NCI, DCPC
Chemoprevention Branch and Agent Development Committee

CLINICAL DEVELOPMENT PLAN:

N-(4-HYDROXYPHENYL)RETINAMIDE (4-HPR)

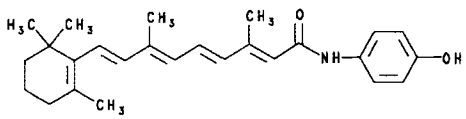
DRUG IDENTIFICATION

CAS Registry No.: 65646-68-6

CAS Name (9CI): all-*trans*-*N*-(4-Hydroxyphenyl)retinamide

Synonyms: Fenretinide
McN-R-1967
RWJ-16434

Structure:



EXECUTIVE SUMMARY

4-HPR is a synthetic amide of all-*trans*-retinoic acid. As a retinoid, 4-HPR is an antiproliferative and differentiation-inducing agent when administered during the promotion and progression phases of carcinogenesis [*e.g.*, 1], although so far it has not been shown to bind retinoic acid receptors. It has been specifically shown to inhibit ODC activity induction [2] and prostaglandin synthesis [3–5], as well as to enhance immune responses [6,7], modulate protein kinase activity [8,9] and cytoskeletal organization [10], decrease circulating insulin-like growth factor-I (IGF-I) [11], and induce apoptosis [1]. 4-HPR is an effective inhibitor of mammary gland, skin, and urinary bladder carcinogenesis in animal models. Concomitantly, both the agent and its less polar metabolites [*e.g.*, *N*-(4-methoxyphenyl)retinamide (4-MPR)] have been demonstrated to accumulate in many of these target tissues. Since 4-HPR is less toxic than other efficacious retinoids, its development as a chemopreventive drug was undertaken by the NCI.

4-HPR has inhibited carcinoma formation in rat mammary glands, hamster lung, rat and mouse prostate, and mouse bladder and liver. These studies are more than adequate to support clinical development of the retinoid as a chemopreventive drug. Additional studies are in progress in transgenic skin and lymphoma models of carcinogenesis. 4-HPR is also effective against the development of premalignant lesions in mouse mammary glands *in vitro* and *in vivo*, and of mouse skin papillomas and rat colon adenomas and aberrant crypt foci *in vivo*. An important aspect of the development of this drug in chemoprevention trials is the identification, standardization and modulation of intermediate biomarkers of carcinogenesis and, ultimately, the validation of these endpoints as surrogates for cancer incidence reduction.

Adequate subchronic and chronic rodent and dog toxicity assays of 4-HPR have been completed. However, treatment-related hemangiosarcomas were seen at doses above the MTD in the two-year mouse carcinogenicity bioassay. A repeat study at doses below the MTD has been undertaken by the

CB. The combination of 4-HPR and tamoxifen citrate is also being tested in 90-day toxicity studies in dogs and rats. No synergistic toxicity was demonstrated in dogs; however, a NOEL was not achieved. The comparable study in rats is in progress.

Phase I trials funded by the Italian National Research Council identified a well-tolerated human dose of 200 mg qd. A dose-related decrease in plasma retinol has been associated with decreased dark adaptation and abnormal rod function (excitation threshold, wave amplification) measured by electroretinogram (ERG) at 200–800 mg 4-HPR qd. The effect appears to be reversible. A three-day drug holiday per month was added in subsequent studies to reduce the potential for ophthalmic toxicity.

NCI-sponsored clinical trials of 4-HPR are summarized in Table I. A Phase III trial is in progress in patients surgically treated for Stage I/II breast cancer to assess prevention of a second primary in the contralateral breast after five years. Four Phase II trials in target tissues other than breast are in progress; a significant aspect of these trials is the identification and evaluation of intermediate biomarkers (histological, genetic, proliferative and differentiation) as surrogate endpoints for long-term cancer chemoprevention trials. A Phase IIa trial evaluating normalization of bladder cell cytology and DNA content showed a decrease in the incidence of aneuploidy in the 4-HPR-treated group; three patients with positive cytology also reverted to normal. Drug has been received to start Phase IIb. Two Phase II trials involving modulation of CIN III and actinic keratosis were recently removed from clinical hold following FDA review of the mouse carcinogenicity data and relevant clinical data from the Phase III trial of 4-HPR. Finally, the protocol for a Phase II trial evaluating modulation of squamous metaplasia/dysplasia in chronic smokers with a prior, resected smoking-related malignancy (lung, head/neck, bladder, *etc.*) has been approved by FDA; the study is awaiting receipt of 4-HPR. Based on the final evaluation of efficacy in the Phase II trials in cervix, bladder, lung and skin, 4-HPR may be further developed in these tissues.

Four additional CB-sponsored Phase II trials began in 1994. One trial with 4-HPR involves modulation of a histological intermediate biomarker (dysplastic oral leukoplakia) as the endpoint. A second Phase II trial is evaluating modulation of histological, genetic and proliferative biomarkers in superficial bladder cancer patients after surgery and BCG treatment. Two additional trials are evaluating the effect of treatment on intermediate biomarkers in the period between cancer diagnosis and surgery. 4-HPR is being administered to biopsy-diagnosed prostate cancer patients until definitive surgery. The remaining trial is evaluating the combination of 4-HPR and tamoxifen citrate in DCIS/breast cancer patients scheduled for surgery. The development of this agent combination by the CB is supported by animal efficacy data in mammary glands; it also takes advantage of potentially complementary mechanisms of retinoids and tamoxifen, such as modulation of growth factors (*e.g.*, TGF-β), and inhibition of prostaglandin and polyamine synthesis.

Other NCI programs are contributing to the development of 4-HPR and tamoxifen as a breast cancer chemopreventive regimen. Two Phase II trials are being administered through the Clinical Oncology Program. The first is a feasibility study of tissue sampling by three methods for assessment of proliferative intermediate biomarkers and their modulation, and of TGF-β isoforms as drug effect measurements, in women at high risk for breast cancer. The other trial will evaluate similar endpoints in areas of CIS and proliferation adjacent to breast cancer; combination treatment will take place between diagnostic biopsy and definitive surgery. Finally, a combination Phase II trial administered by the Eastern Cooperative Oncology Group (ECOG) is being designed. This trial will compare tamoxifen with tamoxifen plus 4-HPR as adjuvant therapy in women surgically treated for node-negative breast cancer.

4-HPR is produced as a proprietary formulation (100 mg/gelatin capsule; Fenretinide) by McNeil Pharmaceutical (Spring House, PA), a division of R.W. Johnson. A Letter of Agreement for the clinical development of 4-HPR, which includes clauses related to supply and formulation, has been negotiated between NCI and McNeil Pharmaceutical.

