The Prostate 29:231–240 (1996)

Comparison of Phytotherapy (Permixon®) With Finasteride in the Treatment of Benign Prostate Hyperplasia: A Randomized International Study of 1,098 Patients

Jean-Christophe Carraro, Jean-Pierre Raynaud, Gary Koch, Geoffrey D. Chisholm, Franco Di Silverio, Pierre Teillac, Fernando Calais Da Silva, Joris Cauquil, Dominique K. Chopin, Freddie C. Hamdy, Miroslav Hanus, Dieter Hauri, Athanasios Kalinteris, Josef Marencak, Antoine Perier, and Paul Perrin

Pierre-Fabre Médicament, Castres (J.C.C., J.C.), University Pierre and Marie Curie, Paris (J.P.R.), Analytica, Paris (A.P.), St. Louis Hospital, Paris (P.T.), Henri-Mondor Hospital, Créteil (D.K.C.), Antiquaille Hospital, Lyon (P.P.), France; Department of Urology, University of Edinburgh, Edinburgh (G.D.C.), Freeman Hospital, Newcastle-upon-Tyne (F.C.H.), UK; University "La Sapienza," Rome, Italy (F.D.S); University of Lisbon, Lisbon, Portugal (F.C.D.S.); Charles University, Urocentrum, Prague, Czech Republic (M.H.); University Hospital, Zürich, Switzerland (D.H.); Aristotle University of Thessaloniki, Thessaloniki, Greece (A.K.); Skalica Hospital, Skalica, Slovakia (J.M.); Department of Biostatistics, University of North Carolina, USA (G.K.)

BACKGROUND. Controversy regarding the relative efficacy of treatments for the relief of the symptoms of benign prostatic hyperplasia (BPH).

METHODS. This was a 6-month double-blind randomized equivalence study that compared the effects of a plant extract (320 mg Permixon®) with those of a 5α-reductase inhibitor (5 mg finasteride) in 1,098 men with moderate BPH using the International Prostate Symptom Score (IPSS) as the primary end-point.

RESULTS. Both Permixon® and finasteride decreased the IPSS (−37% and −39%, respectively), improved quality of life (by 38 and 41%), and increased peak urinary flow rate (+25% and +30%, $P = 0.035$), with no statistical difference in the percent of responders with a 3 ml/sec improvement. Finasteride markedly decreased prostate volume (−18%) and serum PSA levels (−41%); Permixon® improved symptoms with little effect on volume (−6%) and no change in PSA levels. Permixon® fared better than finasteride in a sexual function questionnaire and gave rise to less complaints of decreased libido and impotence.

CONCLUSIONS. Both treatments relieve the symptoms of BPH in about two-thirds of patients but, unlike finasteride, Permixon® has little effect on so-called androgen-dependent parameters. This suggests that other pathways might also be involved in the symptomatology of BPH.

KEY WORDS: **benign prostatic hyperplasia, phytotherapy, lipid/sterol extract of *Serenoa repens*, Permixon®, 5α-reductase inhibitor, finasteride**

Received for publication September 18, 1995; accepted December 20, 1995.

Address reprint requests to Dr. J.C. Carraro, Pierre Fabre Médicament, La Chartreuse, 81106 Castres Cedex, France.

INTRODUCTION

From age 40 years onwards, many men experience a change in their quality of life due to urinary symptoms related to prostate enlargement [1,2]. The management of benign prostate hyperplasia (BPH) of moderate severity is a matter of some controversy [3]. Watchful waiting is considered a safe alternative for those men who wish to delay surgery (transurethral prostatic resection or incision) [4], but could be made more comfortable by palliative medical treatment. Rather than the symptoms per se or the decrease in flow, it is often the bothersomeness of urinary difficulties that matters most to patients [5,6]. Well-informed judgments on the relative merits of different drugs such as 5α-reductase inhibitors [7–9], α-receptor blocking agents [10], and plant extracts [11–15] are thus called for.

Finasteride [7] and other highly specific 5α-reductase inhibitors such as epristeride [8] and turosteride [9] have been recently developed on the premise that the 5α-reduced testosterone metabolite, dihydrotestosterone (DHT), is needed for prostate growth. Androgens do regulate some prostate growth factors [16,17], but there is no sound consistent evidence for higher DHT levels in hyperplastic compared to normal tissue when samples are obtained under physiological conditions [18,19]. Furthermore, the prostatic stroma and epithelium secrete stimulatory and inhibitory diffusible proteins that exert local control and that are nonandrogen-dependent.

Plant extracts are widely used in Europe for symptomatic relief in BPH [11–15]. Their precise mechanism of action is not clear but, because of their mixed composition, they probably exert several types of activity rather than interfere, like finasteride, in an extremely specific manner, with a single molecular target. The lipid/sterol extract from the dwarf palm *Serenoa repens* (LSESr, Permixon®) acts upon prostaglandin metabolism in cultured prostatic cells [20], modulates human 5α-reductase [21], exerts antiedemic activity in animals [22], and displays antiestrogenic activity in humans [23]. This double-blind multicenter trial in 1,098 patients aimed to establish whether finasteride and Permixon® are equivalent in the treatment of BPH of moderate severity.

PATIENTS AND METHODS

Patients

This was a multicenter double-blind equivalence study conducted in 87 urology centers in nine European countries from April 1993–June 1994. The study was approved by the Ethics Committee of each center, and all subjects gave written informed consent. A total of 1,209 men over age 50 years who had BPH and symptoms of associated bladder flow obstruction were enrolled into the study (Table I). Patients who had received α-adrenergic receptor antagonists or *Pygeum africanum* for urological disease had to undergo a 2-week washout period. During the study, diuretics and drugs with antiandrogen properties or acting on α-receptors were considered protocol violations. Drugs with cholinergic, anticholinergic, or anticalcium activity were allowed when not prescribed for any urological pathology.

