

A comparison of fluticasone propionate 200 µg/day with beclomethasone dipropionate 400 µg/day in adult asthma

Leblanc P, Mink S, Keistinen T, Saarelainen PA, Ringdal N, Payne SL. A comparison of fluticasone propionate 200 µg/day with beclomethasone dipropionate 400 µg/day in adult asthma. Allergy 1994; 49: 380–385. © Munksgaard 1994.

A total of 261 patients with symptomatic, mild to moderate asthma were randomized to treatment in this 4-week, double-blind, parallel-group comparison of fluticasone propionate 200 µg/d with beclomethasone dipropionate 400 µg/d. Improvements from both treatments were seen in diary card data. Morning peak expiratory flow rate (PEFR) improved from 375 to 390 and 371 to 382 l/min with fluticasone propionate and beclomethasone dipropionate, respectively. Symptom scores, percentage of symptom-free days and nights, and use of rescue β_2 -agonist medication also improved, as did clinical lung function. With the exception of percentage of rescue-free days, which was greater for beclomethasone dipropionate, none of the differences between the groups were statistically significant. There was a significant difference between treatments in the number of rescue-free days over days 1–28; however, there was no difference between treatments in the number of rescue-free days over days 1–14, nor was there any difference in the number of inhalations of rescue medication used throughout the study. Very few adverse effects were reported. Although all mean plasma cortisol values were within the normal range, they were significantly different between treatments, rising from 402 to 429 nmol/l with fluticasone propionate, and falling from 435 to 394 nmol/l with beclomethasone dipropionate ($P = 0.006$). Mean stimulated cortisol levels 30 min after tetracosactin injection were also significantly greater with fluticasone propionate ($P = 0.024$). In conclusion, fluticasone propionate 200 µg/d is as effective as beclomethasone dipropionate 400 µg/d with less effect on plasma cortisol levels.

P. Leblanc¹, S. Mink², T. Keistinen³,
P. A. Saarelainen⁴, N. Ringdal⁵,
S. L. Payne⁶

¹ Hôpital Laval, Sainte-Foy, Quebec G1V 4GS, Canada; ² University of Manitoba, Winnipeg, Manitoba, Canada; ³ Paivarinne Hospital, 91410 Jokirinne, Finland; ⁴ Laakson Sairaala/Keuhkopoliklinikka, Laakarinkatu 6, 00250 Helsinki, Finland; ⁵ Department of Pulmonary Disease, Molde County Hospital, 6400 Molde, Norway; ⁶ Glaxo Group Research Ltd, Greenford Road, Greenford, Middlesex, UB6 0HE, UK

Key words: asthma; clinical trial; HPA function; inhaled glucocorticosteroid.

Miss S. L. Payne
Glaxo Group Research Ltd
Greenford Road
Greenford, Middlesex UB6 0HE
UK

Accepted for publication 6 August 1993

Since their introduction, inhaled glucocorticosteroids have been increasingly recommended for use in the treatment of asthma, since they are the only inhaled drugs shown to reduce effectively the chronic inflammation of asthma. Nevertheless, because these drugs are associated with certain severe side-effects, there is concern about their increased use. For example, high-dose budesonide and beclomethasone dipropionate have been shown to reduce hypothalamic-pituitary-adrenal (HPA)-axis function and alter bone metabolism (4, 9). Alternative drugs, such as nedocromil sodium and sodium cromoglycate, are not effective replacements for high-dose steroids (14, 19). Thus, inhaled glucocorticosteroids, which are more effective with less systemic activity than their currently available counterparts, are now being developed.

Fluticasone propionate is a topically active glucocorticosteroid which has been shown, *in vitro*, to be more potent than either beclomethasone dipropionate or budesonide (15). Clinical studies of rhinitis (5) and asthma (2, 8) have shown fluticasone propionate to be more effective than beclomethasone dipropionate given at equal doses, while a dose-response study has further suggested that fluticasone propionate is at least twice as potent as beclomethasone dipropionate (6). This study by Dahl et al. (6), in a large, homogeneous population of patients with moderate asthma, clearly demonstrated a dose-response relationship for the therapeutic efficacy of fluticasone propionate over the dose range 200–800 µg daily. In addition, it showed that fluticasone propionate 200 µg/d produced the same increase in morning and evening peak expiratory flow-rate

(PEFR) values as beclomethasone dipropionate 400 µg/d. Furthermore, fluticasone propionate has an oral bioavailability of less than 1% (10), which is lower than that for either budesonide or beclomethasone dipropionate. A recent clinical study (8) in moderate to severe asthmatic patients has shown that fluticasone propionate had no effect on HPA-axis function when given at a dose of 1.5 mg for 12 months.

