Report from the FDA

Fulvestrant in Postmenopausal Women with Advanced Breast Cancer

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Abstract

Purpose: **Patients with hormone-sensitive breast cancer who have responded to tamoxifen (TAM) may receive additional benefit from a second endocrine agent after progression or relapse after TAM therapy. Fulvestrant (FVT; Faslodex; i.m. injection, ICI 182,780; AstraZeneca Pharmaceuticals, Wilmington, DE) was developed as a selective antagonist of estrogen. In postmenopausal women, FVT is reported to inhibit the proliferative effects of estrogen on sensitive tissues and has no apparent measurable estrogenic activity. In this report, we describe the data and analyses supporting marketing approval for FVT by the United States Food and Drug Administration (FDA).**

Experimental Design: **The FDA review of 16 clinical trials and 6 pharmacokinetic trials, as well as preclinical pharmacology and chemistry data, are described. The bases for marketing approval are summarized.**

Results: **Toxicology studies in the mouse, rat, and dog showed minimal toxicity except for antiestrogenic effects. Because of FVT aqueous insolubility, an i.m. formulation, given at monthly intervals, was selected for clinical studies. Pharmacokinetic studies demonstrated sustained concentrations with monthly injection. In *in vitro* studies FVT was extensively metabolized, primarily by hepatic cytochrome P450 3A4. Phase I studies showed minimal toxicity, and the maximal dose (250 mg) was limited by FVT solubility. In two Phase III trials, 851 patients were randomized to either 250 mg FVT i.m. monthly or to anastrozole (ANZ) 1 mg p.o. daily. Ninety-six percent of patients had received TAM previously for early (adjuvant treatment) or advanced breast cancer. Response rates (RR) were 17% for both FVT and ANZ study arms in the North American trial, and were 20% *versus* 15% for FVT *versus* ANZ, respectively, in the European trial. There were no observed differences between study arms with respect to time to progression or survival. The most common FVT adverse events reported as potentially treatment-related were injection site reactions and hot flashes.**

Conclusions: **FVT was approved on April 25, 2002 by the FDA for the treatment of hormone receptor-positive metastatic breast cancer in postmenopausal women with disease progression after antiestrogen therapy. The recommended dose is 250 mg i.m. monthly as a single 5 ml injection or as two concurrent 2.5 ml injections into the buttocks. Approval was based on results of two randomized trials comparing response rates and time to progression of FVT- and ANZ-treated patients. Complete prescribing information is available on the FDA website.**

Introduction

Since the discovery by Beatson (1) in the 19th century that ovarectomy could cause a reduction in breast tumor size, hormonal manipulation has become a cornerstone in the treatment of hormone-sensitive breast cancer (2). TAM[2] (Nolvadex; Astra Zeneca), a nonsteroidal antiestrogen first synthesized in 1963, originally failed as a fertility agent but was subsequently noted to have activity against breast cancer (3). In 1977, TAM was granted United States marketing approval for the treatment of metastatic breast cancer based on tumor responses. TAM has been shown subsequently to reduce the incidence of relapse as well as the occurrence of contralateral breast cancer in patients after surgery for localized disease (4). The reduction in contralateral new tumors led to a study that demonstrated that TAM reduced the risk of invasive breast cancer in women with ductal carcinoma *in situ* and for the reduction in breast cancer incidence in high-risk women (5). After demonstration of safety and efficacy, TAM was granted marketing approval by the United States FDA for these supplemental indications.

When disease progresses after an initial response to hormonal therapy or recurs after adjuvant therapy, subsequent endocrine therapy may provide benefit. Several classes of hormonal agents have demonstrated efficacy in this setting. Progestins were initially used but have side effects of weight gain, edema, and heart failure (6). AIs reduce estrogen production in postmenopausal women by inhibiting the aromatase enzyme, which converts androgens to estrogens. AG was the first AI evaluated for the treatment of breast cancer. A nonselective inhibitor of steroid synthesis, AG was shown to have activity in relapsed metastatic breast cancer but required concomitant corticosteroid administration (7). More selective AIs were developed to inhibit the conversion of androstenedione to estrone

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[2] The abbreviations used are: TAM, tamoxifen; FDA, Food and Drug Administration; AI, aromatase inhibitor; AG, aminoglutethamide; LZ, letrozole; AZ, anastrozole; FVT, fulvestrant; ER, estrogen receptor; TTP, time to progression; MA, megesterol acetate; RR, response rate; PgR, progesterone receptor; CI, confidence interval; PS, performance status.