PRECLINICAL EFFICACY STUDIES

More than sufficient evidence of carcinogenesis inhibition has been obtained *in vivo* in the CB preclinical testing program. The agent appears to act primarily during the promotion and progression phases of carcinogenesis. In completed studies, 4-HPR reduced tumor incidence or multiplicity in the MNU- (0.5 mmol/kg diet, or *ca.* 0.025 mmol/kg-bw/day) and DMBA-induced rat mammary gland (1 mmol/kg diet, or *ca.* 0.05 mmol/kg-bw/day), DEN-induced hamster lung (1 mmol/kg diet, or *ca.* 0.12 mmol/kg-bw/day), [12] and DMBA-in-

duced/TPA-promoted mouse skin (0.75 mmol/kg diet, or *ca.* 0.09 mmol/kg-bw/day) models of carcinogenesis. Studies of 4-HPR in the NNK- and B(*a*)P-induced mouse lung, and transgenic mouse lymphoma (*pim* oncogene) and skin (*ras*/keratin K1) models of carcinogenesis have been initiated. Preliminary results from the lymphoma model suggest that 4-HPR alone and in combination with DFMO improved survival following initiation with ENU [11]; histopathological evaluation is in progress. In short-term test systems, the agent inhibited chemically induced morphological transformation of rat tracheal epithelial cells (B(*a*)P), and human foreskin fibroblasts (platelet-derived growth factor) and epithelial cells (propane sultone). 4-HPR also inhibited anchorage-independent growth in the human lung tumor A427 cell assay and formation of hyperplastic alveolar nodules (HAN) in mouse mammary organ cultures (DMBA).

In published reports, 4-HPR inhibited rat colon (DMH) [14], mouse liver (DEN) [15], rat mammary gland (DMBA, MNU) [16–24], mouse skin (DMBA/TPA) [2,25,26], mouse bladder (OH-BBN) [18,27], mouse prostate (*ras/myc* transduction) [28], and rat prostate (MNU/testosterone) [29] carcinogenesis. Interestingly, both independent and CB-sponsored studies found that MNU-induced rat mammary tumor development could be enhanced or unaffected by 4-HPR in rats fed a semipurified diet (*i.e.*, AIN-76A) rather than a grain-based diet (Wayne Lab Blox, NIH-07) [24,30]. The pharmacokinetics appeared to be altered, with lower levels of circulating drug [24]. This suggests that dietary interactions should be considered in clinical trials of 4-HPR.

Assessment of 4-HPR in a battery of CB-funded *in vivo* intermediate biomarker assays is also in progress. In completed studies, the agent inhibited formation of spontaneous HAN in mouse mammary glands [31] and AOM-induced aberrant crypt foci in rat colon (391 mg/kg diet, or *ca.* 0.05 mmol/kg-bw/day). The endpoints in assays in progress include enzyme-altered foci in the hamster buccal pouch (DMBA); histological changes in the B(*a*)P/silicone-implanted hamster lung; premalignant lesions, and oncogene and PCNA expression in rat mammary glands (MNU); K-*ras* mutations in the hamster pancreas (BOP); and dysplasia and epidermal growth factor receptor (EGFR) levels in the rat urinary bladder (OH-BBN). Published reports have also demonstrated modulation of histological intermediate biomarkers by 4-HPR, *i.e.*, mouse skin papillomas [2,25,26] and rat colon adenomas [14]. A proliferation-related intermediate biomarker, ODC activity, was modulated in TPA-promoted mouse skin [2].

In the standard MNU-induced rat mammary gland model, both CB-sponsored and independent studies [21] have shown that combining tamoxifen with 4-HPR enhances inhibition of carcinogenesis compared with 4-HPR alone. In CB-funded studies, dietary 4-HPR (1 mmol/kg diet, or *ca.* 0.05 mmol/kg-bw/day) with tamoxifen citrate (0.5 mg/kg diet) showed synergistic activity against MNU-induced mammary carcinogenesis in older rats [32]. Interestingly, a similar combination (4-HPR, po; tamoxifen, sc) was even more effective in an adjuvant study using the induction of subsequent mammary carcinomas following surgical removal of the first cancer as the endpoint. Synergistic combinations in other organ systems with 4-HPR include DFMO, oltipraz [33], β-carotene plus oltipraz [33], β-carotene plus vitamin A, and sodium selenite plus vitamin E in hamster lung, and with oltipraz or DFMO in mouse bladder [34].

PRECLINICAL SAFETY STUDIES

Safety NCI has sponsored acute toxicity studies in rats and 30-day and 90-day oral toxicity studies in rats and dogs. McNeil Pharmaceutical has provided results of one-year toxicity studies in the same species. In the one-year rat study, the NOEL by dietary admixture was 10 mg/kg-bw/day (0.026 mmol/kg-bw/day). In the one-year toxicity study in dogs, moderate increases in serum cholesterol were dose-related at 10, 90 and 800 mg 4-HPR/kg-bw/day administered by capsule. Carcinogenicity studies in rats and mice have been performed by the CB. Reproductive and developmental studies (FDA Segment I, II, III) of 4-HPR have been performed by the manufacturer.

Final results are available from the carcinogenicity portion of the CB-sponsored two-year rodent bioassays. In the rat study of 10, 30 and 100 mg 4-HPR/kg-bw/day (0.03, 0.08, and 0.3 mmol/kg-bw/day), treatment-related benign pheochromocytomas were observed only at the two highest doses. Non-neoplastic microscopic changes in the liver, heart and kidneys were also identified at all doses at the one-year interim and two-year terminal sacrifices. In contrast, hemangiosarcomas occurred at all dose levels (100, 300 and 1,000 mg 4-HPR/kg-bw/day, or 0.3, 0.8 and 2.6 mmol/kg-bw/day) in the mouse study. The incidence appears to be treatment-related, and suggests that doses above the MTD were used for lifespan administration. Since the tumor incidence in

females (16%) at the lowest dose (100 mg/kg-bw/day) approached control values (5%), the assay will be repeated at doses of 10, 30 and 100 mg/kg-bw/day. Parallel groups at the highest and lowest dose will be placed on basal diet for three days/month to model the treatment interruption protocol used in clinical trials. All doses are still higher than planned human exposure of 200 mg qd (*ca.* 0.007 mmol/kg-bw qd).

