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NCI, DCPC
Chemoprevention Branch and Agent Development Committee

CLINICAL DEVELOPMENT PLAN: (+)-VOROZOLE

DRUG IDENTIFICATION

CAS Registry No.: 129731-10-8

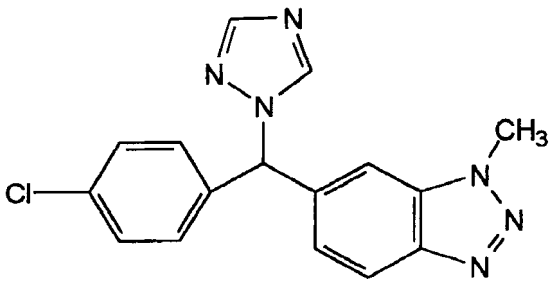
CAS Name (9CI): (S)-6-((4-Chlorophenyl)-1*H*-1,2,4-triazol-1-ylmethyl)-1-methyl-1*H*-benzotriazole

Synonyms: R 83842

Related Compounds:
Vorozole Racemate (R 76713)

***Molecular* Wt.:** 324.8

Structure:



EXECUTIVE SUMMARY

Estrogens have been implicated in the growth and development of certain breast and endometrial cancers, and possibly prostate cancer. Limiting the availability of estrogens by use of estrogen-receptor antagonists (*e.g.*, tamoxifen), or inhibiting estrogen biosynthesis, are potential mechanisms for inhibiting estrogen-dependent tumor cell proliferation. One target for such inhibition is aromatase, an enzyme complex consisting of a cytochrome P450 heme protein and a flavoprotein NADPH cytochrome P450 reductase, which catalyzes the conversion of androstenedione and testosterone to estrone and estrogen, respectively [1]. Aromatase is located in the endoplasmic reticulum of ovary, adipose, breast, prostate, and other peripheral tissues, and has been found at elevated concentrations in breast cancer tumors [2]. Both (+)-vorozole (R 83842) and racemic vorozole (R 76713) have been potent, specific aromatase inhibitors in preclinical *in vitro* and *in vivo* studies and in preliminary clinical studies; activity of the racemate is attributed to the dextroenantiomer, (+)-vorozole [2].

The primary advantages of (+)-vorozole over certain other aromatase inhibitors, such as aminoglutethimide (AG) and 4-hydroxyandrostenedione (4-OHA), are its specificity for inhibiting estrogen synthesis at concentrations which have little effect on other steroid biosynthetic enzymes, its potency, and its relative lack of toxicity [3,4]. Clinical effectiveness of aromatase inhibitors as chemotherapeutic agents was first established with AG; however, toxicity from AG includes nausea, lethargy, ataxia, rash, and blood dyscrasia [3]. AG inhibits synthesis of mineralocorticoids and glucocorticoids [4], requires co-treatment with cortisol replacement therapy [5], and is ineffective against ovarian estrogen production [2]. Clinical effectiveness has also been demonstrated with 4-OHA [5]; however, this compound has limited potential as a chemopreventive agent because

it cannot be administered orally [4], whereas (+)-vorozole is readily absorbed on oral administration. In addition, (+)-vorozole inhibits aromatase activity *in vitro* at concentrations 30- and 1,000-times lower than 4-OHA and AG, respectively [2].

The NCI, Chemoprevention Branch has investigated the chemopreventive activity of (+)-vorozole in the MNU-induced rat mammary gland model and found it effective at inhibiting the formation of tumors. In published *in vivo* studies with established tumors, vorozole racemate and/or (+)-vorozole have been shown to cause growth inhibition or regression in existing tumors in the DMBA- and MNU-induced rat mammary tumor models.

Limited published information on preclinical toxicity and pharmacokinetics is available. Increased ovarian weights and some modulation of other hormone levels (decreased progesterone and increased LH, FSH, androstenedione and testosterone levels) have been reported infrequently at dose levels similar to those required to reduce serum estradiol levels. (+)-Vorozole is well tolerated and apparently well absorbed via oral administration.

No NCI, Chemoprevention Branch-sponsored clinical studies with (+)-vorozole have been undertaken. In published Phase I trials with men and women (pre- and postmenopausal), aromatase inhibition has been successfully demonstrated with (+)-vorozole or vorozole racemate with no reported toxicity and a short biological half-life (hours). Recent Phase II trials with (+)-vorozole indicate some efficacy as a therapeutic agent in breast cancer patients who had relapsed following tamoxifen therapy; daily administration of (+)-vorozole was very well tolerated, with limited, mild clinical side effects.

