NCI, DCPC
Chemoprevention Branch and Agent Development Committee

CLINICAL DEVELOPMENT PLAN:

PROSCAR®
(Active Ingredient: Finasteride)

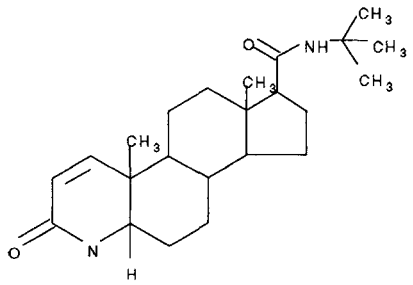
DRUG IDENTIFICATION

CAS Registry No.: 98319-26-7

CAS Name (9CI): *N*-(1,1-Dimethylethyl-3-oxo-(5α,17β)-4-azaandrost-1-ene-17-carboxamide

Synonyms: 17β-*N*-*t*-Butylcarbamoyl-4-aza-5α-androst-1-en-3-one
Finasteride
L-652,931
N-(2-Methyl-2-propyl)-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide
MK-906

Structure:



EXECUTIVE SUMMARY

Proscar® is an azasteroid approved for the treatment of symptomatic benign prostatic hyperplasia (BPH) [1,2]. It is a competitive inhibitor of the intracellular enzyme Δ^4-3-ketosteroid 5α-reductase (5α-reductase), which converts testosterone to 5α-dihydrotestosterone (DHT) in the prostate, seminal vesicles and other sexual organs, liver, genital skin, and frontal scalp. DHT has greater affinity for the androgen receptor than testosterone, and the DHT-receptor complex in turn has a higher affinity for DNA binding sites. The major functions of DHT are male sex differentiation in the fetus and development and maintenance of the prostate during and after puberty. To illustrate, males with an inherited 5α-reductase deficiency are born with ambiguous external genitalia (pseudohermaphroditism), and are often raised as girls. With puberty, however, normal testosterone-dependent male development occurs, including increased penis size, libido and muscle mass, spermatogenesis, and voice change [reviewed in 3]. Lack of DHT-mediated processes is demonstrated by scant beard growth, very small prostate gland, and no male pattern baldness. More importantly, no cases of BPH or prostate cancer have been reported in this group despite normal to high serum testosterone

levels. Although the specific dependence of prostate cancer development on DHT has not been established, 5α-reductase inhibition appears to be a useful strategy for prevention or delay. Because of the low frequency of adverse effects, Proscar® was considered for further development as a prostate cancer chemopreventive drug.

No preclinical efficacy studies on Proscar® have been sponsored by the CB and none were found in the literature. The limited published information has shown no effect on the growth rate or final weight of implanted rat prostate tumors. However, Proscar® decreased prostate size in normal rats and dogs, as well as older dogs with spontaneous prostatic hyperplasia.

Carcinogenicity studies on Proscar® have been performed by Merck, Sharp & Dohme. In a 19-month mouse study, 250 mg/kg-bw/day (671 μmol/kg-bw/day) produced testicular Leydig cell adenomas. At a tenth of that dose, Leydig cell hyperplasia was obtained, which appeared to result from stimulation of these cells to produce testosterone by increased luteinizing hormone (LH) levels. The NOEL for this effect was 2.5 mg/kg-bw/day (6.7 μmol/kg-bw/day), 3.5-fold higher than the estimated clinical dose (5 mg qd, or *ca.* 1.9 μmol/kg-bw qd). In human trials, no significant increases in serum LH in Proscar®-treated groups *vs* placebo groups have been observed.

Reproductive and developmental toxicity studies have also been performed by Merck, Sharp & Dohme. No effects on fertility, testicular histology or mating performance were observed in male rats except for defective copulatory plugs in mated females. The latter is not relevant for species which do not rely on this method of sperm transport (*e.g.*, rabbits, humans). Because of the pharmacological action of Proscar®, developmental toxicities were anticipated. In male offspring of female rats treated on gestation days 16 and 17, formation of external genitalia was affected, including increased incidences of hypospadias, cleft prepuce and decreased anogenital distance.

Phase II and III trials and an extension trial sponsored by the manufacturer to determine the effectiveness of Proscar® in BPH treatment have demonstrated a low frequency (5–10%) of adverse effects. These are primarily related to sexual function, such as loss of libido, decreased ejaculate volume, and impotence.

A Phase III cancer chemoprevention trial (Prostate Cancer Prevention Trial) funded by the Cooperative Community Oncology Program and Cancer and Leukemia Group B of the NCI is in the accrual phase. The endpoints in a projected target population of 18,000 healthy men >55 years of age (9,000/arm) are prostate cancer incidence, grade and stage, BPH incidence and severity, mortality, serum prostate-specific antigen (PSA) levels, and quality of life measurements. Risk factors for prostate cancer will be assessed retrospectively.