The CB will not sponsor studies specifically addressing reproductive and developmental toxicity unless those performed by McNeil Pharmaceutical are inadequate. One CB-sponsored chemoprevention study found normal estrus cycles in female rats at doses to 782 mg/kg diet (*ca.* 0.1 mmol/kg-bw/day) [16]. In a published study, spermatogenic arrest and testicular tubule necrosis were observed in mice and rats receiving the 21-day LD_{50} (NOS) [35]. McNeil Pharmaceutical [36] has performed Segment I reproductive performance and fertility studies in rats. No effect on male performance, estrus, pregnancy rate, gestation length and litter size and sex ratio were found. Published Segment II studies found that 4-HPR is teratogenic in rats and rabbits, although it was less potent than retinoic acid [37,38]. Specific effects included resorptions, craniofacial abnormalities, and hemorrhagic and cardiac vessel defects. The NOEL in rats and rabbits was 0.05 mmol/kg-bw/day. A Segment III study in rats by McNeil Pharmaceutical found intraocular hemorrhage, cataracts and microphthalmia at doses of 20–800 mg 4-HPR/kg-bw/day (0.05–2.0 mmol/kg-bw/day). Phase II trials should stipulate use of dependable birth control (*e.g.*, Norplant, IUD) for female participants.

To support clinical development of combinations of 4-HPR with tamoxifen, the CB has sponsored 90-day toxicity studies in rats and dogs. In female Beagle dogs, no synergistic toxicity was observed with a capsule formulation of the combined agents (0.03, 0.3 and 2.1 mmol 4-HPR/kg-bw/day plus 0.4, 4 and 32 mg tamoxifen citrate/kg-bw/day, respectively); however, a NOEL was not established, primarily due to tamoxifen-related histopathology. The comparable study in Sprague-Dawley rats with 0.03–1.0 mmol 4-HPR/kg-bw/day plus 0.4–16 mg tamoxifen citrate/kg-bw/day is being repeated due to protocol deficiencies.

ADME In studies reported in the literature, absorption was low and variable after oral administration of 4-HPR in rodents, and C_{max} occurred in four hours [39]. The parent drug was extensively metabolized to less polar compounds, such as the primary metabolite 4-MPR [39,40]. Due to the lipophilicity of the metabolites, 4-HPR had a substantially longer elimination half-life than all-*trans*-retinoic acid (12 hrs *vs.* 20 min) [39].

Differences in the metabolism of 4-HPR appear to exist across species. Comparison of proposed pathways revealed similarities between rats and dogs [36]. Rats and mice, however, appear to show substantial differences in the metabolism of 4-HPR [41]. Mice tended to produce more metabolites and significantly higher tissue concentrations of them than rats. However, in both species, the tissues with greatest drug concentrations were bladder, liver and mammary glands [39].

CLINICAL SAFETY: PHASE I STUDIES

The CB has not funded Phase I studies of 4-HPR; however, such studies are addressed in the manufacturer's IND. A dose-titration study (100, 200, and 300 mg qd for 6 months) was funded by the Italian National Research Council to identify the highest tolerable long-term dose [42–47]; at the two highest doses, a low incidence (8%) of visual disturbances was obtained [42]. As a result, McNeil Pharmaceutical suggested a three-day drug holiday per month to avoid the potential ophthalmic toxicity, and no further adverse effects were reported in the remaining 6 months of the Phase I trial at a dose of 200 mg qd with the drug holiday. The NCI, DCPC began a Phase III trial of 4-HPR in March 1987 using the same regimen in women with resected breast cancer. Eleven of the Phase II trials which are in progress or planned include measures of the adverse effects noted in the Italian dose-titration study and may provide additional data on an effective, safe dosing regimen.

Drug Effect Measurement In both the ADME studies supported by McNeil Pharmaceutical [36, 48–50] and the Phase I trials supported by the Italian National Research Council [42–45], the most sensitive drug effect measurement was plasma retinol levels. The relationship between dose and plasma retinol appears to be linear over 100–300 mg 4-HPR qd (*ca.* 0.004–0.01 mmol/kg-bw qd). The onset and reversal of the effect were rapid. The ongoing and planned Phase II studies will provide a further opportunity to validate and standardize the methods for sample handling and plasma retinol measurement. An HPLC method used in the Phase III breast cancer chemoprevention trial allows separation of 4-HPR, 4-MPR and retinol.

One problem with using plasma retinol as a drug effect measurement is that functional vitamin

A deficiency manifests as ophthalmic toxicity (see **Safety** below); the 4-HPR dose used in clinical trials should have as small an effect on this endpoint as possible. A second problem is that the levels may not decrease linearly at doses under 100 mg qd, a possibility with 4-HPR doses used in future combination regimens. However, both retinoids and tamoxifen decrease plasma IGF-I [11,51–53] and induce different tissue TGF-β isoforms [54,55], which may serve as a substitute drug effect measurements. For example, tamoxifen predominantly induces TGF-β1 and retinoids induce TGF-β2 and -β3; the combination may then achieve a greater total induction of TGF-β. The utility of this approach needs to be investigated in dose-titration studies.

Safety In the NCI-funded Phase III breast and Phase IIa bladder trials and the Italian Phase I trial, the main toxicities were ophthalmic disturbances (decreased dark adaptation, abnormal ERG), plasma retinol reduction, and minor dermatological complaints. The dose used in the bladder study (200 mg qd, three-day holiday/month) produced a 33% incidence of nyctalopia which was not considered to be severe enough to reduce or end treatment. After extension of the Italian Phase I trial to 30 months, a low incidence (4%) of ophthalmic disturbances was observed using the same dosing regimen [43,44]. In the Phase III trial, 1,398 of the 2,803 evaluable patients had been treated with 200 mg 4-HPR qd with a three-day drug holiday for an average of three years by February 22, 1993, and only 3.6% had interrupted drug intake due to adverse effects [52]. In preliminary results, mild and moderately diminished dark adaptation occurred at plasma retinol levels of 160 and 100 ng/ml, respectively; however, only half of the subjects reported symptoms [52,56]. A recently published analysis of the vanguard cohort in the Phase III trial showed a 65% reduction in mean retinol levels to 170 ng/ml after 5 years of 4-HPR treatment [57]. This suggests that altering the dose regimen or using combinations of agents at lower doses should be evaluated to reach a NOEL in clinical trials.

In published studies at doses of ≥200 mg qd, the most common adverse reactions occur in the gastrointestinal tract (nausea), skin (pruritus, rash, dryness) and eyes (dryness, night blindness, light sensitivity, abnormal ERG), and clinical chemistry (increased serum cholesterol and triglycerides, decreased retinol and retinol binding protein (RBP) levels) [47,58–61]. At the doses used in clinical trials, these reactions appear to be reversible upon reduction or withdrawal of the drug in the absence of preexisting conditions.