Vorozole is available through the Janssen Research Foundation in Spring House, PA and Beerse, Belgium. For clinical testing, vorozole racemate and (+)-vorozole have been supplied as tablets (1, 2.5, and 5 mg). In animal testing, vorozole racemate and (+)-vorozole have been formulated in polyethyleneglycol and water. No other sources of (+)-vorozole have been identified.

The NCI, Chemoprevention Branch has tentatively planned short-term Phase II studies in breast and/or prostate cancer patients in the period between diagnosis and surgery. (+)-Vorozole is not currently marketed in the US as a pharmaceutical product for any indication; therefore, it has no history of regulatory activity. An agreement with the Janssen Research Foundation may be required for further development of this agent.

PRECLINICAL EFFICACY STUDIES

(+)-Vorozole inhibited tumor formation in the MNU-induced rat mammary gland model, and (+)-vorozole and/or vorozole racemate inhibited tumor growth in both the MNU- and DMBA-induced rat mammary gland models. (+)-Vorozole and vorozole racemate activity and specificity as aromatase inhibitors have been demonstrated in numerous *in vitro* and *in vivo* studies. (+)-Vorozole has clearly been the active component in the racemic mixture in all test systems.

In NCI, Chemoprevention Branch-*sponsored* chemoprevention studies, oral administration of 2.5 or 5 mg (+)-vorozole/kg-bw/day (7.7 or 15 μmol/kg-bw/day) was highly effective, inhibiting tumorigenesis in the MNU-induced rat mammary gland model by >90% at both doses [6]. At 2.5 mg/kg-bw/day (7.7 μmol/kg-bw/day), continual treatment (study duration=150 days) with (+)-vorozole was found to be more effective than short-term (30–60 days) or intermittent (21 days on/21 days off) dosing schedules [7]. A separate study was recently initiated to investigate lower doses (0.08–1.25 mg/kg-bw, or 0.25– 3.85 μmol/kg-bw) in the same model. In the *in vitro* MMOC assay, (+)-vorozole was not effective; the inactivity in MMOC may be due to the lack of aromatase in the mammary culture system.

In a published chemotherapy study, the growth of existing tumors was inhibited by administration of 400 mg vorozole racemate/kg diet (*ca.* 62 μmol/kg-bw/day) in the MNU-induced rat mammary gland model; the response was similar to that obtained by ovariectomy [8]. In the DMBA-induced rat mammary gland model, ig administration of 1 mg vorozole racemate/kg-bw twice daily (6 μmol/kg-bw/day) caused both regression of established tumors and inhibition of new tumor formation [9]. In the same model, 2.5 mg (+)-vorozole/kg-bw twice daily (15 μmol/kg-bw/day) was shown to be as effective at reducing the multiplicity (tumors/animal), volume, and weight of tumors as ovariectomy, and more effective than similar doses of vorozole racemate; (–)-vorozole was ineffective [10].

Aromatase inhibition and reduction of estrogen/estradiol levels by (+)-vorozole and/or vorozole racemate have been demonstrated *in vivo* in rats, mice, and monkeys. Serum estradiol levels were sig-

nificantly reduced to levels comparable to ovariectomized animals by 0.2 mg vorozole racemate/kg-bw twice daily (1.2 μmol/kg-bw/day) in female rats bearing DMBA-induced mammary tumors [10]. Estradiol levels were also significantly reduced by doses of 5 mg vorozole racemate/kg-bw twice daily (31 μmol/kg-bw/day) in normal female rats [9], and by doses of 0.001 mg (+)-vorozole/kg-bw/day (0.003 μmol/kg-bw/day) in pregnant mare serum gonadotropin-injected female rats [11]. In human JEG-3 choriocarcinoma (malignant trophoblast) tumors grown in female nude mice, vorozole racemate significantly reduced aromatase activity after single oral doses of 0.25 or 5 mg/kg-bw (0.8 or 15 μmol/kg-bw) [12]. In male cynomolgus monkeys, single iv injections of 0.003 mg vorozole racemate/kg-bw (0.009 μmol/kg-bw) inhibited the conversion of androstenedione to estrone [13].

