

Castillo Grau & Asociados

ABOGADOS

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Señores
DIRECCION DE NUEVAS CREACIONES
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Bogotá, D.C.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 13-284465- -00008-0000

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Re.: Código 011-378-444
Expediente No. 13-284.465
Fase nacional de Solicitud
de Patente PCT
PEARL THERAPEUTICS, INC.

En relación con el expediente de la referencia y dando cumplimiento a la última providencia recaída sobre este asunto por medio del presente escrito me permito manifestarles lo siguiente:

1. De conformidad con precisas instrucciones de mi representada, se adjunta un nuevo capítulo reivindicatorio el cual se encuentra íntegramente soportado en la descripción.
2. La nueva reivindicación 1 reclama una composición para uso en el tratamiento de una enfermedad o desorden pulmonar. Todas las demás reivindicaciones dependen de la cláusula 1, de tal manera que la materia ahora reclamada es íntegramente patentable.
3. Con respecto a los argumentos y objeciones tanto a la oposición y esa Dirección, la sociedad solicitante se permite efectuar las siguientes precisiones y comentarios sobre el particular.
4. Esa Dirección ha hecho referencia a los argumentos del Opositor con respecto a la novedad y nivel inventivo a la luz de Weers (US2008/0226564), Clarke (US2010/0034890), Nilsson (US2005/0042174), y Mahler (Mahler et al., Effectiveness of Fluticasone Propionate and Salmeterol Combination Delivered via the Diskus Device in the Treatment of Chronic Obstructive Pulmonary Disease, Am. J. Respir.

Crit. Care Med. 166: 1084-1091, 2002). No entendimos cuáles reivindicaciones fueron rechazadas sobre esta base, y la parte Opositora no presentó argumentos que indicaran cómo el estado de la técnica afecta la novedad y el nivel inventivo de las reivindicaciones. No obstante, las reivindicaciones modificadas son novedosas e inventivas con respecto a los antecedentes citados. Por las razones que se esgrimen en detalle más adelante, ninguno de los antecedentes citados enseña las características citadas en las reivindicaciones. Más aún, de la revisión de las enseñanzas encontradas en los antecedentes citados, ya sea que los antecedentes citados se consideren aisladamente o en combinación, la persona medianamente versada en la materia técnica correspondiente no encontraría las características del objeto reivindicado o alguna motivación para modificar las enseñanzas de los antecedentes citados en una forma que pudiera llegar al objeto reivindicado.

Tal como queda modificada, la reivindicación independiente reza así:

1 Una co-suspensión farmacéuticamente aceptable que comprende;
un medio de suspensión que comprende un propelente farmacéuticamente aceptable, una primera especie de partículas respirables del agente activo que comprende glucopirrolato o una sal, éster, isómero o solvato farmacéuticamente aceptable de la misma, una segunda especie de partículas respirables del agente activo que comprende formoterol o una sal, éster, isómero o solvato farmacéuticamente aceptable de la misma, una o más especies de partículas suspensoras respirables, que se caracterizan porque la primera y la segunda especie de partículas respirables del agente activo y las partículas suspensoras respirables se localizan conjuntamente para formar una co-suspensión dentro del medio de suspensión, para usar en el tratamiento de una enfermedad o trastorno pulmonar mediante la administración de la co-suspensión al paciente dos veces al día como un aerosol respirable, que se caracteriza porque una cantidad terapéuticamente efectiva del glucopirrolato o la sal, éster, isómero o solvato farmacéuticamente aceptable de la misma y

formoterol o la sal, éster, isómero o solvato farmacéuticamente aceptable de la misma, que comprende no más de 150 µg del glucopirrolato o la sal, éster, isómero o solvato farmacéuticamente aceptable del mismo y no más de 12 µg de formoterol o la sal, éster, isómero o solvato farmacéuticamente aceptable del mismo, se le da al paciente en cada administración y que se caracteriza porque la administración de la co-suspensión al paciente se traduce en un incremento de IC de 250 mL o más.

Todas las demás reivindicaciones dependen directa o indirectamente de la reivindicación 1 y, por tanto, incorporan todas las características citadas en la reivindicación 1.

5. Weers (US2008/0226564)

Weers destaca las partículas respirables que incorporan agentes activos: "En contraposición, el estado de la técnica intenta proporcionar suspensiones estabilizadas que requieren excipientes (es decir, surfactantes) que son solubles en el medio de suspensión, la presente invención da cabida a las dispersiones estabilizadas, por lo menos en parte, mediante la inmovilización de los agentes bioactivos y los excipientes dentro de la matriz estructural de las microestructuras huecas, porosas". Ver Weers, página 5, párrafo [0057] (el énfasis es nuestro). En la página 8, párrafo [0074], Weers revela que "las microestructuras perforadas de preferencia comprenden por lo menos un agente bioactivo". Ver también la página 10, párrafos [0086] y [0087]. En la página 10, párrafo [0090], Weers revela además suspensiones en las cuales la microestructura perforada "puede comprender, incorporar, adsorber, absorber, estar recubierta con o estar formada por el agente bioactivo". Cada uno de los ejemplos presentados en Weers enseña procesos para preparar partículas respirables que incorporan un agente activo, y todas las materias primas usadas en el proceso de secado por aerosol incluyen material excipiente y un agente activo. Ver, p.ej., Weers, página 16, párrafos [0141]-[0142]; página 17, [0148].

Las enseñanzas de Weers, y los ejemplos experimentales incluidos en el antecedente, destacan específicamente las ventajas alcanzadas por la formación de microestructuras porosas que incorporan el o los agentes activos que se van a administrar. Por ejemplo, en la página 4, párrafo [0051], Weers enseña que "el medio de suspensión es capaz de permear [las microestructuras perforadas], creando así una "homodispersión", que se caracteriza porque las fases continua y dispersada son sustancialmente indistinguible". Weers además apunta a las ventajas de formar una "homodispersión" en la cual la densidad de las partículas incluidas en el medio de suspensión se aproximan estrechamente a la densidad del medio mismo y la suspensión no incluye partículas heterogéneas, que dan lugar a una desaceleración de la separación de la emulsión o la sedimentación de las partículas. Ver, p.ej., Weers, página 4, párrafo [0051].

Las co-suspensiones citadas en las reivindicaciones de la presente solicitud no son homodispersiones como las indicadas por Weers, e incorporan dos especies diferentes de partículas heterogéneas – partículas del agente activo, y partículas suspensoras con características específicamente definidas. A diferencia de los abordajes a la formulación defendidos por Weers, las partículas del agente activo y las partículas suspensoras empleadas en el objeto reivindicado de la presente solicitud se forman por separado y exhiben densidades que son diferentes entre sí y del medio de suspensión. A pesar de las diferencias de densidad, las partículas del agente activo y las partículas suspensoras respirables de las co-suspensiones de acuerdo con las reivindicaciones modificadas se localizan conjuntamente dentro del medio de suspensión.

Por tal razón, Weers no describe la co-suspensión definida en las reivindicaciones modificadas, y al destacar los beneficios de las homodispersiones y las composiciones en suspensión que utilizan partículas de excipiente que incorporan

agentes activos, Weers en realidad aleja a la persona medianamente versada en la materia técnica correspondiente del objeto reivindicado.