A short-term Phase II chemoprevention trial with a 5α-reductase inhibitor has been funded by the CB. Biopsy-proven prostate cancer patients will be treated during the two-week to one-month interval before a scheduled prostatectomy. The endpoints are modulation of intermediate biomarkers such as PIN grade, ploidy, nuclear mor-phometry, and proliferation indices (Ki-67, MIB-1).

Drug and placebo as 5 mg coated tablets are being supplied for the Phase III Prostate Cancer Chemoprevention Trial by Merck, Sharp & Dohme. An agreement with the manufacturer to supply drug and placebo will need to be arranged for any future clinical chemoprevention trials.

PRECLINICAL EFFICACY STUDIES

No preclinical efficacy studies have been sponsored by the CB. All the following data has been obtained from the published literature, which includes information made available by Merck, Sharp & Dohme. These are not chemoprevention studies; however, they evaluate the effect of Proscar® on tissue proliferation. This effect may be related to inhibition or delay of carcinogenesis.

In published studies, the effect of Proscar® on male rats implanted (sc) with the Dunning rat prostatic carcinoma R-3327 was evaluated [4,5]. Treatment with 25 mg/kg-bw/day (67.1 μmol/kg-bw/day) for up to 42 days had no significant effect on tumor growth and final weight, although tumor DHT was reduced. In contrast, Proscar® decreased the weight of the ventral prostate in both intact rats and castrated rats given testosterone. In addition, the drug has been shown to significantly decrease the size of the prostate in young dogs [6,7], as well as in elderly dogs with spontaneous prostatic hyperplasia [6]. In humans, BPH is not considered a premalignant lesion; however, it may respond to similar proliferative influences.

It should be noted that efficacy studies in rats and dogs may not be directly applicable to humans. Significant species differences in prostatic 5α-reductase enzymes exist, including pH profiles, affinities for 4-azasteroidal inhibitors, and sensitivities to mercuric sulfhydryl reagents [8]. For example, the IC_{50}s for Proscar® inhibition of 5α-re-

ductase in prostate homogenates from the three species are as follows: rat, 6.8×10^{-9} M; human, 1.0×10^{-8} M; and dog, 4.0×10^{-6} M. In addition, rat and human enzymes show only 60% amino acid sequence homology [9]. In spite of these differences, however, Proscar® is a potent competitive inhibitor of 5α-reductase in rats, dogs and humans.

PRECLINICAL SAFETY STUDIES

No preclinical toxicity studies have been sponsored by the CB. In published studies, no toxicity has been reported in males at doses comparable to the human dose (5 mg qd or *ca.* 0.2 μmol/kg-bw qd). Leydig cell hyperplasia was reported in mice only at doses 35-fold higher than the human therapeutic dose for BPH. Developmental toxicity was the only significant effect obtained at doses near the human dose; male rat fetuses exposed *in utero* developed abnormal external genitalia. Thus, women of reproductive age should avoid even dermal exposure to Proscar®.

ADME Limited preclinical pharmacokinetic data are available. In studies by the manufacturer, oral Proscar® is well-absorbed by the rat, dog and monkey [10]. Metabolites were found in the plasma, urine and feces of these species and humans. In rat hepatic microsomes, Proscar® is hydroxylated at the *t*-butyl group, which is further oxidized to the carboxylic acid *in vivo*, the major metabolite in rat liver and bile and human plasma [11]. The steroid rings are also hydroxylated at the 6-position; this metabolite has been found in rat plasma and human plasma and urine [10,11].

Safety Several carcinogenicity studies on Proscar® have been performed by Merck, Sharp & Dohme. No carcinogenic effect was observed in two-year studies in male (160 mg/kg-bw/day, or 430 μmol/kg-bw/day) or female (320 mg/kg-bw/day, or 859 μmol/kg-bw/day) Sprague-Dawley rats [2,12]. Based on pharmacokinetic parameters (AUC), these doses produced systemic exposures of 111- and 274-times that in humans receiving 5 mg qd. In a 19-month study in male CD-1 mice given 250 mg/kg-bw/day (671 μmol/kg-bw/day), a statistically significant increase in testicular Leydig cell adenomas was observed [13]. At 25 mg/kg-bw/day (67.1 μmol/kg-bw/day), the frequency of Leydig cell hyperplasia increased. This effect was correlated with a 2–3-fold increase in LH levels; the latter stimulates the Leydig cells to produce testosterone. The NOEL for Leydig cell hyperplasia in mice was 2.5 mg/kg-bw/day (6.7 μmol/kg-bw/day), or 3.5-fold the clinical dose. The NOEL in rats and dogs treated for one year was 20 mg/kg-bw/day (53.7 μmol/kg-bw/day, or 28-fold the clinical dose) and 40 mg/kg-bw/day (107.4 μmol/kg-bw/day, or 57-fold the human dose), respectively.

