Drug Class Review
Long-acting beta-agonists salmeterol and formoterol in the treatment of COPD and asthma

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel
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Salmeterol (Glaxo-SmithKline) and formoterol (Novartis) are the two long-acting beta-agonists presently on the market. The purpose of this review is to determine whether these 2 agents can be competed.

FDA-approved indications

	Salmeterol MDI	Salmeterol inhalation powder	Formoterol inhalation powder
Asthma	Maintenance treatment of asthma and in the prevention of bronchospasm in patients ≥ 12 years old	Maintenance treatment of asthma and in the prevention of bronchospasm in patients ≥ 4 years old	Maintenance treatment of asthma and in the prevention of bronchospasm in patients ≥ 5 years old
Exercise-induced bronchospasm (EIB)	Prevention of EIB in patients ≥ 12 years old	Prevention of EIB in patients ≥ 4 years old	Prevention EIB in patients ≥ 12 years old
COPD	Maintenance treatment of bronchospasm associated with COPD		Maintenance treatment of bronchoconstriction in patients with COPD

DOSE

Salmeterol and formoterol should not be used in patients whose asthma can be managed by occasional use of inhaled, short-acting beta2-agonists. They should not be initiated in patients with significantly worsening or acutely deteriorating asthma nor should they be used as a substitute for inhaled or oral corticosteroids.

	Salmeterol MDI	Salmeterol Diskus	Formoterol Aerolizer
Asthma maintenance	2 puffs (42mcg) q 12h	1 inhalation (50mcg) q12h	1 inhalation (12mcg) q12h
Prevention of EIB	2 puffs (42mcg) 30min prior to exercise; no additional doses should be used for 12 hours	1 inhalation (50mcg) 30min prior to exercise; no additional doses should be used for 12 hours	1 inhalation (12mcg) 30min prior to exercise; no additional doses should be used for 12 hours
COPD maintenance	2 puffs (42mcg) q 12h		1 inhalation (12mcg) q12h

EFFICACY

Literature reviewed:
Because the majority of patients with obstructive airway disease seen in the VA have COPD, all published COPD trials were reviewed. The asthma articles were limited to trials comparing salmeterol and formoterol.

Comparative studies with salmeterol vs. formoterol in asthma

Several inhalation drug delivery systems exist for administration of dry powders. In the U.S., formoterol dry powder is delivered by the Aerolizer™ system and salmeterol, by the Diskus™ system (also marketed as the Accuhaler in some countries). No clinical trial has compared formoterol Aerolizer with salmeterol Diskus; however, 1 pharmacoeconomic and 2 quality of life and studies used these delivery devices in their comparative trials. (Novartis study 073, Gause, Jones 1998) Many of the comparative trials used formoterol Turbuhaler and salmeterol Diskhaler, the dry powder systems available in Europe.

There are 2 longer-term trials and several single-dose or short-term studies. The single-dose or short-term studies found salmeterol and formoterol to be comparable (Lipworth 2000, van Noord 1996, Rabe 1993). In the longer-term studies, Vervloet et al. found PEF, rescue medication use, morning and evening symptom scores and asthma exacerbation rates to be similar between salmeterol and formoterol. Campbell et al. also found similar improvement in PEF between formoterol, salmeterol via dry powder and salmeterol via metered-dose inhaler. Morning asthma symptom scores were slightly better in the patients receiving

formoterol compared to those receiving salmeterol as the dry powder. However, there was no difference between formoterol and salmeterol via metered-dose or between the 2 salmeterol groups.

Comparative pharmacoeconomic studies in asthma

Direct and indirect costs were compared between formoterol and salmeterol in a European. The sum of the direct and indirect costs were converted to 1995 U.S. dollars and were $1559.22 ± 2759.74 for formoterol and $1735.56 ± 3561.97 for salmeterol per patient per year. Because delivery of care may be different in Europe than the U.S. this study may not truly represent costs in the U.S. study (Rutten van-Molken 1998)

In a poster presentation by Gause, the costs of rescue asthma-related medications and other respiratory-related medications was determined using a computerized drug database and patient diaries. Total cost for formoterol $470 ± 335 (95% CI 433, 514) was significantly less than salmeterol $545 ± 385 (95% CI 500, 594).

Comparative quality of life studies in asthma

In addition to their pharmacoeconomic analysis, Rutten-van Molken et al. looked at quality of life outcomes. Using the St. Georges Respiratory Questionnaire, 64% on formoterol and 62% on salmeterol achieved a clinically relevant improvement defined as a ≥ 4% improvement in overall score.

In study 073 (data on file at Novartis), no difference in Asthma Quality of Life Questionnaire score and the Morinsky Compliance score were found between formoterol and salmeterol. Compliance improved from baseline by 20.2% in the formoterol group and 19.9% in the salmeterol group at 6 months

Using the St. Georges Respiratory Questionnaire, Jones found that the change in scores for each section (symptoms, activity, impacts) improved from baseline in both groups with no significant difference between the 2 treatments.

Studies with salmeterol or formoterol in COPD

Single-dose studies

Placebo studies	Salmeterol vs. placebo (Ramirez-Venegas et al.) Formoterol vs placebo (Maesen et al)
Comparator with ipratropium and/or combination with ipratropium	Salmeterol vs. ipratropium vs. placebo (Patakas et al.) Salmeterol vs. ipratropium vs.salmeterol + ipratropium vs. placebo (Matera et al.) Formoterol vs. ipratropium vs. formoterol + ipratropium vs. placebo (Sichlitidis et al.)
Comparator salmeterol vs. formoterol	Salmeterol vs. formoterol vs. placebo (Celik et al.) Salmeterol vs. formoterol vs. placebo (Cazzola et al. 1995)

Work of breathing and airway resistance were improved in patients with poorly reversible COPD receiving formoterol compared to placebo (Maesen 1999). In patients with partially reversible COPD, salmeterol increased airflow (as measured by FEV1 and FVC) and reduced hyperinflation (as measured by FRC and RV) compared to placebo (Ramirez-Venegas 1997).

During exercise treadmill testing, both ipratropium 120mcg (6 puffs) and salmeterol 50mcg produced similar improvement in airflow obstruction, recovery from post-exercise oxyhemoglobin desaturation, and in the sensation of dyspnea (Patakas1998)

In 2 studies, ipratropium 40mcg was found to be inferior, as measured by the peak increase in FEV1 and FEV1 area under the curve, to salmeterol or formoterol (Matera 1996). The combination of formoterol 12mcg or salmeterol 50mcg with ipratropium 40mcg failed to demonstrate a synergistic effect (Sichlitidis 1999).

The 2 small single-dose studies comparing salmeterol and formoterol were performed in patients with partially reversible COPD. The number of patients who achieved ≥ 15% increase in FEV1 at 15 minutes was similar for salmeterol and formoterol. Both studies showed peak increase in FEV1 to be at 1 hour for formoterol and 2 hours for salmeterol. However, the peak bronchodilation achieved was similar

between the 2 drugs. Celik et al. found the 12-hour FEV1 area under the curve to be similar between the 2 drugs whereas Cazzola et al found the FEV1 area under the curve to be greater with salmeterol. This may be due to the slightly longer duration of effect that was seen in this study with salmeterol.

Short-term studies (3-4 weeks)

Placebo studies	Salmeterol vs. placebo (Ulrik et al.) Salmeterol vs. placebo (Grove et al.)
Add-on with ipratopium	Formoterol + ipratropium vs. albuterol + ipratropium (D'Urzo et al.)

Two 4-week studies compared salmeterol to placebo in patients with poorly reversible COPD. In one study, morning peak flow, morning and evening asthma symptoms scores, rescue albuterol use, and subjective patient assessment were significantly better with salmeterol than with placebo (Ulrik 1995). In the second study, pulmonary function, 6-minute walking and cycle ergometry were assessed. There was a small increase in FEV1 with salmeterol, which was maintained for 4 weeks (Grove 1996). Compared with placebo, there was no significance difference in distance walked or with bicycle ergometry; however, patients perceived less exertion with salmeterol after chronic dosing.

D'Urzo et al. compared formoterol 12mcg BID + ipratropium 40mcg QID to albuterol 200mcg QID + ipratropium 40mcg QID in a cross-over study of patients with poorly reversible COPD. The premedication morning peak flow, FEV1, 6-hour FEV1 area under the curve, and asthma symptom scores were higher or improved with the formoterol/ipratropium combination. Exacerbation rates and rescue inhaler use did not differ significantly between the 2 treatments.

Long-term studies (3-12 months)

Placebo study	Salmeterol vs. placebo (Boyd et al.)
Comparator with ipratropium	Salmeterol vs. ipratropium vs. placebo (Mahler et al) Salmeterol vs. ipratropium vs. placebo (Rennard et al.) Formoterol vs. ipratropium vs. placebo (Dahl et al.)
Comparator with theophylline	Salmeterol vs. theophylline (Di Lorenzo et al) Formoterol vs. theophylline (abstract)
Add-on studies	Salmeterol vs. salmeterol +ipratropium vs. placebo (van Noord et al.) Salmeterol + theophylline vs. salmeterol vs. theophylline (ZuWallack et al) Salmeterol vs. salmeterol + fluticasone vs. salmeterol + theophylline (Cazzola et al.)

In a 16-week study in patients with poorly reversible COPD, salmeterol 50mcg and 100mcg BID improved morning asthma symptom score, FEV1, and rescue inhaler use more than placebo. After a 6-minute walk, more patients in the salmeterol 50mcg group had a Borg score for breathlessness of <3 than did the group receiving salmeterol 100mcg or placebo. However, there was no difference in the distance walked between the 3 groups nor was there a difference in COPD exacerbation rates (Boyd 1997). In a separate publication looking at quality of life, improvement using the St. George Respiratory Questionnaire was seen in the group receiving salmeterol 50mcg (Jones 1997). The Medical Outcomes Study Short Form 36 (SF-36) was also used which showed a worsening score in some components of the SF-36.