These *in vivo* studies have been supported by *in vitro* studies indicating vorozole racemate and (+)-vorozole as potent, selective inhibitors of aromatase activity, with little effect on other steroid biosyntheses. Inhibition of aromatase activity by (+)-vorozole and/or vorozole racemate has been demonstrated *in vitro* in FSH-stimulated rat granulosa cells [11], and in human placental microsomes [2] and in choriocarcinoma [12], ovarian, adipose stromal, testicular and adrenal cell cultures [14].

PRECLINICAL SAFETY STUDIES

No toxicity studies with (+)-vorozole have been sponsored by the NCI, Chemoprevention Branch. However, in a Chemoprevention Branch-sponsored efficacy study in female rats, oral administration of 5 mg (+)-vorozole/kg-bw/day (15 μmol/kg-bw/day) resulted in increased body weights and muscularity, chronic diestrus, slightly increased ovarian weights, and decreased uterine weights; one (1/20) rat was sacrificed because of a kidney mass [6].

(+)-Vorozole is not currently marketed as a pharmaceutical product, and no specific toxicity or ADME data have been published on this compound; however, animal studies examining estrogen/estradiol levels have not reported severe toxicity from oral administration of either vorozole racemate or (+)-vorozole at doses of 0.001–20 mg/kg-bw/day (0.003–62 μmol/kg-bw/day). Female rats treated orally with vorozole racemate showed a significant increase in ovarian weights at the 20 mg/kg-bw/day (62 μmol/kg-bw/day) dose level; however, no effect on ovarian weights was produced by the lower dose (5 mg/kg-bw twice daily, or 31 μmol/kg-bw/day), which was the lowest estrogen-inhibiting dose [9].

One of the advantages of (+)-vorozole over other aromatase inhibitors currently in use as chemotherapeutic agents is its specificity; doses of (+)-vorozole necessary to affect the biosynthesis of other steroids are generally 10–10,000 times higher than those which inhibit aromatase activity. However, in a few studies, effects on other steroid biosyntheses were observed at doses near the lowest aromatase-inhibiting dose. In normal female rats, progesterone levels were significantly decreased and LH levels were significantly increased by doses of 1–5 mg vorozole racemate/kg-bw/day (3–15 μmol/kg-bw/day), whereas a dose of 5 mg/kg-bw/day was required to significantly reduce serum estradiol levels [9]. In female rats bearing DMBA-induced mammary tumors, oral administration of vorozole racemate resulted in significantly increased levels of testosterone and androstenedione at 0.2 mg/kg-bw/day (0.6 μmol/kg-bw/day), significantly increased LH levels at 1 mg/kg-bw/day, and significantly increased FSH levels at 5 mg/kg-bw/day; 0.2 mg/kg-bw/day was sufficient to significantly reduce serum estradiol levels [10].

CLINICAL SAFETY: PHASE I/II STUDIES

No NCI, Chemoprevention Branch-sponsored Phase I studies have been performed. Four Phase I trials involving single oral doses ranging from 0.25–20 mg (0.01–1.0 μmol/kw-bw) of vorozole racemate or (+)-vorozole have been reported in the literature; in all studies, vorozole was well tolerated and estrogen/estrone levels were significantly inhibited.

Drug Effect Measurement: Aromatase inhibition by single oral doses of 1–20 mg (+)-vorozole or vorozole racemate was reported in four published Phase I pilot studies in males and pre- and postmenopausal females. Estradiol levels were reduced to detection limits in normal male volunteers (n=4) 4–8 hours after a single oral dose of 5 or 10 mg vorozole racemate (*ca.* 0.22–0.44 μmol/kg-bw) [8]. After a single oral dose of 2.5 or 5 mg (+)-vorozole (*ca.* 0.11–0.22 μmol/kg-bw) in male volunteers (n=6), maximum suppression of estradiol was observed at 24 hours; lower doses (0.25–1 mg; *ca.* 0.01–0.04 μmol/kg-bw) were less effective [15]. In healthy, premenopausal women (n=15), a single oral dose of 20 mg vorozole racemate (*ca.* 1.0 μmol/kg-

bw) significantly reduced plasma estradiol levels >60% after 8 hours [8]. Inhibition of aromatase activity by single, oral doses of 1–5 mg vorozole racemate (*ca.* 0.05–0.22 μmol/kg-bw) was evaluated in postmenopausal women (n=12) by the conversion of labelled androstenedione to estrone; almost complete inhibition of aromatase activity was demonstrated over a four-day period [16]. Dose-related effects on aromatase activity or estradiol levels from doses below 1 mg (+)-vorozole or vorozole racemate have not been conclusively reported in the literature.

