Abbott

XINLAY™ (atrasentan hydrochloride)

ONCOLOGIC DRUGS ADVISORY COMMITTEE BRIEFING DOCUMENT

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NDA 21-491

Treatment of patients with hormone-refractory prostate cancer metastatic to bone

Oncologic Drugs Advisory Committee
Briefing Document for Atrasentan (Xinlay™)

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List of Abbreviations

ACE	angiotensin-converting enzyme
ADT	androgen-deprivation therapy
BSI	Bone Scan Index
CI	confidence interval
CT	computed tomography
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment in Cancer
ET-1	endothelin-1
FACT-P	Functional Assessment of Cancer Therapy – Prostate
ET_A, ET_B	endothelin receptor subtypes
HR	hazard ratio
HRPC	hormone-refractory prostate cancer
IDMC	independent data monitoring committee
LDH	lactic dehydrogenase
MI	myocardial infarction
NSAID	nonsteroidal anti-inflammatory drug
PCS	prostate cancer subscore
WBC	white blood cell

1.0 Executive Summary

Proposed Indication: Atrasentan is indicated for treatment of patients with hormone-refractory prostate cancer metastatic to bone.

Prostate cancer is the most commonly diagnosed non-skin cancer in the United States, with 232,090 new cases diagnosed annually. After lung cancer, prostate cancer is the second most common cause of cancer-related death among American men, resulting in 30,466 deaths per year.[1] After receiving standard androgen-deprivation therapy (ADT), 75% to 85% of patients with advanced, non-localized cancer develop hormone-refractory disease,[2] and 85% of HRPC patients ultimately develop metastatic disease, predominantly in bone.[3] Bone metastases are complicated by severe intractable pain, vertebral compression, and pathological fractures. Of the more than 30,000 men who die annually of prostate cancer, most have metastatic hormone-refractory disease and a large number experience severe pain. Currently, there are few treatment options for men with metastatic HRPC. Treatment has focused on pain palliation with opiate analgesics, radiation therapy, or radiopharmaceuticals. Docetaxel/prednisone prolongs survival by 2.5 months, but all patients inevitably relapse and require palliative care. Despite the survival benefit for HRPC of docetaxel/prednisone, only about 50% of patients with metastatic HRPC ever receive chemotherapy.[4] Zoledronic acid, a bisphosphonate, reduces the incidence of skeletal-related events in patients with bone metastases by 11%, but does not affect disease progression. Many of these treatments must be administered in a clinic or hospital setting. Clearly these patients would benefit from an easily administered and well-tolerated therapy that also delays disease progression.

Endothelin-1 (ET-1) was isolated in 1988 and described as a potent vasoconstrictor. In 1995, following the observation that seminal fluid contained the highest concentrations of ET-1 of any body fluid, it was noted that men with metastatic HRPC had significantly higher plasma concentrations of ET-1 than healthy controls or men with localized prostate cancer.[5] The observation that prostate cancer tissue expresses the ET_A receptor, a key receptor for ET-1, further suggested a role for ET-1 in HRPC progression. In 1996,

following these observations, Abbott began clinical development of atrasentan (Xinlay™), as a novel therapeutic agent for prostate cancer.

The clinical development of atrasentan, including the choice of endpoints, is reflective of the scientific understanding of endothelin biology current at the time the studies were designed. As is common in fields of rapidly expanding knowledge, new findings came to light during the conduct of the studies presented in this document. In 2003, the Guise group at the University of Virginia published results prominently implicating ET-1 in the pathogenesis of bone metastases and found that atrasentan could inhibit osteoblast proliferation through ET_A receptor antagonism.[6] These observations support the hypothesis that atrasentan could provide benefit particularly in patients with HRPC metastatic to bone.

The clinical program for atrasentan comprises more than 35 studies, including 4 randomized, double-blind, placebo-controlled studies in HRPC. Abbott's clinical program for atrasentan encompasses studies in patients at various stages of HRPC:

- Non-metastatic HRPC — M00-244 (ongoing)
- Asymptomatic or minimally symptomatic metastatic HRPC — M96-594 and M00-211
- Symptomatic metastatic HRPC — M00-500

Two of the randomized, double-blind, placebo-controlled studies were multinational trials conducted in men with metastatic HRPC with time to disease progression as the primary endpoint; they were conducted in patients who were either asymptomatic (M96-594) or free of cancer-related pain (M00-211) and these form the basis for the review of atrasentan's efficacy in treating metastatic HRPC. Results from a phase 2 study conducted in men with symptomatic metastatic HRPC (M96-500 with pain response as the primary endpoint) were also submitted as part of the NDA and are included in the safety discussion. In addition, atrasentan is currently being studied in a trial of 941 men with non-metastatic HRPC (M00-244).

A significant benefit was observed in time to disease progression, the primary endpoint, in a protocol-specified evaluable population in each study, even though the treatment effect in favor of atrasentan did not achieve statistical significance in the intent-to-treat population of either study. Most importantly, an analysis of patients from study M00-211 with confirmed bone metastases at baseline demonstrated a significant delay in disease progression with atrasentan compared with placebo, which was supported by data from study M96-594.

Time to disease progression was a composite endpoint of radiographic and clinical measures. Evaluation of the treatment effect on each major component demonstrated a beneficial effect of atrasentan on delaying clinical progression events in both the intent-to-treat and confirmed bone metastatic populations. This finding is also consistent with the role of atrasentan in blocking the effect of endothelin-1 on osteoblast proliferation and resultant disorganized new bone growth in the bone microenvironment, the site of most metastases in prostate cancer patients.

Results of secondary analyses, such as slowing the increase in biomarkers of tumor burden and disease, bone alkaline phosphatase and PSA, factors with known prognostic importance in advanced prostate cancer, support the positive effect of atrasentan on delaying disease progression in the bone metastatic population. Patients initially randomized to atrasentan had a median survival of 20.5 months versus 20.1 months for those randomized to placebo in study M00-211. Even though the study was not designed to detect a survival benefit, the overall survival observed in this study compares favorably with the median survival of 18.0 and 18.9 months reported with docetaxel in combination with estramustine and prednisone, respectively.[7–8] Analysis of changes in quality of life over time demonstrated comparatively less decline with atrasentan therapy on patient-reported outcomes of disease-specific pain. Other analyses show that atrasentan postponed the time to 50% deterioration in pain-related quality of life scores and delayed the onset of bone pain. The results herein provide evidence that atrasentan has particular clinical benefit in men with metastatic HRPC that has metastasized to bone.

In HRPC patients with bone metastases, atrasentan provides these benefits:

- 19% reduction in risk of experiencing disease progression
  - Estimated 25.4% relative difference in progression-free rate at 3 months and 31.6% at 6 months
- 32% reduction in risk of experiencing clinical progression events
- 21% reduction in risk of an adverse event of bone pain
- 36% reduction in risk of experiencing a 50% decline in pain-related quality of life as measured by the FACT-P PCS pain questions

Atrasentan delivers these benefits in the context of once-daily oral administration and manageable tolerability with no renal or hepatic toxicities and no bone marrow suppression. Atrasentan has a manageable safety profile for this progressive disease in this predominantly elderly population. The most notable adverse event identified is heart failure, which is mechanistically understandable given the fluid retention effects of atrasentan. Incidents of heart failure occurred early in the course of therapy and are recognizable, allowing for appropriate medical management. Myocardial infarction, although uncommon, was more frequently observed in the atrasentan arm of the double-blind, placebo-controlled portion of study M00-211, with the majority of events occurring in patients with significant previous cardiovascular history or extenuating and/or concomitant intervening problems. The most common adverse effects of rhinitis, headache, and peripheral edema are associated with the known vasodilatory properties of selective ET_A receptor antagonists and resultant fluid retention. These events were generally mild to moderate in intensity and few patients discontinued atrasentan as a result.

The weight of evidence suggests that atrasentan provides measurable clinical benefit with a manageable safety profile for patients with metastatic HRPC disease in bone.