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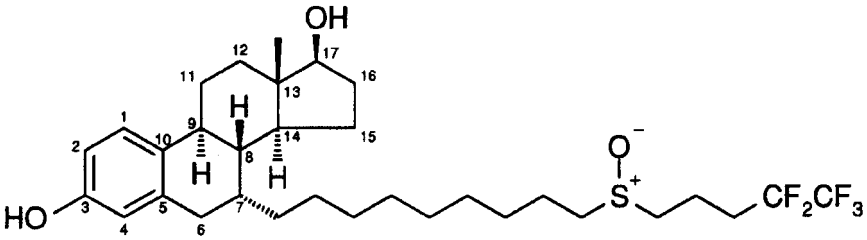

Fig. 1 Structure of FVT. 7α-[9-[(4,4,5,5,5-Pentafluoropentyl)sulfinyl]nonyl]estra-1,3,5 (10)-triene-3,17β-diol.

specifically, with fewer associated side effects. Three products have subsequently gained marketing approval: exemestane, a steroidal inhibitor of aromatase, and the nonsteroidal AIs LZ and AZ (8). Clinical trials comparing TAM with several of the AIs as the initial treatment for metastatic breast cancer have demonstrated that AIs are at least as effective as TAM and may produce fewer serious adverse events, such as venous thromboembolism (9).

TAM possesses agonist as well as antagonist estrogenic activity, and is classified as a selective ER modulator (10, 11). Partial estrogenic activity may theoretically provide beneficial effects, such as delaying or preventing osteoporosis, but also may increase the risk of adverse side effects including thrombosis, endometrial hyperplasia, carcinoma, and sarcoma (12, 13). Discontinuation of TAM may also produce withdrawal responses in breast cancer patients, and this is thought to be a result of partial estrogenic effects (14). TAM clinical trial results in the adjuvant and risk reduction settings have revealed a small but finite estrogenic risk pattern, including an increased risk of venous thromboembolism and endometrial cancer. The adverse estrogenic effects of TAM led to the search for more potent and specific estrogen inhibitors. Toremifine (Fareston; Shire US, Florence, KY), a nonsteroidal antiestrogen approved in 1997 for the initial treatment of metastatic breast cancer, was developed with this intent. However, Toremifine is also a partial estrogen agonist and has some estrogenic effects including increased risk of thrombophlebitis. In comparative studies, the efficacy and tolerability of toremifene and TAM were similar (15). Raloxifene (Evista; Eli Lilly & Co, Indianapolis, IN) is a selective ER modulator that causes activation of certain estrogenic pathways and blockade of others. Raloxofene has received marketing approval for the treatment and prevention of osteoporosis in postmenopausal women but has not demonstrated efficacy for the treatment of breast cancer. Raloxifene is being studied for the reduction of breast cancer risk in the Study of TAM and Raloxifene Trial. FVT was developed in the search for a specific antiestrogen with high ER affinity without estrogenic effects (16).

Chemistry. FVT is a steroid and is the active component of Faslodex Injection. FVT is designated chemically as 7α-[9-[(4,4,5,5,5-Pentafluoropentyl)sulfinyl]nonyl]estra-1,3,5 (10)-triene-3,17β-diol. It is a white powder, with the molecular formula $C_{32}H_{47}F_5O_3S$, and a molecular weight 606.77. The structure is shown in Fig. 1. FVT is a mixture of 2 diastereoisomers, ICI 182,780 Sulfoxide A (ICI 208,926) and ICI 182,780 Sulfoxide B (ICI 208,927) in the ratio of ~45:55. Both diastereoisomers are pharmacologically active and of similar potency. FVT is highly lipophilic and does not ionize at physiological pH. Oral delivery was explored in animals and humans using a range of formulation types, but it was not possible to achieve adequate bioavailability by this route. A nonaqueous cosolvent-based long-acting depot formulation was developed i.m. for clinical study. Faslodex is commercially supplied as two 5-ml prefilled syringes containing 2.5 ml (50 mg/ml) or one 5 ml prefilled syringe containing 5 ml (50 mg/ml). The prefilled syringe is composed of a 5-ml clear glass barrel and fitted with a tamper evident closure. The recommended storage temperature range is 2°C-8°C (36°F-46°F).

Pharmacology and Toxicology. FVT binds to ERs in a competitive manner, with affinity comparable with estradiol. *In vitro* studies with several cell lines showed a putative decrease in measurable ER protein after a 48-h incubation, when assessed by an indirect immunofluorescence staining technique. FVT is a reversible inhibitor of the growth of estrogen-sensitive human breast cancer cells and TAM-resistant cells *in vitro*. In a series of *in vivo* xenograft studies, FVT delayed the establishment of tumors from xenografts of human breast cancer MCF-7 cells, inhibited the growth of established estrogen-sensitive xenografts, and inhibited the growth of TAM-resistant breast tumors in nude mice. It is important to note that *in vitro*, cultured MCF-7/LCC9 FVT-resistant cells were also TAM resistant. *In vivo*, FVT-resistant tumors transplanted into castrated mice showed cross-resistance to TAM. In nontumor-bearing tissues, FVT blocked the tropic actions of endogenous and exogenous estrogens in rodents and monkeys, as well as blocked the uterotropic action of TAM in the rat.

