Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

**Search Strategy**

Two information scientists jointly searched the external databases, MEDLINE, EMBASE, and an internal AstraZeneca product literature database, Planet, for randomised controlled trials comparing budesonide with or without formoterol against placebo or formoterol alone in patients with chronic obstructive pulmonary disease (COPD) which was defined by a clinical diagnosis COPD or current or former smoker [≥10 pack-years] plus a forced expiratory volume in 1s (FEV$_1$) to forced vital capacity (FVC) ratio <0.7. The content in Planet is obtained from a variety of sources, including RCS (Thomson Reuters) and commercial databases licensed to AstraZeneca (e.g. MEDLINE, Current Contents, BIOSIS, EMBASE) as well as from internal AstraZeneca sources (up to Dec. 31, 2008) to identify any potentially relevant articles. The content in Planet within the respiratory field can be accessed via the medical database section using http://www.az-air.com/. The search included Medical Subject Headings and free text terms for COPD (study population); use of budesonide and/or Pulmicort or budesonide and formoterol and/or Symbicort (study intervention); and placebo or formoterol controlled (including Oxis and Foradil) double-blind studies (study design). There were no language or date restrictions.

Two reviewers (US, AT) independently screened the studies for inclusion, retrieved potentially relevant studies, and determined study eligibility, and included only those studies that enrolled adults with COPD (as defined by clinical diagnosis of COPD or as current or former smokers [≥10 pack-years] and an FEV$_1$ to FVC ratio <0.7). Trials enrolling patients with asthma or evidence of reversibility by standard bronchodilator testing were excluded. Additional inclusion criteria were: double-bind studies comparing budesonide or budesonide and formoterol with placebo or formoterol alone and studies
that were of at least 6 months’ duration, as the possibility of evaluating a relationship between pneumonia events and ICS therapy is limited in trials of shorter duration. Using this strategy, seven trials were identified and their patient-level data were obtained and analysed.
Supplement Figure 1. A Summary of Study Flow and Selection

183 articles identified by initial search

160 excluded based on review of title and abstract
- 61: Not controlled double-blind clinical trial with budesonide and placebo/non-ICS as comparator
- 13: No participants with COPD
- 48: Duplicate
- 38: Study duration < 6 months

23 full text retrieved and screened for detailed evaluation

16 excluded based on detailed evaluation
- 6: Not controlled double-blind clinical trial with budesonide and placebo/non-ICS as comparator
- 4: Duplicate
- 1: Study duration < 6 months
- 5: Did not include information on pneumonia AE

7 included in analysis

AE, adverse event; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid
**Definition of serious adverse event**

A serious adverse event is an adverse event occurring during any study phase (i.e. run-in, treatment, follow-up) and at any dose of the investigational product, comparator, or placebo, which fulfils one or more of the following criteria: 1) results in death; 2) is immediately life-threatening; 3) requires in-subject hospitalisation or prolongs an existing hospitalisation; 4) results in persistent or significant disability or incapacity; or congenital abnormality/birth defect; 5) is an important medical event that may jeopardise the subject; or 6) may require medical intervention to prevent one of the outcomes listed above.
**Definition of pneumonia**

Pneumonia for the present analysis was defined as any adverse event (serious or non-serious) coded according to the Medical Dictionary for Regulatory Activities (MedDRA; version 9) preferred terms “pneumonia”, “bronchopneumonia”, “lobar pneumonia”, “lung infection”, “pneumonia staphylococcal”, or “pneumonia pneumococcal”. A patient reporting at least one adverse event of one or more of the MedDRA terms listed above were identified as having pneumonia adverse event (i.e. multiple occurrence of either term regardless of seriousness, or coexistence of two or more pneumonia terms, counts as one patient with pneumonia adverse event).
Definitions of post-treatment events for the individual studies

The methodology for collecting adverse events (including serious adverse event) after last dose (post-treatment adverse event) has varied over time for the studies included in this analysis. For the older studies (Pauwels and colleagues,17 Bourbeau and colleagues,16 and Vestbo and colleagues6), no specific handling of post-treatment adverse events was applied, and in Pauwel’s study,17 the protocol stated that events occurring 15 days or more after last dose were not to be considered adverse events. From these studies, any adverse event (e.g. headache, tremor, pneumonia, etc.) occurring between day 1 and day 15 after last dose were treated as on-treatment adverse events and included as such in the adverse event tables for on-treatment adverse events in the study reports and associated publications where relevant. In the dry powder inhaler studies,12, 13, any adverse event reported from day 1 after last dose and onwards was reported at the discretion of the investigator, which mainly but not solely captured serious adverse events. In these studies patients with post-treatment adverse events have a post-treatment period (of individual length) following the active treatment period recorded in the study database, while patients with no post-treatment adverse events have no recorded post-treatment period. The post-treatment events are readily identifiable in the study database, but have been presented as adverse events together with the on-treatment adverse events in the adverse event tables in the study reports and associated publications. The pressurised metered dose inhaler (pMDI) studies14, 15 used a different approach. In these studies all patients were to be contacted via telephone 4 weeks after last dose. Therefore all patients have a post-treatment period and a higher reporting rate of all types of adverse events during this
period because of the active reporting, compared with the less solicited approach used in the other trials.

