A PARADIGM SHIFT IN COPD MANAGEMENT

Role of TRELEGY Ellipta (ICS/LAMA/LABA) single inhaler triple therapy

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AUS/TLY/0076 approved June 2018

GlaxoSmithKline Australia PTY LTD, MEL VIC. ABN 47 100 162 481

Exacerbations are a prominent feature of COPD

More frequent and severe as lung function decreases[1]

Most common reason for hospitalisation[2]

Associated with increased risk of mortality[3]

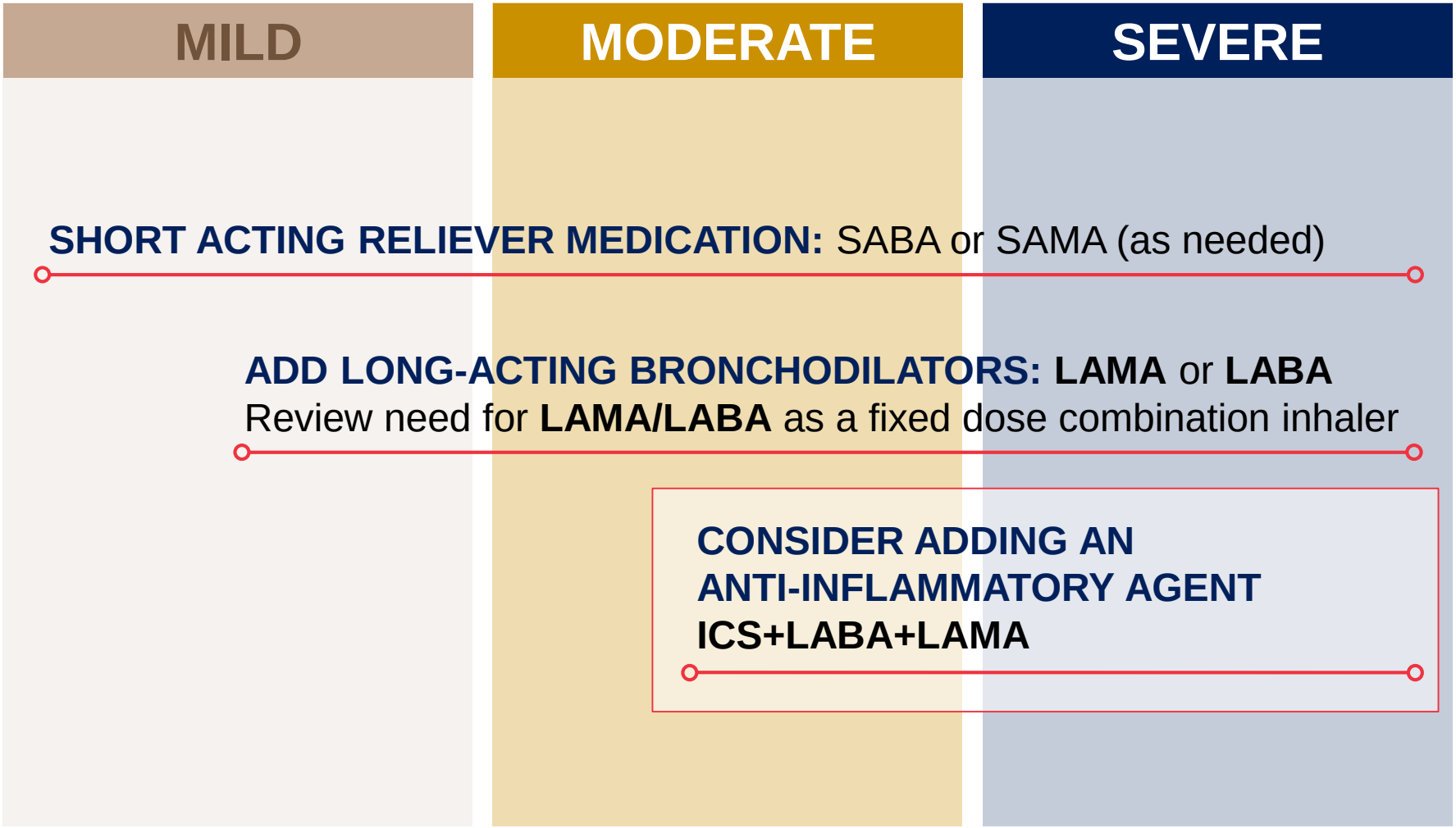
Major contributor to the economic burden[4,5]

The strongest predictor of a patient's future exacerbation frequency is the number of exacerbations they have had in the previous year[1]

Preventing and treating exacerbations continues to be a management goal in COPD to help reduce risk[6]

[1.] Hurst JR et al. N Engl J Med. 2010; 363:1128-1138; [2.] Mapel D et al. Pharmacoeconomics 2012; 30: 869-885; [3.] Suissa S et al. Thorax 2012; 67:957-963; [4.] Pasquale M et al. Int J Chron Obstruct Pulmon Dis. 2012; 7:757-764; [5.] Yu A et al. J Med Econ. 2011; 14:315-323; [6.] Global Strategy for the Diagnosis, Management and Prevention of COPD (GOLD) report 2018. Available at http://goldcopd.org/ Accessed Feburary 2018.

COPDX: Consider adding an anti-inflammatory agent for moderate to severe COPD

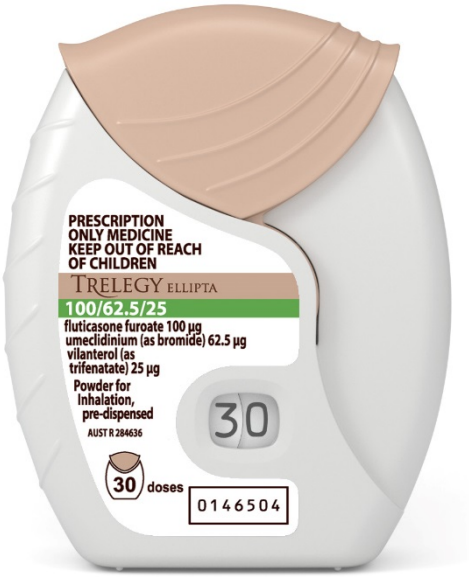


COPD: chronic obstructive pulmonary disease, SABA: short-acting beta2-agonist, SAMA: short-acting muscarinic antagonist, LAMA: long-acting muscarinic antagonist, LABA: long-acting beta2-agonist, ICS: inhaled corticosteroids.