Two 12-week studies compared salmeterol to ipratropium and placebo (Mahler 1999, Rennard 2001) and one compared formoterol to ipratropium and placebo (Dahl 2001). Approximately 60% of the patients in the salmeterol studies demonstrated reversibility to albuterol. The primary endpoints for both studies were 12-hour FEV1 area under the curve and severity of dyspnea using the baseline dyspnea index (BDI) from which the transition dyspnea index (TDI) is determined. Rennard found 12-hour area under the curve to be similar for salmeterol and ipratropium, whereas Mahler found it to be higher with salmeterol only at weeks 4 and 8. Both studies demonstrated improvement in dyspnea and decrease in rescue albuterol use for the salmeterol and ipratropium groups. Neither study was able to demonstrate a difference for distance walked in 6 minutes, the Borg dyspnea score, or in the percentage of patients with COPD exacerbations. Overall quality of life using the Chronic Respiratory Disease Questionnaire (CRDQ) improved significantly for salmeterol and ipratropium in the Mahler study, whereas the Rennard study, the score improved in all groups including placebo. The percent of patients achieving a clinically meaningful increase in score of ≥ 10 was 46%, 39%, and 27% for salmeterol, ipratropium, and placebo respectively in the Mahler study and 46%, 41%, 38% in the Rennard study.

The formoterol study compared formoterol 12mcg and 24mcg BID to ipratropium 40mcg QID. The 12-hour area under the curve was higher in the 3 active treatment arms than placebo. However both formoterol doses were significantly higher than ipratropium. Pre-dose morning peak flow, rescue albuterol use, and quality of life improved significantly more in the formoterol groups than in the ipratropium and placebo groups. The percentages of patients requiring oral steroids, antibiotics, or hospitalization were not different among the 4 groups.

Two studies compared salmeterol or formoterol with theophylline. In an open-label study, DiLorenzo found morning peak flow increasing significantly more with salmeterol (45L/min) than with theophylline (25L/min). Evening peak flow increased with no significant difference between the 2 treatments. The percent of symptom free days and nights increased from baseline with both treatments; however, the increase was significantly greater with salmeterol compared to theophylline. Adverse events and COPD exacerbations were similar for both groups; however, serious adverse events were twice as high in the theophylline group (4% vs. 8.3%).

Presented as an abstract, the FICOPD II group compared formoterol 12mcg, 24mcg, theophylline, and placebo in a 12-month part double-blind (formoterol groups and placebo) and open-label (theophylline) trial. Approximately half the patients were considered to have a reversible component to their disease. In all 3 active groups, FEV1 area under the curve was superior to placebo. Formoterol 12mcg was superior to theophylline and formoterol 24mcg for the first 6 months. The differences in peak flow for formoterol 12mcg and 24mcg from theophylline were 10L/min and 17L/min respectively. Although clinically small, the difference of 17L/min with formoterol 24mcg was considered statistically significant. Use of rescue inhalers decreased in all groups, but was significant only for the formoterol groups. The number of COPD-related hospitalizations and improvement in quality of life and symptom scores did not differ significantly between the active treatment groups.

Salmeterol 50mcg BID was compared to the combination of salmeterol 50mcg BID and ipratropium 40mcg QID and placebo in a 12-week trial (van Noord 2000). Compared to placebo, morning symptom score and peak flow and rescue inhaler use improved significantly in the 2 active treatment groups. The difference between salmeterol alone and the combination was not significant. The only parameter where the combination was better than salmeterol alone was in the improvement of specific airway conductance. The exacerbation rate was 23%, 13%, and 36% for salmeterol, the combination and placebo respectively. Significance was found only between the combination and placebo.

ZuWallack compared the combination of salmeterol and theophylline to each agent alone. Approximately 50% of the patients were considered to have reversible disease. FEV1 area under the curve, transition dyspnea index, rescue albuterol use, peak flow, and treatment satisfaction were significantly better with the combination than with monotherapy with either agent. Symptom-free days, and exacerbation rates were better in the combination group than with theophylline alone. Increased heart rate and adverse GI events were higher in the groups receiving theophylline.

In a 3-month open-label trial, salmeterol + fluticasone led to a greater increase in FEV1 compared to baseline than did salmeterol alone or the combination of salmeterol + theophylline. Response to further bronchodilation with albuterol 400mcg and 800mcg was maintained in all groups despite pretreatment with salmeterol (Cazzola 2000).

Drug delivery devices

Peak inspiratory flow rate

In order for DPIs to deaggregate and disperse during inhalation, a minimum inspiratory flow rate is needed. When tested at a fixed flow rate of 60L/min for 3 seconds, 47mcg of salmeterol was delivered. Patients with severe obstructive airway disease having FEV1 ranging from 0.35-0.92L and 20-30% predicted were tested to see the peak inspiratory flow (PIF) they are able to generate through the resistive load of the Diskus. The mean PIF generated was 82.4L/min (range 46.1-115.3) and the mean emitted dose was 46mcg (range 45-51). When formoterol was tested at a fixed flow rate of 60L/min for 2 seconds, 10mcg of drug was delivered. PIF achievable through the Aerolizer was evaluated in 33 adult and adolescent

patients and 32 pediatric patients with mild-moderate asthma. In the adult-adolescent group, mean PIFR was 117.82L/min (range 34-188) and 99.66L/min (range 43-187) for pediatric patients. Approximately 90% of patients were able to generate a PIFR exceeding 60L/min.

Able to view only the abstract (article in Polish), PIFR was tested in 165 COPD patients and 119 asthmatic children through the Diskus and the Aerolizer. An optimum PIFR value adequate for the Diskus resistance was attained by 100% of the patients. With the Aerolizer, only 21.1% of the patients were able to achieve an optimum PIFR. (Kokot 2000).

Availability

The Diskus is a round plastic device containing 60 doses of salmeterol 50mcg preloaded by the manufacturer. A dose indicator on top allows the patient to know the number of remaining doses. Once removed from its moisture protective foil over wrap pouch, it should not be used beyond 1 month.

Each Aerolizer comes with 60 aluminum blister packed capsules of formoterol 12mcg. Prior to dispensing, formoterol capsules should be stored in a refrigerator. Once dispensed, the patient may store at room temperature for 4 months. Each dry powder capsule must be removed from the blister and placed into the Aerolizer. Upon inhaling, the patient should hear a whirring noise and experience a sweet taste. The capsule may be visually inspected to make sure the entire contents were delivered.

Salmeterol is also available as a metered dose inhaler. In a large randomized 12-week study, comparable efficacy and safety was demonstrated for salmeterol MDI and salmeterol Diskus (Wolfe 2000). Although formoterol is not available as a MDI in the U.S., many studies presented in this review used the MDI; therefore, it would be important to know how the dry powder and MDI compare. In a small crossover study, formoterol dry powder and MDI equally increased peak expiratory flow rate. (Ullman 1996)

Patient satisfaction

Although there are 2 quality of life studies comparing formoterol Aerolizer with salmeterol Diskus, neither study evaluated patient satisfaction or preference (Jones 1998 and Novartis Study 073)

In a 3-month, open, uncontrolled trial in 1380 asthmatic patients, investigators assessed correct use of formoterol Aerolizer by observing patient technique and providing responses to 8 questions on correct use. The answer was yes to all 8 questions after 1-2 weeks of treatment in 79.2% of patients, in 87.2% after 1 month, and in 90.8% after 3 months of treatment. After 1-2 weeks of treatment 91.1% of patients felt the inhaler was easy or very easy to use, 8.1% felt it was fairly easy, and 0.8% found it difficult to use. After 3 months of use, the percentages were 92.5%, 6.8%, and 0.7% respectively. Over 90% of the patients were compliant with their treatment. (Clauzel 1998)

One hundred and fifty nine asthmatic patients who were regular and experienced users of MDIs, but with no history of dry powder inhaler use were randomized to Diskus inhaler or Turbuhaler. Ninety seven percent of patients found their current MDI easy or very easy to use. Sixty-eight percent indicated that they would have been quite or very happy to have a Diskus inhaler prescribed. The features most cited were perceived ease of use, the dose counter, and shape of device. (Schlaeppi 1996)

A study in 48 asthmatics that were dry powder naïve compared patient acceptance of the Accuhaler versus the MDI. The Diskus and the Accuhaler are the same device marketed by different companies. After the first instruction, 66.7% of patients were able to demonstrate correct use of the inhaler. After 4 weeks, more patients preferred the Accuhaler because of the dose counter and a perceived ease of use compared to the MDI. (Liam 2000)

Several studies compared the dry powder inhalers available in the U.S. to their counterparts used in other countries (Diskus to Diskhaler and Aerolizer to Turbohaler). A Canadian study found that peak flow with salmeterol administered by Diskus was equivalent to that administered by Diskhaler. However, more patients found the Diskus easier to use and preferred it to the Diskhaler (73% vs. 15%). (Boulet 1995)
Two studies compared formoterol via Aerolizer vs. Turbuhaler. Clinical efficacy was similar between formoterol administered by either device; however, 98% of those using the Aerolizer performed all

the essential inhalation maneuvers correctly vs. 86% using the Turbuhaler. (Eliraz 2001 and Lotval 1999)

Two recent systematic reviews (BMJ Oct. 2001) looked at delivery of β_2-agonists and corticosteroids by MDI versus other hand held inhaler devices. The authors found marked heterogeneity in patient preference. This may be because different dry powder inhalers were used in the studies. In the corticosteroid review, 2 studies used a Rotahaler, which was significantly less preferred to the MDI, and 2 used a Turbohaler, which was significantly preferred to the MDI. In the β_2-agonist review, 3 trials found adults preferring MDIs to the Rotahaler, 2 trials showed preference for the Turbuhaler over the MDIs and 1 showed preference for the MDI over a multidose dry powder inhaler.

SAFETY

Formoterol

The tables below are from the manufacturers package insert. The formoterol table for asthma is from 5,824 patients enrolled in multiple-dose controlled clinical trials of whom 1,985 were receiving formoterol 12mcg BID. The table for COPD is from 2 pivotal multiple dose trials that enrolled 1634 patients of whom 405 were treated with formoterol 12mcg BID. Both tables show adverse events where the frequency was ≥ 1% for formoterol and where the rates exceeded that of placebo.

Asthma

	Formoterol	Placebo
Infection viral (%)	17.2	17.1
Bronchitis (%)	4.6	4.3
Chest infection (%)	2.7	0.4
Dyspnea (%)	2.1	1.7
Chest pain (%)	1.9	1.3
Tremor (%)	1.9	0.4
Dizziness (%)	1.6	1.5
Insomnia (%)	1.5	0.8
Tonsillitis (%)	1.2	0.7
Rash (%)	1.1	0.7
Dysphonia (%)	1.0	0.9

COPD

	Formoterol	Placebo
URI (%)	7.4	5.7
Back pain (%)	4.2	4
Pharyngitis (%)	3.5	2.4
Chest pain (%)	3.2	2.1
Sinusitis (%)	2.7	1.7
Fever (%)	2.2	1.4
Leg cramps (%)	1.7	0.5
Muscle cramps (%)	1.7	0
Anxiety (%)	1.5	1.2
Pruritis (%)	1.5	1.0
Dry mouth (%)	1.2	1.0

Salmeterol MDI

The salmeterol MDI table for asthma is from 556 patients enrolled in 2 large, 12-week clinical trials where salmeterol was dosed at 42mcg BID (n=184) and albuterol at 180mcg QID. The COPD trial had 816 patients enrolled in 2 large 12-week trials of whom 267 were receiving salmeterol 42mcg BID. Both table show all adverse events that occurred at a rate of ≥ 3% for salmeterol and where the rates exceeded that of placebo.