A Phase I trial of the combination of 20 mg tamoxifen qd with increasing doses of 4-HPR has been published [62]. In consecutive cohorts of three metastatic breast cancer patients, the levels of 4-HPR were 100, 200, 300, and 400 mg qd with a three-day drug holiday per month. Duration of treatment ranged from 2–14 months, with six patients receiving ≥6 months of therapy. Adverse effects (anemia, altered hepatic enzymes) were felt to be due to progressive disease, and all combinations were safe and well-tolerated. No ophthalmic or dermatological effects were observed.

ADME Data in the literature appear to correspond to studies undertaken by McNeil Pharmaceutical [36,48–50]. In both normal volunteers and cancer patients, the time to maximum plasma concentration of the parent drug after administration of 200 mg 4-HPR was 4–8 hrs, with the major metabolite, 4-MPR, peaking about four hours later. C_{max} and AUC appeared to be linear and proportional to dose following a single administration of 4-HPR (25–600 mg, or 0.0009–0.02 mmol). The pharmacokinetic parameters for the dose used in most clinical trials (200 mg) are $AUC_{(0\text{-}24)}$= 4.5 μmol/L·hr and C_{max}=70.5 μg/ml; these values change significantly if the dose is administered following a high-fat diet. The elimination $t_{½}$ was 16–20 hours for 4-HPR and 22 hours for the metabolite.

The kinetics of the parent drug do not appear to change with multiple daily doses (5 months); plasma steady-state was reached with the second dose. It has been suggested that the kinetics of 4-MPR are nonlinear following multiple doses, indicating accumulation; however, the vanguard cohort in the Phase III trial had the same plasma $t_{½}$ for 4-MPR after 28 days and 5 years of 4-HPR treatment [57].

CLINICAL EFFICACY: PHASE II/III STUDIES

Proposed, current and completed NCI-funded clinical trials of 4-HPR are summarized in Table I. One Phase I trial has been completed (see above), and a Phase III trial is in progress in surgically treated breast cancer patients. Seven Phase II trials are ongoing in high-risk bladder, lung, oral cavity, prostate, cervix and skin cohorts, and two additional Phase II trials in a lung and an oral cavity cohort are planned for 1995. Finally, four trials of combinations of 4-HPR and tamoxifen are in progress in breast cancer cohorts under several programs at NCI (ECOG, CB and DCT).

The Phase III clinical trial (Dr. U. Veronesi, Istituto Nazionale Tumori) of 4-HPR to evaluate chemoprevention of a second primary breast cancer in patients with a previously resected cancer in the contralateral breast began in March 1987, and accrual has stopped at 2,972 patients [63]. An interim analysis of patients in the fourth year of intervention was scheduled to begin in June 1993, but information is as yet unavailable. The trial involves five years of intervention with 200 mg 4-HPR qd with a two-year follow-up period.

The NCI-sponsored Phase II trials of 4-HPR in progress are in the early stages. A significant aspect of these trials is the identification, standardization and modulation of intermediate biomarkers as surrogate endpoints for cancer incidence reduction. The Phase IIa portion of a trial (Dr. A. Decensi, National Institute for Cancer Research, Italy) in patients with resected superficial bladder cancer evaluated the feasibility of using genetic (ploidy), proliferative (S-phase fraction) and histological (cytological grade) intermediate biomarkers [64,65]. The results were very promising. Using cells obtained from bladder washings, improvement was obtained in ploidy and cytology in a portion of the 4-HPR-treated group. Drug has been received to begin the IIb portion of the trial.

The protocols for three funded Phase II trials to study 4-HPR modulation of intermediate biomarkers in skin, cervix and lung were recently approved by the FDA. A trial (Dr. B.A. Conley, University of Maryland) in patients with >15 actinic keratosis lesions will investigate improvement of the clinical lesion, and modulation of histological and other intermediate biomarkers (PCNA, ODC, EGFR) in the skin. Histological regression will also be correlated with changes in other types of intermediate biomarkers (PCNA, DNA content, *ras* expression, EGFR, TGF-α, TGF-β, involucrin and transglutaminase) in a Phase II study of CIN III (Dr. M.F. Mitchell, University of Texas, M.D. Anderson Cancer Center) after 6 months of 4-HPR. Finally, the third Phase II trial (Dr. W.K. Hong, University of Texas, M.D. Anderson Cancer Center) will evaluate improvement of squamous metaplasia/dysplasia in chronic smokers with prior resected lung, head/neck or bladder cancer, as well as modulation of genetic and proliferation biomarkers. All these studies will attempt to identify biomarkers most closely related to premalignancy in a specific tissue, and, second, determine their modulation by 4-HPR.

Four CB-administered Phase II trials of 4-HPR alone or in combination with tamoxifen began in 1994. One cohort is to receive adjuvant 4-HPR treatment following surgery and BCG for superficial bladder cancer. A second Phase II trial is evaluating the effect of 4-HPR on clinical aspects, and histological and other biomarkers in dysplastic oral leukoplakia. In women with recently diagnosed ductal carcinoma *in situ* (DCIS) or carcinoma of the breast, modulation of histological lesions and related biomarkers (nuclear pleomorphism index, ploidy, proliferation index) by 4-HPR and tamoxifen administered between the diagnostic core biopsy and resulting surgery are being evaluated in the third trial. Finally, in the fourth trial, prostate cancer patients are administered the retinoid up to 8 weeks between diagnostic biopsy and radical prostatectomy; modulation of histological (*e.g.*, PIN, nuclear polymorphism) and other intermediate biomarkers are the endpoints. This will replace a previous trial of two doses of 4-HPR in men with elevated PSA, but a negative biopsy for carcinoma. Recruitment was stopped due to a possible increase in prostate tumors; however, no placebo control group had been included for comparison.

Phase II trials of 4-HPR combined with tamoxifen in cohorts at high risk for breast cancer are a priority at NCI. As mentioned above, the CB recently funded a trial in which women with DCIS or breast carcinoma are administered the combination between diagnostic core biopsy and definitive surgery. The Clinical Oncology Program has a trial (Dr. J. O'Shaughnessy, NCI) in progress in a similar cohort in which modulation of intermediate biomarkers is evaluated in DCIS and proliferative lesions adjacent to the carcinoma. A second trial (Dr. J. O'Shaughnessy) administered under the same program is comparing three types of tissue sampling for measurement of endpoints in women at increased risk for breast cancer. The effect of 4-HPR and tamoxifen on drug effect measurements and intermediate biomarkers in breast tissue, as well as adverse effects on the endometrium, are being evaluated. Finally, the Cooperative Clinical Oncology Program (*i.e.*, ECOG) is assessing tamoxifen *vs* tamoxifen plus 4-HPR as adjuvant treatments in women surgically treated for node-negative breast cancer.

