

Drugs to Treat Asthma or Chronic Obstructive Pulmonary Disease (COPD)

Preliminary Scan Report #2

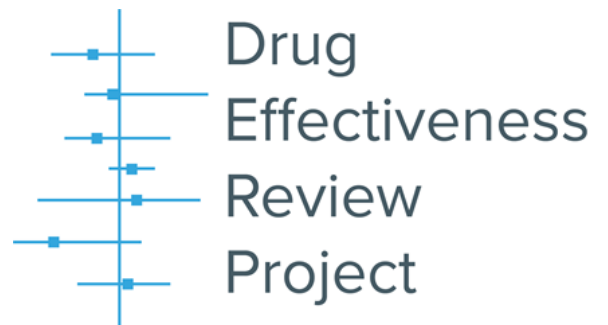
June 2018

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Objective

The purpose of this literature scan is to preview the volume and nature of new research that has emerged since the last full review on this topic. The literature search for this scan focuses on new randomized controlled trials and comparative effectiveness reviews, as well as actions taken by the U.S. Food and Drug Administration (FDA) since the last report. Comprehensive searches, quality assessment, and synthesis of evidence would follow only if DERP Participating Organizations agreed to proceed with a full report update or other review product.

Topic History

Update #1: June 2016, searches through November 2015

Scan # 1: June 2017

Scope and Key Questions

The scope of the review and key questions were originally developed and refined by the Pacific Northwest Evidence-based Practice Center (EPC) with input from DERP Participating Organizations, which ensure that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The EPC adapted the scope and key questions to guide this update scan:

1. What is the comparative efficacy and effectiveness *within-class* and *across-class* of long-acting inhaled and long-acting oral medications used to treat outpatients with asthma or chronic obstructive pulmonary disease (COPD)?
2. What is the comparative *within-class* and *across-class* tolerability and frequency of adverse events of long-acting inhaled and long-acting oral medications used to treat outpatients with asthma or chronic obstructive pulmonary disease (COPD)?
3. Are there subgroups of patients [e.g. groups defined by demographics (age, racial groups, gender), asthma or COPD severity, comorbidities, other medications (drug-drug interactions), smoking status, genetics, or pregnancy] for which asthma or COPD controller medications differ in efficacy, effectiveness, or frequency of adverse events?

Inclusion Criteria

Populations

- Adult or pediatric (≥12 months) patients with persistent or chronic asthma
- Adult patients (≥18 years) with COPD

Interventions

Table 1. Included Interventions

Drug Class	Active Ingredient	Trade Name	Dosage Form	FDA Approval Date
Long-acting beta-2 agonists (LABA)	Arformoterol tartrate (ARF)	Brovana	Nebulizer	10/06/2006
	Formoterol fumarate (FOR; formerly fomoterol)	Foradil Perforomist (aerolizer and certihaler)	DPI DPI	09/25/2001
	Indacaterol maleate (IND)	Arcapta	DPI	07/01/2011
	Olodaterol HCl (OLO)	Striverdi Respimat	SMI	07/31/2014
	Salmeterol xinafoate (SAL)	Serevent	DPI	09/19/1997
Long-acting muscarinic antagonists (LAMA)	Acclidinium (ACL)	Tudorza Pressair	DPI	07/23/2012
	Glycopyrrolate bromide (GLY)	Seebri Breezhaler Lonhala Magnair	DPI Nebulizer	10/29/2015
	Tiotropium bromide (TIO)	Spiriva Spiriva Respimat	DPI SMI	01/30/2004
	Umeclidinium bromide (UME)	Incruse Ellipta	DPI	04/30/2014
Inhaled corticosteroids (ICS)	Beclomethasone (BEC)	QVAR QVAR Redihaler	MDI MDI	09/15/2000
	Budesonide (BUD)	Pulmicort Respules Pulmicort Flexhaler	Nebulizer DPI	08/08/2000
	Ciclesonide (CIC)	Alvesco	MDI	01/10/2008
	Flunisolide hemihydrate (FLUN)	Aerospan HFA	MDI	01/27/2006
	Fluticasone furoate (FF)	Arnuity Ellipta	DPI	08/20/2014
	Fluticasone propionate	Flovent Armonair Respiclick	MDI, DPI MDPI	3/27/1996
	Mometasone furoate (MOM)	Asmanex Twisthaler Asmanex HFA	DPI MDI	03/30/2005
ICS/LABA	Formoterol/budesonide (FOR)	Symbicort	MDI, pMDI	07/21/2006

	Formoterol/mometasone furoate (FOR/MOM)	Dulera	MDI	06/22/2010
	Salmeterol xinafoate/ fluticasone propionate (SAL/FP)	Advair Diskus	DPI	08/24/2000
		Advair HFA	MDI	
		Airduo Respiclick	DPI	
	Vilanterol/fluticasone furoate (VIL/FF)	Breo Ellipta	DPI	05/10/2013
LABA/LAMA	Indacaterol/glycopyrrolate (IND/GLY)	Utibron Noeohaler	DPI	10/29/2015
	Olodaterol Hcl/tiotropium bromide (OLO/TIO)	Stiolto Respimat	SMI	05/21/2015
	Umeclidinium bromide/vilanterol trifenate (UME/VIL)	Anoro Ellipta	DPI	12/18/2013
	Formoterol/glycopyrrolate (FOR/GLY)	Bevespi Aerosphere	MDI	04/25/2016
ICS/LAMA/ LABA	Fluticasone furoate/ umeclidinium bromide/ vilanterol trifenate (FF/VIL/UME)	Trelegy Ellipta	DPI	09/18/2017
Leukotriene modifiers	Montelukast sodium (MON)	Singulair	Tablet	02/20/1998
	Zileuton (SIL)	Zyflo	Tablet	12/09/1996
		Zyflo CR	Tablet	
	Zafirlukast (ZAR)	Accolate	Tablet	09/26/1996
Phosphodiesterase-4 inhibitor	Roflumilast (ROF)	Daliresp	Tablet	02/28/2011

Abbreviations: CR, controlled release; DPI, dry-powder inhaler; FDA, U.S. Food & Drug Administration; MDI, metered-dose inhaler; MDPI, multi-dose powder inhaler; pMDI, pressurized metered-dose inhaler; SMI, soft mist inhaler

Shaded drugs new this scan

Comparators

- Head-to-head comparison of included interventions, including one drug, 2 devices
- *Excluded: add-on therapy (e.g., comparing fixed-dose combination A/B to either included drug (A or B but not both), fixed dose combination product vs. components at same dose (A/B vs. A+B).*

Benefits Outcomes

- Asthma and COPD control (e.g., exacerbations, days/nights/frequency of symptoms, frequency of rescue medication use, courses of oral steroids)
- Quality of life assessed using validated scales
- Functioning (i.e., ability to participate in work, school, sports, or physical activity, improved sleep)
- Emergency department/urgent medical care visits

- Hospitalization (all-cause, unless otherwise specified)
- Decreasing mortality

Harms Outcomes

- Overall adverse events reported
- Withdrawals due to adverse events
- Specific adverse events (e.g., growth suppression, bone mineral density, osteoporosis/fractures, ocular toxicity, suppression of the HPA axis, pneumonia, anaphylaxis, death)

Study Designs

- Randomized controlled trials of at least 12 weeks in duration and N≥100
 - *Excluded: studies comparing classes of drugs without comparing the individual drug products*
 - *Excluded: placebo-controlled trials, active-controlled trials*
- Comparative effectiveness reviews
 - Good-quality, covering all or most of topic scope, and with search dates in the last 2 years
- *Excluded from preliminary update scan (may be included in reports): observational studies*

Setting

Outpatient

Methods for Scan

Literature Search

To identify relevant citations, we searched Ovid MEDLINE®, Ovid MEDLINE® In-Process & Other Non-Indexed Citations, and the Cochrane Central Registry of Controlled Trials from March 2017 through May Week 2 2018 using terms for specific included drugs and limits for English language and humans. Literature searches included any new drugs identified in the present scan (shaded in Table 1). We also searched the FDA website (<http://www.fda.gov/medwatch/safety.htm>) to identify new drugs, new populations, and new serious harms (i.e., boxed warnings). To identify new drugs, we also searched CenterWatch (<http://www.centerwatch.com>), a privately-owned database of clinical trials information, and conducted a limited internet search. To identify comparative effectiveness reviews, we searched the websites of the Agency for Healthcare Research and Quality (<http://www.ahrq.gov/>) (<http://www.effectivehealthcare.ahrq.gov/>), the Canadian Agency for Drugs and Technology in Health (<http://www.cadth.ca/>), and the VA Evidence-based Synthesis Program (<http://www.hsrd.research.va.gov/publications/esp/reports.cfm>). All citations were imported into an electronic database (EndNote X8) and duplicate citations were removed.