Adapted from: https://lungfoundation.com.au/wp-content/uploads/2017/10/LFA-Stepwise-Management-of-COPD_0817_WEB.pdf

Introducing Trelegy Ellipta (ICS/LAMA/LABA)

The only Triple Therapy in a single inhaler for the treatment of COPD*[1]



Trelegy combines the therapeutic effects of **an anti-inflammatory** (fluticasone furoate - ICS) and **two long-acting bronchodilators** (umeclidinium-LAMA, vilanterol-LABA) in a single inhaler for the treatment of moderate to severe COPD*[1]

*Trelegy Ellipta is indicated for the maintenance treatment of adults with moderate to severe COPD who require treatment with LAMA+LABA+ICS.Trelegy ELLIPTA is not indicated for the initiation of therapy in COPD.

[1]Trelegy Ellipta Product Information.

IMPACT: A landmark study[1,2]

IMPACT TRIAL

Over 10,000 patients who have a history of at **least 1 exacerbation** in the past 12 months*

First to compare TRELEGY (ICS/ LAMA/ LABA) **in a single inhaler** with ANORO (LAMA/LABA) and BREO (ICS/LABA)

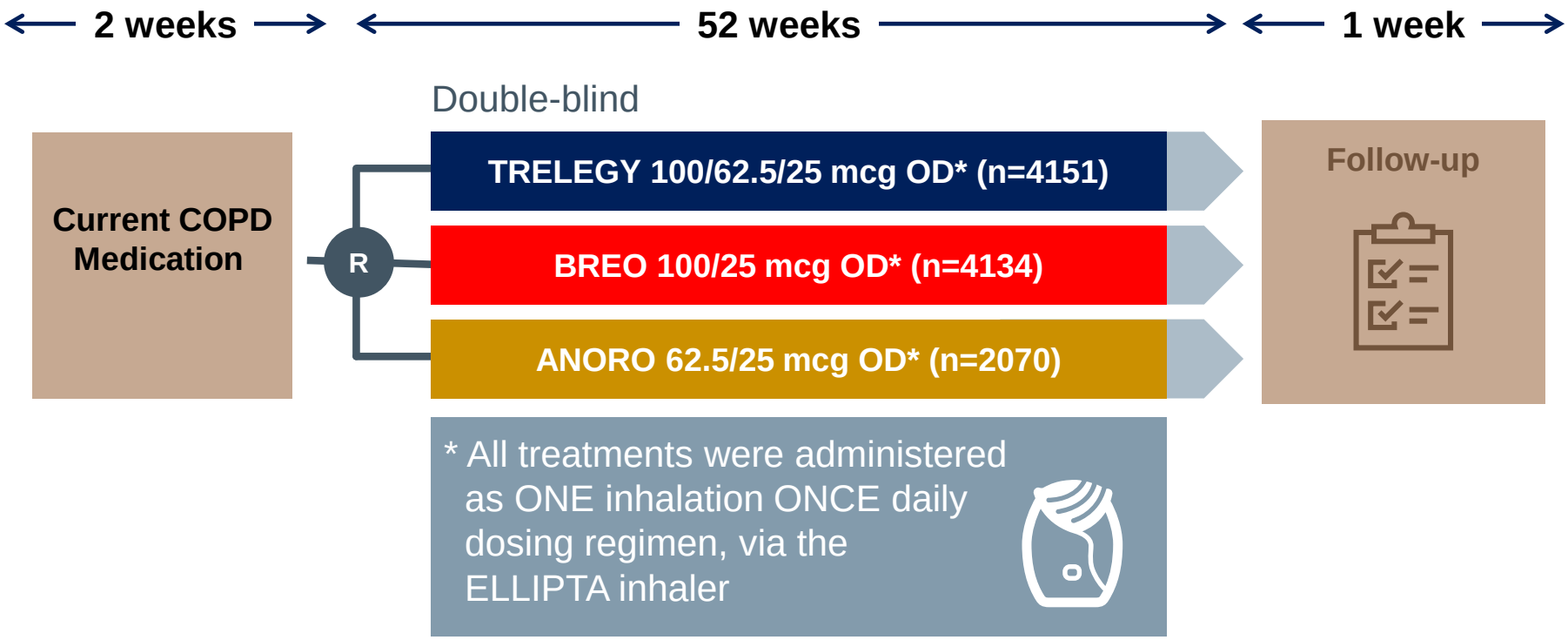
- Provides robust data applicable to symptomatic patients with COPD and a history of exacerbations
- Helps to ensure that the right patient receives the right treatment*

*IMPACT inclusion criteria: FEV_1 <50% +≥ 1 mod/sev exacerbation in the past year OR FEV_1 ≥50% and <80% + ≥ 2 moderate or ≥ 1 severe exacerbation in the past year.