The sponsor has asserted that FVT is a "pure" antiestrogen, which acts as an ER down-regulator. This claim was based on *in vitro* studies in FVT-treated tumor cell lines showing a decrease in measurable ER protein, as assessed by an indirect immunofluorescence staining technique. However, there was no data presented to demonstrate that the immunoreactivity of the "receptor" was independent of conformation changes associated with ligand binding. Thus, the possibility that FVT may change the conformation of the receptor and, thus, its immunoreactivity, without actually decreasing the amount of receptor protein present, cannot be excluded. In clinical specimens from women with primary breast cancer, the administration of FVT (50 mg, 125 mg, or 250 mg single i.m.) or TAM (20 mg/day p.o. for 14–22 days) produced dose-dependent reductions in ER expression (by immunofluorescence staining) as compared with placebo. However, the reduction in ER expression caused by FVT was significantly greater than that of TAM only at the highest dose of FVT (250 mg) tested (17). The FDA concluded that insufficient evidence had been presented to demonstrate that FVT represents a new class of ER down-regulators.

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Absorption, Distribution, Metabolism, and Excretion. Distribution, elimination, and metabolism were investigated in rat and dog using a metabolically stable radiolabeled form of FVT. FVT was well absorbed and widely distributed after i.m. administration, and was eliminated almost entirely in feces in both rats and dogs. Metabolism was qualitatively similar in rats, dogs, and humans. FVT was rapidly cleared by the hepatobiliary route with excretion primarily via the feces (~90%). Renal elimination was negligible (<1%).

Toxicology. Nonclinical toxicity studies included acute (single dose) toxicity studies in rodents and multiple dose toxicity studies in rats and dogs of up to 6 and 12 months duration, respectively. The relative doses of FVT used in the long-term studies in rats and in dogs were ~4-fold higher than the proposed clinical dose (250 mg/month or185 mg/m^2/month). Drug exposure (area under the curve) ranged from 4- to 10-fold, and C_{max} ranged from 9- to 38-fold higher in animals than the values attained in clinical testing. In rats and dogs, atrophy of the uterus, cervix, and vagina was observed after long-term dosing. Ovarian changes included increase in the size and number of Graafian follicles and a reduction in the number of active or regressing corpora lutea. An absence of clinical signs of estrous activity was recorded in the 12-month dog study with evidence of reversibility. In male rats after 6 months of dosing, a loss of spermatozoa from the seminiferous tubules, seminiferous tubular atrophy, and degenerative changes in the epididymides were seen. Changes in the testes and epididymides had not recovered by the end of a 4-week recovery period.

Carcinogenesis and Mutagenesis. A 2-year carcinogenesis study was conducted in female and male rats, which demonstrated an increased incidence of benign ovarian granulosa cell tumors and testicular Leydig cell tumors, consistent with the pharmacology-related endocrine feedback alterations in gonadotropin levels caused by antiestrogens. FVT was not mutagenic or clastogenic in *in vitro* tests or *in vivo* micronucleus test in the rat.

Pregnancy. In pregnant female rats, administration of doses of ≥0.01 mg/kg/day FVT (~100-fold lower than the human recommended dose on a body surface area basis) caused a reduction in female fertility and in embryonic survival. Similarly, rabbits failed to maintain pregnancy when dosed with FVT during the period of organogenesis. FVT caused an increased incidence of fetal abnormalities and variations in rats and rabbits, respectively, when administered during the period of organogenesis. FVT has been shown to cross the placenta after single i.m. doses of 6.0 mg/m^2 in rats and 3 mg/m^2 in rabbits resulting in fetal tissue drug concentrations 2 h after dosing of 76 and 97% compared with maternal plasma, respectively. Lastly, FVT is found in rat milk at levels significantly higher than those in rat plasma. The maximal drug exposure in pups from FVT-treated lactating dams was estimated as 10.3% of the administered dose. FVT is labeled pregnancy category D and, because of the potential for fetal harm and loss of the pregnancy, is contraindicated in pregnant women. There are currently no studies in pregnant women.

Clinical Pharmacology and Pharmacokinetics. In clinical use, drug exposure is controlled by the properties of the formulation: the elimination half-life is ~40 days after i.m. injection of the marketed product compared with 19 h after injection of an i.v. formulation. The ratio of C_{max}:C_{trough} for a 5-ml i.m. injection and a 28-day interdose interval is ~2.5, and levels approach approximate steady-state after 3 doses. The pharmacokinetics of the 250-mg dose were similar when administered as either a single 5-ml or as two 2.5-ml injections. FVT is highly bound (99%) to plasma proteins (predominantly lipoproteins) and has a large steady-state volume of distribution (approximately 3–5 liter/kg), which suggests that the distribution of the compound is largely extravascular. No clear relationship has been established between efficacy measurements (TTP, objective response) and pharmacokinetic parameters such as C_{max}, C_{min}, area under the curve, and clearance.

