An overview of the

FLAME Study

DOI: 10.1056/NEJMoa1516385

Wedzicha JA et al., Indacaterol–Glycopyrronium versus Salmeterol–Fluticasone for COPD

N Engl J Med 2016; 374:2222-2234

ONCE DAILY
Pr ultibro® breezhaler®
indacaterol maleate/glycopyrronium bromide
inhalation powder

ULTIBRO BREEZHALER (indacaterol maleate and glycopyrronium bromide) is a combination of a long-acting beta$_2$-agonist (LABA) and a long-acting muscarinic antagonist (LAMA), indicated for the long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema, and for the reduction of exacerbations of COPD in patients with a history of exacerbations.[1]

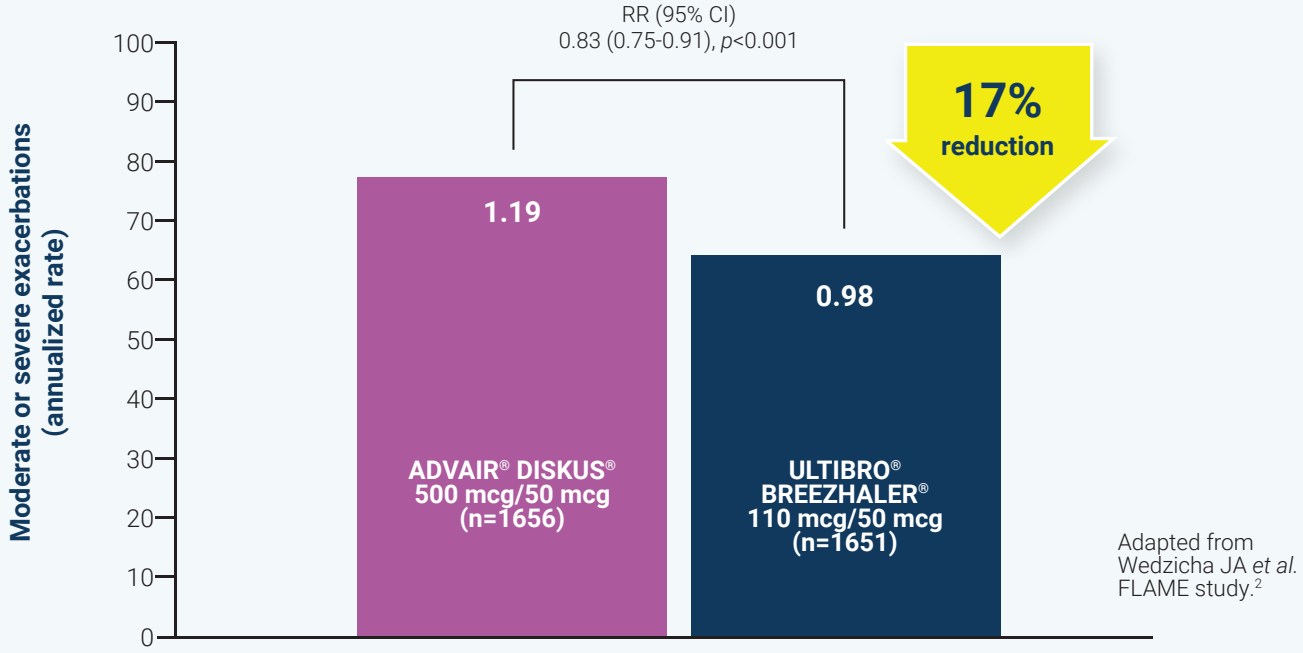
The FLAME Study: **A 52-week, randomized, double-blind, double-dummy, non-inferiority trial**

- Patients who had COPD with a history of at least one exacerbation during the previous year were randomly assigned to receive either **ULTIBRO® BREEZHALER®** once-daily (n=1680) or **ADVAIR® DISKUS®** (fluticasone/salmeterol [SFC] 500/50 mcg BID; n=1682) twice-daily.
- The primary endpoint was the annual rate of all COPD exacerbations.

* A COPD exacerbation was considered of mild severity if a worsening of symptoms that met the symptom criteria was not treated with systemic corticosteroids and/or antibiotics; moderate, if a worsening of symptoms that met the symptom criteria was treated with systemic glucocorticosteroids or antibiotics or both; and severe, if hospitalization was required or a visit to the emergency department that lasted > 24 hours in addition to treatment with systemic glucocorticoids, antibiotics or both. RR = Relative Risk; CI = Confidence Interval.

