NCI, DCPC
Chemoprevention Branch and Agent Development Committee

CLINICAL DEVELOPMENT PLAN:

OLTIPRAZ

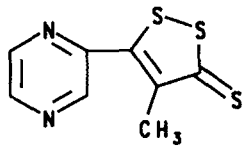
DRUG IDENTIFICATION

CAS Registry No.: 64224-21-1

CAS Name (9CI): 4-Methyl-5-pyrazinyl-3*H*-1,2-dithiol-3-thione

Synonyms: RP 35972

Structure:



EXECUTIVE SUMMARY

Oltipraz, a synthetic dithiolthione, is structurally related to naturally occurring dithiolthiones found in cruciferous vegetables; consumption of these vegetables has been associated with decreased risk for colon cancers [reviewed in 1]. This highly lipophilic drug was originally developed by Rhône Poulenc Santé to treat schistosomiasis. Studies on the mechanism of antischistosomal activity revealed that oltipraz decreases GSH stores in worms [2]. In contrast, the drug increases GSH levels in rodents in several target organs; it also enhances phase II metabolic enzyme expression in animals, particularly the GSH-*S*-transferases (GST) [reviewed in 3,4]. Oltipraz is now widely regarded as a prototypic phase II enzyme inducer for chemoprevention studies. Based on these activities, it was originally thought that the drug would only exhibit anti-initiating activity in animal cancer models; however, recent studies have found it to be active at both the initiation and post-initiation stages of carcinogenesis [5]. Because of its gastrointestinal (GI) accumulation, excretion of metabolites via the urine, and significant chemopreventive activity in hamster lung and rat mammary cancer models, the target tissues of greatest clinical interest are colon, bladder, lung, and breast.

Oltipraz is an effective chemopreventive agent in a wide variety of animal cancer models including lung, bladder, colon, liver, skin, and mammary gland. These studies are sufficient to support the development of the drug as a chemopreventive agent. Additional preclinical efficacy studies evaluating inhibition of prostate, colon and lung tumor formation and modulation of intermediate biomarkers of carcinogenesis in lung and pancreas are being conducted by the NCI.

Plasma pharmacokinetics of oltipraz appear to vary between species, sex, and individuals. In mice and humans, the dose is concentrated in the GI tract, bile, urine, liver and kidneys during the first 24 hours. Humans, monkeys, rats and mice appear to metabolize the drug extensively, and metabolites are excreted primarily in the urine. It is unknown if one of the metabolites is the active drug. One CB-sponsored Phase I trial has also suggested enterohepatic circulation, saturable GI absorption, and two metabolic phenotypes (extensive and limited metabolizers) in humans.

One-year preclinical toxicology studies in rats and dogs sponsored by the CB have been com-

pleted. Additional results made available by Rhône Poulenc Santé include 90-day studies in monkeys and Segment II reproductive toxicity in rats. The FDA may require carcinogenicity studies to be completed prior to initiating any clinical study in which oltipraz is administered chronically for more than one year. Segment I and III reproductive studies will be required prior to submission of an NDA.

Phase I clinical trials sponsored by the CB are summarized in Table I. Based on completed Phase I chronic dosing studies, the MTD appears to be approximately 125 mg qd; additional Phase I studies at lower doses are in progress. The major adverse effects—GI distress, fingertip pain and nail discoloration—are reversed when treatment is stopped. Long-term clinical development will depend on identification of a dosing regimen with acceptable toxicity.

Two Phase II trials of oltipraz began in 1994; one involves previous respiratory tract cancer patients, and the second involves subjects at high risk for aflatoxin B_1 (AFB_1)-associated liver cancer. Three Phase II trials are planned for 1995 in breast, bladder and lung cohorts.

The NCI has purchased bulk oltipraz from Rhône Poulenc Santé. The available supply is sufficient for studies in progress and the two Phase II clinical trials started in 1994. Rhône Poulenc holds all patents on oltipraz, and recently agreed to supply additional drug for the planned trials.