Some patients experienced fever and/or worsening of chronic obstructive pulmonary disease and therefore discontinued the study. A few days later pneumonia was diagnosed. Such patients have been included and counted as a patient with pneumonia event in this analysis. In order to stick to a worst-case approach we defined the duration of the post-treatment period as 15 days and censored our main analysis at this time point. The choice of 15 days as the cut-off is based on an assessment of the current knowledge of the duration of the pharmacodynamic effects of glucocorticoids, particularly with respect to regulation of transcription factors involved in pro- and/or anti-inflammatory properties, and on the well-known natural history of pneumonia induced by relevant bacterial species. Based on the methodology for reporting post-treatment events used in the individual studies almost all relevant “on-treatment +15 days” pneumonia serious adverse events and most pneumonia adverse events will be captured. As part of the sensitivity analysis, adverse events reported after day 15 and onwards have also been identified and named post-study adverse events in this paper. These events originate solely from the two pMDI studies.\textsuperscript{14,15}
Supplement Figure 2. Monthly Breakdown of Pneumonia Adverse Events in the Budesonide Trials (Exclusive of Tashkin et al’s Study15)

Only 12 month trials were included in the analysis.

As countries in the southern hemisphere have an “inverted” calendar pattern to their seasonality, the calendar year for these countries has been standardised to countries in the northern hemisphere.

% Of Total Pneumonia AE

Adjusted Calendar Month

AE, adverse event
**Supplement Table 1:** The occurrence of pneumonia as adverse event or serious adverse event in the individual trials during the full duration of the study

<table>
<thead>
<tr>
<th>Study</th>
<th>No. on ICS</th>
<th>No. not on ICS</th>
<th>No. with pneumonia AE on ICS</th>
<th>No. with pneumonia AE in controls</th>
<th>No. with pneumonia SAE on ICS</th>
<th>No. with pneumonia SAE in controls</th>
<th>No. who prematurely discontinued ICS</th>
<th>No. who prematurely discontinued in controls</th>
<th>Person-years on ICS</th>
<th>Person-years in controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Szafranski et al.(^{12})</td>
<td>406</td>
<td>406</td>
<td>20 (4·9)</td>
<td>15 (3·7)</td>
<td>9 (2·2)</td>
<td>10 (2·5)</td>
<td>121 (29.8)</td>
<td>154 (37.9)</td>
<td>328·58</td>
<td>306·97</td>
</tr>
<tr>
<td>Calverley et al.(^{13})</td>
<td>511</td>
<td>511</td>
<td>15 (2·9)</td>
<td>9 (1·8)</td>
<td>9 (1·8)</td>
<td>7 (1·4)</td>
<td>176 (34.4)</td>
<td>217 (42.5)</td>
<td>388·15</td>
<td>346·81</td>
</tr>
<tr>
<td>Rennard et al.(^{14})</td>
<td>988</td>
<td>976</td>
<td>41 (4·1)</td>
<td>44 (4·5)</td>
<td>18 (1·8)</td>
<td>21 (2·2)</td>
<td>277 (28.0)</td>
<td>332 (34.0)</td>
<td>817·24</td>
<td>746·60</td>
</tr>
<tr>
<td>Tashkin et al.(^{15})</td>
<td>1120</td>
<td>584</td>
<td>24 (2·1)</td>
<td>11 (1·9)</td>
<td>12 (1·1)</td>
<td>6 (1·0)</td>
<td>188 (16.8)</td>
<td>138 (23.6)</td>
<td>506·84</td>
<td>246·47</td>
</tr>
<tr>
<td>Bourbeau et al.(^{16})</td>
<td>38</td>
<td>37</td>
<td>3 (7·9)</td>
<td>4 (10·8)</td>
<td>2 (5·3)</td>
<td>4 (10·8)</td>
<td>12 (31.6)</td>
<td>17 (45.6)</td>
<td>30·16</td>
<td>26·55</td>
</tr>
<tr>
<td>Pauwels et al.(^{17})</td>
<td>593</td>
<td>582</td>
<td>33 (5·6)</td>
<td>16 (2·7)</td>
<td>8 (1·3)</td>
<td>3 (0·5)</td>
<td>135 (22.8)</td>
<td>128 (22.0)</td>
<td>1501·99</td>
<td>1505·44</td>
</tr>
<tr>
<td>Vestbo et al.(^{6})</td>
<td>145</td>
<td>145</td>
<td>16 (11)</td>
<td>24 (17)</td>
<td>0 (0)</td>
<td>1 (0·7)</td>
<td>36 (24.8)</td>
<td>51 (35.2)</td>
<td>360·72</td>
<td>325·04</td>
</tr>
</tbody>
</table>