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

Results

New Drugs

None since last report

New Formulations and Indications

Glycopyrrolate bromide (Lonhala Magnair) – approved on 12/5/2017 for COPD

Fluticasone furoate/umeclidinium bromide/vilanterol trifenate (Trelegy Ellipta) – once daily treatment for COPD approved on 9/18/2017

Beclomethasone (QVAR Redihaler) – approved on 8/3/2017 for asthmatic patients ≥ 4 years old

Fluticasone propionate (Armonair Respiclick) – approved on 1/27/2017 for asthmatic patients ≥ 12 years old

Salmeterol xinafoate/fluticasone propionate (Airduo Respiclick) – approved on 1/27/2017 for asthmatic patients ≥ 12 years old

Formoterol/glycopyrrolate (Bevespi Aero Sphere) – a new combination of ICS with LAMA approved on 4/25/2016 for COPD

New Serious Harms (i.e., Boxed Warnings)

No new Boxed Warning.

ICS/LABA (Advair Diskus®, Advair HPA, Breo Ellipta, Dulera, Symbicort®) – On 12/20/2017, previous boxed warnings that LABA used in combination with ICS significantly increase the risk of asthma-related hospitalizations, intubation, or asthma-related deaths, compared to ICS alone, was removed from these ICS/LABA products.

Comparative Effectiveness Reviews

We identified 1 new potentially relevant AHRQ comparative effectiveness review update on intermittent ICS with or without LAMA for asthma. See Appendix A for abstract and full citation.

Sobieraj DM, et al. Intermittent Inhaled Corticosteroids and Long-Acting Muscarinic Antagonists for Asthma. Comparative Effectiveness Review. AHRQ Publication No. 17(18)-EHC027-EF. March 2018.

Randomized Controlled Trials

Trials identified since the most recent Full Report

Table 2 shows new head-to-head RCTs identified since the last update report. Eleven trials compared the same drug in different delivery devices (7 new this scan). Thirteen trials compared 2 or more included drugs, with 10 of these studies identified for this scan. Many of the trials compared 2 drugs in the same class, or 2 drug combinations from the same classes. Two trials (Lipson 2017 and Papi 2018) compared triple therapy with an ICS, LABA, and LAMA to dual therapy with different drugs in 2 of those classes. One of these trials (Lipson 2017) tested 3 drugs recently approved as a fixed-dose combination product (Trelegy Ellipta). In addition, we have identified 18 secondary publications of previously-included trials (16 new this scan).

Table 2. New head-to-head trials

Shading indicates new studies found in this scan.

Author, Year Trial name	N Duration	Population	Comparison
Head-to-head delivery device			
Amar, 2016 NCT02031640	N=NR 12 weeks	Persistent asthma	Beclomethasone dipropionate BAI vs. MDI
Bernstein, 2017 NCT01576718	N=640 12 weeks	Adults and adolescents (≥ 12 years) with severe, persistent asthma	Fluticasone propionate MDPI vs. Fluticasone propionate DPI vs. Placebo MDPI
Bremner, 2018 NCT02729051	N=1,055 24 weeks	Adults (≥ 40 years) with COPD	Fluticasone furoate/Umeclidinium/Vilanterol vs. Fluticasone furoate/Vilanterol plus Umeclidinium in 2 inhalers
Bouloukaki, 2016	N=200 6 months	Mild-to-moderate COPD	Tiotropium SMI vs. DPI
Chan, 2017	N=NR 12 weeks	Adults with COPD	Fluticasone propionate/Salmeterol single-dose vs. multi-dose inhaler
Chan, 2017	N=NR 12 weeks	Asthma	Fluticasone propionate/Salmeterol single-dose vs. multi-dose inhaler
Kerwin, 2017	N=622 12 weeks	Adults and adolescents (≥ 12 years) with uncontrolled, persistent asthma	Fluticasone propionate MDPI vs. Fluticasone propionate DPI vs. Placebo MDPI
Mansfield, 2017	N=674 26 weeks	Adults and adolescents (≥ 12 years) with persistent asthma	Fluticasone propionate(MDPI) vs. Fluticasone propionate (HFA) and Fluticasone propionate/Salmeterol (MDPI) vs. Fluticasone propionate/Salmeterol (DPI)
Srichana, 2016	N=200 3 months	Mild-to-moderate asthma	Budesonide DPI vs. pMDI
Vandewalker, 2017	N=628 12 weeks	Children (4-11 years) with asthma	Beclomethasone dipropionate BAI vs. Beclomethasone dipropionate MDI
Wise, 2013 Dahl, 2015 Wise, 2015 TIOSPIR NCT01126437	N=17,135 2.3 years	COPD	Tiotropium DPI vs. Tiotropium MDI

Head-to-head drug			
Bernstein, 2017 NCT02301975	N=1,504 24 weeks	Adults and adolescents with controlled asthma	Fluticasone furoate/Vilanterol vs. Fluticasone propionate/Salmeterol vs. Fluticasone propionate
Feldman, 2016	N=1,017 12 weeks	COPD	Umeclidinium vs. Tiotropium
Ferguson, 2017	N=1,086 48 weeks	Moderate-to-very severe COPD	Glycopyrrolate vs. Tiotropium
Hsieh, 2017	N=253 12 weeks	Moderate-to-severe asthma	Beclomethasone/Formoterol vs. Fluticasone/Salmeterol
Kalberg, 2016 NCT02257385	N=NR 12 weeks	Moderate-to-severe COPD	Umeclidinium/Vilanterol vs. Tiotropium plus Indacaterol
Kerwin, 2017 NCT01899742	N=494 Duration: NR	Moderate COPD	Umeclidinium/Vilanterol vs. Tiotropium
Lin, 2017	N=317 12 weeks	Adults with persistent, severe asthma	Fluticasone propionate vs. Budesonide
Lipson, 2017 NCT02345161	N=1,810 24 weeks	COPD	Fluticasone furoate/Umeclidinium/Vilanterol vs. Budesonide/Formoterol
Oliver, 2016	N=593 12 weeks	Children (5-11 years) with asthma	Fluticasone propionate vs. Fluticasone furoate
Papi, 2018 NCT02579850	N=1,532 52 weeks	Symptomatic COPD	Beclomethasone dipropionate/Formoterol fumarate/Glycopyrronium vs. Indacaterol/ Glycopyrronium
Usmani, 2017	N=225 12 weeks	Asthma	Fluticasone propionate/Salmeterol vs. Fluticasone propionate/ Formoterol fumarate dehydrate
Vestbo, 2016 SUMMIT	N=16,4845 1.8 years	COPD with increased risk of cardiovascular disease	Fluticasone furoate vs. Vilanterol vs. Fluticasone furoate/Vilanterol
Wedzicha, 2016 NCT01782326	N=3,362 1 year	COPD	Indacaterol/Glycopyrronium once-daily vs. Salmeterol/Fluticasone twice-daily

Abbreviations: BAI, breath-actuated inhaler; DPI, dry powder inhaler; HFA, hydrofluoroalkane; MDI, metered-dose inhaler; MDPI, multi-dose powder inhaler; NR, not reported; pMDI, pressurized metered dose inhaler; SMI, soft mist

Summary

Since the last update report, the FDA has approved 6 new formulations of, or indications for existing drugs, including a new fixed-dose combination product of 3 drugs. There have been no new boxed warnings, but a warning including increased risk of asthma-related death was removed from ICS/LABA combination products. One 2018 comparative effectiveness review of ICS and LAMA drugs was identified. We have identified 13 new head-to-head trials of included drugs (10 new this scan), and 11 trials of the same drug in different delivery devices (7 new this scan). Two of the trials compared triple therapy with an ICS, LABA and LAMA to dual therapy with different drugs in those classes.

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Preliminary Scan Report #2 Appendices

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APPENDIX A. New Comparative Effectiveness Reviews

Sobieraj DM, Baker WL, Weeda ER, Nguyen E, Coleman CI, White CM, Lazarus SC, Blake KV, Lang JE. Intermittent Inhaled Corticosteroids and Long-Acting Muscarinic Antagonists for Asthma. Comparative Effectiveness Review No. 194. (Prepared by the University of Connecticut Evidence-based Practice Center under Contract No. 290-2015-00012-I.) AHRQ Publication No. 17(18)-EHC027-EF. Rockville, MD: Agency for Healthcare Research and Quality; March 2018. Posted final reports are located on the [Effective Health Care Program search page](#). DOI: <https://doi.org/10.23970/AHRQEPCCER194>.

Structured Abstract

Objective. To assess efficacy of intermittent inhaled corticosteroid (ICS) therapy in different populations (0 to 4 years old with recurrent wheezing, 5 years and older with persistent asthma, with or without long-acting beta agonist [LABA]), and to assess efficacy of added long-acting muscarinic antagonist (LAMA) in patients 12 years and older with uncontrolled, persistent asthma.

Data sources. MEDLINE®, Embase®, Cochrane Central, and Cochrane Database of Systematic Reviews bibliographic databases from earliest date through March 23, 2017; hand searches of references of relevant studies; www.clinicaltrials.gov and the International Controlled Trials Registry Platform.

Review methods. Two investigators screened abstracts of identified references for eligibility and subsequently reviewed full-text files. We abstracted data, performed meta-analyses when appropriate, assessed the risk of bias of each individual study, and graded the strength of evidence for each comparison and outcome. Outcomes for which data were extracted included exacerbations, mortality, asthma control composite scores, spirometry, asthma-specific quality of life, and rescue medication use.