Concomitantly, no evidence of mutagenicity was observed in an *in vitro* bacterial mutagenesis assay or a mammalian cell mutagenesis assay at maximum concentrations of 450–550 μM Proscar® [2,12]. Chromosomal aberrations increased slightly in Chinese hamster ovary (CHO) cells treated *in vitro* at the same levels [2]; however, these concentrations correspond to 4,000–5,000 times the peak plasma levels of men administered 5 mg Proscar®. Further, no treatment-related increases in chromosomal aberrations were obtained in mice given doses of 671 μmol/kg-bw/day in the carcinogenicity study.

Proscar® produces reproductive and developmental effects in the males of all species tested, although effects on fertility were not always observed. Sexually mature male rats (15–16 weeks old) given 80 mg/kg-bw/day (214.7 μmol/kg-bw/day) for 24–34 weeks or young males (4–6 weeks old) given 20–80 mg/kg-bw/day (53.7–214.7 μmol/kg-bw/day) for 12 weeks produced defective copulatory plugs in mated females [14,15]. This is a direct result of Proscar®-induced inhibition of prostate and seminal vesicle secretions; no effects on testicular histology, sperm function, or mating performance were observed. In contrast, mature male rabbits treated with doses up to 80 mg/kg-bw/day (214.7 μmol/kg-bw/day) for 12 weeks showed no effects on fertility [2]; this species does not rely on copulatory plugs for sperm transport.

Developmental toxicity was assessed by Merck, Sharp & Dohme by administration of 0.01–100 mg finasteride/kg-bw/day (0.03–268 μmol/kg-bw/day, ig, suspended in 0.5% aqueous methylcellulose) to female rats [16,17]. Following treatment on gestation days 16 and 17, dose-related incidences of hypospadias, cleft prepuce and decreased anogenital distance in male offspring were obtained. The threshold dose was near 0.1 mg/kg-bw/day (0.3 μmol/kg-bw/day), with 100% incidence at the highest dose. The effects were not explained by the slight decreases in maternal body weight at doses at or above 3 mg/kg-bw/day (8 μmol/kg-bw/day). Thus, 5α-reductase appears to be important in the development of male external genitalia, specifically formation of a medial mesenchymal plate to push the urogenital sinus to the tip of the genital tubercle [17]. No abnormalities were observed in female offspring.

CLINICAL SAFETY: PHASE I STUDIES

The CB has not funded any Phase I clinical studies of Proscar®. All the following data have been obtained from the published literature, which includes information made available by Merck, Sharp & Dohme. The major adverse effects in men were related to sexual function; however, the decrease in PSA levels could mask the presence of prostate cancer. With multiple doses, plasma levels of Proscar® rise slowly, and a beneficial effect may not be seen for six months.

Drug Effect Measurement The most obvious drug effect measurement is serum DHT; however, the dose-response curve is shallow. In healthy male volunteers, a dose-related decrease in DHT (50–65%) was observed only at single oral doses of <10 mg [12,18]; doses between 10 and 100 mg produced a 75–82% reduction in circulating androgen [19]. In BPH patients, maximum suppression was reached after 14 days of dosing, and persisted with continued treatment [20]. After 6–24 months of 5 mg Proscar® qd, circulating DHT levels were decreased by 70–80% [2,21,22]. In addition, this biological effect of Proscar® persists longer than plasma drug levels. Serum DHT returned to baseline about 12 weeks after discontinuing treatment of BPH patients [12]. Although DHT levels may not be useful in estimating compliance, serum DHT appears to correlate highly with intraprostatic levels (r=0.92) [23].

An alternative drug effect measurement is serum PSA. This measurement decreased 50% and 48% in BPH patients receiving 5 mg and 1 mg Proscar® qd, respectively, for >3 months. Thus, the dose-response curve may also be shallow, and the time to effect even longer than that for DHT.

Safety Male subjects have received single doses of Proscar® up to 400 mg (15.3 μmol/kg-bw) and multiple doses up to 80 mg qd (3.1 μmol/kg-bw) for three months without adverse effects [2]. In BPH patients treated with 5 mg Proscar® (0.2 μmol/kg-bw) qd for 12–36 months in U.S. and international Phase II and III clinical trials, the majority of adverse reactions were related to sexual function. Significantly higher incidences of impotence, decreased libido, and decreased ejaculate volume were reported as compared with placebo groups; however, the rates were all 5–10% and two-thirds of cases appeared to resolve with extended treatment (≥2 years) [1,12,17,24]. The cause of these effects is unknown since mean circulating testosterone levels increased 10% [2].