Weers no enseña las co-suspensiones de las reivindicaciones, que tienen las partículas del agente activo y las partículas suspensoras separadas, y que tienen los efectos sobre la capacidad inspiratoria (IC) o el volumen espiratorio forzado en un segundo (FEV 1) que se citan en las reivindicaciones.

6. Clarke (US2010/0034890)

Clarke (US2010/0034890) revela composiciones farmacéuticas que comprenden formoterol y propionato de fluticasona y su uso en el tratamiento de las enfermedades inflamatorias u obstructivas de las vías respiratorias. Clarke no prevé las reivindicaciones modificadas. Clarke no revela composiciones que comprenden glucopirrolato o partículas suspensoras, como las citadas en la reivindicación 1. La composición ejemplar para ser administrada por un inhalador de dosis medidas (MDI) que se muestra en el Ejemplo 1 de Clarke comprende etanol como cosolvente y HFA como a propelente, pero no revela, sugiere, o siquiera contempla los agentes activos o las partículas suspensoras de la reivindicación 1.

7. Nilsson (US2005/0042174)

Nilsson (US2005/0042174) revela métodos para la administración de medicamentos en forma de polvo seco usando un dispositivo inhalador de polvo seco. En primer lugar, Nilsson no prevé el objeto de las reivindicaciones modificadas. Nilsson no revela partículas suspensoras, la administración de glucopirrolato, o una suspensión que comprende un propelente. Segundo, Nilsson, solo o en combinación con los otros antecedentes, no sugiere o tan siquiera contempla las co-suspensiones de las reivindicaciones modificadas. Además, dadas las diferencias entre las plataformas de administración de suspensión de polvo seco y aerosol (como un inhalador de dosis medidas), la persona medianamente versada en la materia técnica correspondiente no miraría a la tecnología de polvo seco para desarrollar suspensiones en aerosol.

Por tal razón, ya sea que se considere solo o en combinación con los otros antecedentes, Nilsson no motivaría a la persona medianamente versada en la materia técnica correspondiente a desarrollar las co-suspensiones de la reivindicación 1.

8. Mahler (Mahler et al., Effectiveness of Fluticasone Propionate and Salmeterol Combination Delivered via the Diskus Device in the Treatment of Chronic Obstructive Pulmonary Disease, Am. J. Respir. Crit. Care Med. 166: 1084-1091, 2002)

Adjuntamos a este escrito una copia del documento de Mahler para referencia Effectiveness of Fluticasone Propionate and Salmeterol Combination Delivered via the Diskus Device in the Treatment of Chronic Obstructive Pulmonary Disease, Am. J. Respir. Crit. Care Med. 166: 1084-1091, 2002). Mahler enseña una terapia combinada con propionato de fluticasona y salmeterol, administrados como polvo seco. Mahler no revela, sugiere, o tan siquiera contempla las partículas suspensoras, la administración de glucopirrolato, o una suspensión en aerosol que tenga los efectos sobre la IC o el FEV 1 que se citan en las reivindicaciones. Como se anotó arriba, la persona medianamente versada en la materia técnica correspondiente no miraría a la tecnología del polvo seco para desarrollar suspensiones en aerosol. Por tal razón, Mahler, solo o en combinación con los otros antecedentes, no prevé las reivindicaciones de la presente solicitud. Además, las reivindicaciones de la presente solicitud tienen nivel inventivo sobre Mahler y los demás antecedentes.

9. La formulación de agentes activos para administración pulmonar desde un inhalador de dosis medidas plantea un desafío bastante impredecible. Esto es especialmente cierto para los medicamentos de alta potencia a dosis bajas en los cuales incluso una pequeña declinación del material medicamentoso administrable debido a inestabilidad física, inestabilidad química, o la mera pérdida del fármaco en las interfaces de las superficies internas del inhalador de dosis medidas puede redundar en que el paciente reciba una dosis inferior a la terapéutica de un medicamento que necesita. Los antecedentes citados no enseñan ni sugieren las co-suspensiones de las reivindicaciones modificadas.

Adjunto el comprobante de pago por concepto de 6 reivindicaciones adicionales por valor de \$ 192,000.00 , recibo No. 42,302

Renuncio al término faltante de traslado, y les solicito otorgar el privilegio de patente de invención aquí tramitado..

De Ustedes Atentamente,



LUIS FELIPE CASTILLO GIBSONE
T.P. No. 68.995 del C.S.J.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800.176.089-2

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**Industria y Comercio**
SUPERINTENDENCIA

RECIBO DE CAJA

No. 15 - 0042302

Bogotá D.C., Abril 17 de 2015 - 11:40:37

RECIBIDO DE : CASTILLO GRAU & ASOCIADOS LTDA.

NI 800.098.704

*** Soporte del Pago ***

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*** Conceptos Pagados ***

CANT. RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
6 50005-01-01 SOLICITUDES	1607 REIVINDICACION PATENTE UNITARIA ADICIONAL A LAS 10 INIC	32.000.00	192.000.00
			\$192.000.00

SON: **CIENTO NOVENTA Y DOS MIL PESOS MONEDA CORRIENTE***

Responsable: 

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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Reivindicaciones

1. Una co-suspensión farmacéuticamente aceptable que comprende;

un medio de suspensión que comprende un propelente farmacéuticamente aceptable

una primera especie de partículas respirables del agente activo que comprende glucopirrolato o una sal, éster, isómero o solvato farmacéuticamente aceptable de la misma.

una segunda especie de partículas respirables del agente activo que comprende formoterol o una sal, éster, isómero o solvato farmacéuticamente aceptable de la misma, una o más especies de partículas suspensoras respirables, que se caracteriza porque la primera y la segunda especies de partículas respirables del agente activo y las partículas suspensoras respirables se localizan conjuntamente para formar una co-suspensión dentro del medio de suspensión, para usar en el tratamiento de una enfermedad o trastorno pulmonar mediante la administración de la co-suspensión al paciente dos veces al día como un aerosol respirable, que se caracteriza porque una cantidad terapéuticamente efectiva del glucopirrolato o la sal, éster, isómero o solvato farmacéuticamente aceptable de la misma y formoterol o la sal, éster, isómero o solvato farmacéuticamente aceptable de la misma, que comprende no más de 36 µg del glucopirrolato o la sal, éster, isómero o solvato farmacéuticamente aceptable de la misma y no más de 12 µg del formoterol o la sal, éster, isómero o solvato farmacéuticamente aceptable de la misma se le administra al paciente en cada administración, y

que se caracteriza porque la administración de la co-suspensión al paciente se traduce en un incremento de la FEV1 de por lo menos 250 mL dentro de un tiempo seleccionado de entre 0,5 horas o menos, 1 hora o menos, y 1.5 horas o menos.

2. Una co-suspensión farmacéuticamente aceptable para usarla de acuerdo con la reivindicación 1 que se caracteriza porque la administración de la co-suspensión al

paciente se traduce en un incremento de FEV1 de por lo menos 300 mL dentro de un tiempo seleccionado de entre 0,5 horas o menos, 1 hora o menos, y 1.5 horas o menos.