In four published Phase I/II multidose trials with postmenopausal women (n=21–29), 1–5 mg (+)-vorozole or vorozole racemate qd (*ca.* 0.05– 0.24 μmol/kg-bw qd) significantly decreased estradiol levels to near or below detection levels after one month of dosing.

Safety: Doses of 0.25–20 mg (+)-vorozole or vorozole racemate (*ca.* 0.01–1.0 μmol/kg-bw) have been well tolerated with no reported side effects in all single-dose clinical studies.

Side effects reported from multiple dosing with 1–5 mg (+)-vorozole or vorozole racemate qd (*ca.* 0.05–0.24 μmol/kg-bw qd) in four Phase II studies in postmenopausal, advanced breast cancer patients (n=24–29 per study) have included malaise, headache, nausea, anorexia, fluid retention, alopecia, light-headedness, hot flashes, GI symptoms, allergic skin reactions, and yeast infections; these effects have all been reported as mild and limited for median treatment durations of 1–24 months [4,17–19]. Some of these side effects (malaise, headache, nausea, fluid retention, light-headedness, and hot flashes) are expected from decreased estrogen levels in postmenopausal women.

Limited effects on non-target steroid levels have been reported from one Phase I and three Phase II multidose studies (1–5 mg (+)-vorozole or vorozole racemate qd, or *ca.* 0.05–0.24 μmol/kg-bw qd) in postmenopausal, advanced breast cancer patients [4,15, 17–19]. Significantly increased LH and FSH levels and significantly decreased cortisol and sex hormone binding globulin (SHBG) were observed after one month of 1–5 mg (+)-vorozole or vorozole racemate qd [4,15,17]; otherwise, no effects on other steroid levels (aldosterone, androstenedione, 17α-hydroxyprogesterone, testosterone, or thyroid-stimulating hormone) have been reported in these Phase I/II studies.

ADME: (+)-Vorozole and vorozole racemate are readily absorbed following oral administration. Peak plasma levels are reached within one hour of administration, then vorozole decays biphasically, with a terminal $t_{½}$ of less than 8 hours [8,15]. In a Phase I study with healthy male volunteers, single oral doses of 0.25–5 mg (+)-vorozole (*ca.* 0.01– 0.22 μmol/kg-bw) resulted in a dose-related increase in plasma levels (C_{max}=3.68–107 ng/ml) [15]. In a separate Phase I trial in healthy males, peak plasma levels were 80 and 156 ng/ml for doses of 5 and 10 mg vorozole racemate (*ca.* 0.22– 0.44 μmol/kg-bw), respectively [8].

In two multidose Phase II studies with postmenopausal, advanced breast cancer patients, trough plasma vorozole levels after one month of daily administration were 2.9, 12.0, and 57.5 ng/ml for doses of 1, 2.5, and 5 mg (+)-vorozole qd (*ca.* 0.05– 0.24 μmol/kg-bw qd), respectively [4]. In a separate study, daily doses of 2.5 mg (+)-vorozole qd (*ca.* 0.12 μmol/kg-bw qd) showed consistent steady-state trough levels from 1 to 12 months [17].

CLINICAL EFFICACY: PHASE II STUDIES

No Phase II clinical efficacy studies examining (+)-vorozole as a chemopreventive agent have been sponsored by the NCI, Chemoprevention Branch or published in the literature.

Four Phase II chemotherapeutic clinical studies are currently ongoing or have recently been completed to examine the efficacy of (+)-vorozole or vorozole racemate in advanced breast cancer patients. Temporary disease response or stabilization was observed in 57– 63% of all evaluable patients treated for 1–24 months with doses of 1–5 mg (+)-vorozole qd (*ca.* 0.05–0.24 μmol/kg-bw qd); serum estradiol levels were significantly suppressed, and all doses were well tolerated [4,17–19].

PHARMACODYNAMICS

The relationship between a defined decrease in estrogen levels and clinical effectiveness has not yet been clearly demonstrated. The lowest dose of (+)-vorozole reported to decrease estradiol levels in female rats was 0.001 mg/kg-bw/day (0.003 μmol/kg-bw/day) [11]. In chemotherapy studies reported in the literature, doses of 2–5 mg (+)-vorozole or vorozole racemate/kg-bw/day (6–15 μmol/kg-bw/day) were required to cause regression of existing tumors [8–10]; efficacy was not demonstrated at lower doses (0.2–0.63 mg/kg-bw twice daily, or 1.2–

3.9 μmol/kg-bw/day). The threshold aromatase inhibition necessary for tumor inhibition in animals has not been defined. Doses of 2.5 or 5 mg (+)-vorozole/kg-bw/day (7.7 or 15 μmol/kg-bw/day) effectively inhibited tumorigenesis in the MNU-induced rat mammary gland tumor model [6]. No results from chemopreventive studies at lower doses have been reported.

