### Evidence Table 15. Pharmacologic Therapy: Bronchodilators—Safety of Long-Acting Beta₂-Agonists

**Abbreviations used in table:**
- **AE**: adverse event
- **AG**: adrenoceptor agonists
- **AQLQ**: Asthma Quality of Life Questionnaire
- **AUC**: area under the curve
- **COPD**: chronic obstructive pulmonary disease
- **DAE**: discontinuation due to adverse event
- **DPI**: dry powder inhaler
- **ED**: emergency department
- **FEF<sub>25%-75%</sub>**: forced expiratory flow between 25% and 75% of vital capacity
- **FEV<sub>1</sub>**: forced expiratory volume in 1 sec.
- **FVC**: forced vital capacity
- **ICS**: inhaled corticosteroid
- **IGCS**: inhaled glucocorticosteroid
- **ITT**: intent-to-treat
- **LABA**: long-acting beta₂-agonists
- **MDI**: metered-dose inhaled
- **OCS**: oral corticosteroid
- **PEF**: peak expiratory flow
- **RR**: relative risk
- **SABA**: short-acting beta-agonist
- **SAE**: serious adverse event

* indicates primary outcome
### Evidence Table 15. Pharmacologic Therapy: Bronchodilators—Safety of Long-Acting Beta2-Agonists

<table>
<thead>
<tr>
<th>Citation (Sponsor)</th>
<th>Study Design</th>
<th>Purpose/ Objective</th>
<th>Study N (Number/ Evaluate d)</th>
<th>Population Characteristic s</th>
<th>Asthma Severity at Baseline (if Reported)</th>
<th>Treatment</th>
<th>Dose</th>
<th>Duration of Active Treatment; Duration of PlaceboIntervention/Off-Treatment Followup</th>
<th>Lung Function</th>
<th>Vital Signs/ Cardiovascular/ Clinical Laboratory Values</th>
<th>Exacerbations/ Symptoms</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipworth et al.</td>
<td>Randomized placebo-controlled crossover study</td>
<td>To compare the effects of regular treatment with inhaled formoterol or oral zafirlukast on bronchial hyperresponsiveness and on airway inflammation in patients who were homozygous for the glycine-16 allele and who were already being treated with inhaled corticosteroids</td>
<td>24 (24)</td>
<td>Age 19-66 yr, mean = 39 yr Gender 37% male, 63% female</td>
<td>Mild-to-moderate asthma Homozygous for glycine-16 allele and being treated with ICS FEV1, % pred. mean = 76</td>
<td>Formoterol fumarate with placebo tablets twice daily</td>
<td>12 mcg</td>
<td>5 weeks (each treatment 1 week with 1-week wash out between treatments) after 1-week run-in period</td>
<td>No difference in geometric mean methacholine provocative doses between formoterol (1.9-fold) and zafirlukast (1.5-fold) groups after 1 week of treatment Compared with placebo, zafirlukast produced 1.7-fold difference in geometric mean exhaled nitric oxide (p &lt; 0.05), and formoterol produced a 1.2-fold difference (p &gt; 0.05). In difference between formoterol and zafirlukast in improvement in PEF</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Bensch et al.</td>
<td>Multicenter, randomized, double-blind, placebo-controlled study comparing formoterol dry powder inhaler with albuterol metered-dose inhaler. Ann Allergy Asthma Immunol 2001;86(1):19-27.</td>
<td>To evaluate the doses of formoterol administered via the Aerolizer inhaler in parallel, group study (25 clinical sites in the United States)</td>
<td>541 (458 completed, 535 in efficacy analysis, 541 in ITT analysis)</td>
<td>Age &gt;12 yr, mean = 35.5 yr Gender 41% male, 59% female Ethnicity 88% Caucasian, 6% Black, 7% Other</td>
<td>Mild-to-moderate persistent asthma Duration of asthma mean = 18.9 yr 51% ICS 17% maintenance theophylline FEV1, % pred. mean = 66</td>
<td>Formoterol (F-12) (n=136)</td>
<td>12 mcg twice daily via Aerolizer</td>
<td>12 weeks after 2-week single-blind, placebo lead-in period</td>
<td>No clinically significant changes in mean blood pressure or pulse rate Clinical laboratory test results indicated no clinically significant mean changes and no significant differences among the groups.</td>
<td>Greater percentage of symptom-free treatment days for F-12 (62%) and F-24 (59%) vs. placebo (33%), p &lt;0.001. Albuterol and placebo groups differed (p=0.008). Percentage of days without nocturnal awakenings greater for F-12 (72%) and F-24 (59%) vs. placebo (33%), p &lt;0.001. Albuterol and placebo groups differed (p=0.008).</td>
<td>No difference in AE reported: 68% of F-12, 76% of F-24, 70% of albuterol, and 71% of placebo groups. 3 withdrew from F-12, 6 from F-24, 5 from albuterol, and 6 from placebo for asthma-related AE.</td>
<td></td>
</tr>
</tbody>
</table>
### Citation (Sponsor)


### Study Design

One retrospective chart review and two prospective observational studies.