1. Pascoe SJ et al. Eur Respir J 2016; 48: 320-330; 2. Lipson DA et al. New Engl J Med 2018

Study Design

IMPACT TRIAL



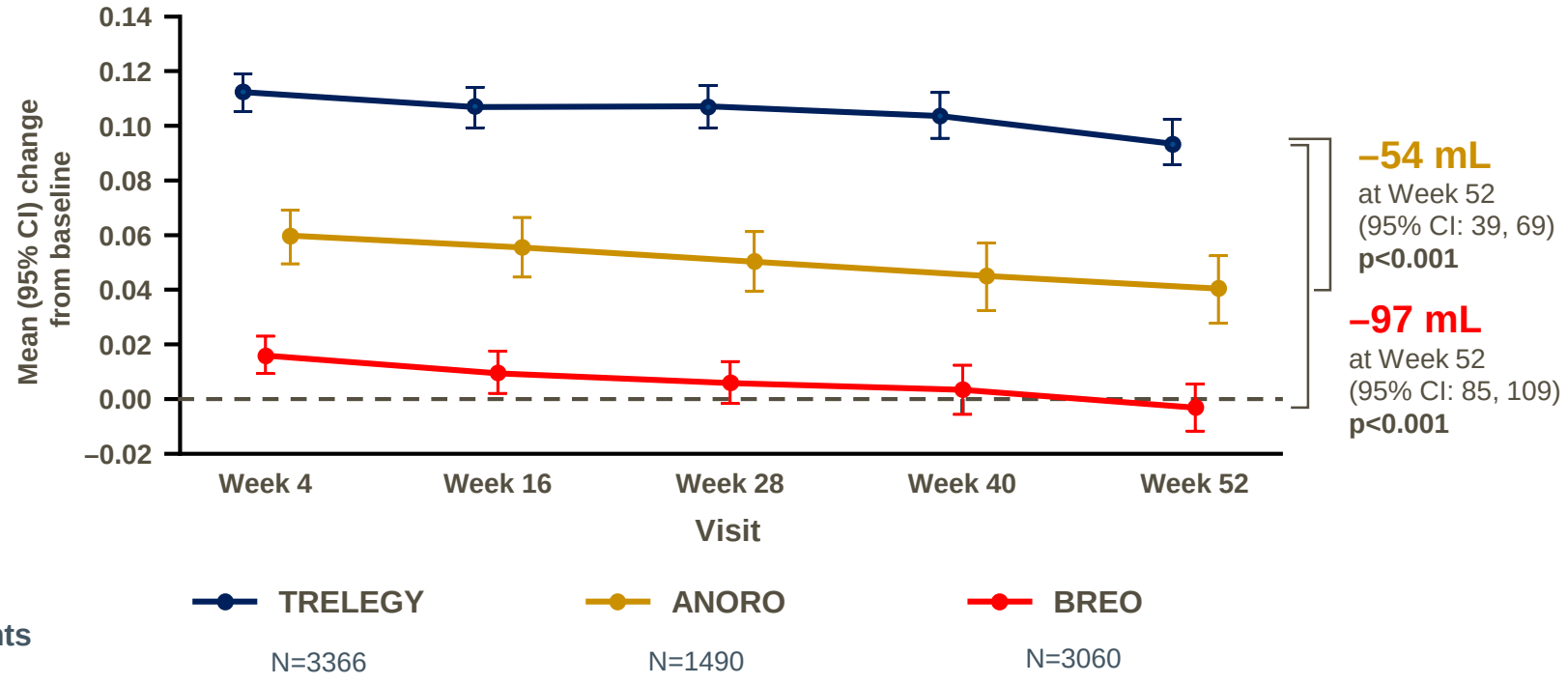
TRELEGY: fluticasone furoate/umeclidinium /vilanterol 100/62.5/ 25mcg once daily (ICS/LAMA/LABA)

BREO: fluticasone furoate/vilanterol 100/ 25mcg once daily (ICS/LABA)

ANORO: umeclidinium /vilanterol 100/ 25mcg once daily (LAMA/LABA)

Lipson DA et al. New Engl J Med 2018

Secondary endpoint: Change from baseline trough FEV_1 at week 52[1,2]



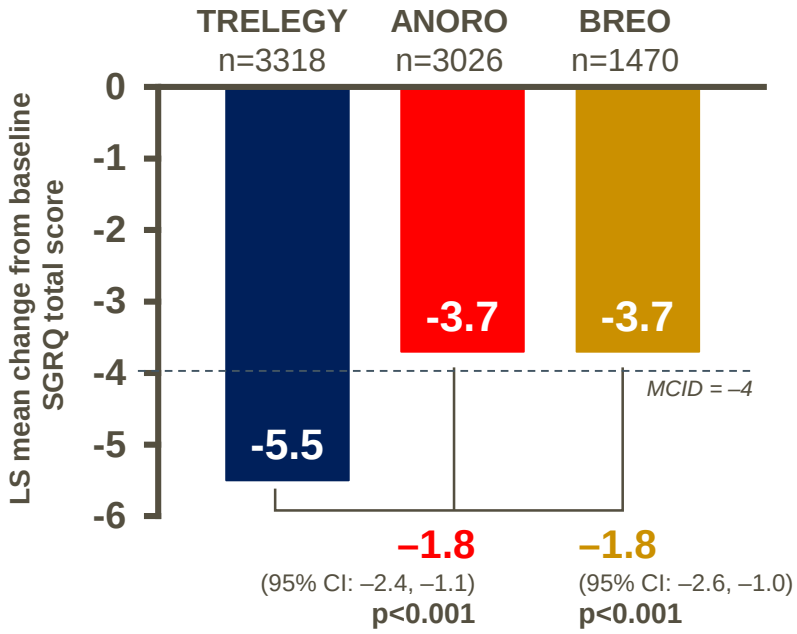
No. of patients evaluated:

TRELEGY	ANORO	BREO
N=3366	N=1490	N=3060

Lipson DA, et al. *N Engl J Med*. 2018; 2. GlaxoSmithKline. Date on file: RF/TLY/0096/17(1).

HRQoL (SGRQ)[1]

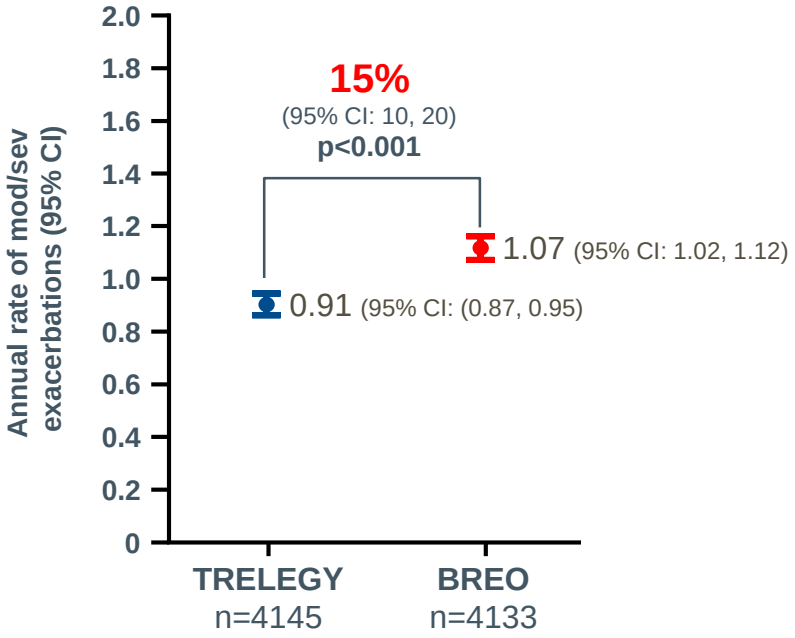
Improvement in HRQoL (SGRQ) and greater likelihood of response with FF/UMEC/VI vs FF/VI and vs UMEC/VI*