Asthma

	Salmeterol	Albuterol	Placebo
URI (%)	14	16	13
Nasopharyngitis (%)	14	11	12
Disease of nasal cavity/sinus (%)	6	1	4
Sinus headache (%)	4	<1	2
Stomachache (%)	4	0	0
Headache	28	27	23
Tremor (%)	4	3	2
Cough (%)	7	3	6
Lower respiratory infection (%)	4	2	2

COPD

	Salmeterol	Albuterol	Placebo
URI (%)	9	9	7
Sore throat (%)	8	6	3
Diarrhea (%)	5	4	3
Back pain (%)	4	3	3
Headache (%)	12	8	10
Chest congestion (%)	4	3	4

Salmeterol Diskus

The salmeterol Diskus table for asthma is from 451 patients enrolled in 2 large 12-week clinical trials.

Patients in the salmeterol group (n=149) were dosed at 50mcg BID and albuterol at 180mcg QID. The table shows all adverse events that occurred at a rate of ≥ 3% for salmeterol and where the rates exceeded that of placebo.

Asthma

	Salmeterol	Albuterol MDI	Placebo
Nasal/sinus congestion (%)	9	8	6
Rhinitis (%)	5	4	4
Headache (%)	13	12	9
Asthma (%)	3	<1	1
Tracheitis/bronchitis (%)	7	3	4
Influenza (%)	5	5	2

Salmeterol vs. formoterol comparative trials

The table below shows the adverse events from the two larger comparative asthma trials of salmeterol versus formoterol.

Vervloet et al.

	Formoterol 12mcg BID	Salmeterol 50mcg BID
Overall adverse events	79%	80%
Drug-related adverse events	13%	9%

The most common drug-related adverse events were headache (formoterol n=7 and salmeterol n=11), tremor (formoterol n=5, salmeterol n=2) and palpitations (formoterol n=4, salmeterol n=0)

Campbell et al.

	Formoterol 12mcg BID	Salmeterol 50mcg BID (Accuhaler)	Salmeterol 50mcg BID MDI
Respiratory system	40%	43%	43%
Central/peripheral nervous system	10%	9%	8%
Body as a whole	17%	10%	13%

Cardiac safety

Cardiac arrhythmias are common in patients with COPD. Hypoxemia, hypercapnia, acid-base disturbances, and use of beta-agonist may contribute to this risk. It therefore is important to know what effect long-acting beta-agonists have in patients with these risk factors. In a single-dose crossover study, Cazzola studied 12 patients with COPD and preexisting mild-moderate cardiac arrhythmias and hypoxemia. The beta-agonists significantly increased heart rate compared to placebo. However, the greatest increase was seen with formoterol 24mcg. Similarly, supraventricular or ventricular premature beats occurred at a higher rate with formoterol 24mcg.

Formoterol 24mcg significantly reduced plasma potassium level more than salmeterol 50mcg and formoterol 12mcg. The maximum decrease was 1.12, 0.45, and 0.49mmol/L respectively. The authors conclude that although the long-acting beta-agonist may have adverse cardiac effects, salmeterol 50mcg and formoterol 12mcg have a higher margin of safety than formoterol 24mcg. One must keep in mind that this was a single-dose study, and the effects of chronic administration are unknown. In another study, 8 patients with reversible airway disease without preexisting cardiac disease were given salmeterol 50mcg BID for 3 days followed by 100mcg BID for 3 days. 24-h Holter monitoring did not demonstrate any clinically relevant change in heart rate, or in the number of supraventricular or ventricular premature beats. (Tranfa 1998)

Salmeterol versus formoterol – Asthma trials

TRIAL	INCLUSION	DOSE	MEASURED OUTCOMES	BASELINE CHARACTERISTICS	RESULTS
Palmqvist 1999 R, DB, DD, CO, PC **Salmeterol vs. formoterol** N=18	18-70y/o confirmed dx asthma stable dose ICS 200-1600 mcg/d (budesonide or equivalent) for ≥ 1 month not currently smoking FEV1 ≥ 70% pred Dose of methacholine producing 20%↓ in FEV1 < 200mcg (PD_{20}) QTc interval < 0.46 sec	3-12 day washout between treatment arms Cumulative admin of: FOR 12mcg + 48mg + 60mcg (total 120mcg) via Aerolizer vs. SAL 50mcg + 200mcg + 250mcg (total 500mcg) via Diskhaler vs. placebo EKG, serum K+, HR measured 50 min post each dose and 110min post cumulative dose. Methacholine challenge 60min post- each dose	1° outcome Difference in maximal PD_{20} methacholine between salmeterol and formoterol, subtracted by the corresponding placebo day value 2° outcomes FEV1 serum K+ HR QTc 1 hr post-dose tremor score	**FEV1 %pred** – 90.9% (range 70-122%) **PD_{20}** - 52.3mcg (range 12.2 – 200mcg) **ICS (mcg/day)-** N=8, 4, 1, 1, 1 for BUD 400, BUD 800, FLU 500, FLU 1000, BDP 400 respectively **Serum K+** - 4.1 ± 0.1 mmol/L **HR**- 66-68 beats/min **QTc**- 0.4 ± 0.005 sec Mean	3 pts. withdrew 1 pt. severe airflow obstr during methacholine provocation, 1 pt. beta-agonist induced AE, 1 pt. deterioration in asthma during washout period **PD_{20} – Formoterol**- dose-response relationship observed with maximal protective effect seen at the highest dose. **Salmeterol** - maximal protective effect was seen after the 250mcg dose with no increased effect with 500mcg. The maximal protective effect on PD_{20} for formoterol was almost two doubling doses higher than for salmeterol **Placebo** – no significant difference after each dose. **Mean FEV1%pred after dose 1, 2, 3** – FOR- 94, 93,92; SAL 93, 91, 91 **Serum K+(lowest value observed)-** FOR 120mcg – 3.4 ± 0.1 (3.1-3.9); SAL 500mcg – 3.7 ± 0.1 (3.3 –3.9)* **HR (highest value observed)** – FOR 120mcg 79 ± 3 beats/min at 50 min.; SAL 500mcg 80 ± 3 beats/min at 110 min. **QTc (longest value)-** FOR 120mcg 0.419 ± 0.007 (range 0.37-0.48); SAL 500 0.423 ± 0.006 (range 0.38-0.45) Tremor score – sig. tremor noted for both drugs at second dose-step. At third-dose step, FOR > SAL* *Sig FOR vs. SAL
Campbell 1999 R, CO, multicenter **Salmeterol vs. formoterol** 8 weeks first arm, 4 weeks second arm N=469	≥ 12y/o Documented dx of asthma ICS ≥ 200mcg/d ≥ 4weeks PRN SABA Meet the following during the run-in period: •≥10% diurnal variation in PEF **or** SABA ≥ bid on at least 4 of the last 7 days of run-in •≥ 15% ↑ in PEF with SABA	7-14 day run-in FOR 12mcg BID via Turbohaler vs. SAL 50mcg BID via Accuhaler vs. SAL 50mcg BID via MDI x 8 weeks This period was followed by a 4-week cross-over period. Patients who had received SAL in the previous 8 weeks were given FOR and patients who had received FOR were given SAL via Accuhaler or MDI	Δ from run-in to 8 weeks in PEFam Δ from run-in to 4 weeks in PEFam PEFpm as recorded in daily diary cards after 8 weeks Daytime asthma symptoms after 4 weeks Patient preference questionnaire	**%Smoking (never/ex/current)-** FOR 48/28/24; SAL-DPI 48/32/20; SAL-MDI 49/28/23 **PEF**- FOR 373.8 (94.5); SAL-DPI 384.9 (100.1); SAL-MDI 372.1 (94) Mean (SD)	<table><tr><th></th><th>FOR</th><th>SAL-DPI</th><th>SAL-MDI</th></tr><tr><td>Δ PEFam (8 weeks)</td><td>+9.5%*</td><td>+8.7%*</td><td>+9.4%*</td></tr><tr><td>Δ PEFam (4 weeks)</td><td>+9.5%*</td><td>+6.5%*</td><td>+9.4%*</td></tr><tr><td>PEFpm</td><td>+6.5%*</td><td>+4.6%*</td><td>+8.3%*</td></tr><tr><td>am asthma sx (4 wks)</td><td>-0.54^</td><td>-0.35</td><td>NS vs. FOR or SAL-DPI</td></tr><tr><td>Pt.preference</td><td colspan="3">•Turbohaler more convenient to carry around than the Accuhaler (P<0.0001) •More pts. preferred the Turbohaler over the MDI if given the choice (P=0.0168)</td></tr></table> *significant vs. baseline ^significant vs. salmeterol MDI differences between groups for PEF results NS

