Drug Class Review

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

Preliminary Scan Report #1

June 2017

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OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant to assist with Participating Organizations’ consideration of allocating resources toward a full report update, a single drug addendum, or a summary review. Comprehensive review, quality assessment, and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report 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. Other important studies could exist.

Date of Last Update Report

Update #1: June 2016 (searches through November 2015)

Date of Last Preliminary Update Scan Report

None since most recent update report

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 with input from a statewide panel of experts (pharmacists, primary care clinicians, and representatives of the public). Subsequently, the key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The Participating Organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The Participating Organizations approved the following key questions to guide this review:

1. What is the comparative within-class and across-class efficacy and effectiveness 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 to 18 years) patients with persistent or chronic asthma.
- Adult patients with COPD (≥18 years).

**Interventions**

<table>
<thead>
<tr>
<th>Table 1. Included interventions</th>
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<tr>
<td><strong>Drug type</strong></td>
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<tr>
<td>Long-acting beta-2 agonists</td>
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<td>Fixed-dose combination products</td>
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<td>Leukotriene modifiers</td>
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<td>Drug type</td>
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<tr>
<td>Zafirlukast</td>
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<td>Phosphodiesterase-4 inhibitor</td>
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Abbreviations: DPI, dry powder inhaler; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonists; LAMA, long-acting muscarinic antagonists MDI, metered dose inhaler; SMI, soft mist inhaler.

* The LAMA category includes anticholinergic drugs as well as those specific for muscarinic receptors.

*b Note, the active ingredient is glycopyrronium. 15.6 mg of glycopyrrolate bromide = 12.5 mg glycopyrrolate.


The list of included drugs (above) is limited to formulations and brand names available in the United States, and in general we have included only studies of these drugs. In some cases however, we have included evidence from outside the United States, where we judge that a similar product is available here. For example, a fixed-dose product combining budesonide and formoterol in an MDI is available in the United States (Symbicort®), while in other countries the same combination is also available in a DPI (Symbicort® Turbohaler® or Turbuhaler®).

Budesonide and formoterol are each available individually via DPI in the United States and could be used to deliver the equivalent drug combination and doses; we have therefore included Turbuhaler® evidence in the most recent update report. Similarly, we have included doses that are available for use in the United States, and eliminated doses that are either not available or have been explicitly deemed unsafe or ineffective.

**Comparisons**
- Head-to-head.
- 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]), FDCP vs. components at same dose (A/B vs. A+B).

**Efficacy and Effectiveness 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.
- 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.

**Adverse Event 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**
- Efficacy/Effectiveness:
  - Randomized controlled clinical trials of at least 12 weeks duration and N≥100.
    - Head-to-head trials only (placebo-controlled trials excluded).
  - Recent comparative good-quality systematic reviews.
Search dates May 2014 or later.

- Adverse Events:
  - Randomized controlled clinical trials of at least 12 weeks duration and N≥100.
    - Head-to-head trials only.
  - Recent comparative good-quality systematic reviews.
    - Search dates May 2014 or later.
  - Observational studies of at least 6 months duration and N≥1,000.

Excluded:

- *Placebo-controlled trials, active controlled trials (included drug is compared with a non-placebo medication which is not an included drug), non-comparative observational studies, non-comparative systematic reviews.*

- *Studies that compare one class of drug against another without comparing the individual drug products will be excluded.*

**Setting**

- Enrolled in study as outpatients (will not exclude for prior hospitalization).
- *Excluded: patients studied while hospitalized or while having an acute asthma or COPD exacerbation.*

**METHODS**

**Literature Search**

To identify relevant citations, we searched Ovid MEDLINE® and Ovid MEDLINE® In-Process & Other Non-Indexed Citations from October 2015 through May 2017 using terms for specific included drugs and limits for English language and humans. Literature searches included any new drugs identified in the present scan in addition to those included in Table 1. We also searched the FDA website (http://www.fda.gov/medwatch/safety.htm) for identification of new drugs, new populations, and new serious harms (e.g., 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/), the VA Evidence-based Synthesis Program (http://www.hsrdrresearch.va.gov/publications/esp/reports.cfm), and University of York Centre for Reviews and Dissemination (http://www.york.ac.uk/inst/crd/crdreports.htm - “Our Publications” and “Our Databases”). All citations were imported into an electronic database (EndNote X7) and duplicate citations were removed.