The present study was designed to compare the efficacy of fluticasone propionate 200 µg/d with that of beclomethasone dipropionate 400 µg/d in adult patients with mild to moderate asthma.

Material and methods

Patients

A total of 301 patients entered this double-blind, parallel-group study. The patients (Table 1) had mild to moderate asthma and demonstrated a peak expiratory flow variability during the 2-week run-in period of >20% or a bronchodilator response of >15%. The patients also suffered symptoms on at least 4 days or nights of the run-in period. Patients were excluded if, during the month preceding the study, they had required more than a daily dose of 400 µg budesonide or beclomethasone dipropionate, or had required oral glucocorticosteroids within 1 month of the study. In addition, patients who did not tolerate rescue inhaled β_2 -agonist on an "as required" basis, were pregnant or lactating, or suffered from a severe concurrent disease were excluded.

Assessments

Diary cards. During the run-in and 4-week treatment periods, patients completed daily record cards every

morning and evening, recording the highest of three PEFR measurements, before taking medication. In addition, they recorded the severity of their asthma symptoms. Daytime asthma symptoms were rated on a four-point scale, ranging from 0 (very well, no symptoms) to 3 (asthma bad, not able to carry out daily activities as usual). Nighttime asthma symptoms were similarly classified, ranging from 0 (slept through the night) to 3 (bad night, kept awake most of the time by asthma). Patients also kept a note of their consumption of trial, concomitant, and rescue medication.

Clinic visits. At each clinic visit, PEFR, forced expiratory volume in 1 s (FEV₁), and forced vital capacity (FVC) were measured after withholding bronchodilator therapy for 4 h if possible. In addition, the incidence of adverse effects was assessed by questioning the patients, physical examination, and biochemical and hematologic analysis of blood samples. Morning plasma cortisols were also measured, and, in 167 patients, a short tetracosactrin test was performed.

Protocol

Patients who fulfilled the entry criteria during the 2-week run-in period were randomized to receive treatment with either fluticasone propionate 100 µg twice daily or beclomethasone dipropionate 200 µg twice daily via a metered dose inhaler for 4 weeks in place of their usual inhaled glucocorticosteroid. Patients were allowed to use a spacer device, but this was at the discretion of their physicians. During the 4-week study period, the patients kept diary cards and attended clinic visits every 2 weeks, with a follow-up visit 2 weeks after cessation of treatment. Throughout the study, the regular inhaled β_2 -agonist was withdrawn and replaced with a salbutamol metered dose-inhaler, which was to be used for relief only. All other concomitant medication was unchanged.

Statistical analysis

All the data presented here are for the total randomized population, on "an intent-to-treat" basis and were analyzed with the SAS (Release 6.03) program and procedures. Power calculations showed that 300 patients would be needed to show a difference of 17 l/min in PEFR with a power of 90%. Daily PEFR, clinical lung function, and plasma cortisols were analyzed by analysis of covariance, adjusting for base line, spacer use, and treatment. The percentage of symptom-free days and nights and rescue-free days was analyzed by Wilcoxon rank sum test with the Van Elteren method for country adjust-

Table 1. Patient characteristics

Variable	Fluticasone propionate 200 µg/d	Beclomethasone dipropionate 400 µg/d
No. of patients	129	132
Sex % M/F	54/46%	52/48%
White	97%	99%
Age median (range; years)	46 (19–80)	46 (18–74)
% Asthma <5/>5 years	47/53%	48/52%
Spacer used (%)	15%	16%
%Pred PEFR	83%	83%
%Pred FEV ₁	73%	71%
Prestudy asthma medications (%)		
Inhaled β_2 -agonists	88%	86%
Oral β_2 -agonists	5%	8%
Inhaled glucocorticosteroids	61%	60%
Methylxanthines	42%	52%
Sodium cromoglycate	4%	5%
Other	12%	15%

ments (13). The incidence of adverse drug effects was analyzed by Mantel Haenszel and Fisher's exact test (12). Predicted lung function values were calculated from the patient's sex, age, and height by standard formulas (16).

