

# KRONOS PIVOTAL TRIAL



BREZTRI AEROSPHERE is indicated for the long-term maintenance treatment to reduce exacerbations of COPD and treat airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema, who are not adequately treated by a combination of an ICS/LABA or a combination of LAMA/LABA.<sup>1</sup>

## Study design<sup>1</sup>

- 24 weeks
- Randomized, double-blind, multicentre, chronic-dosing, parallel-group design

## Patient population<sup>1</sup>

### Key inclusion criteria

- Patients with moderate to very severe COPD
- Prior history of exacerbations was not required
- Baseline FEV<sub>1</sub> ≥25% to <80% of predicted normal

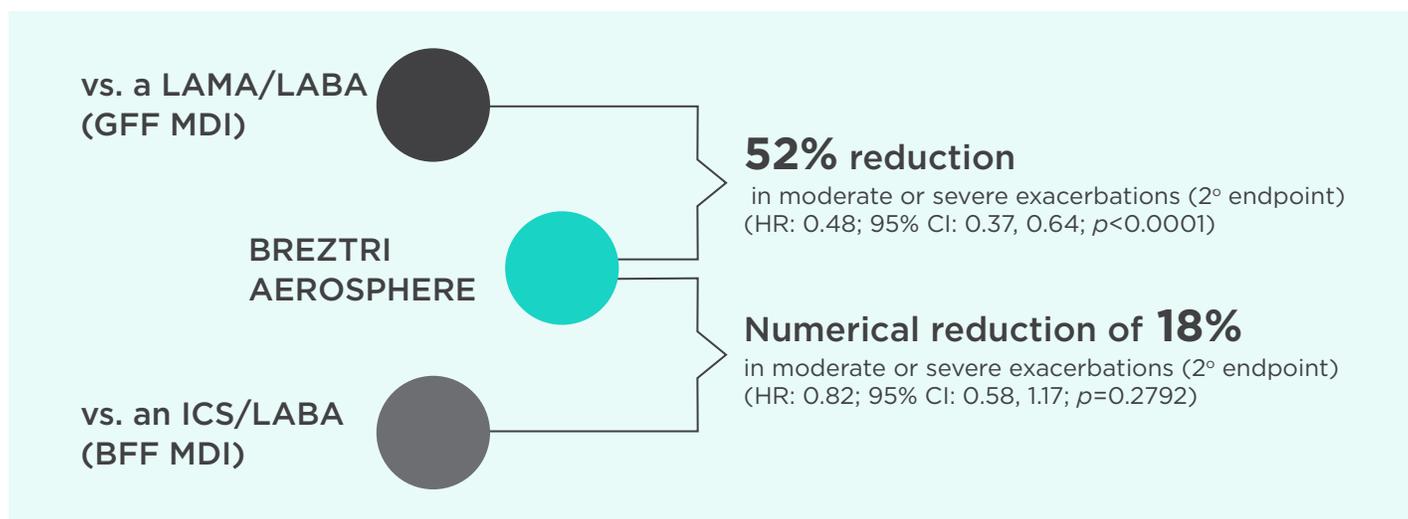
	<b>BREZTRI AEROSPHERE</b> budesonide 320 mcg / glycopyrronium 14.4 mcg / formoterol fumarate dihydrate 10 mcg, BID (ICS/LAMA/LABA)	<b>Glycopyrronium</b> 14.4 mcg / formoterol fumarate dihydrate 10 mcg, BID (GFF MDI; LAMA/LABA)	<b>Budesonide</b> 320 mcg / formoterol fumarate dihydrate 10 mcg, BID (BFF MDI; ICS/ LABA)	<b>Open-label budesonide</b> 400 mcg / formoterol fumarate dihydrate 12 mcg, BID (open-label DPI ICS/LABA)
<b>1,896 patients randomized</b>	n=639	n=625	n=314	n=318

BID: twice daily; BFF: budesonide/formoterol fumarate dihydrate; COPD: chronic obstructive pulmonary disease; DPI: dry powder for inhalation; FEV<sub>1</sub>: forced expiratory volume in 1 second; GFF: glycopyrronium/formoterol fumarate dihydrate; ICS: inhaled corticosteroid; LABA: long-acting beta<sub>2</sub>-agonist; LAMA: long-acting muscarinic antagonist; MDI: metered-dose inhaler.