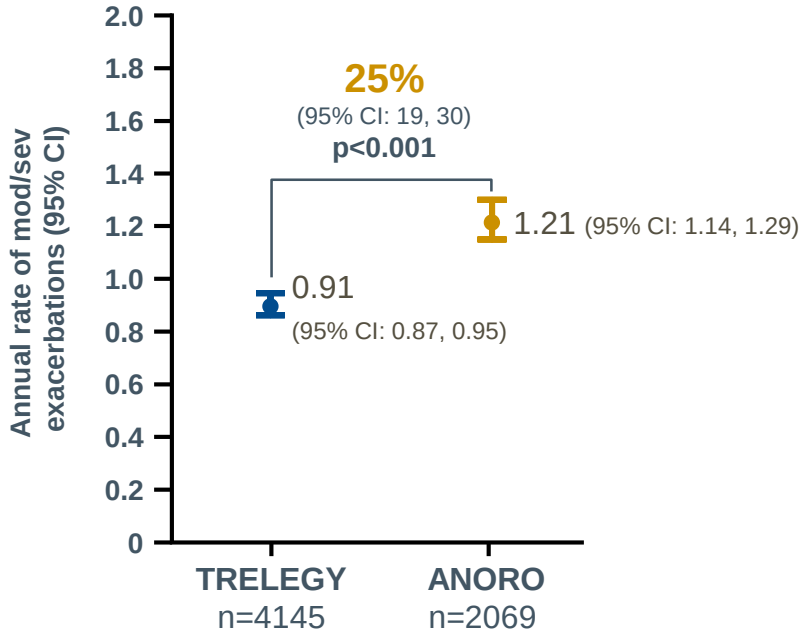


1. Lipson DA et al. NEJM 2018;378:1671-1680; 2. DoF RF/TLY/0096/17.

* SGRQ responder defined as a ≥4 unit decrease from baseline in SGRQ total score
Note: The n reflects the number of patients included in each analysis from the ITT population. Patients were excluded if they had predefined data missing; this varied according to the analysis. The ITT population comprised: 4151 patients treated with FF/UMEC/VI, 4134 patients treated with FF/VI and 2070 patients treated with UMEC/VI.
HRQoL, health-related quality of life; OR, odds ratio; SGRQ, St George's Respiratory Questionnaire.

Primary efficacy endpoint: Moderate/severe exacerbations



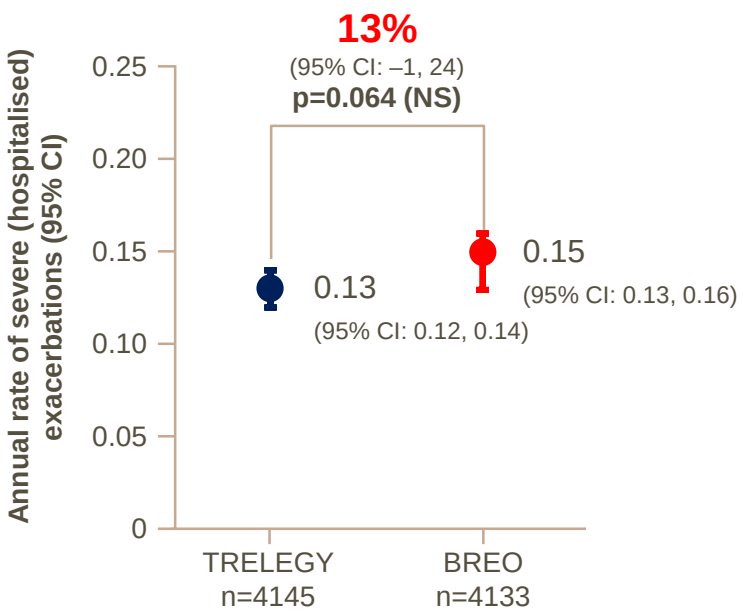


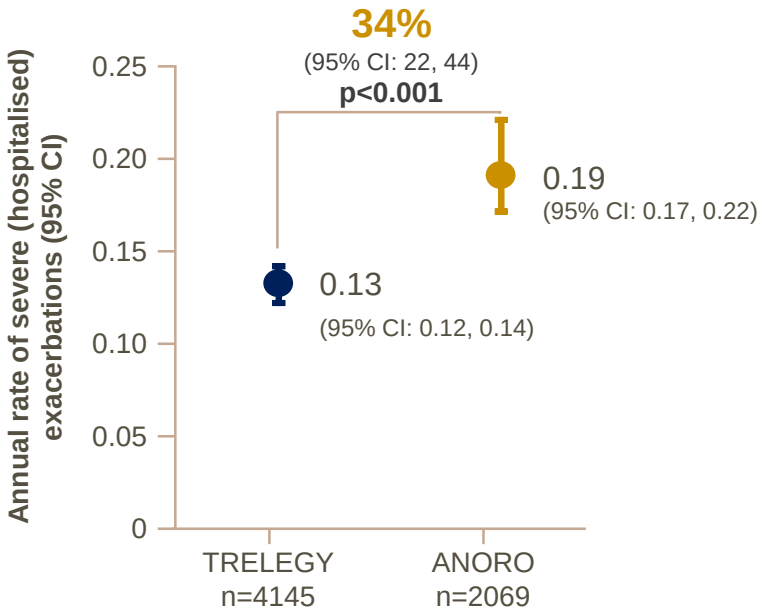
Note: The n reflects the number of patients included in each analysis from the ITT population. Patients were excluded if they had predefined data missing; this varied according to the analysis. The ITT population comprised: 4151 patients treated with TRELEGY, 4134 patients treated with BREO and 2070 patients treated with ANORO.Trelegy (FF/UMEC/VI) FF, fluticasone furoate; UMEC, umeclidinium; VI, vilanterol. Anoro (UMEC/VI) , Breo (FF/VI)

Lipson DA, et al. *N Engl J Med*. 2018.

