Dose-Ranging Study of the Safety and Pharmacokinetics of Atrasentan in Patients with Refractory Malignancies

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ABSTRACT

Purpose: **Atrasentan is an orally bioavailable selective antagonist of the endothelin receptor ET_A. Due to the potential activity of this agent against prostate cancer, the majority of subjects enrolled in prior studies had been male. This Phase I study sought to determine the toxicity and pharmacokinetics of daily atrasentan in a population of both female and male subjects with advanced malignancies.**

Experimental Design: **Patients with refractory malignancies received atrasentan once daily at doses ranging from 5 mg to 75 mg. At least 3 subjects were treated at each dose level before enrollment began at the next higher dose level. Enrollment for specific dose levels was expanded if any subject experienced serious drug-related toxicity. Plasma concentration profiles for atrasentan were determined after dosing on days 1 and 28.**

Results: **Thirty-five patients received atrasentan at doses from 5 mg to 75 mg. The most frequent drug-related adverse events were headache (60%), rhinitis (49%), and peripheral edema (31%). These toxicities were mild to moderate in severity and reversible on cessation of treatment. Dose escalation was stopped at the 75-mg dose level due to the occurrence of three severe adverse events (2 hyponatremia and 1 hypotension). Atrasentan was rapidly absorbed after oral administration; mean time to maximum observed concentration ranged from 0.3 to 1.7 h. Terminal elimination half-life averaged 26 h. No significant difference between sexes was found in any atrasentan pharmacokinetic parameter tested, including maximum observed plasma concentration, time to maximum observed concentration, minimum observed plasma concentration, area under the plasma concentration-time curve, and elimination rate constant.**

Conclusions: **Atrasentan is well tolerated in both female and male cancer patients at doses of up to 60 mg/day with dose-limiting toxicity observed at 75 mg/day. The most frequently observed toxicities were headache, rhinitis, and edema. There was no statistically significant difference in atrasentan pharmacokinetics between sexes.**

INTRODUCTION

The endothelins (ET) are 21-amino acid peptides that were originally identified as vasoconstrictors produced in endothelial cells (1). Subsequently, the ETs have been found to contribute to cell proliferation and hormone production through G protein-coupled pathways and have been detected in elevated amounts in several malignancies (2, 3). ETs are thought to act in endocrine-responsive tissues, and hormonally influenced changes in circulating ET levels have been described. In cancer, dysfunction of ET regulation has been implicated in several hormonally regulated cancers including prostate, ovarian, and cervical cancers (4–7). ET plasma concentrations have been shown to be significantly elevated in metastatic prostate cancer. ETs may act as an antiapoptotic factor in certain malignancies (8).

ET-1 is the main isoform of ETs identified in mammalian tissues and fluids and is found in many epithelial-derived tumors. ET-1 is known to act synergistically with a number of cell growth factors such as platelet-derived growth factor, basic fibroblast growth factor, epidermal growth factor, transforming growth factors, and insulin-like growth factor-I thereby possibly influencing neoplastic growth. Two subtypes of G protein-coupled receptors have been identified: ET_A and ET_B. ET_A binds ET-1 with a higher affinity than the other ET isoforms, and this system has been implicated in tumor growth, angiogenesis, nociception, and bone deposition (5, 9). ET_B receptors mediate vasomotor tone and function as a clearance receptor (10).

Atrasentan is an orally bioavailable selective antagonist of the ET_A receptor (11). In preclinical studies, atrasentan has inhibited ET-1-induced biological responses that are mediated through the ET_A receptor, and it is postulated that the agent may retard the progression of cancer through the same mechanism. Atrasentan has been evaluated principally in patients with hormone-refractory prostate cancer, and safety data in female patients is limited. ET levels are higher in men than in women and seem to be influenced by sex hormones, as evidenced by changes in ET levels that occur during the menstrual cycle and pregnancy (12, 13). Additionally, the ratio and density of ET receptors in the vasculature may be different in men and women, and the ET_B receptor seems to contribute differently to resting vascular tone in males *versus* females (14, 15). These differ-

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ences in ET levels and expression of ET receptors create a potential for sex-related differences in atrasentan toxicity. Because dysregulation of ET regulation has been implicated in several female-specific or predominant malignancies including ovarian, cervical, and breast cancers, investigation of atrasentan in these diseases may be warranted (4–7, 16). To additionally examine the safety, tolerability, and pharmacokinetics of this drug, we initiated a phase I dose-escalation study of chronic daily atrasentan in a population of both female and male patients with refractory malignancies.