Vervloet 1998 R, open, Pr Multicenter **Salmeterol vs. formoterol** N=482 6 months ITT for primary endpoint	Dx reversible obstructive airway disease ≥ 1yr ≥ 18 y/o ICS ≥ 400mcg/d (if fluticasone ≥ 200mcg/d) ≥ 4 weeks *Pts. with COPD included if bronchial reversibility demonstrated*	2 week run-in FOR 12mcg bid via Aerolizer vs. SAL 50mcg bid via Diskhaler *ICS continued at a constant dose*	1° outcome pre-dose PEFam during last 7 days of tx 2° outcome use of rescue meds am/pm pre-dose PEF am/pm symptom scores	**%Smoking (current/ex/never)-** FOR 14.9/29/56; SAL 15.8/32/52.3 **dur of disease (y)-** FOR 15.8; SAL 16.3 **PEFam –**FOR 377 (110-670); SAL 371 (89-749) **PEFpm** – FOR 388 (97-744); SAL 384 (149-800) **Day-time rescue med use-** FOR 2.1 (0-17.6); SAL 1.9 (0-15.1) **Nighttime rescue med use-** FOR 1.2 (0-10.9); SAL 1.1 (0-10.9) **Am sx score** – FOR 0.9 (0-4); SAL 0.8 (0-3.7) **Pm sx score** – FOR 0.6 (0-4); SAL 0.5 (0-3) Mean (range)	**Dropouts** – FOR 10%; SAL 12.5% **Predose PEFam difference between FOR and SAL (95% CI)** -8.69, 9.84 L/min which is in predefined range for equivalence **Pre-dose PEFpm (FOR-SAL)** – difference was statistically significant in favor of FOR at months 2, 3, and 4 only and were 7.27, 10.45, 10.51 L/min respectively **Rescue med use** – decreased by half in both groups **Am and pm sx scores-** both groups had similar improvements **Asthma exacerbation** – For 17%; SAL 22%
Lipworth 2000 R, DB, DD, CO Salmeterol vs. formoterol N=18 1 week per arm	18-65y/o stable mild-mod persistent asthma ≥ 12 mos. FEV_1 > 60% pred PD_{20} < 500mcg ≥ 4x ↑ in PD_{20}, 30min post albuterol 400mcg stable dose of ICS ≥ 3 mos. non smoker for ≥ 12 mos. pts. expressing homozygous glycine-16 β_2–receptor polymorphism	SAL 50mcg bid x 1 week via Accuhaler FOR 12mcg bid x 1 week via Turbohaler Placebo Accuhaler and placebo Turbohaler bid x 1 week 1-week washout between treatments. During washout, pts. were allowed to use prn ipratropium	1° outcome PD_{20} - 12hrs post 1st dose and last dose 2° outcome FEV_1 -12hrs post 1st dose and last dose PEFam/PEFpm Rescue inhaler use	FEV_1 – 2.54 ± 0.17 L % predicted – 76.9 ± 2.5 FEF_{25-75} - 2.26 ± 0.21 L/s Pre-albuterol PD_{20} - 54± 14mcg Post-albuterol PD_{20} - 559 ± 170mcg ICS – 644 ± 118mcg N= 14, 2, 2 for BDP, BUD, FLU respectively Mean (SEM)	<table><tr><th></th><th>Formoterol</th><th>Salmeterol</th></tr><tr><td>PD_{20} 1st dose (95% CI)</td><td>↑ by 1.9 fold ^ (1.1, 3.2)</td><td>↑ by 1.6 fold^ (1.1, 2.2)</td></tr><tr><td>PD_{20} last dose 95% CI)</td><td>↑ by 1.9 fold (1.3, 2.8)</td><td>↑ by 1.6 fold (1.2, 2.3)</td></tr><tr><td>FEV_1 (L)</td><td>2.63^/2.48</td><td>2.59^/2.57</td></tr><tr><td>PEFam/PEFpm</td><td>422/425^</td><td>422/430^</td></tr><tr><td>Rescue inhaler use</td><td colspan="2">No signif difference between the 3 groups (data not shown)</td></tr></table>Measurements for methacholine challenge and FEV1 taken 12 hours after dose ^significant vs. placebo
Van Noord 1996 R, DB, CO **Formoterol vs. salmeterol** N=30 12 hour periods each arm	Age 18-70 years Subjects in stable phase of asthma Baseline FEV1 of 40-80% of predicted value and not varying more than 15% over the three study days Reversibility in FEV1 more than 15% of the baseline value after 200 mcg of inhaled salbutamol	Single dose study of Salbutamol 200mcg vs. Formoterol 24mcg vs. Salmeterol 50mcga all drugs delivered via MDI and chamber *Allowed to cont. nedcromil, cromolyn, ICS, oral steroids, and antihistamines*	FEV1 FVC Airway resistance (R_{aw}) Airway conductance (sG_{aw})		**Onset of action (sG_{aw})** •Salbutamol: ↑ in sG_{aw} of 44% (P<0.0001) after 1 min. and a maximum ↑ of 100% after 30 minutes, followed by a slow decline •Formoterol: ↑ in sG_{aw} of 44% (P<0.0001) after 1 min and a maximum ↑ of 135% after 2 hours, followed by a slowly declining plateau •Salmeterol: ↑ in sG_{aw} of 16% (P<0.0001) after 3 min and a maximum ↑ of 111% between 2 and 4 hours **Duration of action (FEV1, FVC, R_{aw}, sG_{aw})** •No difference between the AUC for formoterol and salmeterol •When compared with salbutamol, the AUC for both formoterol and salmeterol are significantly greater (P<0.02)

Rabe 1993 R, DB, PC, CO **Formoterol vs. salmeterol** N=12 2 separate phases of study: 30 minutes 24 hour	Asthma as defined by ATS Cannot be using ICS or oral steroids, theo, or mast cell stabilizers	Single dose study- 30 min follow-up Formoterol 12mcg Formoterol 24mcg Salmeterol 50mcg Salmeterol 100mcg Placebo All admin via MDI Single dose study- 24 hour follow-up Formoterol 12mcg Salmeterol 50mcg placebo	FEV1 $PC_{20}FEV_1$ – concentration of methacholine necessary to decrease FEV1 by 20%		**Dose-finding Study** •All doses of formoterol and salmeterol equally decreased airway responsiveness to inhaled methacholine compared with placebo (P<0.0001) •Compared with placebo, all doses of both agents significantly increased FEV1 after 10 minutes (P<0.001) and 30 minutes (P<0.003) **24-hour Study** •Compared with placebo, salmeterol improved FEV1 significantly at 0.5, 4, and 12 hours (P<0.0024) but not at 8, 16, 20, or 24 hours •Formoterol improved FEV1 significantly at 0.5 and 4 hours (P<0.0024) but not at 8, 12, 16, 20, or 24 hours •There was no statistical differences between the two agents with respect to bronchodilation over 24 hours •Compared with placebo, salmeterol 50 mcg significantly increased $PC_{20}FEV_1$ over 24 hours (P<0.0024) •Formoterol 12 mcg increased $PC_{20}FEV_1$ for up to 20 hours but did not have a significant effect at 24 hours

Salmeterol vs. formoterol pharmacoeconomic and quality of life studies

<table>
<tr><th>TRIAL</th><th>INCLUSION</th><th>DOSE</th><th>MEASUREMENTS</th><th>DEMOGRAPHICS</th><th>RESULTS</th></tr>
<tr>
<td>Rutten-van Molken 1998
R, open label, Pr multicenter
Formoterol vs. salmeterol
N=482
6 months
ITT</td>
<td>18 years of age or older
Diagnosis of asthma ≥ 1 year
ICS ≥ 400mcg/day or 200mcg/day for fluticasone for ≥ 1 month prior to screening</td>
<td>Formoterol 12mcg bid via Aerolizer vs. salmeterol 50mcg bid via Diskhaler

Cont. ICS at same dose
Prn albuterol allowed</td>
<td>Direct and indirect medical costs
Episode free days (EFDs)
%patients reaching a clinically relevant improvement in quality of life on the St. Georges Respiratory Questionnaire</td>
<td>See Vervloet 1998

SGRQ – Formoterol 35 (18); Salmeterol 35 (17)

Mean (SD)</td>
<td>
<table>
<tr><th></th><th>Formoterol</th><th>Salmeterol</th></tr>
<tr><td>Total direct cost</td><td>698.86* (1442.54)</td><td>808.62 (1961.17)</td></tr>
<tr><td>Indirect cost</td><td>860.51</td><td>925.09</td></tr>
<tr><td>Direct + indirect cost</td><td>1559.22 (2759.74)</td><td>1735.57 (3561.97)</td></tr>
<tr><td># of EFD</td><td>97 (64)</td><td>95 (62)</td></tr>
<tr><td>% reaching improvement QOL</td><td>64%</td><td>62%</td></tr>
</table>
*significant vs. salmeterol
costs converted to 1995 U.S. dollars
mean (SD)
</td>
</tr>
<tr>
<td>Study 073 (Data on file Novartis)
Formoterol vs. salmeterol
N=527
6 months</td>
<td>18-75 y/o moderate-moderately severe asthma</td>
<td>Formoterol 12mcg bid via Aerolizer vs. salmeterol 50mcg bid via Diskus</td>
<td>Asthma Quality of Life Questionnaire (AQLQ)
Morisky Compliance Score</td>
<td>FEV1 %pred- FOR 64.4 (11.4); SAL 63.4 (11)

Mean (SD)</td>
<td>No difference in AQLQ scores between formoterol and salmeterol
Compliance improved from baseline by 20.2% in the formoterol group and 19.9% in the salmeterol group at 6 months</td>
</tr>
<tr>
<td>Gause (poster presentation)
Formoterol vs. salmeterol
N=527
6 months</td>
<td>18-75 y/o moderate-moderately severe asthma</td>
<td>Formoterol 12mcg bid via Aerolizer vs. salmeterol 50mcg bid via Diskus</td>
<td>Estimate the cost of:
Rescue asthma- related medications
Other respiratory-related medication use

Used computerized drug database and patient diary for rescue meds</td>
<td>FEV1 %pred- FOR 64.4 (11.4); SAL 63.4 (11)

Mean (SD)</td>
<td>
<table>
<tr><th></th><th>Formoterol</th><th>Salmeterol</th></tr>
<tr><td>Rescue med</td><td>$14± 9
(95% CI 12, 16)*</td><td>$19 ± 25
(95% CI 16, 22)</td></tr>
<tr><td>Non-rescue asthma-related</td><td>$334 ± 251
(95% CI 307, 370)</td><td>$350 ± 240
(95% CI 323, 381)</td></tr>
<tr><td>Other respiratory-related</td><td>$122
(95% CI 101, 144)*</td><td>$176 ± 252
(95% CI 148, 210)</td></tr>
<tr><td>Total respiratory</td><td>$470 ± 335
(433, 514)*</td><td>$545 ± 385
(500, 594)</td></tr>
</table>
</td>
</tr>
<tr>
<td>Jones 1998
R, Open label, Pr Multicenter
Formoterol vs. salmeterol
N=482
6 months</td>
<td>Reversible obstructive airway disease
Currently receiving ICS and on demand SABA</td>
<td>Formoterol 12mcg bid via Aerolizer vs. salmeterol 50mcg bid via Diskus</td>
<td>QOL using St. George's Respiratory Questionnaire (divided into 3 sections: symptom, activity, impacts)</td>
<td>Duration of asthma (y) – FOR 15.8; SAL 16.3
PEFam (L/min) - FOR 377; SAL 371
PEFpm (L/min) – FOR 388; SAL 384
QOL score (total)- FOR 34.6; SAL 35.2</td>
<td>Change in scores for each section (symptoms, activity, impacts) improved from baseline in both groups; no significant difference between groups