Treatments

Permixon® (referred to by trade name to distinguish it from other extracts) is a hexane extract of the American dwarf palm *Serenoa repens*. Its main components are free (90%) and esterified (7%) fatty acids (of which about half are unsaturated C_{18} fatty acids), sterols, polyprenic compounds, flavonoids and other substances. It was administered for 26 weeks at a dose of 160 mg (bid, morning and evening) and compared to the finasteride (Proscar®) dose (5 mg, morning) recommended by the manufacturers. To guarantee the double-blind design, patients received either Permixon® plus placebo bid, or finasteride plus placebo (morning) with two placebos (evening). Patients within each center were randomly assigned to receive either Permixon® or finasteride according to a computer-generated randomization code.

Protocol and Evaluation Procedures

Each patient was evaluated prior to entry and at 6, 13, and 26 weeks by the same investigator. At each of these visits, peak (Q_{max}) and mean urinary flow rates were measured, the International Prostate Symptom Score (IPSS) was determined, and the patient was asked to complete quality of life and sexual function questionnaires. Additionally, at weeks 13 and 26, patients underwent transrectal and abdominal ultrasound examinations to assess prostatic volume and postvoid residual urine as well as blood sampling for standard blood tests and serum prostate-specific antigen (PSA) assay.

Measurements of peak and mean urinary flow rates were used in the analysis only if at least 200 ml (or 150 ml for men with insulin-dependent diabetes) of urine were voided as advocated by Drach et al. [24] for screening. The IPSS, recommended as a standard by the International Consultation on BPH and "patronized" by the World Health Organization, is based on answers to seven questions (on urgency, daytime and nighttime urinary frequency, hesitancy, intermittency, sensation of incomplete voiding, and force of urine stream). Each answer to this seven-item ques-

TABLE I. Inclusion and Exclusion Criteria

Inclusion	BPH diagnosed by digital rectal examination and not requiring surgery
	International Prostate Symptom Score (IPSS) >6
	Maximum urinary flow between 4–15 ml/sec for a urine volume of at least 150 ml, with a postvoiding residue of <200 ml
	Prostate >25 ml
	Serum prostate-specific antigen (PSA) <10 ng/ml for prostates ≤60 ml, and <15 ng/ml for prostates >60 ml (measured before or 3 days after rectal examination and transrectal ultrasound)
	Good physical and mental condition
Exclusion	Cancer of the prostate
	Known history of bladder disease (cancer, surgery of the bladder neck, or neurogenic disturbances)
	Lower urinary tract pathology or infection
	Any disease potentially affecting micturition
	Abnormal liver function (twice the upper normal limit of serum aminotransferases and/or bilirubin, creatinine >160 μmol/l)
	Diuretics or drugs with antiandrogenic or α-receptor properties administered during the preceding 3 months for nonurological diseases (hypertension, or cerebrovascular insufficiency)
	Prior treatment with either finasteride or Permixon®

tionnaire was rated from 0–5. This test has been shown to have excellent psychometric properties of reliability and validity [25] and was the primary endpoint of our study. As counselled by the International Consensus Group, quality of life was assessed on the basis of the patient's answer to the question: "If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?" The answers were rated on a 0–6-point scale, where the highest score corresponded to the gloomiest perception. The sexual function questionnaire probed interest in sex, quality of erection, achieving orgasm, and ejaculation, each rated on a 0–5 point scale.

Baseline serum PSA (inclusion criterion) was determined by immunoassay in each participating center. PSA levels throughout treatment and repeat baseline values were determined in a central laboratory (St. Louis Hospital, Paris) with a solid-phase, two-site immunoradiometric assay (Hybritech Tandem®-R) (upper limit of normal, 4 ng/ml; within and between CV, 2.7% and 5.6% respectively, at 3.0 ng/ml).

Statistical Analysis

Statistical analyses focused on an intention-to-treat population which included all randomized patients who used the study drug and for whom at least one posttreatment evaluation was available. The results were based on data actually obtained at visits. For comparisons between the two treatments for the IPSS, these results were similar to those for the last posttreatment visit of all patients in the intention-to-treat population with adjustment for the time interval during which the last value occurred (not reported). They were also similar to results for a per protocol population with exclusion of patients (or visits) not strictly meeting study entry criteria, not complying with scheduled dates for visits or treatment duration, or using prohibited medications (not reported).

Baseline characteristics of the patients, study parameters at 26 weeks, and prevalence of intercurrent conditions were expressed as means, standard deviations, and ranges of minimum to maximum values for quantities with essentially continuous distributions, and as frequency tables and percentage distributions for categorical characteristics. Similarity of treatment groups was confirmed with one-way analysis of variance (ANOVA) for all baseline characteristics except quality of life, for which the Wilcoxon rank sum test was used. Comparisons between treatments for prevalence of intercurrent conditions were made with Fisher's exact test for 2×2 frequency tables.

The changes from baseline during the 26-week treatment period for the total symptom, quality of life, and total sexual function scores, and for the urodynamic and prostate parameters, were analyzed with an ANOVA which had components for study centers (centers with <12 patients were pooled with others in the same region), treatment, and the baseline for the study parameter. The principal result from the ANOVA for each study parameter was a two-sided 0.95 confidence interval for the difference between treatments for the changes from baseline. For the total symptom score, the inclusion of this confidence interval within the interval from -2 to $+2$ was the primary criterion for inferring statistical equivalence of the two treatments. The ANOVA for residual urine volume and prostate parameters was also applied to logarithmic values in order to address skewness of distributions and percent changes from baseline. The criterion for statistical significance for statistical tests from ANOVA was two-sided $P \leq 0.05$. The findings were confirmed with corresponding nonparametric analyses for rank transformation (not reported).