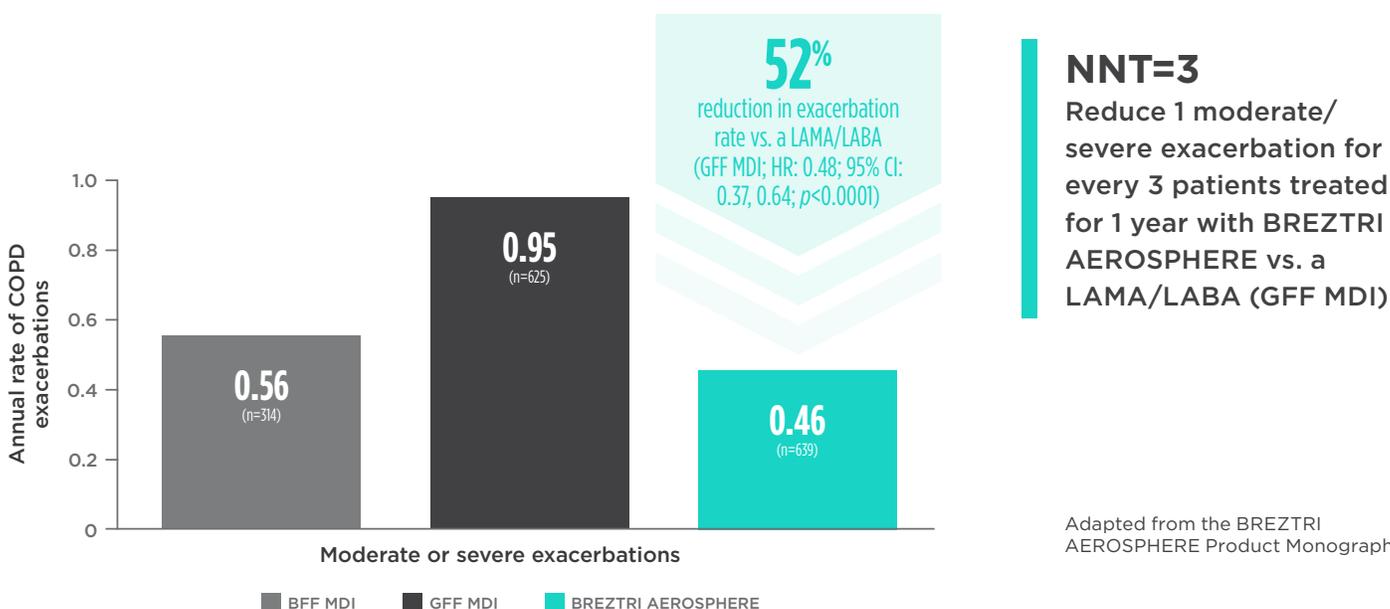
# POWERFUL REDUCTION OBSERVED IN MODERATE OR SEVERE EXACERBATION RATE VS. A LAMA/LABA (GFF MDI) (2° ENDPOINT)<sup>1,2</sup>

## Primary endpoints:

- FEV<sub>1</sub> area under the curve from 0-4 hours (FEV<sub>1</sub> AUC<sub>0-4</sub>) vs. BFF MDI
- Change from baseline in morning pre-dose trough FEV<sub>1</sub> over 24 weeks vs. GFF MDI



## Annual rate of moderate or severe COPD exacerbations (2° endpoint)<sup>1,2</sup>



Numerical reduction of 18% in exacerbation rate vs. an ICS/LABA (BFF MDI; HR: 0.82; 95% CI: 0.58, 1.17;  $p = 0.2792$ )

# NUMERICAL IMPROVEMENTS IN BREATHLESSNESS (TDI FOCAL SCORE) AND PATIENT QUALITY OF LIFE (SGRQ) WERE OBSERVED OVER 24 WEEKS VS. A LAMA/LABA (GFF MDI) AND VS. AN ICS/LABA (BFF MDI) (2° ENDPOINT)<sup>1</sup>



## Breathlessness

(change from baseline in TDI focal score over 24 weeks)<sup>2</sup>

**1.25**

BREZTRI  
AEROSPHERE

**1.07**

(95% CI: -0.07,  
0.43;  $p=0.1621$ )  
LAMA/LABA

**1.01**

(95% CI: -0.07,  
0.54;  $p=0.1283$ )  
ICS/LABA

A  $\geq 1$ -unit change in the TDI focal score is clinically important.<sup>3</sup>



## Quality of life

(change from baseline in SGRQ score over 24 weeks)<sup>2</sup>

**-7.5**

BREZTRI  
AEROSPHERE

**-6.3**

(95% CI: -2.30,  
-0.15;  $p=0.0259$ )  
LAMA/LABA

**-7.1**

(95% CI: -1.78,  
0.87;  $p=0.5036$ )  
ICS/LABA

A decrease in the SGRQ score represents improvement.