Exacerbations leading to hospitalisation (severe)

Significant reduction in the annual rate of severe exacerbations with FF/UMEC/VI vs FF/VI, and vs UMEC/VI



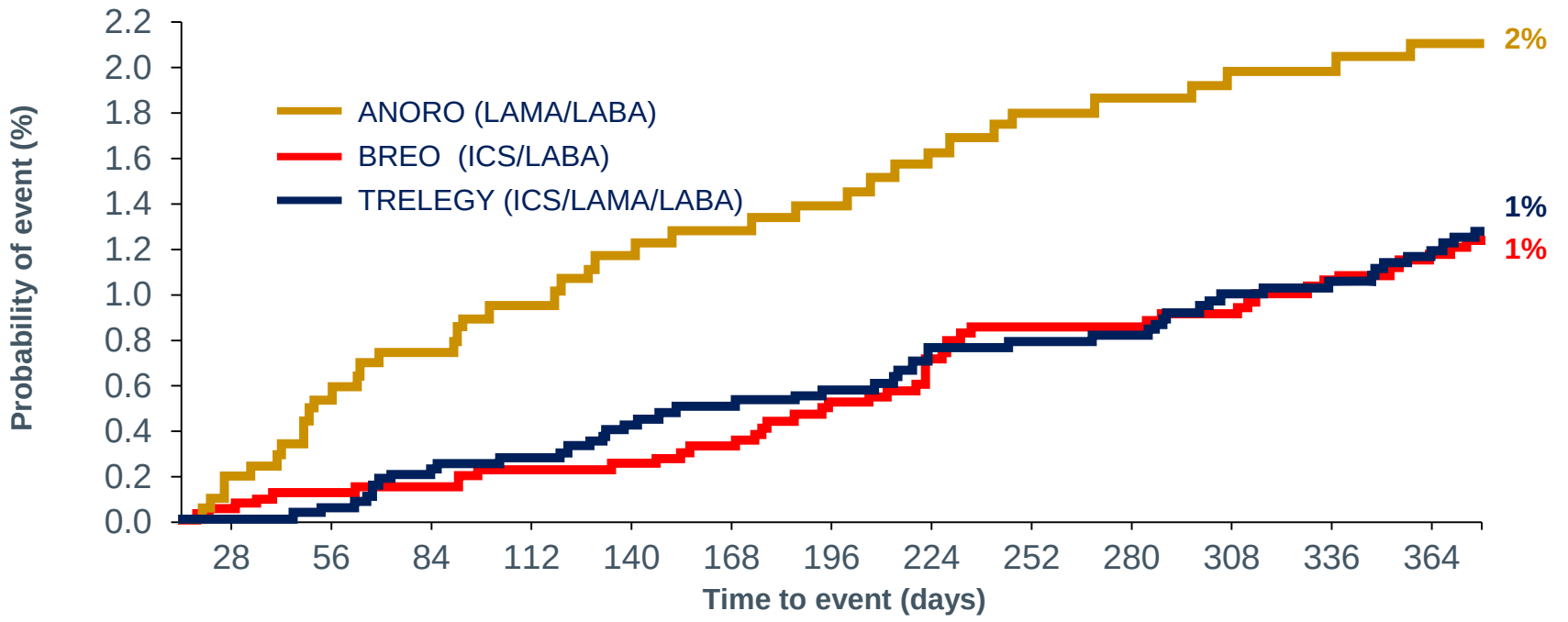


Note: The n reflects the number of patients included in each analysis from the ITT population. Patients were excluded if they had predefined data missing; this varied according to the analysis. The ITT population comprised: 4151 patients treated with FF/UMEC/VI, 4134 patients treated with FF/VI and 2070 patients treated with UMEC/VI.

FF, fluticasone furoate; UMEC, umeclidinium; VI, vilanterol; FEV_1, forced expiratory volume in 1 second; CI, confidence interval; ITT, intention-to-treat; NS, Not Statistically Significant.

Lipson DA et al. NEJM 2018;378:1671-1680

Protocol-defined other endpoint: All-cause mortality (on-treatment data)



Relative risk reduction:		
TRELEGY vs ANORO:	**42%** HR 0.58 (95% CI: 0.38, 0.88) **p=0.011**	
BREO vs ANORO:	**39%** HR 0.61 (95% CI: 0.40, 0.63) **p=0.022**	

The IMPACT study was not designed to study all-cause mortality as a primary outcome, however, all-cause mortality was a pre-specified endpoint (ITT population)

On-treatment refers to data derived from patients who completed the study

When off-treatment data are included in the analysis, status is available for 9781 (94.4%) of the total study population at week 52. Data for the remaining 5.6% of patients are currently being sought