TABLE II. Baseline Characteristics at Time of Recruitment*

Characteristic	Treatment group	
	Permixon®	Finasteride
No. randomized	553	545
No. completing study	467	484
Age (years)	64.3 (49–87)	64.7 (49–88)
Body mass index[a]	26.0 (17–38)	25.9 (18–36)
IPSS score (0–35 points)	15.7 ± 5.8	15.7 ± 5.7
Quality of life score (0–6 points)	3.63 ± 1.28	3.66 ± 1.17
Sexual function score (0–20 points)	8.4 ± 5.5	8.5 ± 5.5
Peak urinary flow (ml/sec)	10.6 ± 2.8	10.8 ± 3.1
Mean urinary flow (ml/sec)	5.4 ± 2.1	5.5 ± 2.3
Total voided volume (ml)	247 ± 111	241 ± 104
Residual volume (ml)	52 ± 44	52 ± 44
Prostate volume (ml)	43.0 ± 19.6	44.0 ± 20.6
Serum PSA (ng/ml)	3.26 ± 3.41	3.23 ± 3.34

*Plus-or-minus values are means ±SD. No statistically significant difference was noted between the two groups in any parameter (test: one-way ANOVA except for quality of life, for which the Wilcoxon rank sum test was used).
[a]Weight in kg/(height in m)^2.

RESULTS

Recruitment, Baseline Characteristics, and Withdrawals

A total of 1,098 patients was randomized to treatment: 553 were assigned to receive Permixon®, and 545 to receive finasteride. The intention-to-treat analysis was performed on the 1,069 patients who had been evaluated at baseline, had received the study drug, and had been reevaluated at least once (536 in the Permixon®-treated group, 533 in the finasteride-treated group). Of these, 951 completed the study; 467 patients had received Permixon® and 484 finasteride. The baseline characteristics of the men enrolled in the two treatment groups (Table II) were similar in all respects, with no statistically significant difference noted in any parameter. During the study, 86 (16%) of the men in the group receiving Permixon® and 61 (11%) of those receiving finasteride withdrew from the study (Table III). The difference in withdrawals between the two groups was statistically significant for absolute values, but not for cumulative dropout rates for any reason.

Treatment Outcome

Both treatments decreased the total IPSS according to a similar pattern and to a similar extent (Fig. 1A). The fall in score was rapid. The decrease with respect to baseline was 22% ($P < 0.001$) at 6 weeks and reached nearly 40% at 26 weeks (Table IV). At this time, a >30% decrease, a −4-point decrease, or a 2-point increase in total score (35 points) were experienced by 59%, 63%, and 6%, respectively, of patients receiving Permixon® and 61%, 67%, and 7%, respectively of those receiving finasteride. Improvements in the individual items of the IPSS questionnaire (any decrease in score) were recorded in 47–67% of patients, depending upon the item. Whichever of the above modes was chosen to express the results at 26 weeks, the responses obtained with both drugs were not statistically different.

Over 50% of patients (53% and 55% in the Permixon® and finasteride treatment groups, respectively) felt their quality of life had improved (≥1 point decrease in the 6-point score) after 6 weeks of treatment, and about 70% after 26 weeks (69% and 73%, respectively). The absolute value of the score declined, as shown in Figure 1B, to yield highly similar decreases at 26 weeks (Table IV). No statistically significant difference between the two treatments was observed at any moment in time.

Only one patient in each treatment group withdrew from the study because of sexual problems. However, patients receiving finasteride experienced a statistically significant deterioration in sexual function score compared to those receiving Permixon®. The difference between the two groups, which was in favor of Permixon® for all four items of the questionnaire, was noted from the first follow-up visit at 6 weeks (Fig. 1D) and remained significant at 26 weeks (Table IV).

The peak urinary flow-rate Q_{max} increased in both treatment groups (Fig. 1C). Statistically significant mean increases were recorded at 26 weeks with a difference between treatments in favor of finasteride ($P = 0.035$) (Table IV). At 26 weeks, Q_{max} had increased by >3 ml/sec in 36% of Permixon®-treated patients (n = 464) and 39% of finasteride-treated patients (n = 477). The corresponding figures for a >30% increase in Q_{max} were 36% and 41%. The mean urinary flow rate also increased significantly above baseline at 6 weeks in both treatment groups, but remained virtually stable thereafter (not shown). At 26 weeks, the mean increases were not statistically different between treatments (Table IV). In the absence of any adjustment to baseline and center, the mean absolute residual volume increased at 26 weeks with Permixon® (+7.9 ml) and decreased with finasteride (−3.8 ml). To compare treatments, the results were adjusted, skewness was reduced by a log transformation, and the geometric means of the ratios of the 26-week to baseline values were calculated (0.91

TABLE III. Withdrawals

Reason for withdrawal	Permixon®	Finasteride
Side effects	28	14
Lack of efficacy	0	2
Patient decision	28	20
Lost to follow-up	5	7
Other	25	18
Total	86 (16%)	61 (11%)

for Permixon® (95% confidence interval (CI), 0.79; 1.05); 0.72 for finasteride (95% CI, 0.62; 0.82)). Although both treatments decreased residual volume, the reduction was greater with finasteride (P = 0.017).

Symptoms and urodynamics agreed in severity in just over half the patients in each treatment group at baseline, when we used a cutoff level of 18 for the IPSS and 10 ml/sec for Q_{max} (Table V). At 26 weeks, irrespective of treatment, the high IPSS-low Q_{max} fraction had fallen from around 13% to 3–4%, whereas the low IPSS-high Q_{max} fraction had risen from 40% to above 60%, i.e., symptoms and urodynamics now agreed in two thirds of the patients in both treatment groups.

Both treatments reduced the size of the prostate. At 13 weeks, the reduction induced by finasteride (−16%) was significantly greater than that due to Permixon® (−7%) ($P < 0.001$ in a between-group comparison). No further reduction was induced by either treatment at 26 weeks (Table VI). PSA levels fell markedly ($P < 0.001$) after 13 and 26 weeks of finasteride therapy, but remained unchanged with Permixon® (Table VI).

Intercurrent Clinical Events

After randomization, two deaths occurred, one with each drug, but neither was deemed drug-related. An 80-year-old patient with a history of heart disease suffered a heart attack 2 months after initiation of treatment with Permixon® and died. A 78-year-old patient with no previous signs of cardiovascular disease suffered a fatal myocardial infarction after 149 days of treatment with finasteride.