### Purpose/ Objective

To describe clinical features and cardiac function among patients with bronchial asthma during long-term oral beta-2-agonist and long-term oral beta-2-agonist.

### Study N (Number Evaluable)

#### Study 1: Retrospective, 143 patients
- **Study 2:** Prospective, 45 of the 143 patients
- **Study 3:** 11 of the 45 in a withdrawal study

### Population Characteristics

**Study 1: Age**
- **mean = 54 yr**

**Study 2: Age**
- **mean = 47 yr**
  - **Gender**
    - **51% male, 49% female**

**Study 3: Age**
- **mean = 55 yr**
  - **Gender**
    - **51% male, 49% female**

### Asthma Severity at Baseline (if Reported)

#### Study 1 Chart Review:
- **Study 1:** Prescribed theophylline for 61 patients, 58 (96%) of 61 patients received oral beta-2-agonists.

#### Study 2:
- **Study 2:** Prescribed theophylline for 44 patients, 41 (93%) of 44 patients received oral beta-2-agonists.

#### Study 3:
- **Study 3:** Prescribed theophylline for 29 patients, 27 (93%) of 29 patients received oral beta-2-agonists.

### Treatment

**Study 1 Chart Review:**
- **Study 1:** 74 cases treated with oral beta-2-agonists and 69 without oral beta-2-agonists.

**Study 2:**
- **Study 2:** 26/74 cases treated with oral beta-2-agonists.

**Study 3:**
- **Study 3:** 22/69 without oral beta-2-agonists.

### Dose

**Study 1:**
- **Study 1:** FEV1 % pred. mean ± SD: 64 ± 11 L:
  - **Study 1:** 3.1

**Study 2:**
- **Study 2:** FEV1 % pred. mean ± SD: 75 ± 12 L:
  - **Study 2:** 3.3

**Study 3:**
- **Study 3:** Inhaled beta-2-agonists: 21 healthy volunteers.

### Duration of Active Treatment: Duration of Postintervention/Def-Treatment Followup

**Study 1:**
- **Study 1:** 2-week washout in group 1 than in group 3 (control).

**Study 2:**
- **Study 2:** 2-week washout in group 1 than in group 3 (control).

**Study 3:**
- **Study 3:** 2-week washout in group 1 than in group 3 (control).

### Lung Function

**Study 1:**
- **Study 1:** FEV1 significantly lower in group 1 than in group 3 (control).

**Study 2:**
- **Study 2:** FEV1 significantly lower in group 1 than in group 3 (control).

**Study 3:**
- **Study 3:** FEV1 significantly lower in group 1 than in group 3 (control).

### Vital Signs/ Cardiovascular/ Clinical Laboratory Values

- **Study 1:** No difference in mean arterial pressure between those with and without oral beta-2-agonists.

### Exacerbations/ Symptoms

- **Study 1:** No incidence of nonfatal heart failure associated with oral beta-2-agonists.

### Safety

- **Study 1:** Incidence of nonfatal heart failure associated with oral beta-2-agonists.


### Surveillance cohort study (general practice patients in England)

To determine age- and gender-specific asthma death rates in patients prescribed the LABAs salmeterol and bimatoprost.

#### Prescribed Salmeterol (n=15,400)
- **Age**
  - **Median = 55 yr**
  - **Gender**
    - **51% male, 49% female**

#### Prescribed Salmeterol (n=15,400)
- **Age**
  - **Median = 60 yr**
  - **Gender**
    - **55% male, 45% female**

#### Prescribed Bimatoprost (n=8,098)
- **Age**
  - **Median = 60 yr**
  - **Gender**
    - **55% male, 45% female**

### At least 1 prescription between December 1990 and May 1991

### In the cohorts combined, the death rate was 2.33 (95% CI 1.84 to 2.84) per 10,000 patient-months of observation: 2.40 (95% CI 1.74 to 3.46) for males and 3.08 (95% CI 2.21 to 3.98) for females per 10,000 patient-months of observation. Rate ratio 0.78, p<0.18. Rates highest for those 60-69 and 80-89 yr.
To examine the systemic effects of single and chronic doses of salbutamol 100 mcg were allowed. Inhaled formoterol dry powder in children with persistent asthma. Ann Allergy Asthma Immunol 2002;89(2): 180–190. (Novartis)

**Study Design**
- Multicenter randomized, double-blind, reference-controlled parallel groups trial (42 centers in 5 countries)

**Population Characteristics**
- **Age**: >18 yr, mean = 47 yr
- **Gender**: 40% male, 60% female
- **Ethnicity**: Not reported