Other possible adverse effects result from inhibition of 5α-reductase conversion of other neutral steroids, such as cortisol. A year-long Phase II treatment study in BPH patients reported a low incidence of laboratory value abnormalities. These included increased serum creatinine, calcium, potassium, and urea nitrogen, or increased red and white blood cell counts [20]. Unfortunately, a comparison of the incidence of these effects between the treatment and placebo groups was not reported.

An additional consideration is that the decrease in serum PSA levels in Proscar®-treated BPH patients may mask the presence of undetected prostate cancer. In two Phase III efficacy studies in BPH patients, three-quarters of men who were found to have prostate cancer had reductions in PSA levels during 1–2 years of treatment with 5 mg Proscar® qd [25]. However, a more recent study found that the predictive value of PSA normalized to MRI-determined prostate volume increased in BPH patients following treatment with Proscar® for 12 months [26]. This appears to result from the greater contribution of adenocarcinoma (3.5 ng/ml/g tissue) than BPH (0.3 ng/ml/g tissue) to circulating PSA [27].

ADME The bioavailability of the 5 mg tablet formulation of Proscar® averaged 63% compared with constantrate iv infusion [12]. After a single oral 5 mg dose, absorption occurred rapidly; a C_{max} of 37 ng/ml was achieved within 1–2 hrs. The $AUC_{0\text{-}24}$ was 0.4 μg·hr/ml [2]. With higher doses, the C_{max}, $AUC_{0\text{-}24}$, and t_{max} increased. For example, C_{max}= 0.92 μg/ml, t_{max}=2–4 hrs, and $AUC_{0\text{-}24}$= 12.9 μg·hr/ml after a 200 mg dose [28]. Approximately 90% of circulating Proscar® is bound to plasma proteins [12]. The majority of this is as the lipophilic parent drug, with approximately 12% as a less active monohydroxylated metabolite produced by the liver. Distribution to peripheral tissues (including brain) also occurred as demonstrated by a V_d of 76 L after constant infusion of 5 mg over one hour; however, Proscar® does not appear to concentrate in seminal fluid [2,29].

The plasma elimination $t_{½}$ after a single 5 mg dose was 6 hours [2]; with doses of 200 mg and 400 mg, this parameter increased to 17.3 and 13.4 hrs, respectively [28]. Excretion occurred by both the urinary (39% of dose) and fecal (57% of dose) routes at doses of 5–38 mg [2,30]. No parent drug was found in urine; the major isolated compound was the monocarboxylic acid metabolite [2].

With multiple doses, the plasma kinetics of Proscar® demonstrated a slow accumulation phase.

The AUC and C_{max} increased slowly during the first four daily doses of 10 mg, but did not accumulate further after one week [12]. After dosing with 5 mg qd for 17 days, plasma concentrations were 47% and 54% higher than after the initial dose in men 45–60 years old and >70 years old, respectively [2]. The mean trough concentrations after 17 days were 6.2 ng/ml and 8.1 ng/ml, respectively, in these two groups. Although the elimination rate appeared to decrease in the elderly, no dosage adjustment was deemed necessary.

CLINICAL EFFICACY: PHASE II/III STUDIES

The CB has not funded clinical efficacy studies of Proscar® as a cancer chemopreventive. A Phase III chemoprevention trial (Drs. C. Coltman and O. Brawley) sponsored by the NCI, DCPC Cooperative Community Oncology Program is underway to determine the effect of Proscar® treatment for seven years on prostate cancer and other endpoints in healthy older men. In addition, a manufacturer-sponsored Phase II trial is examining the effect of Proscar® on PSA levels in men who have undergone radical prostatectomy for non-metastatic prostate cancer. Finally, the CB is considering a Phase II trial in prostate cancer patients scheduled for prostatectomy with intermediate biomarkers as the endpoints, as discussed below.

The Phase III Prostate Cancer Prevention Trial is being coordinated by the Southwestern Oncology Group (SWOG) in collaboration with the Eastern Community Oncology Group (ECOG) and Cancer and Leukemia Group B [31]. This trial will determine the effect of 5 mg Proscar® qd for seven years on prostate cancer incidence, grade and stage, BPH incidence and severity, overall and prostate-specific mortality, quality of life measurements (*e.g.*, sexual and urinary function), prostatic transurethral resection (TURP) incidence, and serum PSA levels [32,33]. An additional aspect of the trial will be a retrospective assessment of risk factors for prostate cancer. Over the three-year randomization period, a total of 18,000 men >55 years of age from 222 sites will enter the treatment and placebo arms (9,000/arm). Subjects with a normal digital rectal exam (DRE) and PSA below 3.0 ng/ml will be stratified within each arm by age, race, and history of first-degree relative with prostate cancer. A DRE and PSA assay will be performed yearly; after seven years, a prostate biopsy will be obtained. Since the start of the study on October 18, 1993, 2,500 subjects have been recruited, which is ahead of schedule [34].