3. Una co-suspensión farmacéuticamente aceptable para usarla de acuerdo con la reivindicación 1 o la reivindicación 2, que se caracteriza porque la co-suspensión es apropiada para administrarla con un inhalador de dosis medidas y que se caracteriza porque:

el medio de suspensión comprende un propelente HFA farmacéuticamente aceptable sustancialmente libre de materiales adicionales; y

las partículas suspensoras respirables comprenden un material fosfolípido que es sustancialmente insoluble en el propelente, que se caracteriza porque la masa total de las partículas suspensoras respirables supera la masa total de la primera y la segunda especies de partículas respirables del agente activo.

4. Una co-suspensión farmacéuticamente aceptable para usarla de acuerdo con cualquiera de las reivindicaciones precedentes, que se caracteriza porque la enfermedad o trastorno pulmonar se selecciona de entre por lo menos una de entre el grupo compuesto por asma, EPOC, rinitis alérgica, sinusitis, vasoconstricción pulmonar, inflamación, alergias, dificultad respiratoria, síndrome de dificultad respiratoria, hipertensión pulmonar, inflamación pulmonar experimentada con la fibrosis quística, y obstrucción pulmonar experimentada con la fibrosis quística.

5. Una co-suspensión farmacéuticamente aceptable para usarla de acuerdo con cualquiera de las reivindicaciones precedentes, que se caracteriza porque la enfermedad o trastorno pulmonar es EPOC.

6. Una co-suspensión farmacéuticamente aceptable para usarla de acuerdo con cualquiera de las reivindicaciones precedentes, que se caracteriza porque el glucopirrolato se encuentra en cualquier forma cristalina.

7. Una co-suspensión farmacéuticamente aceptable para usarla de acuerdo con cualquiera de las reivindicaciones precedentes, que se caracteriza porque el formoterol se encuentra en cualquier forma cristalina.

8. Una co-suspensión farmacéuticamente aceptable para usarla de acuerdo con cualquiera de las reivindicaciones precedentes que se caracteriza porque la proporción de la masa total de las partículas suspensoras respirables a la masa total de la primera y la segunda especies de partículas respirables del agente activo va desde arriba de 1 y hasta 200.

9. Una co-suspensión farmacéuticamente aceptable para usarla de acuerdo con la reivindicación 8, que se caracteriza porque la proporción de la masa total de las partículas suspensoras respirables a la masa total de la primera y la segunda especies de partículas respirables del agente activo se selecciona de entre los intervalos de entre 10 y 200, entre 60 y 200, entre 15 y 60, y entre 15 y 170.

10. Una co-suspensión farmacéuticamente aceptable para usarla de acuerdo con cualquiera de las reivindicaciones precedentes, que se caracteriza porque la co-suspensión comprende una sal farmacéuticamente aceptable de glucopirrolato seleccionado de entre sales fluoruro, cloruro, bromuro, yoduro, nitrato, sulfato, fosfato, formato, acetato, trifluoroacetato, propionato, butirato, lactato, citrato, tartrato, malato, maleato, succinato, benzoato, p-clorobenzoato, difenil-acetato o trifenilacetato, o-hidroxibenzoato, p-hidroxibenzoato, 1-hidroxinaftaleno-2-carboxilato, 3-hidroxinaftaleno-2-carboxilato, metanosulfonato, y bencenosulfonato.

11. Una co-suspensión farmacéuticamente aceptable para usarla de acuerdo con la reivindicación 10, que se caracteriza porque la sal farmacéuticamente aceptable de glucopirrolato se selecciona de entre sales de fluoruro, cloruro, bromuro y yoduro.

12. Una co-suspensión farmacéuticamente aceptable para usarla de acuerdo con cualquiera de las reivindicaciones precedentes, que se caracteriza porque la sal farmacéuticamente aceptable de glucopirrolato es bromuro de 3-[(ciclopentil-hidroxifenilacetil)oxi]-1.1-dimetilpirrolidinio.

13. Una co-suspensión farmacéuticamente aceptable para usarla de acuerdo con cualquiera de las reivindicaciones precedentes, que se caracteriza porque la co-suspensión comprende una sal farmacéuticamente aceptable de formoterol seleccionada de entre sales de los ácidos clorhídrico, bromhídrico, sulfúrico, fosfórico, fumárico, maleico, acético, láctico, cítrico, tartárico, ascórbico, succínico, glutárico, glucónico, tricarballico, oleico, benzoico, p-metoxibenzoico, salicílico, o- y p-hidroxibenzoico, p-clorobenzoico, metanosulfónico, p-toluenosulfónico y 3-hidroxi-2-naftaleno carboxílico.

14. Una co-suspensión farmacéuticamente aceptable para usarla de acuerdo con la reivindicación 13, que se caracteriza porque la sal farmacéuticamente aceptable de formoterol es fumarato de formoterol.

15. Una co-suspensión farmacéuticamente aceptable para usarla de acuerdo con cualquiera de las reivindicaciones precedentes que se caracteriza porque la administración de la co-suspensión al paciente se traduce en un incremento de IC de 200 mL o mayor.

16. Una co-suspensión farmacéuticamente aceptable para usarla de acuerdo con cualquiera de las reivindicaciones precedentes que se caracteriza porque la administración de la co-suspensión al paciente se traduce en un incremento de IC de 300 mL o mayor.

Effectiveness of Fluticasone Propionate and Salmeterol Combination Delivered via the Diskus Device in the Treatment of Chronic Obstructive Pulmonary Disease

Donald A. Mahler, Patrick Wire, Donald Horstman, Chal-Ni Chang, Julie Yates, Tracy Fischer, and Tushar Shah

Dartmouth Hitchcock Medical Center, Lebanon, New Hampshire; and GlaxoSmithKline, Research Triangle Park, North Carolina

This randomized controlled trial examined the benefits of combining an inhaled corticosteroid, fluticasone propionate (F), with an inhaled long-acting β_2 -agonist, salmeterol (S), to treat the inflammatory and bronchoconstrictive components of chronic obstructive pulmonary disease (COPD). A total of 691 patients with COPD received the combination of F and S (FSC), S (50 mcg), F (500 mcg), or placebo twice daily via the Diskus device for 24 weeks. A significantly greater increase in predose FEV₁ at the endpoint was observed after FSC (156 ml) compared with S (107 ml, $p = 0.012$) and placebo (-4 ml, $p < 0.0001$). A significantly greater increase in 2-hour postdose FEV₁ at the endpoint was observed after treatment with FSC (261 ml) compared with F (138 ml, $p < 0.001$) and placebo (28 ml, $p < 0.001$). There were greater improvements in the Transition Dyspnea Index with FSC (2.1) compared with F (1.3, $p = 0.033$), S (0.9, $p < 0.001$), and placebo (0.4, $p < 0.0001$). The incidence of adverse effects (except for an increase in oral candidiasis with FSC and F) was similar among the treatment groups. We conclude that FSC improved lung function and reduced the severity of dyspnea compared with individual components and placebo.

Keywords: chronic obstructive pulmonary disease; β_2 -agonist; inhaled corticosteroid; Transition Dyspnea Index

Chronic obstructive pulmonary disease (COPD) is a disease state that is characterized by inflammation and airflow obstruction leading to chronic bronchitis and/or emphysema (1). Patients with COPD experience exertional breathlessness caused by mucous secretion, edema of the airway wall, a loss of attachments to the terminal airways, and bronchoconstriction. As only smoking cessation has been shown to modify the progressive decline in lung function in patients with COPD, pharmacologic therapy has focused on the treatment of airway obstruction to improve symptoms, primarily dyspnea, as well as health status (2).