Results

Of the 301 patients who entered the study, 261 were randomized to treatment. Forty patients were withdrawn before the start of treatment: 33 were ineligible; six were withdrawn because of poor compliance and one because of an adverse effect. After randomization, five patients in each treatment group withdrew. In the fluticasone propionate group, the reasons for withdrawal were asthma (two patients) and noncompliance (three patients). In the beclomethasone dipropionate group, the reasons were asthma (four patients) and adverse effect (one patient). Treatment groups were well matched in all respects (Table 1). None of the patients were aged less than 18 years, 41% were aged over 50 years, and 10% were over 65 years. Approximately 60% of the patients in either treatment group had previously received inhaled glucocorticosteroids, and approximately 50% were concomitantly receiving methylxanthine preparations. Around 15% of the patients in each treatment group used spacer devices during the study, but the analysis showed that this factor had no influence on the results.

Diary card data

Fig. 1 shows the morning and evening PEFR with fluticasone propionate and beclomethasone dipropionate, demonstrating that over the 4 weeks of treatment, PEFR increased with both drugs. The improvements for fluticasone propionate (FP) and beclomethasone dipropionate (BDP), respectively, were as follows: morning PEFR, 375–390 and 371–382 l/min (adjusted mean difference FP–BDP = 4 l/min; 95% CI –4, 12 l/min); evening PEFR, 398–408 and 390–398 l/min (adjusted mean difference FP–BDP = 2 l/min; 95% CI –6, 10 l/min). The differences between treatments were not significant (Table 2). In terms of percentage of predicted values, these improvements for fluticasone propionate and beclomethasone dipropionate, respectively, were as follows: morning PEFR 82–85% and 81–84%; evening PEFR, 87–89% and 86–87%.

Likewise, the percentage of symptom-free days rose from 18% to 33% and from 22% to 35%, and the percentage of symptom-free nights from 46% to 61% and from 51% to 61% for fluticasone propionate and beclomethasone dipropionate, respectively; the differences between treatments were not significant (Table 2). There was a general improve-

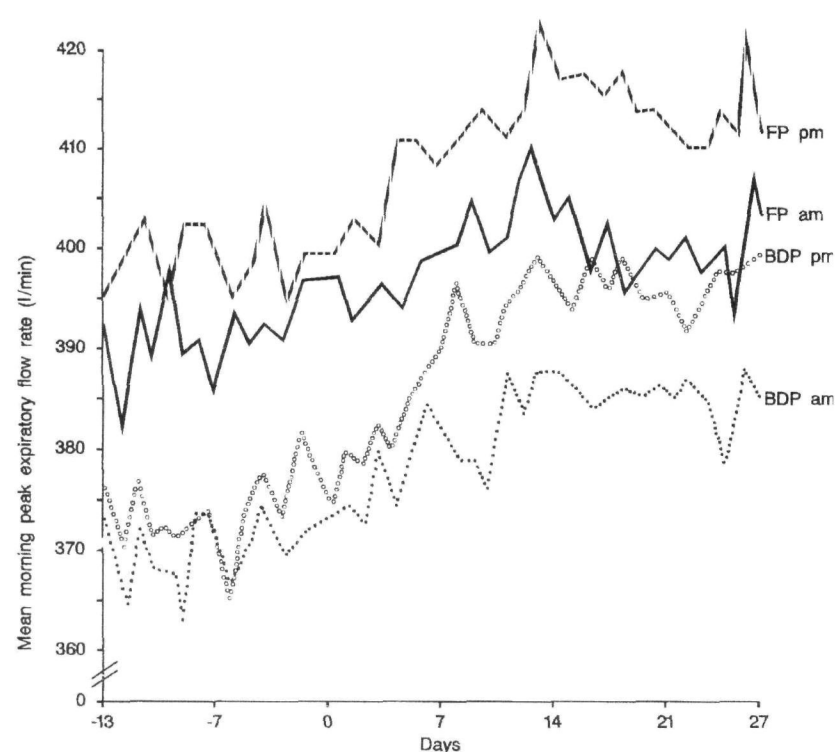


Fig. 1. Mean morning (am) and evening (pm) peak expiratory flow rate (l/min) during run-in and over 4-week treatment period with fluticasone propionate 200 µg/d (FP) and beclomethasone dipropionate 400 µg/d (BDP).

ment in both treatment groups, less than 10% of patients recording symptom scores of 2 or more.

