mg/kg (480 mg/m^2), or 160 mg/kg (960 mg/m^2) show no evidence of a clastogenic or aneugenic effect.

5. Epithelial Irritation Studies:

A. Five Day Intravenous Irritation Study in Rabbits (Test No. 946105):

CGS 20267 was administered intravenously at a daily dose of 0.5 mg/animal daily for five days into the right ear of male rabbits and on day 5 only in the left ear. Control animals received 1 ml placebo on the same dosing schedule. On microscopic examination minimal to slight subacute inflammation with minimal hemorrhage around the site of the venous puncture in all animals including controls whose right ear was injected daily for five days. At the injection site in the left ear (one time injection) none to slight edema was noted in the perivascular area. The conclusion of these studies is that CGS 20267 is not an irritant.

B. Acute Eye Irritation / Corrosion Study in the Rabbit (Test No. 946922):

CGS 20267 at a dose of 32 mg/animal (0.01 ml volume) was placed into the left conjunctival sac of each animal and the eye observed for irritation. Signs of ocular irritation were observed at 73 hours in the iris and the conjunctiva, but by seven days no evidence of ocular irritation was observed.

C. Acute Dermal Irritation / Corrosion Study in the Rabbit (Test No. 946923)

CGS 20267 was applied at a dose of 0.5 g / animal to the shaved skin of the study animals. Animals were observed at 1, 24, 48, and 72 hours and scored using the OECD scoring system. No skin irritation was observed.

6. Radiolabeled Distribution Studies:

A. Absorption and Disposition of [^{14}C]CGS 20267 in Male Mice:

One mg of [^{14}C]CGS 20267 was administered intravenous or orally to male mice and the tissue distribution examined at five minutes after the intravenous dose and six hours after the oral dose. With either route of administration at the time of sacrifice the highest concentrations of radiolabel were in the liver and the adrenals. With IV administrations the concentrations were 5-10 times higher than the blood. With the oral dose concentrations of total radioactivity was 5 -17 times higher than in the blood. Renal excretion accounted for 82% of the intravenous dose and 79% of the oral dose with > 90% of the excretion occurring within the first 72 hours. Major metabolites included unchanged parent compound and the O-glucuronide of CGP 44645 in a 4:1 ratio. Free CGD 44645 represented less than 5% of the dose.

B. Absorption and Distribution of [^{14}C]CGS 20267 in Rats and Dogs:

After oral administration [^{14}C]CGS 20267 was totally absorbed in the rat and 80 -90% absorbed in the dog. In the rat the plasma concentration - time profile was characterized by a broad plateau with a terminal half-life of 7 - 9 hours. In the dog the terminal half-life was 60-90 hours. Rat adrenals and livers had the highest concentration of radioactivity. Daily doses of 30 mg/kg (640 mg/m^2) for thirty days increased the plasma and tissue concentration by 3 - 8 fold with the decline in concentration after cessation of dosing similar to that for a single dose. By ninety-six hours 97% of a single dose was excreted with excretion equally distributed between the urine and the feces. In the dog excretion was not complete by day 7.

C. Absorption and Disposition of [^{14}C]CGS 20267 in Female Rats:

With an oral dose of 1 mg/kg the absorption was at least 95%. With intravenous injection a relatively constant concentration of radioactivity was present from 5 minutes to 8 hours, while with the oral dose the relatively constant concentration was maintained for 4 -24 hours. After 24 hours the levels of radioactivity declined exponentially with a half life of 40 - 50 hours. Distribution of the radiolabel was similar after intravenous and oral administration. Concentration of radiolabel in the adrenals was thirteen times greater that the blood, four times greater in blood, and three times greater in other tissues. About equal excretion of radiolabel occurred in the urine and feces with either route of administration. Excretion was slow with 90% of the dose excreted over seven days after dosing. With biliary duct cannulation 10-20% of the dose was excreted in the bile, 34 - 40% in urine, and 4 -16% in the feces in the first 96 hours.

D. CGS 20267: Long Term Elimination of [^{14}C]CGS 20267 in Female Rats

After the first dose the concentration of ^{14}C labeled drug was two -six fold higher in tissues that in the blood. In the stomach, skin, and eye levels of radioactivity at two weeks were two - five times higher than in all other organs. Levels in other organs were less than 1% of the twenty-four values. Radioactivity declined slowly in all organs and tissues. Excretion of radioactivity was slow and by day 7, 79 - 87% of the dose was recovered in the excreta with about equal amount in the urine and feces.

7. Pharmacokinetic Information in Animals:

A. CSG 20267: Plasma Kinetics of Unchanged CGS 20267 in Rats Following Intravenous and Oral Administration of a Single 1 mg/kg Dose:

CGS 20267 was rapidly absorbed after oral or intravenous administration with an estimated bioavailability of 100% in a study in male rats.

B. CGS 20267: Disposition of CGS 20267 and its Metabolite, CGP 44645, in Rats and Dogs after I.V. or Oral Administration of [^{14}C]CGS 20267.

In the dogs after a dose of 0.1 mg/kg (2.0 mg/m^2) intravenously and orally the concentration of

[^{14}C]CGS 20267 was the same as the total radioactivity indicating that the systemic exposure to metabolites was low. In the rat urine (from rats treated with 0.1 and 1.0 mg/kg i.v. and p.o. single dose) and dog urine the sum of CGS 20267 and CGP 44645 as determined by a cold HPLC method was equal to the amount of radioactivity in the urine for each species.

C. Plasma Concentrations in Male and Female Mice on Week 2 and 10 following CGS 20267 Oral Administration via Gavage of Daily Doses of 0.6 (1.8), 6 (18), or 60 (180) mg/kg Body Weight (mg/m^2) in a Thirteen Week Toxicity Study:

The pharmacokinetic profiles for CGS 20267 were similar for both male and female mice at weeks 2 and 10. AUC and C_{max} increased proportionally with increasing dose.

D. CGS 20267: Letrozole Plasma Concentration in Male and Female Mice on Weeks 26, 54, and 78 following Letrozole Oral Administration by Gavage of Daily Doses of 0.6 (1.8), 6 (18), and 60 (180) mg/kg Body Weight (mg/m^2) in a 104 Week Oral Carcinogenicity Study

On weeks 26, 54, and 78 a dose proportional increase in plasma concentration of similar magnitude was observed for both sexes. No accumulation of CGS 20267 in mice was observed on repeat dosing for 78 weeks. Exposure increased with increasing dose (overproportional AUC).

E. Letrozole Plasma Concentration in Male and Female Rats on Days 1 and 14 Following Letrozole Intravenous Administration of Daily Doses of 0.03 (0.18), 0.3 (1.8), and 3 (18) mg/kg Body Weight (mg/m^2) in a 14-Day Toxicity Study

Plasma levels of CGS 20267 were determined on days 1 and 14. CGS C_{max} and AUC were approximately proportional to the dose. Exposure was higher in female than males, with the day 14 drug accumulation higher in females.

F. Plasma Concentration of Unchanged CGS 20267 in Rats Following Oral Administration of a Single 0.3 (1.8), 3 (18), and 30 (180) mg/kg (mg/m^2) Doses. Investigation on the Presence of the Potential Hydroxy Metabolite, CG 44645 in Plasma

CGS was rapidly absorbed after oral administration with the plasma AUC of the parent drug proportional to dose. Low concentrations of CGP 44645 were detected in the plasma after the 30 mg/kg (180 mg/m^2) dose.

G. Plasma Concentration of Unchanged CGS 20267 in Rats Following Oral Administration of a Single and Repeated Doses of 0.3 (1.8), 3 (18), and 30 (180) mg/kg (mg/m^2) Once Daily for Thirty Days

After the 0.3 (1.8) and the 3.0 (18) mg/kg (mg/m^2) dose CGS 20267 accumulated slightly more (2-4 times more) than predicted from the single dose study. No modification of kinetics were

observed after the 30 mg/kg (180 mg/m^2) dose.

H. Letrozole Plasma Concentrations in Female Rabbits on Gestation Day 17 following Letrozole Oral Daily Doses of 0.06 (0.66), 0.6 (6.6), and 6 (66) mg/kg Body Weight (mg/m^2) on Days 7 - 19 of Gestation to Evaluate Effects of Embryo and Fetal Development in a Dose-Range Finding Study

Plasma C_{max} and AUC (0 - 24 h) of CGS 20267 were dose proportional for the 0.06 and 0.6 mg/kg doses. C_{max} and AUC (0 - 24 h) parameters for the 6 mg/kg dose were greater than for the two lower doses; plasma clearance was reduced at the higher dose.

I. Letrozole Plasma Concentrations in Male and Female Dogs on Days 1 and 14 following Letrozole Intravenous Administration of Daily Doses of 0.02 (0.4), 0.2 (4.0), and 2 (40) mg/kg Body Weight (mg/m^2) in a Fourteen Day Toxicity Study

Interanimal variability in the kinetics of letrozole was low. C_{max} and AUC (0 - 24 h) was proportional to the dose. No major difference were observed in either gender. Accumulation was apparent after 14 days of administration.

K. Plasma Concentration in Male and Female Dogs on Days 1, 182, and 364 Following CGS 20267 Administration of Single and Repeat Once Daily Doses of 0.03 (0.6), 0.3 (6.0), and 3 (60) mg/kg (mg/m^2) in a Six / Twelve Month Toxicity Study

On day 1 C_{max} and AUC (0 - 24 h) were proportional to the dose in males and females. On days 182 and 364 concentrations (C_{max}) at all dose levels were similar with trough concentrations proportional to the dose. In comparison to day 1, the AUC (0 - 24 h) on days 182 and 364 were higher for males and females.

L. Letrozole Plasma Concentrations in Male and Female Rats on Weeks 14, 53, and 78 Following Letrozole Oral Administration via Gavage of Daily Doses of 0.1 mg (0.6), 1.0 mg (6.0), and 10 (60) mg/kg (mg/m^2) Body Weight in a One Hundred Four Week Carcinogenicity Study

Systemic exposure to CGS 20267 increased with increasing dose and was higher in female than in male rats. Dose proportionality was seen at the 0.1 and 1.0 mg/kg/day dose, while at the 10 mg/kg/day dose the AUC was under proportional.