Two clinical trials of 4-HPR sponsored by other organizations are in progress in Italy. A study evaluating 200 mg 4-HPR qd with a three-day drug holiday/month for one year in preventing recurrences and new lesions and carcinomas in patients surgically treated for oral leukoplakia began in 1988 [63,66]. Preliminary results from 137 random-

ized subjects show that the risk of recurrence and new occurrences of oral leukoplakia are 6% in the treatment arm and 30% in the control arm [63]. A preliminary study using topical application of the same dose to oral leukoplakia and lichen planus demonstrated at least 75% clinical response within a month [67]. A second study is evaluating oral 200 mg 4-HPR qd in terms of decreasing recurrences or new occurrences of basal cell carcinoma of the head and neck after surgical excision [63,68]. As of June 1993, 709 patients had been randomized [63].

PHARMACODYNAMICS

The concentrations of 4-HPR in mouse tissues following multiple doses (0.012 mmol/kg-bw/day for 5 days, iv) were highest in the bladder, as follows: bladder, 8.2 mg/g; liver, 4.1 mg/g; mammary glands, 2.7 mg/g; and serum, 0.7 mg/ml [41]. Following oral treatment of mice (0.025 mmol 4-HPR/kg-bw/day for 3 days), the tissue AUCs were 13.4, 60.5 and 77.3 μg·hr/g tissue for bladder, mammary glands and liver, respectively, and 14.1 μg·hr/ml for serum [69]. In published reports, 4-HPR inhibited bladder, liver and mammary gland carcinogenesis in the mouse, the same tissues with high parent drug concentrations. Rat tissue concentrations followed the same order after multiple iv doses (0.012 mmol/kg-bw/day for 5 days), although the values were higher than in the mouse: serum, 1.8 mg/ml; mammary glands, 6.3 mg/g tissue; liver, 11.5 mg/g tissue; and bladder, 35.4 mg/g tissue [41]. In this species, chemopreventive efficacy has been observed in the mammary glands.

Since the major metabolites of 4-HPR are less polar, they tend to accumulate in tissue. The major sites of distribution are fat, mammary glands, bladder, skin and kidney; although the liver concentration is also high, it is not a storage site [41,69]. In the mouse, chemopreventive efficacy has been demonstrated in four tissues (mammary glands, bladder, skin, liver) with high 4-MPR accumulation. Following iv administration [41], the proportion of tissue retinoids represented by 4-MPR approached that of the parent drug. For example, 4-MPR and 4-HPR were each approximately 43% of retinoids in the mammary glands; in the bladder, 33% and 44% of tissue retinoids were 4-MPR and 4-HPR, respectively. In the rat, a smaller proportion of tissue retinoids was represented by metabolites. In the mammary gland, only 6.3% was 4-MPR, while more than 82% was parent drug.

Although 4-MPR and 4-HPR have been shown to share at least one retinoid activity (reverse keratinization of vitamin A-deficient rat trachea organ culture) [40], the relative chemopreventive efficacy/toxicity of the specific metabolites has not been extensively investigated. 4-HPR has been shown to inhibit ODC activity induction and prostaglandin synthesis, as well as to modulate protein kinase activity and immunoglobulin secretion; however, it is unknown if it is actually acting as a prodrug. The CB may consider sponsoring studies which correlate tissue levels of specific metabolites and parent drug with efficacy after chemopreventive doses of oral 4-HPR. Another question for investigation is whether binding to retinoic acid receptors is necessary for efficacy, and, if so, which metabolites are responsible.

The relative contribution of 4-HPR and the major metabolite, 4-MPR, to the proposed chemopreventive efficacy in human breast tissue is unknown. In a study of 9 participants in the Phase I trial of women at risk for a second primary cancer in the contralateral breast, both 4-HPR and 4-MPR concentrated in breast tissue compared with plasma, but to different degrees [70]. The ratio of 4-MPR to 4-HPR was close to unity in plasma, but increased to 5.7 in breast tissue. 4-MPR was stored primarily (85%) in the fat cell fraction. It should be noted that a relationship between plasma 4-MPR and toxicity was suggested recently in a Phase III trial subset; increased circulating 4-MPR was a major determinant of decreased retinol in elderly women who had a high percentage of adipose tissue [71].

In a subset of Phase III participants, 4-HPR treatment has been shown to decrease circulating IGF-I levels significantly, especially in younger women [52]. Preliminary data suggest that the chemopreventive activity of this drug is also most evident in women <45 years of age. The relationship of IGF-I reduction to circulating 4-HPR and 4-MPR levels, as well as to breast cancer risk reduction, should be investigated for 4-HPR alone and in combination with tamoxifen.

PROPOSED STRATEGY FOR CLINICAL DEVELOPMENT

Drug Effect Measurement Issues

Consideration should be given to replacing retinol or RBP as drug effect measurements. These endpoints are related to toxicity, and may not be altered at lower doses. Since serum IGF-I is altered

by both 4-HPR and tamoxifen, it should be investigated as a drug effect measurement in dose-titration studies using either a single agent or combination protocol.

Currently, tissue TGF-β isoforms are being evaluated as substitute drug effect measurements in a Clinical Oncology Program-administered Phase II trial of 4-HPR combined with tamoxifen. Since tamoxifen predominantly induces TGF-β1 and retinoids induce TGF-β2 and -β3, the combination may achieve a greater total induction of TGF-β.

Safety Issues

Although the threshold for ophthalmic toxicity was 200 mg qd in a published Phase I trial, decreased dark adaptation and abnormal ERG continue to be reported at this dose, even with the three-day drug holiday/month. These conditions result from a significant decrease in plasma retinol. The changes appear to be reversible. One pharmacokinetic study demonstrated that plasma retinol normalized between three and seven days after 4-HPR treatment interruption [46]. Recent analysis of the vanguard cohort in the Phase III breast cancer chemoprevention trial demonstrated that plasma retinol increased from 38% of baseline to 71% after the three-day treatment interruption [57]. In a Phase III trial subset, dark adaptation did not recover sufficiently within the three days [56]. Thus, three days of drug holiday after each 28 days of 4-HPR treatment may not prevent ophthalmic toxicity. The dose titration portion of the Phase II trial in actinic keratosis patients may define the optimal dosing strategy by correlating adverse reactions with plasma retinol levels. Also, drug combinations (*e.g.*, 4-HPR and tamoxifen) are planned for future clinical trials to decrease the potential for toxicity while retaining efficacy.