Maintenance treatment with bronchodilators, including β_2 -agonists, anticholinergic agents, and theophylline, has long been the standard of care, as these agents treat the bronchoconstriction associated with COPD. In the United States, the long-acting β_2 -agonists salmeterol (S) (Serevent Diskus; GlaxoSmithKline, Research Triangle Park, NC) and formoterol are currently approved for long-term, twice-daily maintenance treatment of bronchoconstriction associated with COPD. However, many patients remain symptomatic despite optimal use of bronchodilators.

The presence of inflammation in the airways supports the

rationale for instituting antiinflammatory therapy with an inhaled corticosteroid (3). Inhaled corticosteroid use has been shown to reduce inflammation associated with COPD (4–8). These studies have shown that inhaled corticosteroids, including fluticasone propionate (F) (Flovent Diskus; GlaxoSmithKline) (5, 8), have resulted in improvements in a variety of inflammatory indices in bronchoalveolar lavage (4, 7) and in sputum (5, 6, 8). Long-term studies of inhaled corticosteroids in patients with COPD have demonstrated improvements in FEV₁ (9–11) and reductions in exacerbations (9, 11) and rate of decline in health status (11). To date, no medication has been shown to alter the rate of decline of FEV₁ (9–12). These scientific and clinical data provided the foundation for the recent evidence-based Global Initiative for Chronic Obstructive Lung Disease Guidelines, sponsored by the National Heart, Lung, and Blood Institute and the World Health Organization (2). These guidelines recommend the use of inhaled corticosteroids in patients with moderate to severe COPD with significant symptoms who demonstrate a positive response to inhaled corticosteroid therapy or who experience repeated exacerbations (2).

The combination of F and S (FSC) (Advair Diskus; GlaxoSmithKline) would be expected to treat both the inflammatory and bronchoconstriction aspects of COPD. Delivery of these medications together as an inhalation powder in the Diskus device, administered as one inhalation twice daily, may help simplify treatment regimens and may also improve patient adherence compared with currently available COPD treatments.

The purpose of this study was to assess the effectiveness and safety of FSC and its individual components in the treatment of COPD. Specifically, our hypothesis was that combination therapy with FSC would increase airflow, reduce symptoms (including dyspnea), and improve health status over a 24-week period compared with the individual components and placebo.

METHODS

Patients

Patients were 40 years of age or older, were current or former smokers with a 20 pack-year or more history, and had a diagnosis of COPD (1). Inclusion criteria required a baseline FEV₁/FVC of 70% or less and a baseline FEV₁ of less than 65% of predicted but more than 0.70 L. Patients were required to have daily cough productive of sputum for 3 months of the year for 2 consecutive years and dyspnea. Specific exclusion criteria were current diagnosis of asthma, oral corticosteroid use within the past 6 weeks, abnormal clinically significant electrocardiogram, long-term oxygen therapy, moderate or severe exacerbation during the run-in, and any clinically significant medical disorder.

Study Design

This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter trial (protocol number SFCA3006). Patients began a 2-week, single-blind, run-in period during which they received placebo via Diskus and albuterol (metered-dose inhaler and/or nebulas; Ven-

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Supported by GlaxoSmithKline.

Correspondence and requests for reprints should be addressed to Donald A. Mahler, M.D., Dartmouth Hitchcock Medical Center, Section of Pulmonary and Critical Care Medicine, 1 Medical Center Drive, Lebanon, NH 03756-0001. E-mail: donald.a.mahler@hitchcock.org

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tolin Inhalation Aerosol; GlaxoSmithKline) on an as-needed basis, and discontinued use of corticosteroids and bronchodilators, with the exception of stable regimens of theophylline. After the run-in period, eligible patients were randomized as follows: F, 500 mcg; S, 50 mcg; F plus S combination, 500 and 50 mcg, respectively; or placebo via the Diskus device twice daily for 24 weeks. Patients were also given as-needed albuterol. Randomization was stratified by reversibility and investigative site to ensure a balance between treatment groups at each site and in terms of the number of reversible patients. Patients were evaluated weekly for the first 4 weeks of treatment, every 2 weeks until Week 8, and then every 4 weeks until study completion.

The primary efficacy measures were change in predose FEV₁ values for the comparisons of FSC to S and of F to placebo, and change in 2-hour postdose FEV₁ values for the comparisons of FSC to F and of S to placebo. Other efficacy parameters included morning peak expiratory flow (PEF), supplemental albuterol use, dyspnea assessed by the Transition Dyspnea Index (TDI) (13), the Chronic Bronchitis Symptom Questionnaire (14, 15), and exacerbations defined by treatment. Health status was evaluated using the Chronic Respiratory Disease Questionnaire (CRDQ) (16).

Safety was assessed using adverse events reporting, electrocardiograms, 24-hour Holter monitoring, vital signs, clinical laboratory evaluations, oropharyngeal examination, and short cosyntropin (Cortrosyn for injection; Organon, Inc., West Orange, NJ) stimulation testing (17).

The protocol was approved by the institutional review boards for each site, and all patients provided written informed consent.

Statistical Methods

Study enrollment was planned for 700 patients (175 per treatment group) at 65 centers. This sample size provided more than 90% power to detect differences between treatment groups of 100 ml in both predose and 2-hour postdose FEV₁ at the endpoint. The endpoint was

defined as the last on-treatment postbaseline assessment excluding any data from the discontinuation visit.

Differences between treatments at the endpoint and all other time points in the change from baseline in predose and postdose FEV₁, the Chronic Bronchitis Symptom Questionnaire, and the CRDQ were estimated and analyzed using contrasts from analysis of covariance adjusting for baseline and investigator. Estimation and analysis of differences in the Baseline Dyspnea Index/TDI were performed using contrasts with analysis of variance. Time to exacerbation was analyzed using Wald chi-square tests based on a Cox proportional hazards model with age and baseline FEV₁ as covariates. Overall average and monthly average morning PEF, nighttime awakenings, and albuterol use were analyzed using the van Elteren modification of the Wilcoxon test (18).

RESULTS

Study Population

Of the 1,352 patients screened in this study, 691 were randomized and treated. Seventeen patients at one investigative site were unevaluable because of poor study practices, and of the remaining 674 patients, 645 had an evaluable baseline assessment and at least one postbaseline assessment other than the discontinuation visit and were therefore included in the primary efficacy evaluation. A total of 234 patients (38%, 28%, 40%, and 32% for placebo, S, F, and FSC groups, respectively) were discontinued from the study. The most common reasons for discontinuation were adverse events (9.4%, 6.9%, 12.5%, and 6.7%), an exacerbation of COPD (8.8%, 5.6%, 10.1%, and 8.5%), and protocol violations (4.4%, 6.3%, 8.3%, and 4.6%), which was primarily the use of excluded medications. Demographic and