FVT is extensively metabolized. Of the metabolites characterized in human plasma, only the 17-keto compound demonstrates significant antiestrogenic activity, and its activity is 4.5-fold lower than that of the parent compound. In *in vitro* studies, [^{14}C]FVT metabolism was markedly reduced by ketoconazole, a selective inhibitor of CYP 3A4. Furafylline, sulfaphenazole, omeprazole, and quinidine, selective chemical inhibitors of CYP 1A2, 2C9, 2C19, and 2D6, respectively, had no obvious inhibitory effect on [^{14}C]FVT metabolism. FVT did not inhibit CYP enzymes *in vitro* and, thus, would not be expected to raise concentrations of concurrently administered drugs metabolized by CYP enzymes. This was verified by a clinical pharmacokinetic trial of the coadministration of midazolam (metabolized by CYP 3A4) and therapeutic doses of FVT. A clinical pharmacokinetic trial with rifampin showed that the pharmacokinetics of FVT are unlikely to be affected by cytochrome P450 inducers. No meaningful differences in FVT pharmacokinetic parameters were seen between male and female subjects or among subjects with different ethnic backgrounds. Mild renal insufficiency and mild hepatic insufficiency had no apparent effect on the FVT pharmacokinetics. Pharmacokinetic data were not available in patients with moderate or severe hepatic impairment.

Regulatory Background. Before FVT, marketing approvals of hormonal agents for second-line treatment of advanced breast cancer have been based on comparisons to treatment with a progestin, MA, or the nonselective AI, AG (Table 1). ANZ treatment produced objective RRs comparable with, or better than, MA treatment. Two clinical trials compared ANZ and MA for second-line hormonal treatment. There was no significant difference in RRs in either trial, although in one trial the observed RR was numerically higher in the ANZ group (10% *versus* 5%). TTP was similar in treatment arms of both studies (Table 1). No second line hormonal breast cancer treatment has thus far demonstrated a significantly improved RR compared with either AG or MA. However, in single trials, LZ and exemestane treatments each demonstrated prolonged TTP compared with MA treatment (18). In the studies supporting FVT marketing approval, monthly i.m. administration of FVT was compared with daily oral administration of a selective AI, ANZ, in a population of patients whose cancer had progressed on TAM therapy for advanced disease or had relapsed after adjuvant TAM therapy.

Clinical Studies. The FVT application included data from 1877 patients in multiple clinical trials treated with either FVT or with a control treatment (ANZ, TAM, or goserelin acetate. Patients (850) were randomized to FVT or ANZ in

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Table 1 FVT compared with other hormonal drugs approved for second-line treatment of metastatic breast cancer[a]

Hormone	FVT				AZ				Exemestane		LZ	
Number of efficacy trials in NDA	2				2				1 Phase III, 2 Phase-II		1 pivotal, 1 confirmatory	
Design	Open-label		Double blind		Randomized controlled				Randomized double-blind		Randomized controlled	
Statistical analysis	Noninferiority				Superiority				Noninferiority		Superiority	
Sample size	451		400		764				769		552	
	Trial 0020		Trial 0021		Trial 0004		Trial 0005		EX	MG	L	MG
	FVT	AZ	FVT	AZ	AZ	MG[b]	AZ	MG				
Dose (mg)[c]	250[d]	1	250[d]	1	1	160	1	160	25	160	2.5	160
ER + status	70%	76%	83%	80%	85%	79%	62%	58%	67%	68%	57%	
RR (CR + PR)	20%	15%	17%	17%	10%	5.5%	10%	10%	15%	12.4%	24%	16%
Odds ratio 95% CI *P*	1.46 (0.89, 2.41) $P = 0.13$		1.0 (0.59, 1.70 $P = 1.0$		1.95 (0.65, 5.91) $P = 0.17$		0.99 (0.40–2.50) $P = 0.99$		—		1.58 (0.94–2.66) $P = 0.06$	
Difference in RR 95% CI	5.42 (−1.44, 14.8)		−0.02 (−6.28, 8.87)		—		—		−2.6 (−7.5, +2.3)		—	
TTP median days	166	156	165	103	170	151	132	120	142	116	170	168
Hazard ratio CI, *P*	0.98 (0.79–1.21) $P = 0.84$		0.92 (0.74–1.14) $P = 0.43$		0.89 (0.61–1.3) $P = 0.48$		1.04 (0.74–1.46) $P = 0.82$		0.84 (0.71–0.99) $P = 0.037$		0.77 (0.60–0.98) $P = 0.03$	

[a] Table provided courtesy Drs. Rajeshwari Sridhara, Susan Honig, and Patricia Cortazar.
[b] MG, megace; EX, examestene; CR, complete response; PR, partial response.
[c] Daily dose in mg p.o.
[d] Monthly dose i.m.