M. Plasma Concentrations in Male and Female Rats on Days 1. 207, and 365 Following CGS 20267 Administration of Single and Repeated Once Daily Doses of 0.3 (1.8), 3.0 (18), and 30 (180) mg/kg (mg/m^2) in a Six / Twelve Month Toxicity Study

On day 1 plasma concentrations were higher in female than male rats. AUC was dose proportional in male and female rats. Accumulation of CGS 20267 was apparent for the 0.3 (1.8)

and the 3.0 (18.0) mg/kg (mg/m^2) dose with an increase in the two to three fold increase in the AUC. At the 30 mg/kg/day (180 mg/m^2/d) no accumulation was observed.

N. Trough Plasma Concentrations of Unchanged CGS 20267 in Dogs Given Repeated Doses of 0, 0.03 (0.6), 0.3 (6.0), and 3 (60) mg/kg (mg/m^2) Once Daily for Three Months. Investigations on the Presence on the Hydroxymetabolite, CGP 44645, in Plasma.

Trough plasma concentrations of CGS 20267 increased proportionally with dose. At three to five fold increase in trough concentration was observed with the increase greater in male than female dogs. No gender differences were observed at the 0.03 mg/kg/day (0.6 mg/m^2/day) dose level. The carbinol metabolite was not present in the dog plasma.

8. Other Metabolic Studies

A. Protein Binding Studies:

In vitro binding studies were performed in the following species: mouse, rat, dog, and baboon. Binding to serum proteins was low *in vitro*, about 50 - 60% in all animal species and was comparable to that observed in human serum (60%). In human blood CGS 20267 is bound mainly to albumin with negligible binding to *a*-1-acid glycoprotein and gamma-globulins. In human blood CGS 20267 is reversibly taken up into erythrocytes where the concentration is 80% of the plasma concentration.

B. *In Vitro* Metabolism by Human Liver Slices:

At concentrations of 0.2, 20, and 200 *u*M metabolism of CGS 20267 was low; the glucuronide of the carbinol metabolite , CGP44645 was a minor component and represented 1.4% or less of the total applied radioactivity.

C. Cytochrome Metabolism and Other Studies:

[^{14}C]CGS 20267 in rat and human liver microsomes was metabolized to the radiolabeled carbinol metabolite [^{14}C]CGS 44645. The rate of metabolism of CGS 20267 to the carbinol metabolit was slow with wide variability (4-5 fold) and the formation of the carbinol metabolite was not saturable but increased almost proportionally up to 200 umol/l of substrate concentration. Ketoconazole was observed to be a potent inhibitor of biotransformation in both rat and human liver microsomes. Inhibition by ketoconazole was not complete suggesting that a P450 isozyme not sensitive to ketoconazole may contribute to [^{14}C]CGS 20267 biotransformation. CYP3A4 and CYP2A6 were involved in drug transformation.

When male rats were administered 5 mg/kg (30 mg/m^2) once daily for 3, 6, 10, 20, and 30 days by gavage or 50 mg/kg (300 g/m^2) by gavage for 3 or 30 days the following changes were observed in liver metabolism. At the 5 mg/kg (30 mg/m^2) dose CGS 20267 was characterized as

a weak phenobarbital-type inducer. No macroscopic changes in the liver were observed. At 50 mg/kg absolute liver weight was increased with alterations in liver protein content and certain drug metabolizing enzymes. Major treatment related effects include moderately elevated microsomal cytochrome p-450 and morphine UDP-glucuronosyltransferase activities, moderately increased CY2B1, CY2B2, CYP3A1, and CYP3A2 and induction of CY2B1 / CY2B2-dependent pentoxyresorufin O-depentylase and 16*B*-hydroxylase activities. These findings indicate that CGS 20267 at the 50 mg/kg dose level is a potent phenobarbital-type inducer of cytochromes.

In a pilot three week study of the hepatic microsomal enzyme induction in female rats treated with oral doses of 0.05 (0.3), 0.5 (3.0), or 5 (30) mg/kg (mg/m^2) given by gavage for 21 consecutive days finding were observed in all dose groups. One control group was treated with phenobarbital 10 mg/ml. In rats treated at $\geq$ 0.5 mg/kg increased terminal body weights with increased liver weights with increase in specific enzyme fractions of the microsomal proteins (thyroxine UDP-glucuronosyl transferase and testosterone 6-*B* hydroxylase) and histological findings of centrilobular hepatocellular hypertrophy were observed. At > 5 mg/kg specific fractions of the microsomal protein which were increased included: total cytochrome P450; testosterone 6-*B* hydroxylase; pentoxyresorufin O-dealkylase, ethoxylresorufin O-dealkylase, increased benzyloxyresorufin O-dealkylase, CYB2B1, and CYP3A1 protein. At 5 mg/kg liver weights were increased with increase in the microsomal fraction apecifically the microsomal protein fraction due to induction of the enzymes mentioned above. Similar changes were observed in the phenobarbital control group.

Spectral interaction of CGS 20267 were observed with microsomal cytochrome P450 from female liver donors which demonstrated that CGS 20267 binds to the ferric form of the heme moiety. When CGS 20267 was incubated with human liver microsomal fractions the compound was shown to competitively inhibit CYP2A6 (K_i = 0.12 *u*M) and CYP2C19 (K_i = 9.0 *u*M) P450 isozymes in the human liver. Inhibition of CYP1A2, CYP2CP, CYP2D6, CYP2E1, CYP3A4/5 and CYP4A9/11 was not apparent.

While CGS 20267 inhibits aromatase, its metabolite CGP 44645 does not inhibit aromatase *in vitro* at a concentration of 100 *u*M. Weak inhibition was observed at 1000 *u*M. Comparative studies of CGS 20267 versus aminoglutethimide using immature female rat uteri indicate that CGS 20267 is 10;000 - 30,000 times more potent then aminoglutethimide. The effect of CGS 20267 on steroidogenesis in an *in vitro* assay utilizing hamster ovary slices indicates that the concentration of CGS 20267 which reduced estradiol production by 50% was 0.015 *u*M, while progesterone and testosterone synthesis were reduced by 50% with a concentration of > 350 *u*M. In the same assay system aminoglutethimide concentrations of 14 *u*M reduced estrogen concentrations by 50%, 20 *u*M reduced progesterone production by 50%, and 150 *u*M reduced testosterone production by 50%. With rat adrenal tissue aminoglutethimide reduced corticosterone production by 50% with a concentration of 44 *u*M and aldosterone production by 50% at a concentration of 130 *u*M. For CGS 20267 concentrations > 350 *u*M were required to inhibit corticosterone production and concentrations $\geq$ 210 *u*M were required to inhibit

aldosterone production.

Early *in vitro* studies done to assess the antiestrogen effect in rats treated at doses of 0.03 (0.18), 0.1 (0.6), and 1 (6) mg/kg (mg/m^2) serum LH and target organs (ovaries, uterus, and pituitary) a dose dependent disruption of ovarian cyclicity, a significant reduction in ovarian weight, increase in serum LH, an increase in body weight, dose dependent decrease in pituitary weight were noted. A dose of 1 mg/kg day resulted in decreased uterine weight and increase in LH concentrations similar to those seen in untreated ovariectomized rats. To determine the effect on the plasma corticosterone and aldosterone male rats were treated with 0.04 (0.24), 0.4 (2.4), and 4 (24) mg/kg (mg/m^2). Treatment at these dose levels did not effect the corticosterone or aldosterone production in male rats. When compared to CGS 63606 (anastrozole) CGS 20267 significantly reduced uterine weights in adult cyclic female rats at a dose of 1 mg/kg (6 mg/m^2) while CGS 63606 did not at doses of 1 and 10 mg/kg (6 and 60 mg/m^2) affect uterine weight.

In studies in female adult rats bearing DMBA and NMU induced estrogen-dependent mammary carcinomas treatment with letrozole 0.03 (0.18) mg/kg (mg/m^2) or 0.3 (1.8) mg/kg (mg/m^2) caused regression of established tumors, suppressed the emergence of new tumors, caused regression in uterine weight, depressed serum estradiol levels, and resulted in a dose dependent increase in serum LH levels. In a second study the antitumor effect of CGS 20267 (letrozole) was compared to the antitumor effect of CGP 63606 (anastrozole) in Sprague-Dawley rats. At doses between 0.3 (1.8) and 1.0 (6.0) mg/kg (mg/m^2) CGS 20267 caused significant regression of existing tumors, prevented formation of new tumors, and reduced uterine weight while CGP 63606 showed only marginal antitumor effect in the DMBA model at doses up to 10 (60) mg/kg (mg/m^2) with no effect on uterine weight.

Pharmacological effects on other body systems were also evaluated. Very high intravenous doses, i.e. from 3 (36) to 30 (360) mg/kg (mg/m^2) in cats caused cardiac arrhythmias with an increased incidence of arrhythmias reported at higher doses. One death due to arrhythmia was observed at the 30 mg/kg dose. EKG changes included prolonged PQ interval, increased in QRS and St max, and increased number of PVCs at higher doses. Transient decrease in blood pressure after intravenous administration was noted. Respiratory rate was slightly decreased at the 0.03 and 1 mg/kg dose while at the 10 mg/kg and the 30 mg/kg dose levels the respiratory rate was more diminished. No urinary or electrolyte abnormalities were noted. A concentration of 350 *u*M CGS 20267 was reported to cause a marked increase in the force of contraction of the left atria with a marginal increase in left atrial contractile force observed at 35 *u*M. Pretreatment of the atria with propranolol attenuated with positive inotropic and chronotropic response suggesting that the cardiostimulatory response of letrozole is due to catecholamine release. Concentrations of 35 to 350 *u*M did not alter smooth muscle tone when tested in the guinea pig ileum. Blood glucose concentrations in male rats were not affected by concentrations between 0.1 (0.6) and 3 (18) mg/kg (mg/m^2).