**Study N (Number Evaluable)**: 357 (ITT analysis)

**Treatment**
- **Arm 1**: Formoterol (n=176; 146 completed)
  - Formoterol 9 mcg bid + budesonide 4.5 mcg as needed
  - 12 weeks after single-blind 2-week run-in during which all patients received formoterol 9 mcg bid and terbutaline 0.5 mg as needed

- **Arm 2**: Terbutaline (n=181; 150 completed)
  - Terbutaline 0.5 mg bid + terbutaline 0.5 mg as needed

**Dose**
- Formoterol
  - 9 mcg bid + budesonide 4.5 mcg as needed
- Terbutaline
  - 0.5 mg bid + terbutaline 0.5 mg as needed

**Duration of Active Treatment; Duration of Postintervention/Differential Treatment Followup**
- Morning and evening PEF did not change in either group from run-in period. No difference between groups in development of tolerance

**Lung Function**
- *Mean changes in serum potassium level, pulse rate, systolic and diastolic blood pressure, and PR interval did not differ between groups. Terbutaline group had greater increases in cardiac frequency (2.6 beats/min, p=0.03). Cardiac frequency-adjusted QTc did not differ between groups (p=0.82). No changes in mean hematology or clinical chemistry laboratory values for either reliever*

**Vital Signs/ Cardiovascular/ Clinical Laboratory Values**
- *Mean serum potassium level, pulse rate, systolic and diastolic blood pressure, and PR interval did not differ between groups. Mean reduction in daytime reliever use (0.21 inhalations/day) compared with terbutaline group (not significant). Nocturnal reliever use did not differ between groups. Severe exacerbation for 34 in formoterol group and 39 in terbutaline group*

**Safety**
- Formoterol group decreased reliever use by 0.21 inhalations/day compared with terbutaline group (not significant)
- 7 SAE in formoterol group and 1 in terbutaline. Only 1 in formoterol group possibly related to study drug.

**Study N (Number Evaluable)**: 296 (Evaluable)

**Characteristics**
- Percent smokers: 35.7% ex-smokers, 64.3% nonsmokers
- Mean age: 21–59 yr, mean = 39.6 yr
- Gender: 57% female, 43% male

**Ethnicity**
- 60% female
- 40% male

**Duration of asthma**
- 52 yr, = 21.7 yr

**Duration of active treatment**
- 4 weeks between test days

**Baseline (if Reported)**
- *Mean serum potassium level, pulse rate, systolic and diastolic blood pressure, and PR interval did not differ between groups. No clinically relevant differences between active treatments*

**Study N (Number Evaluable)**: 14 (randomized, double-blind, double-dummy, cross-over, placebo-controlled study)


**Study Design**
- Randomized, double-blind, double-dummy, cross-over, placebo-controlled study

**Population Characteristics**
- **Age**: 21–59 yr, mean = 39.6 yr
- **Gender**: 43% male, 57% female
- **Smoking**: 64.3% nonsmokers, 35.7% ex-smokers

**Study N (Number Evaluable)**: 14

**Treatment**
- **Arm 1**: Budesonide/formoterol
  - 1.600/45 mcg
  - Up to 12 weeks (1–4 weeks between test days)
  - No received maintenance dose of budesonide/formoterol 1800/45 mcg twice daily
  - *Mean serum potassium levels remained within normal range for all treatments. Changes in serum potassium, pulse rate, blood pressure, QTc, blood glucose, and plasma lactate with budesonide/formoterol vs. placebo were significant but not clinically meaningful. No clinically relevant differences between active treatments*

- **Arm 2**: Formoterol
  - 45 mcg

- **Arm 3**: Placebo

**Duration of Active Treatment; Duration of Postintervention/Differential Treatment Followup**
- AE similar after each treatment and generally mild. No SAE reported.
### Boonsawat et al.  

#### Purpose/ Objective
To compare the efficacy and safety of maximum recommended dose of formoterol with predicted equivalent dose of salbutamol in patients presenting to an ER with acute severe bronchospasm.

#### Study Design
Multicenter, randomized, double-blind, double-dummy, parallel-groups study (5 emergency departments in Thailand).