The percentage of rescue-free days rose from 21% to 33% and 18% to 35% with fluticasone propionate and beclomethasone dipropionate, respectively. The difference between treatments was significant in favor of beclomethasone dipropionate ($P = 0.05$). However, there was no difference between treatments in the number of rescue-free days over days 1–14, nor was there any difference between treatments in the number of inhalations of rescue medication used throughout the study. The number of times rescue medication was used in a 14-d period decreased from 65 to 44 and from 63 to 48 times with fluticasone propionate and beclomethasone dipropionate, respectively. Therefore, it is likely that the one statistical difference occurred by chance.

Clinical data

Clinical lung function (PEFR, FEV_1 , and FVC) increased with both treatments from base-line values, and the respective values for fluticasone propionate and beclomethasone dipropionate were as follows: clinical PEFR, 388–411 and 379–392 l/min; FEV_1 , 2.34–2.46 and 2.21–2.29 l; FVC, 3.45–3.53 and 3.34–3.38 l (Table 3). There were no significant differences between treatments.

Safety

Adverse drug effects were reported by 24% of patients taking fluticasone propionate and 35% of patients taking beclomethasone dipropionate. In 2% of

Table 2. Diary card data

Variable	Fluticasone propionate 200 µg/d			Beclomethasone dipropionate 400 µg/d			Difference in adjusted means s(95% CI) FP-BDP	P value
	Base-line mean (n)	Means after treatment (n)	Adjusted means* (n)	Base-line mean (n)	Means after treatment (n)	Adjusted means* (n)		
AM PEFR (l/min)	375 (126)	390 (126)	392 (126)	371 (127)	382 (127)	388 (127)	4 (-4, 12)	0.368
PM PEFR (l/min)	398 (126)	408 (126)	406 (126)	390 (129)	398 (129)	404 (129)	2 (-6, 10)	0.605
% Symptom-free days	18% (125)	33% (125)	—	22% (128)	35% (128)	—	—	0.550
% Symptom-free nights	46% (125)	61% (125)	—	51% (128)	61% (128)	—	—	0.338
% Rescue-free days	21% (116)	33% (116)	—	18% (122)	35% (122)	—	—	0.050 ^a
Mean use salb/14 d	65 (116)	44 (116)	—	63 (122)	48 (122)	—	—	0.228

* Mean adjusted for base line, country, and use of spacer.

Mean use salb/14 d=number of times rescue medication was used, averaged over 14 d.

^a Statistically significant, in favor of beclomethasone dipropionate.

—=Not calculated.

Table 3. Clinical lung function at base line and after 4 weeks' treatment

Variable	Fluticasone propionate 200 µg/d (n= 123)			Beclomethasone dipropionate 400 µg/d (n= 132)			Difference in adjusted means s(95% CI)	P value
	Base-line mean	Means after treatment	Adjusted means*	Base-line mean	Means after treatment	Adjusted means*		
PEFR (l/min)	388	411	402	379	392	392	10 (-6, 26)	0.205
%Pred	84	89	87	83	86	85	2 (-1, 6)	0.167
FEV ₁ (l)	2.34	2.46	2.41	2.21	2.29	2.36	0.04 (-0.04, 0.13)	0.313
%Pred	74	78	77	70	73	75	1 (-1, 4)	0.325
FVC (l)	3.45	3.53	3.49	3.34	3.38	3.44	0.05 (-0.06, 0.15)	0.367
%Pred	90	92	91	89	89	90	1 (-1, 4)	0.372

* Mean adjusted for base line, country, and use of spacer.

%Pred= % predicted normal value.

patients taking fluticasone propionate and 4% of patients taking beclomethasone dipropionate, these drug effects were severe, with the same percentage of patients withdrawing from the study because of adverse effects in each treatment group. The most common (>4%) and pharmacologically predictable effects are shown in Table 4.