TABLE 1. KEY DEMOGRAPHICS AND CHARACTERISTICS AT SCREENING

Variable	Placebo (n = 181) n (%)	S 50 mcg (n = 160) n (%)	F 500 mcg (n = 168) n (%)	FSC (n = 165) n (%)
Sex				
Male	136 (75)	103 (64)	103 (61)	103 (62)
Female	45 (25)	57 (36)	65 (39)	62 (38)
Age, yr				
Mean	64.0	63.5	64.4	61.9
Range	44-90	40-84	42-82	40-86
Race				
White	166 (92)	152 (95)	156 (93)	156 (95)
Black	11 (6)	6 (4)	8 (5)	7 (4)
Asian/other	4 (2)	2 (1)	4 (2)	2 (1)
MMRC dyspnea score				
2	129 (71)	90 (56)	112 (67)	108 (65)
3	47 (26)	62 (39)	51 (30)	55 (33)
4	5 (3)	8 (5)	5 (3)	2 (1)
Use of inhaled steroids at screen	33 (18)	49 (31)	42 (25)	46 (28)
Duration of COPD, yr				
Median	6.00	6.00	5.00	5.00
Range	1-36	1-46	1-35	1-41
Diagnosis of emphysema	142 (78)	125 (78)	123 (74)	123 (75)
Smoking status				
Former smoker	84 (46)	86 (54)	91 (54)	89 (54)
Current smoker	97 (54)	74 (46)	77 (46)	76 (46)
Pack-years smoked				
Median	60.0	52.5	54.0	55.0
Range	20.0-165.0	20.0-193.0	20.0-200.0	15.0-150.0
Spirometry				
Mean FEV ₁ , ml	1,317	1,237	1,233	1,268
Mean FEV ₁ % predicted	41	40	41	41
Mean FEV ₁ /FVC	0.49	0.49	0.48	0.49
Bronchodilator response, %				
Mean	19.3	21.2	19.2	20.6

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; F = fluticasone propionate; FSC = fluticasone propionate combined with salmeterol; MMRC = Modified Medical Research Council (score of 2 or more required for study entry); S = salmeterol.

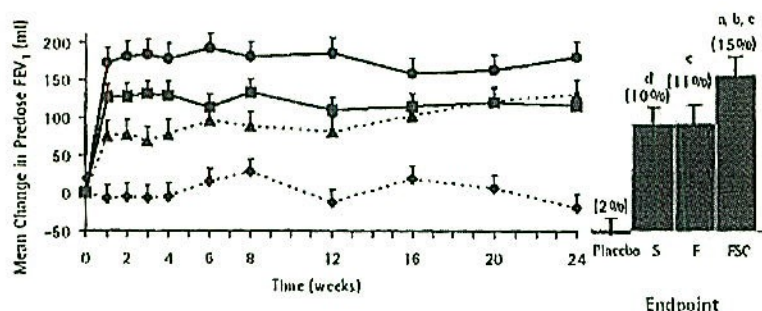


Figure 1. Improvement in predose FEV₁ with FSC (circles) compared with the individual components and placebo (diamonds). Values from weeks 1–24 are mean + SEM. a = FSC versus placebo, $p < 0.001$. b = FSC versus S (squares), $p = 0.012$. c = FSC versus F (triangles), $p = 0.038$. d = S versus placebo, $p < 0.001$. e = F versus placebo, $p < 0.001$.

Patients Remaining in Study:

Placebo	181	127	112
S	159	131	114
F	166	121	99
FSC	163	132	113

disease characteristics at screening are provided in Table 1. Screening spirometry results were comparable across treatment groups. The percentage of patients exhibiting reversibility to albuterol, defined as an increase of 12% or more and 200 ml in FEV₁, was similar across treatment groups, ranging from 51% in the S group to 56% in the placebo group.

Treatment compliance was high and comparable across the treatment groups. Approximately 90% of the patients had an individual adherence of 80% or more as measured by the dose counter on the Diskus device.

Lung Function

Predose FEV₁. A significantly greater increase in predose FEV₁ at the endpoint (the last treatment value) was observed after treatment with FSC (156 ml) compared with S (107 ml, $p = 0.012$) and placebo (−4 ml, $p < 0.001$) (Figure 1). The increase in predose FEV₁ at the endpoint after treatment with FSC was 14.5% over baseline. Significantly greater increases in predose FEV₁ were observed for treatment with FSC compared with that for S beginning at Week 1 (173 versus 127 ml, respectively, $p = 0.032$) and at most other time points throughout the study. A significantly greater increase in predose FEV₁ was also observed for treatment with F versus placebo at the endpoint (109 versus −4 ml, respectively, $p < 0.001$), as well as at all assessment points throughout the study, with the exception of Week 8. Estimated differences between treatment groups at the endpoint are summarized in Table 2.

Two-hour postdose FEV₁. A significantly greater increase in

2-hour postdose FEV₁ at the endpoint was observed after treatment with FSC (261 ml) compared with F (138 ml, $p < 0.001$) and placebo (28 ml, $p < 0.001$) (Figure 2). The increase in 2-hour postdose FEV₁ at the endpoint after treatment with FSC was 24.2% over baseline. Significantly greater increases in 2-hour postdose FEV₁ were observed at Day 1 and throughout the study during treatment with FSC compared with F. Significantly greater increases in 2-hour postdose FEV₁ were observed for the S treatment group versus placebo (233 versus 28 ml, respectively, $p \leq 0.024$) at the endpoint and at all assessment points throughout the study. Estimated differences between treatment groups at the endpoint are summarized in Table 2.

Response by reversibility. Patients who demonstrated reversibility of airway obstruction with albuterol had slightly better improvements in predose FEV₁, 2-hour postdose FEV₁, and TDI with individual components as well as with FSC. Although the magnitude of effect in nonreversible patients was somewhat lower, the effects were still clinically meaningful (Table 3).

Morning PEF rate. Increases in morning PEF on Day 2, approximately 24 hours after the initiation of treatment, were greater for FSC compared with F, S, and placebo ($p < 0.005$) (Figure 3). Greater increases in morning PEF were observed throughout the 24-week treatment period with FSC compared with F, S, and placebo. The mean overall change from baseline in morning PEF with FSC treatment (31.9 L/min) was greater than the sum of the mean changes from baseline observed with the individual components, 12.9 and 16.8 L/min for F ($p < 0.001$) and S ($p < 0.001$), respectively. Mean overall changes from

TABLE 2. ESTIMATED DIFFERENCES IN EFFICACY PARAMETERS AT ENDPOINT

Evaluation	Treatment Group Comparison				
	FSC versus P	FSC versus F	FSC versus S	F versus P	S versus P
Predose FEV ₁	159*	54*	67*	105*	92*
2-hour postdose FEV ₁	231*	129*	40	101*	191*
TDI	1.7*	0.7*	1.2*	1.0*	0.5
CRDQ	5.3*	4.8*	1.6	0.5	3.8
CBSQ	0.6*	0.4	0.2	0.2	0.3

Definition of abbreviations: CBSQ = Chronic Bronchitis Syndrome Questionnaire; CRDQ = Chronic Respiratory Disease Questionnaire; F = fluticasone propionate; FSC = fluticasone propionate and salmeterol combined; P = placebo; S = salmeterol; TDI = Transition Dyspnea Index.

* $p < 0.05$.