The serious clinical events leading to dropouts, and which might have been related to treatment although this was considered unlikely by the investigator, were an incidence of acute prostatitis in a 65-year-old patient receiving Permixon® and a spastic reaction of the left hand accompanied by facial twitching in a 79-year-old patient receiving finasteride. Acute cholecystitis in a 71-year-old patient receiving Permixon® did not result in discontinuation of treatment, and was also considered unlikely to be treatment-related. Less serious clinical events, whether drug-related or not, with an occurrence rate within a treatment group of 1% or more, are given in Table VII. Hypertension was common. Other frequent observations were decreased libido and impotence which affected, respectively, 3.0% and 2.8% of the finasteride-treated patients, and 2.2% and 1.5% of the Permixon®-treated patients. The lower incidences recorded with Permixon® for these parameters are in line with its better response in the sexual function questionnaire (see Table IV). Dysuria was more frequent in the finasteride-treated men and urinary retention in the Permixon®-treated men, but the difference in occurrence rates between treatments did not exceed 1% for these complications. Of the 7 patients with urinary retention in the Permixon® treated-group, 3 underwent surgery (two open prostatectomies and one transurethral prostatic resection). One of the 3 men with urinary retention among the patients receiving finasteride also underwent transurethral prostatic resection. There were no significant changes in any of the standard blood tests with either treatment.

DISCUSSION

The results of this double-blind randomized study demonstrate that 320 mg daily of Permixon® and 5 mg of finasteride are equally effective in the management of BPH. At 26 weeks, both treatments induced similar decreases in the absolute value of the total IPSS (37% and 39%, respectively), with two thirds of the patients responding in each treatment group. Improvements in IPSS were reflected in a less gloomy perception of urinary difficulties, about 70% of patients expressing increased satisfaction with their quality of life regardless of treatment. Finasteride led to higher mean Q_{max} rates at 26 weeks than Permixon®, but the numbers of responders were comparable in both treatment groups for both the selected response criteria (a 30% or 3-ml increase in Q_{max}). A recent factor analysis of data derived from a large-scale study [6] has stressed yet again the low agreement between symptoms and urodynamics. These two variables were in agreement in half our patients before treatment and in two thirds of our patients after treatment, in line with the observations of Barry et al. [2], who found that symptom severity was not correlated with uroflowmetry at baseline, but that reduction of symptoms with treatment did correlate with improvements in uroflowmetry.

It has been suggested that the lack of correlation between symptoms and urodynamics could be due to

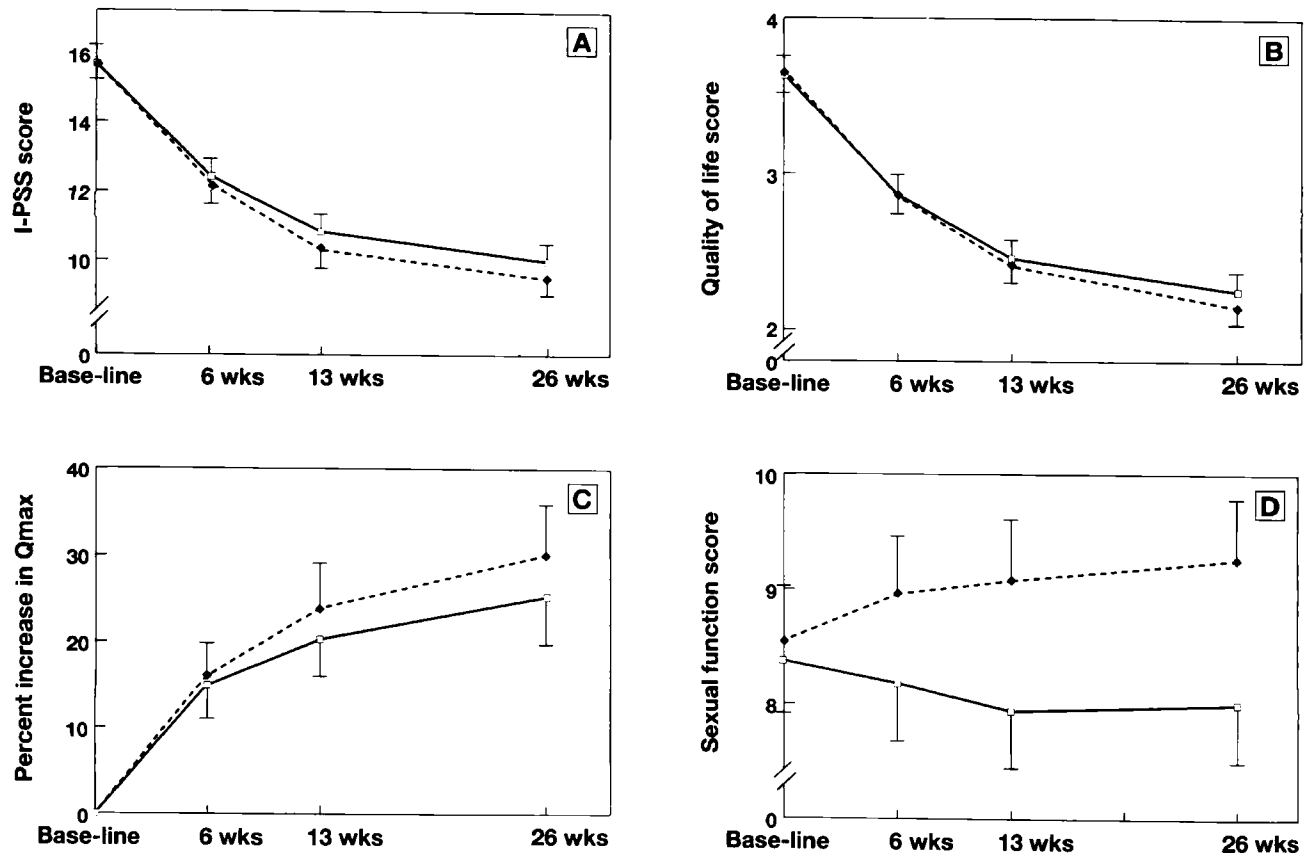

Fig. 1. Mean total IPSS (**A**), mean quality of life score (**B**), percentage of increase in mean peak urinary flow (**C**), and mean sexual function score (**D**), in men with BPH receiving either 320 mg Permixon® (open squares) or 5 mg finasteride (solid diamonds) (±0.95 confidence intervals).