Pharmacodynamics Issues

Consideration should be given to the biologically effective dose of 4-HPR and/or 4-MPR. It has been shown that systemic metabolism of 4-HPR is necessary for chemoprevention of skin tumors and that high levels of 4-MPR accumulate in other target organs (mammary gland, bladder). The chemopreventive and the toxicological potential of 4-MPR is unknown. This aspect may need to be incorporated into the planned Phase II trials. Investigation of a small subset of Phase I trial participants scheduled for tumor removal or breast reconstruction suggested that 4-MPR accumulates in this tissue approximately 6-fold higher than the parent drug [70]. It is unknown if the metabolite binds to any retinoic acid receptors or if this binding is necessary for chemopreventive efficacy.

Regulatory Issues

Two Phase II trial applications (actinic keratosis, CIN III) were recently removed from clinical hold following FDA review of the final results of the first mouse carcinogenicity assay, and determination of availability to NCI of patient follow-up data from the Phase III breast cancer trial. The mouse carcinogenicity study showed a treatment-related incidence of hemangiosarcomas at doses which appear to be above the MTD. A protocol for repeating the mouse carcinogenicity study at lower doses has been funded by the CB, with parallel groups incorporating the three-day drug holiday protocol used in clinical trials. These doses are still approximately 3–30-fold higher than the clinical dose. It should be noted that no change in the incidence of non-breast second primary tumors *vs.* control have been reported in the Phase III breast trial after up to 5 years of 4-HPR treatment [57].

Intermediate Biomarker Issues

Seven Phase II trials are assessing modulation of intermediate biomarkers by 4-HPR. For example, the Phase IIb trial in actinic keratosis patients will correlate modulation of clinical, histological and intermediate biomarkers with AUC at the dose selected from Phase IIa. This information will contribute to validation of individual markers as surrogate endpoints for long-term trials, as well as determine the 4-HPR dose required.

Supply and Formulation Issues

A Letter of Agreement for the clinical development of 4-HPR has been negotiated between NCI, DCPC and McNeil Pharmaceutical. The terms of this agreement include clauses addressing the acquisition and formulation of 4-HPR, which is under patent. Sufficient drug is available to support the clinical development outlined below and additional drug will be acquired to support Phase III development as appropriate.

Clinical Studies Issues

Clinical development of 4-HPR as a breast cancer chemopreventive drug by the CB will be lim-

ited to short-term trials involving modulation of intermediate biomarkers, pending results from the ongoing Phase II trial. Based on this strategy, a Phase II trial was recently funded to evaluate the effect of the retinoid with and without tamoxifen citrate when administered during the 2–4 week period between diagnostic biopsy and definitive surgery for DCIS or carcinoma; histological (*e.g.*, nuclear polymorphism, DCIS), proliferative (*e.g.*, PCNA, S-phase fraction) and genetic (*e.g.*, ploidy) biomarkers will be compared in the two tissue samples.

A second strategy is development of 4-HPR as a chemopreventive for target organs in which animal efficacy data exist. Funded Phase II studies include protocols investigating modulation of premalignant lesions in the skin (actinic keratosis), lung (squamous metaplasia/dysplasia), oral cavity (dysplastic leukoplakia), bladder (BCG-treated cohort), and prostate (PIN in presurgery cohort). A Phase II trial investigating modulation of premalignant lesions in the cervix (CIN III) was also included because CIN III is well-characterized, has a low confounding rate of regression (<10%) [72], a relatively long latency for progression (10–13 years) [72], and the tissue is more easily accessible than breast, prostate or lung.

Finally, development of the combination of 4-HPR and tamoxifen for modulation of premalignant breast lesions and breast cancer risk is a high priority. Complementary mechanisms may allow lower doses of both agents to decrease potential toxicity while retaining efficacy. One CB-sponsored Phase II trial as well as two Phase II trials and one Phase III trial sponsored by other NCI programs are contributing to this strategy.

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Table I. Clinical Trials of 4-HPR Sponsored/Funded by NCI

Study No. Title (PI) Period of Performance IND No.	Cancer Target	Study Population No. of Subjects	Doses Study Duration	Endpoints	Remarks
Phase I (Safety, ADME)					
UO1-CA-38567-07 Subset of Phase III Breast Cancer Chemoprevention with Synthetic Retinoid HPR (Dr. Umberto Veronesi, Istituto Nazionale Tumori, Italy) IND 24,019 (McNeil Pharmaceutical)	---	Previously resected, unilateral Stage I/II breast cancer 13 women	Oral 200 mg qd with 3-day holiday/month for 31–41 months	Drug effect measurements: Plasma retinol, 4-HPR, 4-MPR Safety: Vitamin E levels	Study complete Retinol reduced to 16% of baseline; no effect on vitamin E Published report: [72]
Phase II (Dose titration, efficacy, intermediate biomarkers)					
UO1-CA-56457-01 Phase IIa DNA Content Modulation by 4-HPR in Bladder Tumors (Dr. Andrea Decensi, National Institute for Cancer Research, Italy) 10/89–5/92 IND 39,812 (NCI)	Bladder	Resected transitional cell carcinoma (Stage Ta, T1, TIS) 29 patients	Oral 200 mg qd with 3-day holiday/month for 31 months	Intermediate biomarkers: Cytomorphology, ploidy and S-phase fraction in bladder washings Safety: ERG	Safety and pilot study complete Proportion of patients with aneuploid cells or abnormal cytology decreased compared with controls Published report: [64,65]

Table I. Clinical Trials of 4-HPR Sponsored/Funded by NCI, DCPC *(continued)*

Study No. Title (PI) Period of Performance IND No.	Cancer Target	Study Population No. of Subjects	Doses Study Duration	Endpoints	Remarks
Phase II (Dose titration, efficacy, intermediate biomarkers) *(continued)*					
UO1-CA-56457-01 Phase IIb DNA Content Modulation by 4-HPR in Bladder Tumors (Dr. Andrea Decensi, National Institute for Cancer Research, Italy) 8/92–7/95 IND 39,812	Bladder	Patients with resected transitional cell carcinoma (Stage Ta, T1, TIS) 90 patients	Oral 200 mg qd with 3-day holiday/month for 2 years	Intermediate biomarkers: Cytomorphology, ploidy and S-phase fraction, TGF-β in bladder washings Drug effect measurements: Plasma retinol, 4-HPR, 4-MPR Safety: ERG, hematology, clinical chemistry, urinalysis	Study in progress
New Study *N*-4-(Hydroxyphenyl)retinamide (4-HPR) in Patients Previously Treated with BCG for Superficial Bladder Cancer for Modulation of Surrogate Endpoint Biomarkers (Dr. Charles A. Coltman, Southwest Oncology Group Institute for Research and Care) 9/94– IND 39,812	Bladder	Previous superficial bladder cancer patients (Ta grades 1, 2; T1; TIS) scheduled for BCG 100 patients (50/arm)	Oral 200 mg qd with 3-day holiday/month for 1 year 24 months	Efficacy: Regression of histological lesions Intermediate biomarkers (*e.g.*, ploidy, PCNA, Ki-67, S-phase fraction, nuclear polymorphism)	Modulation of histological lesions and other intermediate biomarkers