Results. We included 56 unique studies (54 randomized controlled trials, 2 observational studies) in this review. Compared to rescue short-acting beta-agonist (SABA) use, adding intermittent ICS reduces the risk of exacerbation requiring oral steroids and improves caregiver quality of life in children less than 5 years old with recurrent wheezing in the setting of a respiratory tract infection (RTI). In patients 12 years and older with persistent asthma, differences in intermittent ICS versus controller use of ICS were not detected, although few studies provided evidence, leading to primarily low strength of evidence ratings. Using ICS and LABA as both a controller and quick relief therapy reduced the risk of exacerbations and improved symptom control in patients 12 years and older compared to ICS controller (with or without LABA). Data in patients 4 to 11 years old suggest lower risk of exacerbations with ICS and LABA controller and

quick relief use, but with a lower strength of evidence than in the older population. In patients 12 years and older with uncontrolled, persistent asthma, LAMA versus placebo as add-on to ICS reduces the risk of exacerbations requiring systemic corticosteroids and improves lung function measure through spirometry. Current evidence does not suggest that a difference exists in the efficacy of LAMA versus LABA as add-on to ICS. Triple therapy of ICS, LAMA, and LABA improves lung function measured through spirometry, although the risk of exacerbation was not different versus ICS and LABA.

Conclusions. Intermittent ICS added to SABA during an RTI provides benefit to patients less than 5 years of age with recurrent wheezing. In patients 12 years and older with persistent asthma, differences in intermittent ICS versus controller use of ICS were not detected, although few studies provided evidence for this question. In patients 12 years and older with persistent asthma, using ICS and LABA as both a controller and quick relief therapy may be more effective at preventing exacerbations than ICS controller (with or without LABA). LAMA is effective in the management of uncontrolled, persistent asthma in patients 12 years of age and older, and current evidence does not suggest a difference between LAMA and LABA as add-on to ICS.

Appendix B. New Active-Controlled Trials

Head-to-head delivery device (n=11)

Amar, N. J., et al. (2016). "Safety and efficacy of beclomethasone dipropionate delivered by breath-actuated or metered-dose inhaler for persistent asthma." Allergy & Asthma Proceedings **37**(5): 359-369.

BACKGROUND: Breath-actuated inhalers (BAI) have been developed to simplify the delivery of inhaled medication.

OBJECTIVE: To evaluate the safety and efficacy of beclomethasone dipropionate hydrofluoroalkane BAI and metered-dose inhaler (MDI) versus placebo in patients who previously used a mid- to high-dose inhaled corticosteroid or inhaled corticosteroid/long-acting beta agonist for persistent asthma.

METHODS: This phase III study included five treatment groups: placebo, and four beclomethasone dipropionate groups (BAI 320 mug/day, BAI 640 mug/day, MDI 320 mug/day, and MDI 640 mug/day). Efficacy over 12 weeks was assessed by spirometry, peak flow measurements, and other clinical end points. Safety was assessed by adverse events.

RESULTS: Baseline-adjusted trough morning forced expiratory volume in 1 second area under the effect curve from time 0 to 12 weeks (primary end point) was increased in the BAI 320 and BAI 640 mug/day groups and the MDI 640 mug/day group versus placebo (not significant). Clinically important improvements were noted in morning and evening peak expiratory flow and decreased rescue medications. More patients who received placebo than patients in active treatment groups withdrew due to meeting the stopping criteria for worsening asthma. Patients in the active treatment groups experienced a greater decrease in asthma symptoms than patients in the placebo group. Quality of life and Asthma Control Test scores improved in the active treatment groups compared with the placebo group ($p < 0.0074$). The most common adverse events ($>5\%$ in any group) were oral candidiasis and upper respiratory tract infection.

CONCLUSION: Clinical benefits for patients who used BAI 320 and 640 mug/day and MDI 640 mug/day were demonstrated. The safety profiles of BAI 320 and 640 mug/day were comparable with that of the MDI. These benefits and the continued need for better symptom control among patients with asthma support the continued development of this controller medication. ClinicalTrials.gov identifier NCT02031640.

Bernstein, D. I., et al. (2017). "Safety, efficacy, and dose response of fluticasone propionate delivered via the novel MDPI in patients with severe asthma: a randomized, controlled, dose-ranging study." Journal of Asthma **54**(6): 559-569.

METHODS: Patients with persistent asthma despite use of high-dose inhaled corticosteroids were randomized to Fp MDPI 50, 100, 200, or 400 mcg; Fp DPI 250 mcg; or placebo MDPI twice daily for 12 weeks. The primary outcome measure was change from baseline in trough forced expiratory volume in 1 second (FEV1). **RESULTS:** Six hundred forty patients were randomized; 459 (72%) completed the study. Numerical dose-related improvements in FEV1 were observed. **CONCLUSIONS:** Clinical benefit observed with Fp MDPI in patients with persistent asthma was comparable to Fp DPI. Safety was reassuring with no unexpected findings. These results support further evaluation of Fp MDPI in asthma. (ClinicalTrials.gov identifier NCT01576718; EudraCT number 2010-023601-35). **OBJECTIVE:** Evaluate fluticasone propionate (Fp) using a novel, inhalation-driven, multidose dry powder inhaler (MDPI) in patients with severe persistent asthma, versus placebo MDPI and Fp dry powder inhaler (DPI).

Bremner, P. R., et al. (2018). "Single-inhaler fluticasone furoate/umeclidinium/vilanterol versus fluticasone furoate/vilanterol plus umeclidinium using two inhalers for chronic obstructive pulmonary disease: a randomized non-inferiority study." *Respiratory Research* **19**(1): 19.

BACKGROUND: Single-inhaler fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) 100/62.5/25 mug has been shown to improve lung function and health status, and reduce exacerbations, versus budesonide/formoterol in patients with chronic obstructive pulmonary disease (COPD). We evaluated the non-inferiority of single-inhaler FF/UMEC/VI versus FF/VI + UMEC using two inhalers. **METHODS:** Eligible patients with COPD (aged ≥ 40 years; ≥ 1 moderate/severe exacerbation in the 12 months before screening) were randomized (1:1; stratified by the number of long-acting bronchodilators [0, 1 or 2] per day during run-in) to receive 24-week FF/UMEC/VI 100/62.5/25 mug and placebo or FF/VI 100/25 mug + UMEC 62.5 mug; all treatments/placebo were delivered using the ELLIPTA inhaler once-daily in the morning. Primary endpoint: change from baseline in trough forced expiratory volume in 1 s (FEV1) at Week 24. The non-inferiority margin for the lower 95% confidence limit was set at - 50 mL. **RESULTS:** A total of 1055 patients (844 [80%] of whom were enrolled on combination maintenance therapy) were randomized to receive FF/UMEC/VI (n = 527) or FF/VI + UMEC (n = 528). Mean change from baseline in trough FEV1 at Week 24 was 113 mL (95% CI 91, 135) for FF/UMEC/VI and 95 mL (95% CI 72, 117) for FF/VI + UMEC; the between-treatment difference of 18 mL (95% CI -13, 50) confirmed FF/UMEC/VI's was considered non-inferior to FF/VI + UMEC. At Week 24, the proportion of responders based on St George's Respiratory Questionnaire Total score was 50% (FF/UMEC/VI) and 51% (FF/VI + UMEC); the proportion of responders based on the Transitional Dyspnea Index focal score was similar (56% both groups). A similar proportion of patients experienced a moderate/severe exacerbation in the FF/UMEC/VI (24%) and FF/VI + UMEC (27%) groups; the hazard ratio for time to first moderate/severe exacerbation with FF/UMEC/VI

versus FF/VI + UMEC was 0.87 (95% CI 0.68, 1.12). The incidence of adverse events was comparable in both groups (48%); the incidence of serious adverse events was 10% (FF/UMEC/VI) and 11% (FF/VI + UMEC). CONCLUSIONS: Single-inhaler triple therapy (FF/UMEC/VI) is non-inferior to two inhalers (FF/VI + UMEC) on trough FEV1 change from baseline at 24 weeks. Results were similar on all other measures of efficacy, health-related quality of life, and safety. TRIAL REGISTRATION: GSK study CTT200812; ClinicalTrials.gov NCT02729051 (submitted 31 March 2016).

Bouloukaki, I., et al. (2016). "Tiotropium Respimat Soft Mist Inhaler versus HandiHaler to improve sleeping oxygen saturation and sleep quality in COPD." Sleep & Breathing **20**(2): 605-612.

PURPOSE: Patients with chronic obstructive pulmonary disease (COPD) have poor sleep quality as a result of various alterations in oxygenation parameters and sleep macro- and micro-architecture. There is a shortage of data to support the efficacy of long-acting inhaled anticholinergic agents in improving these adverse effects, which are known to have a negative impact on clinical outcomes. We aimed to compare the tiotropium Respimat Soft Mist Inhaler and the HandiHaler in terms of their effects on sleeping oxygen saturation (SaO₂) and sleep quality in patients with COPD.