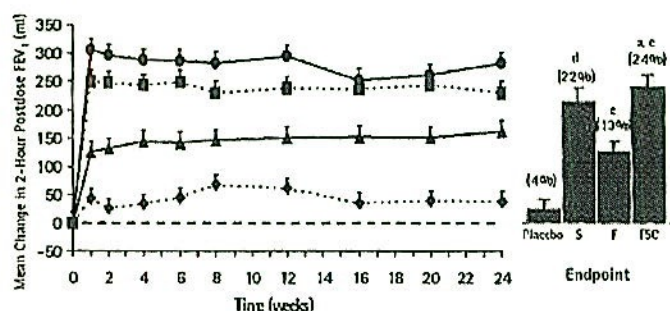


Figure 2. Improvement in 2-hour postdose FEV₁ with FSC (circles) compared with the individual components and placebo (diamonds). Values from Weeks 1–24 are mean + SEM. *a* = FSC versus placebo, *p* < 0.001. *c* = FSC versus F (triangles), *p* < 0.001. *d* = S (squares) versus placebo, *p* < 0.001. *e* = F versus placebo, *p* < 0.001.

baseline were also significantly greater for both F and S versus placebo (*p* < 0.001).

Dyspnea

The mean Baseline Dyspnea Index scores for the placebo, FSC, F, and S groups were 5.8, 6.2, 6.0, and 5.9, respectively, indicating a moderate level of dyspnea for most patients at the beginning of the treatment period. At the endpoint, the mean TDI score for treatment with FSC (2.1) was greater than that after treatment with F (1.3, *p* = 0.033) and was significantly greater than that after treatment with S (0.9, *p* < 0.001) and placebo (0.4, *p* < 0.001) (Figure 4). The estimated difference between FSC and S and between FSC and placebo exceeded the predefined criteria for clinical importance of 1 unit or more (13, 19). Significant differences in TDI scores were observed as early as Week 1 with FSC as compared with F, S, and placebo.

At the endpoint, TDI scores were significantly greater for F (1.3, *p* = 0.002), but not S, compared with placebo. Estimated differences between treatment groups at the endpoint are summarized in Table 2.

Supplemental Albuterol Use

Significant reductions in overall albuterol use (i.e., number of inhalations per day and percentage of days without albuterol use) were observed during treatment with FSC compared with F and placebo. A significant reduction in overall albuterol use was also observed after treatment with S compared with placebo and with F compared with placebo (Table 4).

A significant increase in the overall percentage of nights with no awakenings requiring albuterol was observed for treatment with FSC, F, and S compared with placebo (*p* < 0.001).

Health Status

Baseline mean overall CRDQ scores were 86.2 in the placebo group, 87.1 in the FSC group, 88.5 in the F group, and 87.6 in the S group. At the endpoint, treatment with FSC resulted in a clinically important increase from baseline in mean overall CRDQ score (10.0) that was significantly greater compared with the placebo (5.0, *p* = 0.007) and F (4.8, *p* = 0.017) groups, but not with S (8.0). Clinically important increases in dyspnea score (4.2), fatigue score (2.0), and physical summary score (6.1) were observed after treatment with FSC. These increases were also statistically significant versus the F and placebo treatment groups (*p* ≤ 0.016). Estimated differences between treatment groups at the endpoint are summarized in Table 2.

Other Endpoints

There were no consistent differences among treatments for changes in symptoms of chronic bronchitis (Chronic Bronchitis Symptom Questionnaire). Estimated differences between treatment groups at the endpoint are summarized in Table 2. There were no statistically significant differences between treatment groups in time to exacerbation.

Safety

The average time patients remained in the study was 124 days in the placebo group, 141 days in the S group, 127 days in the F group, and 138 days in the FSC group.

A total of 515 patients (75%) experienced at least one adverse event during the study (Table 5). A greater percentage of patients in the F and the FSC groups experienced candidiasis (mouth/throat) based on visual inspection compared with the placebo and S groups, as expected with the use of an inhaled corticosteroid.

TABLE 3. RESPONSE BY REVERSIBILITY* TO ALBUTEROL AT THE ENDPOINT

	Placebo	S	F	FSC
Predose FEV ₁ (ml)				
Reversible	-1 (25)	132 (26)	123 (26)	191 (30)
Nonreversible	-8 (23)	80 (23)	93 (27)	116 (21)
Two-hour postdose FEV ₁ (ml)				
Reversible	29 (26)	287 (32)	161 (27)	319 (32)
Nonreversible	28 (23)	175 (30)	111 (25)	195 (24)
TDI				
Reversible	0.3 (0.3)	1.3 (0.4)	1.5 (0.3)	2.2 (0.4)
Nonreversible	0.4 (0.3)	0.5 (0.4)	1.0 (0.4)	1.9 (0.4)

Definition of abbreviations: F = fluticasone propionate; FSC = fluticasone propionate and salmeterol combined; S = salmeterol; T = Transition Dyspnea Index.

* Reversibility defined as an increase of 12% and 200 ml in FEV₁ following albuterol 400 mcg.

Values are mean change from baseline (SE).

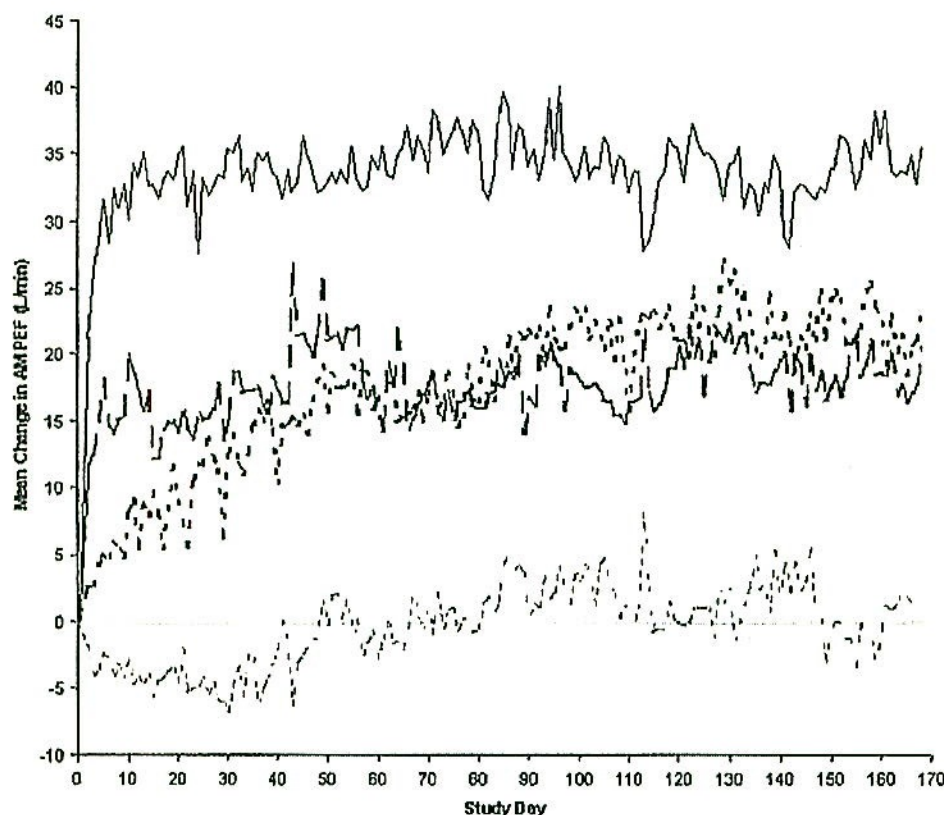


Figure 3. Mean change in the morning PEF rate. Base-line morning PEF values were 269.5 L/min in the placebo (medium dashed line) group, 254.0 L/min in the FSC (solid line) group, 243.7 L/min in the F (short dashed line) group, and 252.1 L/min in the S (long dashed line) group. Treatment with FSC provided significantly greater improvement compared with placebo, F, and S ($p \leq 0.001$). SEMs ranged from 2.6 to 6.3 L/min.