All mean plasma cortisol values were above the lower limit of the normal range (140 nmol/l) before and after treatment. However, plasma cortisols were significantly different between treatments, rising from 402 to 429 nmol/l with fluticasone propionate (n= 108), and falling from 435 to 394 nmol/l with beclomethasone dipropionate (n= 114) (ratio FP/BDP= 1.15, 95% CI 1.04, 1.28; P= 0.006). In some patients, an optional tetracosactrin test was performed. The results showed that stimulated cortisol levels 30 min after tetracosactrin injection were also significantly different, being 786 and 811 nmol/l, be-

fore and after treatment for patients taking fluticasone propionate (n= 80), and 757 and 724 nmol/l before and after treatment for patients taking beclomethasone dipropionate (n= 87; ratio FP/BDP= 1.09, 95% CI 1.01, 1.18; P= 0.024). No clinically significant changes were detected in the routine

Table 4. Most common (≥4%) and pharmacologically predictable adverse effects

Adverse effect	Fluticasone propionate 200 µg/d (%)	Beclomethasone dipropionate 400 µg/d (%)
No. of patients	129	132
Headache	5 (4)	1 (< 1)
Asthma	3 (2)	5 (4)
Oral candidiasis*	5 (4)	7 (5)
Hoarseness*	0	2 (2)

* Pharmacologically predictable adverse effects.

laboratory hematology, biochemistry, and urinalysis, and there was no difference between treatments.

Discussion

This study shows that fluticasone propionate 200 µg/d is at least as effective as beclomethasone dipropionate 400 µg/d in the control of mild to moderate asthma in adult patients. This was evident from diary PEFr measurements and reduced symptom scores. There was a difference in favor of beclomethasone dipropionate for the percentage of rescue-free days over the 28-d study period. This, however, was probably attributable to chance, since there was no difference between treatments in the percentage of rescue-free days over days 1–14, nor was there any difference in the number of inhalations of rescue medication throughout the study. In addition, clinical lung function was equally increased on both treatments.

Unstimulated and stimulated plasma cortisols, although all within the normal range, were significantly greater in patients taking fluticasone propionate than in those taking beclomethasone dipropionate. These data are compatible with the preclinical (10, 15) and clinical studies (1) which have shown fluticasone propionate to be more potent than beclomethasone dipropionate with less effect on plasma cortisol levels.

The results of this study confirm both the efficacy and safety of fluticasone propionate, as well as its superior potency to beclomethasone dipropionate, in the treatment of adult asthmatic patients. Previous comparative studies have frequently failed to distinguish between beclomethasone dipropionate and budesonide in terms of efficacy and safety at therapeutic doses (3, 7, 11, 17, 18). However, many of the comparisons have involved small numbers of patients, and this may have made it difficult to detect any significant differences in treatment. In addition, few studies have succeeded in showing a dose-response relationship for inhaled glucocorticosteroids (9), a relationship which in the case of fluticasone propionate has been demonstrated over the dose range 200–800 µg/d (6). In that study, fluticasone propionate 200 µg/d was shown to be equivalent, in improvement in lung function, to beclomethasone dipropionate 400 µg/d. Although the study reported here failed to reach its target of 300 evaluable patients which would have given it power to detect a true difference, all the efficacy variables, with the exception of the percentage of rescue-free days, favored fluticasone propionate. Therefore, it is unlikely that beclomethasone dipropionate 400 µg/d is more effective than fluticasone propionate 200 µg/d. Furthermore, in both treatment groups, there was still room for improvement in PEFr and symptom

scores, implying that the top of the dose-response curve had not been reached. In addition, there were fewer adverse effects and systemic effects in the fluticasone propionate group than in the beclomethasone dipropionate group, demonstrating that fluticasone propionate has greater efficacy without increasing the risk of adverse effects.

Acknowledgments

We would like to thank the following for their assistance with the study: Dr K. Sertl (Austria); Dr D. A. Lindsay (Australia); Dr B. Dewispelaere, Dr D. Coolen (Belgium); Dr G. F. MacDonald, Dr R. Grossman (Canada); Dr B. Keogh, Dr L. Clancy (Ireland); Prof. A. E. Rubin (Israel); Prof. L. M. Fabbri, Prof. S. Bianco, Prof. G. Gunella, Prof. C. Giuntini (Italy); Dr K. Holten, Dr P. Gottschalk (Norway); Dr D. H. Mahlo, Dr H. G. Fenner, Dr P. Arens, Dr H. J. Taenzer, Dr T. Gebhardt, Dr F. Fuetting, Dr J. Kandziora, Dr D. Hahn, Dr L. Leonhardt (Germany).