PRECLINICAL EFFICACY STUDIES

Oltipraz has demonstrated chemopreventive activity in many different animal models of carcinogenesis; these data are sufficient to support clinical development of the agent. In studies sponsored by the CB, the drug inhibited development of tumors induced by DEN (600 mg/kg diet, or *ca.* 0.3 mmol/kg-bw/day) and MNU (300 mg/kg diet, or *ca.* 0.2 mmol/kg-bw/day) in hamster lung, AOM in rat colon (100 mg/kg diet, or *ca.* 0.02 mmol/kg-bw/day), MAM acetate in mouse colon (960 mg/kg diet, or *ca.* 0.6 mmol/kg-bw/day), DMBA (250 mg/kg diet, or *ca.* 0.06 mmol/kg-bw/day) and MNU (100 mg/kg diet, or *ca.* 0.02 mmol/kg-bw/day) in rat mammary glands, DMBA in mouse skin (0.2% in diet, or *ca.* 1.2 mmol/kg-bw/day) [6], and OH-BBN in mouse bladder (125 and 250 mg/kg diet, or *ca.* 0.07 and 0.1 mmol/kg-bw/day). Further support for its chemopreventive activity comes from published studies of efficacy against tumors induced by B(*a*)P, DEN, or uracil mustard in mouse lung [7], B(*a*)P in mouse forestomach [7], and AOM in rat colon [8]. The best-documented chemopreventive activity is against AFB_1-induced malignant lesions in rat liver [4,9]. Oltipraz is currently being evaluated by the CB in additional animal carcinogenesis models in rat colon (PhIP) and prostate and A/J mouse lung (B(*a*)P).

The efficacy of combinations of oltipraz with several other agents is also under investigation by the CB. Oltipraz has shown synergistic chemopreventive activity with DFMO in mouse bladder [10], with β-carotene in hamster lung [11], with 4-HPR in both mouse bladder and hamster lung [10,11], and with carbenoxolone in rat mammary gland.

Assessment of the effects of oltipraz on the development of intermediate biomarkers of carcinogenesis in animal models may identify surrogate endpoints for cancer incidence to be used in future clinical trials. In tests sponsored by the CB, oltipraz inhibited the development of foci of aberrant crypts, putative biomarkers of colon carcinogenesis in AOM-treated rats. In independent studies, the agent was also effective against AFB_1-induced enzyme-altered foci (GGT- and GST-π-positive foci), putative premalignant lesions in rat liver [12,13]. CB-sponsored studies are in progress to examine oltipraz's effects on intermediate biomarkers in hamster and mouse lung and hamster pancreas, such as precancerous lesions and oncogene expression.

PRECLINICAL SAFETY STUDIES

Toxicity CB-sponsored one-year oral toxicity studies in rats and dogs have been completed. Results of oral studies in mice (acute), rats (acute, 90-day, segment II teratology), rabbits (acute, segment II teratology), hamsters (5-day), dogs (acute, 30-day), and monkeys (30-day, 90-day) have been provided by Rhône Poulenc Santé; results of genotoxicity studies have also been made available. Carcinogenicity and Segment I and III reproductive studies will be needed in order to complete the toxicity profile.

In one-year oral studies, the NOEL in rats was 10 mg/kg-bw/day (0.04 mmol/kg-bw/day); significant increases in relative liver weight which correlated with hepatic hypertrophy were observed at the two higher doses (30 and 60 mg/kg-bw/day, or 0.13 and 0.27 mmol/kg-bw/day). In dogs, the NOEL was 5 mg/kg-bw/day (0.02 mmol/kg-bw/day); significant weight loss occurred in the two high dose groups (15 and 60 mg/kg-bw/day, or

0.07 and 0.27 mmol/kg-bw/day) in females.

Both the CB and Rhône Poulenc Santé observed red/orange feces and urine as well as staining of body surfaces in the anogenital region of animals treated with oltipraz. This is presumably due to excretion of the red parent compound and/or its metabolites. Yellow discoloration of adipose tissues has also been noted.

Results of some of the preclinical toxicity studies conducted by Rhône Poulenc Santé have been summarized by Leroy *et al.* [14]. In a series of multidose studies, oltipraz was well-tolerated for one month at oral doses of 50 mg/kg-bw/day in dogs and 100 mg/kg-bw/day in monkeys based on the results of clinical, biochemical, hematological, and pathological examinations. A 90-day study in rats administered 150 mg/kg-bw/day showed a slight reduction of body weight gain with no mortality; 50 mg/kg-bw/day was reportedly well-tolerated. Reproductive and developmental toxicity studies in animals have also been conducted by Rhône Poulenc Santé; oltipraz reportedly had negative embryotoxic and teratogenic findings [15]. The experimental details of these studies and others [mice (acute), rats (acute, Segment II teratology), rabbits (acute, Segment II teratology), hamsters (5-day), dogs (acute, 30-day), and monkeys (30-day, 90-day)] have been provided to the CB by Rhône Poulenc Santé.

No adequate carcinogenicity studies have been reported in the literature. It should be noted, however, that oltipraz was reported to be nonmutagenic with or without metabolic activation in the Ames assay with *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100 [14]. The experimental details of this and other genotoxicity studies have been made available by Rhône Poulenc Santé.