imprecision of measurements, and that repeat baseline determinations are required. Our mean baseline IPSS of 15.7 is consistent with the 16.8 rating (range, 2–35) published by Barry et al. [2], who presented the same questionnaire to 198 consecutive outpatients of slightly higher average age (66.9 years), and is also consistent with the 14.9 and 15.1 ratings in a recent β-sitosterol study by Berges et al. [15]. Moreover, our peak and mean urinary flow rates at entry (10.7 and 5.5 ml/sec, respectively) are virtually identical to published values (10.2 and 5.1 ml/sec, in Barry et al. [2]; 10.2 and 5.8, in Berges et al. [15]). Mean values for prostate size (51.8 g), PSA (4.05 ng/ml), and especially postvoid residual urine (109 ml) were higher in Barry et al. [2] but comparable in Berges et al. [15]. The divergence in PSA values might be explained by exclusion from our study of patients with very high PSA levels and suspected cancer of the prostate. Residual volume is known to be an unreliable measurement, with poor reproducibility [26].

Although Permixon® and finasteride achieve comparable clinical effectiveness on symptoms and urinary flow rates, their mechanisms of action differ. Finasteride was designed as a highly specific and potent competitive inhibitor of 5α-reduction of testosterone into DHT and, by extension, of the androgen (i.e., DHT)-dependent component of BPH. Finasteride markedly decreases plasma and tissue DHT at 6 months with no effect on plasma testosterone levels [27], although early increases in testosterone have been recorded in some studies [7]. Our study confirmed the androgen-inhibitory action of finasteride. We noted decreases in prostate volume (ca. −18% at 26 weeks) and in PSA levels which are in good agreement with those found in previous studies [28–30]. The fall in PSA, a glycoprotein secreted by the epithelial cells of the prostate gland, could be related to lower epithelial cell function and thus to reduced prostate size. DHT is also thought to contribute to male sexual behavior [31]. Finasteride was less well-perceived than Permixon® in the sexual function questionnaire and led to a greater occurrence of decreased libido, impotence, and ejaculatory disorders.

Permixon® inhibits prostate 5α-reductase activity in vitro by a noncompetitive mechanism [21] but, at clinically relevant doses, has little effect on DHT lev-

TABLE IV. Outcome Variables at Presentation and 26 Weeks of Permixon® or Finasteride Treatment†

	Baseline	26 weeks	Percent change of mean	95% CI of adjusted mean change	95% CI of difference between groups and *P* value[a]
IPSS score					
Permixon®	15.7 ± 5.9	9.9 ± 5.4*	−37%	−6.2; −5.4	−0.17; 0.96
Finasteride	15.7 ± 5.7	9.5 ± 5.5*	−39%	−6.6; −5.8	0.17
Quality of life score					
Permixon®	3.63 ± 1.28	2.25 ± 1.29*	−38%	−1.5; −1.3	−0.04; 0.24
Finasteride	3.66 ± 1.17	2.15 ± 1.26*	−41%	−1.6; −1.4	0.14
Sexual function score					
Permixon®	8.4 ± 5.5	7.9 ± 5.4 (NS)	−6%	−0.7; −0.1	−1.52; −0.71
Finasteride	8.6 ± 5.5	9.3 ± 5.7**	+9%	0.5; 1.0	<0.001
Peak urinary flow (ml/sec)					
Permixon®	10.6 ± 2.8	13.3 ± 6.7*	+25%	2.1; 3.1	−1.46; −0.05
Finasteride	10.8 ± 3.1	14.0 ± 7.4*	+30%	2.8; 3.8	0.035
Mean urinary flow (ml/sec)					
Permixon®	5.4 ± 2.1	6.2 ± 3.3*	+15%	0.6; 1.1	−0.67; 0.14
Finasteride	5.5 ± 2.3	6.6 ± 3.7*	+20%	0.8; 1.4	0.21

†NS, not significant; *$P < 0.001$; **$P < 0.01$.
[a]Statistical significance of difference between adjusted means of treatments (adjusted to baseline and center effect) is given by ANOVA.

TABLE V. Classification of Patients at Presentation and at 26 Weeks According to Symptoms and Urodynamics*

	Patients at baseline			Patients at 26 weeks		
	IPSS <18	IPSS ≥18	N	IPSS <18	IPSS ≥18	N
Permixon®						
Q_{max} <10 ml/sec	25.5%	13.5%	214	30%	4%	156
Q_{max} ≥10	40%	21%	336	63%	4%	308
N	359	191	550	427	37	464
Finasteride						
Q_{max} <10	25%	12%	201	25%	3%	135
Q_{max} ≥10	40%	23%	344	66%	5%	342
N	355	190	545	438	39	477

*Percentages may not add up to 100% because of rounding of figures.

els and none on testosterone levels [32]. Its complex composition might account for manifold activities in the prostate. For instance, the antiandrogenic, antiedemic, and antiestrogenic activities that have been reported for Permixon® [22,23] might explain its capacity to reduce prostate size, albeit to a lesser extent than finasteride, and without any significant impact on PSA levels. Unpublished observations suggest that Permixon® is as active as finasteride on medium-sized and small prostates, but is less inhibitory on very large prostates. This difference might be at the origin of the higher incidence of urinary retention we noted with Permixon® in this study.