Table I. Clinical Trials of 4-HPR Sponsored/Funded by NCI, DCPC *(continued)*

Study No. Title (PI) Period of Performance IND No.	Cancer Target	Study Population No. of Subjects	Doses Study Duration	Endpoints	Remarks
Phase II (Dose titration, efficacy, intermediate biomarkers) *(continued)*					
New Study Phase II Clinical Trial of *N*-(4-Hydroxyphenyl)retinamide (4-HPR) and Tamoxifen in Breast Neoplasia, Administration During the Period Between Diagnostic Core Biopsy and Definitive Surgery (Dr. Kapil Dhingra, Univ. of Texas, M.D. Anderson Cancer Center) 9/94– IND 39,812	Breast	Women with biopsy-proven DCIS or carcinoma <10 mm diameter scheduled for surgery 100 patients (50/arm)	Oral 200 mg 4-HPR + 20 mg tamoxifen citrate qd; or 200 mg 4-HPR qd; or 20 mg tamoxifen citrate qd; or placebo between core biopsy and surgical excision (2–4 weeks) 18 months	Intermediate biomarkers (*e.g.*, DCIS grade, ploidy, PCNA, Ki-67, S-phase fraction, nuclear polymorphism)	Modulation of DCIS and other intermediate biomarkers
NIH 94C-0056D Pilot Chemoprevention Study of Tamoxifen and Fenretinide in Subjects at High Risk for Developing Invasive Breast Cancer (Dr. Joyce O'Shaughnessy, Clinical Oncology Program, NCI) 1994– IND 40,294	Breast	Women at increased risk for breast cancer from LCIS, resected DCIS, atypical hyperplasia with 1° relative, or familial risk pattern 25 women	Oral 200 mg 4-HPR qd with 3-day holiday/month during months 1–4 + 20 mg tamoxifen qd during months 2–24	Drug effect measurement: Tissue TGF-β isoforms Intermediate biomarkers: Proliferation biomarkers (*e.g.*, PCNA, Ki-67) Safety: Endometrial biopsy and ultrasound, ophthalmic assessment	Feasibility study of tissue sampling by guided needle biopsy, nipple aspiration and 4-quadrant fine needle aspiration for biomarker and drug effect measurements

Table I. Clinical Trials of 4-HPR Sponsored/Funded by NCI, DCPC *(continued)*

Study No. Title (PI) Period of Performance IND No.	Cancer Target	Study Population No. of Subjects	Doses Study Duration	Endpoints	Remarks
Phase II (Dose titration, efficacy, intermediate biomarkers) *(continued)*					
New Study A Pilot Trial of Tamoxifen and 4-HPR (4-*N*-(Hydroxy)phenyl retinamide) in Patients with Newly Diagnosed Breast Cancer (Dr. Joyce O'Shaughnessy, Clinical Oncology Program, NCI, at University of Maryland) 1994– IND 40,294	Breast	Women with newly diagnosed DCIS or breast cancer 20 patients	Oral 200 mg 4-HPR + 20 mg tamoxifen citrate qd between diagnostic biopsy and surgical excision (<25 days)	Drug effect measurement: Tissue TGF-β isoforms Intermediate biomarkers: Histological, proliferation (cyclin D1 and E, MIB-1, EGFR, IGF-I), and genetic (p53, *erb*B-2)	Study of biomarker modulation in areas of proliferation and CIS adjacent to cancer
NO1-CN-25433-01 A Randomized Double-blind Study of *N*-4-Hydroxyphenylretinamide (4-HPR) *versus* Placebo in Patients with Cervical Intraepithelial Neoplasia (CIN) Grade 3 (Dr. Michele F. Mitchell, Univ. of Texas, M.D. Anderson Cancer Center) 9/92–9/94 IND 39,812	Cervix	CIN III patients 60 patients	Oral 200 mg qd with 3-day holiday/month for 6 months, then cross-over of placebo to 4-HPR for 6 months 1 year	Efficacy: CIN III regression Other intermediate biomarkers: DNA content, micronucleated cell frequency, *ras* expression, PCNA, EGFR, involucrin, TGF-α, TGF-β, and RAR in lesions and normal cervical tissue Safety: Hematology, clinical chemistry, ERG Drug effect measurements: Plasma retinol, 4-HPR, 4-MPR	Protocol submitted to FDA

Table I. Clinical Trials of 4-HPR Sponsored/Funded by NCI, DCPC *(continued)*

Study No. Title (PI) Period of Performance IND No.	Cancer Target	Study Population No. of Subjects	Doses Study Duration	Endpoints	Remarks
Phase II (Dose titration, efficacy, intermediate biomarkers) *(continued)*					
NO1-CN-25433-03 A Randomized Double-Blind Study of *N*-4-Hydroxyphenylretinamide (4-HPR) *versus* Placebo in Chronic Smokers with Squamous Metaplasia/Dysplasia in the Bronchial Epithelium (Dr. Waun K. Hong, Univ. of Texas, M.D. Anderson Cancer Center) 6/93–6/96 IND 39,812	Lung	Chronic smokers with prior resected head/neck, lung, or bladder cancer who display bronchial squamous metaplasia (index ≥15%) or dysplasia 100 smokers	Oral 200 mg qd with 3-day holiday/month for 6 months 3 years	Efficacy: Histological regression Other intermediate biomarkers: Micronucleated cell frequency, ploidy, p53 mutation, PCNA, EGFR, mutagen sensitivity Safety: Clinical chemistry, hematology Drug effect measurements: Plasma retinol, 4-HPR	Patient accrual in progress
Planned Study Chemoprevention of Second Primary Aerodigestive Cancer in Prior Resected Patients 1995	Lung	Patients with previously resected Stage 1 lung cancer 100 patients	4-HPR + oltipraz 4 years	---	Study not yet designed