ADME No ADME studies have been conducted by the CB. Studies conducted by Rhône Poulenc Santé in several animal species at high doses have appeared in the literature [16,17]. Species and sex differences are evident. After ig administration of single, high doses of 20 mg [^{14}C]-oltipraz/kg-bw (0.09 mmol/kg-bw) to monkeys, 50 mg/kg-bw (0.2 mmol/kg-bw) to rats, or 250 mg/kg-bw (1.1 mmol/kg-bw) to mice infected with *Schistosoma mansoni*, t_{max} was 3 hrs in monkeys and rats and 12 hrs in mice. The plasma $t_{½}$ was 3.5, 7, 2.5, and 4 hrs in male monkeys, female monkeys, rats, and infected mice, respectively. The C_{max} also varied greatly in monkeys, and similar to the $t_{½}$, appeared to be sex dependent; C_{max} was 3.5 and 6 μg/L for the two females and 34 and 123 μg/L for the two males. In rats and infected mice, C_{max} was 1.7 and 14.0 mg/L, respectively [17].

Oltipraz metabolism appears to proceed via rearrangement of the dithiolthione ring and sulfoxidation; 13 urinary and plasma metabolites were identified among these three species [16,17]. As anticipated for this highly lipophilic compound, the parent moiety was the principal fecal metabolite, although it accounted for <1% of the original oltipraz dose. During the first 24 hours, radioactivity from oltipraz was concentrated in the GI tract, bile, urine, liver, and kidneys of infected mice. Similar results have been obtained in human studies [18]. The metabolite pattern in the monkey most closely resembles that in humans. Major metabolites are being synthesized for use as analytical standards in clinical ADME studies.

CLINICAL SAFETY: PHASE I STUDIES

Four Phase I studies have been sponsored by the CB (see Table I), and two of these studies have been completed. In one completed study (Dr. N. Dimitrov, Michigan State University), normal subjects were treated orally with single (1, 2, or 3 mg/kg-bw) or multiple (1–3 mg/kg-bw qd for 10 days) doses of oltipraz. The use of a loading dose to achieve steady-state levels at these low doses was also examined. In the second study (Dr. A.B. Benson, Northwestern University Cancer Center), patients with previously resected adenomatous colon polyps or first-degree relatives of breast cancer patients were treated with single oral doses (125, 250, 375, and 500 mg) or chronic doses (125 and 250 mg qd for six months).

Two Phase I studies are currently in progress. One study (Dr. A.B. Benson) is examining toxicity and pharmacokinetics of lower, single oral doses of 20, 50, 100, or 125 mg in normal subjects. Chronic administration of the same doses (qd for six months; dose escalation study) in patients at increased risk for colorectal or breast cancer is also being investigated. The second study (Dr. P. O'Dwyer, Fox Chase Cancer Center) is examining toxicity and pharmacokinetics after administration of single oral doses (125, 250, 500 and 1,000 mg/m^2) in patients at increased risk for colorectal cancer; a multidose step is being designed. These single dose studies are being carried out in anticipation of future intermittent dosing studies.

Drug Effect Measurement No drug effect measurements related to oltipraz were examined in either of the two completed Phase I studies. Both of the ongoing Phase I studies are measuring GSH

levels and GST activity in lymphocytes and colorectal biopsies as drug effects; one study is also assessing NAD(P)H:quinone reductase and γ-glutamylcysteine synthetase (γGCS) mRNA in the same tissues. Preliminary results (Dr. P. O'Dwyer) suggest that single oltipraz doses of 250–1,000 mg/m^2 (0.03–0.1 mmol/kg-bw) did not affect GSH levels or GST activity in lymphocytes; rectal GST increased only after the 250 mg/m^2 dose [19]. Lymphocyte NAD(P)H:quinone reductase and γGCS induction peaked 2–4 days after oltipraz administration (means of 4.5- and 7-fold, respectively), but the responses were unrelated to dose. Further evaluation of these measurements at lower doses is underway.

Safety GI symptoms are the most common side effects observed after treatment with oltipraz; however, the dose-limiting toxicity is acute fingertip pain and fingernail discoloration. In a CB-sponsored study (Dr. N. Dimitrov), oral doses of up to 2 mg/kg-bw qd (0.009 mmol/kg-bw) administered for 5, 10, or 28 days were generally well-tolerated by small groups of normal subjects (n=3/dose) [18]. Flatulence was reported by 2/3 patients treated with 2 mg/kg-bw qd for 10 days. Numbness and pain in the fingers followed by dark blue stripes on the nails were observed in one subject after 7 days of treatment with 1.5 mg/kg-bw qd (0.007 mmol/kg-bw). These changes were reversed 10 days after withdrawal of the drug.

