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New products

Series editors: Donald Y. M. Leung, MD, PhD, Harold S. Nelson, MD, Stanley J. Szefer, MD, Philip S. Norman, MD, and Andrea Apter, MD, MSc

Efficacy and safety overview of a new inhaled corticosteroid, QVAR (hydrofluoroalkane-beclomethasone extrafine inhalation aerosol), in asthma

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Efficacy and safety overview of a new inhaled corticosteroid, QVAR (hydrofluoroalkane-beclomethasone extrafine inhalation aerosol), in asthma

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Chlorofluorocarbon (CFC)-containing inhalers are gradually being phased out and replaced with hydrofluoroalkane (HFA)-based alternatives. The reformulation provided the opportunity to improve the inhalation technology and physical characteristics of corticosteroid formulations. QVAR contains HFA-beclomethasone dipropionate (HFA-BDP) with the steroid in solution rather than suspension, which, in combination with improved inhaler technology, produces an extrafine aerosol with a mass median aerodynamic diameter of 1.1 μm (smaller than the 3.5–4.0 μm found with CFC-BDP). It was predicted and demonstrated that the smaller particle size of QVAR would be deposited in the lung to a greater extent than that found with CFC-BDP, particularly in the small airway, a major site of inflammation. Increased lung deposition of QVAR permits a reduction in dosage relative to CFC-BDP. Clinical evidence confirms that adult and elderly patients required approximately half the dose of QVAR to achieve the same degree of asthma

control as with CFC-BDP. In long-term assessments, patients taking CFC-BDP could be switched to QVAR at half the daily dose without exacerbation of their asthma symptoms. QVAR was associated with a low overall incidence of side effects and, at the maximum recommended dose of 640 $\mu\text{g}/\text{d}$, caused no more adrenal suppression than 672 $\mu\text{g}/\text{d}$ CFC-BDP. (*J Allergy Clin Immunol* 2000;106:1209–26.)

Key words: Chlorofluorocarbon propellant, hydrofluoroalkane propellant, QVAR, inhaled corticosteroids, beclomethasone, fluticasone, budesonide, efficacy, safety

Inhaled corticosteroids form an integral part of asthma management and are the most effective long-term therapy available for mild, moderate, or severe-persistent asthma.¹ Beclomethasone dipropionate (BDP) continues to be one of the most commonly prescribed inhaled corticosteroids, a suspension aerosol formulation with chlorofluorocarbon (CFC) propellants. However, recognition that CFC propellants deplete the ozone layer has led to their production being gradually phased out under the Montreal Protocol on Substances that Deplete the Ozone Layer.²

To meet the need to find a replacement for CFCs in pressurized (“press and breathe”) metered-dose inhalers (pMDIs), BDP has been reformulated with a non-CFC propellant, hydrofluoroalkane-134a (HFA; QVAR, 3M Pharmaceuticals), which has no ozone-depleting potential.³ This reformulation has provided the opportunity to improve the inhalation technology and the physical characteristics of the BDP formulation, with the aim of enhancing the efficiency of BDP delivery to the respiratory tract. Improved delivery is a vital feature because there is evidence that airway inflammation occurs in both the large and small airways in patients with asthma.^{4–6} There is a potential for improved drug effect if it is capable of reaching all areas of the lungs where pathologic and physiologic changes have taken place. Furthermore, the Food and Drug Administration approval process requires that replacement products demonstrate comparability to the corresponding CFC product, so that patients and physicians can expect similar efficacy and safety from the new formulations.^{1,7}

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Editor's note: This article initiates a series of special contributions to *The Journal of Allergy and Clinical Immunology* that will address state-of-the-art topics and concepts in the use of new medications/devices for the treatment of allergic and immunologic diseases. These New Products articles will appear regularly in the next several volumes. To ensure that statements of efficacy are evidence-based and there is no commercial bias, each of these articles will be critically reviewed by 2 clinical researchers and/or Editorial Board members who have not been associated with development of the new product.

The authors disclose that they have served as consultants to 3M and have received grant support in the past to investigate QVAR's mechanisms of action and clinical efficacy. They have prepared this report to present factual, unbiased information and attest that their associations with the developers of QVAR have not influenced this report, nor do they constitute commercial or personal conflict of interest.

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Abbreviations used

AUC:	Area under the curve
BDP:	Beclomethasone dipropionate
CFC:	Chlorofluorocarbon
FEF _{25%-75%} :	Forced expiratory flow, midexpiratory phase
FP:	Fluticasone propionate
HFA:	Hydrofluoroalkane
HPA:	Hypothalamic-pituitary-adrenal
PEF:	Peak expiratory flow
pMDI:	Pressurized metered-dose inhaler
T _{max} :	Time to maximum serum concentration

In the HFA-based formulation, BDP is in solution rather than in suspension, as is the case with CFC-containing preparations. In combination with the improved inhaler technology, QVAR is expelled as an extrafine aerosol, with a smaller mean particle size than that of CFC-BDP. This allows more of the inhaled drug to be delivered to the central and peripheral airways and reduces deposition in the oropharynx, as shown by Leach et al.⁸

PATHOPHYSIOLOGY AND SCIENTIFIC RATIONALE

There is accumulating evidence that the airway inflammation and remodeling that characterize asthma occur in all parts of the airway from mainstem bronchi to bronchioles.⁴

Small airways have an internal perimeter of at most 2 mm. Changes in the function of these airways are difficult to assess because of the lack of specificity, sensitivity, and consistency of pulmonary function tests.^{9,10} Consequently, the contribution of small airway dysfunction in asthma is unresolved. Nevertheless, newer techniques, such as high-resolution computed tomography, have advanced our ability to assess abnormalities in peripheral airways and their response to treatment (see "The importance of treating the small airways").

A number of cell types have been characterized in the inflammatory infiltrate of the airways of patients with asthma, including eosinophils, mast cells, macrophages, T cells, and neutrophils,^{4,11} as well as mesenchymal cells, such as fibroblasts, smooth muscle cells, and endothelial cells.¹⁰ Indeed, eosinophil infiltration has been demonstrated in the alveoli of patients with nocturnal asthma.^{12,13} In addition, the inflammatory process has been shown to be more severe in the small than in the large airways, which is consistent with the observation that the former are major sites of obstruction.⁴ Confirmation of these findings comes from postmortem tissue analysis, which indicates that there is significantly more disease in the small airway of patients with asthma than in control subjects ($P < .01$) in terms of greater lumen occlusion, higher smooth muscle thickness ($P < .001$), and inflammatory infiltrate involving mononuclear cells ($P < .001$) and eosinophils.¹⁴

Current management guidelines for asthma therapy recommend treatment with inhaled corticosteroids for long-term asthma control. Recognition of asthma as a

disease of the entire respiratory tract suggests that improved inhaler systems are needed that permit drug delivery to be targeted to both central and peripheral airways and thus enable inflammation to be treated uniformly throughout the airways.

PHARMACEUTICS

The 2 main disadvantages of pMDIs over other inhalation devices are the relatively high throat deposition of drug and the *cold-Freon* effect (ie, the cold and uncomfortable feeling at the back of the throat on inhalation, which may prevent the patient from inhaling the full dose of corticosteroid). Both of these adverse effects arise from a high-velocity forceful blast impacting on the oropharynx.¹⁵ The need to change propellant provided the opportunity to improve pMDI technology because it necessitated a reappraisal of the inhaler device components (formulation, metering valve, container, and actuator).¹⁶

Commercially available formulations of BDP in CFC propellants are suspensions producing particles with a mass median aerodynamic diameter of approximately 3.5 to 4.0 μm in diameter and typically delivering no more than 15% of the inhaled dose to the lungs.¹⁷ The remainder is deposited in the oropharynx, providing little therapeutic benefit, and may be associated with unwanted dysphonia, oropharyngeal candidiasis, and systemic effects if swallowed.¹⁸ By comparison, mass median aerodynamic diameter values for other inhaled corticosteroids in pMDIs include 2.5 μm for fluticasone¹⁹ and 2.4 to 4.0 μm for budesonide.²⁰

Some CFC-BDP formulations contain a small amount of surfactant, such as oleic acid, to aid suspension characteristics, which may be responsible for the cough and wheeze experienced by a few patients after inhalation.²¹ QVAR contains BDP uniformly dissolved in HFA propellant (with no need for a surfactant), which, in combination with improved pMDI technology, produces an extrafine aerosol with a mass median aerodynamic diameter of 1.1 μm . QVAR is available as pMDI and breath-actuated Autohaler (3M Pharmaceuticals) devices containing the same formulation of BDP dissolved in HFA propellant. Unless otherwise specified, all studies described in this review were performed with the pMDI. The inhalers are produced in 2 strengths, delivering ex-valve doses of 50 or 100 μg , respectively (ie, the dose emitted from the inhaler valve into the mouthpiece of the actuator), which is equivalent to ex-actuator doses of 40 or 80 μg , respectively. The ex-actuator dose is the amount ejected from the mouthpiece of the inhaler and, for consistency, ex-actuator doses will be adopted throughout this review.