2.0 Introduction

2.1 Hormone-Refractory Prostate Cancer: Epidemiology and Treatment

Prostate cancer is the most commonly diagnosed non-skin cancer in the United States and is second only to lung cancer as a common cause of cancer-related death in men (30,466 annually).[1] Following androgen-deprivation therapy (ADT), 75% to 85% of patients with advanced, non-localized cancer ultimately develop hormone-refractory disease (HRPC), with 85% of these patients exhibiting radiographic evidence of metastases in bone.[2,3] Bone metastases from prostate cancer are typically osteoblastic, with increased uptake on radioscintigraphy. Progressive debilitating bone pain, along with serious skeletal complications, such as spinal cord compression, pathologic fractures, and neurological deficit, are major morbidities for these patients. Seventy-five percent of patients will develop pain and 55% of those dying from prostate cancer will require opiate analgesia in the last 3 months of life.[9] Bone pain can be continuous or intermittent, vary diurnally, and be migratory in nature, and it can severely limit activity. Its optimal management is complex and frequently not completely satisfactory to patients, their families, and their physicians. Aspirin-related compounds such as nonsteroidal anti-inflammatory drugs (NSAIDs) are the first-line treatment choice, but most commonly, opiate analgesia becomes necessary.[10,11] Response to opiate analgesics and other systemic therapies is variable and inconsistent. Further, in a study of the utilization of palliative care in cancer, 90% of HRPC patients required opioid analgesics in the final month before death.[9]

Prevention or delay of the excruciating pain that requires opiates clearly is a desirable therapeutic objective. Initiation of opiate analgesia itself is associated with a poor prognosis and an increased chance of dying within 1 year.[12] Some of the common adverse effects of opioid analgesics include sedation, agitation, confusion, constipation, nausea, and vomiting. Localized external beam radiation therapy is frequently required for palliation, but the widespread nature of bone metastases in HRPC means that *diffuse* skeletal pain remains a major problem. Only 35% of patients will gain even partial relief from radiation therapy, and 20% will not respond at all.[13]

Most patients facing the prospect of progression of metastatic HRPC to severe pain have limited treatment options. In addition to opiates, secondary hormonal therapy, radiation therapy, radiopharmaceuticals, and chemotherapy with docetaxel or mitoxantrone in combination with prednisone are used to control pain. Zoledronic acid reduces the occurrence of skeletal-related events associated with advanced prostate cancer and long-term ADT, but does not affect disease progression.[14]

Docetaxel in combination with prednisone was approved in May 2004 for the treatment of patients with androgen independent (hormone-refractory) metastatic prostate cancer. Independent data provided from OncoTrack (Oncology, Inc., a comprehensive patient records database that tracks drug utilization and cancer patient characteristics),[4] indicated that in 2004 only 48% of HRPC patients received chemotherapy. The remaining 52% were treated with non-chemotherapy modalities. Of those who received chemotherapy, 65% (362/554) received docetaxel; the remaining 35% used non- docetaxel containing regimens.

In 2005, this demographic remains unchanged. Forty-seven percent of HRPC patients received chemotherapy, while 53% did not. As expected, the use of docetaxel among chemotherapy-treated patients increased from 65% in 2004 to 74% in 2005 following its approval for the treatment of HRPC. While usage of docetaxel specifically increased among patients who elect to receive chemotherapy, the pool of patients who do not receive chemotherapy has remained unchanged over a 2-year period.

Docetaxel and mitoxantrone treatments require close monitoring and must be administered by health care professionals. Men with metastatic HRPC progress rapidly with a median survival of approximately 18 months with standard of care.[7,8] The delay in both time to disease progression and time to developing pain and the slowed deterioration in quality of life provided by atrasentan demonstrate that it represents an important addition to the limited treatment options available to men with metastatic HRPC.

2.2 Rationale for the Development of Atrasentan

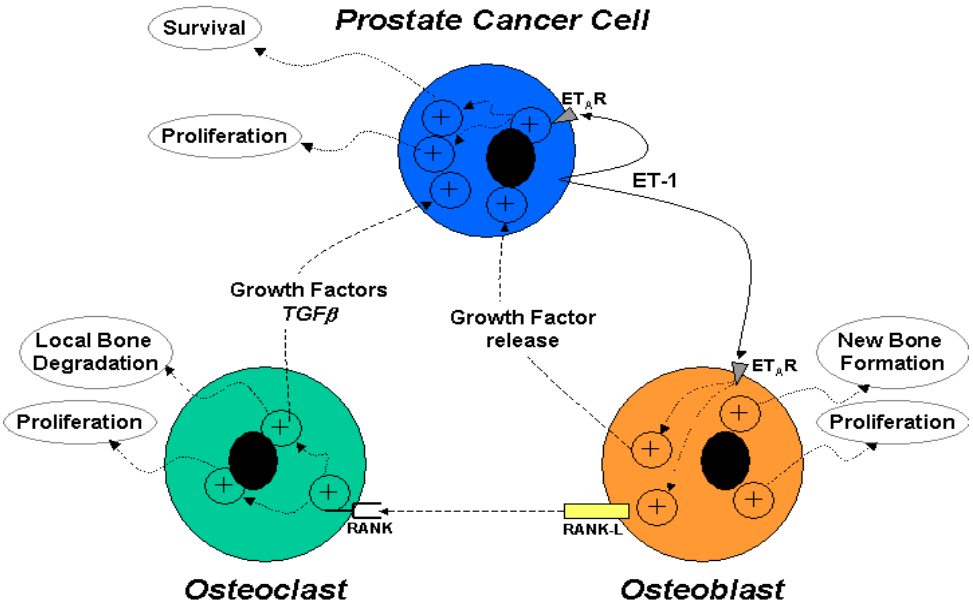
The endothelin (ET) axis consists of 3 peptides, ET-1, ET-2, and ET-3, and two G-protein–linked endothelin receptors, ET_A and ET_B, that mediate their effects.[15] These peptides were originally identified due to their vasoactive properties. ET_A receptors bind ET-1 with a higher affinity than ET-2 and ET-3,[16] while ET_B receptors bind all 3 peptides with a similar affinity.[15]

ET-1 is the primary endothelin isoform identified in mammalian tissues and fluids and is the most potent endogenous vasoconstrictor known. ET-1 increases vascular permeability and stimulates the proliferation of vascular smooth-muscle cells, cardiocytes, and fibroblasts. Excessive ET-1 is associated with cardiovascular and non-cardiovascular diseases, including myocardial damage due to vascular insult, heart failure, pulmonary hypertension, and postischemic renal failure.[17–20] Given the impact of ET-1 on the growth of vascular cells, it is not surprising that the initial hypotheses regarding the role of the endothelin axis in the development of prostate cancer centered on mitogenesis. Nelson and coworkers observed that prostate cancer cells secrete ET-1 and that circulating ET-1 levels are elevated in hormone-refractory prostate cancer (HRPC) and are even higher in metastatic disease than in localized disease.[5] They also noted that ET-1 acts as a modest mitogen and a stronger comitogenic agent on prostate cancer cells in vitro, acting through the ET_A receptor.[5,21] ET receptor populations on normal prostatic epithelium undergo a phenotypic shift in HRPC, transforming from ET_B-rich to ET_A-rich.[21] These observations, indicating that ET axis blockade should reduce prostate cancer cell proliferation, originally led Abbott to initiate clinical trials of the selective ET_A receptor antagonist atrasentan in HRPC, and shaped the design of those trials.