In the other completed clinical study (Dr. A.B. Benson), the most commonly reported side effects after doses of 125 or 250 mg qd (*ca.* 0.008 or 0.03 mmol/kg-bw) for six months were GI in nature and included nausea, diarrhea, flatulence, bloating, and stomach pain. Cases of paresthesia, photosensitivity, and lines on thumbnails were also observed. The lowest dose tested, 125 mg qd, was suggested as the MTD on chronic administration. This investigator is currently examining the safety of lower doses of the drug (<0.008 mmol/kg-bw).

At higher doses, GI disturbances were also the major side effects. In preliminary results from a CB-sponsored Phase I trial (Dr. P. O'Dwyer) of single doses of 250, 500 and 1,000 mg/m^2 (*ca.* 0.03, 0.05 and 0.1 mmol/kg-bw), one patient reported nausea at each of the two highest doses and one patient had low grade diarrhea at the second highest dose. During clinical trials of even higher single doses of oltipraz as an antischistosomal (generally 10–35 mg/kg-bw, or 0.04–0.15 mmol/kg-bw) [15,20–25], GI disturbances were reported. Central nervous system effects such as headache, paresthesia and malaise were also observed. Acute finger pain, apparently associated with exposure to sunlight and sometimes resulting in photo-onycholysis (loosening of the fingernails), allegedly prompted the manufacturer to remove the drug from further clinical trials for this indication [26].

ADME In a CB-sponsored study (Dr. N. Dimitrov), normal volunteers were administered single, relatively low doses of 1, 2, or 3 mg/kg-bw (0.004, 0.009 or 0.013 mmol/kg-bw) [18]. Peak serum concentrations (C_{max}=16, 61 and 205 ng/ml at 1, 2 and 3 mg/kg-bw, respectively) were achieved in 2.5–4 hrs; the serum $t_{½}$ was short, about 4–5 hrs. Steady-state concentrations could not be achieved after 10 daily doses of 1, 2, or 3 mg/kg-bw. Loading doses of 1.5 and 2 mg/kg-bw bid on the first day, followed by maintenance doses of 1.5 and 2 mg/kg-bw qd, respectively, for 9 or 27 days, were reported to result in steady-state serum levels; however, a similar dosing schedule with 1 mg/kg-bw did not achieve steady-state.

Significant interindividual variations in blood levels were observed in both completed Phase I studies (Drs. Dimitrov and Benson) and one Phase I trial in progress. In the second completed trial (Dr. A.B. Benson), peak plasma levels were 348 and 1,049 ng/ml after single doses of 125 and 250 mg (*ca.* 0.008 and 0.016 mmol/kg-bw) [27]. Preliminary results from the trial in progress (Dr. P. O' Dwyer) show that C_{max} ranged from 71–1,150 ng/ml at doses of *ca.* 0.03–0.1 mmol/kg-bw, with harmonic mean $t_{½}$=7.6 hrs [19]. Multiple plasma oltipraz peaks were observed in some patients, possibly resulting from enterohepatic circulation. Also, plasma AUC did not increase linearly with dose, suggesting saturable absorption. Based on these results, a dose of 125 mg (*ca.* 0.008 mmol/kg-bw) was added to the protocol, and subjects are being accrued.

Oltipraz metabolism was also investigated in the latter trial (Dr. P.O' Dwyer). Preliminary results show extensive metabolism, with significant formation of a desulfurated metabolite (M3) [19]. AUC ratios of M3/oltipraz were variable: 0.43, 1.01 and 0.73 for doses of 250, 500 and 1,000 mg/m^2 (*ca.* 0.03, 0.05 and 0.1 mmol/kg-bw), respectively. The data suggest that two phenotypes of oltipraz metabolizers have been identified.

In studies by Rhône Poulenc Santé, less than 1% of the administered dose was eliminated in urine as unchanged parent compound in schistosomiasis patients treated with single oral doses of 0.50, 0.75, or 1 g. In feces, the parent compound was the principal compound identified. As in animals, the principal routes of oltipraz metabolism were identified

as rearrangement of the dithiolthione ring and sulfoxidation.

As a lipophilic and highly water-insoluble drug, the absorption of oltipraz would be expected to increase significantly when it is co-administered with a fatty meal. However, findings on this point are inconsistent. In one study, the absorption of a 25 mg/kg-bw (0.1 mmol/kg-bw) dose of oltipraz administered with a low- or high-fat meal was significantly higher than when it was administered after a 12-hour fast [28]. In a second crossover study, plasma oltipraz was elevated in all (n=3) subjects six hours after administration of the first 2 mg/kg-bw (0.009 mmol/kg-bw) dose with a high-fat meal when compared with a low-fat meal [18]. However, the difference in plasma levels was not sustained over three subsequent days of oltipraz intake concurrent with a high-fat diet.