The two QVAR devices were bioequivalent for both rate and extent of total beclomethasone absorption (ie, BDP and its metabolites) and maximum plasma concentration in a study of 49 patients with asthma; the results of this study met the statistical criteria for dose-strength proportionality.²²

In a comparison of the plume characteristics of a range of inhaler devices, QVAR pMDI and the QVAR Autohaler had favorable characteristics,¹⁵ which suggested a decreased likelihood of patients experiencing the cold-Freon effect.

First-use priming of QVAR devices requires 2 actuations, and this is not required again unless stored without use for more than 10 days. Because QVAR inhalers contain a solution of BDP, they do not need to be shaken between uses. QVAR is designed to be used without a spacer, but for those patients who desire it, QVAR pMDI is compatible with the AeroChamber spacer.²³

LUNG DEPOSITION STUDIES

Lung deposition studies have been performed by using radiolabeled aerosol BDP to determine the drug distribution within the lungs on inhalation. Subjects were required to demonstrate reproducible pMDI technique. The fine particle fraction ($<4.7\ \mu\text{m}$) and mass median aerodynamic diameters for QVAR and CFC-BDP and radiolabeled analogs were measured by using the Anderson Cascade Impactor. Drug deposition was measured by using gamma scintigraphy.

In 16 patients with mild asthma receiving technetium 99m-radiolabeled QVAR (40 μg from a standard pMDI), most BDP was deposited in the lungs ($56\% \pm 9\%$), with a comparatively small amount in the oropharynx ($33\% \pm 9\%$), confirming the pattern observed in healthy volunteers.⁸ CFC-BDP was mainly deposited in the oropharynx.

Lung delivery of QVAR was assessed at varying degrees of pMDI discoordination (ie, actuation at different times during the inspiratory process).²⁴ Although increasing degrees of discoordination (time to actuation after beginning inspiration) led to a lower total lung deposition (59% at 0.2 seconds vs 32% at 2.5 seconds), there was no difference in the relative distribution of QVAR within the lungs (peripheral deposition of 29% at 0.2 seconds and 31% at 2.5 seconds). The results indicate that there is a forgiving aspect to the use of the QVAR pMDI, which seems to maintain a homogeneous distribution of drug even when inhalation technique is poor and may reduce the need for a spacer device to overcome pMDI coordination difficulties.

The QVAR Autohaler was designed for patients who have difficulty coordinating inspiration and actuation. An open-label study investigated the deposition of QVAR from an Autohaler (1 or 2 puffs from an 80- μg strength device).²⁵ In 12 men with mild-to-moderate stable asthma who were receiving CFC-BDP (336 μg) ex-valve deposition of radiolabeled QVAR was highest in the lungs ($54\% \pm 7\%$) compared with the oropharynx ($18\% \pm 7\%$).

Lung deposition of QVAR was also compared with CFC-BDP from pMDIs in a randomized, cross-over, single-blind study in 10 patients with stable asthma.¹⁷ On separate days, each subject underwent a 133-Xenon and a ventilation-perfusion scan to delineate lung borders. The respective percentage deposition of QVAR and CFC-BDP in the lungs was $52\% \pm 10\%$ and $16\% \pm 9\%$,

and the corresponding values in the oropharynx were $25\% \pm 8\%$ and $60\% \pm 13\%$.

The deposition properties of technetium 99m-radiolabeled QVAR, CFC-based fluticasone propionate (CFC-FP), and CFC-BDP were compared in a group of 9 healthy volunteers by using a standardized inhalation technique.²⁶ Lung deposition was highest for QVAR (53%), followed by CFC-FP (13%) and CFC-BDP (4% , Fig 1). Oropharyngeal deposition was correspondingly lower for QVAR than the other pMDIs.

These radiolabeled images demonstrate that QVAR was deposited in the central and peripheral airways, whereas CFC-FP was deposited primarily in the central and intermediate airways and CFC-BDP in the large central airway. A mean lung deposition of 22% (range, 10% – 36%) was noted with FP in normal subjects assessed by means of positron emission tomography.²⁷ Triamcinolone delivered from a pMDI with an integrated spacer resulted in a lung deposition of 14% ,²⁸ whereas that from a budesonide pMDI with attached spacer was 34% ,²⁹ and the amount from a flunisolide pMDI and spacer was 26% (31% to oropharynx).³⁰

According to these findings, the possibility that QVAR would provide a wider therapeutic benefit in patients with asthma was investigated.

PHARMACOKINETICS

The potential influence of the greater lung delivery with QVAR compared with CFC-BDP on BDP pharmacokinetics was examined in 23 patients with mild asthma who completed an open, single-dose, randomized, 3-way, cross-over study.³¹ A serum assay for total beclomethasone (ie, BDP plus 17-beclomethasone monopropionate and 21-beclomethasone monopropionate metabolites) was used, which identified only low levels of beclomethasone in the serum, with the majority being BDP metabolites (over 90% of the material in the total beclomethasone was 17-beclomethasone monopropionate).

As shown in Table I, the maximum serum concentration and the area under the curve (AUC) for total beclomethasone after inhalation of 320 μg of QVAR were approximately twice those obtained after 160 μg of QVAR. Furthermore, the maximum serum concentration and AUC of total beclomethasone parameters of 336 μg of CFC-BDP resembled those of 160 μg of QVAR more closely than those of 320 μg of QVAR. However, time to maximum plasma concentration (T_{max}) was later with CFC-BDP than QVAR (2 hours vs 0.6 hours). This rapid T_{max} with QVAR reflects the immediate absorption through the lung compared with the slower absorption through the gut (ie, primarily oropharyngeal deposition) with CFC-BDP. The increased systemic bioavailability of QVAR results from an increased deposition of BDP in the lower respiratory tract. This may imply that there is the potential for increased systemic side effects from QVAR compared with CFC-BDP at the same microgram dose.

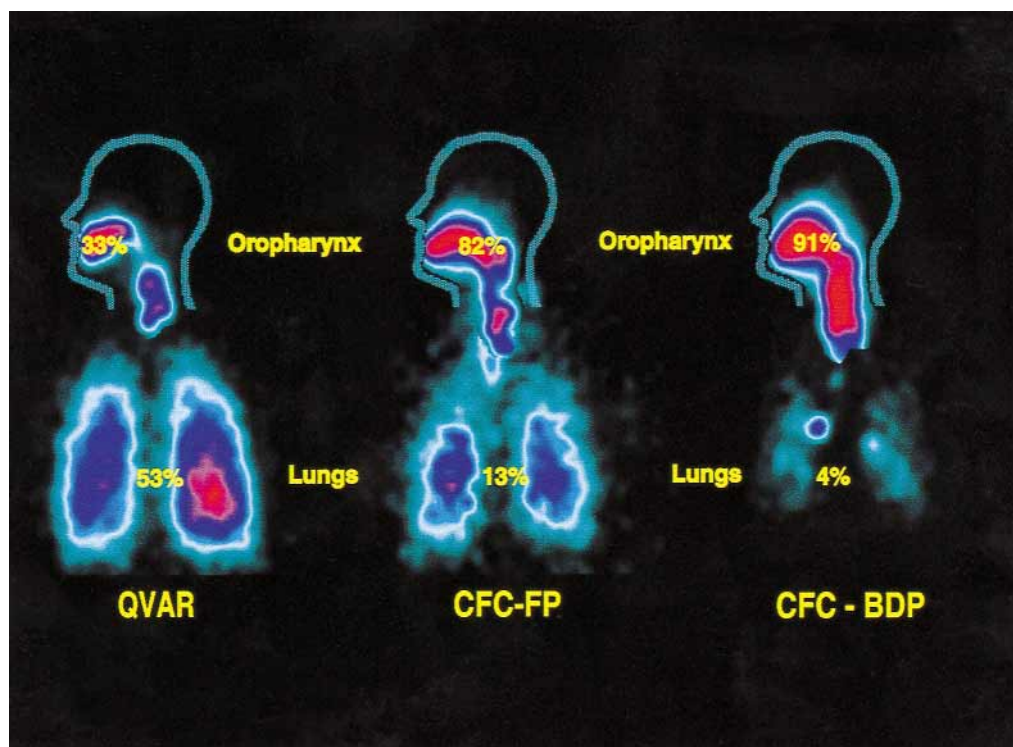


FIG 1. Deposition of radiolabeled steroid after inhalation of QVAR, CFC-FP, and CFC-BDP.²⁶

TABLE I. Comparative total beclomethasone pharmacokinetic parameters (mean $\pm$ SD)

Parameter	QVAR (160 μ g)	QVAR (320 μ g)	CFC-BDP (336 μ g)
C_{max} (ng/mL)	0.57 ± 0.2	1.15 ± 0.38	0.38 ± 0.16
AUC (ng $\cdot$ mL ⁻¹ $\cdot$ h ⁻¹)	2.06 ± 0.55	4.33 ± 1.13	1.76 ± 0.87
T_{max} (h)	0.60 ± 0.30	0.80 ± 0.50	2.0 ± 0.50

Data from Harrison et al.³¹

The study was performed with a pMDI, and the data represent systemic absorption of total beclomethasone (ie, BDP plus 17-beclomethasone monopropionate and 21-beclomethasone monopropionate metabolites).