In clinical trials, aromatase inhibition has been demonstrated from single oral doses of 0.25–5 mg (+)-vorozole (*ca.* 0.01–0.22 μmol/kg-bw), while some chemotherapeutic response has been reported from doses of 1 mg (+)-vorozole qd (*ca.* 0.05 μmol/kg-bw qd). Inconsistent chemotherapeutic response has not been attributed to inadequate plasma vorozole levels [17]. Instead, responsiveness may be related to estrogen-dependence; tumors which have not developed estrogen-independence are likely to be more sensitive to modulation of estrogen levels by (+)-vorozole treatment. Potentially, even lower doses of (+)-vorozole could be effective at earlier stages of tumorigenesis, since the cells would be more likely to be estrogen-dependent.

PROPOSED STRATEGY FOR CLINICAL *DEVELOPMENT*

Drug Effect Measurement Issues

Since the proposed mechanism of chemopreventive efficacy is the suppression of circulating estrogen levels, clinical studies should include monitoring of plasma estrogen levels; however, the correlation between estrogen levels and clinical effectiveness has not yet been clearly demonstrated. Dowsett [3] argues that the best measurements of aromatase inhibition *in vivo* are plasma estradiol levels because estradiol is the most potent estrogen, plasma is the most relevant and easily available fluid, and highly sensitive methods have been developed for this assay.

Effects on aromatase activity (conversion of androstenedione to estrone) can also be measured directly; however, methods reported for this measurement involve injection of radiolabeled substrates [16], which is impractical for most clinical trials.

Safety Issues

Both (+)-vorozole and vorozole racemate have been well tolerated in all clinical studies. No side effects have been reported from single oral dosing studies. Side effects reported in multidose Phase II studies included headache, nausea, anorexia, hot flashes, GI symptoms, allergic skin reactions, and yeast infections; generally these effects have been reported as mild and limited. Some of the side effects reported are expected from decreased estrogen levels in postmenopausal women.

Two studies with rats reported effects on ovarian weights from chronic oral administration of (+)-vorozole or vorozole racemate. In an NCI, Chemoprevention Branch-sponsored efficacy study in rats, oral administration of 5 mg (+)-vorozole/kg-bw/day (15 μmol/kg-bw/day) resulted in chronic diestrus, slightly increased ovarian weight and decreased uterine weights [6]. A study with female rats treated orally with vorozole racemate found a significant increase in ovarian weight at the 20 mg/kg-bw/day (62 μmol/kg-bw/day) dose level; however, no effect on ovarian weight was produced at the lowest estrogen-inhibiting dose of 5 mg/kg-bw/day (15 μmol/kg-bw/day) [9]. It is unclear what the long-term effects of ovarian proliferation are in humans.

While one of the advantages of (+)-vorozole over other aromatase inhibitors is its specificity, effects on the biosynthesis of other steroids have been observed in a few animal studies at dose levels near the lowest aromatase-inhibiting levels. Preclinical and clinical effects of (+)-vorozole and/or vorozole racemate on androstenedione, cortisol, FSH, LH, progesterone, SHBG, and testosterone indicate the necessity of monitoring hormonal levels during clinical trials. Decreased estrogen levels from (+)-vorozole administration appear to stimulate a positive feedback effect on FSH and LH synthesis.

The long-term effects of (+)-vorozole administration are unknown; estrogen-sensitive parameters such as decreased bone mass and increased risk for heart disease have not been addressed.

Pharmacodynamics Issues

Insufficient data are available to correlate plasma vorozole and estrogen levels to either aromatase activity, chemopreventive efficacy, or toxicity. Evidence from limited data indicate that single oral doses as low as 0.001 mg (+)-vorozole/kg-bw (0.003 μmol/kg-bw/day) in rats and 0.25 mg qd (*ca.* 0.01 μmol/kg-bw qd) in clinical studies were sufficient to observe some reduction in estradiol levels, while doses of 2–5 mg (+)-vorozole or vorozole racemate/kg-bw/day (*ca.* 6–15 μmol/kg-bw/day) in rats

and 1 mg (+)-vorozole qd (*ca.* 0.05 μmol/kg-bw qd) in humans were required for mammary tumor regression. These results imply that relatively high inhibition of aromatase activity is required to achieve therapeutic efficacy with this compound. The minimum decrease in estradiol to obtain chemopreventive activity, without undue effect on the ovary, needs to be established. No ADME studies in animals have been published.