11. Lipson DA, et al. N Engl J Med. 2018; 2. Lipson DA, et al. ATS abstract

Safety analysis

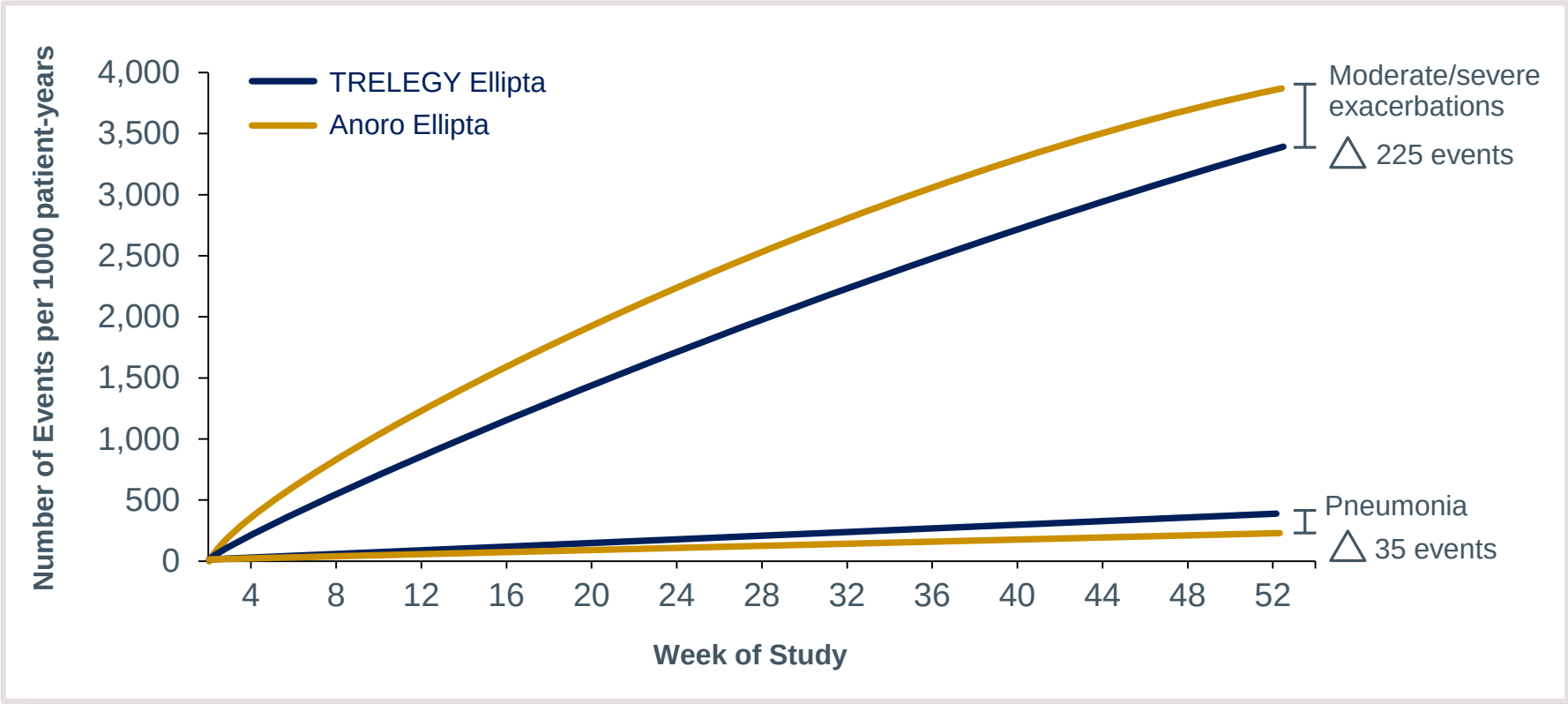
IMPACT TRIAL

	TRELEGY N=4151 (%)	BREO N=4134 (%)	ANORO N=2070 (%)
Adverse event of special interest			
Pneumonia	8%	7%	5%
On-treatment serious adverse event			
Worsening of COPD	11%	11%	13%
Pneumonia resulting in hospitalisation	4%	4%	3%

Lipson DA et al. New Engl J Med 2018 and Supplement

Benefits vs Risks with TRELEGY Ellipta in COPD

Number of on-treatment events in the non fatal pneumonia adverse events of special interest group and number of on-treatment moderate/severe exacerbations over 52 weeks (ITT population)[15]



The rate of pneumonia was 95.8 and 61.2 events per 1000 patients-years with TRELEGY Ellipta vs Anoro Ellipta respectively; where as the rate of moderate or severe COPD exacerbations was 922.8 and 1147.6 per 100 patient-years, respectively.
Note: the number of events in the Anoro treatment group has been doubled to account for the 2:2:1 randomization scheme for TRELEGY, Breo, Anoro.
DOF: Number of On-Treatment Events in the Pneumonia Adverse Events of Special Interest Group and Number of On-Treatment Moderate/Severe Exacerbations (2018N368847_00)

Evidence based treatment decisions in COPD

Ensuring the right patient receives the right treatment

Symptomatic without a history of exacerbations

ANORO[1,2] (LAMA/LABA)
dual bronchodilation

Symptomatic with history of ≥ 2 exacerbations in previous 12 months

TRELEGY (ICS/LAMA/LABA)
dual bronchodilation + anti-inflammatory[1,3-7]

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD) report 2017; Available at http://goldcopd.org Accessed February 2018; 2. Oba Y et al. *Throax* 2016; 71:15-25; 3. Liu Y et al. *Eur J Intern Med*. 2014; 25:491-495; 4. Rodrigo GJ et al. *Pulm Pharmacol Ther*. 2012; 25:40-47; 5. Lipson DA et al. *Am J Resp Crit Care* 2017; 6. Singh D et al. *Lancet* 2016; 388:963-973; 7. Vestbo J et al. *Lancet* 2017; 389:1919-1929.

PBS Clinical Criteria for Trelegy:

- Patient must have a forced expiratory volume in 1 second (FEV_1) less than 50% of predicted normal prior to therapy

AND

- Patient must have a history of repeated exacerbations with significant symptoms despite regular bronchodilator therapy with a long acting muscarinic antagonist (LAMA) and a long acting beta-2 agonist (LABA) or an inhaled corticosteroid (ICS) and a LABA.

OR

- Patient must have been stabilised on a combination of a LAMA, a LABA and an ICS for this condition

Anoro Ellipta PBS Information: Authority required (STREAMLINED). Refer to PBS Schedule for full authority information.

STREAMLINED AUTHORITY CODE 5763
Please review Product Information before prescribing.
For Full Product Information or visit au.gsk.com

Anoro® Ellipta® (umeclidinium bromide/vilanterol trifenatate) 62.5 mcg umeclidinium/25 mcg vilanterol inhalation powder. Minimum Product Information. INDICATIONS: As a long-term once daily maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD). CONTRAINDICATIONS: Hypersensitivity to the active ingredient or any excipients, patients with severe milk-protein allergy. PRECAUTIONS: Should not be used in asthma. Can cause paradoxical bronchospasm - if this occurs, treatment should be discontinued and alternative therapy instituted if necessary. Should not be used for the relief of acute symptoms of bronchospasm. Use with caution in patients with severe cardiovascular disorders, particularly cardiac arrhythmias. See full PI. Use with caution in patients with narrow-angle glaucoma or urinary retention. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. Pregnancy – Cat B3. Lactation – unknown whether umeclidinium or vilanterol are excreted in human milk. Paediatric – should not be used in children. INTERACTIONS: Beta-blockers, strong CYP3A4 inhibitors, P-glycoprotein inhibitors. ADVERSE EFFECTS: Cough, pharyngitis, constipation, dry mouth, UTI, URTI. Others see full PI. DOSAGE: One oral inhalation, via Anoro Ellipta inhaler, once a day. Do not use Anoro Ellipta more than once every 24 hours. Should be taken at the same time every day. No dosage adjustment is required in elderly, impaired renal function, mild or moderate hepatic impairment. Not recommended in children. Min PI v2.0.