**Study Selection**

We included only potentially relevant randomized controlled trials and comparative effectiveness reviews. One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.
RESULTS

New Drugs

Identified in this Preliminary Update Scan
No newly approved drugs in classes included in the last report.

Note: Three new biologic drugs have now been approved. These drugs are not currently within the scope of this report. We report them here for the participants understanding of the field. Medline searches for trials of these drugs yielded 2 citations of reslizumab, 14 citations of mepolizumab, and 108 citations of omalizumab.

Reslizumab (Cinqair®): interleukin-5 antagonist monoclonal antibody approved in injection form on 3/23/2016 and indicated for add-on maintenance treatment of patients with severe asthma ages 18 years and older, and with an eosinophilic phenotype.

Mepolizumab (Nucala®): interleukin-5 antagonist monoclonal antibody approved in injection form on 11/4/2015 and indicated for add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype.

Omalizumab (Xolair®): recombinant DNA-derived humanized IgG1κ monoclonal antibody approved in injection form on 6/20/2003 and indicated for adults and adolescents (≥12 years of age) with moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids.

Identified in previous Preliminary Update Scans
No scan since most recent update report

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

Identified in this Preliminary Update Scan
None identified.

Identified in previous Preliminary Update Scans
No scan since most recent update report

Comparative Effectiveness Reviews

Identified in this Preliminary Update Scan
We identified 1 ongoing potentially relevant comparative effectiveness review that could be used to answer specific pieces of an update report. The protocol of this review states that the review will compare inhaled corticosteroids, long-acting beta-2 agonists, and long-acting muscarinic antagonists as controller therapy, but does not appear to include all fixed-dose combination products or leukotriene modifiers. The key questions and inclusion criteria for this ongoing review are included in Appendix A. The date of completion for this report is unknown.

**Identified in previous Preliminary Update Scans**
No other scans since most recent update report

**Randomized Controlled Trials**

**Trials identified since the most recent Full Report**
Medline searches for this scan yielded 283 citations. Of those, 10 head-to-head trials were considered potentially relevant and includable in this scan. These included 5 drug versus drug trials (4 in patients with COPD) and 1 in patients with asthma-COPD overlap syndrome, and 5 device versus device trials (same drug) with 2 in patients with COPD and 3 in patients with asthma. Study durations of the head-to-head trials ranged from 12 weeks to approximately 2 years and sample sizes ranged from 16 to 17,135 participants. Additional study characteristics are listed in Tables 2 and 3, below. Please see Appendix B for abstracts.

**Table 2. New head-to-head trials (N=10)**

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Duration</th>
<th>Comparison</th>
<th>Population</th>
<th>Focus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wise, 2013</td>
<td>17,135</td>
<td>2.3 years</td>
<td>Tiotropium HandiHaler vs. tiotropium Respimat</td>
<td>COPD</td>
<td>Risk of death, first COPD exacerbation, cardiovascular safety</td>
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<tr>
<td>Dahl, 2015</td>
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<td></td>
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<td>Wise, 2015</td>
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<tr>
<td>TIOSPIR NCT01126437</td>
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<tr>
<td>Bouloukaki, 2016</td>
<td>200</td>
<td>6 months</td>
<td>Tiotropium soft mist inhaler vs. HandiHaler</td>
<td>COPD (mild-to-moderate)</td>
<td>Sleep quality</td>
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<tr>
<td>Srichana, 2016</td>
<td>36</td>
<td>3 months</td>
<td>Budesonide via DPI vs. pMDI</td>
<td>Asthma (mild-to-moderate)</td>
<td>Severity of symptoms, adverse events, frequency of rescue medication use</td>
</tr>
<tr>
<td>Virchow, 2016 NCT01803555</td>
<td>574</td>
<td>12 weeks</td>
<td>Budesonide/formoterol via Spiromax vs. Turbuhaler</td>
<td>Asthma (persistent; adults and adolescents &gt;12 years old)</td>
<td>Symptom-free and rescue-free 24-hour periods, adverse events</td>
</tr>
<tr>
<td>Amar, 2016 NCT02031640</td>
<td>NR</td>
<td>12 weeks</td>
<td>Beclomethasone dipropionate via breath-actuated vs. metered dose inhaler</td>
<td>Asthma (persistent)</td>
<td>Frequency of symptoms and rescue medication use, adverse events</td>
</tr>
<tr>
<td>Ishiura, 2015</td>
<td>16</td>
<td>12 weeks</td>
<td>Fluticasone furoate/vilanterol once-daily vs. fluticasone propionate/salmeterol twice-daily</td>
<td>Asthma-COPD overlap syndrome</td>
<td>COPD assessment test, asthma control test</td>
</tr>
<tr>
<td>Feldman, 2016</td>
<td>1,017</td>
<td>12 weeks</td>
<td>Umeclidinium vs. tiotropium</td>
<td>COPD</td>
<td>Patient reported outcomes from Transition Dyspnea Index, St. George’s Respiratory Questionnaire, and COPD Assessment Test; adverse events</td>
</tr>
</tbody>
</table>
### SUMMARY