CLINICAL EFFICACY: PHASE II STUDIES

Two CB-funded Phase II trials started in 1994; evaluation and modulation of intermediate biomarkers are major aspects of these trials. As shown in Table I, one trial (Dr. P.E. Engstrom, Fox Chase Cancer Center) involves patients with previously resected lung or respiratory tract cancers. The cohort for the other trial (Dr. T.W. Kensler, Johns Hopkins University School of Hygiene and Public Health) involves individuals in Qidong, China at high risk for liver cancer from AFB_1 exposure.

Three Phase II trials are planned for 1995. The cohorts include biopsy-diagnosed breast cancer patients in the period prior to definitive surgery, bladder cancer patients treated by surgery and BCG, and patients with a surgically resected lung cancer. Any additional Phase II trials proposed will be evaluated critically for relevance, priority and need.

PHARMACODYNAMICS

In preclinical studies, oltipraz inhibited carcinogenesis in rat colon, bladder and mammary glands at doses of 0.02–0.06 mmol/kg-bw/day, which is within the range of the one-year rat NOEL—0.04 mmol/kg-bw/day. The effective rat doses produced steady state serum concentrations of 300–600 ng/ml [8]. In comparison, a single dose of 125 mg (*ca.* 0.008 mmol/kg-bw), produced a peak plasma level of 350 ng/ml in a Phase I trial (Dr. A.B. Benson) [27]. This dose is reported to be the human MTD on chronic (six month) administration. The rat data suggest that human chemopreventive efficacy without significant adverse reactions is attainable at doses below the MTD. A Phase I trial in progress is evaluating the toxicity of doses of 20, 50, and 100 mg qd (*ca.* 0.001, 0.003, and 0.006 mmol/kg-bw qd); thus far, toxicity has not been seen at doses as high as 60 mg qd (*ca.* 0.004 mmol/kg-bw qd). It is possible that the efficacy of lower doses will be evaluated in future Phase II trials.

PROPOSED STRATEGY FOR CLINICAL DEVELOPMENT

Drug Effect Measurement Issues

Major effects of oltipraz in animals include elevated GSH levels and GST activity [reviewed in 29]; increases in these parameters in urine, peripheral blood, or tissue may serve as appropriate drug effect measurements for clinical trials. Both of the ongoing Phase I studies are measuring GSH levels and GST activity in lymphocytes and colorectal biopsies as drug effects; one study is also assessing NAD(P)H:quinone reductase and γGCS mRNA in the same tissues. Preliminary results suggest that single oltipraz doses did not consistently affect GSH levels in lymphocytes or GST activity in lymphocytes and rectal mucosa. Lymphocyte γGCS mRNAs and NAD(P)H:quinone reductase were induced, but the responses were unrelated to dose. Further evaluation of these measurements after chronic administration and at lower doses is underway.

The special characteristics of the proposed measurements should be considered. For example, the GSTs are a family of enzymes. In humans, three major classes are present in the cytosol: α, μ, and π [29]. Activity measurements, most commonly using 1-chloro-2,4-dinitrobenzene, do not allow characterization of individual isozymes. This characterization may be necessary to establish accurate drug effect measurements. In humans, the distribution of isozymes varies and is dependent on several factors, including tissue and cell type [30]. Measurements in white blood cells or other easily accessible body fluids/tissues may not accurately reflect specific changes in target tissues. However, recent preliminary results suggest that total blood lymphocyte GST activity (measured with 1-chloro-2,4-dinitrobenzene) correlated with colorectal mucosal activity (coefficent=0.82) [31].

Safety Issues

In its initial review of the original CB oltipraz chemoprevention IND 33,148, the FDA cited phototoxicity as a major concern and called for adequate monitoring of subjects. Phototoxicity in schistosomiasis studies was associated with finger pain, discoloration of finger nails, and paresthesia of the extremities. By one account, the incidence of these effects was reported to be as high as 30% of treated patients. Similar adverse events have occurred in chemoprevention chronic dosing studies, along with photosensitivity and increased susceptibility to sunburn. The majority of adverse effects have been GI upsets.

Modification of dosing schedules or the dosage form itself may be effective in reducing adverse effects. For example, in animals, short-term exposure to oltipraz results in sustained increases in GST activity [32]. Therefore, continual exposure to the drug may not be necessary for chemopreventive activity. Intermittent dosing may decrease toxicity. Further, it appears to be feasible to substantially improve the bioavailability of the dosage form so that greater and more reliable absorption will occur with less drug. This would also decrease toxicity.