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Table 2 Demographic characteristics

Demographic characteristic	Trial 0021 North American		Trial 0020 European	
	FVT 250 mg $n = 206$	AZ 1 mg $n = 194$	FVT 250 mg $n = 222$	AZ 1 mg $n = 229$
Age (y)				
Mean	63	62	63	64
SD	11	12	10	11
Age distribution, *n* (%)				
<45	12 (5.8)	12 (6.2)	8 (3.6)	8 (3.5)
≥45 to <65	96 (46.6)	102 (52.6)	107 (48.2)	103 (45.0)
≥65 to <75	61 (29.6)	48 (24.7)	74 (33.3)	77 (33.6)
≥75	37 (18.0)	32 (16.5)	33 (14.9)	41 (17.9)
Weight (kg)				
Mean	71.7	72.7	68.9	67.8
SD	14.7	16.3	13.0	11.8
Race (%)				
White	177 (85.9)	157 (80.9)	214 (96.4)	218 (95.2)
Black	20 (9.7)	24 (12.4)	0	0
Hispanic	8 (3.9)	10 (5.2)	0	1 (0.4)
Asian/Oriental	0	1 (0.5)	1 (0.5)	2 (0.9)
Other	1 (0.5)	2 (1.0)	7 (3.2)	8 (3.5)
WHO performance status, *n* (%)				
0	90 (43.7)	84 (43.3)	104 (46.8)	104 (45.4)
1	94 (45.6)	95 (49.0)	93 (41.9)	98 (42.8)
2	21 (10.2)	15 (7.7)	25 (11.3)	27 (11.8)

pivotal efficacy trials. A total of 1178 patients were exposed to FVT and were included in the safety evaluation. The largest group included the 591 patients who were included in the pivotal efficacy trials, and these patients also received the longest exposures to FVT.

Phase I and II Studies. Initial Phase I clinical trials with FVT were conducted with a short-acting formulation given as either a single i.m. dose or multiple daily doses. FVT was given to healthy postmenopausal women to assess the endocrine effects and antiestrogenic effects of FVT on the reproductive tract. FVT 250 mg prevented estrogen-stimulated endometrial thickening as measured by ultrasound. In a study of premenopausal patients undergoing hysterectomies for benign gynecological disease, 12 weeks of FVT was compared with placebo or 12 weeks of goserelin acetate, a gonadotropin-releasing hormone agonist, which suppresses ovarian function in premenopausal women. FVT had no measurable effect on the endometrium compared with placebo, whereas Goserelin caused thinning and atrophy of the endometrium. In premenopausal women, FVT had no significant effects on hypothalamic-pituitary axis hormones and no observed effects on the ovarian function. There were no changes in markers of bone resorption (cross-linked N-telopeptides free deoxypyridinoline).

In a small randomized Phase II study, postmenopausal women undergoing surgical resection of ER-positive breast cancers were randomized to treatment with FVT or TAM before surgery. Excised tumors were examined for changes in proliferative index, as well as for ER and PgR levels. FVT caused a decrease in both ER and PgR levels, whereas TAM caused a decrease in measurable ER but not PgR. Both drugs caused a similar decrease in the Ki67 proliferative labeling index in tumors, consistent with ER activity suppression (19).

Phase III Studies. The FVT marketing application included two randomized, controlled clinical studies in postmenopausal women with locally advanced or metastatic breast cancer: a North American double-blinded study and a predominantly European open-label study. All of the patients had disease progression after previous therapy with an antiestrogen in the adjuvant or advanced disease setting. The majority of patients in these trials had ER+ and/or PgR+ tumors. Patients who had ER−/PgR− or unknown disease must have shown prior response to endocrine therapy. Eligibility criteria required the presence of at least one measurable or evaluable lesion. In both trials patients were randomized to receive either FVT 250 mg i.m. monthly or ANZ 1 mg p.o. daily. The North American trial was a double-blind, double-dummy randomized trial conducted in 400 postmenopausal women in the United States and Canada (20). The European trial was an open-label, randomized trial conducted in 451 patients in Europe, Scandinavia, Australia, and South Africa (21). Patients on the FVT arm of the North American trial received two injections (2 × 2.5 ml), one into each buttock, of the long-acting depot formulation. In the European trial, FVT patients received a single injection (1 × 5 ml). In both trials, an additional study arm evaluated the FVT dose of 125 mg/month. This arm was discontinued when an early interim analysis demonstrated a low RR.

The initial primary end point of the studies was TTP, and the studies were designed to evaluate the hypothesis that FVT treatment results in a longer TTP than ANZ. RR was evaluated as a secondary end point. Survival was also compared on the study arms, but the studies did not have sufficient statistical power to detect small survival differences. Patients were to continue treatment until disease progression, with tumor assessments monthly for the first 3 months and every 3 months

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Table 3 Baseline disease characteristics