Since the last update report on this topic, we have identified no newly approved drugs, serious harms (boxed warnings), or completed comparative effectiveness reviews. We have identified the protocol for 1 ongoing comparative effectiveness review by the Agency for Healthcare Research and Quality, which will compare inhaled corticosteroids, long-acting beta-2 agonists, and long-acting muscarinic antagonists as controller therapy. The publication date for this review is unknown.

We have identified 10 head-to-head trials published since the last DERP report, of which, 5 compared head-to-head delivery methods, while 5 evaluated head-to-head drug comparisons. Of these, 4 represent comparisons that were not included in the last report update.
APPENDIX A. ONGOING POTENTIALLY RELEVANT COMPARATIVE EFFECTIVENESS REVIEW


Key Question 1a: What is the comparative effectiveness of intermittent ICS compared to no treatment, pharmacologic or non-pharmacologic therapy in children 0 to 4 years old with recurrent wheezing?

Key Question 1b: What is the comparative effectiveness of intermittent ICS compared to ICS controller therapy in patients 5 years of age and older with persistent asthma?

Key Question 1c: What is the comparative effectiveness of ICS with LABA used as both controller and quick relief therapy compared to ICS with or without LABA used as controller therapy in patients 5 years of age and older with persistent asthma?

Key Question 2a: What is the comparative effectiveness of LAMA as add on to ICS controller therapy compared to placebo or increased ICS dose in patients 12 years of age and older with uncontrolled, persistent asthma?

Key Question 2b: What is the comparative effectiveness of LAMA compared to other controller therapy as add on to ICS in patients 12 years of age and older with uncontrolled, persistent asthma?

Key Question 2c: What is the comparative effectiveness of LAMA as add on to ICS plus LABA compared to ICS plus LABA as controller therapy in patients 12 years of age and older with uncontrolled, persistent asthma?

For the above KQs, the following PICOTS criteria apply:

Populations
We will include all patients that meet the KQ specific criteria regardless of gender, race and ethnicity.
• KQ1a: Children 0 to 4 years of age with recurrent wheezing
• KQ1b-c: Patients 5 years of age and older with persistent asthma
• KQ2a-c: Patients 12 years of age and older with uncontrolled, persistent asthma

Interventions
This review is focused on pharmacologic interventions within the following classes of inhaled medications: ICS, LABA, and LAMA (Table 1). In addition, some of the pharmacologic interventions include more than one class of medications, in which case one drug from each of the specified classes is combined. Medications were selected if used for asthma management (regardless of FDA approval).
The interventions for each of the KQs is as follows:
• KQ1a-b: Intermittent ICS dosing
• KQ1c: ICS+LABA used as controller and quick relief therapy
• KQ2a-b: ICS+LAMA as controller therapy
• KQ2c: ICS+LABA+LAMA as controller therapy

Table 2 demonstrates the interventions and comparators for each KQ in a tabular format. The definitions of “intermittent”, “controller therapy” and “quick relief therapy” are provided above as well as section VI. Definitions of Terms.