Interaction of CGS 20267 with neurotransmitters *in vitro* was studied with standard radioligand binding assays. No interaction or negligible interaction was noted with the *a*1-adrenergic, *a*2-

adrenergic, *B*-adrenergic, 5-HT_1-, 5-HT_2-, and histamine-1, and muscarinic cholinergic receptors at a concentration of 10 *u*M. This concentration is about five magnitudes higher than the IC_{50} for aromatase inhibition *in vitro*. *In vivo* evaluation of the CNS was conducted in adult male mice with a doses of 0.3 (0.9), 1 (3), 3 (9), or 10 (30) mg/kg (mg/m^2) with the mice followed up to twenty-four hours following doses. Similar testing using the same dose levels were performed in rats. Studies to evaluate CNS function included observation for behavior changes, sedation, and memory impairment, mobility, rotorod movement, potentiation of ethanol-induced narcosis, and passive avoidance of male mice to electric footshock, and body temperature changes. No abnormalities were observed in any testing except for body temperature evaluation. Two hours post dosing body temperature rose significantly in treated rats with a rapid return to normal. Since the antitumor dose which is effective in the rat is about 30 *u*g/kg, CGS 20267 appears to have a high therapeutic index.

LITERATURE REVIEW OF SECOND-LINE HORMONAL THERAPY

Table L-1 contains background information on second line hormonal therapy in advanced breast cancer and is based on Exhibit 12.2-1 (Vol.1.71) in the NDA.

L-1: Studies of Megestrol as Second Line Therapy in Advanced Breast Cancer

Drug / Treatment Schedule	*No. of Patients*	*Response Rate*	*Reference*
Megestrol 40 mg QID	48	31%	Ross et al. Cancer 49: 413 - 417, 1982
Megestrol 160 mg daily	37	25%	Blackledge et al. Eur J Cancer Clin Oncol 22;1091-1094, 1986
Megestrol 40 mg QID	30	23%	Ettinger et al. Semin Oncol 13: 9-14, 1986
Megestrol 40 mg QID	38	5%	Muss et al. JCO 6: 1089-1106, 1988
Megestrol 160 mg BID	221	16%	Robertson et al. Eur J Cancer Clin Oncol 25: 469-475, 1989
Megestrol 160 mg daily vs Megestrol 800 mg daily	86 84	10% 27%	Muss et al. JCO 8: 1797- 1805, 1990

In studies conducted in patients with advanced breast cancer some of whom had prior hormonal therapy for advanced disease, the response rate for megestrol ranges from 5 - 31%.

L-2: Comparative Studies of Second Line Hormonal Therapy in Breast Cancer

Drug / Treatment Schedule	No. Patients	Response Rate	Reference
Aminoglutethimide 250 BID vs Megestrol 160 mg/day	76 / arm 74 / arm	34 % 31%	Lundgrunden et al. Breast Cancer Res Treat 14(2):201-206,1989
Megestrol 80 mg BID vs Medroxyprogesterone acetate 500 mg BID	48 / arm 44 / arm	48% 44%	Willemse et al. Eur J Cancer 26:337- 343, 1990
Aminoglutethimide 125 mg BID vs Medroxyprogesterone acetate 250 mg BID	106 / arm 112 / arm	27% 31%	Canny et al. JNCI 80:1147-1151, 1988
Fadrozole 0.5 mg BID vs. Fadrozole 1.0 mg BID vs Fadrozole 2.0 mg BID	(Total-350)	18% 18% 13%	Hoffken et al. Ann Oncol 3 Suppl 5: Abstract 294, 1992
Fadrozole 0.5 mg BID vs Fadrozole 2.0	Total-78)	23% ?	Raats et al. JCO 10: 111-116, 1992
Fadrozole 1 mg BID vs Megestrol 40 mg QID	195 / arm 184/ arm	11% 16%	(Protocol 03) PDR:Physician's Desk Reference , 1996
Fadrozole 1 mg BID vs Megestrol 40 mg QID	150/arm 148/arm	13% 12%	(Protocol 06) FDA Oncology Advisory Drug Committee Meeting, Oct 16, 1995
Anastrozole 1 mg vs Anastrozole 10 mg vs Megestrol 40 mg QID	128 / arm 130 / arm 128 / arm	10% 5% 6%	(Trial 0004) PDR:Physician's Desk Reference, 1996

L-2: Comparative Studies of Second Line Hormonal Therapy in Breast Cancer

Drug / Treatment Schedule	No. Patients	Response Rate	Reference
Anastrozole 1 mg vs Anastrozole 10 mg vs Megestrol 40 mg QID	135 / arm 118 / arm 125 / arm	10% 13% 10%	(Trial 0005) PDR: Physician's Desk Reference, 1996

As shown in Table L-2 in comparative trials the response rates for megestrol acetate range from 6- 31%, for aminogluthemide from 27-34%, for the aromatase inhibitor fadrozole 11-23%; and for the aromatase inhibitor anastrozole (Arimidex™) from 5-13%.

SUMMARY: PHASE I / II STUDIES IN ADVANCED BREAST CANCER

Four phase I / II clinical trial were conducted and one phase II comparative trial of letrozole 0.5 mg vs letrozole 2.5 mg. Clinical trial reports for each of the Phase I / II trials: AR/BC1, AR/PS1, Protocol 01, and AR/ST1 are included in this section of the Review as well as the Clinical Trial Report for AR/ES1, a comparative phase II trial. In each of these trial letrozole treatment in significant suppression of estrogen synthesis without any effect on adrenal or thyroid function. In postmenopausal patients with hormone receptor positive or receptor unknown breast cancer who had receive previous therapies objective response of some duration were observed. No frequent serious or life-threatening adverse experiences were observed and letrozole was felt to be well tolerated by the investigators involved in these studies. In the comparative phase II study AR/ES1 forty-six patients were randomized to therapy with either letrozole 0.5 mg or 2.5 mg. The objective response rate was greater in the 0.5 mg arm and the toxicity profile was comparable in both arms.

Trial AR/BC I: Clinical Trial Report

I. Description:

This phase I trial conducted at the was performed primarily to: 1) determine the general tolerability and toxicity of CGS 20267 after multiple administrations; 2) determine the minimum effective dose of CGS 20267 which achieves maximal estrogen suppression: 3) determine the effects of CGS 20267 after multiple administrations on other hormones (cortisol, 17-hydroxyprogesterone, FSH, LH, TSH, and androstenedione); and, 4) investigate the pharmacokinetic profile of CGS 20267 after multiple administrations. A secondary endpoint was to collect data on the antitumor activity of CGS 20267.

The study was conducted in two part. In the first twenty-eight days of the trial (Core Trial) patients were enrolled at one of three dose levels: 0.1 mg, 0.5mg, or 2.5 mg and observed for suppression of estrogen levels, evaluation of other hormone levels, and occurrence of adverse events. Patients who did not progress during the first twenty-eight days of the trial were continued on study drug until progression occurred (Extension Trial). The Core Trial was conducted between September 11, 1991 and December 11, 1991. The Extension Trial was conducted between March 11, 1991 and was ongoing at the data cutoff date of August 4, 1993.

Inclusion criteria included: complaint postmenopausal women < 80 years; postmenopausal status; presence of loco-regional recurrence or progression of metastatic breast cancer not responsive to conventional anticancer therapy; histological or cytological proof of breast cancer; WHO performance status ≤ 2; and, written informed consent. Exclusion criteria include: rapidly progressive metastases; life expectancy < 3 months; presence of endocrine disorders such as diabetes mellitus, confirmed hyper- or hypothyroidism, Cushing's syndrome, or Addison's disease (treated or untreated); significant renal dysfunction (creatinine ≥ 1.5 x ULN); significant

hepatic dysfunction (total bilirubin $\geq$ 1.5 ULN or transaminases $\geq$ 3x ULN); hematologic disorders (Hgb < 9.5 mg%, WBC < 3000/ul, neutrophils < 1500/ul, platelets < 100,000/ul, prothrombin time > 1.5 x ULN); total calcium > 2.75 mmol/L; cardiac decompensation; other concurrent malignancies; concomitant anti-cancer treatments such as chemotherapy, bisphosphonates, immunotherapy, or other hormonal agents. A washout period of four weeks for chemotherapy and six weeks for a depot preparation was required.

Patients were assessed with case histories prior to treatment; clinical examination including weight, blood pressure, pulse rate, and body temperature prior to treatment and weekly; ECG monthly; blood samples including hematology and blood chemistry prior to treatment and weekly; estrone and estradiol prior to treatment, on first and second day of treatment, and weekly; cortisol, aldosterone, 17-hydroxyprogesterone, FSH, LH, TSH, and androstenedione prior to treatment and on day 28; letrozole levels prior to treatment, first day of therapy, and then weekly; urinanalysis prior to treatment and day 28; chest and skeletal xrays. bone scan, liver ultrasound, measurements and photographs of visible lesions at study entry, concomitant medication was recorded prior to entry and then weekly, adverse experiences were reported weekly, severity of pain and performance status monthly, and tablet count weeks 2, 3, and 4. Patients were hospitalized on day 0 and on day 28 for assessment of pharmacokinetic profile.

On the extention trial patients had a clinical evaluation every three months with weight, blood pressure, pulse rate, body temperature, ECG, laboratory evaluations including hematology and blood chemistry, drug levels, chest and skeletal xrays, bone scan, liver ultrasound, measurements of superficial or palpable lesions, concomitant medication, adverse experiences, performance status, pain severity, tumor response, and tablet count.

Seven patients were selected at each dose level (total enrollment: twenty-one) and followed weekly for four weeks for degree of estrogen suppression. A sample size of six patients per dose level was required to demonstrate with 80% power a 50% reduction in serum estrone and estradiol production statistically significance at the 5% level. The Bonferroni correction was used with each of four weekly measurements with the $p = 0.0125$. Tumor response was evaluated using the UICC criteria with overall response a measure of response in all involved tissues. Time to event definitions used in the extension portion of the trial were standard.

II. Results:

A. Core Trial:

1. Demographics:

Twenty-one patients were entered on the core study between the ages of 39 and 82 years (median: 62 years). All patients were postmenopausal. The disease free interval ranged from 0 - 117 months. Five of the twenty-one patients were receptor positive, two were negative, and fourteen were unknown. Six of the twenty-one patients had no surgery and all six received

tamoxifen as therapy. Fifteen had surgical treatment to the primary. In addition sixteen patients had radiotherapy, five receiving adjuvant radiotherapy. Nine patients had adjuvant antiestrogen therapy, none had adjuvant chemotherapy. Eight patients did not receive therapeutic treatment for advanced disease. Of the thirteen patients who received therapeutic treatment for advanced disease seven received hormonal therapy only, one chemotherapy only, and five both. Of these thirteen patients two had only one therapeutic treatment, three patients had two therapeutic treatments, and eight patients had three or more treatments. Dominant site of disease was visceral in four patients, bone in one patient, and soft tissue in sixteen patients. Two minor protocol violations occurred: an eighty-two year old women was enrolled on study (upper limit of age is 80 years) and one patient had neutropenia at study entry (not clinically relevant).