More recent studies have clarified another key role of the ET axis in prostate cancer, noting a unique relationship between tumor-derived ET-1 and bone remodeling. High levels of both ET-1 and the ET_A receptor characterize cancers associated with osteoblastic phenotypes (notably prostate and breast). Of particular relevance to osteoblastic bone metastases in prostate cancer, osteoblasts express the ET_A receptor at

high density (10^5 to 10^6 receptors per cell), and ET-1 drives osteoblast proliferation and new bone formation through ET_A receptor activation in vitro and in vivo.[6,22–25] Active osteoblasts in turn generate growth factors, which reciprocally exacerbate local metastatic tumor proliferation, either directly or indirectly through the osteoclasts via the receptor activator of NFκB (RANK) pathway[6,24,25] (Figure 1). Endothelin stimulates the proliferation of osteoblasts in culture[26] and increases the expression of the phenotype-related proteins osteocalcin and osteopontin in an osteosarcoma cell line.[27]

Figure 1. Prostate Cancer Cell–Osteoblast–Osteoclast Interaction Within the Bone Compartment Microenvironment



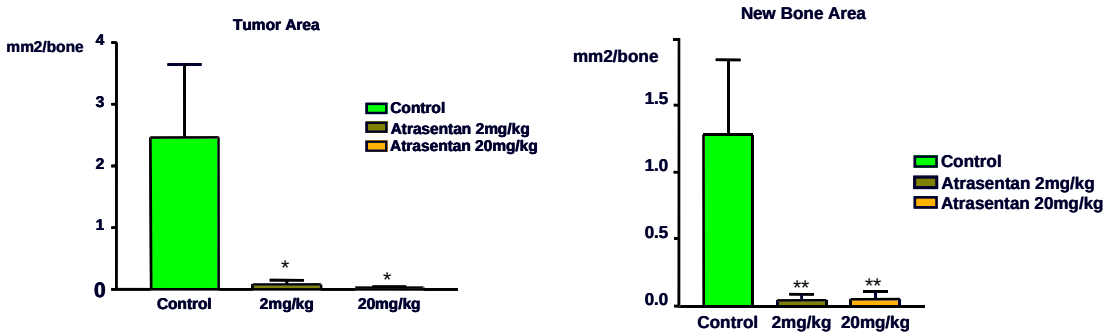
ET-1 = endothelin 1; ET_AR = endothelin A receptor; TGFβ = transforming growth factor β; RANK = receptor activator of NFκB; RANK-L = RANK ligand

Tumor-derived ET-1 stimulates osteoblast proliferation and new bone formation via the ET_A receptor. Activated osteoblasts release growth factors that in turn promote cancer cell proliferation and survival, setting up a vicious cycle. Osteoblasts and tumor cells can also stimulate osteoclasts through the RANK pathway, and activated osteoclasts degrade bone, releasing latent tumor growth factors, such as TGFβ.

Until recently, efforts to validate this hypothesis in vivo have been hampered by the paucity of animal models that reflect the natural history and progression of prostate cancer. Standard human prostate cancer cell lines, even those (such as PC3) that secrete osteoblastic factors, generally produce osteolytic tumors when injected into animals. Nelson and coworkers employed the WISH cell line, a rapidly growing osteoblastic line of amniotic lineage.[28] Intratibial injection of these cells produces substantial new bone growth over a 14-day period. Treatment with A-127722, the racemate of atrasentan, substantially reduced new bone formation. The results of the study suggested for the first time that ET_A receptor blockade could inhibit a tumor-driven osteoblastic response in vivo.

The most compelling data regarding the critical role of the ET axis in the formation of osteoblastic bone metastases emerge from work with 2 in vivo models. The first utilizes the ZR-75-1 tumor line, an ET-1–secreting breast cancer cell line that forms osteoblastic tumors in mice. In vitro work demonstrated that the ZR-75-1 tumor line stimulated bone formation that could be completely inhibited by atrasentan.[6] Mice receiving intracardiac injections of ZR-75-1 develop osteoblastic metastases over a period of 3 to 6 months. Atrasentan administered in the drinking water reduced tumor volume and new bone formation compared with vehicle (Figure 2).[6,28]

Figure 2. Endothelin A Receptor Blockade with Atrasentan Inhibited Tumor and New Bone Formation in ZR-75-1 Cell Line



*,** $P \leq .05$ and.01, respectively.
Source: Yin et al. Proc Natl Acad Sci USA 2003;100(19):10954–9.

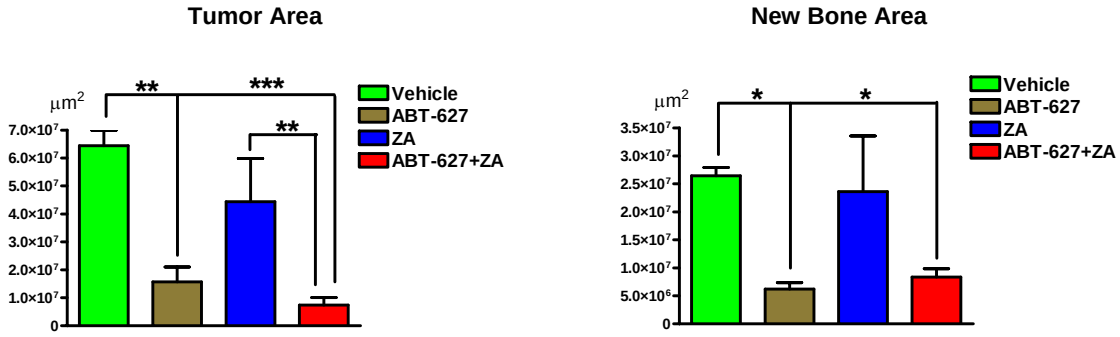
Importantly, the tumor burden in the bone is also reduced by ET_A blockade, suggesting that atrasentan has interrupted the tumor/osteoblast feedback loop. An ET_B receptor antagonist has no effect in this model. Putting their results in the context of the other experiments described here, the authors state:

> We propose the following mechanism by which ET-1 promotes osteoblastic bone metastases: metastatic cancer cells in the bone microenvironment secrete ET-1, which binds to the ET_A receptor and stimulates osteoblast proliferation and new bone formation. The stimulation of osteoblast activity enriches the local microenvironment with growth factors, which in turn could increase tumor burden and ET-1 secretion. This hypothesis proposes that the net effect is a vicious cycle, which increases osteoblastic bone metastases.[6]

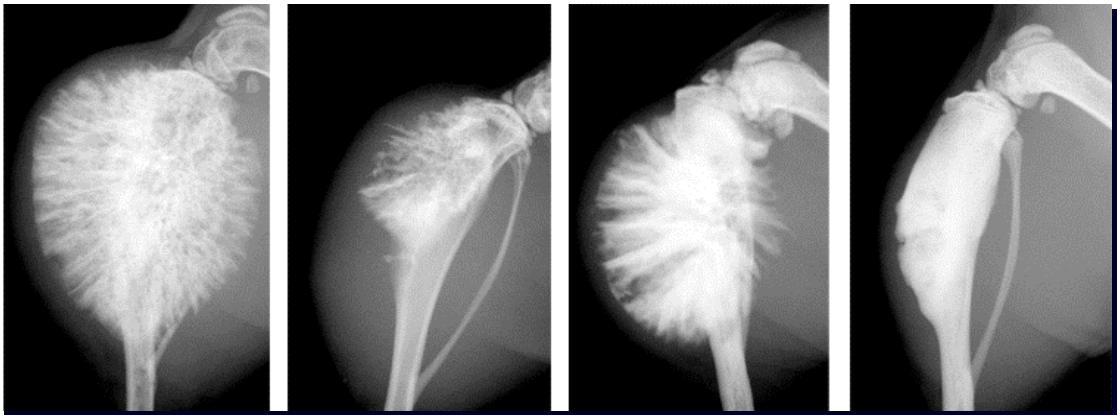
The above preclinical results indicate that the endothelin axis may play a unique synergistic role in the development of osteoblastic metastases, in tumors such as prostate cancer. This suggests that an ET_A receptor antagonist such as atrasentan might show enhanced activity in bone compared with other domains.

