FULFIL Trial: Once-Daily Triple Therapy for Patients with Chronic Obstructive Pulmonary Disease

BACKGROUND

- The Global Initiative for Chronic Obstructive Lung Disease guidelines recommends inhaled triple therapy (ICS/LAMA/LABA) for patients with advanced COPD with persistent symptoms and risk of exacerbations.
- Triple therapy may offer improvements in lung function and quality of life compared with ICS/LABA dual therapy, as well as reduce the number of inhalers used.

OBJECTIVE

- To evaluate the effects of once-daily single-inhaler triple therapy (FF/UMEC/VI) on lung function and health-related quality of life compared with twice-daily dual ICS/LABA therapy (Budesonide/Formoterol) at 24 weeks.

METHODS

- **Design:** Multicenter, phase III, randomized, double-blind, double-dummy, parallel study; Duration: 24 weeks, extension population 52 weeks
- **Inclusion criteria:** 40 years or older with Global Initiative for Chronic Obstructive Lung Disease group D COPD, and either at least two moderate exacerbations or at least one severe exacerbation in the past year, received daily maintenance therapy for at least 3 months
- **Exclusion criteria:** Diagnosis of asthma causing symptoms, unresolved pneumonia or severe COPD exacerbation, COPD from alpha$_1$-antitrypsin deficiency, lung resection within 12 months of screening, respiratory tract infection not resolved within 7 days of screening, abnormal chest X-ray, abnormal and clinically significant 12-lead ECG
- **Primary outcome measures:** Change from baseline in trough FEV_1 and St. George's Respiratory Questionnaire (SGRQ) total score
- **Secondary outcome measures:** Proportion of patients with a clinically meaningful change from baseline in trough FEV_1, SGRQ total score, and Evaluating Respiratory Symptoms in COPD score (E-RS: COPD) and proportion of responders
- **Safety outcome measures:** patient reported adverse events, serious adverse events, adverse events of special interest, major cardiovascular events
- 1811 patients were randomized to receive treatment; 1810 patients in the ITT population
  - 911 patients: one inhalation daily fluticasone furoate/umeclidinium/vilanterol 100 mcg/62.5 mcg/25mcg (ELLIPTA) plus one inhalation twice-daily placebo Turbuhaler
  - 899 patients: one inhalation twice-daily budesonide/formoterol 400 mcg/12 mg (Turbuhaler) plus one inhalation once-daily placebo ELLIPTA
- 688 patients needed per group for a power of 90% with an alpha level of 0.01 to detect a difference between groups of 80 mL for trough FEV_1 (assuming SD 240 mL) and 2.5 units for SGRQ score (assuming SD 12 units)
- Data handling method was intent-to-treat

RESULTS

- 1810 patients were included in the ITT population; 186 patients discontinued treatment; 911 ELLIPTA, 210 continued to 52-week; 899 Turbuhaler, 220 continued to 52-week
- Primary outcome measure: Change in baseline FEV_1 between treatments in favor of ELLIPTA (171 mL; 95% CI, 148-194; $P < 0.001$). Change in SGRQ total score in favor of ELLIPTA (-2.2 units; 95% CI, -3.5 to -1.0; $P < 0.001$)

- **Secondary outcome measures:** OR of achieving an increase of at least 100 mL from baseline in trough FEV_1 versus not achieving in favor of ELLIPTA (OR 4.03; 95% CI 3.27-4.97; P < 0.001); Improvement in SGRQ score OR of response versus nonresponse in favor of ELLIPTA (OR 1.41; 95% CI, 1.16-1.70; P <0.001); Reduction in annualized rate of exacerbations in favor of ELLIPTA (35%; 95% CI, 14-51%; P =0.002); Greater reductions in E-RS in favor ELLIPTA (P < 0.001); ORs for response versus nonresponse in favor of ELLIPTA (ORs 1.59-1.76; P < 0.001)
- **Authors' conclusion:** Results showed that once-daily ELLIPTA offered clinically meaningful and statistically significant improvements at Week 24 in lung function and health-related quality of life compared with Turbuhaler.

STRENGTHS

- Randomized, double-blind, double-dummy, multicenter
- Power appropriate for 24-week duration
- Written consent obtained
- Standardized equipment used for spirometry

LIMITATIONS

- Multiple conflicts of interest
- New guidelines recommend LAMA/LABA combination not ICS/LABA as dual therapy
- No data provided for adherence or success of blinding
- Results reported in overly positive manner and extrapolated inappropriately
- Adverse effects not statistically analyzed
- Authors did not address study limitations

CONCLUSION

- The study showed that once-daily therapy with ELLIPTA improved lung function and health-related quality of life compared to twice-daily Turbuhaler in patients with group D COPD.
    - This should be taken into account when recommending therapy as well as the potential for improved compliance and reduced medication errors. However, this must also be weighed against the cost of the newer ELLIPTA as well as potential long-term adverse effects.
- Further research:
    - In future studies, triple therapy should be compared to a LAMA/LABA combination to assess the efficacy of adding an ICS. If possible, patients' baseline therapies should be controlled for so the outcome measures will only reflect the effect of new therapy. Additionally, inhaler technique and compliance should be assessed to ensure patients are receiving the medications. An effort should be made to maintain an adequate number of patients for an extended period to allow the assessment of efficacy and adverse effects.

Reference: Lipson DA, Barnacle H, Birk R, Brealey N, Locantore N, Lomas DA, et al. FULFIL Trial: Once-Daily Triple Therapy for Patients with Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2017;196(4):438-446.

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