2. Efficacy:

The limits of detection for the estrone assay was 10 pmol/L and for the estradiol assay was 3 pmol/L. Estrone suppression achieved with a dose of 0.1 mg was about 61% of baseline on day 1 with a further decrease to about 78% from baseline on day 28. With 0.5 mg almost maximal suppression was achieved on day seven with levels 78% lower than baseline which was further reduced to 83% from baseline on day 28. With letrozole 2.5 mg 80% suppression of estrone levels occurred at day 7. Changes from baseline at each weekly measurement at each dose level were highly significant. Estradiol suppression reached a maximum suppression of 80% from baseline on day 7 with the 0.1 and the 2.5 mg while with 0.5 mg dose the suppression was only 77% of baseline. Changes from baseline at each time point were highly significant.

With regard to serum cortisol no relevant changes from baseline were observed with 2.5 mg and the 0.5 mg with a 17% change (non-significant) with the 0.1 mg dose. A slight reduction in aldosterone levels was observed with letrozole 2.5 and 0.5 mg, but no change in baseline with letrozole 0.1 mg. No significant changes were observed in 17-hydroxyprogesterone levels at any dose level. With regard to FSH levels thirteen of twenty-one patients showed an increase, five showed a decrease, and three showed no change. With LH levels a small increase from baseline was observed with all three dose levels. TSH levels did not change from baseline over the twenty-eight day period. Serum androstenedione levels remained constant with the 0.1 mg and the 0.5 mg doses, while a non-significant decrease was noted with the 2.5 mg dose level.

Letrozole pharmacokinetics are summarized in the following table:

Table AR/BC1: Pharmacokinetic Data for AR/BC3

Dose (mg)	C_{max} (± SD) (nmol / L)	C_{max} spec [C_{max} / dose]	T_{max} (hours)	AUC (0 - 24 hrs) (h x umol / L)	AUC spec (h x umol / umol)
0.1	4.37 (1.18)	12.49	1 - 2	0.25 (0.13)	0.712
0.5	22.65 (8.66)	12.49	1 - 4	1.18 (0.25)	0.672
2.5	114.4 (34.0)	13.06	1 - 4	8.37 (1.96)	0.995

The pharmacokinetic data in this study is similar to the pharmacokinetic data for the studies in healthy men and healthy postmenopausal women.

3. Safety Data

No changes in blood pressure or pulse rate were observed over time with use of study medication. Preexisting hypertension was not exacerbated. Body weight and temperature were within normal limits. In nineteen patients ECG did not change over the trial period. In two patients no ECG was done on day 28.

Adverse experiences were reported for six patients in the letrozole 0.1 mg group, seven in the letrozole 0.5 mg group, and five in the letrozole 2.5 mg group. No serious adverse events occurred during the first twenty-eight days of trail. The most common symptom was headache which occurred in six patients and was definitely related to drug in one case. The other adverse events were considered unlikely or not related to study drug.

Clinical laboratory evaluations for the first twenty-eight days were as follows: Seven patients had low hemoglobin levels at initiation of study drug. In three patients the values decrease one grade but relationship to study drug is unclear. Six patients had low lymphocyte counts (Grade II or III) at entry which did not worsen during trial. No marked alteration in serum electrolytes persisted over the course of the trial. No abnormalities of creatinine, total protein, urea, phosphorus were reported. One patient developed mild hypokalemia, increased creatinine, increased blood glucose, and hypocalcemia. No patients developed hypocalcemia or abnormalities in phosphate values.

With regard to liver function abnormalities one patient had grade I increases in AST, ALT, and alkaline phosphatase at four weeks which were associated with progression of liver metastases. On other patient developed an increase from Grade I in AST, ALT, and alkaline phosphatase during the first four weeks of therapy probably related to study drug. Prothrombin time and urinanalysis were not affected by study drug.

B. Extension Trial

1. Patient Disposition / Drug Exposure:

Nineteen of twenty-one patients enrolled in the core trial continued on in the extension trial. At the time of data cut-off (August 4, 1993) three patients remained on trial receiving study drug. One death occurred in the letrozole 2.5 mg arm (due to disease progression) and seventeen patients had disease progression. The median duration of treatment on the letrozole 0.1 mg arm was 85 days, on the letrozole 0.5 mg arm was 211 days, and on the letrozole 2.5 mg arm was 240 days. (These durations are slightly inaccurate since the duration of treatment for the three patients remaining on trial was censored at the last visit date.)

2. Efficacy Results:

One patient treated with 2.5 mg had a complete response and seven patients had a partial response (one on the 0.1 mg arm, three on the 0.5 mg arm, and three on the 2.5 mg arm) for an objective response rate of 38%. Three patients were considered to have no change (stable disease), and ten patients (48%) had progressive disease on study. Median duration of objective response was 428 days (95% CI: 288-505 days). Median time to progression was 169 days (95% CI: 84-233 days). For the 0.1 mg dose level median time to progression was 85 days, for the 0.5 mg arm was 211 days, and for the 2.5 mg arm was 220 days. Time to treatment failure was identical to time to progression. No survival information is included.

With regard to pain severity three patients showed an improvement in pain status, seven patients showed a deterioration in pain, and eleven showed no change in pain. Between baseline and final observation two patients showed an improved performance status, nine patients showed a deterioration in performance status, and ten showed no change. In the study report the improvements and / or worsening of the secondary variables was not correlated with tumor response information.

3. Safety Results:

Adverse experiences were reported by all twenty-one patients. Four serious adverse events were reported. One patient developed urticarial rash most likely related to ingestion of dexamethasone and not related to study drug. A second patient developed an acute pulmonary embolus eighteen days after discontinuation of letrozole treatment for progressive disease. Despite heparinization the patient died. This adverse event does not appear to be related to the study drug. A third death occurred on study from possible heart failure or thoracic aortic aneurysm dissection. A fourth patient developed a large pleural effusion which required drainage, had positive cytology, and was considered to be evidence of disease progression.

The most common adverse reactions reported for this trial include: nine headache in seven patients, arthralgia in four patients, eight experiences of back pain in four patients, and six experiences of musculoskeletal pain in four patients. On patient developed an exacerbation of hypertension on study day 245 after start of treatment which was not considered to be related to study drug. Only three of the adverse experiences on the extension trial were considered to be related to study drug, two patients with headache and one patient with dry skin (due to relative estrogen deficiency).

No clinically relevant changes in weight occurred. Four patients had an increase in systolic pressure at some point during the trial and two had diastolic elevations during the trial. Relationship to study drug is unclear.

III. Summary:

In the first portion of this clinical trial all dose levels of letrozole (0.1 mg, 0.5 mg, and 2.5 mg) showed a significant suppression of estrone and estradiol levels with not serious affects on hematological parameters, blood chemistry levels, or other hormones especially adrenocorticol function. The drug was well tolerated. The overall response rate for this phase I/II study is 38% (8/21 patients) which is impressive considering that the majority of patient had previous at least antiestrogen therapy and possibly other hormone therapies and chemotherapies. The duration of response and time to progression reported for this study suggest that this drug is efficacious as second line therapy in breast cancer. The safety profile for this study population is acceptable with no serious adverse events related to the study medication and few mild to moderate adverse events (headache, dry skin) which were related to study drug.

Trial AR/PS1: Clinical Trial Report

I. Description:

This open phase I trial of letrozole 0.5 mg daily in postmenopausal women with advanced breast cancer was conducted in between July 7. 1991 and June 30, 1992. Primary objectives of this trial were to determine the systemic tolerability and toxicity of letrozole and to determine the effects of letrozole 0.5 mg on estrogens (E1. E2), cortisol, and aldosterone. Secondary objectives were to determine the antitumor activity of letrozole. Fourteen postmenopausal women with advanced breast cancer were enrolled based on the statistical knowledge that a sample size of fourteen allows the maximum standard error for the proportion of patients with adverse experiences to be 0.134 and the confidence interval of $\pm$ 0.29.

Inclusion criteria included: informed consent; histologic or cytologic proof of breast cancer; positive or unknown receptor status; and, postmenopausal status with FSH and LH in the postmenopausal range. Exclusion criteria included: rapidly progressing metastatic disease; endocrine disorders such as diabetes mellitus, confirmed hyper- or hypothyroidism, Cushing's syndrome, Addison's disease; significant renal disease (creatinine $\geq$ 1.5 x ULN), hepatic dysfunction (total bilirubin $\geq$ 1.5 x ULN or serum transaminases $\geq$ 3 x ULN); hematologic disorders (WBC < 3000/ul, AGN < 1500/ul, platelets < 100,000/ul, Hgb < 9.5 gm%, prothrombin time > 1.5 x ULN; total serum calcium > 2.75 mmol/L (> 11 mg/dL); or cardiac decompensation; concurrent malignant diseases except carcinoma in situ of the uterus or adequately treated squamous or basal cell carcinoma of the skin; presence of blastic or mixed bone lesions with no other sites of measurable / evaluable disease; contralateral breast cancer as the only lesion; presence of hilar enlargement, plueral effusion, or ascites as the only manifestation of disease; previous treatment with aromatase inhibitors; concomitant anti-cancer therapy or use of investigational new drugs within thirty days of treatment.

Patients were followed for the first twenty-eight days for the hormonal effects and tolerability and for six months in an extension trial for tumor response and tolerability. Tumor response was

assessed using: chest xrays, liver scans, and xrays of suspicious areas on study then at two, three, and six month; bone scans performed every six months; CATs and MRIs done as clinicaly indicated; and, direct measurements (and photographs if applicable) of superficial or palpable tumor on study and at two, three, and six months. Tumor response was assessed utilizing the UICC criteria. WHO performance status was graded at each examination. Laboratory examinations including blood chemistry and hematology at each examination. Fasting blood sugar and prothrombin time were done only at visits 1, 3, and 5. Urinalysis was performed at visits 1 and 3. Endocrine measurements were performed prior to study drug and at each examination up to Examination 5. Pharmacokinetics measurement were not planned in the original protocol, however the protocol was amended to include pharmacokinetics sampling. Plasma samples leftover from the hormone assays were utilized.