The highly comparable activities of Permixon® and finasteride on symptoms and urinary flow, despite the divergent actions on androgen-dependent parameters, highlight once again the observation that symptoms of prostatism and urinary flow rates are not directly related to prostate size. This discrepancy has been noted in earlier studies on finasteride, where a daily dose of 5 mg was needed to improve symptoms and also peak urinary flow rate, even though a dose of 1 mg was as effective as 5 mg in decreasing serum DHT and prostate volume [7]. There are at least two factors that could account for this discrepancy. Firstly, decreases in prostate vol-

TABLE VI. Prostate Parameters at Presentation and at 26 Weeks

			Comparison with baseline			Group comparison	
	Baseline	26 weeks	Adjusted mean ratio 26 weeks/ baseline $\log_e$	95% CI of adjusted mean ratio	Percent change based on adjusted mean ratio	Ratio of adjusted mean ratios	95% CI and *P* value[a]
Prostate volume (ml)							
Permixon®	43.0 ± 19.6	41.5 ± 20.5*	0.94	0.91; 0.96	−6%		
						1.14	1.11; 1.18
Finasteride	44.0 ± 20.6	36.7 ± 17.2*	0.82	0.80; 0.84	−18%		$P < 0.001$
Serum PSA (ng/ml)							
Permixon®	3.26 ± 3.41	3.22 ± 4.00 (NS)	1.02	0.98; 1.05	+3%		
						1.40	1.33; 1.45
Finasteride	3.23 ± 3.34	1.99 ± 1.98*	0.73	0.71; 0.75	−41%		$P < 0.001$

NS, not significant; *$P < 0.001$.
[a]Significant according to ANOVA.

TABLE VII. Main Intercurrent Clinical Events*

	Permixon®, N = 551 (%)	Finasteride, N = 542 (%)
Hypertension	3.1	2.2
Decreased libido	2.2	3.0
Abdominal pain	1.8	2.8
Impotence	1.5	2.8
Back pain	1.6	0.6
Diarrhea	0.9	1.1
Influenza-like symptoms	0.9	1.1
Urinary retention	1.3	0.6
Headache	1.3	0.4
Nausea	0.5	1.1
Constipation	0.4	1.1
Dysuria	0.4	1.1

*Only those events with a 1% or greater incidence are given. No statistically significant differences were noted between the two treatment groups for any intercurrent event.

ume may not necessarily coincide with the zone where BPH tends to develop and which is responsible for urinary obstruction. Secondly, BPH, which is an age-related disease, is triggered by nonandrogenic factors. The much-cited relationships between 5α-reductase deficiency [33], small prostates, and absence of BPH should not be too hastily interpreted as intensified 5α-reductase activity being the sole or even major cause of BPH.

In conclusion, in the treatment of men with mild or moderate symptoms of BPH, Permixon® and finasteride are clinically equivalent. The long-term efficacy of finasteride has been established in placebo-controlled studies; that of Permixon® needs to be confirmed. Because both compounds are equally effective but have divergent mechanisms of action, it is necessary to reevaluate the clinical androgen-dependence of BPH.

REFERENCES

1. Girman CJ, Jacobsen SJ, Guess HA, Oesterling JE, Chute CG, Panser LA, Lieber MM: Natural history of prostatism: Relationship among symptoms, prostate volume and peak urinary flow rate. J Urol 153:1510–1515, 1995.
2. Barry MJ, Cockett ATK, Holtgrewe HL, McDonnell JD, Sihelnik SA, Winfield HN: Relationship of symptoms of prostatism to commonly used physiological and anatomical measures of the severity of benign prostatic hyperplasia. J Urol 150:351–358, 1993.
3. Graversen PH, Gasser TC, Wasson JH, Hinman F Jr, Bruskewitz RC: Controversies about indications for transurethral resection of the prostate. J Urol 141:475–481, 1989.
4. Wasson JH, Reda DJ, Bruskewitz RC, Elinson J, Keller AM, Henderson WG, for the Veterans Affairs Cooperative Study Group on Transurethral Resection of the Prostate: A comparison of transurethral surgery with watchful waiting for moderate symptoms of benign prostatic hyperplasia. N Engl J Med 332:75–79, 1995.
5. Barry MJ, Mulley AG Jr, Fowler FJ, Wennberg JW: Watchful waiting vs. immediate transurethral resection for symptomatic prostatism. The importance of patients' preferences. JAMA 259:3010–3017, 1988.
6. Department of Veterans Affairs Cooperative Study of Transurethral Resection for Benign Prostatic Hyperplasia: A comparison of quality of life with patient reported symptoms and objective findings in men with benign prostatic hyperplasia. J Urol 150:1696–1700, 1993.
7. Gormley GJ, Stoner E, Bruskewitz RC, Imperato-McGinley J, Walsh PC, McDonnell JD, Andriole GL, Geller J, Bracken BR, Tenover JS, Vaughan ED, Pappas F, Taylor A, Binkowitz B, Ng J, for the Finasteride