A new Phase II trial (Dr. S.W. Beenken, University of Alabama) of a 5α-reductase inhibitor was funded in 1994 by the CB. Biopsy-diagnosed prostate cancer patients are treated with the drug for two weeks to one month before their scheduled prostatectomy. This placebo-controlled, blinded study will evaluate intermediate biomarkers as surrogate trial endpoints, plus titrate the dose of the 5α-reductase inhibitor *vs* biomarker response. Possible biomarkers include grade of PIN, Ki-67, MIB-1, ploidy, and nuclear morphometry.

Merck, Sharp & Dohme is sponsoring a Phase II study in 100 non-metastatic prostate cancer patients who have undergone radical prostatectomy [35,36]. The endpoint is the effect of the drug on serum PSA, which is a risk factor for prostate cancer recurrence/metastasis. Proscar® was previously found to produce only a 15–20% decrease in PSA levels in patients with Stage D (*i.e.*, metastatic) prostate cancer; none of the lesions demonstrated regression [37].

PROPOSED STRATEGY FOR CLINICAL DEVELOPMENT

Drug Effect Measurement Issues

The most obvious drug effect measurement is serum DHT; however, the dose-response curve is shallow. In BPH patients, maximum suppression is reached after 14 days of dosing, and persists with continued treatment. In addition, this biological effect of Proscar® persists 12 weeks longer than plasma drug levels. Although DHT levels may not be useful in estimating compliance, serum DHT appears to correlate highly with intraprostatic levels (r=0.92). More information in BPH-free males is needed to determine the utility of serum DHT as a drug effect measurement for chronic Proscar® intake in cancer chemoprevention trials.

An alternative drug effect measurement is decreased serum PSA. However, this measurement also has a shallow dose-response curve and the time to effect is even longer than that for DHT. The Phase III chemoprevention trial should provide more information on the effect of Proscar® on PSA levels in normal subjects.

Safety Issues

Sufficient toxicity studies for clinical development of Proscar® appear to have been performed

by Merck, Sharp & Dohme. It may be possible to rely on approved product labeling information for authorized doses, types of adverse events, preclinical toxicology, *etc.* Additional data, such as clinical chemistry results in an animal toxicity study or clinical data supporting higher doses, may be available in Merck, Sharp & Dohme's IND or NDA files.

Pharmacodynamics Issues

Since the dose-response curve for inhibition of 5α-reductase is shallow, further development of Proscar® should include titration of the tissue effect against doses lower than 5 mg qd. Lower doses may also decrease the incidence of adverse sexual function effects.

Regulatory Issues

No studies exist in the published literature or the CB preclinical testing program investigating the chemopreventive efficacy of Proscar® against prostate carcinogenesis. Negative data exists regarding the drug's effect on established tumors. Conversely, the safety of the drug during chronic intake has been established in several Phase II and III treatment trials in BPH patients, and a seven year Phase III chemoprevention trial is in progress. No regulatory obstacles to further clinical development of Proscar® appear to exist.

Supply and Formulation Issues

Merck, Sharp & Dohme holds the rights to Proscar®, and is supplying the drug and placebo for the Phase III chemoprevention trial funded by the NCI. An agreement with the manufacturer to supply drug and placebo will need to be arranged for any future NCI-sponsored clinical trials. An alternative is the use of another 5α-reductase inhibitor, such as Epristeride (SmithKline Beecham) or 4-hydroxy-4-androstene-3,17-dione (Sigma Chemical Co.).

Intermediate Biomarker Issues

The only intermediate biomarker which has been assessed with Proscar® is serum PSA; however, it is of limited value as a surrogate trial endpoint. PSA is a protease produced by normal, hyperplastic and neoplastic prostatic epithelium for secretion into the seminal fluid. Increased leakage of PSA into the circulation is a result of loss of the basal cell layer in prostatic intraepithelial neoplasia (PIN) and cancer or the increased prostate volume secondary to BPH. Thus, it is a marker of the presence of a tumor or hyperplasia, rather than a causative factor in carcinogenesis.