METHODS: In a randomized, open-label, parallel-group trial involving 200 patients with mild to moderate COPD (resting arterial oxygen tension >60 mmHg while awake), we compared the effects of 6 months' treatment with the two devices on sleeping SaO₂ and sleep quality. Overnight polysomnography and pulmonary function testing were performed at baseline and after 6 months' treatment.

RESULTS: A total of 188 patients completed the trial. Both groups showed significant improvement in minimum sleep SaO₂ and time of sleep spent with SaO₂ below 90 (TST90) compared to baseline. The patients using the Respimat had significantly better TST90 than did those using the HandiHaler. Sleep disturbance was highly variable in these patients, but the sleep stage durations were significantly better in the Respimat group.

CONCLUSIONS: Sleeping SaO₂ can be improved by tiotropium delivered using either the HandiHaler device or the Respimat Soft Mist Inhaler. However, the patients who used the Respimat device had significantly better TST90 and sleep architecture parameters.

Chan, R., et al. (2017). "Assessment of the efficacy and safety of fluticasone propionate and salmeterol delivered as a combination dry powder via a capsule-based inhaler versus a multi-dose inhaler in patients with chronic obstructive pulmonary disease." Pulmonary Pharmacology & Therapeutics **43**: 12-19.

BACKGROUND: This study tested the clinical non-inferiority of the fluticasone propionate/salmeterol combination 50/250 mug (FSC) Rotacaps^{/Rotahaler^{system, a single unit dose inhaler, with}}

the multi-dose FSC Diskus inhaler in adults with chronic obstructive pulmonary disease (COPD).

METHODS: This multi-centre, randomised, double-blind, double-dummy, two-way cross-over study compared 12 weeks' treatment of FSC administered twice daily using Rotacaps/Rotahaler or Diskus. The primary endpoint was change from baseline in trough morning forced expiratory volume in 1 s (FEV₁) at Day 85, and the pre-defined non-inferiority criteria was: the lower limit of the confidence interval (CI) for the treatment difference (Rotacaps/Rotahaler-Diskus) in least squares (LS) mean change from baseline, being greater than -45 mL. Secondary endpoints included change in breathlessness (as measured by transition dyspnoea index (TDI)) and COPD-specific health status measures.

RESULTS: The LS mean increase from baseline in trough FEV₁ at Day 85 was 116 mL in the Rotacaps/Rotahaler group and 91 mL in the Diskus group (difference in model-adjusted LS mean change: 25 mL (95% CI 2 mL, 47 mL)), the lower limit of the CI for the treatment difference being greater than the protocol-defined criterion for non-inferiority i.e. -45 mL. Data for breathlessness, COPD-specific health status and safety parameters were similar following FSC treatment via either inhaler.

CONCLUSIONS: This study demonstrated the clinical non-inferiority of FSC 50/250 mug when administered using Rotacaps/Rotahaler compared with Diskus in patients with COPD. The risk:benefit profile for the two inhalers was comparable.

Chan, R., et al. (2016). "Assessment of the efficacy and safety of fluticasone propionate and salmeterol delivered as a combination dry powder via a capsule-based inhaler and a multi-dose inhaler in patients with asthma." Pulmonary Pharmacology & Therapeutics **41**: 19-24.

BACKGROUND: In developing countries, there is a need for access to affordable inhaled respiratory medicines. This study tested the clinical non-inferiority of fluticasone propionate/salmeterol combination (FSC) 50/250 mug Rotacaps/Rotahaler compared with FSC 50/250 mug Diskus.

METHODS: A multi-centre, randomised, double-blind, double-dummy study evaluated 12 weeks, twice daily treatment of FSC 50/250 mug administered using Rotacaps/Rotahaler or Diskus inhaler in a crossover design in patients with asthma (pre-bronchodilator forced expiratory volume in 1 s (FEV₁) 40%-85% of predicted, FEV₁ reversibility ≥12%, prior stable dose with inhaled corticosteroid (ICS) or ICS/long acting beta-agonist). The primary efficacy endpoint, change from baseline in trough morning FEV₁ at Day 85, was analysed using a model for repeated measures analysis. The pre-defined criterion for non-inferiority was the lower limit of the CI (0.025, one-sided significance level) for the treatment difference (Rotacaps/Rotahaler-Diskus) in least squares (LS) mean change from baseline, being greater than -125 mL. Secondary

endpoints included serial FEV₁ measurements, morning peak expiratory flow (PEF), rescue medication use, day- and night-time asthma symptoms, Asthma Control Test (ACT) scores, and serial cortisol measured over 12 h (area under the curve (AUC₀₋₁₂)).

RESULTS: Treatment with FSC 50/250 mug via Rotacaps/Rotahaler or Diskus resulted in a similar LS mean increase from baseline in trough FEV₁ at Day 85 (231 mL and 203 mL respectively). The difference in the model-adjusted LS mean change was 28 mL (95% CI -24 mL, 80 mL), fulfilling the criterion for non-inferiority. Data for all secondary endpoints were similar for the two treatments, supporting the primary endpoint findings. Both treatments were well tolerated and demonstrated similar safety profiles.

CONCLUSION: This study demonstrated the clinical non-inferiority of FSC 50/250 mug when administered using Rotacaps/Rotahaler compared with administration using Diskus in patients with asthma, and suggests there is no difference in the risk:benefit profile between the two FSC inhalers.

Kerwin, E. M., et al. (2017). "Randomized, dose-ranging study of a fluticasone propionate multidose dry powder inhaler in adolescents and adults with uncontrolled asthma not previously treated with inhaled corticosteroids." *Journal of Asthma* **54**(1): 89-98.

OBJECTIVE: A novel, inhalation-driven, multidose dry powder inhaler (MDPI) eliminates the need to coordinate actuation with inhalation. To characterize dose response, efficacy, and safety of fluticasone propionate (Fp) MDPI, a dose-ranging study was conducted with placebo and active comparators.

METHODS: This 12-week, double-blind, parallel-group study randomized patients aged ≥ 12 years with uncontrolled persistent asthma not previously treated with inhaled corticosteroid therapy (N = 622) to twice-daily treatment with Fp MDPI (12.5, 25, 50, or 100 micro g), placebo MDPI, or open-label Fp dry powder inhaler (DPI) 100 micro g. The primary efficacy endpoint was change from baseline over 12 weeks in trough (morning pre-dose and pre-rescue bronchodilator) forced expiratory volume in 1 second (FEV₁). Blood samples were collected from a patient subset to evaluate pharmacokinetics. Adverse events were monitored.

RESULTS: Fp MDPI 25, 50, and 100 micro g significantly improved change from baseline in trough FEV₁ over 12 weeks compared with placebo (p < 0.01). There were no substantial differences in FEV₁ change from baseline over 12 weeks between any Fp MDPI dose and Fp DPI 100 micro g. Maximum observed concentration (C_{max}) of Fp increased with increasing Fp MDPI doses; time of C_{max} was similar across doses and treatments. Systemic exposures for Fp MDPI 25 and 50 micro g were lower than that for Fp DPI 100 micro g. The safety profile of Fp MDPI was consistent with that of Fp DPI.

CONCLUSIONS: In this study, Fp MDPI 25 and 50 micro g provided comparable efficacy and safety to Fp DPI 100 micro g, with lower systemic exposure.

Mansfield, L., et al. (2017). "A 6-month safety and efficacy study of fluticasone propionate and fluticasone propionate/salmeterol multidose dry powder inhalers in persistent asthma." Allergy & Asthma Proceedings **38**(4): 264-276.

BACKGROUND: A novel multidose dry powder inhaler (MDPI) that is breath actuated, easy, and intuitive to use has been developed for administering fluticasone propionate (Fp) and Fp/salmeterol (FS).

OBJECTIVE: To assess the safety and efficacy of Fp MDPI versus Fp hydrofluoroalkane (HFA) and FS MDPI versus FS dry-powder inhaler (DPI).

METHODS: This phase III, 26-week, open-label, active drug-controlled study enrolled subjects ≥ 12 years old with persistent asthma. Based on entry controller medication (inhaled corticosteroid [ICS] or ICS/long-acting beta-agonist), the subjects were randomized to twice-daily mid-strength Fp MDPI 100 mug or Fp HFA 220 mug, high-strength Fp MDPI 200 mug or Fp HFA 440 mug, mid-strength FS MDPI 100/12.5 mug or FS DPI 250/50 mug, or high-strength FS MDPI 200/12.5 mug or FS DPI 500/50 mug in a 3:1 MDPI to Fp HFA or FS DPI ratio. Safety and efficacy were assessed by adverse events (AE) and pulmonary function and asthma symptoms, respectively.

RESULTS: A total of 674 subjects were randomized. The AE incidence was similar across treatment groups (upper respiratory tract infections, sinusitis, and nasopharyngitis were most frequent). A higher percentage of subjects in the Fp HFA 440 mug and FS DPI 500/50 mug groups had oral candidiasis versus those who received Fp MDPI 200 mug or FS MDPI 200/12.5 mug, respectively. Serious AEs were similar between the treatments, with no unexpected findings. The incidence of asthma exacerbations was low and generally similar between the groups. Noninferiority was established for all Fp MDPI and FS MDPI doses compared with Fp HFA and FS DPI, respectively, for forced expiratory volume in 1 second. Changes in peak expiratory flow, rescue albuterol use, and symptoms were similar between treatments.