PATIENTS AND METHODS

Patients. Subjects were required to have a histologically or cytologically documented diagnosis of a refractory malignancy, have a life expectancy >3 months, and an Eastern Cooperative Oncology Group performance status 0–2. Normal organ function was required, including WBC >2,000/mm^3, absolute neutrophil count >1,000/mm^3, platelet count >50,000/mm^3, hemoglobin >9 g/dl, total bilirubin <1.5 mg/dl, aspartate aminotransferase and alanine aminotransferase $\leq 3 \times$ upper limit of normality, and calculated creatinine clearance $\geq$50 ml/min. Female subjects of childbearing potential were required to have a negative urine pregnancy test, and all of the subjects and their partners were required to use two forms of contraception until 2 months after completion of study participation. Patients must have had no surgery, radiotherapy, chemotherapy, or immunotherapy within 28 days of starting treatment. Treatment with corticosteroids within 4 weeks of treatment was not allowed, except for physiological replacement therapy. Subjects requiring opioids for pain control were required to demonstrate stabilization of pain before study entry. No prior therapy with atrasentan was allowed. Exclusion criteria included brain or spinal cord involvement, active hepatitis A, B, or C or HIV positive, recent significant history of alcoholism or drug addiction, significant intercurrent medical or psychiatric disorder, or history of migraine headaches or chronic headache syndrome. All of the subjects were >18 years of age and gave written informed consent. Enrollment priority was given to female subjects.

Treatment Plan. Atrasentan, in hard gelatin capsule strengths of 2.5 mg and 10 mg, was administered orally once daily until disease progression, toxicity requiring study drug discontinuation, or for a maximum of 12 months, whichever came first. Patients were admitted for 24 h to the Clinical Research Center at the University of Chicago on day 1. Subjects arrived fasted, having taken nothing orally beginning at midnight. Atrasentan was administered on day 1 and withheld on day 2 for the purpose of pharmacokinetic sampling. Plasma samples for atrasentan concentrations were obtained predosing, and 15 min, 30 min, 45 min, 1 h, 1.5 h, 2 h, 4 h, 6 h, 10 h, 16 h, 24 h, 30 h, and 48 h after dosing. A predose sample was obtained on day 14. Dosing was withheld on days 29–31 for repeat pharmacokinetic sampling, including 72-h and 96-h samples in addition to samples at above-mentioned times.

The initial dose level was 5 mg/day, with subsequent planned dose levels of 10, 20, 30, 45, 60, 75, 95, 115, and 140 mg/day. Three subjects were to be enrolled at each dose level. Two subjects within each dose level must have completed at least 14 days of drug administration, and the third subject must have completed at least 7 days of drug administration without any evidence of National Cancer Institute Common Toxicity Criteria grade 3 or 4 drug-related toxicity before dosing at the next higher dose level began. If 1 of the first 3 subjects in a dose level experienced a grade 3 or 4 drug-related toxicity, 3 additional subjects were to be dosed at that level before dosing began at the next higher dose level.

Before enrollment, patients underwent a physical exam and medical history, electrocardiogram, chemistry panel, complete blood count, urinalysis, radiographic assessment, and Brief Pain Inventory assessment. Physical exams were repeated every 28 days, and laboratory studies were repeated every 14 days. Radiological assessment was repeated after 84 days.

The quality of life of the subjects was assessed through the Functional Assessment Cancer Therapy questionnaire (17). Pain assessment for subjects requiring opioid analgesics was based on the daily log of pain of the subjects using the Visual Analog Scale (18). All of the subjects before beginning therapy (19) completed a Brief Pain Inventory-Short Form. Patients with pain requiring the use of opioids were required to enter a stabilization period of no more than 14 days to achieve adequate pain control before day 1 dosing. A subject was considered to have achieved adequate pain control if he/she had 2 of 3 successive days of a pain score $\leq$5 on the Visual Analog Scale, tolerable side effects, and the use of $\leq$4 rescue doses per day.