**Summary total** | **3801** | **3241** | **152 (4·0)** | **123 (3·8)** | **58 (1·5)** | **52 (1·6)** | **945 (24·9)** | **1037 (32·0)** | **3933·68** | **3503·88** |

AE, adverse event; ICS, inhaled corticosteroid; SAE, serious adverse event
Supplement Figure 3. The Adjusted Relationship Between FEV$_1$ % Predicted and Pneumonia as Adverse Event or Serious Adverse Event

a. AE (Adverse Event)  
b. SAE (Serious Adverse Event)
The relative hazard functions were generated using a Cox proportional hazards model in which age, gender, smoking status, and body-mass index were included as covariates.

The hazard ratios can be calculated from this figure by determining the hazard function at a particular FEV₁ % predicted value (e.g. 40%) and dividing it by the hazard function of the reference value (e.g. 80% of predicted). In this example, the HR for adverse event would be ~1.87 and HR for serious adverse event would be ~3.5.
### Supplement Table 2: Sensitivity Analyses

1. Analysis was repeated (as the main analysis) following exclusion of Vestbo’s trial\(^6\) because it did not use a smoking history of 10 pack-years or greater as part of the inclusion criteria. The results of this sensitivity analysis was that the hazard ratio (HR) for pneumonia adverse event was 1.13 (95% CI, 0.86 to 1.49) and for pneumonia serious adverse event was 0.93 (95% CI, 0.86 to 1.38).

2. Analysis was repeated (as the main analysis) following the exclusion of Tashkin’s trial (which was a 6 month study)\(^15\) to mitigate the effects of differential follow-up period. The results of this sensitivity analysis was that the HR for pneumonia adverse event was 1.13 (95% CI, 0.78 to 1.39) and for pneumonia SAE was 0.93 (95% CI, 0.63 to 1.38).

3. Analysis was repeated (as the main analysis) following the exclusion of Calverley’s trial,\(^13\) which had a run-in phase wherein all patients were treated with oral prednisolone (30 mg/d) for 2 weeks to mitigate the effects of oral corticosteroid carry-over effect. The results of this sensitivity analysis was that the HR for pneumonia AE was 1.00 (95% CI, 0.75 to 1.32) and for pneumonia serious adverse event was 0.86 (95% CI, 0.56 to 1.31).

4. HR comparing the effects of budesonide against those of either placebo or formoterol on the risk of pneumonia adverse events or serious adverse events.

Data are shown as HR (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>adverse event</th>
<th>p</th>
<th>serious adverse event</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budesonide vs placebo</td>
<td>0.97 (0.71 to 1.31)</td>
<td>0.827</td>
<td>0.93 (0.58 to 1.48)</td>
<td>0.755</td>
</tr>
<tr>
<td>Budesonide vs formoterol</td>
<td>1.20 (0.82 to 1.77)</td>
<td>0.353</td>
<td>0.86 (0.52 to 1.44)</td>
<td>0.577</td>
</tr>
<tr>
<td>Formoterol vs placebo</td>
<td>0.80 (0.51 to 1.25)</td>
<td>0.319</td>
<td>0.99 (0.55 to 1.79)</td>
<td>0.980</td>
</tr>
</tbody>
</table>

5. The effect of budesonide on the risk of pneumonia adverse events or serious adverse events stratified based on daily dose.

Controls were either formoterol or placebo and the data are shown as HR (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>adverse event</th>
<th>p</th>
<th>serious adverse event</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>320 µg/d vs control*</td>
<td>1.09 (0.63 to 1.90)</td>
<td>0.760</td>
<td>0.80 (0.35 to 1.82)</td>
<td>0.589</td>
</tr>
<tr>
<td>640 µg /d vs control*</td>
<td>1.19 (0.87 to 1.63)</td>
<td>0.287</td>
<td>1.07 (0.67 to 1.71)</td>
<td>0.789</td>
</tr>
<tr>
<td>1280 µg /d vs control*</td>
<td>0.79 (0.12 to 5.17)</td>
<td>0.807</td>
<td>0.79 (0.12 to 5.17)</td>
<td>0.807</td>
</tr>
</tbody>
</table>

*By convention, there are two ways of expressing the daily dose of inhaled products: either as a metered dose or a delivered dose, which is defined as the amount of drug leaving a mouthpiece of an inhaler. There are slight differences in the doses depending on which metric is used. For instance, the delivered dose of 18µg of formoterol corresponds to a metered dose of 24µg and the delivered dose of 320, 640, and 1280µg of budesonide
is equivalent to metered doses of 400, 800, and 1600µg, respectively. For parsimony, in the present study, we have expressed the daily dosage using delivered dose.