CONCLUSION: The safety and efficacy profiles of Fp MDPI and FS MDPI administered at lower doses were generally comparable with those of Fp HFA and FS DPI, respectively, after 26 weeks of treatment. The ClinicalTrials.gov identifier is NCT02175771.

Srichana, T., et al. (2016). "Clinical equivalence of budesonide dry powder inhaler and pressurized metered dose inhaler." The clinical respiratory journal **10**(1): 74-82.

INTRODUCTION: A delivery device is the most important factor that determines the local/systemic bioavailability of inhaled corticosteroids. Dry powder inhalers (DPIs) and pressurized metered dose inhalers (pMDIs) are the most commonly used delivery devices for localized drug delivery to the airways.

OBJECTIVE: This study was to compare the clinical equivalence of budesonide delivered by the Pulmicort Turbuhaler (DPI) and the Aeronide inhaler (pMDI).

MATERIALS AND METHODS: The two inhalers were compared for their pharmaceutical equivalence and clinical equivalence. The in vitro test included the uniformity of the delivered dose and determination of the aerodynamic particle size of budesonide. The in vivo test was carried out in 36 patients with mild to moderate asthma. This was a randomized, single-blinded study conducted for a period of 3 months. This included assessment of the spirometric parameters [forced expiratory volume in 1s (FEV1), forced vital capacity (FVC), peak expiratory flow rate (PEFR), forced expiratory flow 25-75% (FEF25-75)], the severity of asthma symptoms, adverse events, frequency of short-acting inhaled bronchodilator usage and measurement of urinary cortisol levels.

RESULTS: The aerodynamic particle size was slightly different between the two inhalers (2.3+/-0.2micro m for Pulmicort Turbuhaler and 2.2+/-0.2micro m for Aeronide inhaler). Both inhalers passed the uniformity of delivered dose (95.4% and 97.4%) specified in the British Pharmacopoeia. There was no statistically significant difference observed between the two inhalers in terms of the spirometric parameters, symptom-free days, frequency of bronchodilator usage and the level of urinary cortisol.

CONCLUSION: In addition to pharmaceutical equivalence, no clinical difference observed between the two budesonide inhalers.

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Vandewalker, M., et al. (2017). "Efficacy and safety of beclomethasone dipropionate breath-actuated or metered-dose inhaler in pediatric patients with asthma." Allergy & Asthma Proceedings **38**(5): 354-364.

BACKGROUND: Breath-actuated inhalers (BAI) eliminate the need for hand-breath coordination and, therefore, simplify the delivery of inhaled medication.

OBJECTIVE: To evaluate the efficacy and safety of beclomethasone dipropionate BAI and metered-dose inhaler (MDI) versus placebo in pediatric patients ages 4-11 years with persistent asthma.

METHODS: In this double-blind, double-dummy, phase III study, 628 children with persistent asthma were randomly assigned (1:1:1:1) to twice-daily beclomethasone dipropionate (BAI 80 mug/day, BAI 160 mug/day, MDI 80 mug/day, or MDI 160 mug/day) or to placebo. Efficacy over 12 weeks was assessed by spirometry, peak expiratory flow (PEF) measurements and other clinical end points. The primary efficacy end point was the baseline-adjusted trough morning percent predicted forced expiratory volume in 1 second (PPFEV1) area under the effect curve from 0 to 12 weeks (AUEC[0-12 weeks]).

RESULTS: PPFEV1 AUEC(0-12 weeks) showed numerical improvements from baseline in the BAI 80 mug/day and BAI 160 mug/day groups and MDI 80 mug/day and MDI 160 mug/day groups; however, these improvements were not significant versus placebo for any group

after hierarchical testing was applied. Consistent improvements were noted in the active treatment groups versus placebo for the weekly average trough morning and evening PEFs, and with BAI 80 mug/day versus placebo for rescue albuterol/salbutamol use and the total daily asthma symptom score. Most patients indicated that the BAI device was easy or very easy to use. Adverse events were comparable across the groups; the incidence of oral candidiasis ranged from 0.8 to 3.2%.

CONCLUSIONS: Although the primary efficacy end point was not demonstrated, consistent improvements in PEF and other clinical end points were observed with beclomethasone dipropionate BAI, particularly at the 80 mug/day dose. These clinical benefits, combined with the need for better symptom control in children with asthma, supported the development of beclomethasone dipropionate BAI.

Wise, R. A., et al. (2013). "Tiotropium Respimat Inhaler and the Risk of Death in COPD." New England Journal of Medicine. **369**: 1491-1501.

BACKGROUND: Tiotropium delivered at a dose of 5 µg with the Respimat inhaler showed efficacy similar to that of 18 µg of tiotropium delivered with the HandiHaler inhalation device in placebo-controlled trials involving patients with chronic obstructive pulmonary disease(COPD). Although tiotropium HandiHaler was associated with reduced mortality, as compared with placebo, more deaths were reported with tiotropium Respimat than with placebo.

METHODS: In this randomized, double-blind, parallel-group trial involving 17,135 patients with COPD, we evaluated the safety and efficacy of tiotropium Respimat at a once-daily dose of 2.5 µg or 5 µg, as compared with tiotropium HandiHaler at a once-daily dose of 18 µg. Primary end points were the risk of death (noninferiority study, Respimat at a dose of 5 µg or 2.5 µg vs. HandiHaler) and the risk of the first COPD exacerbation (superiority study, Respimat at a dose of 5 µg vs. HandiHaler). We also assessed cardiovascular safety, including safety in patients with stable cardiac disease.

RESULTS: During a mean follow-up of 2.3 years, Respimat was noninferior to HandiHaler with respect to the risk of death (Respimat at a dose of 5 µg vs. HandiHaler: hazard ratio, 0.96; 95% confidence interval [CI], 0.84 to 1.09; Respimat at a dose of 2.5 µg vs. HandiHaler: hazard ratio, 1.00; 95% CI, 0.87 to 1.14) and not superior to HandiHaler with respect to the risk of the first exacerbation (Respimat at a dose of 5 µg vs. HandiHaler: hazard ratio, 0.98; 95% CI, 0.93 to 1.03). Causes of death and incidences of major cardiovascular adverse events were similar in the three groups.

CONCLUSIONS: Tiotropium Respimat at a dose of 5 µg or 2.5 µg had a safety profile and exacerbation efficacy similar to those of tiotropium HandiHaler at a dose of 18 µg in patients with COPD. (Funded by Boehringer Ingelheim; TIOSPIR ClinicalTrials.gov number, [NCT01126437](#)).

Head-to-head drug (n=13)

Bernstein, D., et al. (2017). "Once-daily fluticasone furoate/vilanterol versus twice-daily fluticasone propionate/salmeterol in patients with asthma well controlled on ICS/LABA." Journal of Asthma.

OBJECTIVE: We aimed to demonstrate non-inferiority of once-daily fluticasone furoate/vilanterol 100/25 mug (FF/VI) to twice-daily fluticasone propionate/salmeterol 250/50 mug (FP/SAL) in adults/adolescents with asthma well controlled on inhaled corticosteroid/long-acting beta2 agonist (ICS/LABA). **METHODS:** This was a randomized, double-blind, double-dummy, parallel-group, 24-week study (NCT02301975/GSK study 201378). Patients whose asthma met study-defined criteria for control were randomized 1:1:1 to receive FF/VI, FP/SAL or twice-daily FP 250 mug for 24 weeks. Primary endpoint was change from baseline in evening trough forced expiratory volume in 1 second (FEV1). Secondary endpoints included rescue-/symptom-free 24-hour periods. Safety was also assessed. **RESULTS:** The intent-to-treat (ITT) population included 1504 randomized and treated patients (504 FF/VI; 501 FP/SAL; 499 FP); mean age 43.5 years, 64% female. FF/VI demonstrated non-inferiority (using a margin of -100 mL) to FP/SAL for evening trough FEV1 at Week 24 (ITT: 19 mL [95% confidence interval (CI) -11 to 49]; per protocol population [N = 1336]: 6 mL [95% CI -27 to 40]). Improvement in evening trough FEV1 at Week 24 for both FF/VI (123 mL; $p < 0.001$) and FP/SAL (104 mL; $p < 0.001$) was greater than FP. FF/VI increased rescue-/symptom-free 24-hour periods by 1.2%/1.2% compared with FP/SAL. All treatments were well tolerated. On-treatment adverse event (AE) rates were 43% to 45% across arms; there were no drug-related serious AEs. **CONCLUSIONS:** FF/VI was non-inferior to FP/SAL for evening trough FEV1 at 24 weeks. These data suggest that patients well controlled on FP/SAL could step across to FF/VI without loss of control.

Feldman, G., et al. (2016). "A randomized, blinded study to evaluate the efficacy and safety of umeclidinium 62.5 mug compared with tiotropium 18 mug in patients with COPD." International Journal of Copd **11**: 719-730.