Pharmacodynamics Issues

Because of the drug's high lipophilicity, studies assessing the effects of both dietary and body fat on oltipraz pharmacokinetics should be conducted.

High interindividual variations in blood levels of oltipraz were observed in both completed Phase I studies. Oltipraz is unstable to light and highly lipophilic; this could affect the results of ADME studies. Rigorous standard methodologies for measuring oltipraz in body fluids and tissues should be developed to insure that lipid does not interfere with measurements of oltipraz levels and that storage techniques do not lead to decomposition of the samples. Oltipraz is metabolized to a great extent, thus standard methodologies for detecting oltipraz metabolites must be developed and specific metabolites to be measured in clinical studies must also be determined.

Oltipraz is extensively metabolized in the four species studied. It is unknown if one of the metabolites is the active drug. In order to define effective dosing regimens with miminal toxicity, the active entity and its tissue and plasma pharmacokinetics should be identified.

Regulatory Issues

Carcinogenicity and Segment I and III reproductive studies will need to be completed for Phase II trials of ≥1 year duration.

Supply and Formulation Issues

The bulk oltipraz used in clinical studies was provided by and/or purchased from Rhône Poulenc. Supplies are adequate for studies in progress and for future high priority Phase II studies. NCI has recently reached an agreement with Rhône Poulenc for the purchase of additional oltipraz.

The lipophilicity and aqueous insolubility of oltipraz suggests development of a soft gelatin capsule formulation of oltipraz dissolved or suspended in an oil capsule fill. Such a formulation could substantially reduce the amount of oltipraz needed to provide equivalent absorption, and reduce erratic absorption and adverse GI effects. Such developmental work would require comparison of the old and new dosage forms in dogs, followed by human bioequivalence studies.

Intermediate Biomarker Issues

Successful development of oltipraz as a chemopreventive agent will depend on the identification and validation of intermediate biomarkers that can serve as surrogate endpoints for cancer in clinical studies. Modulation of these endpoints by oltipraz will suggest that the drug has the potential to decrease the risk of cancer in the target organs. Such endpoints may be biochemical, genetic, or histologic in nature and must be validated for the individual target tissues of interest. In rat efficacy studies, oltipraz inhibited development of a histological biomarker of colon carcinogenesis. Ongoing studies are evaluating other types of biomarkers.

Clinical Studies Issues

Oltipraz is thought to be a pure phase II enzyme inducer; however, assays in humans evaluating the effects on phase I enzyme induction should be undertaken (*e.g.*, alterations in steroid metabolism/metabolites).

No further Phase I studies of oltipraz are anticipated at this time. A report summarizing the raw data from the two completed Phase I trials will be prepared for FDA review. The chronic MTD of 125 mg qd (0.008 mmol/kg-bw) determined in one

of the completed Phase I studies is sufficient information to start Phase II trials. Ongoing Phase I studies are evaluating selected drug effect measurements that may be used in subsequent clinical studies. Development of more specific drug effect measurements may be needed. Subsequent Phase II studies will contribute to optimal dosing regimens for chemoprevention studies by evaluating the dose-response of drug effect measurements and/or potential surrogate endpoints.

The efficacy of oltipraz in preclinical models of lung, liver, bladder, colon, and breast carcinogenesis provides evidence that these are likely target organs for Phase II clinical chemoprevention trials. In addition, autoradiographic studies in mice demonstrated that the drug was present in most of these tissues 24 hrs after administration [reviewed in 33]. Finally, GSH levels and GST activities were also enhanced in the same organs. For these reasons, the CB began one Phase II trial in a lung cohort and one in a liver cohort in 1994. Three additional Phase II trials in breast, bladder and lung cohorts are planned for 1995. For example, modulation of intermediate biomarkers will be evaluated in breast and prostate cancer patients receiving oltipraz in the period between diagnostic biopsy and definitive surgery. Also, chemoprevention of premalignant and malignant changes will be investigated in patients with previously resected lung and bladder cancers.

Future clinical trials may evaluate the safety and efficacy of combinations of agents with oltipraz. In preclinical carcinogenesis models, synergistic responses were obtained with DFMO in bladder, with β-carotene in lung, with 4-HPR in both tissues, and with carbenoxolone in mammary glands. Lower doses of each agent may retain efficacy while decreasing potential adverse effects.