Annual rate of moderate or severe exacerbations
(secondary endpoint)

ULTIBRO® BREEZHALER® reduced the annual rate of moderate or severe exacerbation by 17% vs. ADVAIR® DISKUS® at week 52 ($p<0.001$; secondary endpoint)[1-3*]

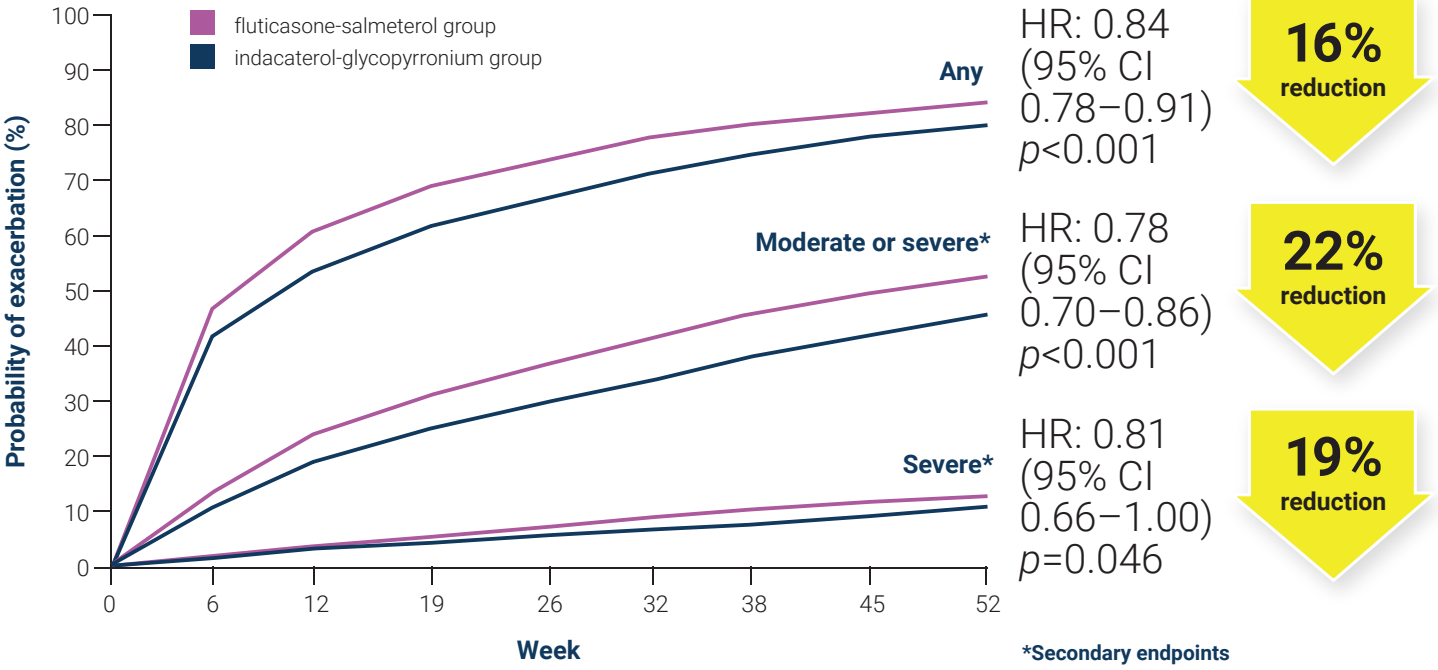


Adapted from Wedzicha JA *et al.* FLAME study.[2]

The annual rate of severe COPD exacerbation for ULTIBRO® BREEZHALER® vs. ADVAIR® DISKUS® did not achieve statistical significance (secondary endpoint).

Time to first moderate or severe exacerbation
(secondary endpoint)

ULTIBRO® BREEZHALER® significantly delayed time-to-first moderate or severe exacerbation vs. ADVAIR® DISKUS®[1,2]*



Adapted from Wedzicha JA *et al.* FLAME study.[2]

THE RESULTS OF STUDY A2318 (FLAME STUDY)

showed that ULTIBRO® BREEZHALER® met the primary study objective of non-inferiority in rate of all COPD exacerbations (mild, moderate, or severe) compared to ADVAIR® DISKUS® (fluticasone/salmeterol 500 mcg/50 mcg) (3.59 vs. 4.03; rate ratio, 0.89, 95% CI:0.83-0.96, *p*=0.003)[1,2]*

* A COPD exacerbation was considered of mild severity if a worsening of symptoms that met the symptom criteria was not treated with systemic corticosteroids and/or antibiotics; moderate, if a worsening of symptoms that met the symptom criteria was treated with systemic glucocorticosteroids or antibiotics or both; and severe, if hospitalization was required or a visit to the emergency department that lasted > 24 hours in addition to treatment with systemic glucocorticoids, antibiotics or both. RR = Relative Risk; CI = Confidence Interval.