BACKGROUND: The long-acting muscarinic antagonists umeclidinium (UMEC) and tiotropium (TIO) are approved once-daily maintenance therapies for COPD. This study investigated the efficacy and safety of UMEC versus TIO in COPD.

METHODS: This was a 12-week, multicenter, randomized, blinded, double-dummy, parallel-group, non-inferiority study. Patients were randomized 1:1 to UMEC 62.5 mug plus placebo or TIO 18 mug plus placebo. The primary end point was trough forced expiratory volume in 1 second (FEV1) at day 85 (non-inferiority margin -50 mL; per-protocol [PP] population). Other end points included weighted mean FEV1 over 0-24 and 12-24 hours post-dose. Patient-reported outcomes comprised Transition Dyspnea Index

score, St George's Respiratory Questionnaire total score, and COPD Assessment Test score. Adverse events were also assessed.

RESULTS: In total, 1,017 patients were randomized to treatment. In the PP population, 489 and 487 patients received UMEC and TIO, respectively. In the PP population, change from baseline in trough FEV1 was greater with UMEC versus TIO at day 85, meeting non-inferiority and superiority margins (difference: 59 mL; 95% confidence interval [CI]: 29-88; $P < 0.001$). Similar results were observed in the intent-to-treat analysis of trough FEV1 at day 85 (53 mL, 95% CI: 25-81; $P < 0.001$). Improvements in weighted mean FEV1 over 0-24 hours post-dose at day 84 were similar with UMEC and TIO but significantly greater with UMEC versus TIO over 12-24 hours post-dose (70 mL; $P = 0.015$). Clinically meaningful improvements in Transition Dyspnea Index and St George's Respiratory Questionnaire were observed with both treatments at all time points. No differences were observed between UMEC and TIO in patient-reported outcomes. Overall incidences of adverse events were similar for UMEC and TIO.

CONCLUSION: UMEC 62.5 mug demonstrated superior efficacy to TIO 18 mug on the primary end point of trough FEV1 at day 85. Safety profiles were similar for both treatments.

Ferguson, G. T., et al. (2017). "Long-term safety of glycopyrrolate/eFlow CS in moderate-to-very-severe COPD: results from the Glycopyrrolate for Obstructive Lung Disease via Electronic Nebulizer (GOLDEN) 5 randomized study." Respiratory Medicine(pagination).

Background: The use of long-acting bronchodilators is an essential component of the management of chronic obstructive pulmonary disease (COPD). The GOLDEN 5 Phase III, randomized, active-controlled, open-label study was conducted to evaluate the long-term safety and tolerability of a nebulized glycopyrrolate formulation (SUN-101) delivered via the investigational eFlow Closed System (eFlow CS) nebulizer in subjects with moderate-to-very-severe COPD. **Methods:** Subjects were randomized in a 4:3 ratio to nebulized glycopyrrolate 50 mug twice daily (BID) or tiotropium 18 mug once daily (OD) and treated for 48 weeks. Subjects represented the general COPD population with real-world characteristics including severe disease, presence of comorbidities, and receiving background COPD therapy. Primary endpoints were the incidence of treatment-emergent adverse events (TEAEs), serious TEAEs, and discontinuations due to TEAEs. Secondary endpoints included the number of subjects with major adverse cardiovascular events (MACE); change from baseline in trough forced expiratory volume in 1 s ($FEV_{1 <inf>1 </inf>}$), and assessment of patient-reported outcomes. **Results:** 1086 subjects received at least one dose of study drug. The overall incidence of TEAEs was comparable for subjects treated with glycopyrrolate (69.4%) or tiotropium (67.0%). Serious TEAEs occurred at similar rates in both treatment groups (glycopyrrolate, 12.3%; tiotropium, 10.5%). The most frequent TEAEs were COPD exacerbation/worsening and cough. Discontinuation due to TEAEs was higher in the

glycopyrrolate group (10.0%) than the tiotropium group (2.8%) and related, in part, to the open-label study design, prior use of long-acting muscarinic antagonists and aerosol-airway interactions. Fewer subjects in the glycopyrrolate group experienced MACE (glycopyrrolate, n = 3 [0.5%]; tiotropium, n = 8 [1.7%]). Nebulized glycopyrrolate treatment resulted in improvements in trough FEV₁ that were maintained over 48 weeks. Patient-reported health outcomes showed improvements, supporting the increases in trough FEV₁. Conclusions: Treatment with nebulized glycopyrrolate was well tolerated over 48 weeks with the most common adverse events being COPD worsening and cough. The overall and cardiac safety and tolerability profile and improvements in pulmonary function and patient-reported health outcomes support the use of nebulized glycopyrrolate as a maintenance treatment for moderate-to-very-severe COPD. Clinical trial registration number: NCT02276222. Copyright (C) 2017 The Authors.

Hsieh, M. J., et al. (2017). "Comparative efficacy and tolerability of beclomethasone/formoterol and fluticasone/salmeterol fixed combination in Taiwanese asthmatic patients." Journal of the Formosan Medical Association / Taiwan yi zhi(pagination).

Background: The study was designed to compare the efficacy and tolerability of a fixed combination of extra-fine beclomethasone and formoterol, with the fixed combination fluticasone and salmeterol in Taiwanese asthmatic patients. Methods: This was a phase III, multicentre, randomized, two-arm parallel groups, controlled study. Patients with moderate to severe asthma were randomized to a 12-week treatment with either beclomethasone 100 mcg plus formoterol 6 mcg (BDP/F) or fluticasone 125 mcg plus salmeterol 25 mcg (FP/S), both delivered 2 inhalations twice daily. The efficacy and tolerability of these two combinations were compared. Results: Among the 253 randomized subjects, 244 patients were evaluable (119 in the BDP/F group and 125 in the FP/S group). A significant improvement from baseline to the end of treatment period was observed in both BDP/F and FP/S groups in forced expiratory volume in the first second (FEV₁), forced vital capacity (FVC), morning and evening peak expiratory flow (PEF), Asthma Control Test (ACT) score and the use of rescue medication. FVC increase from pre-dose was significant after 5 min post inhalation in the BDP/F group only, while statistically significant within group improvement was not achieved until 30 min post inhalation in the FP/S group. Conclusions: The BDP/F combination is comparable in efficacy and tolerability to FP/S combination in Taiwanese asthmatic patients, with the advantage of rapid onset of improvement of FVC, consistent with the faster improvement of pulmonary hyperinflation with BDP/F. Copyright (C) 2017.

Kalberg, C., et al. (2016). "Dual Bronchodilator Therapy with Umeclidinium/Vilanterol Versus Tiotropium plus Indacaterol in Chronic Obstructive Pulmonary Disease: A Randomized Controlled Trial." Drugs in R & D **16**(2): 217-227.

INTRODUCTION: The fixed-dose, long-acting bronchodilator combination of umecclidinium/vilanterol (UMEC/VI) has not previously been compared with a combination of a long-acting muscarinic antagonist and long-acting beta2-agonist in patients with chronic obstructive pulmonary disease (COPD).

METHODS: This 12-week, randomized, blinded, triple-dummy, parallel-group, non-inferiority study compared once-daily UMEC/VI 62.5/25 mcg with once-daily tiotropium (TIO) 18 mcg + indacaterol (IND) 150 mcg in patients with moderate-to-very-severe COPD. The primary endpoint was the trough forced expiratory volume in 1 s (FEV1) on day 85 (predefined non-inferiority margin -50 mL), and the secondary endpoint was the 0- to 6-h weighted mean (WM) FEV1 on day 84. Other efficacy endpoints [including rescue medication use, the Transition Dyspnea Index (TDI) focal score, and the St. George's Respiratory Questionnaire (SGRQ) score] and safety endpoints [adverse events (AEs), vital signs, and COPD exacerbations] were also assessed.

RESULTS: Trough FEV1 improvements were comparable between treatment groups [least squares (LS) mean changes from baseline to day 85: UMEC/VI 172 mL; TIO + IND 171 mL; treatment difference 1 mL; 95 % confidence interval (CI) -29 to 30 mL], demonstrating non-inferiority between UMEC/VI and TIO + IND. The treatments produced similar improvements in the trough FEV1 at other study visits and the 0- to 6-h WM FEV1 (LS mean changes at day 84: UMEC/VI 235 mL; TIO + IND 258 mL; treatment difference -23 mL; 95 % CI -54 to 8 mL). The results for patient-reported measures (rescue medication use, TDI focal score, and SGRQ score) were comparable; both treatments produced clinically meaningful improvements in TDI and SGRQ scores. The incidence of AEs and COPD exacerbations, and changes in vital signs were similar for the two treatments.

CONCLUSION: UMEC/VI and TIO + IND, given once daily, provided similar improvements in lung function and patient-reported outcomes over 12 weeks in patients with COPD, with comparable tolerability and safety profiles.

TRIAL NUMBERS: ClinicalTrials.gov study ID NCT02257385; GSK study no. 116961.

Kerwin, E. M., et al. (2017). "Umeclidinium/vilanterol as step-up therapy from tiotropium in patients with moderate COPD: a randomized, parallel-group, 12-week study." International journal of chronic obstructive pulmonary disease **12**: 745-755.