Tolerability was assessed after 14 and 28 days based on occurrence and severity of adverse experiences; body weight changes; EKG, blood pressure, body temperature and pulse rate measurements; laboratory parameters including hematology, chemistry, and urinalysis. Cortisol and aldosterone levels were followed at 14 and twenty-eight day. Patients who had not progressed at day twenty-eight after initiation of study drug were followed in the extension study for tumor response and study drug tolerability.

II. Results:

A. Demographics:

Fourteen patients completed the tolerability portion of the study. One patient had progressive disease after twenty-eight days so thirteen patients were continued in the extension study. Patients were 42 to 73 years of age, were postmenopausal (duration: 1 - 23 years), with median weight of 61.5 kg (range: 55 - 93 kg). Disease free interval ranged from 14 days to 30 years. Site of first metastasis was soft tissue in eight, bone in four patients, and visceral in one patient. One patient had both nodal and pleural involvement. Eleven of fourteen patients had receptor positive status and three had unknown status. Six patients had a performance status of 0, three patients had performance status of 1, and five patients had a performance status of 2. Eleven patients had breast cancer surgery while three did not. Two patient had adjuvant radiotherapy, one had adjuvant chemotherapy, but none had adjuvant hormonal therapy. Hormonal therapy for advanced disease was given to three patients, chemotherapy for advanced disease to six patient, and five patients had both hormone and chemotherapy for advanced disease.

Four minor protocol violations occurred. One patient had non-aggressive lymphangitic carcinomatosa of the lung (present for one year prior to trial entry). Three patients who were postmenopausal less than five years did not have FSH and LH levels measured, but all had bilateral oophorectomies prior to study enrollment.

B. Efficacy Information:

Plasma estrone levels decreased significantly ($p < 0.0001$) to below the limits of detection (< 2.5 pg/ml) by day 14 and the suppression was sustained throughout treatment. Plasma estradiol was also significantly depressed ($p < 0.0001$) to below the limits of detection (< 2.5 pg/ml) by day 14 and remained so while the patient was on study drug. Mean trough level of letrozole were measured on days 14, 28, 56, and 84. Table AR/PS1 displays the pharmacokinetics data.

Table AR/PS1: Pharmacokinetics Measurements (Plasma Trough Levels) On Study

Day of Blood Collection	Concentration (± SD) in nmol/L	Number
Day 14	44.6 (20.2)	14
Day 28	55.8 (23.8)	14
Day 56	57.6 (31.9)	13
Day 84	59.7 (31.1)	11

The apparent increase in trough levels over the study day 84 suggests that at the letrozole 0.5 mg dose level steady state plasma concentrations are not reached by three months. Cortisol levels and were decreased about 12% from baseline at Day 28 and remained depressed for the remainder of the study. Aldosterone levels increased 19% from baseline by day 14, but returned to baseline by day 28 and then decreased slightly below baseline for the remainder of the study.

After six months of treatment with letrozole responses observed included five partial responses, five patients with stable disease, and four patient with progressive disease. All patients with partial responses had high levels of estrogen receptor positivity on the original tumor and / or metastatic lesions. None of these patients had prior hormonal therapy for either advanced disease or as adjuvant therapy.

C. Safety Information

Three patients had abnormal EKGs at study entry and these remained abnormal without change during the trial. No changes in blood pressure (systolic or diastolic), pulse rate, body weight, or body temperature occurred during the trial. Overall tolerability was considered very acceptable by the investigators.

One patient - complained of mild influenza-like symptoms after two months of treatment which was not considered drug related. No other serious adverse reactions occurred during the study. No death occured during or immediately after study termination.

Five patients had low hemoglobin values at entry onto study which did not vary during the study. Three patients were noted to have a decrease in WBC count during treatment while one patient had an increase in WBC count. One patient developed mild thrombocytosis and another mild thrombocytopenia. No change in prothrombin time was observed. With regard to serum chemistry values, no abnormalities which were not either very minor or present prior to initiation of study drug were observed except in one instance where the patient developed an elevation of

AST at study examination 6. No patients had abnormalities of urinalysis.

III. Summary

In this phase I study 14 postmenopausal patients with advanced breast cancer received letrozole 0.5 mg daily. During the first twenty-eight days hormonal changes were evaluated. Estrone production was significantly reduced from baseline (85%) while estradiol production was significantly suppressed (90%) from baseline. In this study for unclear reasons trough plasma letrozole levels continued to rise during the first 84 days of study. (Increase in trough plasma letrozole levels using letrozole 0.5 mg has not been reported after day 60.) Cortisol levels decreased slightly (12%) but not significantly during the first 14 days of study. Aldosterone levels rose about 14% (not significantly) at day 14 and then were reduced to baseline levels or below by day 28 and after. No abnormalities in vital signs or EKGS were observed. During the extension study one patient developed an unexplained elevation of AST. No other laboratory abnormalities were significantly different from baseline values. With regard to tumor responses five partial responses were observed in patients who were known to be receptor positive. No deaths or serious adverse reactions were reported and one minor adverse experience was reported (flu-like illness) which was not considered to be related to study drug.

Trial 01: Clinical Trial Report

I. Description:

Protocol 01 Core was designed as a single center, open-label, dose-finding trial in postmenopausal women with advanced breast cancer non-responsive to conventional therapy. The primary objectives of the core protocol were to evaluate the safety, tolerability, toxicity of letrozole, the degree of estrogen suppression of the various letrozole doses, the effect of letrozole on adrenal steroidogenesis and thyroid function at letrozole levels which block aromatase activity, and the pharmacokinetics of different doses. In Protocol 01 patients were assigned to one of three treatment groups: Group I Treatment Sequence -letrozole 0.1 mg for six weeks / 0.25 mg for six weeks; Group II Treatment Sequence-letrozole 0.5 mg for six weeks / 1.0 mg for six weeks; and, Group III-letrozole 2.5 mg for six weeks / letrozole 5.0 mg for six weeks. At the end of the twelve week core trial patients who had tumor response or stabilization were allowed to continue on to Protocol 01 Extension. In Protocol 01 Extension the primary objective was to provide continued treatment to patients who responded to letrozole in the core trial while collecting information on the tolerability and toxicity as well as the efficacy of letrozole.

Eligibility criteria for this trial include: female; postmenopausal; > age 17; progressive metastatic breast cancer either receptor positive or receptor unknown status; life expectancy $\geq$ sixteen weeks; WHO performance status ≤ 2; acceptable hematological, hepatic, and calcium levels. Patients were ineligible if they had: receptor status known to be negative; a history of treatment with fadrozole; prior radiotherapy to measurable disease; evidence of brain metastases or lymphangitic carcinomatosus; treatment with prior chemotherapy, hormonal therapy or, steroid

therapy, or other aromatase inhibitors within thirty days; treatment with other investigational agent within thirty days; or, a history of serious medical illness or non-compliance which would make them unreliable study candidates. Concomitant use of other treatments were not allowed.

Patients were evaluated at entry onto trial with the following: medical history including performance status, pain scoring, use of concomitant medications and complete physical exam; symptom assessment; chest xray, EKG, abdominal CT or liver scan, bone scan with xrays of suspicious areas; measurements and photographs of cutaneous lesions; and, laboratory studies including protime, PTT, CBC, serum chemistry, and urinalysis. Patients were followed every two weeks for the first twelve weeks of the trial with evaluation of pain and performance status, queries about adverse events, physical exam, letrozole plasma levels, and laboratory studies. Endocrine studies including serum estrogens, 24 hour urine collection for estrogens and free cortisol, thyroid function studies, plasma renin, cortrosyn test, creatinine, and electrolytes were performed on day one and then every two weeks. Full hormone profiles, plasma estrogen samples (collected over a twenty four hour period) along with urinary estrogen and cortrosyn testing of adrenal function were performed on day 1. day 42, and day 85. Tumor response was with local measurements at six weeks and the complete laboratory testing at twelve weeks.

The proposed sample size was twenty-one patients (seven /group). No statistical assumptions were used in selecting the sample size. Patient were assigned sequential numbers beginning with 001 at visit 1 in the order of presentation with the first seven patients assigned to the first treatment group. The core trial was conducted by from October 21, 1991 until September 30, 1992. The extension trial was conducted from March 10, 1992 until January 20, 1994 by Patients were continued on the dose that they were receiving at the end of the core trial until response to letrozole was lost. The duration of treatment lasted from 112 to 555 days.

II. Results:

A. Patient Disposition and Demographic Data:

Twenty-three patients, all Caucasians, were enrolled on this study. In Group 1 (0.1 / 0.25 mg) six of eight patients completed the core trial (twelve weeks) and continued on to the extension trial, one withdrew consent after one month on study and one died from progressive disease. In Group II (0.5 / 1.0 mg) five of seven patients continued to the extension trial and two were removed for unsatisfactory therapeutic response. In Group III six of eight patients completed the core trial and continued on to the extension trial, one patient was removed for unsatisfactory therapeutic response, and one patient withdrew consent after one month on study.

In Group I for the enrolled eight patients the mean age was 54.6 years (range: years), in Group II for the seven enrolled patients the mean age was 64.4 years (range: years), while in group III for the eight patients enrolled the mean age is 63.5 years (range: years).

Menopause was natural in twelve patients, chemotherapy induced in two patients, and surgically induced in nine patients. Twenty-two had prior surgery for breast cancer, nineteen had prior radiotherapy, twelve had one or more prior chemotherapy regimens, and twenty-one patients had one or more hormonal regimens for advanced disease. Nineteen patients were ER +, three had unknown ER status, and one was ER -, PR+. Fourteen patients had $\geq$ 2 year disease free interval. About half of the patients had measurable disease and half had evaluable disease.