Three patients died during the study; all were in the placebo group. None of the deaths was considered by the investigator to be related to the study drug. The incidence of serious adverse events was low and similar across the treatment groups (4–7%).

Morning plasma cortisol concentrations were obtained before administration of the morning dose of study medication at baseline and then again at end of study. At end of study, the prestimulated morning plasma cortisol concentrations were similar across the treatment groups (Table 6). The number of subjects with an inappropriate cortisol response to stimulation with cosyntropin at Day 1 was zero in the placebo group, zero in the F group, two in the S group, and one in the FSC group. At the endpoint, the number of subjects with an abnormal response was zero in the placebo group, one in the F group, one in the S group, and one in the FSC group.

The incidence of clinically significant electrocardiogram abnormalities was comparable among the treatment groups (four patients in the placebo group, four patients in the F group, two patients in the S group, and three patients in the FSC group). No treatment-related effects on vital signs, QTc, or cardiac rate were observed. The incidence of ventricular ectopic events was similar in the placebo group compared with the active treatment groups at screening and at Week 4. Only five patients experienced significant changes in Holter monitor results (one patient each in the placebo, S, and FSC groups and two patients in the F group).

DISCUSSION

The major findings of this study were as follows: (1) FSC provided significantly greater improvements in predose and 2-hour

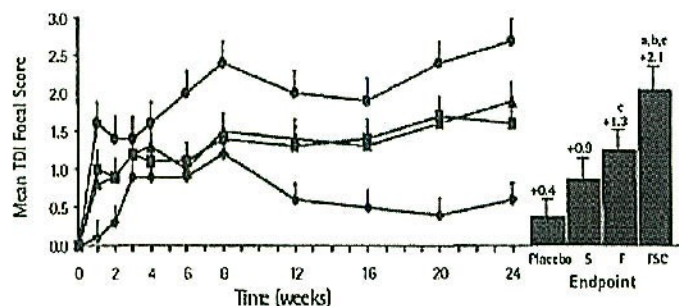


Figure 4. Transition Dyspnea Index—mean focal score. Values from weeks 1–24 are mean $\pm$ SD. a = FSC (circles) versus placebo (diamonds), $p < 0.001$. b = FSC versus S (squares), $p < 0.001$. c = FSC versus F (triangles), $p = 0.033$. e = F versus placebo, $p = 0.002$.

TABLE 4. SUMMARY OF MEAN CHANGES FROM BASELINE IN SUPPLEMENTAL ALBUTEROL USE AND NIGHTTIME AWAKENINGS REQUIRING ALBUTEROL

Time Point	Number of Puffs of Albuterol Used per Day				Percent of Days without Albuterol Use			
	Placebo	S	F	FSC	Placebo	S	F	FSC
Baseline								
n	181	158	166	161	181	158	166	161
Mean	4.9	4.6	4.5	4.2	19.0	21.4	22.1	28.0
Overall								
n	179	157	164	161	179	159	165	165
Mean	5.4	3.6	4.1	3.0	19.5	31.0	28.5	43.7
Mean change	0.5	-0.9*	-0.4*	-1.2 [†]	0.3	9.3*	6.2*	16.3 [‡]
Time Point	Number of Awakenings/Night Requiring Albuterol				Percent of Nights With No Awakenings Requiring Albuterol			
	Placebo	S	F	FSC	Placebo	S	F	FSC
Baseline								
n	177	156	163	157	177	156	163	157
Mean	0.27	0.26	0.24	0.22	82.9	82.2	86.4	84.4
Overall								
n	175	153	162	157	177	157	165	163
Mean	0.36	0.17	0.16	0.19	78.9	89.0	89.5	89.8
Mean change	0.10	-0.09 [‡]	-0.08 [‡]	-0.04 [‡]	-4.3	6.8 [‡]	3.0 [‡]	5.7 [‡]

Definition of abbreviations: F = fluticasone propionate; FSC = fluticasone propionate and salmeterol combined; S = salmeterol.

*p < 0.045 versus placebo.

[†]p < 0.032 versus F 500.

[‡]p < 0.031 versus placebo.

postdose FEV₁ as well as in morning PEF compared with individual agents or placebo. (2) FSC significantly reduced the severity of dyspnea as measured using the TDI compared with S and placebo. (3) There were significant reductions in albuterol use as a rescue medication with FSC compared with F and placebo. (4) FSC resulted in significant increases in health status, as measured using the CRDQ compared with F and placebo. (5) There were no differences in adverse events (except for oral candidiasis in the FSC and F groups) among treatment groups.

The improvements in FEV₁ were apparent with F, S, and FSC after the first week of treatment and continued during the subsequent 24 weeks of the study (Figures 1 and 2). The predose FEV₁ at the endpoint with S was 107 ml (Figure 1), which is comparable to the results previously observed at 12 weeks with this long-acting β_2 -agonist (20, 21). The higher predose FEV₁ values observed with FSC (156 ml) reflect the additional contribution of F, which is presumably caused by an antiinflammatory effect. In a study of 80 patients with COPD, Cazzola and colleagues (22) investigated the addition of F (500 mcg twice daily) to S, and the results of combination therapy suggested a progressive improvement in lung function over a 3-month period com-

pared with S alone. These results observed by Cazzola and associates (22) support our findings with combination therapy.

The enhanced 2-hour postdose FEV₁ with FSC (261 ml) illustrates the additional bronchodilation with S. For example, previous studies have demonstrated that S has its peak bronchodilator effect at 2 hours after the dose (20, 21, 23). Endpoint analysis for both predose and postdose FEV₁ was performed to ensure that the patients prematurely withdrawing from the trial did not impact the robustness of the FEV₁ results. The appropriateness of this analysis was supported by evaluating the data using alternative methods of handling dropouts, including multiple imputation, analysis of only completers, and recursive regression imputation. The significant improvement in morning PEF occurred within 24 hours after beginning treatment (Figure 3) and was higher than salmeterol treatment alone, suggesting an important early contribution from the inhaled corticosteroid. Thus, combination therapy with FSC provided rapid and consistent bronchodilation (predose and 2-hour postdose FEV₁ and morning PEF) throughout the 6 months of the study compared with individual medications and placebo. Improvements in lung function were observed in patients who had reversible as well as

TABLE 5. INCIDENCE OF ADVERSE EVENTS OF 10% OR MORE

Adverse Event	Placebo (n = 185) n (%)	S (n = 164) n (%)	F (n = 173) n (%)	FSC (n = 169) n (%)
Any event	127 (69)	119 (73)	138 (80)	131 (78)
Headaches	25 (14)	30 (18)	35 (20)	30 (18)
URTI	18 (10)	20 (12)	25 (14)	28 (17)
Musculoskeletal pain	23 (12)	21 (13)	13 (8)	20 (12)
Throat irritation	14 (8)	17 (10)	11 (6)	19 (11)
Viral respiratory infections	6 (3)	12 (7)	17 (10)	14 (8)
Candidiasis mouth/throat	1 (< 1)	1 (< 1)	17 (10)	12 (7)

Definition of abbreviations: F = fluticasone propionate; FSC = fluticasone propionate and salmeterol combined; S = salmeterol; URTI = upper respiratory tract infection.