C_{max} Maximum serum concentration.

TABLE II. Total beclomethasone pharmacokinetic parameters after single and steady-state dosing (mean $\pm$ SD)*

Dose	Single (dose 1)		Steady-state (dose 27)		Accumulation ratio [†]
	C_{max} (ng/mL)	AUC (ng $\cdot$ mL ⁻¹ $\cdot$ h ⁻¹)	C_{max} (ng/mL)	AUC (ng $\cdot$ mL ⁻¹ $\cdot$ h ⁻¹)	
QVAR (160 μ g)	0.17 ± 0.1	0.57 ± 0.30	0.20 ± 0.08	0.80 ± 0.18	1.4 ± 0.8
QVAR (320 μ g)	0.45 ± 0.16	1.96 ± 0.80	0.54 ± 0.24	2.11 ± 0.80	1.1 ± 0.4
QVAR (640 μ g)	0.74 ± 0.25	2.85 ± 0.90	0.95 ± 0.36	4.00 ± 1.60	1.3 ± 0.4
CFC-BDP (672 μ g)	0.37 ± 0.2	1.8 ± 0.87	0.44 ± 0.19	2.26 ± 0.70	1.7 ± 1.5

Adapted from Harrison LI, et al. J Pharm Pharmacol 1999;51:263-9.

The study was performed with a pMDI, and the data represent systemic absorption.

C_{max} Maximum serum concentration.

*Total beclomethasone: BDP plus 17-beclomethasone monopropionate and 21-beclomethasone monopropionate metabolites.

[†] C_{max} steady-state/ C_{max} single dose.

In a dose-response study, the pharmacokinetics of QVAR and CFC-BDP were compared in 43 corticosteroid-naïve patients.³² Subjects were randomized to HFA-placebo; 160, 320, or 640 μ g of QVAR; or 672 μ g of CFC-BDP and dosed every 12 hours for 2 weeks. The rate and extent of total beclomethasone absorption increased as the dose of QVAR

rose ($P < .0001$), but there was virtually no accumulation with multiple dosing for the active treatment groups. On the basis of steady-state AUC values, the extent of drug absorption from 640 μ g of QVAR and 672 μ g of CFC-BDP was assessed as a ratio of 1.7:1. The derived pharmacokinetic parameters from this study are listed in Table II.

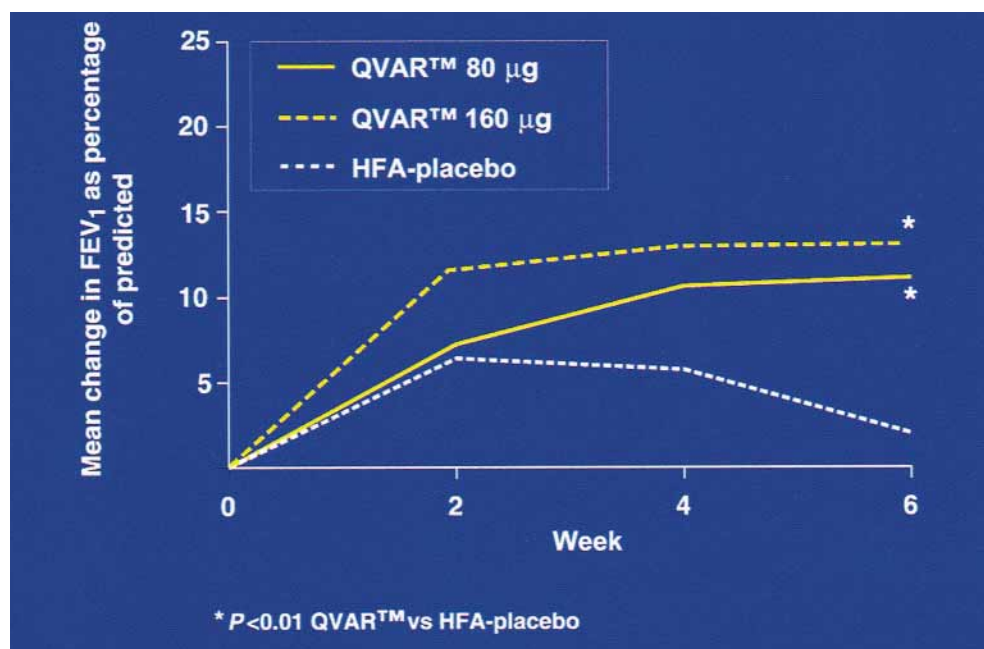


FIG 2. Mean change in FEV₁ percent predicted in patients taking 80 and 160 µg/d QVAR or HFA-placebo. (Reprinted from Hampel F, et al. *J Asthma* 2000;37:389-98.)

EFFICACY

In view of the improved delivery characteristics of QVAR, resulting from the smaller droplet size and reduced impaction in the upper airway, the clinical efficacy of QVAR was evaluated at doses lower than those currently recommended for CFC-BDP.

Design considerations

The clinical efficacy studies with QVAR include a range of broadly representative patient populations that are likely to receive treatment with inhaled corticosteroids in clinical practice. The studies included new patients (ie, those who had not previously received inhaled corticosteroids or steroid-naïve patients), symptomatic patients whose symptoms were inadequately controlled on their current therapy, and also asymptomatic patients (those whose asthma was well controlled but who would be appropriate candidates to be switched to alternative CFC-free therapy).

The altered characteristics of QVAR prompted the need to establish the dose potency of QVAR compared with CFC-BDP and other inhaled corticosteroids. Patients in such studies must be both symptomatic and capable of responding to inhaled corticosteroids, otherwise interpretation of treatment effect and comparison with other drugs will be confounded. In a benchmark comparative dose-response study,³³ patients were found to be responsive to inhaled corticosteroids during a well-controlled washout period before randomization. In another study³⁴ a symptomatic population was given an oral steroid burst to confirm that an improvement in peak flow was achievable before randomization.

Treating new patients with asthma

To define the lower limit of the recommended dose range for QVAR, 270 steroid-naïve patients with mild-to-moderate asthma according to Global Initiative for Asthma guidelines³⁵ were randomized to treatment in a 6-week, blinded, placebo-controlled, multicenter study.³⁶ Of these, 91 received 40 µg of QVAR twice daily, 92 received 80 µg of QVAR twice daily, and 87 received HFA-placebo. At baseline, 57%, 61%, and 52% of these 3 treatment groups, respectively, were women. The mean $\pm$ SD ages of all patients in the 3 groups at baseline were 32.2 ± 10.2 , 35.8 ± 12.1 , and 32.6 ± 12.3 years, and their corresponding FEV₁ percent predicted values at the same assessment point were 75.3%, 75.5%, and 77.1%.

The mean change from baseline in FEV₁ as a percentage of predicted normal value was significantly greater for both QVAR (80 and 160 µg/d) treatment groups than placebo at week 6 (ie, changes of 6.7%, 8.6%, and 0.4%, respectively; $P \leq .01$ active treatment vs placebo; Fig 2). The Jonckheere test for a linear trend indicated a dose response between placebo and 80 and 160 µg/d QVAR ($P \leq .0001$). These results were supported by the significantly greater QVAR-induced improvement in morning peak expiratory flow (PEF) compared with placebo at weeks 3 to 4 and 5 to 6 ($P \leq .01$). The mean change from baseline in morning PEF at weeks 5 to 6 was 29.5 L/min for the 80 µg/d QVAR group, 33.8 L/min for the 160 µg/d QVAR group, and 5.0 L/min for the HFA-placebo group. In addition to improving patients' air flow, 80 µg/d QVAR (a dose currently below the Global Initiative for Asthma recom-