Pharmacokinetic and Statistical Analysis. Atrasentan plasma concentrations were determined using a validated liquid chromatograph/mass spectrometer assay method. Parameter estimates for atrasentan were obtained using noncompartmental methods. The maximum observed plasma concentration, the minimum concentration for the dosing interval (day 28 only), and time to maximum observed concentration were read directly from the plasma concentration-time data. The terminal phase elimination rate constant (β) was obtained using a least-squares linear regression analysis of the terminal log-linear portion of the plasma concentration-time profile. A minimum of three concentration-time points was used to determine β. The terminal elimination half-life was calculated as $\ln(2)/\beta$. The area under the plasma concentration-time curve from time 0 to infinite time (AUC_∞) after dosing on day 1 was calculated as the sum of $AUC_{0\text{-last}}$ and C_{last}/β, where C_{last} is the last measurable plasma concentration. AUC over a dosing interval on day 28 (AUC_{0-24}) was calculated by the linear trapezoidal method. Oral clearance (CL/F, where F is the bioavailability) was calculated by dividing the administered dose by the corresponding AUC. Apparent volume of distribution (V_β) was calculated by dividing CL/F by β.

Atrasentan pharmacokinetic (PK) variables, including time to maximum observed concentration and natural logarithms of dose-normalized maximum observed plasma concentration and AUC_∞ for day 1 and time to maximum observed concentration and natural logarithms of dose-normalized maximum observed plasma concentration, minimum concentration for the dosing interval and AUC_{0-24} for day 28, were analyzed by an analysis of covariance model. The analysis of covariance model was specified with body weight as a covariate and dose level and sex as classification variables, and it allowed different slopes and intercepts for the regression lines with body weight for the two sexes by including an interaction term between body weight and

sex. Changes in logarithms of dose-normalized maximum observed plasma concentration and AUC_{0-24} from day 1 to day 28, as well as the logarithm of dose-normalized day 1 AUC_{∞} subtracted from the logarithm of dose-normalized day 28 AUC_{0-24}, were analyzed by an ANOVA model with factors of dose and sex.

Mean changes from baseline to each visit in laboratory parameters, pain assessments, and quality of life were analyzed by an ANOVA with all of the treatment groups combined and with dose as the factor.

RESULTS

Patient Characteristics. Patient characteristics are shown in Table 1. A total of 35 patients were treated in this study between February 1999 and June 2000. The majority (54%) of subjects were female. This was a heavily pretreated population of patients with 74% having received ≥2 prior chemotherapy regimens. Colorectal cancer was the most common diagnosis, and colorectal, lung, and kidney cancers accounted for the majority of enrolled patients. No prostate cancer patients were enrolled in this study.

Subjects were treated at 7 different dose levels of atrasentan: 5 mg ($n = 3$), 10 mg ($n = 3$), 20 mg ($n = 4$), 30 mg ($n = 3$), 45 mg ($n = 5$), 60 mg ($n = 8$), and 75 mg ($n = 9$). All of the enrolled subjects received at least one dose of atrasentan. Overall, subjects in the study achieved 2045 days of exposure to atrasentan. The majority of subjects discontinued treatment due to disease progression. Dose escalation was discontinued at the 75-mg dose level due to the occurrence of dose-limiting toxicity.

Table 1 Patient characteristics

Characteristic	No.
Total patients	35
Age (years)	
Median	55
Range	26–83
Sex	
Female	19
Male	16
Baseline ECOG[a] performance status	
0	17
1	18
Previous therapy	
Surgery	30
Radiation	17
Biologic therapy	7
Radiopharmaceuticals	1
Prior chemotherapy regimens	
0	2
1	7
2	8
3+	18
Tumor type	
Colorectal	9
Lung	6
Kidney	5
Sarcoma	2
Cervical	2
Pancreatic	2
Head and neck	1
Esophageal	1
Other	7

[a] ECOG, Eastern Cooperative Oncology Group.

Toxicity. Adverse events occurring on this study were graded as mild, moderate, or severe. All of the subjects enrolled in the study experienced at least one adverse event during treatment. The most commonly reported adverse events were headache (23 of 35; 66%), rhinitis (18 of 35; 51%), and peripheral edema (16 of 35; 46%). When stratified by attribution, the most common adverse events that were considered possibly or probably related to study drug administration remained headache (21 of 35; 60%), rhinitis (17 of 35; 49%), and peripheral edema (11 of 35; 31%). Adverse events that were considered possibly or probably related to atrasentan and experienced by ≥10% of subjects are listed in Table 2. The incidences of headache and rhinitis were more pronounced at higher dose levels with 12 of 17 (71%) of patients experiencing headache and 11 of 17 (65%) of patients experiencing rhinitis at the 60 mg and 75 mg dose levels.