AUS//TLY/0076/18 date of approval: June 2018

BREO ELLIPTA PBS Information: Restricted Benefit: COPD

Symptomatic treatment of COPD where the FEV_1 is <50% predicted normal and there is a history of repeated exacerbations with significant symptoms despite regular $ß_2$-agonist bronchodilator therapy.

Note: Patient must not be on a concomitant single agent long acting $ß_2$-agonist.

Product is not indicated for initiation of bronchodilator therapy in COPD.

Please review full product information before prescribing. The product information can be accessed at au.Gsk.Com

Breo Ellipta (fluticasone furoate/vilanterol trifenatate) Minimum Product Information.

INDICATIONS: Asthma: Regular treatment of moderate to severe asthma in patients requiring medium to high dose inhaled corticosteroid (ICS) combined with long acting $ß_2$-agonist (LABAs). Chronic Obstructive Pulmonary Disease (COPD): symptomatic treatment of patients with COPD with a FEV_1 <70% predicted normal (post-bronchodilator) in patients with an exacerbation history despite regular bronchodilator therapy. Breo Ellipta is not indicated for the initiation of bronchodilator therapy in COPD. CONTRAINDICATIONS: Severe milk-protein allergy or hypersensitivity to any of the actives and any excipients. PRECAUTIONS: Long acting $ß_2$-agonists (LABAs) as a class can be associated with an increased risk of asthma death. Patients using Breo Ellipta should not use another medicine containing a LABA (e.g., salmeterol, eformoterol, indacaterol) for any reason. Cannot be used to relieve acute symptoms of asthma or COPD (short acting $ß_2$-agonists should be used for acute attacks). As with other inhalation therapy, the possible occurrence of paradoxical bronchospasm immediately after dosing should be treated with short acting $ß_2$-agonists. As with sympathomimetic drugs, Breo Ellipta should be used with caution in patients with cardiovascular disease. As with all sympathomimetic amines, Breo Ellipta should be used with caution in patients with convulsive disorders or hyperthyroidism. To minimise adverse reactions, ICS should be used at the lowest dose that maintains symptom control. ICS should be used with caution in patients with active or quiescent tuberculosis infections of the respiratory tract; systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex. An increase in pneumonia has been observed in patients with COPD. Beta-adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce adverse cardiovascular effects. Beta-agonist agents may produce transient hyperglycaemia in some patients. Other: fertility, pregnancy (category B3), lactation. INTERACTIONS: Beta-blockers, P-glycoprotein inhibitors, CYP3A4 inhibitors, sympathomimetic medicinal products, monoamine oxidase inhibitors, tricyclic antidepressants. ADVERSE REACTIONS: Very common: headache, nasopharyngitis. Common: URTI, bronchitis, influenza, oral candidiasis of mouth and throat, oropharyngeal pain, sinusitis, pharyngitis, rhinitis, cough, dysphonia, abdominal pain, arthralgia, back pain, pyrexia, muscle spasms. Fractures and pneumonia in patients with COPD. DOSAGE: Prescribers should be aware that 100 mcg of fluticasone furoate is a medium dose of ICS and 200 mcg of fluticasone furoate is a high dose of ICS. Asthma: (Adults and Adolescents ≥ 12 years): 1 inhalation once daily (100/25mcg or 200/25mcg). In patients whose asthma is well controlled and stable the Breo Ellipta dose may carefully be down-titrated to the lowest strength of Breo Ellipta. The next step should consider the cessation of Breo Ellipta and transfer to an appropriate inhaled corticosteroid containing regimen. COPD: 1 inhalation once daily (100/25mcg only). Breo Ellipta 200/25 mcg is not indicated for patients with COPD. Specific patient population: Elderly patients: due to limited data in patients with asthma aged 75 years and older, Breo Ellipta 200/25mcg is not recommended. Moderate to Severe Hepatic Impairment: once daily maximum dose of 100/25mcg. Min PI v3.0.

AUS//TLY/0076/18 date of approval: June 2018

PBS Information: Authority Required(Streamlined 7651) Chronic Obstructive Pulmonary Disease. Criteria Apply. Refer to PBS schedule for full information.

Please review full product information before prescribing.
The product information can be accessed at au.gsk.com

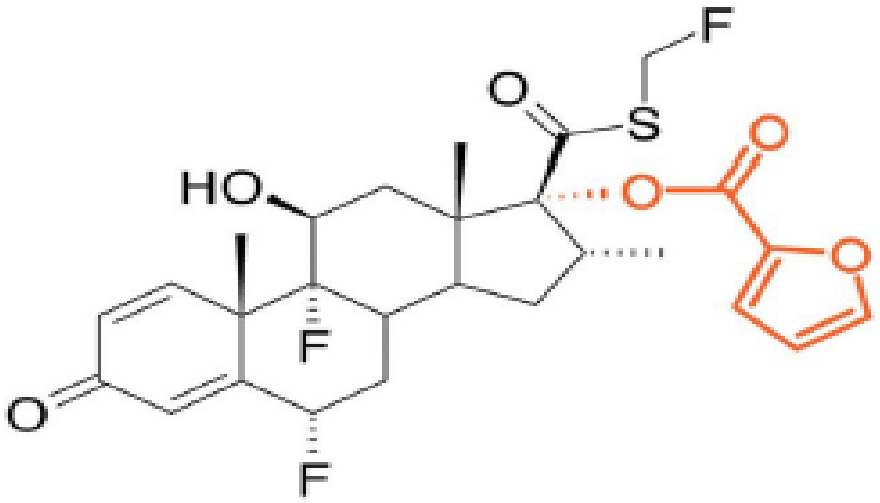
Minimum Product Information. Trelegy Ellipta (Fluticasone furoate/Umeclidinium (as bromide)/Vilanterol (as trifenatate) 100/62.5/25mcg

