reported
- Use of concurrent medications
- Use of a nebulized solution

CONCLUSION

- The study showed that long term LABA use in patients with COPD is safe and is consistent with other treatments.
- LABA use in current practice is typically used in combination with another medication. The use of Formoterol fumarate inhalation solution as monotherapy is limited.
- Future research: Need future studies where the dropout rate isn't over 50%. Also, need a formulation that doesn't require twice daily nebulization. Most formulations that include a LABA are inhalers.

Reference:

Hanania NA, Sethi S, Koltun A, Ward JK, Spanton J, Ng D. Long-term safety and efficacy of formoterol fumarate inhalation solution in patients with moderate-to-severe COPD. Int J Chron Obstruct Pulmon Dis. 2018 Dec 27;14:117-127.

Aaron Hanzes, Doctor of Pharmacy Candidate