#### Study N (Number Evaluable)
86 (84: ITT analysis)

#### Population Characteristics
- **Age**: 18–67 yr; mean = 44 yr
- **Gender**: 27% male, 73% female
- **Ethnicity**: Not reported

#### Study N (Number Included)
S1: 12
S2: 20
S3: 13
S4: 12
S5: 9

#### Study 1: Formoterol DPI
- **Treatment**: Formoterol via Turbulhaler (n=44; 42 completed)
- **Dose**: 18 mcg at 0, 30 and 60 min (54 mcg)
- **Duration of Active Treatment**: 4 hours
- **Lung Function**: No difference in heart rate or QTc

#### Study 2: Salbutamol via MDI (n=44)
- **Dose**: 800 mcg at 0, 30 and 60 min (2400 mcg)
- **Duration of Active Treatment**: 4 hours
- **Lung Function**: No difference in heart rate or QTc

#### Study 3: Formoterol or albuterol via MDI
- **Study 3**: Formoterol or albuterol via MDI
- **Study 4**: Formoterol, albuterol, fenoterol, or placebo by MDI
- **Study 5**: Formoterol or albuterol

#### Study 4: Formoterol or albuterol
- **Study 1**: Formoterol via DPI
- **Study 2**: Single dose of formoterol or placebo
- **Study 3**: Formoterol or albuterol via MDI
- **Study 4**: Formoterol, albuterol, fenoterol, or placebo by MDI
- **Study 5**: Formoterol or albuterol

#### Study 5: Escalating doses formoterol (6, 18, 54 mcg) or albuterol (100, 300, 900 mcg)
- **Study 1**: Single dose with measurements for 48 hours
- **Study 2**: Single dose with measurements for 9 hours
- **Study 3**: Doses increased at 1 hour intervals up to 6 hours, cross over after 2 days washout
- **Study 4**: 5 doses at 30 min intervals; cross over to each of other treatments after 3–7 days washout
- **Study 5**: 2 study days separated by at least 1 week

#### Safety
- Adjusted mean minimum serum potassium was lower in formoterol than in salbutamol group (3.2 vs. 3.5 mmol/L, p = 0.001).
- Adjusted mean average serum potassium was lower with formoterol than salbutamol (p = 0.002).
- No differences in decrease in systolic and diastolic blood pressure.
- No difference in heart rate or QTc.
- Average effect was 43% in salbutamol group (p = 0.05).
- Adjusted mean increase at all time points.

#### Exacerbations/ Symptoms
- Difference in subjective symptom score (3.04) was not significant between groups.
- Mean Acute AQLQ score increased from 2.67 to 5.88 for formoterol group and from 2.49 to 5.69 for salbutamol group (p < 0.05).

#### Adverse Effects
- Ten patients reported a total of 13 mild AEs.

---


#### Review Article
- **Study 1**: 1 open-label, non-comparative study (S1); 1 placebo-controlled, dose-escalation study (S2); and 3 comparative studies (S3–S5)

#### Study 1: Formoterol (OXIS) Turbulhaler as rescue therapy compared with salbutamol in patients with acute severe asthma.

#### Study Design
- **Study N (Number Evaluable)**: 84; ITT
- **Population Characteristics**: 76 men, 4 women
- **Age**: 29 yr; 8 men, 4 women
- **Duration of Active Treatment**: 4 hours
- **Lung Function**: No difference in heart rate or QTc

#### Study 2: Formoterol (OXIS) Turbulhaler as rescue therapy compared with salbutamol in patients with acute severe asthma.

#### Study Design
- **Study N (Number Evaluable)**: 84; ITT
- **Population Characteristics**: 76 men, 4 women
- **Age**: 47.2 yr; 12 men, 1 woman
- **Duration of Active Treatment**: 4 hours
- **Lung Function**: No difference in heart rate or QTc

#### Study 3: Formoterol or albuterol via MDI
- **Study 1**: 120 mcg
- **Study 2**: 112, 24, 48, or 96 mcg
- **Study 3**: Daily doses of 12–228 mcg formoterol or 200–3800 mcg albuterol
- **Study 4**: Formoterol 400 mcg, or fenoterol 400 mcg
- **Study 5**: Escalating doses formoterol (6, 18, 54 mcg) or albuterol (100, 300, 900 mcg)

#### Study 4: Formoterol or albuterol via MDI
- **Study 1**: 120 mcg
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- Adjusted mean minimum serum potassium was lower in formoterol than in salbutamol group (3.2 vs. 3.5 mmol/L, p = 0.001).
- Adjusted mean average serum potassium was lower with formoterol than salbutamol (p = 0.002).
- No differences in decrease in systolic and diastolic blood pressure.
- No difference in heart rate or QTc.

#### Adverse Effects
- Ten patients reported a total of 13 mild AEs.
### Citation (Sponsor)


**Study Design**
- Multicenter, open, randomized, parallel-group study 
  - 1,139 centers in 24 countries
- To assess the safety and effectiveness of formoterol as reliever medication, compared with salbutamol in people with asthma over a wide age range with different degrees of asthma severity and receiving a variety of other maintenance medications
- (16,935 completed study; ITT analysis for 17,862)
- Age: 4–91 yr, mean 39 yr
- Ethnicity: 76% Caucasian, 10% Oriental, 8% other
- Gender: 43% male, 57% female
- Severity judged by medication level: Intermittent, 16% Mild, 35% Moderate, 35% Severe, 15%
- Leukotriene modifiers, 13% xanthines/oral bêta-agonists, 4% oral OCS, 10% others
- 71% Caucasian, 18% African-American, 8% Hispanic, 3% other
- Clinical diagnosis of asthma: Currently taking asthma medications
- Lung Function: Baseline (if reported)