Comparators
We are interested in direct comparisons of therapies as described per KQ. Table 2 demonstrates the intervention and comparator for each KQ in a tabular format. The definition of “controller therapy” is provided above as well as in section VI. Definition of Terms.
• KQ1a: No treatment (placebo or control) OR pharmacologic therapy which includes controller therapy or as needed SABA OR non-pharmacologic therapy. Controller therapies include ICS, inhaled LABA, leukotriene modifiers, cromolyn, methylxanthines, immunomodulators, and systemic corticosteroids. Nonpharmacologic treatment is as per EPR-3 (e.g., avoiding environmental triggers)
• KQ1b: ICS controller therapy • KQ1c: ICS controller therapy OR ICS+LABA controller therapy
• KQ2a: ICS controller therapy, with or without placebo, where the ICS dose is the same or increased relative to the intervention arm dose.
• KQ2b: ICS+another controller therapy, including LABA, leukotriene modifiers, cromolyn, methylxanthines, immunomodulators and systemic corticosteroids.
• KQ2c: ICS+LABA controller therapy

Similar to the interventions, some of the pharmacologic comparators include more than one class of medications, in which case one drug from each of the specified classes is combined. Medications were selected if used for asthma management (regardless of FDA approval).

Outcomes
Within the construct of the outcomes listed, we will include outcomes that fall within one of the listed categories below, using the definitions provided by each study.
• Asthma Control
  o Composite Measures
    - Asthma Control Test (ACT)
    - Asthma Control Questionnaire (ACQ)
  o Spirometry including FEV1, FVC, FEV1/FVC
• Asthma exacerbations
• Asthma-specific quality of life
  o Asthma Quality of Life Questionnaire (AQLQ)
  o Pediatric Asthma Quality of Life Questionnaire (PAQLQ)
  o Pediatric Asthma Caregivers Asthma Quality of Life Questionnaire (PACQLQ)
• Death, all-cause and asthma-specific
• Healthcare utilization
  o Asthma-related hospitalizations, emergency department visits, urgent care visits, outpatient visits
  o Additional asthma-medication use/need (e.g. need for rescue inhaler)
  o Additional resource use related to intervention (personnel time, equipment)

Timing
We will have no minimum study duration or length of follow-up.

Setting
We will have no requirements with respects to study setting.
APPENDIX B. POTENTIALLY RELEVANT NEW TRIALS


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.


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.


OBJECTIVES: This post hoc analysis of TIOtropium Safety and Performance In Respimat (TIOSPIR) evaluated safety and exacerbation efficacy in patients with stable (>2 months) use of tiotropium HandiHaler 18 micro g (HH18) prior to study entry, to evaluate whether there was a difference in risk for patients who switched from HH18 to tiotropium Respimat 2.5 micro g (R2.5) or 5 g (R5).

SETTING: TIOSPIR (n=17,135) was an international, Phase IIIb/IV, randomised, double-blind, parallel-group, event-driven trial.

PARTICIPANTS: Patients from TIOSPIR with chronic obstructive pulmonary disease (COPD) and postbronchodilator ratio of forced expiratory volume in 1 s to forced vital capacity < 0.70, receiving HH18 before study entry, were analysed (n=2784).

INTERVENTIONS: Patients were randomised to once-daily tiotropium R2.5 (n=914), R5 (n=918) or HH18 (n=952) for 2-3 years.

Primary and secondary outcome measures:

PRIMARY OUTCOMES: time to death (safety) and time to first COPD exacerbation (efficacy).

SECONDARY OUTCOMES: number of exacerbations and time to first major adverse cardiovascular event (MACE).

RESULTS: Baseline characteristics were similar in all groups. Respimat had a similar mortality risk versus HH18 (vital status follow-up, HR; 95% CI R2.5: 0.87; 0.64 to 1.17; R5: 0.79; 0.58 to 1.07) with no significant differences in the risk and rates of exacerbations and severe exacerbations across treatment groups. Risk of MACE and fatal MACE was similar for Respimat versus HH18 (HR; 95% CI MACE R2.5: 0.73; 0.47 to 1.15; R5: 0.69; 0.44 to 1.08; fatal MACE R2.5: 0.57; 0.27 to 1.19; R5: 0.67; 0.33 to 1.34). Overall risk of a fatal event (on treatment) was lower for R5 versus HH18 (HR; 95% CI R2.5: 0.78; 0.55 to 1.09; R5: 0.62; 0.43 to 0.89).