In the second in vivo model of ET_A receptor blockade, which used the LuCap23.1 prostate cancer cell line, Guise and coworkers injected nude mice in the tibia with LuCap23.1 and treated them with vehicle, atrasentan, zoledronic acid, or atrasentan + zoledronic acid. Atrasentan treatment resulted in a greater reduction in both tumor area and osteoblast generation than both vehicle and zoledronic acid, and response to the combination therapy on tumor area was greater than either treatment alone (Figure 3).

Figure 3. Endothelin A Receptor Blockade with Atrasentan and Zoledronic Acid Inhibited Tumor and New Bone Formation in LuCap23.1 Cell Line



Histomorphometric analysis of the intratibial LuCap23.1 tumor area and new bone area. Mice treated with either atrasentan (ABT-627) or zoledronic acid (ZA) had less tumor and new bone area than vehicle-treated mice. Combined therapy was more effective in reducing tumor area than either treatment alone. Atrasentan more effectively reduced new bone area compared with combined therapy.
*, **, *** $P \leq .05$, .01, and .001, respectively for difference between treatments.



Radiographic images of the LuCap 23.1 inoculated into the tibia of nude mice, showing extensive osteoblastic reaction and florid new bone formation in vehicle-treated mice (A). Combined treatment with atrasentan (ABT-627) and zoledronic acid (ZA) (D) dramatically reduced the size of the osteoblastic lesion, more than either ABT-627 (B) or ZA (C) alone.
Source: Mohammad et al. Symposium on Skeletal Complications of Malignancy, sponsored by the Paget Foundation and the University of Virginia Health System. Bethesda, Md.: NIH, 28–30 April 2005.

ET-1 appears to mediate other effects relevant to metastatic cancer, including the modulation of pain. In vivo studies demonstrate that sensory neurons express the ET_A

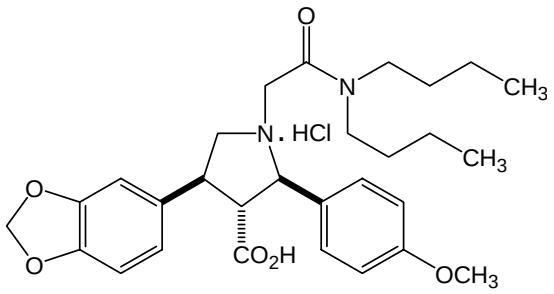
receptor,[29] and in various models of peripheral nociception, ET-1 activation of the ET_A receptor induces a pain response by hypersensitizing nerve terminals to stimuli, thereby causing allodynia.[30–34] The pain caused by ET-1 in vivo was blocked only by morphine and was resistant to milder analgesics.[30] Selective ET_A receptor blockade lessens these nociceptive effects, and in an in vivo bone cancer pain model, atrasentan significantly reduced ongoing and movement-evoked bone cancer pain as well as several neurochemical indices of peripheral and central nociceptor stimulation.[35]

Abbott's understanding of the role of endothelin and the ET_A receptor in the pathogenesis of prostate cancer has undergone a dramatic shift in recent years, influencing the context within which atrasentan's clinical trial experience should be reviewed. A growing body of preclinical evidence has shown that there is a unique role for the endothelin axis in mediating the interplay between osteoblasts and tumor cells within bone metastases. ET-1 secreted by tumor cells stimulates the growth and activity of osteoblasts; in fact, ET-1 secretion is a hallmark of osteoblastic tumors. The osteoblasts respond to this stimulation by secreting their own mitogenic factors, further enriching the local environment. The net result is tumor expansion and a disruption of the osteoclast/osteoblast balance leading to excess deposition of disorganized bone. While many growth factors play a role in this spiraling response, ET-1 signaling through ET_A receptor is central. The evidence suggests that atrasentan may be uniquely effective at this tumor-bone interface.

2.3 Atrasentan Drug Substance and Pharmacokinetics

Atrasentan is a potent (Ki 0.034 nM) and selective endothelin A receptor antagonist that is 1800 times more selective for ET_A than for ET_B (Figure 4).[32,36]

Figure 4. Chemical Structure of Atrasentan



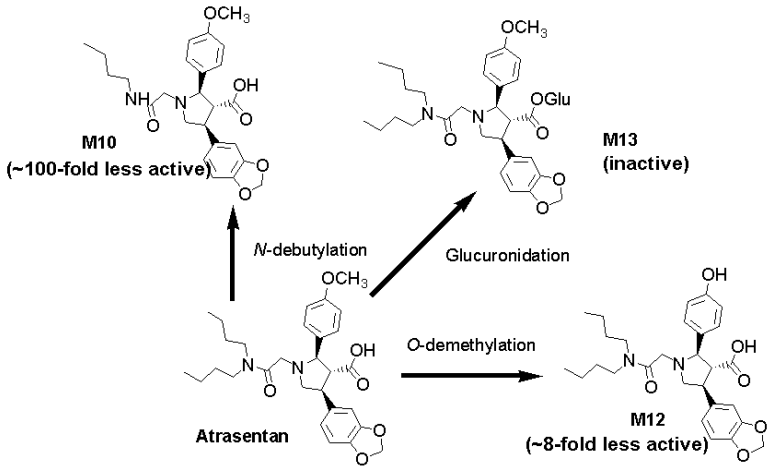
Over a 24-hour dosing interval at steady state, the 10-mg dose achieved a C_{max} of 39 ng/mL and a C_{min} of 13 ng/mL. The area under the curve was 556 ng•hr/mL. With the 2.5-mg dose, over a 24-hour dosing interval at steady state, the C_{max} was 14 ng/mL and the C_{min} was 4 ng/mL. The area under the curve was 247 ng•hr/mL. The in vitro binding of [^{14}C]atrasentan to human plasma proteins at drug concentrations between 0.05 μg/mL and 50 μg/mL was 98.8%. Following a single oral 10-mg dose administered under fasting conditions, absorption was rapid with a median time to maximum plasma concentration (T_{max}) of 0.5 hours. The terminal elimination half-life of approximately 25 hours in humans provides convenient once-daily dosing with steady state concentrations achieved within 7 days.

Daily dosing of orally administered 2.5 mg to 30 mg atrasentan achieved plasma concentrations that exceeded the Ki of atrasentan at the ET_A receptor. Plasma concentrations achieved in this dose range corresponded to concentrations producing physiologic effects in human pharmacodynamic studies and in preclinical studies in vivo.

Atrasentan is extensively glucuronidated, primarily forming the ester glucuronide of parent drug and also the *N*–debutylated derivative. In addition, atrasentan undergoes

oxidative metabolism to form the *N*–debutylated and *O*–demethylated metabolites of parent drug (Figure 5). Hydrolysis of the glucuronide moiety in the intestine would therefore suggest the possibility for enterohepatic cycling. Enzymes of the cytochrome P450 3A (CYP3A) family are the major catalysts of oxidative metabolism of atrasentan.

Figure 5. Metabolism of Atrasentan



Following oral administration of a single 5-mg dose of [^{14}C]atrasentan to adult male human subjects, the primary route of dose elimination was fecal (>90% of the dose), while urinary excretion was minor (4% of the dose). About two thirds of the administered dose was eliminated in the feces as unchanged parent drug and the *O*-demethyl metabolite. Relatively small amounts of the *N*–debutyl and 4 minor unidentified metabolites (each comprising less than 4% of the dose) were excreted. Absence of unchanged parent drug in the urine indicated that the renal clearance of atrasentan in man was negligible.