### Population Characteristics

- Arm 1: Formoterol via Turbuhaler® (n=9,064; 8,260 completed)
- Arm 2: Salbutamol via pMDI or equivalent (n=9,060; 8,413 completed)
- Age: 4–91 yr, mean 39 yr
- Ethnicity: 76% Caucasian, 10% Oriental, 8% other
- Gender: 43% male, 57% female
- Severity judged by medication level: Intermittent, 16% Mild, 35% Moderate, 35% Severe, 15%
- Leukotriene modifiers, 13% xanthines/oral bêta-agonists, 4% oral OCS, 10% others
- 71% Caucasian, 18% African-American, 8% Hispanic, 3% other
- Clinical diagnosis of asthma: Currently taking asthma medications
- Lung Function: Baseline (if reported)

### Study N (Number Evaluable)
- 18,124

### Purpose/ Objective
- To compare the safety and effectiveness of formoterol as reliever medication, compared with salbutamol in people with asthma over a wide age range with different degrees of asthma severity and receiving a variety of other maintenance medications

### Analysis}
- To compare safety and effectiveness of formoterol as reliever medication, compared with salbutamol in people with asthma over a wide age range with different degrees of asthma severity and receiving a variety of other maintenance medications
- To compare safety and effectiveness of formoterol as reliever medication, compared with salbutamol in people with asthma over a wide age range with different degrees of asthma severity and receiving a variety of other maintenance medications

### Data
- Data collected at 4-week intervals for 28 weeks.
- All continued usual asthma therapy.

### Exacerbations/ Symptoms

- Fewer in formoterol (28.6%) experienced exacerbation vs. salbutamol (32.4%).
- Time to first exacerbation longer in formoterol vs. salbutamol, with 14% reduction in relative risk (p<0.001) and 12% reduction for first severe exacerbation (p<0.0013).
- Patients in each age group and each level of baseline asthma medication had longer times to first exacerbation with formoterol compared with salbutamol.
- Significant reduction in percent of days with symptoms for formoterol vs. salbutamol (p<0.03)

### Safety

- *AE for 42% of each group. Fewer asthma-related AE in formoterol (12.3%) than salbutamol (13.5%), p=0.018.
- *No difference in number of asthma-related SAE: formoterol 1.2% vs. salbutamol 1.4%, p=0.39
- *More DAE and asthma-related DAE in formoterol (2.4% & 1.0%) vs. salbutamol (1.3% & 0.5%), p<0.001

### Study Design

- Multicenter, open, randomized, parallel-group study
- To assess the safety and effectiveness of formoterol as reliever medication, compared with salbutamol in people with asthma over a wide age range with different degrees of asthma severity and receiving a variety of other maintenance medications
- 1,139 centers in 24 countries
- To assess the safety and effectiveness of formoterol as reliever medication, compared with salbutamol in people with asthma over a wide age range with different degrees of asthma severity and receiving a variety of other maintenance medications
- 1,139 centers in 24 countries

### Variables

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose</th>
<th>Duration of Active Treatment</th>
<th>Duration of Postintervention/Off Treatment Followup</th>
<th>Lung Function</th>
<th>Vital Signs/Values</th>
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<tbody>
<tr>
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<td></td>
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<tr>
<td>Arm 2</td>
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</tbody>
</table>

### Notes

- *RR based on Life Table Analysis
- *The relative risk for the overall incidence of primary safety outcome events (combined respiratory-related death or life-threatening experience) in Arm 1 relative to Arm 2 was 1.40 (95% CI 0.91–2.14).
- Relative risk of respiratory-related death (2.16, 95% CI 1.05–4.41), asthma-related death (RR 4.37, 95% CI 1.25–15.34), and combined asthma-related death or life-threatening experiences (RR 1.71 95% CI 1.01–2.89) were higher in Arm 1 relative to Arm 2.
- In African-American subpopulation, the RR for combined respiratory-related death or life-threatening experiences (RR 4.10 95% CI 1.54–10.90), combined all cause death or life-threatening experiences (RR 2.17, 95% CI 1.06–4.41), and asthma-related death or life-threatening experiences (RR 4.92, 95% CI 1.68–14.45) were higher for Arm 1 relative to Arm 2.