Additional intermediate biomarkers need to be evaluated in preclinical and short-term clinical trials if Proscar® is developed further as a cancer chemopreventive drug. As suggested at a recent workshop, potential biomarkers include PCNA, MIB-1, ploidy, morphometry (cell size, number of nucleoli, texture, nuclear roundness, apoptotic bodies, chromatin distribution), c-*erb*B-2, and PIN [38].

Clinical Studies Issues

The efficacy of Proscar® in treating BPH has been studied in two 12-month Phase III trials [reviewed in 12,39]. The 5 mg daily dose decreased prostate volume by a mean of only 20%, although serum DHT decreased 80%. The latter effect is the same as that obtained from surgical castration. Symptom improvement, such as increased urinary flow rate, was unpredictable. An open-label extension trial at the completion of the Phase III trials suggested that slight declines in prostate volume and symptoms continued during an additional year of treatment [12]. The lack of a large effect may result from several considerations which may also affect its chemopreventive efficacy. First, two isozymes of 5α-reductase exist in the epithelial cells [40], but Proscar® inhibits only one type 2 [reviewed in 38]. This is the reason that serum and prostatic DHT are not reduced by 100%. It may be necessary to inhibit both isozymes. Second, intraprostatic testosterone increases significantly since it is not metabolized further [41]; this high concentration may overcome its weaker association with the androgen receptor compared with DHT [42] and perhaps promote tumor growth [6]. Finally, normal and hyperplastic prostatic tissues appear to contain more 5α-reductase activity than cancer tissues [6], and enzyme activity does not correlate to tumor grade. Thus, it is unclear what effect Proscar® may have on prostatic adenocarcinoma development. Except for dose-titration and short-term biomarker studies, further clinical development of Proscar® by the CB will await results of both the NCI-funded Phase III prostate cancer prevention trial in healthy older men and the manufacturer-funded trial in prostate cancer patients after radical prostatectomy.