Patients previously excluded from efficacy analyses because of poor study practices (n = 17) are included in the safety analysis.

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TABLE 6. MEAN PRESTIMULATION MORNING PLASMA CORTISOL CONCENTRATIONS

Timepoint	Placebo (n = 185)	S (n = 164)	F (n = 173)	FSC (n = 169)
Day 1	12.8 ± 5.3	12.4 ± 4.9	13.1 ± 4.9	13.7 ± 6.7
End of study	12.9 ± 5.1	11.8 ± 4.3	12.0 ± 5.1	12.1 ± 5.3

Definition of abbreviations: F = fluticasone propionate; FSC = fluticasone propionate and salmeterol combined; S = salmeterol.

Values are mcg/dl (SE).

nonreversible changes in FEV₁ after acute administration of 400 mcg of albuterol (Table 3).

Any increase in expiratory airflow may contribute to improvements in clinical outcomes. In this trial, we measured changes in dyspnea from baseline with the multidimensional TDI. The increase in the TDI score with FSC at the endpoint (2.1) was substantial and exceeded the responses with S (0.9), F (1.3), and placebo (0.4). Furthermore, the estimated differences between FSC and S (1.2) and placebo (1.7) exceeded the change of one unit considered to be the minimum clinically important difference (13, 19), whereas the estimated difference between FSC and F (0.7) approached this one-unit criterion. Greater reductions in the use of rescue albuterol with active treatments compared with placebo throughout the study further substantiate the clinical improvement in dyspnea. The improvements in TDI scores seen with FSC are considerably greater than those reported for any medication studied to date in a major clinical trial in patients with COPD (20, 21, 24–26). Although improvements in the TDI score were greater in the reversible patients, FSC also provided clinically important reductions in dyspnea in those patients considered to be nonreversible (Table 3).

Although we did not investigate the mechanisms for the observed improvement in dyspnea with FSC in this study, it is reasonable to speculate on possible explanations. Previous studies with other bronchodilators, particularly albuterol (27) and ipratropium bromide (28), have shown that the improvements in breathlessness with these medications were due in part to the reduced dynamic hyperinflation that frequently develops in patients with COPD during exertion. The improved respiratory mechanics would diminish elastic recoil and increase the length of the vertical muscle fibers of the diaphragm. These changes would modulate inspiratory effort and reduce the intensity of breathlessness (28, 29). In another study, Ayers and colleagues (30) reported that S (two puffs, 42 mcg) and ipratropium (four puffs, 72 mcg) had similar effects on inspiratory capacity (used to measure dynamic hyperinflation) and ratings of dyspnea during submaximal cycle ergometry, although a placebo arm was not included for comparison with the bronchodilators. Therefore, it is likely that S, as a component of FSC, improved dynamic hyperinflation in our patients, which could have contributed to the observed reduction in dyspnea with combination therapy. Furthermore, Weber's law states that the perception of breathlessness must be increased by a constant fraction of its background value to produce a minimum or perceived change (31). Thus, a greater increase in airway resistance would be required after bronchodilation with FSC for the individual patient to notice a change in the severity of dyspnea.

In the Lung Health Study II, inhaled triamcinolone reduced airway reactivity in response to methacholine in those with mild COPD (12). These patients, most of whom continued to smoke cigarettes, "had fewer respiratory symptoms during the course of the study." Any similar reduction in airway reactivity caused by inhaled F, a component of FSC, might also be expected to

improve breathlessness. Thus, it is plausible that the combination of S (bronchial smooth muscle relaxation) and F (reduction in edema and inflammation within the wall of the airway) as part of combination therapy could work by different mechanisms to enhance airflow, reduce hyperinflation, and improve dyspnea as related to activities of daily living. Certainly, additional studies are needed to investigate these and other possible mechanisms whereby FSC reduces dyspnea.

Health status generally slowly deteriorates in patients with COPD over time (11, 32). In the 6 months of this study, we observed that the score for the CRDQ actually increased with placebo treatment (5.0). The reasons for the increase in the placebo group could be due to patients receiving better medical attention when involved in a clinical trial and/or the increased use of albuterol in the placebo versus the active treatment groups. It is also likely that health status may have declined if the trial lasted for a longer time period. In this trial, we observed greater increases in the scores on the CRDQ with FSC (10.0) compared with S (8.0) and F (4.8) alone. Various investigators have reported that S (50 mcg) twice daily improved health status using either the CRDQ (20, 21, 26) or the St. George's Respiratory Questionnaire (33), although the differences compared with placebo were not always statistically significant. In the Inhaled Steroids in Obstructive Lung Disease trial, Burge and colleagues (11) found that F (500 mcg) twice daily slowed the decline in health status (measured on the St. George's Respiratory Questionnaire) compared with the decline with placebo over a 3-year time period. Our present data with combination therapy are quite consistent with these previous results for S and F used individually. These collective findings support the benefits of FSC for improving health status in patients with COPD.

Exacerbation rates have been shown to be reduced in previous studies evaluating treatment with inhaled corticosteroids (9, 11). However, in this study, patients who experienced an exacerbation resulting in hospitalization or treated with an inhaled or oral corticosteroid during the study period were withdrawn to ensure that the concomitant use of these agents did not confound our ability to assess treatment effects on the primary efficacy measures of FEV₁. This precluded examination of the effect of the treatment on rate of exacerbations. Other study design issues that limited the examination of a treatment effect on exacerbations include not requiring a history of exacerbations as an entry criteria, relatively short treatment duration, and inadequate sample size to discern significant treatment differences. Future studies are needed to confirm the positive findings seen with inhaled corticosteroids in previous trials (9, 11).

The safety profile of FSC was consistent with that observed with the administration of both S plus F and was not different from that for the components alone. The overall adverse event profile of the combination therapy showed no new or unexpected adverse events. There was no evidence that treatment with FSC was associated with any increased risk of clinically relevant hypothalamic-pituitary-adrenal axis suppression, as assessed by cosyntropin stimulation testing, compared with treatment with F, S, or placebo. No unexpected cardiovascular effects, as assessed by Holter monitoring and routine electrocardiogram, were observed in those patients receiving FSC compared with patients receiving S or placebo.

What are the clinical implications of the findings of this study? Based on the Global Initiative for Chronic Obstructive Lung Disease Guidelines, bronchodilator medications are indicated for the treatment of symptoms associated with COPD, whereas inhaled corticosteroids are indicated for airflow limitation that is responsive to a trial period of inhaled glucocorticoid treatment (2). When combined together, these agents treat both the bronchial smooth muscle constriction and the airway inflammation

that are major components causing airflow limitation in this disease. Previous studies have shown both physiologic and/or clinical benefits of inhaled corticosteroids in patients with COPD (9, 11, 12, 22). Our results demonstrate that FSC not only improved airflow obstruction, but also provided clinical benefits as manifested by reduced severity of dyspnea, reduced use of rescue albuterol, and improved health status. We conclude that FSC can provide a useful treatment option for symptomatic patients with COPD.

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