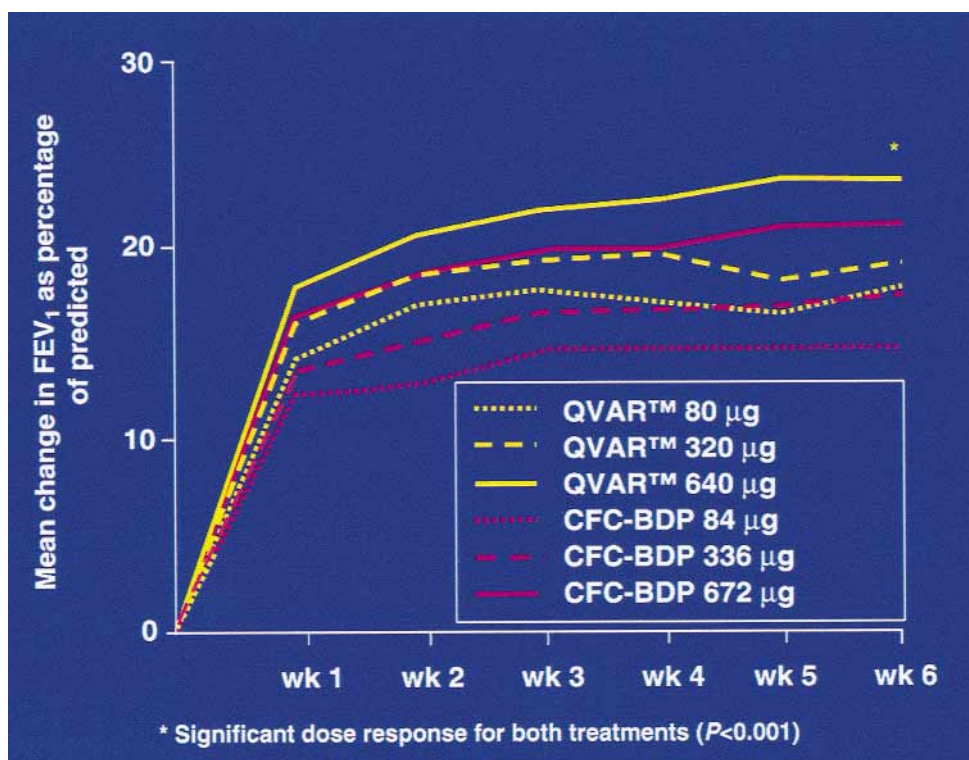


FIG 3. Mean change in baseline in FEV₁ (% of predicted normal) by week for patients receiving 80, 320, and 640 µg/d QVAR or CFC-BDP at equivalent doses. (Reprinted from Busse WW, et al. J Allergy Clin Immunol 1999;104:1215-22.)

TABLE III. Change from baseline in morning PEF (L/min) at weeks 5 to 6 (combined data) in patients with an FEV₁ percent predicted of 60% to 80%

	HFA-placebo (n = 99)	QVAR 80 µg/d (n = 67)	QVAR 160 µg/d (n = 60)	QVAR 320 µg/d (n = 85)	P value
Mean ± SE change from baseline in morning PEF	10.3 ± 5.35	29.7 ± 6.50	38.4 ± 6.87	48.9 ± 5.77	≤.0001

Data from Hampel et al³⁶ and Matthys et al.³⁷

mended guidelines for this patient profile) significantly reduced daily inhaled bronchodilator use (from 3 uses each day at baseline to 2 uses), increased the percentage of nights without sleep disturbance (from 44% of nights at baseline to 65%), and improved wheeze and cough scores (from 1.4-0.8 and 0.9-0.5, respectively) at weeks 5 to 6 (all values: $P \leq .05$ in comparison with HFA-placebo). QVAR at a dose of 160 µg/d also produced a significant improvement in nights without sleep disturbance compared with placebo at weeks 3 to 4 and 5 to 6 (from 50% of nights at baseline to 76%; $P \leq .01$). QVAR was therefore shown to be effective at doses as low as 40 µg twice daily, an advance that may be attributable to the increased amount of drug reaching the lungs.

In another study the efficacy of QVAR was compared with that of placebo in 256 steroid-naïve patients with moderate asthma (Global Initiative for Asthma classifica-

tion) over a period of 6 weeks.³⁷ Patients were randomized to receive 320 µg/d QVAR (4 puffs twice daily from a 40-µg strength inhaler or 2 puffs twice daily from an 80-µg strength inhaler) or placebo. At baseline, the mean ± SD age of the combined QVAR groups was 38.9 ± 11.5 years, whereas that of the placebo group was 41.7 ± 11.9 years. The baseline morning PEF percent predicted values in the same groups were 66.5% and 65.6%, respectively.

Both treatment groups demonstrated a significant change from baseline in FEV₁ ($P \leq .006$) compared with HFA-placebo, with significant control of symptoms seen as early as week 1. Efficacy was maintained throughout the study, and at week 6, a mean improvement in FEV₁ from baseline of 0.29 L was observed for the QVAR-treated groups compared with 0.09 L with HFA-placebo ($P < .006$). Statistically and clinically significant changes from baseline in morning PEF were also observed during

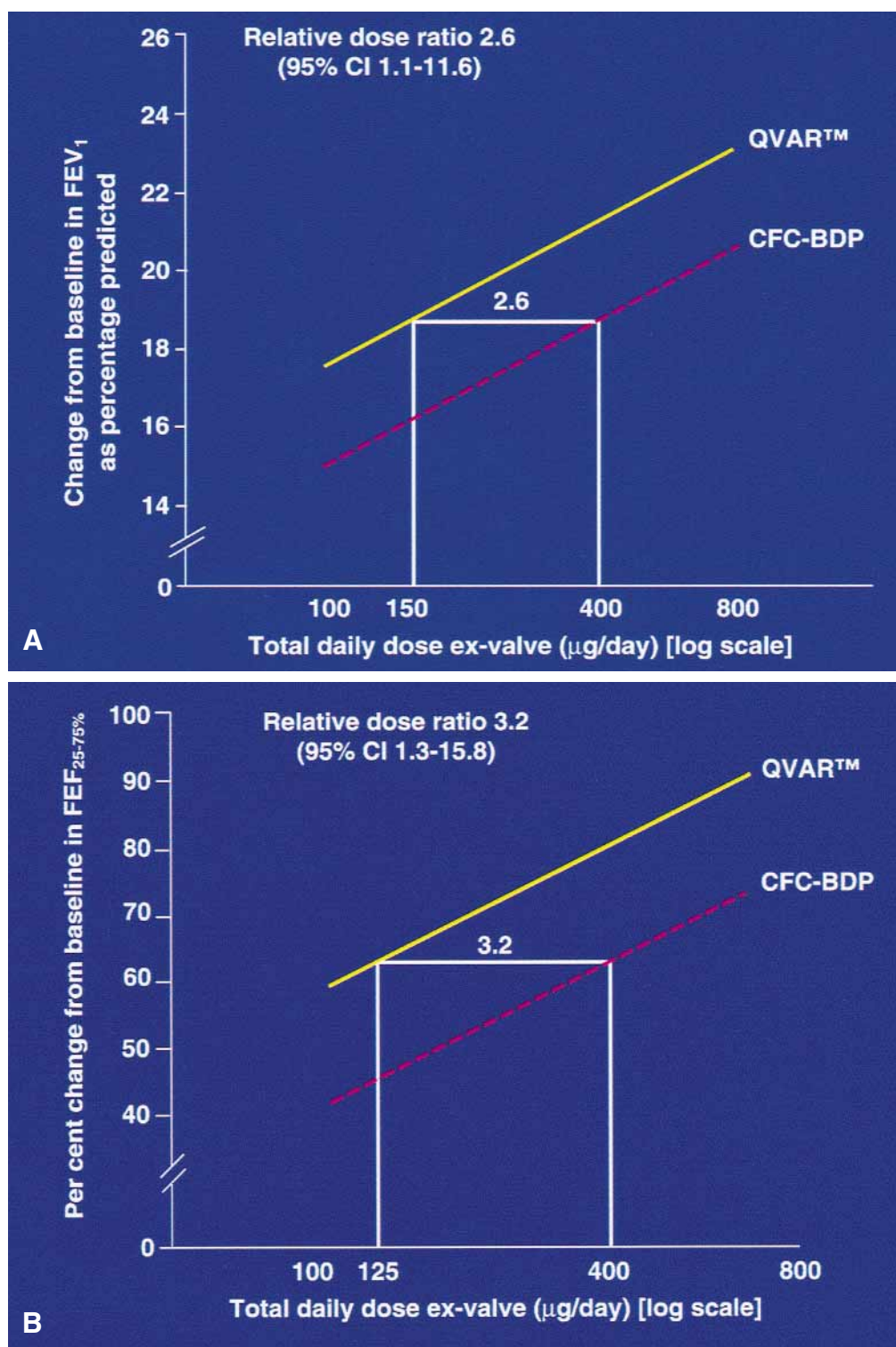


FIG 4. Regression analysis of change from baseline at week 6 in FEV₁ percent predicted (**A**) and FEF_{25-75%} (**B**). (Reprinted from Busse WW, et al. J Allergy Clin Immunol 1999;104:1215-22.)

the study. At weeks 5 to 6, the mean changes from baseline in morning PEF were 47.0 L/min in the QVAR-treated groups and 16.5 L/min in the HFA-placebo group ($P < .001$). The efficacy of QVAR was equivalent whether

the 320 μg/d dose was delivered by 8 puffs of 40 μg or 4 puffs of 80 μg ($P = .017$ for equivalence).