At visit 5 ten patients had the incorrect dose given (the dose was increased prematurely in eight patients in Group I and in five patients in Group II) which invalidated the estrogen level assessments. An additional patient , took an incorrect dose for two weeks during the trial so that her hormone assessment is invalid. This patient also is not evaluable for response since she received radiation to sites of disease. Three patients also violated eligibility criteria: one patient had previous treatment with fadrozole; one patient had negative receptor status; and, a third patient who had been treated for brain metastases was enrolled. This patient within one month of initiation of study drug due to progressive disease. An additional patient who had transphenoidal hypophysectomy and was on a daily dose of Synthroid with elevated T_4 and abnormally low TSH levels. The dose of Synthroid was adjusted and TSH and T_4 levels returned to normal.

B. Efficacy Results:

1. Core Trial:

A decrease from baseline of about 65% in both serum estrone and serum estradiol were observed twenty four hours after administration of the first dose of letrozole. Measurement of estradiol levels over a twenty-four hour period a visit 2 showed a continued decrease from baseline over the twenty four hours at all three dose levels. With regard to serum estradiol levels, each treatment group at visits 3 thru 8 (with one exception - Group II at Visit 8) demonstrated a statistically significant decrease of 84 -95% from baseline in the serum estradiol level. On visit 8 (at twelve weeks) in all three treatment sequences estradiol values were depressed to about 92%. No pattern or difference in the degree of estradiol suppression from baseline was noted in any of three treatment groups. Serum estrone levels in each treatment group were significantly suppressed from baseline except in for Group II at visit 8. Eighty per cent of the study participants in each group had estrone values below the level of detection.

Urinary estradiol was statistically significantly decreased from baseline in all treatment groups except at visit 3 for all Groups, at visit 4 for Group I, at visit 5 for Groups I and II , and visit 7 for Group I. The failure of the estrone values to reach statistical significance level of suppression may have been due to the timing of the study medication ingestion on the day prior to collection. Urinary estrone levels were statistically significant decreased from baseline except for the following time points: at visit 3 for all Groups at visit 4 for Group I, at visit 5 for Groups I and II and visit 7 for Group I, and at visit 8 for Group I. Overall serum and urinary estrogen suppression were adequate to permit response in hormonally sensitive breast cancers.

No clinically significant suppression of basal cortisol levels was detected. Two patients in Group I (letrozole 0.1 / 2.5 mg) did show 50% decreases in basal levels of cortisol at visits 5 and 8 and an additional patient had a decrease in urinary free cortisol and ACTH. In general ACTH levels were in the normal ranges at all times. Seven patients had a decrease from baseline in their aldosterone levels but the aldosterone levels remained in the normal range. No blunting of the aldosterone effect was observed after ACTH challenge (except for one patient who appeared to have blunting a thirty minutes which was not associated with a rise in serum renin.) No abnormalities of serum or urinary electrolytes were noted. Plasma renin activity was below the normal range at visits 2, 5, and 8 for all except two patients who had values well above the normal range but whose aldosterone levels were normal. Thyroid functions were normal except in one patient on Indural with an elevated TSH level without T_3 or T_4 abnormalities and a second patient with abnormal values due to excessive Synthroid (see above). Delta-4 androstenedione, 17-hydroxyprogesterone, 11-deoxycortisol, and DHEA-S were within normal range when evaluated at visits 2, 5, and 8.

ECOG performance status did not vary during study except for Group III during visits 5 - 8 where a decrease was noted probably related to progression of disease. Bone pain scores were variable with not clear pattern of improvement in any group over the study period, however no worsening of bone pain was reported. With regard to narcotic scores improvement was observed in group III over the entire twelve week period, while no change was observed in the other two arms.

Tumor response was followed: one partial response in Group II, seven patients with stable disease (two in Group I, two in Group II, three in Group III), and thirteen patients were judged to have progressive disease. Two patients were not assessable for response.

2. Extension Trial:

No change in the degree of estradiol or estrone suppression was noted in those patients who were continued in the extension trial. A slight increment (not significant) in the degree of estrogen suppression was noted with the increase in dose. No further decrease in urinary estrogen values were observed in the extension trial.

Of the twenty-three patients who entered the core trial, seventeen completed it. Fourteen of the seventeen were continued on Protocol 01 extension. One patient who had a partial response during the core trial continued to have a partial response maintained for nine months in the extension trial, and a second patient achieved a partial response after 8.5 months of treatment which continued for nine months. Six patients had stable disease during the extension trial. Six of these patients had objective progression of disease **during the core trail** but **were continued on the extension trial.** Four of these six progressers were removed from the trial at month 4 (after one month enrollment in the extension trial), while two were continued on trial for six months because of symptomatic improvement. For this reason time to progression and time to treatment failure as calculated by the applicant will not be reported here.

Performance status of the fourteen patients remained constant while on the extension trial. Bone pain scores remained constant during the extension trial with three patients showing an increase due to progression of bony disease. Shortly after the bone pain scores increased patients were removed from trial. Narcotic scores remained constant during the extension trial except in two instances where increasing bone pain was associated with progressive disease.

Cortisol data from visits 11 and 14 along the Cortrosyn testing did not any evidence of suppression of adrenal function in the tested patients.. One patient did have a 50% reduction in baseline values. Serum aldosterone levels were noted to be decreased in three patients in the extension trial with no associated abnormalities of plasma renin or serum electrolytes. Urinary free cortisol, urine creatinine, urine sodium, and potassium were normal at all visits. ACTH levels were within normal limits. Plasma renin levels did not vary form the levels reported in the core trial and in both portions of the trial plasma renin were below the normal range in the six patients tested. No significant abnormalities of thyroid function were reported.

C. Safety Data:

1. Core Trial:

All twenty-three patients were evaluated for safety and twenty-one patients reported one or more adverse experiences. No premature discontinuations occurred which were due to adverse events and / or laboratory abnormalities. No hospitalization due to drug therapy were reported. No adverse events with sequelae or secondary malignancies were observed during this trial.

Three deaths occurred during or within thirty days of study drug discontinuation. One death on study occurred in Group I due to progressive disease after one month on trial. Two other patients died within thirty days of study drug discontinuation due to progressive disease.

Ten patients reported serious adverse reactions only one of which was related to study drug. The one serious adverse event considered to be drug related was the occurrence of grade 3/4 bone pain considered by the investigator to a disease flare related to therapy. Six other serious adverse experiences were grade 3 /4 bone pain related to disease. One patient experienced grade 3/4 ascites, anorexia, and fatigue with severe (grade 3) bleeding from a left breast neoplasm and was later discontinued from trial due to progressive disease. One patients had a grade 4 surgical procedure, insertion of a port-a-cath complicated by a hemothorax. Other grade 3 events which were reported included: aphasia, hemiparesis, asthenia, gastroenteritis, pathological fracture, spinal cord compression, nausea and vomiting.

Most of the adverse experiences which were reported were considered to be related to the patient's underlying disease with bone pain being the most common adverse reaction reported. Table P01-1 provides a frequency distribution of the most common adverse experiences reported by at least two patients whether related to study drug or not in both the core and the extension trail with drug related adverse events in parenthesis in the trial. The most common drug related

adverse event in the core study were hot flushes and nausea.

Table P01-1: Most Common Adverse Experiences on Study with Number Drug Related AEs in Parentheses

Adverse Experiences	0.1 mg / 0.25 mg	0.5 mg / 1.0 mg	2.5 mg / 5.0 mg
Bone Pain	3	3 (1)	4
Nausea	1 (1)	5 (2)	3 (2)
Hot Flushes	4 (4)	1 (1)	-
Vomiting	-	3	1
Asthenia	-	-	2
Alopecia	1 (1)	1 (1)	-
Constipation	1	1	-
Dehydration	-	-	2
Diarrhea	1 (1)	1 (1)	-
Dizziness	-	-	1 (1)
Dyspepsia	-	-	2 (2)
Edema, Peripheral	-	2 (1)	-
Fatigue	1	1	-
Gastroenteritis	-	-	2
Increased Sweating	2	-	-
Leg Cramps	1 (1)	-	-
Pathological Fracture	-	-	2

No significant abnormalities were reported on physical exam after treatment with study drug. Six patients had greater than 5% weight loss and in four of these patients weight loss could be related to progressive disease. In one patient nausea and diarrhea associated with the weight loss may have been due to study drug ingestion, while in one patient the cause of weight loss is unclear. Two patients treated with letrozole 0.25 mg were noted to have a decrease in diastolic blood pressures, no episodes of hypertension were reported. No abnormalities in pulse rate were reported. No new abnormalities in EGK tracing were reported during the course of the trial. On chest xray one patient developed CHF not related to study drug and a second patient developed a small pleural effusion. With regard to laboratory findings no patients had any evidence of grade 4 toxicity (NCI Common Toxicity Criteria). Two patients developed grade 3 hemoglobin changes attributed in both cases to radiation therapy. One patient had persistent grade 3 hyperbilirubinemia which was due to extensive liver metastases (along with widespread disease) and which did not worsen with drug therapy. One patient had grade 3 alkaline phosphatase abnormality due to bony disease. On patient developed grade 3 proteinuria at visit 8 which was not considered to be due to drug therapy.

2. Extension Trial:

In the extension trial no deaths occurred on or within thirty days of study discontinuation. No serious adverse events or laboratory abnormalities lead to trial discontinuations, deaths, or caused second malignancies. The following serious (Grade 3 / 4) adverse events were reported in the extension study. Patient developed worsening of bone pain which had improved on study drug. The increase in bone pain due to progressive disease was reported att visit 11 and lead to discontinuation of study drug at visit 13 with pathological left clavicular fracture, increased weakness, and hypercalcemia. Patient developed back (flank) pain secondary to ureteral obstruction caused by extracorporeal lithotripsy of known renal calculi and fever due to C. albicans fungemia with renal infection. Neither serious AE is related to drug therapy. Patient experienced pericardial effusion and dyspnea due to progressive disease at visit 17. Patient No. 14 had an increase in bony pain due to progressive disease. Patient developed right flank pain due to obstructive hydronephrosis, anemia, right lower quadrant abdominal pain associated with cholelithiasis none of which were related to drug therapy. Patient developed increasing bone pain related to disease progression at visit 11. In Table P01-2 the most common adverse experiences reported on the extension trial are presented and in parentheses the number which are considered related to study drug.