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Table I. Clinical Trials of Oltipraz 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 I (Safety, ADME)					
NO1-CN-85104-01 Phase I Study of Oltipraz (Dr. Nikolay Dimitrov, Michigan State University) 4/89–10/92 IND 33,148	----	Normal subjects; male, female (postmenopausal) 27 subjects (3/dose)	Oral 1, 2, 3 mg/kg-bw qd for 1, 5 and 10 days, with a prescribed diet Loading dose: Oral 1.5 and 2 mg/kg-bw bid on first day, followed by a maintenance dose of 1.5 and 2 mg/kg-bw qd, respectively, for 10 days Chronic dose: 1.5 and 2 mg/kg-bw bid on first day, followed by 1.5 and 2 mg/kg-bw qd, respectively, for 28 days Dietary fat effect (crossover design): 2 mg/kg-bw qd for 4 days concurrent with a low-fat (20%) or high-fat (53%) diet	Safety; single and multi-dose pharmacokinetics; dietary fat effect on bioavailability	Study complete Safety: Fingertip pain, numbness and black fingertips in 1 subject receiving dose of 1.5 mg/kg-bw qd for 7 days Pharmacokinetics: After a single dose, $t_{1/2}$=4.1–5.3 hrs, and t_{max}=2.5–4 hrs; C_{max}=16, 61, and 205 ng/ml at 1, 2, and 3 mg/kg-bw, respectively. AUC also dose-dependent, with rapid elimination (k_e=0.122–0.136 hrs). After 10 daily doses, steady-state plasma levels were not achieved. Using either loading dose regimen, steady-state plasma levels were achieved by day 2. With chronic dosing, no serum oltipraz detected 2 days after the final dose. A high-fat diet increased serum oltipraz levels at 6 hr, but not subsequently Published report: [18]

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

Study No. Title (PI) Period of Performance IND No.	Cancer Target	Study Population No. of Subjects	Dose(s) Study Duration	Endpoints	Remarks
Phase I (Safety, ADME) ***(continued)***					
NO1-CN-85103-01 Phase I Study of 4-Methyl-5-(2-Pyrazinyl)-1,2-Dithiol-3-Thione (Oltipraz; RP 35972) in Male Patients with Previously Resected Colon Polyps and First Degree Relatives of Breast Cancer Patients (Dr. Al B. Benson, Northwestern University Cancer Center) 7/90–10/92 IND 33,148	----	Male patients with previously resected adenomatous colon polyps; first-degree relatives of breast cancer patients 24 men, 16 women	Single dose: Oral 125, 250, 375 and 500 mg (*ca.* 1.8, 3.6, 5.4, 7.1 mg/kg-bw) Multidose: Oral 125 and 250 mg qd (*ca.* 1.8 and 3.6 mg/kg-bw) for 6 months	Safety; single and multiple dose plasma pharmacokinetics	Study complete Chronic MTD: 125 mg qd (*ca.* 1.8 mg/kg-bw) for 6 months. Dose-limiting toxicities include photosensitivity, paresthesia, gastrointestinal disturbances Published report: [34]

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

Study No. Title (PI) Period of Performance IND No.	Cancer Target	Study Population No. of Subjects	Dose(s) Study Duration	Endpoints	Remarks
Phase I (Safety, ADME) *(continued)*					
NO1-CN-15345-01 A Phase I/Pharmacokinetic/Biochemical Trial of the Chemopreventive Agent 4-Methyl-5-(2-Pyrazinyl)-1,2-Dithiol-3-Thione (Oltipraz; RP 35972) (Dr. Peter O'Dwyer, Fox Chase Cancer Center) 9/92–12/94 IND 33,148	----	Subjects at increased risk for colorectal cancer, male and female 5–6 subjects/dose	Single dose: Oral 125–1,000 mg/m^2 qd Multidose: To be determined	Safety; single and multidose pharmacokinetics; metabolic profile; drug effect measurements (GSH levels, GST activity, NAD(P)H:quinone reductase, and γGCS in lymphocytes and colon biopsies)	Study in progress Fourteen patients have completed single doses of 250–1,000 mg/m^2. Preliminary plasma data show AUC did not increase linearly with dose, so subjects are being accrued to a new 125 mg/m^2 dose level. Two phenotypes of oltipraz metabolism identified. Lymphocyte γGCS and NAD(P)H: quinone reductase mRNA induction peaked at 2–4 days, but values were unrelated to dose. No major adverse effects noted; a low incidence of diarrhea and nausea at 500 and 1,000 mg/m^2 Published report: [19]