Furthermore, QVAR treatment resulted in a significant reduction in the mean daily use of a bronchodilator (from

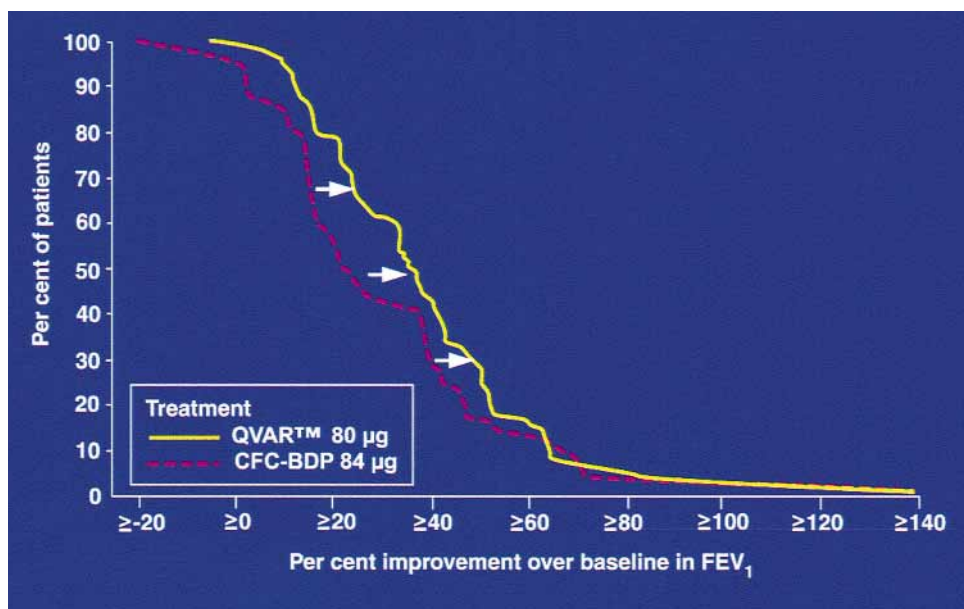


FIG 5. Proportion of patients with increasing improvement in FEV₁ for 80 µg of QVAR versus equal dose of CFC-BDP. (Reprinted from Busse WW, et al. J Allergy Clin Immunol 1999;104:1215-22.)

2.6 uses each day at baseline to 1.3 uses) compared with placebo (from 2.5 uses each day at baseline to 2.3 uses) at weeks 5 to 6 ($P \leq .03$). The mean percentage of nights without sleep disturbance was also improved with QVAR compared with HFA-placebo. The percentage increased from 48.6% at baseline to 77.1% at weeks 5 to 6 in the QVAR group and from 51.0% to 54.6% in the HFA-placebo group. In this study treatment with the same dose from either strength inhaler resulted in equivalent asthma control.

By treating a steroid-naïve patient population with the same degree of asthma severity (FEV₁ 60%-80% predicted), the combined morning PEF results from the studies of Hampel et al³⁶ and Matthys et al³⁷ showed a dose response ($P \leq .0001$, Table III).

Establishing the efficacy-potency ratio with CFC-BDP

In patients with persistent asthma, increasing doses of inhaled corticosteroids are advocated.¹ However, until recently, demonstrating a dose response to inhaled corticosteroids has been elusive, due in part to methodologic difficulties³⁸ and because low doses of inhaled corticosteroids can produce marked improvement in asthma.

An investigation by Busse et al³³ showed that, with an appropriate study design, it is feasible to demonstrate a dose response. This was aided by the requirement for patients after a 7- to 14-day run-in period to display both a fall in FEV₁ and an increase in either symptoms or β -agonist use after discontinuation of their current inhaled corticosteroid and daily clinic assessment (5 days per week) of the primary outcome variable (FEV₁). This thoughtfully designed, blinded, dose-response study

involved 323 patients with moderate and severe asthma (FEV₁, 50%-75%) who were treated with standard inhaled corticosteroids at doses from 336 to 840 µg/d. Patients were randomized to either 84, 336, or 672 µg/d CFC-BDP (Vanceril, Schering/Key Pharmaceuticals) or the same total daily dose of QVAR (80, 320, 640 µg/d) for 6 weeks.

For FEV₁ (percent predicted normal), a significant dose response was seen for both treatments over the dose range from 80 to 672 µg/d ($P < .001$), as shown in Fig 3. A significant dose effect ($P < .05$) was also observed with the percentage change from baseline in FEV₁. At QVAR doses of 80, 320, and 640 µg/d, the percentage changes from baseline in FEV₁ were 33%, 36%, and 47% compared with 29%, 37%, and 38% with the same doses of CFC-BDP.

The dose-response curve for change in FEV₁ percent predicted at week 6 was shifted to the left with QVAR compared with CFC-BDP, and an effect was evident within 1 week of treatment. From these data, it was calculated that it would take 2.6 times (95% confidence interval, 1.1-11.6; Finney's bioassay method) the dose of CFC-BDP to produce the same improvement in FEV₁ obtained with QVAR (Fig 4, A). One of the confirmatory efficacy variables used in the study was the change from baseline in forced expiratory flow, midexpiratory phase (FEF_{25%-75%}), which is thought to be a better measure of small airways function than FEV₁. Although it is less reliable and more effort dependent than FEV₁, it was believed that it would give an indication of the effect of QVAR on the small airways. In terms of this parameter, the dose-response curve for QVAR was also shifted to the left compared with CFC-BDP and, based on the Finney bioassay method, indicated that it would take 3.2

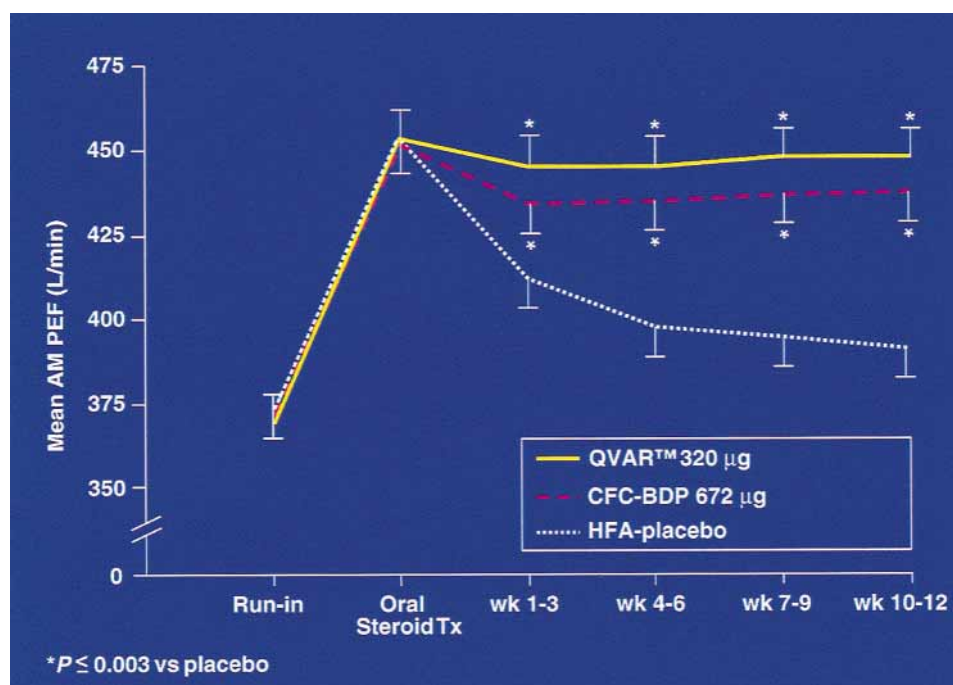


FIG 6. Mean morning PEF (in liters per minute) in patients taking 320 µg/d QVAR or 672 µg/d CFC-BDP or HFA-placebo over 12 weeks. (Reprinted from Gross G, et al. *Chest* 1999;115:343-51.)

times (95% confidence interval, 1.3-15.8) the dose of CFC-BDP to produce the same improvement in $FEF_{25\%-75\%}$ as found with QVAR (Fig 4, B).

Interestingly, 92% of patients treated with 80 µg of QVAR achieved a clinically relevant 12% improvement in FEV_1 compared with only 78% of patients treated with 84 µg of CFC-BDP (Fig 5). Treatment with QVAR not only resulted in greater increases in FEV_1 but also increased the percentage of patients who showed improved airway function.