Demographic characteristic	Trial 0021 North American		Trial 0020 European	
	FVT 250 mg $n = 206$	Anastrozole 1 mg $n = 194$	FVT 250 mg $n = 222$	Anastrozole 1 mg $n = 229$
Baseline tumor assessment, *n* (%)				
Measurable only	35 (17.0)	41 (21.1)	44 (19.8)	55 (24.0)
Any evaluable	169 (82.0)	150 (77.3)	166 (74.8)	161 (70.3)
Measurable + evaluable	79 (38.3)	66 (34.0)	78 (35.1)	79 (34.5)
No measurable or evaluable	2 (1.0)	3 (1.5)	3 (1.4)	5 (2.2)
Sites of metastatic disease, *n* (%)				
Local disease only	1 (0.5%)	2 (1.0%)	5 (2.3%)	6 (2.6%)
Breast	8 (3.9)	8 (4.1)	21 (9.5)	30 (13.1)
Skin and soft tissue	43 (20.9)	41 (21.1)	40 (18.0)	35 (15.3)
Bone	90 (43.7)	85 (43.8)	115 (51.8)	117 (51.1)
Liver involvement	47 (22.8)	45 (23.2)	48 (21.6)	56 (24.5)
Previous treatment, *n* (%)				
Tamoxifen	196 (95.2)	187 (96.4)	215 (97)	225 (98)
Surgery	194 (94.2)	182 (93.8)	204 (91.9)	200 (87.3)
Cytotoxic chemotherapy	129 (62.6)	122 (62.9)	94 (42.3)	98 (42.8)
Loco-regional RT	99 (48.1)	91 (46.9)	128 (57.7)	125 (54.6)
Palliative RT	68 (33.0)	53 (27.3)	40 (18.0)	47 (20.5)
Hormone receptor status				
Total ER+	170 (82.5)	156 (80.4)	156 (70.3)	173 (75.5)
Total PR+	137 (66.5)	119 (61.3)	93 (41.9)	105 (45.9)

thereafter. All of the patients were to be followed until tumor progression or death. For the time-to-event analyses (TTP and survival), time was measured from the randomization date, and hazard ratios were determined. When initial analysis did not support the TTP superiority objective, the sponsor requested approval consideration to be based on a noninferiority analysis. Multiple hormonal drugs in both the first-line and second-line treatment settings have received marketing approval based on a primary comparison of RRs (establishing comparability of the new drug to an approved drug in an adequately powered study) with support from secondary comparisons of TTP and survival (Table 1). The FDA determined that the primary efficacy analysis supporting marketing approval be based on a comparison of RRs and agreed that the approval could be based on a noninferiority analysis of RRs. TTP and survival would be considered as the secondary efficacy endpoints. The primary statistical analysis of the FDA used 95.4% CIs for the difference in RR between the FVT and ANZ groups. Because of the statistical effect of the interim efficacy analyses, 95.4% CIs were used rather than the usual 95% CIs.

Patient Characteristics. Demographic characteristics were similar in the two treatment groups (Table 2). The study population of postmenopausal females was predominantly Caucasian with good baseline PS; >90% had a baseline WHO PS of 0 or 1. Mean age was 63, and slightly fewer patients under 45 were accrued to the European study. Baseline disease characteristics were similar in the two treatment groups (Table 3). Approximately 75% of the patients had ER+ tumors, and the remainder of the patients had disease showing clinical evidence of hormone sensitivity (at least 12 months of adjuvant hormonal treatment, or in the advanced disease setting, hormone-induced tumor remission or tumor stabilization lasting at least 3 months). Over 96% of patients had received TAM previously. Sixty-three percent of patients on the North American trial and 42% of patients on the European trial had received chemotherapy previously. Over 97% of patients had documented metastatic disease at entry.

Efficacy. The FDA verified the reported RRs and TTP of the sponsor using the primary tumor response datasets, and by an audit of data from three study sites by the FDA Division of Scientific Investigation.

TTP. The primary objective of the studies was to demonstrate that patients treated with FVT delayed progression (superiority in TTP) compared with AZ. Kaplan-Meier survival curves for the European and North American trials are shown in Figs. 2 and 3. Although point estimates of median TTPs were longer in the FVT arm in both studies (165 days *versus* 103 days in the North American study and 166 *versus* 156 days in the European study), the risk of progression based on Cox proportional hazards model was not significantly different between the treatment arms in either study (Table 4). The 95.4% CIs were (0.79–1.21) in the European trial and (0.74–1.14) in the North American trial. The upper one-sided 97.7% confidence limit for the hazard ratio (FVT:ANZ) for TTP did not exceed 1.25 and, therefore, a potential deficiency in TTP of >25% for the experimental treatment was ruled out. However, there is no accepted standard for non inferiority of TTP in this setting, because the effects of the active control drug on TTP is not known with any degree of certainty.