Study Group: The effect of finasteride in men with benign prostatic hyperplasia. N Engl J Med 327:1185–1191, 1992.
8. Levy MA, Brandt M, Sheedy KM, Dinh JT, Holt DA, Garrison LM, Bergsma DJ, Metcalf BW: Epristeride is a selective and specific uncompetitive inhibitor of steroid human 5α-reductase isoform 2. J Steroid Biochem Mol Biol 48:197–206, 1994.
9. Di Salle E, Briatico G, Giudici D, Ornati G, Panzeri A: Endocrine properties of the testosterone 5α-reductase inhibitor turosteride (FCE 26073). J Steroid Biochem Mol Biol 48:241–248, 1994.
10. Jardin A, Bensadoun H, Delauche-Cavallier, Attali P, the BPH-ALF Group: Alfuzosin for treatment of benign prostatic hypertrophy. Lancet 337:1457–1461, 1991.
11. Düker EM, Kopanski L, Schweikert HU: Inhibition of 5α-reductase activity by extracts from *Sabal serrulata*. Planta Med [Suppl] 5:Abst L2-2, 1989.
12. Buck AC, Cox R, Rees RWM, Ebeling L, John A: Treatment of outflow tract obstruction due to benign prostatic hyperplasia with the pollen extract, cernilton. Br J Urol 66:398–404, 1990.
13. Fitzpatrick JM, Dreikorn K, Habib F, Mebust WK, Perrin P, Schulze HK: Medical management of benign prostatic hyperplasia other than with hormones of alpha blockers. Prog Clin Biol Res 386:303–309, 1994.
14. Champault G, Patel JC, Bonnard AM: A double-blind trial of an extract of the plant *Serenoa repens* in benign prostatic hyperplasia. Br J Clin Pharmacol 18:461–462, 1984.
15. Berges RR, Windeler, J, Trampisch HJ, Serge T, β-Sitosterol Study Group: Randomised, placebo-controlled, double-blind clinical trial of β-sitosterol in patients with benign prostatic hyperplasia. Lancet 545:1529–1532, 1995.
16. Griffiths K, Eaton CL, Harper ME, Peeling B, Davies P: Steroid hormones and the pathogenesis of benign prostatic hyperplasia. Eur Urol 20:68–77, 1991.
17. Habib FK, Chisholm GD: The role of growth factors in the human prostate. Scand J Urol Nephrol [Suppl] 138: 53–58, 1991.
18. Bruchovsky N, Rennie PS, Batzold FH, Goldenberg SL, Fletcher T, McLoughlin MG: Kinetic parameters of 5α-reductase activity in stroma and epithelium of normal, hyperplastic, and carcinomatous human prostates. J Clin Endocrinol Metab 67:806–816, 1988.
19. Bartsch W, Klein H, Schiemann U, Bauer HW, Voigt KD: Enzymes of androgen formation and degradation in the human prostate. Ann NY Acad Sci 595:53–66, 1990.
20. Ragab A, Ragab-Thomas JMF, Delhon A, Tisne-Versailles J, Gassama-Diagne A, Fauvel J, Cousinier JP, Chap H, Douste-Blazy L: Effects of Permixon® (Sereprostat® in Spain) on phospholipase A2 activity and on arachidonic acid metabolism in cultured prostatic cells. In: "New Trends in Bladder Cancer Chemotherapy. New Trends in BPH Etiopathogenesis." Acta Medica, 1987, pp. 293–296.
21. Délos S, lehlé C, Martin PM, Raynaud JP: Inhibition of the activity of "basic" 5α-reductase (type 1) detected in DU 145 cells and expressed in insect cells. J Steroid Biochem Mol Biol 48: 347–352, 1994.
22. Tayrayre JP, Delhon A, Lauressergues H, Stenger A: Action anti-oedémateuse d'un extrait hexanique de drupes de *Serenoa repens* Batr. Ann Pharm Fr 41:559–570, 1983.
23. Di Silverio F, d'Eramo G, Lubrano C, Flammia GP, Sciarra A, Palma E, Caponera M, Sciarra F: Evidence that *Serenoa repens* extract displays an antiestrogenic activity in prostatic tissue of benign prostatic hypertrophy patients. Eur Urol 21:309–314, 1992.
24. Drach GW, Layton TN, Binard WJ: Male peak urinary flow rate: Relationships to voided volume and age. J Urol 122:210–214, 1979.
25. Barry MJ, Fowler FJ Jr, O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK, Cockett ATK, Measurement Committee of the American Urological Association: The American Urological Association symptom index for benign prostatic hyperplasia. J Urol 148:1549–1557, 1992.
26. Birch NC, Hurst G, Doyle PT: Serial residual volumes in men with prostatic hypertrophy. Br J Urol 62:571, 1988.
27. McConnell JD, Wilson JD, George FW, Geller J, Pappas F, Stoner E: Finasteride, an inhibitor of 5α-reductase, suppresses prostatic dihydrotestosterone in men with benign prostatic hyperplasia. J Clin Endocrinol Metab 74:505–508, 1992.
28. Geller J: Effect of finasteride, a 5α-reductase inhibitor on prostate tissue androgens and prostate-specific antigen. J Clin Endocrinol Metab 71:1552–1555, 1990.
29. Guess HA, Heyse JF, Gormley GJ: The effect of finasteride on prostate-specific antigen in men with benign prostatic hyperplasia. Prostate 22:31–37, 1993.
30. Finasteride Study Group: Finasteride (MK-906) in the treatment of benign prostatic hyperplasia. Prostate 22: 291–299, 1993.
31. Mantzoros CS, Georgiadis El, Trichopoulos D: Contribution of dihydrotestosterone to male sexual behaviour. Br Med J [Clin Res] 310:1289–1290, 1995.
32. Rhodes L, Primka R, Berman C, Vergult G, Gabriel M, Pierre-Malice M, Gibelin B: Comparison of finasteride, a 5α-reductase inhibitor, and various commercial plant extracts in in vitro and in vivo 5α-reductase inhibition. Prostate 22:43–51, 1993.
33. Imperato-McGinley J, Guerrero L, Gautier T, Peterson RE: Steroid 5α-reductase deficiency in man: An inherited form of male pseudohermaphroditism. Science 186:1213–1215, 1974.

APPENDIX

Writing Committee

T. Ojasoo and J.P. Raynaud (University Pierre and Marie Curie, Paris, France); J.C. Carraro (Pierre Fabre Médicament, Castres, France); F.C. Hamdy (Freeman Hospital, Newcastle-upon-Tyne, UK); F.K. Habib (University of Edinburgh Medical School, Edinburgh, UK).

Biostatistics

G. Koch (University of North Carolina, USA); J. Cauquil (Pierre Fabre Médicament, Castres, France); A. Périer (Analytica, Paris, France).