A total of 26 adverse events were graded severe as listed in Table 3. Six subjects experienced severe adverse events that were judged either possibly or probably related to atrasentan by the investigator or the study sponsor. These events (with the respective dose level) were: hypotension (75 mg), hyponatremia (75 mg), pleural effusion (75 mg), fractured arm (75 mg), central nervous system hemorrhage (30 mg), and dyspnea with hypotension (60 mg). Severe events were most prevalent at the 60 and 75 mg/day dose levels, accounting for 19 of the 26 events. Pneumonia, dyspnea, hyponatremia, cough, and headache were the most commonly reported severe events, occurring in ≥2 patients. The remaining severe events occurred as individual episodes. There was no significant difference in severe events among either sex. Four deaths occurred during the trial or the follow-up period. None of these deaths were considered related to atrasentan (2 due to disease progression and 2 due to infection). Twenty-seven patients discontinued treatment for disease progression, and 1 withdrew for personal reasons. Five patients were withdrawn from the study for the following adverse events: pneumonia (20 mg), nausea and vomiting (60 mg), edema and dyspnea (75 mg), hypotension (75 mg), and dyspnea (30 mg).

Dose-Limiting Toxicity. Dose escalation was halted after 9 subjects were treated at the 75-mg dose level. Two subjects at this dose level experienced hyponatremia that was graded as severe, and 1 subject developed hypotension that resulted in a serious adverse event. These events were considered dose-limiting; 2 additional subjects were treated at the 60-mg dose level after these events for additional assessment of this dose level.

Laboratory Evaluation. Previous clinical studies of atrasentan have suggested a mild hemodilution effect as manifested by a decrease in hemoglobin/hematocrit as well as serum albumin and total protein (20, 21). In the current study, no statistically significant changes from baseline across all of the dose levels occurred for hemoglobin or hematocrit after 2 or 4 weeks of atrasentan treatment. There was a mild decrease in albumin and total protein over the first 4 weeks of 0.25 ± 0.09 g/dl ($P = 0.008$) and 0.41 ± 0.14 g/dl ($P = 0.008$), respectively.

PKs. PK parameters are shown in Table 4. Atrasentan was rapidly absorbed after oral administration of 5–75 mg daily

Table 2 Number (%) of subjects experiencing adverse events considered possibly or probably related to treatment and reported by ≥10% of 35 subjects receiving atrasentan

Atrasentan dose Adverse event	5 mg $n = 3$	10 mg $n = 3$	20 mg $n = 4$	30 mg $n = 3$	45 mg $n = 5$	60 mg $n = 8$	75 mg $n = 9$	Total $n = 35$
Headache	1 (33)	1 (33)	3 (75)	1 (33)	3 (60)	4 (50)	8 (89)	21 (60)
Rhinitis	1 (33)		1 (25)	2 (67)	2 (40)	7 (88)	4 (44)	17 (49)
Peripheral edema		1 (33)	1 (25)	2 (67)	1 (20)	4 (50)	2 (22)	11 (31)
Asthenia		2 (67)		1 (33)		3 (38)	2 (22)	8 (23)
Hypotension	1 (33)	1 (33)		1 (33)	1 (20)	1 (13)	3 (33)	8 (23)
Nausea			1 (25)	1 (33)	2 (40)	1 (13)	3 (33)	8 (23)
Vomiting				1 (33)	2 (40)		3 (33)	6 (17)
Anorexia			1 (25)	1 (33)	1 (20)	1 (13)	2 (22)	6 (17)
Anemia	1 (33)			1 (33)		1 (13)	1 (11)	4 (11)

with mean time to maximum observed concentration values ranging from 0.3 to 1.7 h. After peaking, atrasentan plasma concentrations declined biexponentially with a terminal half-life that averaged 26 h. Atrasentan PKs were characterized by a global mean oral clearance of 21 liters/h (SD 14) and apparent volume of distribution of 790 liters (SD 677). Clearance was constant across dose groups ($P = 0.13$, day 1; $P = 0.19$, day 28) and between day 1 and day 28 ($P = 0.54$). There was no statistically significant difference between sexes in any atrasentan PK parameter analyzed (Table 5). The tests of different slopes ($P > 0.07$) and different averages ($P > 0.06$) on the regression lines with body weight between sexes for all of the analyzed PK variables were not statistically significant. Steady-state atrasentan plasma concentrations consistent with biological activity in preclinical models and expected to selectively inhibit ET_A receptors were achieved across the range of doses studied.