### Adherence

- 4.5 mcg per dose as needed
- 200 mcg per dose as needed

### Other

- Formoterol via Turbuhaler®
- Salbutamol via pMDI or equivalent

### Characteristics

- Age: 4–91 yr, mean 39 yr
- Ethnicity: 76% Caucasian, 10% Oriental, 8% other
- Gender: 43% male, 57% female
- Severity judged by medication level: Intermittent, 16% Mild, 35% Moderate, 35% Severe, 15%
- Leukotriene modifiers, 13% xanthines/oral bêta-agonists, 4% oral OCS, 10% others
- 71% Caucasian, 18% African-American, 8% Hispanic, 3% other
- Clinical diagnosis of asthma: Currently taking asthma medications
- Lung Function: Baseline (if reported)

### Analysis

- To compare the safety and effectiveness of formoterol as reliever medication, compared with salbutamol in people with asthma over a wide age range with different degrees of asthma severity and receiving a variety of other maintenance medications
- To compare the safety and effectiveness of formoterol as reliever medication, compared with salbutamol in people with asthma over a wide age range with different degrees of asthma severity and receiving a variety of other maintenance medications
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### Notes

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<td>von Berg et al.</td>
<td>Multicenter, randomized, double-blind, placebo-controlled study (32 centers in 5 countries in Europe)</td>
<td>To investigate the efficacy and tolerability of formoterol Turbuhaler in children. In J Clin Pract 2003;57(10): 852–856.</td>
<td>248 (ITT analysis)</td>
<td>Age 6–17 yr, mean = 11.1 yr</td>
<td>Asthma severity</td>
<td>Formoterol 50 mcg (n=83); 77 completed</td>
<td>9 mcg twice daily</td>
<td>12 weeks after 2-week run-in</td>
<td>Turbutaline 0.025 mg used as relief medication. Normal anti-inflammatory medication or immunotherapy continued throughout the study. No other asthma medication permitted.</td>
<td>*Increase in morning PEF over 12 weeks was greater for formoterol 9 mcg vs. placebo (13.01 L/min; p&lt;0.02); no difference for formoterol 4.5 mcg vs. placebo (11.1 L/min; p=0.051). Average FEV1 over 12 weeks was higher in formoterol 4.5 mcg (5.2%) and 9 mcg (0.7%) than placebo (p&lt;0.05). Mean FEV1 reversibility was greater in placebo from a lower treatment baseline: 9.9% and 9.7% in formoterol 4.5 mcg and 9 mcg vs. 15.1% in placebo.</td>
<td>Decrease in symptom scores were not different between groups. Formoterol groups reduced daytime use of terbutaline during study (p&lt;0.04). Formoterol 9 mcg dose reduced number of nocturnal inhalations (p=0.02) and number of awakenings due to asthma (p=0.04 vs. placebo).</td>
<td>Total of 107 AEs during placebo vs. 84 and 104 in formoterol 4.5 and 9 mcg twice daily. Most mild or moderate. Nine SAE: 3 in formoterol 4.5 mcg, 5 in formoterol 9 mcg, and 1 in placebo; none were related to study drug.</td>
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<td>Pohunek et al.</td>
<td>Multicenter, single-dose randomized, double-blind, double-dummy, placebo-controlled, cross-over study</td>
<td>To compare the efficacy of single doses of formoterol (Oxis) Turbuhaler compared with salmeterol Diskhaler in children with asthma. Pediatr Allergy Immunol 2004;15(1):32–39. (AstraZeneca, Lund, Sweden)</td>
<td>68 (64 completed)</td>
<td>Age 7–17 yr, mean = 11.9 yr</td>
<td>Asthma severity</td>
<td>Formoterol 4.5 mcg (n=48)</td>
<td>9 mcg</td>
<td>12-hour study period</td>
<td>Measurements at 32, 10, 20, 30 min and 1, 2–4, 6, 8, 10, and 12 hours after drug administration.</td>
<td>*All treatments had better effects than placebo in average 12-hour serial FEV1, mean, FEF75, at 12 hours, and maximal FEF, for 12-hour period Formoterol 4.5 mcg and salmeterol did not differ on efficacy parameters. Improvement in effect was dose-related for formoterol 9, 18, and 36 mcg vs. salmeterol. Formoterol at doses 9, 18, and 36 mcg provided better effects for 7–12 year olds than salmeterol (p&lt;0.05) with relatively steep dose-response curve. Less steep dose-response effect for 13–17 year olds with 36 mcg significant vs. 4.5–18 mcg doses (p=0.05). Formoterol dose corresponding to salmeterol 50 mcg for efficacy estimated to be 2.6–3.3 mcg.</td>
<td>Dose-dependent effects for formoterol on pulse, heart rate, and QTc. Salmeterol 50 mcg was estimated to correspond to 7.8–13.5 mcg delivered dose of formoterol.</td>
<td>AE was generally mild or moderate with no difference between treatments.</td>
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**Study N:** Number of participants in the study. **ITT:** Intention-to-treat. **AE:** Adverse event. **ITT analysis:** Analysis of data from all participants who received at least one dose of the study medication, regardless of whether they completed the study. **FEV1:** Forced expiratory volume in one second. **ICS:** Inhaled corticosteroids. **PEF:** Peak expiratory flow. **Pulse:** Heart rate. **QTc:** Corrected QT interval.
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<th>Asthma Severity at Baseline (if Reported)</th>
<th>Treatment</th>
<th>Dose</th>
<th>Duration of Active Treatment; Duration of Postintervention/Off-Treatment Followup</th>
<th>Lung Function</th>
<th>Vital Signs/ Cardiovascular/ Clinical Laboratory Values</th>
<th>Exacerbations/ Symptoms</th>
<th>Safety</th>
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<tbody>
<tr>
<td>Salpeter et al. Cardiovascular effects of beta-agonists in patients with asthma and COPD: a meta-analysis. Chest 2004;125(6): 2309–2321.</td>
<td>Meta-analysis of 33 randomized placebo-controlled trials</td>
<td>To evaluate the cardiovascular effects of beta-agonist use in patients with asthma or chronic obstructive pulmonary disease (COPD)</td>
<td>13 single-dose trials with 232 participants; 20 longer duration trials with 6,623 participants</td>
<td>Single dose trials: Mean age = 56.6 yr. Longer duration trials: Mean age = 52.2 yr.</td>
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<td>*Single dose of beta-agonist increased heart rate by 9.12 beats/min (95% CI 5.32–12.92) compared to placebo. Relative risk for sinus tachycardia was 3.06 (95% CI 1.72–5.50).</td>
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<tr>
<td>Kruse et al. Safety and tolerability of high-dose formoterol (Aerolizer) and salbutamol (pMDI) in patients with mild/moderate, persistent asthma. Plum Pharmacol Ther 2005; 18(3):229–234.</td>
<td>Randomized, double-blind, double-dummy, active-comparator controlled, two-period cross-over study</td>
<td>To compare the safety and tolerability of high-dose formoterol and salbutamol over a 3-day period in patients with asthma, specifically to confirm that there is an acceptable safety margin for formoterol at high doses that may be taken by patients suffering from worsening asthma symptoms over several days</td>
<td>16 (16)</td>
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<thead>
<tr>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Not reported</th>
<th>Weight</th>
<th>FEV1</th>
<th>FEV1/FVC</th>
<th>QTc Interval</th>
<th>Blood glucose</th>
<th>Serum potassium</th>
<th>QTc</th>
<th>ECG</th>
<th>Safety</th>
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<tr>
<td>21–49 yr, mean = 32 yr</td>
<td>81% male, 19% female</td>
<td>Not reported</td>
<td>Weight 78–102 kg, mean = 75.6 kg</td>
<td>Mid (82.6%) or moderate (122.5%) persistent asthma FEV1, 2.04–4.48 L, mean = 3.36 L FEV1/FVC, % pred, 78–102, mean = 89.6 QTc interval, 352–440 ms, mean = 399 ms Serum potassium, 3.96–5.22 mmol/L, mean = 4.51 mmol/L Blood glucose, 3.68–5.22 mmol/L, mean = 4.84 mmol/L</td>
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Patients randomly assigned to treatment sequence; n=16