Important Safety Information for ULTIBRO® BREEZHALER®

Indication:
ULTIBRO BREEZHALER (indacaterol maleate and glycopyrronium bromide) is a combination of a long-acting beta$_2$-agonist (LABA) and a long-acting muscarinic antagonist (LAMA), indicated for the long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema, and for the reduction of exacerbations of COPD in patients with a history of exacerbations.

Clinical use:
- Not indicated for the treatment of acute episodes of bronchospasm
- Not indicated for asthma use
- Can be used at the recommended dose in elderly patients over 65 years of age
- Should not be used in patients under 18 years of age

Contraindications:
- Hypersensitivity to indacaterol maleate or glycopyrronium bromide, or to any other component of ULTIBRO® BREEZHALER®
- Severe hypersensitivity to milk proteins
- Not indicated for treatment of asthma

Most serious warnings and precautions:
Asthma-related death: Increased risk of asthma-related death is considered a class effect with LABAs, including indacaterol maleate. ULTIBRO® BREEZHALER® is not indicated for asthma.

Other relevant warnings and precautions:
- Not indicated for treatment of acute episodes of bronchospasm: patients who have been taking inhaled, short-acting bronchodilators on a regular basis should be instructed to discontinue regular use when beginning treatment with ULTIBRO® BREEZHALER®
- Not indicated for treatment of acutely deteriorating COPD
- Not to be used more often or at higher doses than recommended or with other LABA or LAMA products
- Occurrence of dizziness or blurred vision may influence the ability to drive and use machinery
- Caution in patients with narrow-angle glaucoma: patients should be cautioned to avoid getting the drug powder into their eyes and to be alert of signs and symptoms of acute narrow angle glaucoma
- Caution in urinary retention: risk of prostatic hyperplasia and bladder neck obstruction
- Caution in patients with cardiovascular disorders, coronary insufficiency, acute myocardial infarction, cardiac arrhythmias, and hypertension: ULTIBRO® BREEZHALER® may need to be discontinued
- Caution in patients with a known history of QTc prolongation, risk factors for torsade de pointes, or taking medications known to prolong the QTc interval
- Caution in patients with convulsive disorders, thyrotoxicosis, and patients who are unusually responsive to sympathomimetic amines
- Risk of hypokalemia: monitor serum potassium in patients predisposed to low levels of serum potassium
- Risk of hyperglycemia: monitor blood glucose in diabetic patients
- Risk of immediate hypersensitivity reactions: discontinue immediately and do not rechallenge with ULTIBRO® BREEZHALER®
- Risk of angioedema
- In severe renal impairment (estimated GFR <30 mL/min/1.73m^2) including those with end-stage renal disease requiring dialysis, use only if the expected benefit outweighs the potential risk. Patients should be monitored closely for adverse drug reactions.
- Risk of paradoxical bronchospasm: discontinue immediately
- May inhibit labour: use only if the potential benefit justifies the potential risk
- Pregnancy/nursing and delivery: use only if potential benefit justifies the potential risk
- Caution in patients with severe hepatic impairment
- ULTIBRO® BREEZHALER® capsules must not be swallowed

For more information:
Please consult the Product Monograph at https://pdf.hres.ca/dpd_pm/00054946.PDF for important information relating to adverse events, drug interactions, and dosing information which have not been discussed in this piece. The Product Monograph is also available by calling the Medical Information Department at 1-800-363-8883.

References:

1. ULTIBRO® BREEZHALER® Product Monograph. Novartis Pharmaceuticals Canada Inc., January 27, 2020.
2. Wedzicha JA et al. Indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD. NEJM. Online May 15, 2016.DOI:10.1056/NEJMoa1516385.
3. Wedzicha JA et al. Indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD. Supplementary Appendix. NEJM.Online May 15, 2016. DOI:10.1056/NEJMoa1516385.

COVIS PHARMA

REVIEWED BY PAAB

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