Total score change from baseline – formoterol 8.9; salmeterol 8.1 (NS between groups)</td>
</tr>
</table>

SUMMARY OF STUDIES EVALUATING SALMETEROL/FORMOTEROL FOR TREATMENT OF COPD

<table>
<tr><th>TRIAL</th><th>INCLUSION</th><th>DOSE</th><th>MEASURED OUTCOMES</th><th>DEMOGRAPHICS</th><th>RESULTS</th></tr>
<tr><td>Ramirez-Venegas 1997
R, DB, PC, CO
Salmeterol vs. placebo
N=16
4 hour periods</td><td>Clinically stable COPD with dyspnea for at least 3 months, ↑ in FEV1 ≥200ml and by ≥12% after 180mcg albuterol</td><td>Salmeterol 42mcg as single dose via MDI vs. placebo</td><td>FEV1, FVC, FRC, TLC, RV
Breathlessness scale (CR-10) after breathing against resistive loads
-5 to +5 dyspnea rating

all measurements taken 30 min, 2h, and 4h post-dose</td><td>FEV1 (L)- 0.97 (0.33)
FEV1%pred- 51 (13)
FVC- 2.42 (0.8)
Post-albuterol FEFV1- 1.23 (0.35)
Baseline dyspnea index- 6.0 (1.4)</td><td>Significant increase in FEV1 and FVC vs. placebo
Significant decrease in FRC and RV vs. placebo
No significant in TLC between tx and placebo
CR-10 dyspnea scores significantly lower compared to placebo</td></tr>
<tr><td>Maesen 1999
R, DB, PC, CO
Formoterol vs. Placebo
N=12
Single-dose study</td><td>40-70y/o
smoking history > 10 pack-yrs.
FEV1 % pred – 30-60%, but > 1L
% reversibility < 9% pred after 1mg inhaled terbutaline</td><td>Single-dose
Formoterol 6mcg,
Formoterol 24mcg,
Placebo via turbuhaler</td><td>FEV1
Work of breathing (WoB)
Airway resistance (Raw)
Specific airway conductance (sGaw)</td><td>FEV1- 1.38L (1.0-2.0)
FEV1 %pred- 46.9% (37.3 – 59.9)
FEV1/FVC- 44% (32 – 56)
FEV1 % Reversibility – 5.1 (0.7-8.7)

Mean (range)</td><td><table><tr><th></th><th>F6</th><th>F24</th><th>Placebo</th></tr><tr><td>FEV1 AUC (L · h)</td><td>1.5 (1.02)</td><td>2.68 (2.08)</td><td>0.6 (2.51)</td></tr><tr><td>WoB (kPa·L^{-1}· h)</td><td>-1.33 (1.90)</td><td>-1.34 (2.21)*</td><td>1.21 (1.7)</td></tr><tr><td>Raw (kPa·L^{-1}· s· h)</td><td>-1.14 (1.53)</td><td>-1.18 (1.18)*</td><td>0.17 (1.26)</td></tr><tr><td>sGaw (s $^{-1}$· kPa $^{-1}$ · h)</td><td>1.15 (1.18)</td><td>1.52 (1.45)*</td><td>-0.15 (1.28)</td></tr></table>*significant vs. placebo and F6
mean (SD)</td></tr>
<tr><td>Patakas 1998
R, PC, CO
Ipratropium vs. salmeterol vs. placebo
N=15
Single-dose study</td><td>Stable copd
FEV1 < 65% pred
< 20% reversibility after beta-agonist
DLCO ≤ 65% pred</td><td>Ipratrop 6 puffs,
Salmeterol 50mcg,
Placebo 4 puffs

24 hrs between study periods</td><td>FVC 30 min post dose
FEV1 30 min post dose
Exercise treadmill with Borg scale (BS) to assess breathlessness
1) distance walked at BS 5
2) total distance walked
3) distance walked at BS 0
Δ SaO2 =SaO2 (rest) – Sa02 (nadir during exercise)
recovery time of SaO2</td><td>FEV1 (L)- IPR 0.91 (0.25); SAL 0.89 (0.26); PL 0.94 (0.25)
FEV1 % pred- 33.67%
FVC (L)- IPR 1.69 (0.4); SAL 1.69 (0.36); PL 1.83 (0.34)
FEV1 post-bronchodil – 1.02</td><td><table><tr><th></th><th>IPR</th><th>SAL</th><th>PL</th></tr><tr><td>FVC</td><td>2.08 (0.32)^</td><td>2.06 (0.31)^</td><td>1.83(0.33)</td></tr><tr><td>FEV1</td><td>1.12 (0.35)^</td><td>1.13 (0.24)^</td><td>0.95 (0.24)</td></tr><tr><td>Distance at BS 5 (m)</td><td>237 (74.2)^</td><td>248.2 (92.3)^</td><td>176.2 (59.9)</td></tr><tr><td>Total distance</td><td>350 (67.3)^</td><td>366.5 (78.6)^</td><td>270.4 (73.1)</td></tr><tr><td>Distance at BS 0</td><td>70.8 (61.8)</td><td>80.8 (68.1)^</td><td>42.9 (60.8)</td></tr><tr><td>Δ SaO2</td><td>7.46 (6.3) %</td><td>7.7 (6.1) %</td><td>8.13 (7.3)%</td></tr><tr><td>Recovery time (sec)</td><td>66.6 (33.4)^</td><td>72.6 (31.9)^</td><td>114.4 (53.1)</td></tr></table>Mean (SD)
^sig vs. placebo</td></tr>
<tr><td>Matera 1996
R, SB, CO
Salmeterol vs. ipratropium vs. placebo
N=12
Single-dose</td><td>Clinically stable COPD
Smoking >10ppd
≥40 y/o
FEV1 16-62% pred after withholding bronchodilator</td><td>-Salmeterol 50mcg + placebo
-Ipratropium 40mcg + placebo
-Salmeterol 50mcg + ipratrop 40mcg
-Placebo + placebo</td><td>% change of FEV1 (highest value used) from baseline of that day
AUC of FEV1 over 12 hours</td><td>No differences in baseline spirometry between treatment groups (data not shown)</td><td>FEV1 AUC – SAL 2.67 (0.55)* ^; IPR 1.06 (0.46)*; SAL+IPR 2.71 (0.47)*^
Peak % change in FEV1- SAL 28.8% (5); IPR 26% (9.1); SAL+IPR 28 (4.2)

Mean (SE)
*significant vs. placebo</td></tr>
</table>

		as single dose via MDI + chamber			^significant vs. ipratropium alone
Sichletidis 1999 R, SB, DD, CO, PC **Ipratropium vs. formoterol vs. ipratropium + formoterol** N=27 Single-dose study	Stable copd Smoker or ex-smoker with 10 pack/yr history FEV1 40 - 70% pred FEV1/FVC <70%	•IPR 40mcg •FOR 12mcg •IPR 80mcg •FOR 24mcg •FOR 12mcg + IPR 40mcg •4 puffs PL all doses via MDI	1° endpoint Change in peak FEV1 2° endpoint AUC 0-6hrs AUC 6-12hrs AUC 0-12hrs	**FEV1-** 1.35 L (0.85 –2.37) **% pred-** 52.38% (40.7 – 68.6) **FEV1/FVC**- 60.15% (38.3 – 67.8) Mean (range)	**FEV1 peak Δ** - IPR 40 224.8 (26.1)*^; FOR12 282.6 (25.9)^; IPR80 245.6 (27)*^; FOR24 300.4 (27.7)^; F12 + I40 335.2 (24.6)^; PL 65.6 (2.13)* **FEV1 AUC** – FOR12 and F24 not significantly different from combination; IPR40, IPR80, and placebo significantly different from combination Mean (SE) *significant vs. combination ^significant vs. PL
Celik 1999 R, DB, PC, CO **Formoterol vs. salmeterol vs. placebo** N=22 Single-dose	Mild-severe copd with partially reversible airway obstruction (≥10% reversibility to albuterol 200mcg)	Single-dose Formoterol 12mcg via MDI Salmeterol 50mcg via MDI Min. of 48hrs washout between tx periods May cont. ICS (n=8)	FEV1 @ 10, 20, 60, 120 min, 12 hr FEV1AUC	**Dur of COPD (y)-** 9.1 (3.9) **Smoking (pack-yrs)-** 35.2 (6.8) **FEV1 (L)-** 1.1 (0.2) **FEV1%pred** – 35.4 (9.8) **FEV1/FVC %-** 47 (9.2) **PEF (L/sec)-** 149.1 (46.2) **FEV1 reversible post-albuterol**- 19.3% (3.1%) Mean (SD)	**FEV1↑ @ 10, 20, min** – FOR 0.20*, 0.25*^; SAL 0.11, 0.20*^; PL 0.04, 0.04, 0.02, -0.12 **Maximal FEV1↑** – FOR 0.39^ achieved at 60 min; SAL 0.40 ^ achieved at 120min **FEV1 12 hrs** – FOR 0.25^; SAL 0.22^; PL –0.12 **FEV1 AUC**- FOR 3.5 ± 1.3L/h^,;SAL 3.2 ± 1.2L/h^; PL 1.2 ± 0.5L/h Mean (SD) *sig vs. baseline ^sig vs. PL
Cazzola 1995 R, SB, CO **Salmeterol vs. formoterol vs. placebo** N=12 Single-dose	Current or previous smoker, chronic cough ± sputum production or dyspnea when walking on level ground, FEV1 12-32% pred. (after withholding bronchodil), ≥ 15% ↑ in FEV1 after 200mcg albuterol but < than predicted range	Salmeterol 25, 50, 75 mcg Formoterol 12, 24, 36 mcg as single doses via MDI + chamber	FEV1, FVC, $FEF_{50\ for}$ up to 12 hours	**FEV1 (L)-** 0.58 **FEV1 % pred** – 21.5% **% Reversibility**- 28.9 mean values	• Both active treatments had signif improvement in spirometry over placebo. FEV1 AUC was greater with salmeterol 50mcg than formoterol 12 and 24mcgs. • A dose dependent ↑ in response was seen with formoterol but not salmeterol 50mcg and 75mcg. • Formoterol had earlier peak (1 hr) bronchodilation than salmeterol (2hrs). However, salmeterol 50mcg has a similar mean peak bronchodilation as does formoterol 12 and 24mcgs. • Trend that salmeterol had longer duration of action.
Ulrik 1995 R, DB, PC, CO **Salmeterol vs. placebo** N=66 4 week periods	Smoker, chronic bronchitis (ATS definition), FEV1 1-2L and <60% pred., FEV1/FVC <60%, ↑ in FEV1<15% or < 300ml 30min after albuterol 400mcg, no Δ in FEV1 after 7 day trial of prednisone 30mg. Day and night sx score≥1 on 5 of the last 7 days of run-in.	2-week run-in Salmeterol 50mcg BID via dry powder disk-inhaler vs. placebo prior anticholinergics were withdrawn prn albuterol allowed	1° outcome Peak expiratory flow (PEF) 2° outcomes FEV1, FEV1/FVC Daily diary of sx scores and prn beta-agonist use Subjective effect of tx (on scale of 1-4)	**Smoking pack years-** SAL/PL 42.2 (17.6); PL/SAL 45.2 (18.7) **FEV1 pre-albuterol /post-albuterol-** SAL/PL 1.21 (0.25)/1.37 (0.27); PL/SAL 1.24 (0.27)/1.39 (0.31) **%pred pre-albuterol/post-albuterol**- SAL/PL 46.1 (9.7)/ 50.5 (9.1); PL/SAL 44.6 (8)/52.5 (11.5) mean (SD)	<table><tr><th></th><th>Salmeterol</th><th>Placebo</th></tr><tr><td>PEFam (l/min)</td><td>238 (10)*</td><td>226 (10)</td></tr><tr><td>PEFpm</td><td>242 (10)</td><td>237 (10)</td></tr><tr><td>Am sx score/pm sx score^</td><td>1.0*/0.9*</td><td>1.8/1.6</td></tr><tr><td>Prn albuterol am/pm</td><td>1.7*/0*</td><td>2.6/0.3</td></tr><tr><td>Subjective assessment</td><td colspan="2">SAL > placebo* (data not shown)</td></tr><tr><td>FEV1, FEVI/FVC (measured 24h after SAL or placebo was withheld)</td><td>1.26 L (0.04)/ 53 (1)%</td><td>1.25 L (0.04)/ 52 (1)%</td></tr></table>Mean (SE) *Significant vs. placebo period ^% of days with sx score of zero was same as placebo