A  $\geq 4$ -unit change in the SGRQ score is clinically important.<sup>4</sup>



## POWERFUL and SUSTAINED IMPROVEMENTS observed in trough FEV<sub>1</sub> (1° endpoint)<sup>1</sup>

BREZTRI AEROSPHERE provided statistically significant improvements in trough FEV<sub>1</sub> over 24 weeks vs. a LAMA/LABA (GFF MDI) and an ICS/LABA (BFF MDI)

### Lung function analyses

Trough FEV<sub>1</sub> (mL) over 24 weeks, LS mean change from baseline (SE)

**147 mL**  
**(6.5)**

BREZTRI  
AEROSPHERE  
(n=639)\*

**125 mL**  
**(6.6)**

GFF MDI  
(n=625)\*

**73 mL**  
**(9.2)**

BFF MDI  
(n=314)\*

22 mL improvement vs. a LAMA/LABA (GFF MDI) (95% CI: 4, 39;  $p=0.0139$ )<sup>†</sup>

74 mL improvement vs. an ICS/LABA (BFF MDI) (95% CI: 52, 95;  $p<0.0001$ )<sup>†</sup>

\* Administered orally as two inhalations of BREZTRI AEROSPHERE 160/7.2/5 mcg, GFF MDI 7.2/5 mcg, BFF MDI 160/5 mcg, BID.

<sup>†</sup> Statistically significant.

BFF: budesonide/formoterol fumarate dihydrate; FEV<sub>1</sub>: forced expiratory volume in one second; GFF: glycopyrronium/formoterol fumarate dihydrate; ICS: inhaled corticosteroid; LABA: long-acting beta<sub>2</sub>-agonist; LAMA: long-acting muscarinic antagonist; LS: least squares; MDI: metered-dose inhaler; SE: standard error; SGRQ: St. George's respiratory questionnaire; TDI: transition dyspnea index.

# CHOOSE THE POWERFUL DEMONSTRATED EFFICACY OF BREZTRI AEROSPHERE IN COPD<sup>1</sup>

## **Clinical use:**

BREZTRI AEROSPHERE is not indicated for:

- Treatment of acute episodes of bronchospasm or asthma.
- Use in pediatric patients <18 years of age.

## **Relevant warnings & precautions:**

- Risk of serious asthma-related events, including hospitalization, intubations, and death
- Should not be used in patients with deteriorating COPD
- Excessive use with other LAMA and LABA products
- Anticholinergic activity: Use with caution in patients with symptomatic prostatic hyperplasia, urinary retention, or narrow-angle glaucoma
- Cardiovascular effects, including arrhythmias and changes in pulse and blood pressure, QTc prolongation
- Driving and operating machinery
- Candidiasis
- Risk of systemic effects, including Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, hypokalemia and hyperglycemia, cataract, intraocular pressure, and glaucoma
- Hypercorticism, adrenal suppression
- Adrenal insufficiency in patients transferred from systemic steroid
- Patients with symptomatic prostatic hyperplasia, glaucoma, convulsive disorders, thyrotoxicosis, sensitivity to sympathomimetic amines, severe hepatic impairment/hepatic disease, or urinary retention



- In rare cases, eosinophilic conditions
- Susceptibility or decreased resistance to infections
- Monitoring of hypokalemia, hyperglycemia, bone and ocular effects, and corticosteroid effects in patients with hepatic impairment
- Paradoxical bronchospasm
- Increased risk of pneumonia
- Pregnant and nursing women
- Geriatrics (≥65 years of age)

## **For more information:**

Consult the Product Monograph at [breztri-en.azpm.ca](http://breztri-en.azpm.ca) for important information regarding adverse reactions, drug interactions, and dosing. The Product Monograph is also available by calling AstraZeneca Canada at **1-800-668-6000**.

COPD: chronic obstructive pulmonary disease; LABA: long-acting beta<sub>2</sub>-agonist; LAMA: long-acting muscarinic antagonist.

## **References:**

**1.** BREZTRI AEROSPHERE Product Monograph. AstraZeneca Canada Inc. **2.** Ferguson GT, et al. Triple therapy with budesonide / glycopyrrolate / formoterol fumarate with co-suspension delivery technology versus dual therapies in chronic obstructive pulmonary disease (KRONOS): a double-blind, parallel-group, multicentre, phase 3 randomised controlled trial. *Lancet Respir Med.* 2018(6):747-758. **3.** Witek TJ, et al. Minimal important difference of the transition dyspnoea index in a multinational clinical trial. *Eur Respir J.* 2003(21):267-272. **4.** Chronic Obstructive Pulmonary Disease: Use of the St. George's Respiratory Questionnaire as a PRO Assessment Tool. Food and Drug Administration. March 2018. Available at: [www.fda.gov/files/drugs/published/Chronic-Obstructive-Pulmonary-Disease--Use-of-the-St.-George%E2%80%99s-Respiratory-Questionnaire-as-a-PRO-Assessment-Tool-Guidance-for-Industry.pdf](http://www.fda.gov/files/drugs/published/Chronic-Obstructive-Pulmonary-Disease--Use-of-the-St.-George%E2%80%99s-Respiratory-Questionnaire-as-a-PRO-Assessment-Tool-Guidance-for-Industry.pdf). Retrieved November 30, 2023.

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