| Arm 1 (F) Formoterol Arm 2 (S) Salbutamol (n=16) | 36 mcg (dry powder for inhalation) via Aerolizer® 3 times daily at 5-hour intervals 600 mcg via pressurized MDI 3 times daily at 5-hour intervals | 3 consecutive days with 3-7 day washout period between drugs; 21-day screening period | Similar peak FEV1 values for F and S (p=0.613) F vs. S had higher mean AUC of FEV1 over 72-hour period (302.2 L vs. 277.4 L, p =0.001). Higher mean 24-hour AUC FEV1 for F vs. S for each day (102.3 vs. 93.9 L for 0–24 hours; 101.6 vs. 91.5 L for 24–48 hours; 98.3 vs. 92.1 L for 48–72 hours; at p =0.01) | | | | | | | | |
| Plasma potassium concentration means during F vs. S were 3.4 and 3.6 mmol/L, p <0.001. Mean AUC for 72-hour period was lower during F vs. S (284.3 vs. 296.6 mmol/L, p =0.001). Difference between F and S during 0–24 hours was 90.8 vs. 96.6 mmol/L, p =0.001; and 24–48 hours was 93.3 vs. 97.9 mmol/L, p <0.001, with no difference for 48–73 hour period (p=0.13). Mean AUC for blood glucose over 72 hours was higher for F than S (421.2 vs. 410.8 mmol/L, p=0.009), with only difference in 0–24 hour period (147.6 vs. 139.9 mmol/L, p=0.001). QTc was greater for F vs. S over 72 hours (p <0.001), with maximum values higher for F vs. S (428.8 vs. 417.4 ms, p <0.001). | | | | | | | | |