Treating the symptomatic patient: QVAR (at half daily dose) versus CFC-BDP

The efficacy/potency ratio (as found by Busse et al³³) was tested in a group of 347 patients who were symptomatic and either steroid-naïve or taking inhaled corticosteroids up to 336 µg/d.³⁴ The study design was a 12-week, randomized, parallel-group, blinded, multicenter trial, and all patients had at least moderate asthma consistent with the Global Initiative for Asthma classification. After a 10- to 12-day run-in period to demonstrate asthma symptoms, patients were given a short course of 30 mg/d prednisone to show that they were capable of improvement and steroid responsive. If eligible, patients were randomized to receive either 672 µg of CFC-BDP (Beclovent, GlaxoWellcome Inc) in line with Global Initiative for Asthma guidelines, 320 µg of QVAR (ie, a 2:1 dosing ratio of CFC-BDP to QVAR), or placebo. At baseline, the mean ± SD ages in these groups were 34.8 ± 11.9, 32.5 ± 10.0, and 34.6 ± 9.4 years, respec-

tively. The corresponding baseline FEV_1 percent predicted values were 66.7%, 67.4%, and 67.2%, respectively.

Throughout the 12 weeks of treatment, mean morning PEF was equivalent for 320 µg/d QVAR and 672 µg/d CFC-BDP, and both were significantly greater than with placebo ($P < .003$, Fig 6). Both active treatments maintained, to an equivalent extent, the improvement seen with oral steroids, and this effect was significantly greater than that of placebo ($P \leq .003$). QVAR (320 µg/d) and CFC-BDP (672 µg/d) also provided comparable asthma control, as measured by asthma symptom scores, β -agonist use, and sleep disturbance. These results show that QVAR maintained the improved asthma control after the short burst of oral steroid without the need to step up to the CFC-BDP dose of 672 µg/d.

Another study in 233 patients with moderate-to-severe asthma (according to Global Initiative for Asthma guidelines), which followed a similar design, also demonstrated the ability of QVAR to improve asthma without stepping up to the higher CFC-BDP dose.³⁹ In this trial the randomized treatments were either 640 µg/d QVAR (n = 116) or 1260 µg/d CFC-BDP (n = 117) for 12 weeks.

The primary efficacy variable (mean morning PEF) was equivalent for the 2 treatment groups throughout the study, as were the changes in other measures of pulmonary function, asthma symptom scores, and β -agonist use.

These 2 studies support the notion that QVAR provides equivalent asthma control to CFC-BDP at half the daily dose.

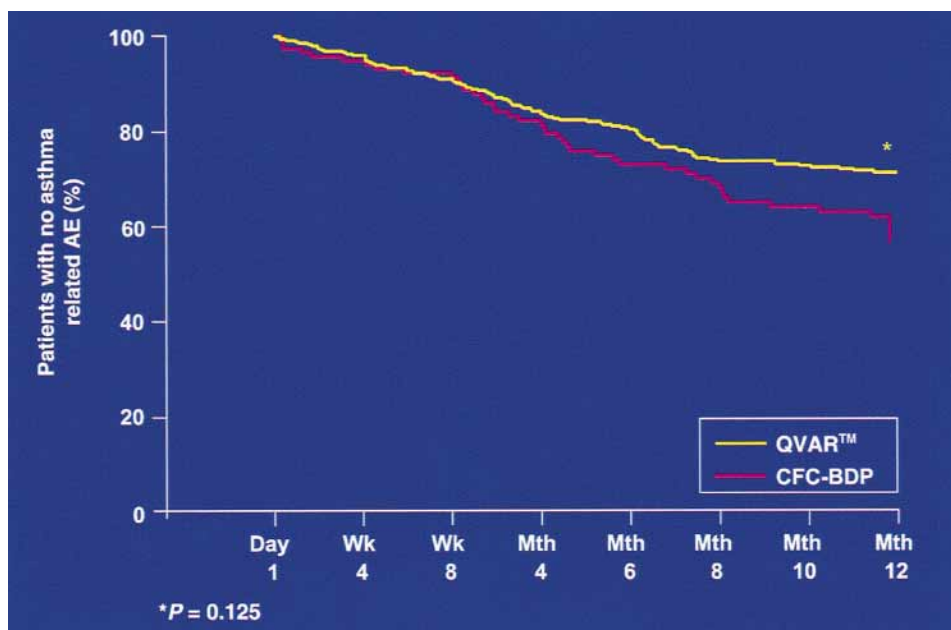


FIG 7. Kaplan-Meier analysis showing time to onset of acute asthma episode or increased asthma symptoms. *P* value indicates no significant difference between the treatments. (Reprinted from Fireman P, et al. *Am J Respir Crit Care Med*. In press.)

Advantages in switching well-controlled patients from CFC-BDP to QVAR

The ongoing phase-out of CFC inhalers means patients will ultimately have to switch to a CFC-free alternative. A 12-month parallel-group study was carried out to determine whether maintenance of asthma control could be achieved by switching patients with asthma from CFC-BDP to QVAR at approximately half their CFC-BDP dose.⁴⁰

The investigation included patients with a 6-month history of asthma and stable symptoms for the past month. During a 2-week run-in period, subjects' symptoms were stabilized on CFC-BDP at the same dose and strength as their previous therapy. They were then randomized to continue CFC-BDP (336-1344 µg/d) at the same dose and strength used during the run-in period (*n* = 119) or switched to approximately half the dose of QVAR (160-640 µg/d, *n* = 354). At baseline, the mean ± SD ages and FEV₁ percent predicted values in the 2 treatment groups were 39.8 ± 14.1 and 39.3 ± 14.1 years and 83.3% and 85.8%, respectively. Objectives of the study included assessment of whether asthma control could be maintained when treatment was switched^{40,41} and, similarly, whether quality of life was maintained over the study period.⁴²

The 2 treatments maintained comparable increases from baseline in morning PEF over 12 months.⁴¹ Measures of pulmonary function, such as FEV₁, FEV_{25%-75%}, and forced vital capacity, also improved, with no significant difference between the 2 treatments. The proportion

of patients who experienced one or more asthma exacerbations during the 12 months of the study was 16.9% in the QVAR group and 22.7% in the CFC-BDP group, despite treatment with QVAR at a dose half that of CFC-BDP. The time to onset of an acute asthma episode or increased asthma symptoms is shown in Fig 7.

In addition to demonstrating maintenance of efficacy, which is necessary for a successful transition program, it is useful to gain a perspective on other patient factors relating to the new treatment. Measurement of health-related quality of life allows the assessment of a wider picture of patient experience. Over the course of this 1-year study, patients' quality of life was measured by using the Juniper Asthma Quality of Life Questionnaire. Using this method, a clinically significant improvement or deterioration in quality of life is defined by a 0.5 or greater increase or reduction in score. At baseline, the mean overall scores with this questionnaire were 5.4 with QVAR and 5.3 with CFC-BDP compared with 5.8 and 5.4 after 1 year, with the difference between treatments being significant at month 12 (*P* = .019), although the size of the mean change was not clinically important. However, on the basis of the clinically meaningful change in score of 0.5 or greater at month 12, the quality of life had deteriorated in significantly more CFC-BDP-treated patients than QVAR-treated patients (19.6% vs 9.1%, *P* = .003).⁴²

The results of this 1-year open-label investigation demonstrated that asthma control continues to be main-