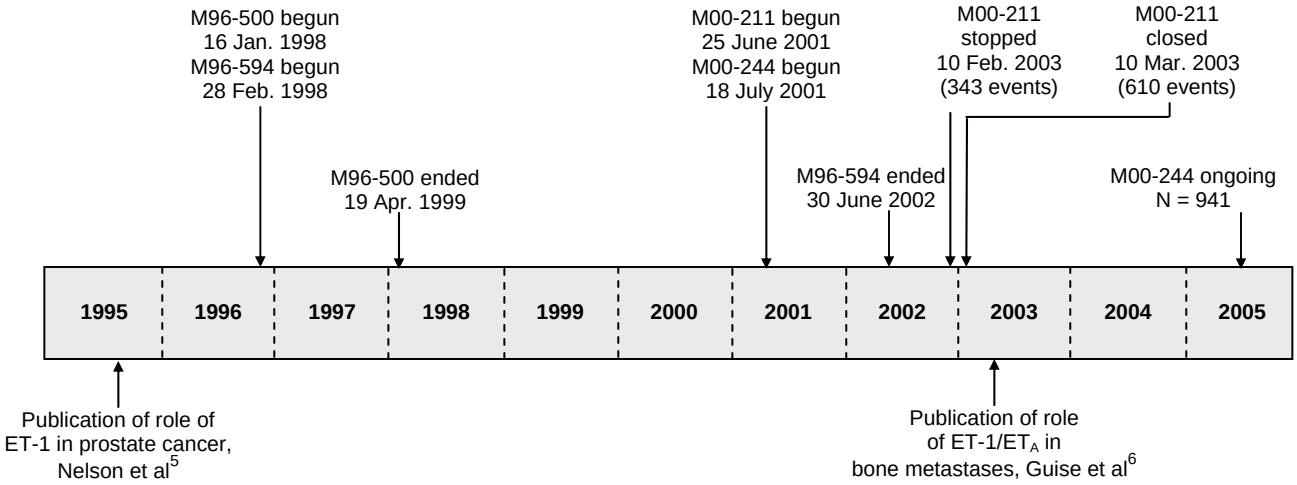
3.0 Clinical Development Program

The clinical development program for atrasentan began in June 1996, encompassing 35 completed or ongoing studies, including 4 studies in HRPC. Atrasentan administration was studied in diverse patient populations, including patients with diabetic nephropathy, congestive heart failure, and hepatic impairment. In 1997, Abbott focused the atrasentan

oncology clinical program on prostate cancer based on compelling evidence for the role of endothelin expression in the disease. In January 1998, 2 randomized placebo-controlled studies were initiated in symptomatic and asymptomatic metastatic HRPC (M96-500 and M96-594, respectively). Study M96-500 was an 84-day trial designed to evaluate the effect of atrasentan on pain in subjects with symptomatic HRPC, which showed that atrasentan had a modest effect on reduction of pain and opioid analgesic use. Study M96-594 was in patients with asymptomatic metastatic HRPC, comparing 2.5 mg and 10 mg atrasentan with placebo. In this study, the 10-mg dose of atrasentan delayed disease progression, particularly in an evaluable population. Based on these findings, Abbott initiated 2 large phase 3 studies in HRPC in June 2001. One of these studies, M00-244, is in patients with non-metastatic HRPC and is ongoing. The second, M00-211, evaluated the effect of atrasentan on disease progression in patients with metastatic HRPC. This study was stopped in February 2003 when an independent data monitoring committee (IDMC) determined that the null hypothesis was not likely to be rejected (more details are provided in section 4.2.2). The results of studies M96-594 and M00-211 form the basis of the efficacy discussion in this document.

Finally, a study in patients with advanced HRPC metastatic to bone is planned to begin in October 2005 in collaboration with the Southwest Oncology Group (SWOG) comparing the effect of combination atrasentan + docetaxel/prednisone with placebo + docetaxel/prednisone on progression-free survival. Secondary endpoints include survival, qualitative and quantitative analyses of toxicity, quality of life, and changes in biomarkers of tumor burden.

A timeline for the clinical program with atrasentan in HRPC is shown in the diagram below.



3.1 Clinical Trials in Metastatic Hormone-Refractory Prostate Cancer

The efficacy of 10 mg atrasentan in patients with metastatic HRPC is demonstrated in 2 randomized, double-blind, placebo-controlled, multinational studies, M00-211 and M96-594. Patients were minimally symptomatic or asymptomatic, respectively. In both studies, the primary endpoint was time to disease progression. These studies are summarized below.

4.0 Efficacy of Atrasentan

4.1 Supportive Study M96-594

4.1.1 Study Design

Study M96-594, initiated in February 1998, was a randomized, double-blind, placebo-controlled, multinational, dose-ranging phase 2 study designed to evaluate the effect of 10 mg and 2.5 mg atrasentan in men with asymptomatic metastatic HRPC. A total of 288

patients were randomized into the study at 74 sites in 9 countries. Sites included both hospital and community practice, with participation by both urologists and oncologists.

Eligibility Criteria

Patients were to have histologic evidence of prostatic adenocarcinoma, metastatic disease, hormone-refractory status (castrate levels of testosterone, ie, <30 ng/dL and a rising PSA or PSA ≥20 ng/mL), sufficient anti-androgen withdrawal, adequate performance status (Eastern Cooperative Oncology Group [ECOG] ≤2), and freedom from pain related to prostate cancer. Patients who had received radionuclides within 12 weeks of randomization were ineligible, as were those who had received radiotherapy or chemotherapy within 28 days before randomization.

The primary endpoint was time to disease progression, described in detail below, as determined by the investigator. A total of 204 patients (68 per treatment arm) was calculated to be sufficient to detect a 50% improvement in time to disease progression in either atrasentan arm compared with the placebo group with 0.2 significance and 76% power. Time to disease progression was defined as the first event from among the following:

Radiographic measures (performed at the investigator's discretion and interpreted locally)
- New measurable bone lesions by bone scan
- Extraskeletal progression measured by CT scan

Clinical measures (adjudicated by the investigator)
- Prostate cancer–related pain requiring opioid analgesics or radiation
- Initiation of chemotherapy
- New symptoms related to tumor growth and requiring intervention
- Other investigator-defined measures of disease progression

Radiographic scans were not scheduled at regular intervals, but were mandated only at baseline and at the time of clinical progression. Additional scans could be performed at the investigator's discretion. Secondary efficacy analyses included changes from baseline at scheduled intervals in biomarkers, quality of life, performance status, and

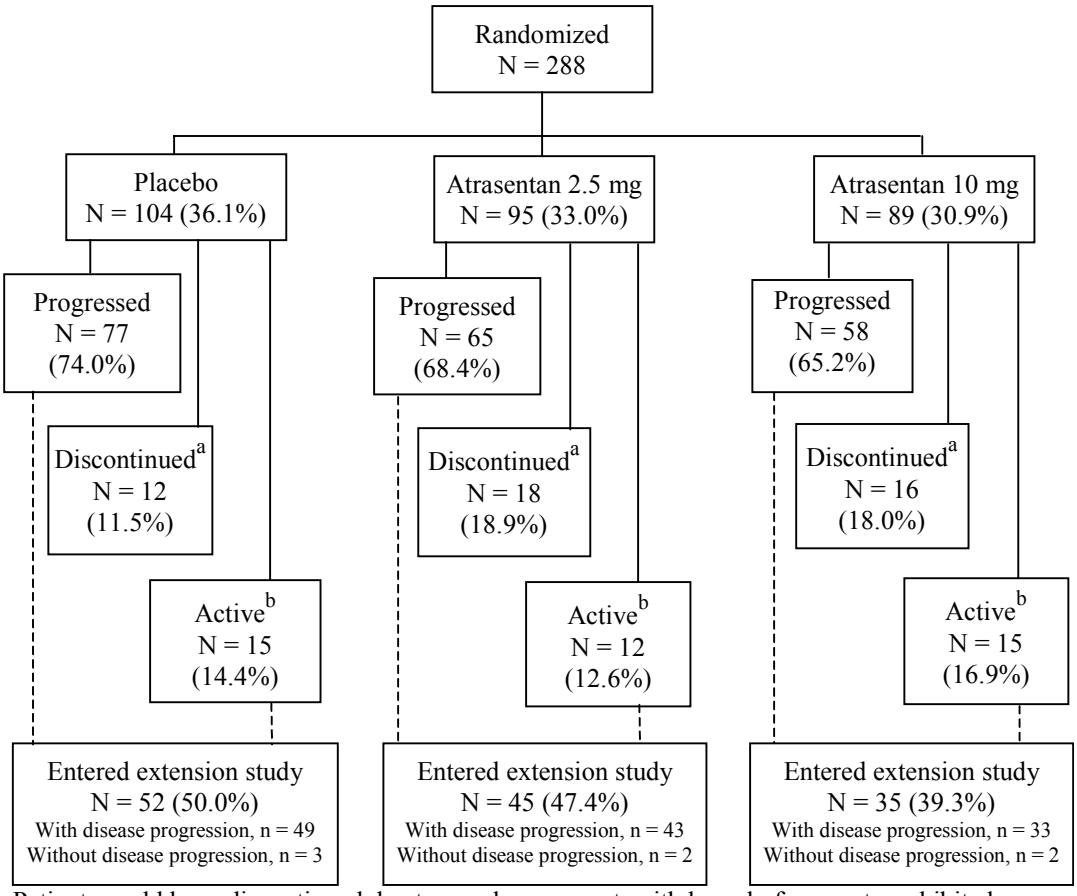
survival. Patients who completed the study were eligible to enroll in an open-label extension study. All protocol-specified analyses were subject to a cutoff of 31 October 1999; all other analyses are performed with no cutoff.