Indications: Maintenance treatment of adults with moderate to severe COPD who require LAMA+LABA+ICS. Not indicated for initiation in COPD. Contraindications: Severe milk-protein allergy or hypersensitivity to any of the ingredients. Precautions: Treatment in accordance with clinical guidelines. Not indicated for asthma. Treatment re-evaluated if pneumonia occurs. Paradoxical bronchospasm, unstable cardiac disease, hepatic impairment, active or quiescent TB, systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex. Narrow angle glaucoma, urinary retention Pregnancy: Category B3. Interactions: Beta-blockers, strong CYP3A4 inhibitors, sympathomimetics, monoamine oxidase inhibitors, tricyclic antidepressants and other LAMAs and LABAs. Adverse Effects: nasopharyngitis, headache, cough, pneumonia, upper respiratory tract infection, influenza, pharyngitis, rhinitis, arthralgia, back pain. Dosage: one inhalation once daily. After inhalation, rinse mouth with water without swallowing. Min PI v1.0 For full product information please contact GlaxoSmithKline Australia Pty Ltd. PO Box 18095, Melbourne, VIC 8003. ABN 47 100 162 481. For information on GSK products or to report an adverse event involving a GSK product, please contact GSK Medical Information on 1800 033 109 Trelegy Ellipta Trademarks are owned by or licensed to the GSK group of companies

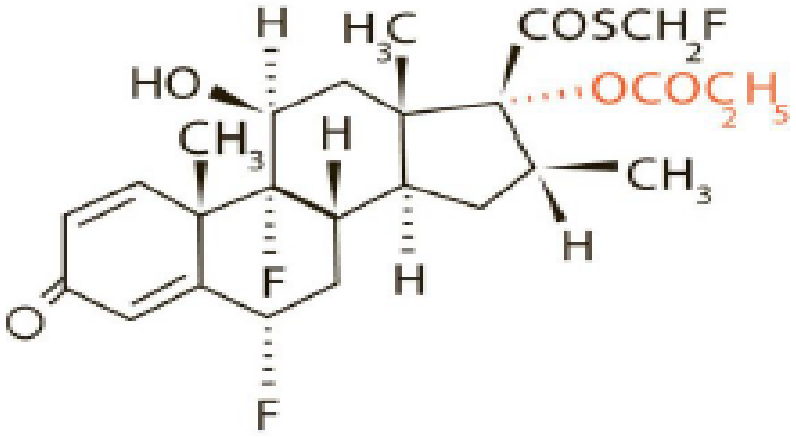
Pharmacological profile

Naming convention of inhaled corticosteroids

- Fluticasone furoate (FF) and fluticasone propionate (FP) are different drugs with distinct properties
- Similarity in names has led to the incorrect assumption that FF and FP have the same active
- FF is active as an intact molecule
- FF is not a pro-drug or salt of fluticasone



Fluticasone furoate

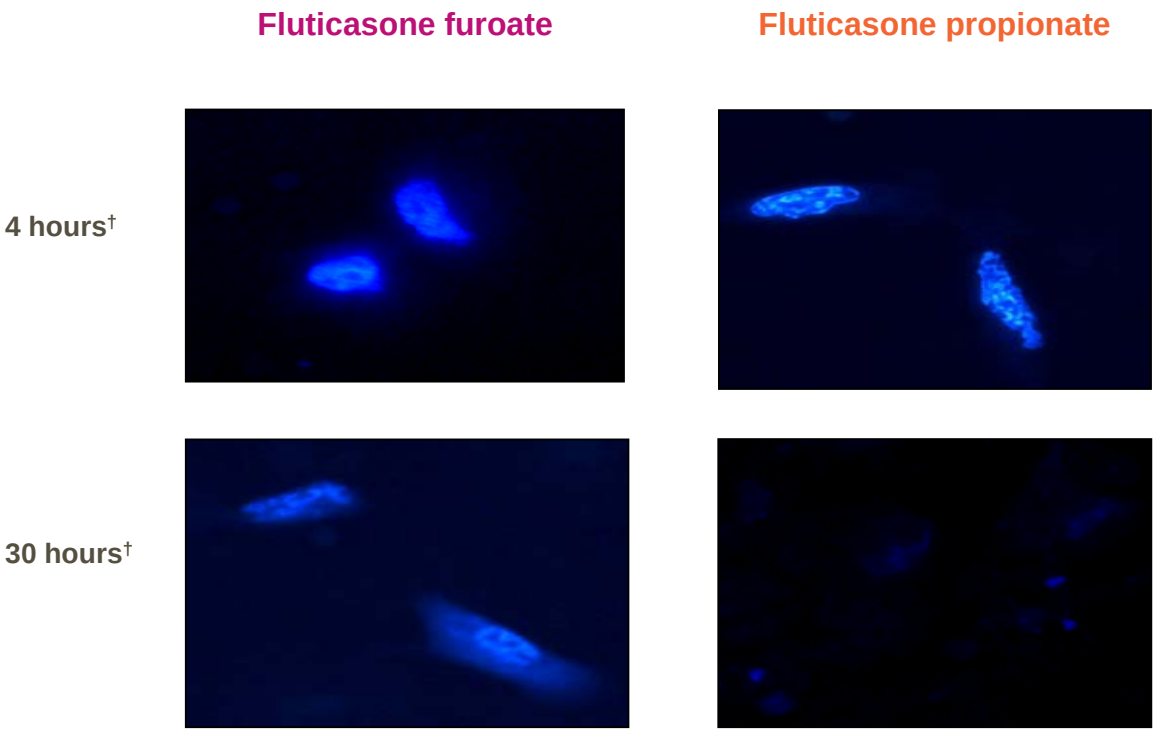


Fluticasone propionate

Adapted from Salter M et al. *Am J Physiol Lung Cell Mol Physiol*. 2007;293:L660–7.

Duration of glucocorticocoid receptor binding: fluticasone furoate vs fluticasone propionate*

**In-vitro data does not necessarily predict clinical effect*



†Study design: yellow fluorescent protein-conjugated GR was overexpressed in BEAS2B cells, and GR nuclear translocation was detected under microscopy over 30 hours.
FF, fluticasone furoate; FP, fluticasone propionate; GR, glucocorticoid receptor; ICS, inhaled corticosteroid

1. Adapted from Rossios C et al. *Eur J Pharmacol*. 2011;670:244–251.