<table>
<tr>
<td>Grove 1996
R, DB, PC, CO
Salmeterol vs. placebo
N=29
4 week periods
ITT</td>
<td>Stable COPD
FEV1 % pred -25-75
5-15% reversibility to albuterol 200mcg, smoking history, not on oral steroids</td>
<td>At least a 1-week run-in

Salmeterol 50mcg BID via MDI vs. placebo (1-week washout)</td>
<td>Spirometry
Helium static lung volume
6 min. walking
Cycle ergometry
all measurements 1 and 6 hours after single dose and after 4 weeks chronic dosing
Borg sx score</td>
<td>FEV1- 1.18 (0.08)
FEV1 %pred- 42 (3)
Reversibility to albuterol- 12.5% (1.3)
ICS use – 86%

Mean (SE)</td>
<td>Dropouts n=5 (17.2%)
Small ↑ FEV1 at 1 and 6 hours and 4 weeks when compared to placebo
FVC > with salmeterol only at 6 hours after single dose.
No diff between groups with static lung volume, in distance walked, and bicycle ergometry. Perceived exertion signif less with salmeterol after chronic dosing.</td>
</tr>
<tr>
<td>D’Urzo 2001
R, DB, DD, CO, multicenter
Formoterol + ipratropium vs. albuterol + ipratropium
N=172
Each arm, 3 weeks
ITT</td>
<td>Outpatient COPD
≥ 40y/o
Current or previous smoker ≥ 10 pack-year of smoking, FEV1 ≤ 65% pred and ≥ 1.0L
FEV1/FVC ≤ 70%, 5-11% reversibility to albuterol 400mcg, sx score >1 on ≥ 3 days out of 7 of last week of run-in, no hosp or ER for exacerbation w/i 1 month</td>
<td>2-week run-in with IPR

Formoterol 12mcg bid via Aerolizer added to ipratropium MDI 40mcg qid + PL MDI qid
Crossover to
Albuterol 200mcg qid + ipratropium 40mcg qid + PL DPI bid

Rescue IPR allowed up to 8 puffs/d</td>
<td><u>1° endpoint</u>
PEFam (premed) over the last week of each tx period
<u>2° endpoint</u>
FEV1
FVC
AUC FEV1 0-6hr
AUC FVC 0-6hr
Sx scores
SGRQ
# of exacerbations</td>
<td>ICS use -40.9%; theo used by 9.4%
FEV1 (prebronchodil)- 1.4L (0.36)
FEV1 % pred (prebronchodil)- 51.3 (10.48)
FEV1/FVC- 52.9 (9.13)
PEFam (prebronchodil)- 259 L/min (80.8)
Total sx score – 5.8
Prn albuterol – 1.9 puffs/d

Mean (SD)</td>
<td>
<table>
<tr><th></th><th>FI</th><th>SI</th><th>FI - SI</th></tr>
<tr><td>PEFam (pre dose) Δ from baseline</td><td>+15.31 (36.1)</td><td>+3.0 (43.1)</td><td>+12.1 (39.3)*</td></tr>
<tr><td>Predose FEV1 (95% CI)</td><td></td><td></td><td>0.116 (0.003, 0.15)*</td></tr>
<tr><td>FEV1 AUC</td><td></td><td></td><td>44.5 (32.3, 56.7)*</td></tr>
<tr><td>Total sx score</td><td></td><td></td><td>-0.6 (-1.01, -0.19)*</td></tr>
<tr><td>Rescue inhaler use</td><td>1.3</td><td>1.5</td><td></td></tr>
<tr><td>% days using 0, 1-2, 3-4, >4 inhalations</td><td>73.3/7.4/8/12.4</td><td>68.8/10.1/8.9/12.2</td><td></td></tr>
<tr><td>QOL total score</td><td></td><td></td><td>-1.52 (-3.18, 0.14)</td></tr>
<tr><td>% exacerb</td><td>65.4</td><td>69.2</td><td></td></tr>
</table>
*significant versus SI
</td>
</tr>
<tr>
<td>Boyd 1997
R, DB, Pr multicenter
Salmeterol vs. placebo
N=674
16 weeks
ITT</td>
<td>Current or previous smoker, 40-75y/o chronic bronchitis (ATS criteria), FEV1≤70% pred. and FEV1/FVC≤60, ↑ in FEV1 5-15% after 400-800mcg albuterol, daytime sx score ≥2 at least 4 of 7 days prior to randomization</td>
<td>2-week run-in

Salmeterol 50mcg or 100mcg BID via MDI +/- spacer
(added to pts. existing therapy)</td>
<td><u>1° outcome</u>
Daytime sx score
<u>2° outcomes</u>
Nighttime sx score
Additional prn bronchodilator
FEV1
6 minute walk
Borg scale of breathlessness
Incidence of exacerbations</td>
<td>%Current/ex-smoker- SAL50 55/45; SAL100 55/45l PL 60/40
FEV1 (L)- SAL 50 1.31 (0.51); SAL100 1.3 (0.53); PL 1.23 (0.47)
FEV1 % reversibility- SAL50 10.8 (9.6); SAL100 10 (8.2); PL 11.2 (11.6)
Median am sx score – 2.0 (all 3 groups)</td>
<td>
<table>
<tr><th></th><th>SAL50</th><th>SAL100</th><th>PL</th></tr>
<tr><td>Withdrawals</td><td>23 (3%)</td><td>27 (4%)</td><td>21 (3%)</td></tr>
<tr><td>Am sx score</td><td>1.0*</td><td>1.0*</td><td>2.0</td></tr>
<tr><td>% ↓ in prn albuterol use</td><td>-24*</td><td>-25*</td><td>-11</td></tr>
<tr><td>Δ FEV1 (ml)</td><td>+70*</td><td>+88*</td><td>- 30</td></tr>
<tr><td>% with Borg score < 3 post 6min walk</td><td>43.7*^</td><td>34.8</td><td>32.6</td></tr>
<tr><td>6min walk</td><td colspan="3">No difference in distance walked between the 3 groups</td></tr>
<tr><td>Exacerbations</td><td>21%</td><td>25%</td><td>26%</td></tr>
</table>
*sig vs. placebo
^sig vs. SAL 100
</td>
</tr>
</table>