Response. No objective responses were observed in this study. One patient with medullary thyroid carcinoma and another with papillary thyroid carcinoma maintained stable disease for 6 months and 13 months, respectively. Sixteen patients had objective evidence of disease progression on follow-up radiographic imaging. Twelve subjects were withdrawn early from treatment with clinical evidence of progressive disease, and 2 patients died from progressive disease while on study. No statistically significant changes in pain response or analgesic use were observed during the study. No statistically significant changes in quality of life parameters as measured by the Functional Assessment Cancer Therapy questionnaire were observed.

DISCUSSION

This Phase I study demonstrates that chronic daily oral dosing of atrasentan is well tolerated in doses of up to 60 mg/day. This is the first study of atrasentan in cancer patients to contain a significant proportion of female subjects. Before this study, atrasentan had been predominately studied in males due to its development for treatment of prostate cancer. No significant differences in toxicity or PKs between the sexes were observed. Given that ET dysregulation has been suggested in

Table 3 Number of subjects experiencing adverse events by dose level

Atrasentan dose Adverse event	5 mg n = 3	10 mg $n = 3$	20 mg $n = 4$	30 mg $n = 3$	45 mg $n = 5$	60 mg $n = 8$	75 mg $n = 9$
Pneumonia			1				2
Dyspnea						2	1
Hyponatremia							2
Cough						1	1
Headache					1	1	
Anemia				1			
Asthenia							1
Bilirubinemia					1		
Chest pain						1	
CNS[a] bleed				1			
Confusion							1
Edema							1
Hepatomegaly							1
Hypotension							1
Nausea and vomiting						1	
Pathological fracture							1
Peripheral edema							1
Sepsis	1						
Shock	1						
Total	2	0	1	2	2	6	13

[a] CNS, central nervous system.

Table 4 Pharmacokinetic parameters of atrasentan in patients with refractory malignancies

Mean values ± SD atrasentan dose (mg).

Parameter	5	10	20	30	45	60	75
Day 1	$n = 3$	$n = 3$	$n = 4$[a]	$n = 3$	$n = 5$[a]	$n = 8$	$n = 9$[a]
T_{max}(h)[b]	0.8 ± 0.3	1.0 ± 0.5	0.9 ± 0.5	1.1 ± 0.4	1.2 ± 0.7	0.8 ± 0.3	0.9 ± 0.4
C_{max}(ng/ml)	91 ± 34	62 ± 53	217 ± 268	234 ± 173	396 ± 207	480 ± 269	857 ± 477
AUC_{∞}(h·ng/ml)	646 ± 344	536 ± 273	1089 ± 940	1527 ± 652	4326 ± 2455	3453 ± 1502	4277 ± 2584
$t_{1/2}$(h)[c]	27.0 ± 10.1	23.2 ± 5.8	18.8 ± 3.7	21.2 ± 8.7	19.1 ± 3.7	16.1 ± 6.3	12.1 ± 4.8
CL/F (liter/h)	9.5 ± 5.3	23.8 ± 15.5	30.4 ± 23.4	22.4 ± 9.9	13.7 ± 8.5	20.1 ± 8.0	24.4 ± 16.6
Day 28	$n = 3$	$n = 3$	$n = 3$[a]	$n = 4$	$n = 3$	$n = 4$	$n = 2$
T_{max}(h)	0.6 ± 0.1	0.8 ± 0.7	0.3 ± 0.1	1.7 ± 1.6	1.5 ± 0.9	0.6 ± 0.1	1.3 ± 1.1
C_{max}(ng/ml)	89 ± 42	99 ± 63	358 ± 305	242 ± 197	544 ± 348	819 ± 338	489 ± 400
C_{min}(ng/ml)	17 ± 13	19 ± 11	40 ± 28	31 ± 21	97 ± 104	50 ± 19	26 ± 4
AUC_{0-24}(h·ng/ml)	580 ± 360	752 ± 430	1591 ± 973	1492 ± 876	5354 ± 5644	3162 ± 1215	2338 ± 1374
$t_{1/2}$(h)[c]	34.1 ± 16.5	26.4 ± 8.6	40.9 ± 3.4	32.0 ± 8.1	30.0 ± 5.0	32.6 ± 15.5	36.1 ± 41.4
CL/F (liter/h)	10.6 ± 4.9	19.7 ± 16.8	20.3 ± 19.0	27.0 ± 15.8	16.0 ± 11.4	22.0 ± 10.8	38.8 ± 22.8

[a] n reduced by one for AUC_{∞}, $t_{1/2}$, and CL/F, because $t_{1/2}$ could not be determined for one of the subjects.