CONCLUSIONS: This analysis indicates that it is safe to switch patients from tiotropium HandiHaler to tiotropium Respimat, and that the efficacy is maintained over the switch.

TRIAL REGISTRATION NUMBER: NCT01126437; Post-results.

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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.


BACKGROUND: Asthma-chronic obstructive pulmonary disease overlap syndrome (ACOS) is important because patients with ACOS have significantly worse outcomes compared with those with asthma or chronic obstructive pulmonary disease (COPD) alone. Inhaled corticosteroids (ICS), together with a long-acting beta2 agonist (LABA), are recommended, but no therapeutic studies for ACOS have been conducted. Recently, fluticasone furoate/vilanterole (FF/VI) has been approved as the first once-daily ICS/LABA combination therapy for asthma and COPD.

METHODS: A 12-week, randomized, open-label cross-over study was conducted in 16 patients with ACOS to compare the effectiveness of once-daily FF/VI 200/25 mug vs. twice-daily fluticasone propionate/salmeterol (FP/SAL) 500/50 mug. The study period included a 4-week run-in, the first 4-week treatment, and the second 4-week treatment. Respiratory functions, including forced expiratory volume in 1 s (FEV1) and respiratory impedance using the forced oscillation technique (FOT), were measured, as was fractional exhaled
nitric oxide (FeNO). A COPD assessment test (CAT) scores and asthma control test (ACT) scores were recorded 0, 4, and 8 weeks after randomization.

RESULTS: The mean values for the FEV1 were 1.33 (+/-0.29) L in the run-in period, 1.38 (+/-0.39) L after the FP/SAL treatment period, and 1.47 (+/-0.38) L after the FF/VI treatment period. The FEV1 value after the FF/VI treatment was significantly greater than the value after the run-in period (p < 0.01). FOT parameters, FeNO levels, CAT scores, ACT scores, and other blood tests were not significantly different during the run-in period, the FP/SAL treatment period, and the FF/VI treatment period.

CONCLUSIONS: FF/VI, the first once-daily ICS/LABA, can provide substantial improvement in lung functions, indicating that FF/VI should be considered for the regular treatment of ACOS.


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.

INTRODUCTION: The treatment of COPD (Chronic Obstructive Pulmonary Disease) aims to improve the patient's well-being and to reduce mortality, morbidity and the development of exacerbations. This study was thus designed to compare the efficacy and tolerability of salmeterol/fluticasone combination with tiotropium in patients with moderate COPD.

MATERIALS AND METHODS: This was an open, prospective, randomized trial in COPD patients whose FEV1 (forced expiratory volume in 1 second) levels were between 80% and 50% predicted. A total of 44 patients who met the inclusion and exclusion criteria and who gave written informed consent were included in the study. At the end of the two-week wash-out period, the patients were randomized to receive either salmeterol 50 micro g/fluticasone 500 micro g combination as dry powder inhaler twice daily (SF Group) or tiotropium dry powder inhaler 18 micro g once daily (T Group) for one year. These were equally distributed in the two groups (22 patients in each study group). At follow-up, the patients were required to come to the outpatient clinic at the third, sixth, ninth and twelfth months.

RESULT: There were no statistically significant difference between the two groups with regards to demographic features and baseline measurements. There were 1.2 +/- 1.7 exacerbations in SF Group and 2.1 +/- 2.2 exacerbations in T Group (p= 0.070). The time to the first exacerbation was 4.2 +/- 4.0 and 4.2 +/- 3.3 months, respectively (p= 0.697). The number of severe exacerbations that resulted in admission to the emergency department or hospital was 0.6 +/- 1.0 and 1.1 +/- 1.4, respectively (p= 0.245).

Significant improvements were observed in CAT (CPOD Assessment Test) scores in both groups during the treatment period (p< 0.0001); but there was no difference between the two groups.

CONCLUSIONS: This study has shown that in patients with moderate COPD, treatment with combined corticosteroid and long-acting beta-2 agonist provides similar improvements in pulmonary function tests, patient-reported outcomes and exercise capacity as compared a long-acting anticholinergics.