Table I. Clinical Trials of 4-HPR Sponsored/Funded by NCI, DCPC *(continued)*

Study No. Title (PI) Period of Performance IND No.	Cancer Target	Study Population No. of Subjects	Doses Study Duration	Endpoints	Remarks
Phase II (Dose titration, efficacy, intermediate biomarkers) *(continued)*					
NO1-CN-25440-02 *N*-4-(Hydroxyphenyl)retinamide (4-HPR) in Oral Dysplastic Leukoplakia (Dr. Barbara A. Conley, Univ. of Maryland Cancer Center) 9/94– IND 39,812	Oral Cavity	Patients with biopsy-proven dysplastic oral leukoplakia 100 patients (50/arm)	Oral 200 mg qd with 3-day holiday/month for 6 months 24 months	Efficacy: Clinical and histological regression of lesions Other intermediate biomarkers (*e.g.*, grade of dysplasia, ploidy, PCNA, Ki-67, S-phase fraction, nuclear polymorphism)	Modulation of histological lesions and other intermediate biomarkers
Planned Study Chemoprevention of New Leukoplakia Lesions (4-HPR or Alternate) 1995	Oral Cavity	Patients with dysplastic oral leukoplakia 100 patients	— 3 years	—	Study not yet designed
CA-22453-15S1 Phase II Chemoprevention Study of Oral Fenretinide (4-HPR) in Patients at Risk for Adenocarcinoma of the Prostate (Dr. Kenneth Pienta, Wayne State Univ.) 4/88–3/96 IND 38,892 (R.W. Johnson)	Prostate	Biopsy negative for carcinoma and serum PSA ≥4 ng/ml 90 men	Oral 100 or 200 mg qd with 3-day holiday/month for 1 year	Efficacy: Prevention of positive biopsy or doubling of PSA Intermediate biomarkers: Nuclear matrix protein; regression of PIN Safety: ERG, clinical chemistry, hematology Drug effect measurements: Plasma RBP, retinol	Nonrandomized safety and intermediate biomarker evaluation at two doses; no placebo control group. Recruitment stopped 8/93 due to possible increase in prostate tumors. Published report: [73]

Table I. Clinical Trials of 4-HPR Sponsored/Funded by NCI, DCPC *(continued)*

Study No. Title (PI) Period of Performance IND No.	Cancer Target	Study Population No. of Subjects	Doses Study Duration	Endpoints	Remarks
Phase II (Dose titration, efficacy, intermediate biomarkers) *(continued)*					
NO1-CN-35577-01 *N*-4-(Hydroxyphenyl)retinamide (4-HPR) in Patients with Prostate Cancer in the Period Prior to Radical Prostatectomy (Presurgical Period): Modulation of Surrogate Endpoint Biomarkers (Dr. Ernest M. Marshall, Univ. of Alabama) 9/94– IND 39,812	Prostate	Patients with biopsy-proven prostate cancer scheduled for radical prostatectomy 100 patients (50/arm)	Oral 200 mg qd with 3-day holiday/month for up to 8 weeks 18 months	Intermediate biomarkers (*e.g.*, PIN grade, ploidy, PCNA, Ki-67, nuclear polymorphism)	Modulation of intermediate biomarkers
NO1-CN-25440-01 Phase IIa Phase II Clinical Trial of 4-Hydroxyphenylretinamide (4-HPR, Fenretinide) in Skin Actinic Keratosis (Dr. Barbara A. Conley, Univ. of Maryland Cancer Center) 9/92– IND 39,812	Skin	Actinic keratosis (>15) patients >45 years of age with Fitzpatrick skin type I or II 57 patients	Oral 200, 300, and 400 mg qd with 3-day drug holiday/month for 3 months	Efficacy: Regression of lesions (clinical, histological) Other intermediate biomarkers: PCNA, ODC, EGFR Drug effect measurements: Plasma retinol, 4-HPR Safety	Safety, dose titration, ADME, preliminary evaluation of intermediate biomarkers. Validation of 4-HPR and 4-MPR assays completed; standardizing retinol assay. Study will begin when drug and placebo received.

Table I. Clinical Trials of 4-HPR Sponsored/Funded by NCI, DCPC *(continued)*

Study No. Title (PI) Period of Performance IND No.	Cancer Target	Study Population No. of Subjects	Doses Study Duration	Endpoints	Remarks
Phase II (Dose titration, efficacy, intermediate biomarkers) *(continued)*					
NO1-CN-25440-01 Phase IIb Phase II Clinical Trial of 4-Hydroxyphenylretinamide (4-HPR, Fenretinide) in Skin Actinic Keratosis (Dr. Barbara A. Conley, Univ. of Maryland Cancer Center) 3/93–9/95 IND 39,812	Skin	Actinic keratosis (>15) patients >45 years of age with Fitzpatrick skin type I or II 26 patients	Oral (optimal dose from Phase IIa) for 6 months	Efficacy: Regression of lesions (clinical, histological) Other intermediate biomarkers: PCNA, ODC mRNA, EGFR mRNA, RAR; correlate with AUC Drug effect measurements: Plasma retinol, 4-HPR	Efficacy and evaluation of intermediate biomarkers at dose selected from IIa. Phase IIa will begin on receipt of the drug and placebo
Phase III (Efficacy, intermediate biomarkers)					
ECOG EB-193 Phase III Double-blind, Placebo-controlled, Prospective Randomized Comparison of Adjuvant Therapy with Tamoxifen *vs.* Tamoxifen and Fenretinide in Postmenopausal women with Involved Axillary Lymph Nodes and Positive Receptors (Dr. Melody A. Cobleigh, Rush-Presbyterian-St. Luke's Medical Center) 1994 IND 40,294	Breast	Women >65 years with surgically treated, node-positive, receptor-positive breast cancer 1,500 women	Oral 20 mg tamoxifen qd a.m., or 20 mg tamoxifen qd a.m. + 400 mg 4-HPR qd p.m. (3-day 4-HPR holiday/month) for 5 years	Efficacy: Survival, disease free survival Safety	Protocol under review

Table I. Clinical Trials of 4-HPR Sponsored/Funded by NCI, DCPC *(continued)*

Study No. Title (PI) Period of Performance IND No.	Cancer Target	Study Population No. of Subjects	Doses Study Duration	Endpoints	Remarks
Phase III (Efficacy, intermediate biomarkers) *(continued)*					
UO1-CA-38567 Breast Cancer Chemoprevention with Synthetic Retinoid HPR (Dr. Umberto Veronesi, Istituto Nazionale Tumori, Italy) 9/84–4/95 IND 24,019 (McNeil Pharmaceutical)	Breast	Previously resected unilateral Stage I/II breast cancer patients with limited lymph node involvement 3,500 patients	Oral 200 mg qd with 3-day holiday/month for 5 years	Efficacy: Incidence and latency of carcinoma in contralateral breast Safety: ERG, plasma RBP	Efficacy study in progress; accrual has ended at 2,972 women Published report: [74]