[b] T_{max}, time to maximum observed concentration; C_{max}, maximum observed plasma concentration; AUC_{∞}, area under the plasma concentration-time curve from time 0 to infinite time; $t_{1/2}$, terminal elimination half-life; CL/F, oral clearance; AUC_{0-24}, area under the plasma concentration-time curve over a dosing interval on Day 28.

[c] Harmonic mean ± pseudo SD.

breast, cervical, and ovarian cancers, additional study in these diseases may be warranted.

The frequently observed adverse events of rhinitis, headache, and edema have been reported previously with ET receptor antagonists and are likely attributable to the vasoactive properties of these agents. Data from a previous Phase I study of atrasentan supported 60 mg as the maximum tolerated dose due to increased incidence of headache coincident with higher dose levels (20). Another Phase I study treated patients with doses of up to 95 mg/day without achieving protocol-defined maximum tolerated dose (21). Rhinitis, headache, and peripheral edema were again the most frequent adverse events, and most cases occurred in patients taking doses of ≥60 mg. The majority of patients treated at the 60- and 75-mg dose levels in our study experienced headache and rhinitis. Whereas these adverse events were not considered severe in nature, they were prominent enough to support a recommended daily dose of <75 mg.

Table 5 Central value estimates of pharmacokinetic parameter by sex

	Central value estimates[a]		
Parameter	Males	Females	*P*
Day 1			
T_{max}[b] (h)	0.9	1.0	0.412
C_{max}[c] (ng/ml/mg)	8	8	0.120[d]
AUC_{∞}[c] (h·ng/ml/mg)	68	58	0.067[d]
Day 28			
T_{max} (h)	0.8	1.0	0.651
C_{max}[c] (ng/ml/mg)	7	11	0.205[d]
AUC_{0-24}[c] (h·ng/ml/mg)	46	65	0.233[d]
C_{min}[c] (ng/ml/mg)	0.8	1.3	0.110[d]

[a] Adjusted means (least-squares means) after adjusting for dose level and body weight in analysis of covariance for T_{max} and antilogarithms of adjusted means in logarithms for others.

[b] T_{max}, time to maximum observed concentration; C_{max}, maximum observed plasma concentration; AUC_{∞}, area under the plasma concentration-time curve from time 0 to infinite time; AUC_{0-24}, area under the plasma concentration-time curve over a dosing interval on Day 28.

[c] Dose-normalized.

[d] Data analyzed on transformed log scale.

The severe adverse events that limited dose escalation in this study were hypotension and hyponatremia, which likewise may be explainable by vasoactive changes induced by atrasentan. Whereas statistically significant decreases in blood pressure were observed sporadically, there were no consistent trends established across dose levels. Blood pressure should be monitored in subjects receiving atrasentan, and adjustment of concomitant antihypertensives may be necessary. Whereas slight decreases in serum albumin and total protein suggest a mild hemodilution effect of atrasentan, no significant fall in hemoglobin or hematocrit was observed.

PK analysis revealed that atrasentan is rapidly absorbed when orally administered and that biologically relevant steady-state concentrations were achieved across all of the dose levels. For example, the mean unbound minimum concentration for the dosing interval for the 10 mg daily regimen was ~10-fold greater than the K_i for the ET_A receptor (0.017 ng/ml; atrasentan is 98.8% bound to plasma proteins). No significant differences in PKs between the sexes were detected. A modest increase in plasma ET concentrations was observed suggesting biological activity, perhaps through displacement of ETs from their receptors or alteration of a feedback pathway (data not shown). Because atrasentan is a selective ET_A antagonist and ET_B is thought to be the primary route of clearance of ETs from the plasma, marked changes in plasma ET concentrations would not be expected.

In conclusion, this study demonstrated that atrasentan doses of up to 60 mg/day are well tolerated by both male and female subjects with advanced cancer. Observed side effects were consistent with vasoactive changes, likely mediated by the ET_A receptor. The efficacy of atrasentan in the treatment of prostate cancer is being investigated in ongoing clinical studies. A dose of 10 mg daily is being used in most of these studies, well within the safe and tolerable range as evidenced by our study. Phase II evaluations of atrasentan may be warranted in other diseases in which ET dysregulation has been suggested as

a factor in tumor growth. Randomized placebo-controlled Phase II studies demonstrated a consistent ability of atrasentan to attenuate the increase in markers of prostate cancer progression such as prostate-specific antigen, alkaline phosphatase, *N*-telopeptides, *C*-telopeptides, deoxypyridinoline, and lactate dehydrogenase (22–24). Phase III trials comparing atrasentan to placebo are nearing completion.

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