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 Aeronee 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+/-0.2μm for Pulmicort Turbuhaler and 2.2+/-0.2μm 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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BACKGROUND: Budesonide and formoterol (BF) Spiromax is a dry powder inhaler designed to deliver BF with maximum ease of use for patients with asthma or chronic obstructive pulmonary disease.

METHODS: A phase 3b, 12-week, multicenter, double-blind, double-dummy, randomized, controlled trial in patients (>12 years) with persistent asthma.

PRIMARY OBJECTIVE: to demonstrate non-inferiority of twice-daily BF Spiromax 160/4.5 mcg to BF Turbuhaler 200/6 mcg in change from baseline to week 12 in morning peak expiratory flow (PEF). Secondary endpoints included: Patient Satisfaction and Preference Questionnaire scores, change from baseline to week 12 in evening PEF, trough forced expiratory volume in one second, percentage of symptom-free and rescue-free 24-hour periods, and safety.

RESULTS: The analysis was based on the per-protocol population (BF Spiromax, n=290; BF Turbuhaler, n=284). The least squares mean change from baseline to week 12 in morning PEF was: BF Spiromax, 18.8 L/min and BF Turbuhaler, 21.8 L/min. Non-inferiority of BF Spiromax vs BF Turbuhaler was demonstrated (the lower limit of the 95% two-sided confidence interval was -9.02 L/min, which is greater than -15 L/min [the criteria specified for non-inferiority]). The mean difference in the total performance domains scores for BF Spiromax vs BF Turbuhaler were 0.248 at baseline and 0.353 at week 12 (both, p <0.001), indicating statistical superiority for BF Spiromax. No statistical or numerical differences were recorded in the total convenience domain score between the two devices. Scores for 'device preference' and 'willingness to continue' supported BF Spiromax at baseline and at week 12 (p=0.0005 vs BF Turbuhaler). No significant between-group differences were observed in the other secondary efficacy endpoints. Both treatments were well tolerated, with no significant differences in adverse events or asthma exacerbations.

CONCLUSIONS: This study demonstrates the non-inferiority of BF Spiromax vs BF Turbuhaler in patients (>12 years) with asthma. More patients preferred the Spiromax device over Turbuhaler for its performance, and were willing to continue therapy with BF Spiromax beyond the 12-week study period.

TRIAL REGISTRATION: NCT01803555; February 28, 2013.

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 μg) plus the LAMA glycopyrronium (50 μg) once daily or the LABA salmeterol (50 μg) plus the inhaled glucocorticoid fluticasone (500 μg) 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.).


BACKGROUND: Patients with chronic obstructive pulmonary disease (COPD) who were naive to anticholinergics before the TIOtropium Safety and Performance In Respimat (TIOSPIR) trial may reflect patients seen in practice, in particular in primary care. In addition, investigating safety in these patients avoids the potential bias in patients who previously received anticholinergics and may be tolerant of their effects.
AIMS: The aim of this study was to evaluate whether patients naive to anticholinergic therapy who were treated with tiotropium Respimat 2.5 or 5mug had different safety and efficacy outcomes than patients treated with tiotropium HandiHaler 18mug.

METHODS: A post hoc analysis of patients who were not receiving anticholinergics before TIOSPIR (N=6,966/17,135) was conducted. Primary end points were risk of death from any cause and risk of COPD exacerbation. Secondary outcomes included severe exacerbation and major adverse cardiovascular events (MACE). Additional analysis of exacerbations was carried out in anticholinergic-naive patients with moderate (GOLD II) disease.

RESULTS: Anticholinergic-naive patients had less severe disease than the total TIOSPIR population. Discontinuations because of anticholinergic side effects were infrequent (0.9% overall). Similar to the primary study, patients in the tiotropium Respimat groups had no difference in the risk of death or risk of any or severe exacerbation than patients treated with tiotropium HandiHaler. Risk of MACE was similar across the Respimat and HandiHaler groups. Rates of exacerbations in the subgroup of patients with moderate disease were similar across the Respimat and HandiHaler groups.

CONCLUSIONS: Tiotropium Respimat and HandiHaler have similar safety and efficacy profiles in patients who are naive to anticholinergic therapy.