References

1. BARNES NC, MARONE G, DI MARIA GU, VISSER S, UTAMA I, PAYNE SL. A comparison of fluticasone propionate 1 mg daily with beclomethasone dipropionate 2 mg daily in the treatment of severe asthma. *Eur Respir J* 1993; 6: 877–84.
2. BAUER K, BANTJE TA, SIPS AP, et al. The effects of inhaled fluticasone propionate (FP), a new potent corticosteroid, in severe asthma. *Eur Respir J* 1988; 1 (Suppl. 2): P201s (Abstract).
3. BJÖRKANDER J, FORMGREN H, JOHANSSON SA, MILLQVIST E. Methodological aspects on clinical trials with inhaled corticosteroids: results of two comparisons between two steroid aerosols in patients with asthma. *Eur J Respir Dis* 1982; 63 (Suppl. 122): 108–17.
4. BOE J, SKOOGH B-E. Is long-term treatment with inhaled steroids hazardous? *Eur Respir J* 1992; 5: 1037–9.
5. BRYSON HM, FAULDS D. Intranasal fluticasone propionate. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in allergic rhinitis. *Drugs* 1992; 43 (5): 760–75.
6. DAHL R, LUNDBACK B, MALO J-L, et al. A dose-ranging study of fluticasone propionate in adult patients with moderate asthma. *Chest* 1993 (in press).
7. EBDEN P, JENKINS A, HOUSTON G, DAVIES BH. Comparison of two high-dose corticosteroid aerosol treatments, beclomethasone dipropionate (1500 mcg) and budesonide (1600 mcg/day) for chronic asthma. *Thorax* 1986; 41: 869–74.
8. FABBRI L, BURGE PS, CROONENBORGH L, et al. Comparison of fluticasone propionate with beclomethasone dipropionate in moderate to severe asthma treated for one year. *Thorax* 1993; 48: 817–23.
9. GEDDES DM. Inhaled corticosteroids: benefits and risks. *Thorax* 1992; 47: 404–7.
10. HARDING SM. The human pharmacology of fluticasone propionate. *Respir Med* 1990; 84 (Suppl. A): 25–9.
11. KEELAN P, FRAME M, GRAY P, KELLY P. Comparison of a new corticosteroid aerosol budesonide, with beclomethasone dipropionate in the treatment of chronic asthma. *Ir Med J* 1984; 77: 244–7.
12. KOCH GG, EDWARDS S. Clinical efficacy trials with categorical data. In: PEACE KE, ed. *Biopharmaceutical statistics for drug development*. New York: Dekker, 1988: 403–58.
13. LEHMANN EL. *Nonparametrics: statistical methods based on ranks*. San Francisco: Holden-Day, 1975: 132–41.

14. MOLEMA J, VAN HERWAARDEN CLA, FOLGERING HTM. Effects of long-term treatment with inhaled cromoglycate and budesonide on bronchial hyperresponsiveness in patients with allergic asthma. *Eur Respir J* 1989; 2: 308–16.
15. PHILLIPS GH. Structure-activity relationships of topically active steroids: the selection of fluticasone propionate. *Respir Med* 1990; 84 (Suppl. A): 19–23.
16. QUANJER PH, DALHUIJSON A, VAN ZOMEREN BC. Summary equations and reference values. *Bull Eur Physiopathol Respir* 1983; 19 (Suppl. 5): 45–51.
17. ROSENHALL L, LUNQUIST G, ADELROTH E, GLENNOW C. Comparison between inhaled and oral corticosteroids in patients with chronic asthma. *Eur J Respir Dis* 1982; 63 (Suppl. 122): 154–62.
18. STIKSA G, GLENNOW C, JOHANNESSON N. An open cross-over trial with budesonide and beclomethasone dipropionate in patients with bronchial asthma. *Eur J Respir Dis* 1982; 63 (Suppl. 122): 266–7.
19. SVEDSEN UG, FROLUND L, MADSEN F, NIELSEN NH. A comparison of the effects of nedocromil sodium and beclomethasone dipropionate on pulmonary function, symptoms, and bronchial responsiveness in patients with asthma. *J Allergy Clin Immunol* 1989; 84: 224–31.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.