Jones 1997 **Salmeterol vs. placebo** Quality of life assessment from Boyd study	See Boyd 1997	See Boyd 1997	St. George's Respiratory Questionnaire(SGRQ) Medical Outcomes Study Short Form 36(SF-36)	**FEV1 (L)-** SAL 50 1.4 (0.5); SAL100 1.4 (0.5); PL 1.3 (0.5) **FEV1%pred-** SAL50 47 (16); SAL100 45 (15); PL 45 (14) **FEV1 % reversibility-** SAL50 10.8 (9.6); SAL100 10 (8.2); PL 11.2 (11.6) **Use of ICS-** 64-68% **SGRQ total score-** SAL50 54 (17); SAL100 56 (18); PL 52 (18)	Salmeterol 50 mcg showed improvement in SGRQ total score and impact score compared to placebo. Components of the SF-36 showed a worsening score with 100mcg dose.
Mahler 1999 R, DB, DD, PC, Pr, multicenter **Salmeterol vs. ipratropium vs. placebo** N=411 12 weeks	≥ 35y/o, ≥ 10 pack-year of smoking, FEV1 > 0.70L and ≤ 65% pred, FEV1/FVC ≤ 70%, grade 1 breathlessness on the Medical Research Council dyspnea scale	Salmeterol 42mcg bid vs. Ipratropium 36mcg qid vs. placebo via MDI *Baseline bronchodil and theo were d/c'd; inh steroids or ≤ 10mg pred was continued* *Prn albuterol allowed* ***Pts. stratified according to response to albuterol 180mcg (FEV1 ↑≥ 12% and ≥ 200ml)***	1° endpoints 12 hr. FEV1-AUC severity of dyspnea using baseline dyspnea index (BDI); change in severity of dyspnea transition dyspnea index (TDI); 2° endpoints 6MW with Borg dyspnea scale to measure breathlessness; patient self-rating of symptoms; HRQL using chronic resp disease questionnaire (CRDQ)	**Dur of COPD (y)** – SAL 7.5 (0.6); IPR 7.3 (0.6); PL 8 (0.7) **FEV1%pred-** SAL 42.1 (1.08); IPR 37 (1.14); PL 40.8 (1.12) **FEV1/FVC-** SAL 0.49 (0.01); IPR 0.46 (0.01); PL 0.49 (0.01) **FEV1 (L)-** SAL 1.36 (1.62); IPR 1.18 (1.42); PL 1.31 (1.54) **% with reversibility to albuterol-** SAL64.4%; IPR 64.7%; PL 65% **prn albuterol (puffs/d)-** SAL 4.6 (0.3); IPR 4.5 (0.3); PL 4.3 (0.3) **BDI-** SAL 5.9; IPR 6.0; PL 6.3 mean (SE)	**Withdrawals-** PL 16%, 7%SAL, 13.5% IPR **FEV1AUC** SAL*^ > IPR* > PL **Imp in TDI scores** sig for IPR and SAL vs. PL (not seen in pts. in the nonresp strata) No changes in the Borg dyspne scale or 6MW for any group **Daily albuterol use** – SAL 2 ± 0.3*; IPR 2.4± 0.3* (not seen in pts. in the nonresp strata) **Pt. Self-assess-** imp seen with all group, but no diff between groups in daytime and nighttime cough + chest tightness. Nighttime SOB SAL better than IPR (p=0.043). **CRDQ-** overall score higher for SAL and IPR vs. PL (P=0.007). Proportion of pts. with ↑ in score of ≥ 10- SAL 46%(p=0.002), IPR 39% (p=0.041), PL 27% **% of pts. with ≥ 1 exacerbation-** SAL 20.7%; IPR 30.8%; PL 32.9% SAL delayed time to first exacerbation compared to IPR and PL *significant vs. placebo ^significant vs. ipratropium at weeks 4 and 8 only
Rennard 2001 R, DB, PC, Pr Multicenter **Salmeterol vs. ipratropium vs. placebo** N=405 12 weeks	35y/o FEV1 > 0.7L FEV1 % pred ≤ 65% Pts. stratified according to response to albuterol (≥ 12% and 200ml ↑ in FEV1) ≥ 1 on MMRC dyspnea scale	Salmeterol 42mcg bid ipratropium 36mcg qid Placebo All given via MDI *May cont. ICS (77% of patients)*	1° endpoints FEV1 AUC 1-12hrs BDI/TDI 2° endpoints FEV1 6-min walk Borg scale (BS) for dyspnea pre- and post-walk CRDQ Exacerbations Sx score (SOB, chest tightness, cough, prn	**FEV1 (pre-albuterol)-** SAL 1.22 (0.04); IPR 1.28 (0.04); PL 1.3 (0.05) **FEV1 (post-albuterol)-** SAL 1.46 (0.04); IPR 1.52 (0.05); PL 1.52 (0.05) **% of pt. with reversibility to albuterol-** SAL 59; IPR 61; PL 57 **% of pts. with reversibility to ipratrop** – SAL 46%; IPR 44%; PL 43% **prn albuterol (puffs/d)-**	**Withdrawals-** SAL 16.7%; IPR 18.1%; PL 21.5% **FEV1 AUC** – SAL=IPR **Duration of action** SAL > IPR **Onset of action** IPR > SAL Overall, albuterol responsive pts had greater response to both SAL and IPR than albuterol unresponsive pts. Effects did not wane with SAL or IPR **TDI-** improvement for SAL and IPR vs. placebo **6-min walk** did not ↑ by more than 10yds for any group pre-walk BS for dyspnea ↓ for SAL vs. PL **BS for dyspnea post-walk** –post-walk scores did not change signif among the 3 groups **% exacerb-** 30.4% PL; 28.8% SAL; 26.8% IPR

<table>
<tr><td></td><td></td><td></td><td>alb, nighttime awakenings)</td><td>SAL 3.6 (0.3); IPR 4.4 (0.3); 4.1 (0.03)
nocturnal awakening – SAL 0.7 (0.08); IPR 0.64 (0.07); PL 0.47 (0.06)
BDI- SAL 5.96; IPR 6.27; PL 6.01</td><td>CRDQ- ↑ in all 3 groups, but did reach signif
% of pts. achieving Δ CRDQ score > 10 from baseline- SAL 46%; IPR 41%; PL 38%
Sx score ↓ in all groups but not sign diff from that seen with PL
Prn alb ↓ in with SAL* or IPR*</td></tr>
<tr><td>Dahl 2001
R, DB, PC, DD
Multicenter
Formoterol vs. ipratropium vs. placebo
N=780
12 weeks
ITT</td><td>COPD per ATS guidelines
Current or previous smoker
≥ 10 pack-year
FEV1 < 70% pred
FEV1 > 750ml
FEV1/FVC < 88%pred
Daytime or nighttime sxs present ≥ 4 of the last 7 days of run-in</td><td>10-21 day placebo run-in
Formoterol 12mcg bid vs. formoterol 24mcg bid via Aerolizer vs. ipratropium 40mcg qid via MDI vs. PL

Pts. able to continue stable dose of ICS</td><td><u>1° endpoint</u>
FEV1 AUC 0-12hrs
<u>2° endpoint</u>
PEF
Predose FEV1
Prn albuterol
Exacerbations (3 levels)
1) days with at least 2 indiv sx scores ≥ 2 and/or 20% ↓ PEF
2) req steroids, antibiotics or O2
3) req. hosp
Total sx score
SGRQ</td><td>Duration of COPD (yrs.) - F12 7.1; F24 7.0; Ipr 7.3; PL 8.7
FEV1 (L)- F12 1.32; F24 1.31; Ipr 1.25; PL 1.26
FEV1 % pred – F12 46; F24 45; Ipr 45; PL 43.9
FEV1/VC % pred – F12 61.2; F24 61.8; Ipr 61.6; PL 59.4
PEFam – F12 255; F24 258; Ipr 243; PL 241
% pts. with reversibility – F12 43.8; F24 44.3; Ipr 39.7; PL 40.5
% using ICS- F12 47%; F24 53%; Ipr 52%; PL 54%</td><td>
<table>
<tr><th></th><th>F12</th><th>F24</th><th>Ipr</th><th>PL</th></tr>
<tr><td>Withdrew</td><td>7%</td><td>12%</td><td>9%</td><td>15%</td></tr>
<tr><td>ΔFEV1 AUC (95% CI)</td><td>223ml*^ (0.174, 0.273)</td><td>194ml*^ (0.145, 0.243)</td><td>137ml* (0.088, 0.186)</td><td></td></tr>
<tr><td>ΔFEV1 AUC (rever/irre ver pts.)</td><td>244*^/137*</td><td>241*^/213*#</td><td></td><td></td></tr>
<tr><td>Predose PEFam</td><td>290*^</td><td>281*^</td><td>254</td><td>243</td></tr>
<tr><td>Prn albut</td><td>1.2*^</td><td>1.7*^</td><td>2.1</td><td>2.5</td></tr>
<tr><td>SGRQ</td><td>-6.6*^</td><td>-4.8*</td><td>-2.7</td><td>-1.5</td></tr>
<tr><td>Req. OCS /antibiotic</td><td>7%/13%</td><td>8%/14%</td><td>10%/14 %</td><td>8%/12%</td></tr>
<tr><td>Hosp. (n)</td><td>2</td><td>2</td><td>6</td><td>4</td></tr>
</table>
*Significant vs. placebo
^significant vs. IPR
#significant vs. F24</td></tr>
<tr><td>DiLorenzo 1998
R, Open label multicenter
Salmeterol vs. theophylline
N=178
3 months and 1 year</td><td>Stable COPD as defined by ATS
Pre-bronch FEV1 50-80% pred
≥ 10% ↑ in FEV1 with alb 200mcg
Daytime + nighttime sx score ≥ 2
Daytime sx score ≥ 1 during run-in</td><td>2 week run-in
Salmeterol 50mcg MDI bid vs. theophylline SR (titrated to 10-20 mcg/ml)

Inhaled or oral steroids (<20mg/d of pred equiv). Mast cell stabilizers, prn albuterol were permitted</td><td><u>1° endpoint</u>
Efficacy and tolerability at 3 months
<u>2° endpoint</u>
Safety profile at 1 yr
QOL (SF-36)</td><td>FEV1 (L)- sal 2.0 (0.6); theo 1.9 (0.5)
FVC (L)- Sal 2.9 (0.9); theo 2.8 (0.7)
PEFam (L/min)- sal 324 (99.7); theo 298.8 (88.7)
PEFpm – sal 340.9 (104.7); theo 314 (89.2)
16.5% of pts. were using inhaled steroids
% days/nights of no prn alb use- sal 15%23%; theo 14%/18%
median % of sx-free days/nights– sal 14.6%23.4%; theo 13.7%/18.4%

Mean (SD)</td><td>
<table>
<tr><th></th><th>Salmeterol</th><th>Theophylline</th></tr>
<tr><td>PEFam @ 3mos</td><td>+45^</td><td>+25</td></tr>
<tr><td>PEFpm @ 3mos</td><td>+39</td><td>+25</td></tr>
<tr><td>% sx-free days/nights @ 3 mos</td><td>59.7%*^/ 67.2%*^</td><td>46.1%*/49.3%*</td></tr>
<tr><td>FEV1 @ 3mos</td><td colspan="2">0.16^ (difference between SAL – theo)</td></tr>
<tr><td>% days/nights of no prn albuterol</td><td>67.4%*^/76%*^</td><td>50%*/60.4%*</td></tr>
<tr><td>MD assessment very effect/effective @ 1mo.</td><td>18.2%^/56.8%^</td><td>2.4%/30.5%</td></tr>
<tr><td>Pt. assessment very effect/effective</td><td>24%^/50.7%^</td><td>9.1%/37.9%</td></tr>
<tr><td>QOL (8 domains)</td><td colspan="2">Both showed improvement, but sal > theo in 3 domains: physical fx, Δ's in health perception, social fx</td></tr>
<tr><td>AEs/severe AEs</td><td>49.5%/4%</td><td>49.4%/8.3%</td></tr>
<tr><td>Incid. COPD exacerb (3mos/12mos)</td><td>3.4%/9%</td><td>2.7%/8.9%</td></tr>
</table>
*significant vs. baseline</td></tr>
</table>