In Phase II clinical trials, plasma vorozole levels of 2.9–95 ng/ml were observed after one month of dosing with 1–5 mg qd (+)-vorozole or vorozole racemate (*ca.* 0.05– 0.24 μmol/kg-bw qd); estradiol levels were significantly inhibited at these doses. Interestingly, in one Phase I study, maximum suppression of estradiol levels occurred after 24 hours, although the mean terminal plasma $t_{1/2}$ for vorozole was less than eight hours [15].

Regulatory Issues

(+)-Vorozole and vorozole racemate are not currently marketed as pharmaceutical products for any indication. Since Janssen has initiated development of both the racemate and the (+)-enantiomer, data from toxicity studies required by the FDA may be available. Also, since the Janssen Research Foundation appears to be the sole source of vorozole, an agreement with them should be sought to allow access to preclinical (*i.e.*, higher dose and longer toxicity studies to characterize adverse effects in rats and dogs) and clinical data to support the proposed NCI studies.

According to the FDA Policy Statement for the Development of New Stereoisomeric Drugs, differences in pharmacokinetics of single enantiomers *versus* racemic mixtures and significant conversion to the other isomer must be evaluated for single enantiomer products developed from marketed racemic mixtures [20]. It is not clear if this requirement is limited to newly resolved enantiomers from racemic mixture products currently on the market. Therefore, it needs to be determined whether the FDA will require that pharmacokinetic and isomeric stability studies be performed with both (+)-vorozole and vorozole racemate.

Intermediate Biomarker Issues

Evidence of mammary tumor regression and inhibition of tumor growth by (+)-vorozole in humans and rats suggests that evaluation of histological biomarkers (*i.e.*, size and grade of DCIS and other lesions and nuclear morphometry) and proliferation markers (PCNA and MIB-1) would be of high interest. Intermediate biomarkers of interest in the prostate include PSA, MIB-1, c-*erb*B-2, PIN, angiogenesis, DNA ploidy, nuclear morphometry and PCNA.

Supply and Formulation Issues

Vorozole is available though the Janssen Research Foundation in Spring House, PA, or Beerse, Belgium. For clinical testing, vorozole racemate and (+)-vorozole have been supplied as tablets (1, 2.5 and 5 mg). In animal testing, vorozole racemate and (+)-vorozole have been diluted in polyethyleneglycol and water. No other sources of (+)-vorozole have been identified.

An agreement with the Janssen Research Foundation may be required for supply of the formulated product.

Clinical Studies Issues

The NCI, Chemoprevention Branch is considering short-term Phase II studies in breast or prostate cancer patients with vorozole administered in the period between diagnostic biopsy and definitive surgery. While the role of estrogen in the development of breast cancer has been extensively investigated, its relationship to prostate cancer is less well understood. Although pharmacological estrogen treatment can lead to prostatic atrophy in rats [21] and has been used successfully to reduce the growth of prostate tumors in humans [22–24], it has also been associated with induction of prostatic hyperplasia [*e.g.*, benign prostate hyperplasia (BPH)] [25, 26]. Since combining estrogen with testosterone is more effective than the latter alone in inducing prostate tumors in rats [*e.g.*, 27], it is hypothesized that estrogen may be required in general for androgen-mediated stimulation of prostatic epithelial proliferation [reviewed in 26]. In support of this theory, the ratio of estrogen to testosterone increases with age, concomitant with increases in incidences of both BPH and prostate cancer. In fact, both estrogen receptors and conversion of testosterone to dihydroxytestosterone occur in the stroma, suggesting a paracrine stromal-epithelial interaction. The proposed Phase II prostate trial would evaluate modulation of intermediate biomarkers of prostate carcinogenesis by aromatase inhibition in comparison with other types of hormonal interventions for androgen blockade (antiandrogen, LHRH

agonist) to determine the most effective strategy. Combining vorozole with a 5α-reductase inhibitor to suppress the estrogen-dependent negative feed-back signal which causes the pituitary-hypothalamic axis to stimulate androgen production may also be desirable.

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