The study was initiated in February 1998 and was completed in June 2002.

4.1.2 Efficacy Results

Patient disposition in study M96-594 as of 31 October 1999 is summarized in Figure 6.

Figure 6. Patient Disposition in Study M96-594



a Patients could have discontinued due to an adverse event, withdrawal of consent, prohibited concomitant medication use, or personal or other reasons.

b Patients were still active as of 31 October 1999.

Patients enrolled in the study ranged in age from 43 to 94 years. A total of 278 patients were Caucasian (97%), 6 (2%) were Black, 2 (1%) were Asian, and 2 (1%) were Hispanic. Baseline characteristics for the placebo and atrasentan treatment arms are summarized in Table 1. The treatment groups were well balanced with no statistically significant differences in demographics or baseline characteristics.

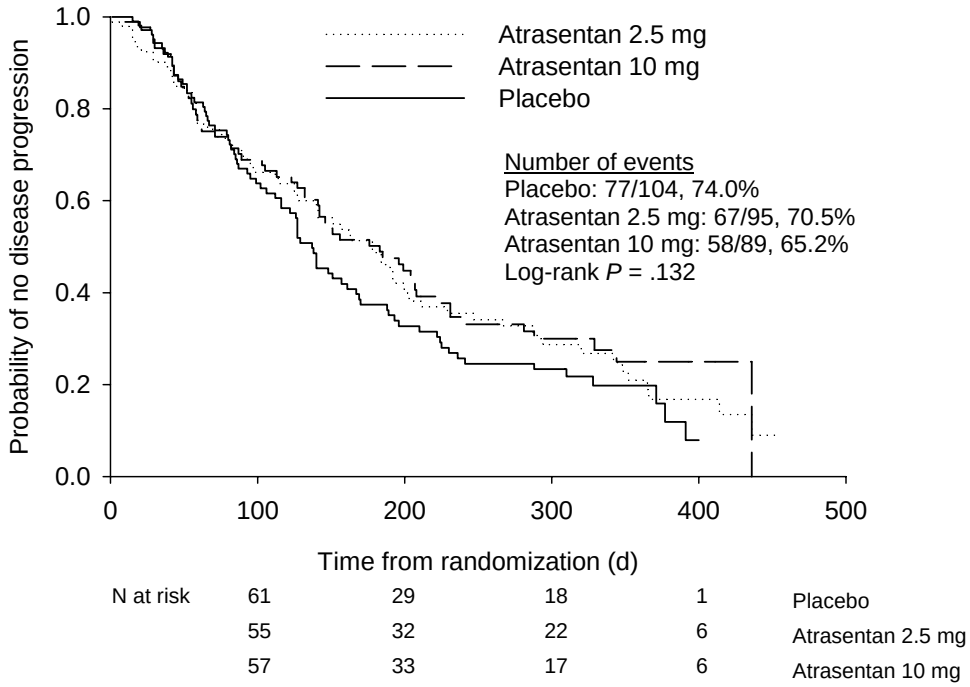
Table 1. Baseline Characteristics: M96-594 Intent-to-Treat Population

	Placebo N = 104		2.5 mg Atrasentan N = 95		10 mg Atrasentan N = 89	
Variable	**Median**	**Range**	**Median**	**Range**	**Median**	**Range**
Age, y	72.0	(54 – 88)	71.0	(52 – 89)	72.0	(43 – 94)
Hemoglobin, g/dL	13.2	(8.2 – 16.0)	13.1	(8.3 – 15.4)	13.5	(9.7 – 15.7)
LDH, IU/L	177	(95 – 420)	173	(93 – 663)	169	(74 – 626)
Bone alkaline phosphatase, ng/mL	15.8	(3.3 – 703.9)	11.9	(4.3 – 253.7)	15.3	(3.3 – 513.4)
PSA, ng/mL	94.1	(0.1 – 7431.0)	70.8	(2.6 – 9374.3)	84.2	(2.4 – 2822.4)
Total Gleason score	7.0	(4.0 – 10.0)	7.0	(3.0 – 10.0)	7.0	(2.0 – 9.0)
Time since diagnosis, y	4.4	(0.1 – 22.9)	3.8	0.4 – 22.5)	5.3	(0.1 – 19.0)
ECOG performance score ≤1	101/104 (97.1%)		89/95 (93.7%)		84/89 (94.4%)	

Primary Endpoint—Time to Disease Progression

In the primary analysis of time to disease progression, the median time to progression was longer for 10 mg atrasentan than for placebo (183 days versus 137 days), although the difference was not statistically significant in the intent-to-treat population (hazard ratio [HR] = .769, 95% CI = [.545, 1.085]) (log-rank *P* = .132). Similar results were observed with 2.5 mg atrasentan relative to placebo (median of 178 days; log-rank *P* = .288), but the signal was not as strong as with the 10 mg dose (2.5 mg versus placebo HR = .836, 95% CI = [.600, 1.165]) (Figure 7).

Figure 7. Time to Disease Progression: M96-594 Intent-to-Treat Population



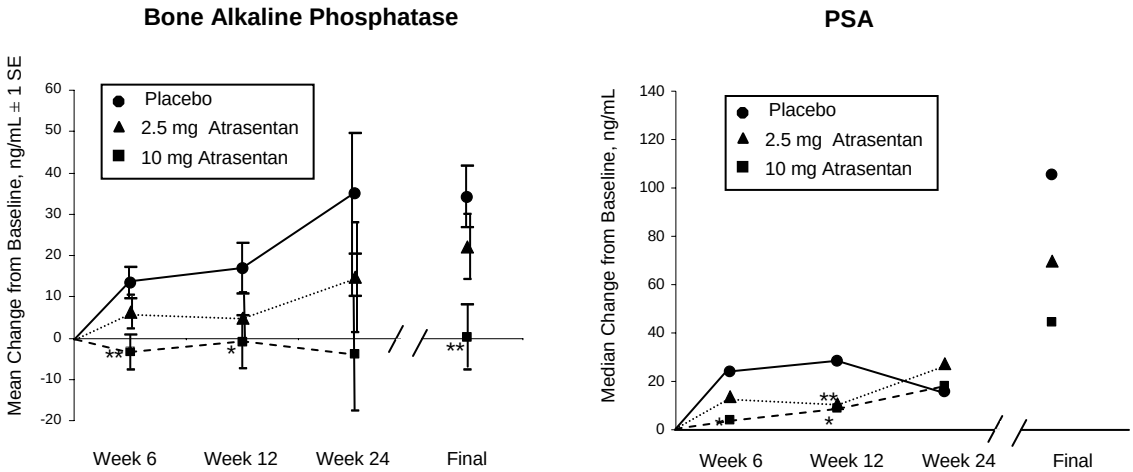
In an analysis of the 84.7% of randomized patients (N = 244)[a] who most strictly met the inclusion and exclusion criteria as defined by the protocol, 10 mg atrasentan demonstrated a statistically significant 67-day delay in median time to disease progression (*P* = .021). In this analysis, 10 mg atrasentan reduced the risk of disease progression by 35% relative to placebo (HR = .654, 95% CI = [.455, .940]) using Cox proportional hazards modeling. The 2.5 mg dose also significantly delayed time to disease progression with a 55-day difference in median time compared with placebo (*P* = .035) and with a 31% reduction in the risk of disease progression relative to placebo (HR = .686, 95% CI = [.481, .977]).

a The definition of the evaluable population and the results of the primary analysis for each study are presented in Appendix B.