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

Study No. Title (PI) Period of Performance IND No.	Cancer Target	Study Population No. of Subjects	Dose(s) Study Duration	Endpoints	Remarks
Phase I (Safety, ADME) *(continued)*					
NO1-CN-25527-01 Phase I Study of 4-Methyl-5-(2-Pyrazinyl)-1,2-Dithiol-3-Thione (Oltipraz; RP 35972) in Male Patients with Previously Resected Colon Polyps and First Degree Relatives of Breast Cancer Patients (Dr. A. B. Benson, Northwestern University Cancer Center) 9/92– IND 33,148	----	Normal subjects 16 subjects Male patients with previously resected colon polyps and first degree relatives of breast cancer patients 25 subjects	Single dose: Oral 20, 50, 100 and 125 mg (*ca.* 0.3, 0.7, 1.4, 1.8 mg/kg-bw) Multidose: Oral 20, 50, 100 and 125 mg qd (0.3, 0.7, 1.4, 1.8 mg/kg-bw) for 6 months	Safety; single and multidose pharmacokinetics; metabolic profile; drug effect measurements [GSH levels and GST activity in lymphocytes and rectal biopsies (colon patients only)].	Study in progress Participants are being accrued for the first (2 normal subjects) and second (13 high-risk) parts of the study Published report: [27]
Phase II (Dose-titration, efficacy, intermediate biomarkers)					
Planned Study Phase IIa/IIb Chemoprevention Trials of Oltipraz in Patients Previously Treated with BCG for Superficial Bladder Cancer 1995 IND 33,148	Bladder	Patients with resected superficial bladder cancer treated with BCG	Oral (doses to be determined) 1 month (Phase IIa)/1 year (Phase IIb)	Efficacy: Tumor recurrence, histopathology Intermediate biomarkers (to be determined)	Efficacy, dose-titration and evaluation of intermediate biomarkers as surrogate endpoints; emphasis on quantitative evaluation of biomarkers by computer-assisted cytomorphometry and cytophotometry

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

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) ***(continued)***					
Planned Study Phase II Oltipraz in Breast Neoplasia: Administration During the Period Between Diagnostic Core Biopsy and Definitive Surgery 1995 IND 33,148	Breast	Patients scheduled for biopsy/surgery (dose and marker evaluation)	--- 1 wk–2 months	---	Study not yet designed
NO1-CN-25437-01 Phase II Clinical Trial of Oltipraz in Individuals at High Risk for Liver Cancer. Modulation of Aflatoxin Biomarkers (Dr. Thomas W. Kensler, Johns Hopkins Univ. School of Hygiene and Public Health) 9/94– IND 33,148	Liver	Subjects exposed to AFB_1 (Qidong Region, China)	Oral 125 mg qd for 2 months Oral 250 and 500 mg, 1x/week for 2 months	Intermediate biomarkers (risk): Urinary aflatoxin-DNA adducts, serum aflatoxin-albumin adducts	Evaluation of intermediate biomarkers and drug effect measurements. Emphasis on biologically effective dose in reducing molecular damage
NO1-CN-25436-01 Oltipraz in Chronic Smokers. Modulation of Surrogate Endpoint Biomarkers (SEB) of the Bronchial Epithelium (Dr. Paul F. Engstrom, Fox Chase Cancer Center) 9/94– IND 33,148	Lung	Chronic smokers and patients after resection of carcinoma of the respiratory tract	Oral 125 mg qd for 6 months	Intermediate biomarkers: Proliferative index, ploidy, nuclear polymorphism index	Efficacy and evaluation of intermediate biomarkers as surrogate endpoints; emphasis on quantitative evaluation of biomarkers by computer-assisted cytomorphometry and cytophotometry

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

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) *(continued)*					
Planned Study Chemoprevention of Second Primary Aerodigestive Cancer in Prior Resected Patients (Oltipraz or 4-HPR) 1995	Lung	Patients with previously resected Stage 1 lung cancer 100 patients	--- 4 years	Efficacy: Histological regression Other intermediate biomarkers: Micronucleated cell frequency, ploidy, p53 mutation, PCNA, EGFR, mutagen sensitivity	---
Planned Study Phase II Chemoprevention Studies of Oltipraz in Patients with Prostate Cancer in the Period Prior to Radical Prostatectomy (Presurgical Period): Modulation of Surrogate Endpoint Biomarkers 1995 IND 33,148	Prostate	Biopsy-diagnosed prostate cancer patients scheduled for prostatectomy	Oral 125 mg qd between diagnostic biopsy and definitive surgery (2–4 wk)	Efficacy: Regression of PIN and other histological biomarkers Other intermediate biomarkers (to be determined)	Evaluation of intermediate biomarkers with emphasis on those that can be measured quantitatively by computer-assisted cytomorphometry and cytophotometry

OLTIPRAZ DEVELOPMENT STATUS