REFERENCES

1. FDC Reports. Merck's Proscar® (finasteride) approved June 19 after 14-month review. *FDC Reports (The Pink Sheet)* 54: 4, 1992.
2. Duffy, M.A. *Physicians' Desk Reference*, 48th Ed., Montvale, New Jersey: Medical Economics Data Production Co., pp. 1532–1534, 1994.
3. Tenover, J.S. Prostates, pates, and pimples. The potential medical uses of steroid 5α-reductase inhibitors. *Endocrinol. Metab. Clin. North Am.* 20: 893–909, 1991.
4. Brooks, J.R., Berman, C., Nguyen, H., Prahalada, S., Primka, R.L., Rasmusson, G.H., and Slater, E.E. Effect of castration, DES, flutamide, and the 5α-reductase inhibitor, MK-906, on the growth of the Dunning rat prostatic carcinoma, R-3327. *Prostate* 18: 215–227, 1991.
5. Pode, D., Weston, W.D., Huryk, R., and Fair, W. Effect of 5α-reductase inhibitors on the rat prostate and prostatic carcinoma. *European Urol.* 18 (Suppl. 1): 177, 1990. (Meeting abstract)
6. Gormley, G.J. Role of 5α-reductase inhibitors in the treatment of advanced prostatic carcinoma. *Urol. Clin. North Am.* 18: 93–98, 1991.
7. Laroque, P.A., Prahalada, S., Gordon, L.R., Noblot, S.M., Bagdon, W.J., Duprat, P., Peter, C.P., and van Zwieten, M.J. Effects of chronic oral administration of a selective 5α-reductase inhibitor, finasteride, on the dog prostate. *Prostate* 24: 93–100, 1994.
8. Liang, T., Cascieri, M.A., Cheung, A.H., Reynolds, G.F., and Rasmusson, G.H. Species differences in prostatic steroid 5α-reductases of rat, dog, and human. *Endocrinology* 117: 571–579, 1985.
9. Andersson, S. and Russel, D.W. Structural and biochemical properties of cloned and expressed human and rat steroid 5α-reductases. *Proc. Natl. Acad. Sci. U.S.A.* 87: 3640–3644, 1990.
10. Carlin, J., Christofalo, P., Arison, B., Berman, C., Brooks, J., Rasmusson, G.F., Rosegay, A., Stoner, E., and VandenHeuvel, W. Metabolism and disposition of MK0906 in animals and man. *Pharmacologist* 29: 149, 1987.
11. Ishii, Y., Mukoyama, H., and Ohtawa, M. *In vitro* biotransformation of finasteride in rat hepatic microsomes: Isolation and characterization of metabolites. *Drug Metab. Dispos.* 22: 79–84, 1994.
12. Sudduth, S.L. and Koronkowski, M.J. Finasteride: The first 5α-reductase inhibitor. *Pharmacotherapy* 13: 309–329, 1993.
13. Prahalada, S., Majka, J.A., Soper, K.A., Nett, T.M., Bagdon, W.J., Peter, C.P., Burek, J.D., MacDonald, J.S., and van Zwieten, M.J. Leydig cell hyperplasia and adenomas in mice treated with finasteride, a 5α-reductase inhibitor: A possible mechanism. *Fundam. Appl. Toxicol.* 22: 211–219, 1994.
14. Cukierski, M.A., Sina, J.L., Prahalada, S., Wise, L.D., Antonello, J.M., MacDonald, J.S., and Robertson, R.T. Decreased fertility in male rats administered the 5α-reductase inhibitor, finasteride, is due to deficits in copulatory plug formation. *Reprod. Toxicol.* 5: 353–362, 1991.
15. Wise, L.D., Minsker, D.H., Cukierski, M.A., Clark, R.L., Prahalada, S., Antonello, J.M., Macdonald, J.S., and Robertson, R.T. Reversible decreases of fertility in male Sprague-Dawley rats treated orally with finasteride, a 5α-reductase inhibitor. *Reprod. Toxicol.* 5: 337–346, 1991.
16. Clark, R.L., Antonello, J.M., Grossman, S.J., Wise, L.D., Anderson, C., Bagdon, W.J., Prahalada, S., MacDonald, J.S., and Robertson, R.T. External genitalia abnormalities in male rats exposed *in utero* to finasteride, a 5α-reductase inhibitor. *Teratology* 42: 91–100, 1990.
17. Clark, R.L., Anderson, C.A., Prahalada, S., Robertson, R.T., Lochry, E.A., Leonard, Y.M., Stevens, J.L., and Hoberman, A.M. Critical developmental periods for effects on male rat genitalia induced by finasteride, a 5α-reductase inhibitor. *Toxicol. Appl. Pharmacol.* 119: 34–40, 1993.
18. Vermeulen, A., Giagulli, V.A., De Schepper, P., Buntinx, A., and Stoner, E. Hormonal effects of an orally active 4-azasteroid inhibitor of 5α-reductase in humans. *Prostate* 14: 45–53, 1989.
19. Rittmaster, R.S., Stoner, E., Thompson, D.L., Nance, D., and Lasseter, K.C. Effect of MK-906, a specific 5α-reductase inhibitor, on serum androgens and androgen conjugates in normal men. *J. Androl.* 10: 259–262, 1989.
20. Gormley, G.J., Stoner, E., Bruskewitz, R.C., Imperato-McGinley, J., Walsh, P.C., McConnell, J.D., Andriole, G.L., Geller, J., Bracken, B.R., Tenover, J.S., Vaughan, E.D., Pappas, F., Taylor, A., Binkowitz, B., and Ng, J. The effect of finasteride in men with benign prostatic hyperplasia. *N. Engl. J. Med.* 327: 1185–1191, 1992.
21. Stoner, E. The clinical development of a 5α-reductase inhibitor, finasteride. *J. Steroid Biochem. Mol. Biol.* 37: 375–378, 1990.
22. The MK-906 Study Group. One-year experience in the treatment of benign prostatic hyperplasia with finasteride. *J. Androl.* 12: 372–375, 1991.
23. Norman, R.W., Coakes, K.E., Wright, A.S., and Rittmaster, R.S. Androgen metabolism in men receiving finasteride before prostatectomy. *J. Urol.* 150: 1736–1739, 1993.
24. Stoner, E. and Members of the Finasteride Study Group. Three-year safety and efficacy data on the use of finasteride in the treatment of benign prostatic hyperplasia. *Urology* 43: 284–294, 1994.
25. Stoner, E., Round, E., Ferguson, D., Gormley, G.J., and the Finasteride Study Group. Clinical experience of the detection of prostate cancer in patients with benign prostatic hyperplasia treated with finasteride. *J. Urol.* 151: 1296–1300, 1994.
26. Gormley, G.J., Stoner, E., Ng, J., Guess, H., Cook, T., and Walsh, P. Effect of finasteride on prostate-specific antigen density. *Urology* 43: 53–59, 1994.
27. Stamey, T.A., Yang, N., Hay, A.R., McNeal, J.E.,

Freiha, F.S., and Redwine, E. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. *N. Engl. J. Med.* 317: 909–916, 1987.