<table>
<tr><td></td><td></td><td></td><td></td><td></td><td>^significant vs. theo</td></tr>
<tr><td>Abstract
R, DB, PC
multicenter
Formoterol vs. theophylline
N= 854
12 months
ITT</td><td>COPD as defined by ATS
Current or previous smoker > 10pack years</td><td>10-21 day run-in
inhaled arms were double-blind; theo arm open-label

formoterol 12mcg bid vs. formoterol 24mcg bid vs. inhaled placebo (all inhalers were via Aerolizer) vs. slow-release theo adjusted to plasma levels</td><td>FEV1 AUC 0-12hrs
PEF
Rescue albuterol use
% bad days defined as sx score ≥ 2 and/or >20% ↓ in PEF from baseline
QOL-SGRQ</td><td>Dur of COPD (y)-F12 9.6; F24 7.9; theo 8.5; PL 7.7
FEV1 (L)- F12 1.36; F24 1.39; theo 1.33; PL 1.4
FEV1 %pred-F12 47, F24 47; theo 46; PL 49
FEV1/FVC- F12 49; F24 49; theo 49; PL 50
PEF (pre-med)- F12 259; F24 251; theo 247; PL 252
% pts. reversible- F12 45; F24 55; theo 49; PL 46
% reversibility- F12 16; F24 19; theo 17; PL 16
prn albuterol (puffs/d)- F12 2.9; F24 2.9; theo 2.7; PL 3.1</td><td>Dropouts %- F12 25; F24 19%; theo 39%; PL 27%
FEV1 AUC- F12, F24, and theo superior to PL; F12 was superior to theo; F24 superior to theo only for the first 6 mos.
Lung function improved with F12 and F24 in poorly reversible pts.
PEF diff from PL- F12 22L/min^; F24 29L/min.^ Theo^ vs. PL signif only for the first 9 mos.
PEF diff from theo- F12 10 L/min; F24 17L/min*
Rescue meds (puffs/d)-F12 1.7^; F24 1.5^; theo 2.2; PL 2.3
% bad days -F12 31.9%^; F24 34.4%^*; theo 39.4%; PL 40.9%
# with one COPD-related hosp- F12 10; F24 5; theo 5; PL 16
# with 2-5 COPD-related hosp- F12 0; F24 0; theo 1; PL 4
QOL- improved total scores with F12, F24, and theo vs. PL
Sx scores- reduced in all active-tx groups, difference did not reach statistical significance

^sig vs. PL
*sig vs. theo</td></tr>
<tr><td>Van Noord 2000
R, DB, PC, DD, Pr, multicenter
Salmeterol vs. salmeterol + ipratropium vs. placebo
N=144
12 weeks
ITT</td><td>Stable COPD according to ATS criteria
Current or ex-smokers
10 pack-years
40-75 y/o
No change in COPD meds ≥ 6 weeks
No change in smoking ≥ 6 months
FEV1 < 75% pred post-albuterol 200mcg
Daytime sx score at end of run-in ≥ 2 on at least 4 out the last 7 days</td><td>2 week run-in (beta-agonist and ipratrop stopped, steroids, theo, prn albuterol allowed)

Salmeterol 50mcg bid vs. salmeterol 50mcg bid + ipratropium 40mcg qid vs. Placebo
given via MDI + chamber</td><td><u>Single dose study</u>
FEV1%pred
Specific airway conductance (sGaw)

<u>12-week study</u>
Am symptom score
Rescue albuterol use
Exacerbation
sGaw
PEFam</td><td>Am sx score-SAL 2.0 (0.1); SAL+IPR 2.0 (0.1); PL 1.9 (0.1)
FEV1 (L)- SAL 1.3 (0.4); SAL+IPR 1.4 (0.4); PL 1.3 (0.4)
FEV1 %pred- SAL 42 (10); SAL+IPR 41 (12); PL 38 (10)
FEV1/FVC- SAL 43 (8); SAL+ IPR- 42 (9); PL 41 (9)
Raw (kPa·L^{-1}) -SAL 0.63 (0.23); SAL+IPR- 0.65 (0.23); PL 0.72 (0.3)
<b>sGaw (kPa·L^{-1}) – SAL 0.35 (0.18); SAL+IPR 0.33 (0.13); PL 0.29 (0.09)
PEFam- SAL 246 (9); SAL+IPR 252 (11); PL 238 (9)

Mean (SD)</td><td>Single-dose study
<table><tr><th></th><th>SAL</th><th>SAL+IPR</th></tr><tr><td>FEV1%pred
peak ↑/@12hr</td><td>7 (0.7)^/
2 (1.0)^</td><td>11 (0.8)^/
3 (0.8)^</td></tr><tr><td>sG(aw)
peak ↑/@12hr</td><td>60 (7.2)%^/
25 (5.6)^</td><td>94 (8.9)^/
25 (5.1)^</td></tr></table>
12-week study
<table><tr><th></th><th>SAL</th><th>SAL+IPR</th><th>PL</th></tr><tr><td>Dropouts (n)</td><td>7</td><td>5</td><td>8</td></tr><tr><td>Am sx score</td><td>1.4 (0.1)^</td><td>1.3 (0.1)^</td><td>1.7 (0.1)</td></tr><tr><td>Prn albuterol</td><td>↓ 65%^</td><td>↓ 69%^</td><td>↓ 24.5%</td></tr><tr><td>exacerbation</td><td>23%</td><td>13%^</td><td>36%</td></tr><tr><td>↑ FEV%pred</td><td>5 (0.9)</td><td>8 (08)</td><td>1 (0.9)</td></tr><tr><td>↑ sG(aw)</td><td>36 (6)%</td><td>61 (6)%*</td><td>16 (6)%</td></tr><tr><td>PEFam</td><td>262 (11)^</td><td>277 (12)^</td><td>236 (9)</td></tr></table>Mean (SE)
^sig vs. placebo
*sig vs. salmeterol</td></tr>
</table>

<table>
<tr>
<td>ZuWallack 2001
R, DB, DD
Multicenter
Salmeterol + theo vs. salmeterol vs. theo
N=943
12 weeks
ITT</td>
<td>≥45y/o
COPD
20 pack-year history
FEV1 ≥ 0.7L
FEV1 % pred ≤ 65%FEV1/FVC ≤70%</td>
<td>Sal 42mcg bid + theo vs. sal 42mcg bid vs. theo

Groups stratified into albuterol resp and nonresp
Theo 10-20mcg/ml

Prn albuterol, stable doses of ICS or oral steroids ≤ 10mg/d were allowed</td>
<td><u>1° endpoint</u>
AUC FEV1 0-12hrs
<u>2° endpoint</u>
BDI/TDI dsypnea rating
PEFam/PEFpm
Sx scores
Prn albuterol
HRQOL
Tx. satisfaction</td>
<td>Dur of COPD – SAL+Theo 6.8 (0.4); SAL 6.7 (0.4); theo 6.6 (0.4)
% current smoker – SAL+theo 42%; SAL 41%; theo 39%
%using ICS- SAL+theo 36%; SAL 36%; theo 39%
FEV1 % pred-SAL+theo 40.8 (0.69); SAL 40.1 (0.74); Theo 40.7 (0.75)

mean (SE)</td>
<td>
<table>
<tr><th></th><th>SAL+ Theo</th><th>SAL</th><th>Theo</th></tr>
<tr><td>Withdrew 2° AE</td><td>6%</td><td>8%</td><td>8%</td></tr>
<tr><td>FEV1 AUC</td><td colspan="3">S+T* > S, T;
S > T only for hours 1-4</td></tr>
<tr><td>CRDQ</td><td>+12.7</td><td>+7.6</td><td>+8.6</td></tr>
<tr><td>% with ≥ 10pt. improvement</td><td>54*</td><td>45</td><td>42</td></tr>
<tr><td>% exacerbations</td><td>15.3*^</td><td>23</td><td>30.5</td></tr>
<tr><td>TDI, prn albuterol, PEF, tx satisfaction</td><td colspan="3">S+T* > S, T</td></tr>
<tr><td>Sx free days</td><td colspan="3">S+T^ > T</td></tr>
</table>
GI AEs and ↑ HR greater in theo groups

*significant vs. theo alone or salmeterol alone
^ significant vs. theo alone</td>
</tr>
<tr>
<td>Cazzola 2000
R, open label
Salmeterol vs. salmeterol + fluticasone vs. salmeterol + theo
N=80
3 months
(only pts. completing 3 mos were included in efficacy analysis)</td>
<td>Well-controlled COPD per ATS definition
On theo with level 10-20mcg/mL
>50y/o
H/O ≥ 20 yr. smoking
≤ 12% reversibility to albuterol 400mcg,
FEV1 < 85% pred post-albuterol</td>
<td>2 week run-in
salmeterol 50mcg bid vs. salmeterol 50mcg bid +fluticasone 250mcg bid vs. salmeterol 50mcg bid + fluticasone 500mcg bid vs. salmeterol 50mcg bid + theo bid (titrated to 10-20mcg/ml)

doses given via MDI + aero chamber</td>
<td>FEV1
FEV1 when given albuterol

AEs not evaluated</td>
<td>Pack-yrs- S 45.1 (41.1-49); S+FP250 42.9 (39.1-46.8); S+FP500 44.4 (41.5-47.4); S+theo 46.8 (43-50.6)
FEV1-no diff between groups</td>
<td>
<table>
<tr><th></th><th>S</th><th>S+FP250</th><th>S+FP500</th><th>S+theo</th></tr>
<tr><td>ΔFEV1 from baseline (95%CI)</td><td>0.163 (0.08, 0.245)</td><td>0.188 (0.089, 0.287)</td><td>0.239 (0.183, 0.296)</td><td>0.157 (0.27, 0.288)</td></tr>
<tr><td>Max ↑ FEV1 over pre-albuterol values</td><td>0.1 (0.0048, 0.152)</td><td>0.188 (0.089, 0.287)</td><td>0.232 (0.163, 0.3)</td><td>0.138 (0.034, 0.233)</td></tr>
<tr><td>Drop-outs (n)</td><td>3</td><td>2</td><td>2</td><td>4</td></tr>
</table>
All tx arms significant vs. baseline.</td>
</tr>
</table>

<u>Abbreviations used in the tables summarizing the clinical trials</u>

R=randomized, DB= double-blind, SB=single-blind, DD=double-dummy, CO=cross-over, PC=placebo-controlled, Pr= parallel; ICS=inhaled corticosteroid, FOR=formoterol, SAL=salmeterol, PL=placebo, PEFam=morning peak expiratory flow, PEFpm=evening peak expiratory flow, AUC=area under the curve

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