Table P01-2: Most Common Adverse Experiences on Study with Number Drug Related AEs in Parentheses

Adverse Experiences	0.1 mg / 0.25 mg	0.5 mg / 1.0 mg	2.5 mg / 5.0 mg
Bone Pain	2	3	2
Nausea	1	0	2 (1)
Hot Flushes	1 (1)	-	-
Vomiting	1	0	1
Headache	1	-	-
Urinary Tract Infection	-	2 (2)	-
Diarrhea	1	-	-
Dyspnea	1	1	-
Edema, Peripheral	1	-	-
Back Pain	-	1	1
Muscle Weakness	1	-	-
Pathological Fracture	1	-	-

No significant abnormalities were noted on physical exam. Two patients with weight loss during the core trial entered the extension trial. One patient was able to gain weight even though discontinued from the study at month 4. A second patient continued to lose weight during the extension trial and was discontinued after four months in the extension trial due to disease

progression which had been recognized in the core trial. No evidence of hypotension or other blood pressures or pulse rates were noted in the extension trial. EKGs were normal or clinically insignificant at discontinuation of the extension trial. With regard to laboratory data only two patients had grade 3 changes during the extension trial and no patients had grade 4 toxicity. One patient had a decrease to grade 3 hemoglobin due to blood loss for a hepatic flexure arterio-venous malformation and decreased WBC and platelet counts due to bone marrow involvement with tumor. One patient had a grade 3 rise in SGOT at visit 13 considered to be unrelated to study drug. Patient was discontinued from study due to progression of disease in the lungs and in bone associated with hypercalcemia. Liver was not evaluated for tumor involvement and bilirubin was normal.

III. Summary:

Protocol 01 enrolled twenty-three patients of whom twenty-one completed the core trial and fourteen were enrolled in the extension trial. Estradiol and estrone suppression was demonstrated at > 90% of baseline at the end of trial. In those hormonal parameters which were evaluated at both dose levels in patients no appreciable difference was noted between the two dose levels on any of the hormonal parameters which were measured. Adrenocortical function was not significantly disturbed by use of aromatase inhibitors. Aldosterone levels although reported to be lower in some treated patients and lowered plasma renin levels observed in some patients in the extension trial did not have any physiological consequences as demonstrated by normal blood pressure measurement, normal pulse rate, and normal electrolytes. Thyroid function was not affected.

Two partial response and six patients with stable disease were reported in this population of postmenopausal women who have been heavily pretreated. One death occurred on study and one within thirty days of study discontinuation both due to progressive disease. One serious adverse event related to study drug was reported in the core trial - bone pain flare which resolved with continued treatment. The most common adverse events related to study drug were nausea and hot flushes. Overall letrozole at the dose levels study in this two part trial appears safe and effective in hormonally responsive advanced breast cancer.

Trial AR/ST1 : Clinical Trial Report

I. Description of Study:

This phase I study is entitled: "CGS 20267 - Non-steroidal Oral Aromatase Inhibitor. Open, randomized, comparative, between patient single center Phase I trial in postmenopausal patients with advanced breast cancer. Investigation on *in-vivo* aromatization during CGS 20267 treatment". The primary objectives of the trial are to compare doses of 0.5 mg and 2.5 mg for: 1) *in-vivo* inhibition of aromatization; 2) tolerability and toxicity; 3) changes in plasma estrogen levels (E1, E2, E1S); and, 4) trough plasma letrozole concentrations. The secondary objective is to collect data on the anti-tumor activity of letrozole. As in the other phase I/II trials the trial is

divided into two parts: a Core Trial where the primary concern is determination of the changes in hormonal levels and a Extention Trial where the antitumor activity, tolerability and safety are of major concern.

In this open, comparative trial in postmenopausal women with loco-regional recurrence or progression of metastatic disease patients were randomly allocated to a once daily oral dose of letrozole 0.5 mg or letrozole 2.5 mg for a six week period. At the end of the six week period if the tumor had not progressed, the patient was given the option of remaining on trial. The study was conducted at the The core trial was conducted between February 18, 1993 and October 21, 1993. The extension trial starting date was February 18, 1993 (day 1 of Core Trial) and was concluded on September 30, 1994. The main outcome variable was the inhibition of aromatization of androstenedione (A) to E1 (estrone) with either dose of letrozole. Secondary outcomes include tumor response data, trough plasma letrozole levels, measures of tolerability (vital signs, EKGs, and adverse experiences).

Inclusion criteria for the trial include: compliant postmenopausal women of all ethnic groups under the age of 80 years with loco-regional recurrence or progression of metastatic breast cancer who might benefit from treatment, histologic or cytologic proof of breast cancer, postmenopausal status, ER or PR positive tumor or receptor unknown tumor, WHO performance status ≤ 2; ability to give informed consent. Exclusion criteria include: rapidly progressive metastases (CNS involvement, lymphangitic carcinomatosis of the lung, inflammatory breast cancer, or hepatic metastases involving more than one-third of the liver; endocrine disorders such as diabetes mellitus, confirmed hypo- or hyperthyroidism, Cushing's disease, or Addison's disease; significant renal dysfunction (creatinine $\geq$ 1.5 x ULN); significant hepatic dysfunction (total bilirubin $\geq$ 1.5 x ULN or transaminases $\geq$ 3 x ULN); significant hematological abnormalities (WBC < 3000 / *ul*; neutrophils < 1500 / *ul* , platelets < 100,000 / *ul*, or Hgb < 9.5 gm%), total serum calcium > 2.75 mmol/L; cardiac decompensation; concurrent malignant disease; hilar enlargement, pleural effusion, or ascites as the sole manifestation of disease; previous treatment with other aromatase inhibitors, other anticancer therapy within four weeks except depot preparations where a six week washout is required, incomplete recovery from the toxicities of previous therapy; concomitant anti-cancer treatments such as chemotherapy, bisphosphonates, immunotherapy, endocrine therapy, or radiotherapy or concomitant therapy with steroids.

Patients were randomized in blocks of four to receive either letrozole 0.5 mg or letrozole 2.5 mg. Patients were evaluated with: history, physical examination at entry; measurement of superficial or palpable lesions with photographs of visible lesions if applicable at entry, on day 46 if enrolled in extension trial and every three months; vital signs, severity of pain and WHO performance status at entry, day 21, day 46 and then every three months if enrolled in the extension trial; ECG at entry and on day 43 (or day 46 if enrolled in the extension trial); chest xray, skeletal xray, liver ultrasound at entry, every three months or oftener if patient symptomatic, bone scan at entry and at month six for those in the extension trial; laboratory examinations including hematology, blood chemistry at entry, day 22, day 43, and if enrolled in the extension trial every three months; urinalysis at entry and on day 43; blood samples for

estrogens at entry, on day 4, on day 22, on day 43, and day 46; pharmacokinetics on day 4, day 22, day 43, and day 46; tracer injection [7-^{3}H-androstenedione and 4-^{14}C-estrone] on day 1 and day 43 with urine collection for 72 hours after tracer injection. Information on adverse experiences was collected on day 4, day 22, day 43, day 46 if enrolled in the expansion trial, and then every three months.

Patients were discontinued from trial for adverse experiences, abnormal laboratory values, abnormal test procedures, unsatisfactory therapeutic effects, condition did not warrant further treatment, failure to meet protocol eligibility requirements, non-compliance, withdrawal of consent, loss to follow-up, administrative problems, and death.

The sample size was calculated on the inhibition of aromatization of androstenedione (A) to E1 with 0.5 and 2.5 mg letrozole. Inhibition of 90% of aromatization is required for clinical benefit. A dose of letrozole 0.5 mg is expected to inhibit aromatization by 85% and a dose of 2.5 mg is expected to inhibit aromatization by 95%. Studies with the aromatase inhibitor, fadrozole indicate a standard deviation of 7% around the measurements of *in vivo* aromatase inhibition. Assuming a Type I error of 10% ($a = 0.10$), a power of 90% ($B = 0.10$) and a standard deviation of 7% six patients per dose-group are required for an absolute difference of 10% I inhibition to be detected as statistically significant with a one-sided test.

II. Results of Study:

A. Core Trial

1. Demographic Data:

Six patients were randomized to the 0.5 mg arm and seven patients to the 2.5 mg arm. Two patients discontinued at examination 5 (day 46) due to unsatisfactory therapeutic response. Two minor protocol violations occurred: One patient had amenorrhea for less than 5 years but had bilateral oophorectomy so was definitely postmenopausal and two patients has been treated with aminoglutethimide > six months prior to enrollment on trial. Mean age of patients on this trial was 59.5 years (range: years); average weight was 63.6 kg (range: kg). All patients had WHO performance status of 0-2 and either slight of no pain. Four patients had abnormal EKGs at baseline: two with sinus tachycardia, one with left ventricular hypertrophy, and one with unspecified abnormalities. Three patients had diastolic hypertension and with two also having systolic hypertension. All patients were postmenopausal. All patients had advanced breast cancer with twelve of the thirteen patients having surgery. Five patients were receptor positive and eight were receptor unknown. Five patients had a disease free interval greater than two years and five patients had a disease free interval less than two years. All patients had hormonal and / or chemotherapy with eleven patients having hormonal therapy for advanced disease. Two patients had received aminoglutethimide for advanced disease prior to entry on this study. The dominant site of advanced disease was soft tissue (46%) in five patients, bone was second in four patients (31%), and visceral disease was dominant in three patients.

2. Efficacy:

Efficacy of *in-vivo* inhibition of aromatase was always greater than 98% regardless of the dose. The p-values and confidence intervals showed no significant differences between the dose groups in terms of the percentage of aromatization inhibition. A statistically significant decrease in estrone and estradiol levels from baseline occurred at each time point with both the 0.5 and the 2.5 mg dose levels. The average estrone levels were suppressed 80% from baseline for both dose levels. Estradiol measurement indicated an 80% suppression from baseline for the 0.5 mg dose level, however at the 2.5 mg dose level estradiol suppression was 80% from baseline at day 22 but only 68% from baseline at day 43/46. Methodological errors are considered to be the cause of the abnormality on day 43/46.

Tumor responses were reviewed for the core trial at six weeks. One patient was considered unassessable. Four patients had progressive disease, four had no change in tumor status, and four were considered responders (three partial and one complete). Two patients (both on the letrozole 0.5 mg arm) of the four with progressive disease were removed from trial at this point. The other two patient with progressive disease were allowed to continue in the extension.

The mean plasma letrozole levels for each dose level are shown in Table AR/ST1.