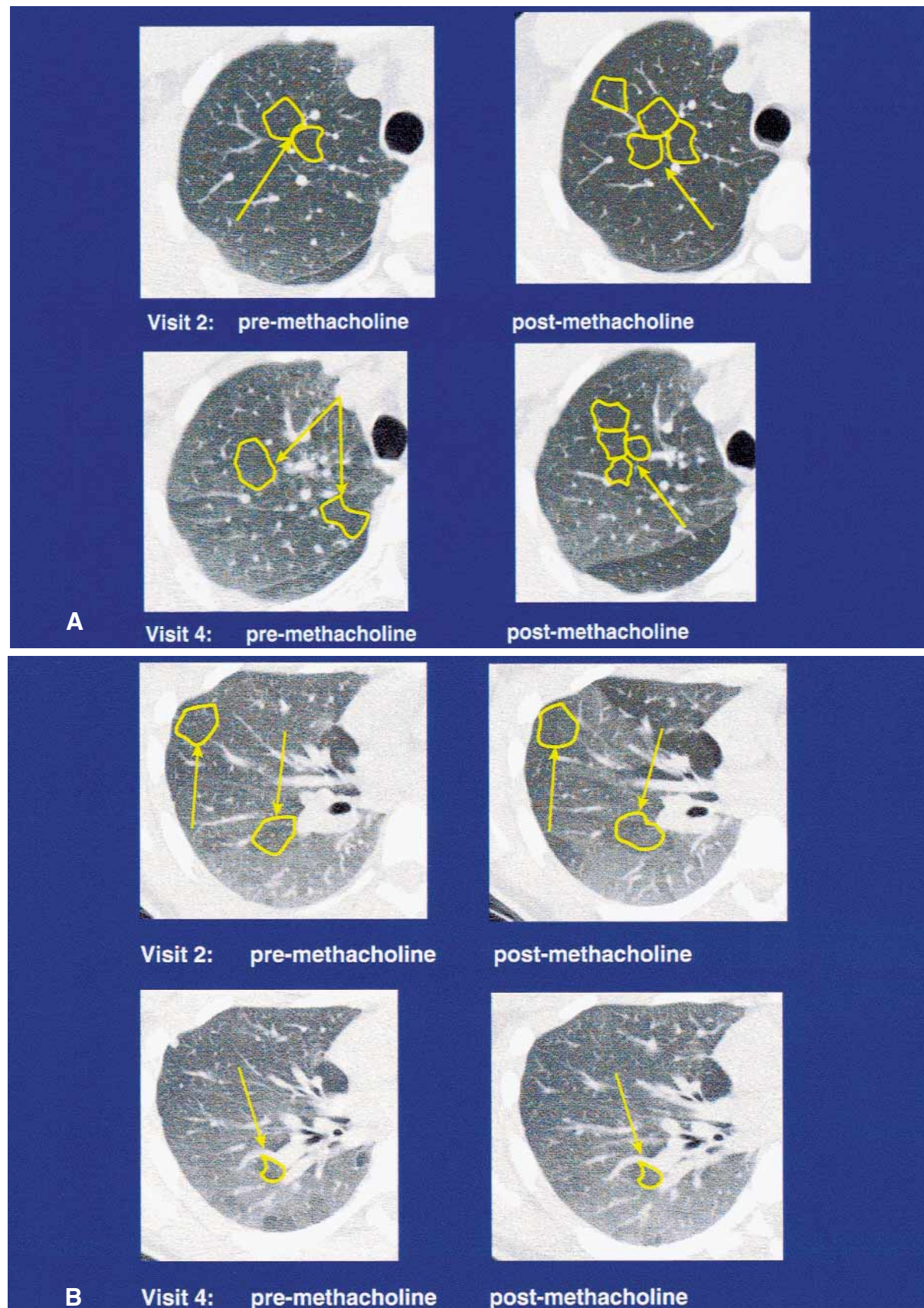


FIG 8. High-resolution computed tomography images before and after methacholine challenge at visits 2 (pretreatment baseline visit) and 4 (posttreatment visit) in a CFC-BDP-treated patient (**A**) and a QVAR-treated patient (**B**). Arrows show regions of trapped air; not all such regions have been highlighted. (Reprinted from Goldin JG, et al. *J Allergy Clin Immunol* 1999;104:S258-67.)

TABLE IV. Median lung attenuation values (Hounsfield units) before and after methacholine challenge at baseline and after 4 weeks of treatment with QVAR or CFC-BDP

	Baseline			After treatment			Change in response
	Before methacholine	After methacholine	Change	Before methacholine	After methacholine	Change	
QVAR (n = 11)	-692* ± 68	-721 ± 70	-29	-646 ± 57	-663 ± 80	-17	12†
CFC-BDP (n = 9)	-690 ± 93	-716 ± 84	-26	-680 ± 75	-740 ± 80	-60	34

Adapted from Goldin JG, et al. *J Allergy Clin Immunol* 1999;104:S258-67.

Results presented for patients who inhaled the same concentration of methacholine at both visits.

*Mean ± 1 SD.

†Significantly different from change in response to methacholine in CFC-BDP-treated patients ($P = .04$).

tained in patients who have switched from CFC-BDP to QVAR and that the proportion of patients who had one or more asthma exacerbations was similar while the switch resulted in improved maintenance of asthma-related quality of life.

THE IMPORTANCE OF TREATING THE SMALL AIRWAYS

Small airway involvement has been demonstrated both physiologically and histopathologically (see "Pathophysiology and scientific rationale"), with evidence of small airway wall remodeling, but the clinical significance of these findings remains unclear.

Conventional CFC-based steroid-suspension aerosols may not adequately suppress inflammation in the small airway, presumably because of the reduced penetration of larger particles into these branches. Testing this hypothesis is difficult, and methods have not been fully validated.

One method proposed is the use of high-resolution computed tomography. This technique was used to assess the relative efficacy of QVAR (160 µg/d) and CFC-BDP (168 µg/d) on small airway hyperreactivity in patients with mild-to-moderate asthma.⁴³ High-resolution computed tomography was performed at baseline and after 4 weeks of inhaled corticosteroid treatment before and after a bronchoconstrictor (methacholine) challenge. Quantitative assessment of the changes in distribution of lung attenuation was performed by using lung attenuation curve analysis as an indirect measure of possible changes in small airways caliber. QVAR-treated subjects (n = 16) showed a significant reduction in regional hyperinflation, whereas CFC-BDP-treated subjects (n = 15) showed no difference. Comparison between the post-treatment QVAR and CFC-BDP subjects showed significantly less methacholine-induced air trapping in the QVAR-treated group (Fig 8, A and B, and Table IV).

This study demonstrated a greater ability for QVAR than CFC-BDP to reduce regional air trapping and to reduce regional airway hyperreactivity; this may be a result of the more effective delivery of BDP to the lung periphery. With the exception of a decline in breathlessness, which was significantly greater in the QVAR group than in the CFC-BDP group ($P < .05$), the reduction in regional hyperinflation

was not associated with clinical improvements in most traditional lung function and asthma symptom scores because the study was not of sufficient size to show a difference in these parameters. High-resolution computed tomography is a sensitive technique; however, further studies are required to assess its clinical usefulness.

A preliminary study has examined the effects of the improved deposition of QVAR on the cells of the small airways. The effects of QVAR (320 µg twice daily) or CFC-BDP (336 µg twice daily) on the production of the inflammatory cytokine TNF-α by alveolar macrophages in response to inflammatory stimulants, such as lipopolysaccharide, derived from nonpathogenic (*AraLAM*) or virulent (*ManLAM*) mycobacteria and LPS derived from gram-negative bacteria were examined.⁴⁴

Alveolar macrophages were cultured after harvesting from healthy nonsmoking volunteers by using fiberoptic bronchoscopy and bronchoalveolar lavage before and after 2 weeks of treatment with QVAR (n = 10) or CFC-BDP (n = 10). QVAR significantly suppressed the production of TNF-α by LPS- and *ManLAM*-stimulated alveolar macrophages ($P < .001$ and $P < .02$, respectively), although no effect was observed with *AraLAM*. CFC-BDP had no significant effect on TNF-α production stimulated by any preparation. This is the first demonstration of an immunomodulatory effect on alveolar macrophages by inhaled corticosteroids and suggests that the improved deposition of QVAR in the peripheral airways and the alveoli may be capable of modulating the inflammatory response of alveolar macrophages.⁴⁴ Further experiments are required to support these findings, for example, after 6 weeks of inhaled corticosteroid therapy and in patients with asthma.

Further evaluation of the benefits of QVAR in treating the inflammation in the smaller airway is underway.

SAFETY OF QVAR

Because QVAR is a new formulation, the safety and tolerability of both the propellant and active constituent have been extensively monitored. However, because BDP is already well characterized as a result of its wide clinical use over the preceding 3 decades, it was not anticipated that any important issues would emerge for

Image available in print only

FIG 9. Dose response of percentage suppression of morning plasma cortisol level (meta-analysis of 4 studies). (Reprinted from Lipworth BJ. *Respir Med* 2000;94[Suppl D]:S21-6.)

the active entity. Nevertheless, it was considered that there may have been changes in the tolerability profile relating to the reduced deposition in the oropharynx and the enhanced delivery of the drug to the lungs. The long-term study previously described^{41,42} assessed the use of QVAR in high doses (640 µg), although no dose response was found. A long-term study has been completed and is awaiting publication.

Acute tolerability

HFA has been shown to be safe in animal toxicology studies,^{45,46} healthy volunteers,^{47,48} and patients with asthma.^{49,50} It has been approved for use in inhalers in more than 40 countries, and therefore in combination with BDP it was considered unlikely to generate any new safety concerns.⁵⁰

The acute topical safety of QVAR was assessed in a single-dose cross-over study of 18 patients who received 8 puffs each of QVAR (160 µg), HFA-placebo, CFC-BDP (210 µg), or CFC-placebo on each of 4 study days. This represented twice the maximum amount of propellant and drug likely to be taken at one time.^{50,51} There were no significant differences between the cough counts per minute between these formulations, although a trend toward higher counts was noted with CFC-BDP. In addition, there were no significant differences in the percentage change of FEV₁ from baseline between the treatment groups.

Systemic effects

Treatment with inhaled corticosteroids may give rise to systemic adverse events associated with suppression of adrenal function, particularly when used in high doses.

The effects of QVAR on the hypothalamic-pituitary-adrenal (HPA) axis have been assessed as a marker of potential systemic activity.