Secondary Endpoints—Changes in Biomarkers

Atrasentan significantly attenuated the increase in biomarkers related to disease progression, bone alkaline phosphatase and PSA, both of which have been correlated with poor outcome (Figure 8).[37,38]

Figure 8. Change from Baseline in Biomarkers: M96-594 Intent-to-Treat Population



*,** $P \leq .05$ and $P \leq .01$ for the difference between treatment arms

Time to PSA progression, defined as an increase ≥50% from baseline on 2 occasions at least 2 weeks apart, was also analyzed. The treatment difference was significant for 10 mg atrasentan and was more pronounced than with the 2.5 mg dose (Table 2).

Table 2. Time to PSA Progression: M96-594 Intent-to-Treat Population

Treatment Arm	Number of Events (%)	Median, days	HR (95% CI)	*P* Value
Placebo	68/102 (66.7%)	71		
2.5 mg Atrasentan	52/88 (59.1%)	141	.706 (.491, 1.016)	.055
10 mg Atrasentan	41/86 (47.7%)	155	.553 (.373, .819)	.002

Summary of Phase 2 Experience

Decisions affecting the design of the phase 3 study, M00-211, were based on the results and conduct of the dose-ranging study, M96-594. The 10 mg dose was selected for further development because of its measurably greater effect on disease biomarkers and a similar adverse event profile relative to the 2.5 mg dose (see section 5.3). Second, the weighted log-rank statistical test, $G^{1,1}$ (described by Fleming et al[39]), was selected for use in the primary analysis in study M00-211 based on the results from this study. Third, a decision was made to address the FDA's concerns about the potential effect that PSA changes may have exerted on triggering discretionary radiographic scans and thus influencing time to disease progression. In study M00-211, Abbott prespecified that scans be performed at 12-week intervals. This decision had unanticipated consequences, which are discussed in greater detail below.

4.2 Pivotal Study M00-211

4.2.1 Study Design

Study M00-211, initiated in June 2001, was a randomized, double-blind, placebo-controlled, multinational phase 3 study designed to evaluate the effect of 10 mg atrasentan in men with metastatic HRPC. A total of 809 patients were ultimately randomized at 179 sites in 18 countries. Sites included both hospital and community practice, with participation by both urologists and oncologists.

Eligibility Criteria

Patients were to have histologic evidence of prostatic adenocarcinoma, independently reviewed evidence of metastatic disease, hormone-refractory status (castrate levels of testosterone, ie, <50 ng/dL[40] and a rising PSA or a PSA value ≥20 ng/mL), sufficient anti-androgen withdrawal, adequate performance status (Karnofsky ≥70), and freedom from prostate cancer–related pain requiring opiates. A central radiologist independently reviewed all baseline scans to confirm the presence and location of metastases. Patients who received chemotherapy or radionuclide therapy were ineligible, as were those who received local therapy to the prostatic bed or radiation therapy or steroids within 6 months of randomization. Patients who received hormone therapies or bisphosphonates within 4 weeks were likewise ineligible.

The primary endpoint was time to disease progression. Time to disease progression was defined as the first independently confirmed event from among the following:

Radiographic measures

New measurable bone lesions	At least 2 new lesions determined by bone scan scheduled every 12 weeks
New measurable soft-tissue lesions	One new lesion or changes to existing lesion(s) determined by computed tomography (CT) scan or magnetic resonance imaging (MRI) using modified RECIST criteria

Clinical measures

Metastatic pain	Prostate cancer–related pain as demonstrated by evidence of disease at the site and requiring opiates (single dose of intravenous, intramuscular, or subcutaneous opioids or oral or transdermal opioids administered for 10 out of 14 days), chemotherapy, radiotherapy, radionuclide therapy, or glucocorticoids (≥5 mg oral prednisone for 10 out of 14 days or a doubling of the current dose for 10 out of 14 days for patients on chronic steroid therapy)
Skeletal-related event	A clinically manifested skeletal-related event with evidence of disease at the site (a pathologic or vertebral compression facture not related to trauma, prophylactic radiation, or surgery for an impending fracture, or spinal cord compression)
New intervention	Progression requiring other intervention, eg, urinary tract obstruction, malignant pleural effusion, brain metastases, or other similar events, and not including an increase in PSA

The composite endpoint was established in consultation with academic experts, regulatory agencies, and practicing physicians. A 12-week schedule for bone scans, although deviating from usual clinical practice, was implemented in order to minimize the potential influence of rising PSA on the acquisition of scans. The threshold for disease progression by bone scan of at least 2 new lesions was determined in consultation with the FDA. The study was designed to capture all events of disease progression as rigorously as possible. Independent radiologists centrally reviewed all bone and CT scans, and disease progression based on scans required concurrence by 2 of the radiologists. In addition, all disease progression events (radiographic and clinical) required review and confirmation by an independent oncologist.

Protocol-specified secondary analyses were mean change from baseline to final value in bone alkaline phosphatase, time to PSA progression, mean rate of change in Bone Scan Index, and survival. Other protocol-specified analyses included time to bone alkaline phosphatase progression and longitudinal analyses of PSA, as well as quality of life based on patient-reported outcome measures.

4.2.2 Sample Size, Power, and Other Statistical Considerations

An estimated 650 events were needed to achieve 90% power to detect a treatment difference similar to that observed between 10 mg atrasentan and placebo in study M96-594 at $\alpha = .05$. The number of patients required for this study was projected to be 1000. The ultimate enrollment of 809 patients represents the largest placebo-controlled study in men with metastatic HRPC and presented logistical challenges previously not experienced with this patient population. There are a few important considerations that are highly relevant to the interpretability of study M00-211.

1. In study M96-594, an exploratory analysis of time to disease progression had been performed using the $G^{1,1}$ test statistic, a variant of the log-rank test described by Fleming et al.[39] The $G^{1,1}$ test statistic reduces the weight given to events that occur very early or very late in time-to-progression distributions. This statistic was chosen due to the shape of the disease progression curve (greatest separation

between treatment at the median) as observed in study M96-594.

Based on the anticipation that the time to disease progression curve would be similar in study M00-211, the $G^{1,1}$ statistic was the protocol-specified primary analysis for the endpoint of time to disease progression. Unfortunately, the impact of the protocol-defined 12-week scheduling of radiographic scans resulted in approximately 50% of patients completing the study at the time of their first scan (around 12 weeks). Thus, in retrospect, the $G^{1,1}$ statistic was no longer optimal and the median statistic is not a good indicator of the treatment effect of atrasentan. To present results in a more clinically relevant fashion, Cox proportional hazards modeling, which describes the relative risk across the entire distribution of events, was used. The $G^{1,1}$ statistic and the more traditional log-rank test statistic are also presented for study M00-211 in this document.

2. An IDMC met 4 times during the course of the study and performed 3 formal interim analyses after the start of accrual. On 27 September 2002, the IDMC recommended that further enrollment was not necessary. At its January 2003 meeting, the IDMC recommended that the study be stopped on 10 February 2003. The IDMC determined that the null hypothesis was not likely to be rejected for the primary endpoint in the intent-to-treat population. Their decision was based on data from 809 patients, 343 of whom had documented disease progression as of 11 December 2002. Investigators were notified and all active patients were to discontinue the study within 4 weeks. In the weeks immediately following the January meeting, the committee members were provided with updated tables that included endpoint information for approximately 500 patients in order to ensure that all available data were considered. When remaining data were collected and independently adjudicated, a total of 610 patients had experienced confirmed disease progression events. The study blind was broken on 16 May 2003. Patients who completed the study by experiencing an event of disease progression or who were still active in the study were eligible to enroll in an open-label extension study.