47 mild AEs and 2 moderate AEs: 23 reports (8 patients) with F and 26 reports (9 patients) with S. No SAE reported.
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<td>Nelson et al. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest 2006;2(8):15–26 (SMART trial)</td>
<td>Randomized, double-blind, placebo-controlled, observational study (8,163 sites in the United States; 1,316 investigators randomized subjects into trial)</td>
<td>To compare the safety of salmeterol inhalate or placebo added to usual asthma care</td>
<td>26,355 (26,355 TT)</td>
<td>Age 12–100 yr; mean = 39.1 yr Gender 36% male, 64% female Ethnicity 71% Caucasian, 18% African-American, 6% Hispanic, 1% Asian, 2% other</td>
<td>Diagnosis of asthma Mean duration of asthma = 16.3 yr Currently receiving prescription asthma medication No previous use of inhaled LABAs PEF mean = 355.3 L/min PEF % pred. mean = 83.9 in previous 12 months: 26% asthma ED visits, 8% hospitalization, 61% weekly symptoms of nocturnal asthma ICS use: 47% overall, 49% of Caucasians, and 38% of African-Americans</td>
<td>Arm 1 (B) Salmeterol via MDI (n=13,176)</td>
<td>42 mcg twice daily</td>
<td>28 weeks Single clinic visit when subjects were given a 28-week supply of study medication, instructed on proper use of MDI, and instructed to continue use of current asthma medications. Study medications to be taken approximately 12 hours apart, and a new inhaler to be used every 4 weeks. Subjects contacted every 4 weeks by telephone for data collection. Compliance not reinforced during study contact.</td>
<td>Evaluable (n=6,163 sites in the United States)</td>
<td>2006;129(1):27–38.</td>
<td>No difference in number of subjects with respiratory-related death or life-threatening experiences over 28 weeks period (RR 1.395, 95% CI 0.91 to 2.14). Differences between S and P in number of respiratory-related deaths (24 vs. 11, RR 2.16, 95% CI 1.06 to 4.41), asthma-related deaths (13 vs. 3, RR 4.34, 95% CI 1.25 to 15.34), and combined asthma-related deaths or life-threatening experiences (37 vs. 22, RR 1.71, 95% CI 1.01 to 2.89). No differences among Caucasians, but among African-Americans, differences between S and P for number of respiratory-related deaths (20 vs. 5, RR 4.1, 95% CI 1.54 to 10.00) and combined asthma-related deaths or life-threatening experiences (19 vs. 4, RR 4.9, 95% CI 1.68 to 14.45). Differences for S vs. P in time to first SAE causing discontinuation (S survival rate, 95.6%; P survival rate, 96.2%; p=0.022)</td>
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<tr>
<td>Wolte et al. Formoterol, 24 mcg bid, and serious asthma exacerbations: similar rates compared with formoterol, 12 mcg bid, with and without extra doses taken on demand, and placebo. Chest 2006;129(1):27–38.</td>
<td>Multicenter, placebo-controlled, parallel-group study by (184 exacerbation asthma clinics in the United States)</td>
<td>To determine whether high-dose formoterol, 24 mcg bid, was associated with more asthma exacerbations compared with lower formoterol doses in patients with stable persistent asthma</td>
<td>2,085 (2,085 TT)</td>
<td>Age 12–82 yr; mean = 38.1 yr; 15% 12–18 yr, 79% 19–64 yr, 5% 65–74 yr, 1% &gt;74 yr Gender 45% male, 55% female Ethnicity 79% Caucasian, 13% African-American, 2% Oriental, 6% other</td>
<td>Persistent stable asthma Duration of asthma 0–80 yr; mean = 20.5 yr PEF, Vs. 51 L; mean = 2.37 L PEF, % pred. 85.2–123.6; mean = 88.8</td>
<td>Arm 1 (F-24) Formoterol high dose (n=527)</td>
<td>24 mcg bid, with 2 additional 12 mcg daily doses as needed 12 mcg bid</td>
<td>16 weeks Medications administered by inhalation from a single-dose DPI between 6 and 9 a.m. and between 6 and 9 p.m. Patients in double-blind groups were allowed rescue medication; patients in F/D were allowed up to 4 puff/day of inhaler as rescue medication after receiving 2 additional 12 mcg doses on demand.</td>
<td>No clinically meaningful differences between groups in pulse rate or blood pressure</td>
<td>No differences between groups in serious exacerbation (p &gt;0.21). Lower proportion in F/D vs. P with serious exacerbation requiring systemic corticosteroids (4.4% vs. 8.8%, p =0.006). No other groups differed. No difference in proportion experiencing serious exacerbation or discontinuing due to asthma-related AE or having an asthma-related ED visit (p &gt;0.25)</td>
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Proportion with any asthma-related AE was similar in F-24 and F-12 and not different from P (13.7% and 14.0% vs. 15.9%, p >0.38); fewer had asthma-related AE in F/D vs. P (10.3% vs. 18.6%, p=0.009).