The effect of treatment on the HPA axis was evaluated by 3 methods: 24-hour urinary free cortisol excretion; urinary cortisol/creatinine ratios; and morning plasma cortisol level. The former measure is considered to be the more sensitive and reliable test for this purpose.⁵²

An initial dose-finding study of 43 patients (described earlier in "Pharmacokinetics") also assessed the mean percentage change in 24-hour urinary free cortisol excretion. The results suggested that QVAR at a maximum recommended dose of 640 µg/d caused no more adrenal suppression than a 672 µg/d dose of CFC-BDP.³²

Two of the 12-week trials (described earlier in "Clinical efficacy") included measurements of morning plasma cortisol concentrations.^{34,39} In one investigation involving 347 patients, over 96% of patients in each of the 3 treatment groups (320 µg/d QVAR, HFA-placebo, and 672 µg/d CFC-BDP) had plasma cortisol levels within the normal reference range after 12 weeks of therapy.³³ In the second study (n = 233) comparing 640 µg/d QVAR with 1260 µg/d CFC-BDP, significantly fewer QVAR-treated subjects (4.4%) had below normal morning plasma cortisol levels than CFC-BDP-treated patients (14.6%, *P* = .024).³⁹ Fig 9 illustrates the results of a meta-analysis of morning plasma cortisol from 4 studies comparing QVAR with CFC-BDP, indicating no clinically significant suppression with QVAR below a dose of 640 µg/d, the maximum recommended dose of QVAR.⁵³ Contrary to the pharmacokinetic results, these findings provide reassurance that the increased deposition of drug in the lungs with the new formulation does

TABLE V. Incidence of adverse events in patients receiving QVAR, CFC-BDP, or HFA-placebo in large clinical trials (up to 12 weeks' duration)

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not adversely affect adrenal function.⁵⁴ This may be due to the difference in absorption profiles of the products such that a shorter rise time (ie, T_{max} ; Table I) for QVAR compared with CFC-BDP provides less stimulus to the HPA axis to change its output of corticotropin-releasing hormone and adrenocorticotrophic hormone.⁵⁵

Morning plasma cortisol levels were evaluated in the 12-month open-label study described previously (see "Advantages in switching well-controlled patients from CFC-BDP to QVAR").⁴¹ These patients had been stabilized on CFC-BDP during a 2-week run-in period and then were randomized to continue on their CFC-BDP or switched to approximately half the dose of QVAR. The results show that group mean levels increased from baseline at all time points, and there were no significant differences between the 2 groups at month 12.⁴¹ There was also no significant difference in the proportion of patients with morning plasma cortisol levels below the lower normal limits. Less than 1% of patients treated with QVAR in this study had an abnormal response to cosyntropin stimulation after 12 months' treatment. As a further evaluation of HPA axis suppression, the same investigators measured osteocalcin levels. These levels decreased slightly from baseline to a similar extent in both treatment groups (approximately 0.1 ng/mL after 12 months). A decrease was also demonstrated with budesonide in a 12-month study.⁵⁶ Data are not yet available assessing the effect of QVAR on bone density in adults over time.

Adverse events

The incidence of adverse events in 5 large, phase III, clinical trials has been summarized by Thompson et al.⁵⁰ Treatment groups included QVAR, CFC-BDP, and HFA-placebo.

As shown in Table V, in multiple-dose studies of 6 or 12 weeks' duration, the overall number of patients reporting at least one adverse event was significantly lower in patients treated with QVAR (46%) than those receiving CFC-BDP (59%, $P < .001$). The incidence of adverse events in the HFA-placebo group was significantly lower ($P = .024$) than those in the CFC-BDP group but not significantly different from those in the QVAR group. The incidence of events categorized as *inhalation route disorders* (incorporating cough and dysphonia, both commonly associated with BDP when it is deposited in the oropharynx) was significantly lower with QVAR than CFC-BDP ($P = .042$). The most frequent respiratory system adverse events were found in the HFA-placebo and CFC-BDP groups, 36% and 37%, respectively, as opposed to 25% with QVAR ($P \leq .05$ vs CFC-BDP). Most adverse events were mild-to-moderate in intensity, with severe adverse events (mainly respiratory system disorders) reported by 4% of patients in the QVAR group, 7% of patients in the CFC-BDP group, and 9% of patients in the HFA-placebo group.

Similar numbers of patients from each active treatment group withdrew from the studies (8% with QVAR and 10% with CFC-BDP), which were less than in the HFA-placebo group (21%).

The low incidence of adverse events with QVAR compares favorably with CFC-BDP and the reformulation of BDP by using HFA as the propellant has not raised any new safety concerns. The differences between groups may, in part (eg, those with rhinitis), reflect the difference in sample sizes.

The incidence and profiles of adverse events were also found to be comparable during the immediate switch period between patients continuing to take CFC-BDP and those transferred to QVAR.⁴⁰

These data indicate that comparable tolerability can be expected with CFC-BDP and QVAR by using half the daily dose. On the basis of long-term comparison data with CFC-BDP and QVAR, the tolerability profiles are maintained over 12 months.

PATIENT PREFERENCES

With the phasing out of CFC propellants, patients will be required to replace their existing pMDI with a CFC-free device. As part of the 12-month study described previously,⁴¹ patient opinions on the acceptability and the ease of switching from their CFC-BDP pMDI to QVAR pMDI were assessed by means of 2 questionnaires.⁵⁷ The initial questionnaire concerned the CFC-inhaler used before the study and was completed after the run-in period. The follow-up questionnaire concerned the QVAR pMDI and was completed 1 month after randomization.

Overall, 235 (88%) of 267 patients who were assigned to QVAR pMDI found this to be an acceptable alternative to CFC-BDP, and 150 subjects recorded that QVAR had advantages over the CFC-containing inhaler (fewer puffs, lack of CFC, and better mouthpiece). In addition, 96% (256/267) of patients found it easy to switch to the new pMDI.

CONCLUDING REMARKS

The need to reformulate BDP has provided the opportunity to improve current therapies. With traditional CFC-BDP, where most of the drug is deposited in the oropharynx and is swallowed, studies now suggest that airway inflammation may not have been adequately treated. The findings that a lower daily steroid dose in QVAR is associated with improved delivery, even when discoordination is present, as well as comparable efficacy, tolerability, and no change in adrenal suppression up to 640 µg/d, will prompt further clinical investigations to provide the necessary confirmation.

The increased deposition of BDP in the lungs with the new formulation permits a reduction in dosage relative to CFC-BDP. Across the dose range from 84 to 672 µg/d, a 2.6 times higher dose of CFC-BDP is required to achieve the same level of efficacy as QVAR. QVAR has demonstrable efficacy in well-controlled trials when compared with CFC-BDP and placebo in patients with varying degrees of asthma severity, and in a range of patient types, including steroid-naïve, symptomatic, and asymptomatic subjects. These studies were robustly designed for their respective circumstances (eg, ensuring that patients were steroid responsive to permit an optimum assessment of the effects of the medications studied). Moreover, to reduce bias, randomization and maintenance of blinding were enforced when it was not considered ethically possible to perform double-blind placebo-controlled trials.

Long-term assessment of efficacy and tolerability was also essential for a chronic condition, such as asthma. In long-term assessments comparing CFC-BDP with QVAR at

half the daily dose, patients could be switched to QVAR without exacerbation of their asthma symptoms during the switch period, and this control was maintained in the long term. Patient preference information has confirmed that QVAR is an acceptable alternative to CFC-BDP and that the switch is easy to make. An assessment of patients' quality of life showed an improvement for QVAR-treated patients. No new safety issues relating to QVAR emerged during the clinical trials program. Additional studies evaluating the effect of QVAR in children with asthma are currently in progress; however, QVAR at present is not indicated for pediatric use.

Regardless of the circumstances of the individual efficacy trials, the outcomes were remarkably consistent and provide evidence to support the hypothesis that increasing the delivery of BDP to the central and peripheral airways is associated with added benefit for patients because of a reduction in the daily dose required for asthma control. This outcome is in line with current treatment guidelines.

The safety profile of QVAR at the maximum recommended dose of 640 µg/d was found to be similar to that observed with CFC-BDP up to 672 µg/d.

The therapeutic ratio (benefit/risk) of an inhaled corticosteroid can be estimated from the ratio of clinical to systemic effects.⁵⁸ The clinical effect is assumed to depend only on the deposition in the airway, whereas the systemic effect depends on the amount of corticosteroid deposited in and systemically absorbed from the lungs and the amount absorbed from the gastrointestinal tract. Assuming that the clinical effect was to improve because of increased deposition but at a lower dose of inhaled corticosteroid (as with QVAR) and that the systemic effects were to be similar or better (as observed with QVAR), then it is tempting to speculate that a treatment displaying a favorably improved therapeutic ratio is now available. Nevertheless, caution is required until further clinical assessments have been performed that investigate this feature of QVAR more specifically.

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