28. Carlin, J.R., Christofalo, P., and Vandenheuvel, W.J.A. High performance liquid chromatography determination of *N*-(2-methyl-2-propyl)-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide, a 4-azasteroid, in human plasma from a Phase I study. *J. Chromatogr.* 427: 79–91, 1988.
29. Steiner, J.F. Finasteride: A 5α-reductase inhibitor. *Clin. Pharm.* 12: 15–23, 1993.
30. Carlin, J.R., Höglund, P., Eriksson, L.-O., Christofalo, P., Gregoire, S.L., Taylor, A.M., and Andersson, K.-E. Disposition and pharmacokinetics of [^{14}C]finasteride after oral administration in humans. *Drug Metab. Dispos.* 20: 148–155, 1992.
31. Reynolds, T. Prostate cancer prevention trial launched. *J. Natl. Cancer Inst.* 85: 1633–1634, 1993.
32. PDQ *Physicians' Data Query*. Available online via the National Library of Medicine (NLM), September 1994.
33. Brawley, O.W., Ford, L.G., Thompson, I., Perlman, J.A., and Kramer, B.S. 5-α-Reductase inhibition and prostate cancer prevention. *Cancer Epidemiol. Biomarkers Prev.* 3: 177–182, 1994.
34. FDC Reports. Axion distributing Proscar® for prostate cancer prevention trial. *FDC Reports (The Pink Sheet)* 55: TG10–TG11, 1993.
35. Jenks, S. Optimism expressed over prostate drug. *J. Natl. Cancer Inst.* 83: 1712–1713, 1991.
36. FDC Reports. Merck's Proscar® (finasteride) undergoing Phase II study. *FDC Reports (The Pink Sheet)* 54: T&G4–T&G5, 1992.
37. Fair, W.R., Presti, J.C., Jr., Sogani, P., Andriole, G., Seidmon, E.J., Ferguson, D., and Gormley, G.J. Multicenter, randomized, double-blind, placebo controlled study to investigate the effect of finasteride (MK0906) on stage D prostate cancer. *J. Urol.* 45: 317A, abstract no. 419, 1991.
38. Bostwick, D.G., Burke, H.B., Wheeler, T.M., Chung, L.W.K., Bookstein, R., Pretlow, T.G., Nagle, R.B., Montironi, R., Lieber, M.M., Veltri, R.W., Grizzle, W.E., and Grignon, D.J. The most promising surrogate endpoint biomarkers for screening candidate chemopreventive compounds for prostatic adenocarcinomas in short-term Phase II clinical trials. *J. Cell. Biochem.* 19 (Suppl.): 283–289, 1994.
39. Rittmaster, R.S. Finasteride. *N. Engl. J. Med.* 330: 120–125, 1994.
40. Jenkins, E.P., Andersson, S., Imperato-McGinley, J., Wilson, J.D., and Russell, D.W. Genetic and pharmacological evidence for more than one human steroid 5α-reductase. *J. Clin. Invest.* 89: 293–300, 1992.
41. 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.
42. Grino, P.B., Griffin, J.E., and Wilson, J.D. Testosterone at high concentrations interacts with the human androgen receptor similarly to dihydrotestosterone. *Endocrinology* 126: 1165–1172, 1990.

Table I. Clinical Trials of Proscar® Sponsored/Funded by NCI, DCPC

Study No. Title (PI) Period of Performance IND No.	Cancer Target	Study Population No. of Subjects	Dose(s) Study Duration	Endpoints	Remarks
Phase II (Dose-titration, efficacy, intermediate biomarkers)					
New Study Chemoprevention Trial of 5α-Reductase Inhibitors in Patients with Prostate Cancer in the Period Prior to Radical Prostatectomy (Presurgical Period): Modulation of Surrogate Endpoint Biomarkers (Dr. Samuel W. Beenken, Univ. of Alabama) 9/94–	Prostate	Biopsy-proven prostate cancer patients scheduled for prostatectomy 100 patients (50/arm)	Oral maximum nontoxic dose of a 5α-reductase inhibitor for 2 weeks to 1 month	Efficacy: PIN grade, other intermediate biomarkers	Evaluation of intermediate biomarkers with emphasis on those measured quantitatively by computer-assisted cytomorphometry and cytophotometry
Phase III (Efficacy, intermediate biomarkers)					
U01-CA-37429 *(not Chemoprevention Branch)* Prostate Cancer Prevention Trial (Dr. Charles A. Coltman, Jr., SWOG; Dr. Otis Brawley, NIH, NCI Coordinator) 10/93–10/03	Prostate	Men ≥55 years of age with normal DRE, and PSA below 3 ng/ml 18,000 men (9,000/arm)	Oral 5 mg qd for 7 years 10 years	Efficacy: Prostate cancer incidence, grade and stage; BPH incidence and severity; overall and prostate-specific mortality; TURP incidence Risk factors: Serum PSA, other factors	Study in progress, with accrual ahead of schedule (2,500) Published reports: [24,31,33]

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