RRs. In Table 4, the RRs for FVT and ANZ RRs are shown to be 20% and 15%, respectively, in the European trial, and 17% in both treatment arms in the North American trial. RRs were not significantly different between treatment arms. For each of the trials, an analysis of the 95.4% CIs of the difference in RRs between FVT and ANZ was able to rule out a 10% absolute difference in favor of ANZ. (The estimated differences were 5.42% and −0.02% for the North American and European trials, respectively.) This criterion for noninferi-

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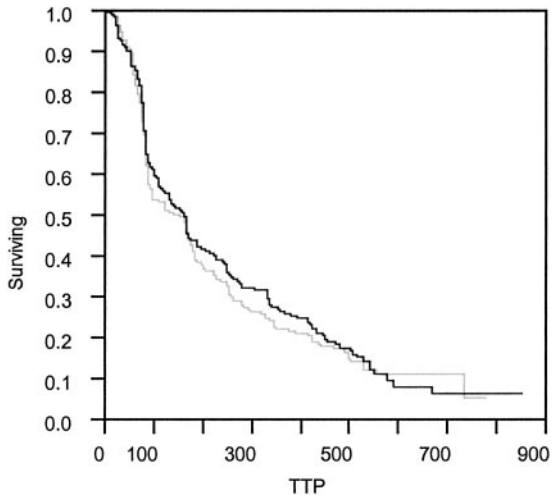

Fig. 2 Kaplan-Meier Plot of TTP (intention to treat Population) for the European trial. ▬, fulvestrant; ——, anastrozole.

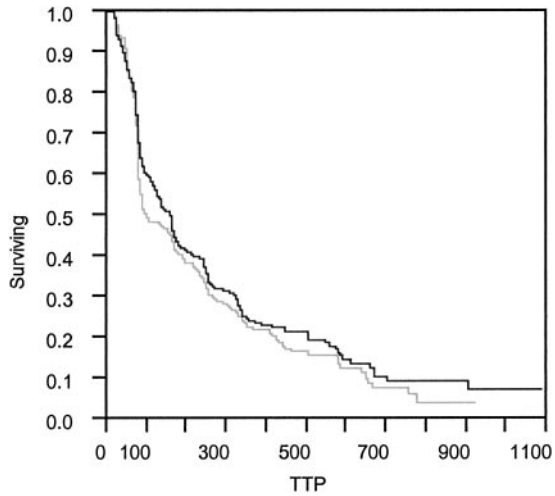

Fig. 3 Kaplan-Meier Plot of TTP (intention to treat Population) for the North American trial. ▬, fulvestrant; ——, anastrozole.

Table 4 Efficacy data from ANZ Phase III trials, ITT population

	Trial 0021 United States—double blind		Trial 0020 Europe—open label	
	FVT 250 mg (n = 206)	ANZ 1 mg (n = 194)	FVT 250 mg (n = 222)	ANZ 1 mg (n = 229)
Number (%) CR + PR	35 (17.0%)	33 (17.0%)	45 (20.3%)	34 (14.9%)
OR: (FAS/ANA)[a]	1.0 (P = .996)		1.46 (P = 0.13)	
95.4% CI	(0.59, 1.70)		(0.89, 2.41)	
% Difference in RR (FVT-ANZ)	−0.02		5.42	
95.4% CI	(−6.28, 8.87)		(−1.44, 14.77)	
Median TTP (days)	165	103	166	156
Hazard ratio (FVT/ANZ)[b]	0.92 (P = 0.43)		0.98 (P = 0.84)	
95.4% CI	(0.74 to 1.14)		(0.79 to 1.21)	

[a] Odds ratio, logistic-regression model without baseline covariates.
[b] Cox proportional-hazards model with baseline covariates: age, PS, measurable compared with nonmeasurable disease, receptor status, previous response to hormone therapy, previous use of cytotoxic chemotherapy, and use of bisphosphonate therapy for bone disease.

ority has been accepted in previous applications for the hormonal treatment of breast cancer (Table 1).

Safety. Safety and tolerability of FVT was evaluated in all 1178 patients who were exposed to FVT, with the longest exposures in 423 subjects in two Phase III trials. Median treatment duration was 6 months, with individual FVT exposure up to 3 years. Relatively few serious adverse events were reported to be drug-related in either treatment group. The incidence and types of adverse events, regardless of attributed causality to the study drugs, were generally similar in FVT- and ANZ-treated patients (Table 5). FVT local injection reactions included mild transient pain and inflammation, and were more common with the 2 × 2.5 ml injections compared with the single 5-ml injection (27% *versus* 8%, respectively). However, these observations were from different trials, and cross-trial comparisons are suspect. A small increase in joint disorders was reported in ANZ-treated patients. An increase in FVT thromboembolic adverse events reported at an interim analysis was not substantiated in the final safety analysis. The most common side effects were weakness, asthenia, headache, hot flashes, vasodilatation, back pain, nausea, vomiting, and diarrhea (Table 6).

Discussion and Conclusions. The initial primary objective of the FVT pivotal trials was to determine whether TTP was significantly increased in patients given FVT compared with patients given ANZ using a Cox proportional hazards model. A secondary objective was to compare RRs. When initial analysis did not support the TTP superiority objective, FDA determined that a comparison of RRs could be the primary efficacy analysis supporting marketing approval.[3] In the past, hormonal drugs in both the first-line and second-line treatment of breast cancer have been granted marketing approval based on a primary comparison of RRs (see Table 1). A noninferiority analysis is

[3] Points to consider on switching between superiority and non inferiority. EMEA committee for proprietary medicinal products. Internet address: http://www.emea.eu.int/index/indexh1.htm.