Table AR/ST1: Mean Letrozole Plasma Trough Levels in Nmol/L (± SD)

Dose (mg/day)	Treatment Day		
	Day 22	Day 43	Day 46
0.5 mg	61.9 (± 17.2)	55.7 (± 16.1)	47.9 (± 16.7)
2.5 m	359 (± 59)	432 (± 134)	435 (± 160)

Plasma levels are similar to those reported in other studies for the same dose levels. Trough levels increased with dose with a slight dose overproportionality for the 2.5 mg/day dose as compared to the 0.5 mg/day dose.

3. Safety Data:

No patients died on study. Six patients reported adverse experiences during the core trial. Patient [redacted] reported bone pain of moderate severity of three years duration was reported at visit 2 but was improved at visit 3 and not considered related to study drug. Patient [redacted] complained of moderate bone pain which started two days before study drug and was improved on visit 2, and ended the day after visit 2. Patient [redacted] bone pain was not considered to be related to study drug. Patient [redacted] developed hot flushes of mild severity on day 7 which persisted beyond day 46 which was possibly (probably related to study drug.) Patient [redacted] had preexisting diarrhea of moderate severity treated with loperamide on visit 2 then codeine. Diarrhea resolved with a lactose free diet. Barium enema was normal. Diarrhea was not assumed to have any relationship to study drug.

Patient [redacted] had worsening back pain during trial not related to study drug. Patient [redacted] had skin irritation on the left chest wall in the area of two tumor ulcers. Skin irritation was treated with antihistamines, and skin irritation was noted to improve by visit 5. Skin irritation was not considered related to study drug.

The following serious adverse reactions were noted. Patient [redacted] treated with letrozole 0.5 mg developed numbness and tingling in the right buttocks and thigh due to impending spinal cord compression. This SAE was not considered related to study drug. Patient [redacted] treated with letrozole 0.5 mg developed severe lymphedema in the left arm around day 28 which worsened until day 43, developed progressive left neck pain which required hospitalization on day 43, and was removed from trial for progressive disease at day 46. Patient 10 treated with letrozole 2.5 mg developed severe Herpes zoster starting about day 8 and requiring hospitalization and acyclovir therapy. No relationship to study drug is assumed.

No clinically relevant changes in vital signs, performance status, pain severity, and ECG parameters are noted. No significant changes in hematological or biochemical laboratory parameters were reported except for the alkaline phosphatase in one patient. Alkaline phosphatase was increased at visit 4 and visit 5 in this patient with known bone metastases considered to have progressive bony disease.

B. Extension Study:

1. Demographics:

Eleven patients were treated in the extension trial, four on letrozole 0.5 mg and seven on the 2.5 mg arm. Two of these eleven had evidence of progressive disease at entry on to the extension trial both in the letrozole 2.5 mg group. At the study cutoff date (September 30, 1994) three patients continued on trial, nine had discontinued. Eight patients were discontinued due to progression of disease, while one patient died. Data from all thirteen patients are included in the efficacy results in this section.

2. Efficacy Information:

Tumor response is as follows: three complete responses (CRs), two partial responses, three patients had disease stabilization (NC), and five patients had progressive disease (PD). Two complete responders, one partial responder, and one patient with stable disease (NC) remained on trial at the data cut-off date. Median duration of response could not be estimated since three of the five responders remained on study. Individual durations of response are for the complete responders reported at 92+ days, 259+ days, 325+ days and for the partial responders reported at 153 and 448+ days. For the three patients with no change the median duration of no change was 430 days. Median time to progression was 153 days and the median time to treatment failure was identical. No survival information is available.

3. Safety Information:

One death was reported while on trial. Patient [redacted] a seventy-six year old female died suddenly while on study due to probable MI. Patient had received more than eighteen months of trial treatment. Death is not considered related to study drug. The following serious adverse events were reported in the extension trial. Patient [redacted] experienced nausea, vomiting, and gall stone ileus six months after the start of study drug which was treated with laparotomy and enterotomy, antibiotics, non-steroidal anti-inflammatory agents, analgesics, bronchodilator, diuretics, dopamine, and antiemetics. Six months later (twelfth month on study drug) patient developed severe abdominal pain diagnosed as diverticulitis. Three months later (after study cut-off date) patient was admitted with abdominal pain, jaundice, and laboratory evidence of hepatorenal failure. Cytology on the abdominal fluid was positive for malignant cells. Patient died six days later due to progressive disease with hepato-renal failure.

Adverse events reported in the extension trial include the following. Patient [redacted] complained of persistent moderate bone pain not related to study medication. Patient [redacted] had mild right clavicular pain starting at month 8 and not considered related to study drug. Patient [redacted] had persistent hot flushes from visit 3 on which at visit 7 were not considered related to study drug (?). Patient [redacted] developed moderate cough with chest infection which was reported 4 months after start of study drug with recovery on antibiotic therapy which are not considered related to study drug. Patient [redacted] reported diarrhea found during the course of the study to be due to lactose intolerance. Patient [redacted] also had marked increase in bony pain due to disease progression not related to study drug. Patient [redacted] had continued skin irritation and tumor ulceration on left chest wall requiring moisten dressings and antihistamines and not related to study drug. Patient [redacted] had moderate nausea after four months on study due to disease progression which was not related to study drug. Patient [redacted] reported moderate soft tissue pain in the right side of the neck after three months on therapy which was related to disease progression and had no relationship to study drug. Patient [redacted] reported mild neck pain which developed after three months on study and persisted for six months, pain in the hands, feet, and left shoulder after eight months of trial treatment, mild dyspepsia at visit 9, and mild increase in serum calcium at visit 10. Patient remained on study drug at cut-off and none of the above adverse reactions are considered due to study drug.

III. Summary:

The primary objective of this study was to show inhibition of aromatase activity *in vivo* in postmenopausal patients with advanced breast cancer treated with doses of letrozole 0.5 mg or 2.5 mg. Both doses resulted in greater than 98% suppression of aromatization as shown by measurements of estrone and estradiol after administration of drug. Other objectives were to show the efficacy and safety of letrozole. Five patients had CR or PR and four remained on drug at study cutoff suggesting letrozole is an efficacious agent in advanced breast cancer in previously treated patient with a long duration of response. Safety data revealed few adverse experiences which could be related to drug therapy none of which were serious in nature. The one death on study does not appear related to study drug therapy.

Clinical Trial Report: AR/ES1, a Phase II Study

Introduction:

In the original NDA submission the study report, protocol and the data listings for Trial AR/ES1 the only Phase II study were not included. The information from this trial is of interest since this was randomized trial of low (0.5 mg) versus high dose (2.5 mg) letrozole and was requested from the applicant. Four volumes (Doc. ID. BZ) were submitted on September 9, 1996 for review.

Protocol Summary:

Study Title: AR/ES1: Double Blind, Between Patient, Multicenter, Phase II, Endocrine Trial Comparing Once Daily Doses of 0.5 mg and 2.5 mg CGS 20 267 in Postmenopausal Patients with Advanced Breast Cancer

Trial Objectives:

1) Examine estrogen (E1, E2, and E1S) measurements over 3 months with treatment of CGS 20267.
2) Evaluate the effects of CGS 20267 after multiple applications (doses) on cortisol and aldosterone levels using the Synacthen™-test.
3) Confirm and complement the endocrine results form the one month Phase I trial in postmenopausal women (AR/BC1).
4) Evaluate the effect of CGS 20 267 on other endocrine parameters.
5) Assess the trough plasma drug concentration levels during treatment with daily doses of 0.5 and 2.5 mg CGS 20 267.
6) Evaluate the tolerability of CGS 20 267.
7) Collect data on antitumor activity.

Trial Design:

Randomized double blind, between patient Phase II endocrine trial in two centers in which patients took two tablets (two 0.25 mg CGS 20 267 tablets or one 2.5 mg and one placebo tablet) daily. All tablets were of the same appearance and taste. Patients must not have received any anti-cancer treatment for three weeks prior to initiation of the trial. Patient visits are scheduled for Day 0, Day 14, and Months 1, 2, 3, and 6.

Patient Selection:

Eligibility Criteria:

Postmenopausal women

Histological or cytological diagnosis of breast cancer
Advanced breast cancer with either locally progressive disease, advanced disease, loco-regional recurrence not curable by surgery or radiotherapy or progressive metastatic disease
Receptor positive or unknown
Documented measurable and / or evaluable disease with objective evidence of progression of disease
History of progression with adjuvant antiestrogen therapy for more than six months or w/in twelve months of discontinuation of antiestrogen therapy or progression while on antiestrogens with advanced disease
WHO performance status > 2
Life expectancy > 3 months
Washout period of $\geq$ 3 weeks since previous anticancer treatment
Signed informed consent

Exclusion Criteria

Rapidly progressive metastatic disease
Endocrine disorders: Diabetes mellitus with blood sugars $\geq$ 1.4 g/L, confirmed hyper or hypothyroidism, Cushing's syndrome, Addison's disease (treated or untreated)
Uncontrolled cardiac disease or unstable angina
Renal Dysfunction : Creatinine $\geq$ 1.5x ULN
Hepatic Dysfunction: Tot. Bili. $\geq$ 1.5x ULN; Transaminases $\geq$ 2.6x ULN; Hgb < 10 g/dl; WBC < 3.0 x 10^9/ul (AGC < 1.5 x 10^9/ul); Plts. $\leq$ 75 x 10^9/ul
Calcium $\geq$ 11.6 mg/dl ($\geq$ 2.75 mmols/L)
Concurrent malignant diseases
Sole manifestation of disease: hilar enlargement, pleural effusion, or ascites
More than one regimen of cytotoxic chemotherapy
Previous first line endocrine therapy other than antiestrogens for advanced disease
Incomplete recovery from toxicities of previous therapy
Discontinuation of topical investigational new drugs < 7 days prior to entry
Discontinuation of systemic investigational new drugs < 30 days prior to entry
Failure to discontinue antiestrogens or other anticancer drugs prior to the start of trial medication
Concomitant use of other anticancer treatments (chemotherapy, immunotherapy, biological response modifiers, and/or endocrine therapy including steroids)

Laboratory Investigations:

Pre-Study:

Hematology[1]

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[1] Hemoglobin, Hematocrit, WBC and differential, Platelet