METHODS: In this randomized, blinded, double-dummy, parallel-group study (NCT01899742), patients (N=494) who were prescribed TIO for ≥ 3 months at screening (forced expiratory volume in 1 s [FEV RESULTS: Compared with TIO, UMEC/VI produced greater improvements in trough FEV CONCLUSION: UMEC/VI step-up therapy provides clinical benefit over TIO monotherapy in patients with moderate COPD who are symptomatic on TIO alone. **INTRODUCTION:** Patients with COPD who remain symptomatic on long-acting bronchodilator monotherapy may benefit from step-up therapy to a long-acting bronchodilator combination. This study evaluated the efficacy

and safety of umeclidinium (UMEC)/vilanterol (VI) in patients with moderate COPD who remained symptomatic on tiotropium (TIO).

Lin, J., et al. (2017). "Comparison of fluticasone propionate with budesonide administered via nebulizer: a randomized controlled trial in patients with severe persistent asthma." Journal of Thoracic Disease **9**(2): 372-385.

Background: This study compared the efficacy and safety of fluticasone propionate (FP) inhalation solution with budesonide (BUD) suspension for inhalation administered via nebulizer, in Chinese adult patients with severe, persistent asthma. **Methods:** This was a multicenter, randomized, active-controlled, single-blind, parallel-group study, conducted at 26 clinical sites in China. Participants were randomized 1:1 to FP nebulizer 1 mg twice daily or BUD 2 mg twice daily via nebulizer for 12 weeks. **Results:** A total of 317 adult patients were randomized. The primary endpoint was mean change in morning peak expiratory flow (PEF) over weeks 1-12 from baseline, and analyzed in the ITT (n=315) and PP populations (n=283). Week 12 PEF increase from baseline was 26.7 L/min (14.1%) and 28.0 L/min (15.3%) in the ITT population, and 29.1 L/min (15.7%) and 30.1 L/min (16.2%) in the PP population, in the FP and BUD groups, respectively; all improvements were of clinical significance. Lower limits of the two-sided 95% CIs for the least squares (LS) mean treatment difference (FP minus BUD) were -12.19 L/min (ITT) and -12.95 L/min (PP), both above the pre-specified non-inferiority criteria -12.00 L/min and not clinically meaningful. There was no significant difference in the week 12 mean FEV1 increase between the FP and BUD groups (0.237 L/16.79% vs. 0.236 L/17.73%). Lower limits of the 95% CIs for LS mean treatment difference in morning PEF change from baseline over weeks 1-4 in a post hoc analysis were -10.41 and -11.96 L/min in the ITT and PP populations respectively; both above -12.00 L/min. A review of safety data indicated that rates of AEs, SAEs, and drug-related AEs were similar between two groups. **Conclusions:** The 12-week treatment of FP inhalation solution administered via nebulizer is safe and effectively for treating severe, persistent asthma in Chinese patients over 12 week. Copyright (C) Journal of Thoracic Disease. All rights reserved.

Lipson, D. A., et al. (2017). "FULFIL Trial: once-Daily Triple Therapy for Patients with Chronic Obstructive Pulmonary Disease." American Journal of Respiratory and Critical Care Medicine **196**(4): 438-446.

OBJECTIVES: We compared the effects of once-daily triple therapy on lung function and health-related quality of life with twice-daily ICS/LABA therapy in patients with COPD. **METHODS:** The FULFIL (Lung Function and Quality of Life Assessment in Chronic Obstructive Pulmonary Disease with Closed Triple Therapy) trial was a randomized, double-blind, double-dummy study comparing 24 weeks of once-daily triple therapy (fluticasone furoate/umeclidinium/vilanterol 100 [μg]/62.5 [μg]/25 [μg]; ELLIPTA

inhaler) with twice-daily ICS/LABA therapy (budesonide/formoterol 400 [mu]g/12 [mu]g; Turbuhaler). A patient subgroup remained on blinded treatment for up to 52 weeks. Co-primary endpoints were change from baseline in trough FEV MEASUREMENTS AND MAIN RESULTS: In the intent-to-treat population (n = 1,810) at Week 24 for triple therapy (n = 911) and ICS/LABA therapy (n = 899), mean changes from baseline in FEV CONCLUSIONS: These results support the benefits of single-inhaler triple therapy compared with ICS/LABA therapy in patients with advanced COPD. Clinical trial registered with www.clinicaltrials.gov (NCT02345161). RATIONALE: Randomized data comparing triple therapy with dual inhaled corticosteroid (ICS)/long-acting [beta]

Oliver, A. J., et al. (2016). "Randomized Trial of Once-Daily Fluticasone Furoate in Children with Inadequately Controlled Asthma." *Journal of pediatrics* **178**: 246-253.e242.

OBJECTIVE: To evaluate the dose-response, efficacy, and safety of fluticasone furoate (FF; 25micro g, 50micro g, and 100micro g), administered once daily in the evening during a 12-week treatment period to children with inadequately controlled asthma.

STUDY DESIGN: This was a Phase IIb, multicenter, stratified, randomized, double-blind, double-dummy, parallel-group, placebo- and active-controlled study in children aged 5-11 years with inadequately controlled asthma. The study comprised a 4-week run-in period, 12-week treatment period, and 1-week follow-up period. Children were randomized to receive either placebo once daily, fluticasone propionate (FP) 100micro g twice daily, FF 25micro g, FF 50micro g, or FF 100micro g each once daily in the evening. Primary endpoint was the mean change from baseline in daily morning peak expiratory flow (PEF) averaged over weeks 1-12. Adverse events (AEs) also were investigated.

RESULTS: In total, 593 children were included in the intent-to-treat population. The difference vs placebo in change from baseline daily morning PEF averaged over weeks 1-12 was statistically significant for the FF 25, FF 50, FF 100, and FP 100 groups (18.6L/min, 19.5L/min, 12.5L/min, and 14.0L/min, respectively; $P < .001$ for all). The incidence of AEs was greater in the FF groups (32%-36%) than in the placebo group (29%); the most frequent AE was cough.

CONCLUSION: FF and FP resulted in significant improvements in morning PEF compared with placebo, suggesting that they are effective treatments for children with inadequately controlled asthma. All treatments were well tolerated; no new safety concerns were identified.

TRIAL REGISTRATION: ClinicalTrials.gov:NCT01563029.

Papi, A., et al. (2018). "Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial." *Lancet* **391**(10125): 1076-1084.

Background: Evidence is scarce on the relative risk-benefit of inhaled triple therapy, consisting of inhaled corticosteroid, long-acting muscarinic antagonist, and long-acting beta₂-agonist, versus dual bronchodilation for chronic obstructive pulmonary disease (COPD). We aimed to compare a single-inhaler triple combination of beclometasone dipropionate, formoterol fumarate, and glycopyrronium (BDP/FF/G) versus a single-inhaler dual bronchodilator combination of indacaterol plus glycopyrronium (IND/GLY) in terms of the rate of moderate-to-severe COPD exacerbations over 52 weeks of treatment. Methods: This randomised, parallel-group, double-blind, double-dummy study was done at 187 sites across 17 countries. Eligible patients had symptomatic COPD, severe or very severe airflow limitation, at least one moderate or severe exacerbation in the previous year, and were receiving inhaled maintenance medication. After a 2 week run-in period with one inhalation per day of IND/GLY (85 mug/43 mug), patients were randomly assigned (1:1), via an interactive response technology system, to receive 52 weeks of treatment with two inhalations of extrafine BDP/FF/G (87 mug/5 mug/9 mug) twice per day or one inhalation of IND/GLY (85 mug/43 mug) per day. Randomisation was stratified by country and severity of airflow limitation. The primary endpoint was the rate of moderate-to-severe COPD exacerbations across 52 weeks of treatment in all randomised patients who received at least one dose of study drug and had at least one post-baseline efficacy assessment. Safety was assessed in all patients who received at least one dose of study drug. This study is registered with ClinicalTrials.gov, number NCT02579850. Findings: Between May, 29 2015, and July 10, 2017, 1532 patients received BDP/FF/G (n=764) or IND/GLY (n=768). Moderate-to-severe exacerbation rates were 0.50 per patient per year (95% CI 0.45-0.57) for BDP/FF/G and 0.59 per patient per year (0.53-0.67) for IND/GLY, giving a rate ratio of 0.848 (0.723-0.995, p=0.043) in favour of BDP/FF/G. Adverse events were reported by 490 (64%) of 764 patients receiving BDP/FF/G and 516 (67%) of 768 patients receiving IND/GLY. Pneumonia occurred in 28 (4%) patients receiving BDP/FF/G versus 27 (4%) patients receiving IND/GLY. One treatment-related serious adverse event occurred in each group: dysuria in a patient receiving BDP/FF/G and atrial fibrillation in a patient receiving IND/GLY. Interpretation: In patients with symptomatic COPD, severe or very severe airflow limitation, and an exacerbation history despite maintenance therapy, extrafine BDP/FF/G significantly reduced the rate of moderate-to-severe exacerbations compared with IND/GLY, without increasing the risk of pneumonia. Funding: Chiesi Farmaceutici. Copyright (C) 2018 Elsevier Ltd

Usmani, O. S., et al. (2017). "A Randomized Pragmatic Trial of Changing to and Stepping Down Fluticasone/Formoterol in Asthma." *The Journal of Allergy & Clinical Immunology in Practice* 5(5): 1378-1387.e1375.