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Table 5 Common (>1%) events attributed to FVT treatment

Very Common (incidence rate >10%)	
Whole body	Injection-site reactions, including transient pain and inflammation (when administered as two 2.5-ml injections)
	Hot flashes
Common (incidence rate from 1–10%)	
Whole body	Injection-site reactions, including transient pain and inflammation (when administered as one 5-ml injection)
	Asthenia
	Headache
Gastrointestinal	Gastrointestinal disturbance, including nausea, vomiting, diarrhea and anorexia
Skin and appendages	Rash
Urogenital	Urinary tract infection

Table 6 Combined trials adverse events[a] ≥5%

Body system and adverse event	FVT 250 mg (n = 423)	ANZ 1 mg (n = 423)
	% of patients reporting adverse event[b]	
Body as a whole	68.3	67.6
Asthenia	22.7	27.0
Pain	18.9	20.3
Headache	15.4	16.8
Back pain	14.4	13.2
Abdominal pain	11.8	11.6
Injection site pain[c]	10.9	6.6
Pelvic pain	9.9	9.0
Chest pain	7.1	5.0
Flu syndrome	7.1	6.4
Fever	6.4	6.4
Accidental injury	4.5	5.7
Cardiovascular	30.3	27.9
Vasodilatation	17.7	17.3
Digestive	51.5	48.0
Nausea	26.0	25.3
Vomiting	13.0	11.8
Constipation	12.5	10.6
Diarrhea	12.3	12.8
Anorexia	9.0	10.9
Hematologic and lymphatic	13.7	13.5
Anemia	4.5	5.0
Metabolic and nutritional	18.2	17.7
Peripheral edema	9.0	10.2
Musculoskeletal	25.5	27.9
Bone pain	15.8	13.7
Arthritis	2.8	6.1
Nervous	34.3	33.8
Dizziness	6.9	6.6
Insomnia	6.9	8.5
Paresthesia	6.4	7.6
Depression	5.7	6.9
Anxiety	5.0	3.8
Respiratory	38.5	33.6
Pharyngitis	16.1	11.6
Dyspnea	14.9	12.3
Cough increased	10.4	10.4
Skin and appendages	22.2	23.4
Rash	7.3	8.0
Sweating	5.0	5.2
Urogenital	18.2	14.9
Urinary tract infection	6.1	3.5

[a] Regardless of investigator attributed causality.
[b] Patients may have more than one adverse event.
[c] Only those ANZ patients who were in trial 0021 received placebo injections.

designed to rule out the loss of a specified portion of the known effect of the active control. FVT and ANZ RRs were each 17% in North American trial, and were 20% and 15%, respectively, in the European trial. Analysis of the difference in RRs by logistic regression model ruled out an absolute difference in response of >10% with respect to ANZ in each of the two pivotal trials for the NDA using two-sided 95.4% CIs. Tumor responses provided *prima facia* evidence of efficacy with additional support from secondary comparisons of TTP and survival (22). There is no accepted regulatory standard for noninferiority with regard to TTP in this setting because the effect of the active control drugs on TTP is not known. A 25% increase in the risk of progression was excluded with two-sided 95.4% CIs.

In this study population of postmenopausal women with locally advanced or metastatic breast cancer, both FVT and ANZ were well-tolerated, and most adverse events were not serious. Less than 3% of all patients in either treatment group withdrew because of adverse events. The most common drug-related events were injection site reactions and hot flashes. More local injection site reactions were reported in the North American study, which used 2 × 2.5 ml injections, compared with the single 5-ml injection used in the European study. It is not known if the differences are because of different reporting policies between Europe and North America.

FVT was approved on April 25, 2002 by the FDA for the treatment of hormone receptor-positive metastatic breast cancer in postmenopausal women with disease progression after antiestrogen therapy. The recommended dose is 250 mg i.m. monthly as a single 5-ml injection or as two concurrent 2.5 ml injections into the buttocks. Approval was based on results of two randomized trials comparing RR and TTP of FVT- and ANZ-treated patients. Complete prescribing information is available.[4]

Marketing approval of FVT provides an additional treatment option for breast cancer patients with disease failing TAM therapy. The FVT i.m. formulation provides the advantage of infrequent dosing and improved compliance but the disadvantage of local toxicity at the injection site. Although the availability of a parenteral hormonal treatment for breast cancer may increase compliance for some patients, this cannot be the basis for marketing approval. The requirement for approval is documented safety and efficacy; although compliance may affect efficacy, that effect must be demonstrated. Questions remain regarding the role of FVT treatment in other breast cancer settings, in particular, efficacy in first-line treatment of breast cancer has not been established. Similarly, the efficacy of FVT in those patients whose disease has failed treatment with AIs is unknown.

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[4] Internet address: http://www.fda.gov/cder/approval/index.htm.

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