Administration

P. Deschaseaux (Pierre Fabre Médicament, Castres, France).

Participating Investigators and Medical Centers

L. Alno (Clinique Volney, Rennes, France), A. Arnold (Queen Elisabeth Hospital, Birmingham, UK), J. Aubert (C.H.U. La Miletrie, Poitiers, France), W. Aulitzky (Landeskrankenanstalten Urologie, Salzburg, Austria), E. Bassi (H.C. Civile Conegliano, Treviso, Italy), J. Benchetrit (Clinique Croix St. Michel, Montauban, France), T. Billebaud (Hôpital Intercommunal, Créteil, France), J.C. Bobillon (Clinique Mutualiste, Lyon, France), J. Bollmann (Fribourg, Switzerland), H. Botto (Hôpital Foch, Suresnes, France), C. Breuer (Canton Spital, Liesthal, Switzerland), A.C. Buck (Glasgow Royal Infirmary, Glasgow, UK), H. Cabane (Hôpital Gouin, Clichy, France), P.O. Cadi (Bourgoin, France), F. Calais Da Silva (Lisbon, Portugal), G. Cariou (Hôpital des Diaconesses, Paris, France), J.M. Casanova (Paris, France), I. Chami (Clinique Ste. Marguerite, Paray-le-Monial, France), P. Chauveau (Clinique Urologique, St. Sebastien sur Loire, France), G. Chisholm (Western General Hospital, Edinburgh, UK), D.K. Chopin (Hôpital Mondor, Créteil, France), R. Claude (Clinique St. François, Montluçon, France), P. Clerc (Clinique Regnier, La Rochelle, France), P. Coloby (Hôpital Réné Dubos, Pontoise, France), J.P. Cosson (Clinique de Francheville, Périgueux, France), D. Cracco (Centre Hospitalier Général, Valenciennes, France), J. Davin (Clinique Ste. Catherine, Avignon, France), A. Dell'Adami (H. Cattarina, Trieste, Italy), V. Delmas (C.H.U. Bichat, Paris, France), E. Delorme (Clinique de Bourgogne, Saint-Remy, France), B. Denis (Clinique de Marly, Marly-le-Roi, France), V. Di Santo (H. Miunni Acquaviva, Delle-Fonti-Bari, Italy), F. Di Silverio (University "La Sapienza", Rome, Italy), J.M. Dubernard (Hôpital St. Luc, Lyon, France), J.P. Dulac (Clinique du Tonkin, Villeurbanne, France), M. Egli, (Limatthal Spital Schlieren, Zurich, Switzerland), R. Faye (Clinique de l'Esperance, Angers, France), U. Ferrando (H. Aggiore di "S. Giovanni Batista," Turin, Italy), F. Foroutan (A.O. Krankenhaus Urologie Wiener, Neustadt, Austria), X. Giannakopoulos (Panepistimiako Nosokomeio, Ioannina, Greece), P. Glemain (C.H.U., Nantes, France), R.C. Gouveia (Libo, Portugal), D. Grasset (C.H.U., Montpellier, France), G. Grechi (Universita di Firenze, Florence, Italy), F. Hamdy (Freeman Hospital, Newcastle-upon-Tyne, UK), M. Hanus (Urocentrum, Prague, Czech Republic), D. Hauri (Universitatsspital, Zurich, Switzerland), J. Hermabessiere (Centre Médical République, Clermont-Ferrand, France), W. Horninger (Universität Klinik für Urologie, Innsbruck, Austria), C. Issaris (Geneva, Switzerland), R. Jaques (Hôpital Saint Luc, Lyon, France), A. Kalinderis (Kentrikon Nosokomeion, Thessalonika, Greece), G. Kepenekian (Hôpital Saint Joseph, Lyon, France), D. Lambert (Clinique Marzet, Pau, France), P. Lansiaux (Hôpital Bellan, Paris, France), T. Lanz (Clinique de St. Quentin, Trappes, France), B. Le Portz (Clinique du Sacre Coeur, Vannes, France), C. Leleu (Clinique Ste. Marthe, Angouleme, France), B. Lobel (Hôpital Pontchaillou, Rennes, France), A. Mandressi (H. Civile, Busto Arsizio, Italy), A. Manganelli (H.L. Scotte, Sienna, Italy), M. Marberger (Urologische Univ. Klinik, Vienna, Austria), B. Marc (Clinique St. Privat, Beziers, France), J. Marencak (Skalica Hospital, Skalica, Slovakia), B. Mauroy (Centre Hospitalier, Roubaix, France), M. Monsallier (Lyon, France), G.B. Muraro (I.N.R.C.A., Florence, Italy), J.L. N'Guyen Qui (Salon-de-Provence, France), J.F. Olivo (Clinique de la Sagesse, Rennes, France), P. Palascak (C.H. Paul Morel, Vesoul, France), V. Pansadoro (Imario Reparto di Urologia, Rome, Italy), M. Pavone Macalusso (Policlinico Dell'Universita, Palermo, Italy), P. Perrin (Hôpital de l'Antiquaille, Lyon, France), T. Piechaud (Clinique St. Augustin, Bordeaux, France), A. Pinna (H. "S. Francesco," Nuoro, Italy), A. Prawerman (Clinique de Champagne, Reims, France), M. Reis (Porto, Portugal), C. Richaud (Hôpital Nord, Marseille, France), G. Robinson (General Infirmary, West Yorkshire, UK), A. Roggia (H. "S. Antonio Abate," Gallarate-Varese, Italy), H. Rozenberg (Hôpital Victor Jousselin, Dreux, France), J.L. Sachot (Polyclinique Sevigne, Cesson Sevigne, France), L. Sauvage (Centre Hospitalier, Seclin, France), V. Scetbon (Paris, France), F. Segura (Polyclinique, Villeneuve-St.-Georges, France), G. Severini (H.S. "Maria delle Croci," Ravenna, Italy), G. Signorelli (H. "Riviera del Brenta," Dolo-Venezia, Italy), W. Stackl (Urologie Krankenanstalt Rudolfstiftung, Vienna, Austria), S. Striano (H. Civile, Caserta, Italy), U. Studer (Anna Seiler-Haus, Bern, Switzerland), P. Teillac (Hôpital St. Louis, Paris, France), R. Tenaglia (H. "SS. Annunziata," Chieti, Italy), J. Tostain (Centre d'Urologie, Saint-Etienne, France), T. Tsintavis (Tzanio Hospital, Piraeus, Greece), J.M. Turblin (Hôpital, St. Quentin, France), and A. Villers (Clinique Esquirol, Agen, France).