BACKGROUND: Guidelines recommend reducing treatment in patients with well-controlled asthma after 3 months of stability. However, there is inadequate real-life data to guide physicians on therapy change in daily practice.

OBJECTIVE: To assess asthma control after change to and step-down of fluticasone propionate/formoterol fumarate dihydrate (FP/FOR) in real-life patients.

METHODS: In a randomized controlled, pragmatic, open-label trial, 225 well-controlled patients with asthma were randomized (1:2) to maintain high-dose fluticasone propionate/salmeterol xinafoate (FP/SAL, 1000/100 mug) or switch to FP/FOR (1000/40 mug) daily for 12 weeks (phase 1). One hundred sixteen patients stable on FP/FOR at week 12 were subsequently randomized (1:1) to maintain this therapy, or stepped down to FP/FOR (500/20 mug) daily for 12 weeks (phase 2). The primary end point was the 7-question Asthma Control Questionnaire (ACQ7) score.

RESULTS: In phase 1, FP/FOR (1000/40 mug) (n = 126) was noninferior to FP/SAL (1000/100 mug) (n = 73) for ACQ7 (difference in means, -0.12; 95% CI, -0.32 to 0.09). In phase 2, FP/FOR (500/20 mug) (n = 52) was noninferior to FP/FOR (1000/40 mug) (n = 52) for ACQ7 (difference in means, 0.01; 95% CI, -0.20 to 0.22). There was no significant difference in exacerbation rate between the groups in either phase. However, 1 to 2 exacerbations in 12 months before phase 1 were associated with the occurrence of an exacerbation after step-down (P = .007).

CONCLUSIONS: In patients with well-controlled asthma, a change from FP/SAL to FP/FOR did not compromise asthma control. Step-down of FP/FOR was well tolerated; however, in contrast to current guidelines, our data suggest caution in stepping down patients uncontrolled in the last 12 months. Larger step-down studies are required to confirm these findings.

Vestbo, J. et al. (2016). "Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomized controlled trial." *Lancet* **387**(10030): 1817-1826.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) often coexists with cardiovascular disease. Treatments for airflow limitation might improve survival and both respiratory and cardiovascular outcomes. The aim of this study was to assess whether inhaled treatment with a combined treatment of the corticosteroid, fluticasone furoate, and the long-acting β agonist, vilanterol could improve survival compared with placebo in patients with moderate COPD and heightened cardiovascular risk.

METHODS : In this double-blind randomised controlled trial (SUMMIT) done in 1368 centres in 43 countries, eligible patients were aged 40-80 years and had a post-bronchodilator forced expiratory volume in 1 s (FEV1) between 50% and 70% of the predicted value, a ratio of post-bronchodilator FEV1 to forced vital capacity (FVC) of 0.70 or less, a smoking history of at least 10 pack-years, and a score of 2 or greater on the modified Medical

Research Council dyspnoea scale. Patients had to have a history, or be at increased risk, of cardiovascular disease. Enrolled patients were randomly assigned (1:1:1:1) through a centralised randomisation service in permuted blocks to receive once daily inhaled placebo, fluticasone furoate (100 µg), vilanterol (25 µg), or the combination of fluticasone furoate (100 µg) and vilanterol (25 µg). The primary outcome was all-cause mortality, and secondary outcomes were on-treatment rate of decline in forced expiratory volume in 1 s (FEV1) and a composite of cardiovascular events. Safety analyses were performed on the safety population (all patients who took at least one dose of study drug) and efficacy analyses were performed on the intention-to-treat population (safety population minus sites excluded with Good Clinical Practice violations). This study is registered with ClinicalTrials.gov, number [NCT01313676](https://clinicaltrials.gov/ct2/show/study/NCT01313676).

FINDINGS: Between Jan 24, 2011, and March 12, 2014, 23 835 patients were screened, of whom 16 590 were randomised. 16 485 patients were included in the intention-to-treat efficacy population; 4111 in the placebo group, 4135 in the fluticasone furoate group, 4118 in the vilanterol group, and 4121 in the combination group. Compared with placebo, all-cause mortality was unaffected by combination therapy (hazard ratio [HR] 0.88 [95% CI 0.74-1.04]; 12% relative reduction; $p=0.137$) or the components (fluticasone furoate, HR 0.91 [0.77-1.08]; $p=0.284$; vilanterol, 0.96 [0.81-1.14]; $p=0.655$), and therefore secondary outcomes should be interpreted with caution. Rate of decline in FEV1 was reduced by combination therapy (38 mL per year [SE 2.4] vs 46 mL per year [2.5] for placebo, difference 8 mL per year [95% CI 1-15]) with similar findings for fluticasone furoate (difference 8 mL per year [95% CI 1-14]), but not vilanterol (difference -2 mL per year [95% CI -8 to 5]). Combination therapy had no effect on composite cardiovascular events (HR 0.93 [95% CI 0.75-1.14]) with similar findings for fluticasone furoate (0.90 [0.72-1.11]) and vilanterol (0.99 [0.80-1.22]). All treatments reduced the rate of moderate and severe exacerbation. No reported excess risks of pneumonia (5% in the placebo group, 6% in the combination group, 5% in the fluticasone furoate group, and 4% in the vilanterol group) or adverse cardiac events (17% in the placebo group, 18% in the combination group, and 17% in the fluticasone furoate group, and 17% in the vilanterol group) were noted in the treatment groups.

INTERPRETATION: In patients with moderate COPD and heightened cardiovascular risk, treatment with fluticasone furoate and vilanterol did not affect mortality or cardiovascular outcomes, reduced exacerbations, and was well tolerated. Fluticasone furoate, alone or in combination with vilanterol, seemed to reduce FEV1 decline.

FUNDING: GlaxoSmithKline.

Wedzicha, J. A., et al. (2016). "Indacaterol-Glycopyrronium versus Salmeterol-Fluticasone for COPD." *New England Journal of Medicine* **374**(23): 2222-2234.

BACKGROUND: Most guidelines recommend either a long-acting beta-agonist (LABA) plus an inhaled glucocorticoid or a long-acting muscarinic antagonist (LAMA) as the first-choice treatment for patients with chronic obstructive pulmonary disease (COPD) who have a high risk of exacerbations. The role of treatment with a LABA-LAMA regimen in these patients is unclear.

METHODS: We conducted a 52-week, randomized, double-blind, double-dummy, noninferiority trial. Patients who had COPD with a history of at least one exacerbation during the previous year were randomly assigned to receive, by inhalation, either the LABA indacaterol (110 mug) plus the LAMA glycopyrronium (50 mug) once daily or the LABA salmeterol (50 mug) plus the inhaled glucocorticoid fluticasone (500 mug) twice daily. The primary outcome was the annual rate of all COPD exacerbations.

RESULTS: A total of 1680 patients were assigned to the indacaterol-glycopyrronium group, and 1682 to the salmeterol-fluticasone group. Indacaterol-glycopyrronium showed not only noninferiority but also superiority to salmeterol-fluticasone in reducing the annual rate of all COPD exacerbations; the rate was 11% lower in the indacaterol-glycopyrronium group than in the salmeterol-fluticasone group (3.59 vs. 4.03; rate ratio, 0.89; 95% confidence interval [CI], 0.83 to 0.96; $P=0.003$). The indacaterol-glycopyrronium group had a longer time to the first exacerbation than did the salmeterol-fluticasone group (71 days [95% CI, 60 to 82] vs. 51 days [95% CI, 46 to 57]; hazard ratio, 0.84 [95% CI, 0.78 to 0.91], representing a 16% lower risk; $P<0.001$). The annual rate of moderate or severe exacerbations was lower in the indacaterol-glycopyrronium group than in the salmeterol-fluticasone group (0.98 vs. 1.19; rate ratio, 0.83; 95% CI, 0.75 to 0.91; $P<0.001$), and the time to the first moderate or severe exacerbation was longer in the indacaterol-glycopyrronium group than in the salmeterol-fluticasone group (hazard ratio, 0.78; 95% CI, 0.70 to 0.86; $P<0.001$), as was the time to the first severe exacerbation (hazard ratio, 0.81; 95% CI, 0.66 to 1.00; $P=0.046$). The effect of indacaterol-glycopyrronium versus salmeterol-fluticasone on the rate of COPD exacerbations was independent of the baseline blood eosinophil count. The incidence of adverse events and deaths was similar in the two groups. The incidence of pneumonia was 3.2% in the indacaterol-glycopyrronium group and 4.8% in the salmeterol-fluticasone group ($P=0.02$).

CONCLUSIONS: Indacaterol-glycopyrronium was more effective than salmeterol-fluticasone in preventing COPD exacerbations in patients with a history of exacerbation during the previous year. (Funded by Novartis; FLAME ClinicalTrials.gov number, NCT01782326.).