3. As in other therapeutic areas, scientific advances parallel drug development efforts. In the case of study M00-211, publication of important preclinical results in mid-2003 increased Abbott's understanding of the relationship between the ET_A receptor, prostate cancer cells, and osteoblasts, pointing to a potentially clinically important role for atrasentan in patients with bone metastases. These data emerged after the initiation of study M00-211. Abbott decided to examine the effect of atrasentan in a population of patients with metastatic disease in bone because of the potential clinical relevance of these findings. Although the decision to analyze these data was not specified in the protocol and was made after the study was unblinded, patients were assigned to this population before the blind was broken, and the criteria by which they were assigned complied fully with protocol-defined procedures for radiographic assessment, ie, an independent reviewer determined which patients had metastatic disease in bone at baseline. The protocol did not allow for multiple comparison adjustments for these analyses.

4. In addition, once patients experienced one event of disease progression, the protocol did not require that their data be captured for other disease progression events. This prevents a full analysis of the time to each of the 5 components of the endpoint. However, as very few patients left the study prior to completing the first radiographic evaluation, sensitivity analyses of patient data through the first radiographic scan provide an opportunity to identify patterns in the major components of the primary endpoint. These analyses revealed results that were maintained through the remainder of the study; they are presented below in section 4.2.3.1.

We have analyzed the study using protocol-specified methods as well as with these scientific and objective considerations. Through these analyses, this document presents an aggregate body of data demonstrating a measurable clinical benefit with 10 mg atrasentan for metastatic HRPC patients, particularly for those with metastases to bone.

4.2.3 Efficacy Results

The format of the efficacy presentation is as follows. Results are presented for the intent-to-treat population on the protocol-specified primary endpoint, time to disease progression, with additional separate analyses of the 2 major components of the endpoint:

- Radiographic progression events
- Clinical progression events

Sensitivity analyses of results through the date of the first scheduled radiographic scan are then presented in order to clarify the clinical benefit of atrasentan. The first section concludes with results for an evaluable patient population.

Results for these same analyses focusing on the 85% of patients from study M00-211 with bone metastases (a scientifically justifiable group) are then presented, followed by corroborative results for time to disease progression in patients from study M96-594 with abnormal baseline bone scans.

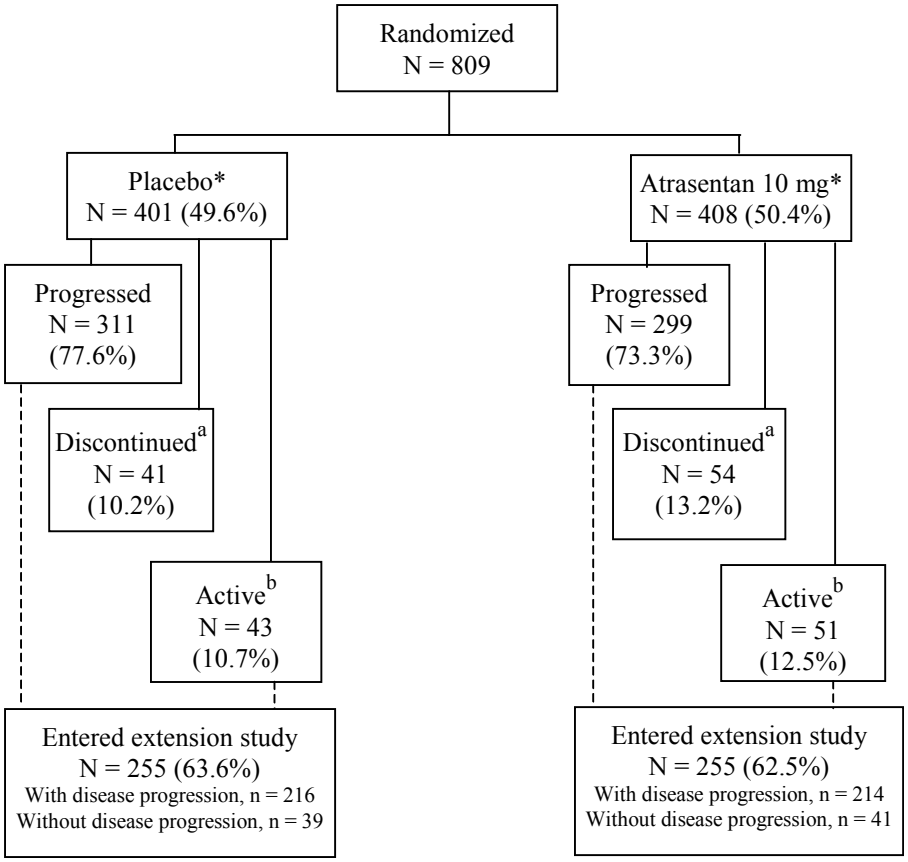
Results are then presented for the protocol-specified secondary analyses and other prespecified analyses of quality of life for the bone metastatic and intent-to-treat populations. Results for other relevant patient populations defined by metastatic status are presented for the primary endpoint at the conclusion of the protocol-specified endpoint discussion. The section concludes with 3 exploratory time-to-event analyses in the intent-to-treat and bone metastatic populations corroborating the clinical benefit of atrasentan:

- Time to 50% worsening of pain-related patient-reported quality of life outcome measures
- Time to first opioid initiation
- Time to first adverse event of bone pain

Finally, results of an integrated study-stratified log-rank analysis of studies M00-211 and M96-594 are presented to further delineate the clinical benefit of atrasentan in men with metastatic HRPC. These results were submitted in the NDA in December 2004.

Patient disposition in study M00-211 as of 10 February 2003 is summarized in Figure 9.

Figure 9. Patient Disposition in Study M00-211



* Note: Four patients in each treatment arm were randomized into the study, but never received study drug. Two placebo-treated patients lack study drug completion pages and are not counted among those who progressed, discontinued, or were still active.

a Patients could have discontinued due to an adverse event, withdrawal of consent, abnormal radiographic findings, or other reason.

b Of patients who were still active on 10 February 2003, 39 from the placebo arm and 41 from the atrasentan arm enrolled in the open-label extension study.

Patients enrolled in the study (N = 809) ranged in age from 45 to 93 years. A total of 770 patients (95%) were Caucasian and 26 (3%) were Black. There were no statistically significant differences in demographics between the 2 treatment groups. The baseline characteristics were well balanced, especially for those variables of importance in prostate cancer (Table 3).

Table 3. Baseline Characteristics: M00-211 Intent-to-Treat Population

	Placebo N = 401		Atrasentan N = 408	
Variable	**Median**	**Range**	**Median**	**Range**
Age, y	72.0	(45.0 – 92.0)	73.0	(45.0 – 93.0)
Hemoglobin, g/dL	13.2	(9.1 – 18.1)	13.4	(9.3 – 17.4)
LDH, IU/L	188	(108 – 2365)	186	(97 – 1318)
Bone alkaline phosphatase, ng/mL	24.8	(2.0 – 1599.0)	25.5	(2.0 – 1903.8)
PSA, ng/mL	79.6	(2.2 – 5424.8)	69.8	(1.7 – 5784.0)
Total Gleason score	7.0	(2.0 – 10.0)	7.0	(3.0 – 10.0)
Time since diagnosis, y	4.8	(0.1 – 23.2)	5.0	(0.3 – 23.7)
Karnofsky performance status ≥90	348/401 (86.8%)		358/408 (87.7%)	

Baseline characteristics for patients in study M00-211 were largely similar to those for patients in study M96-594.

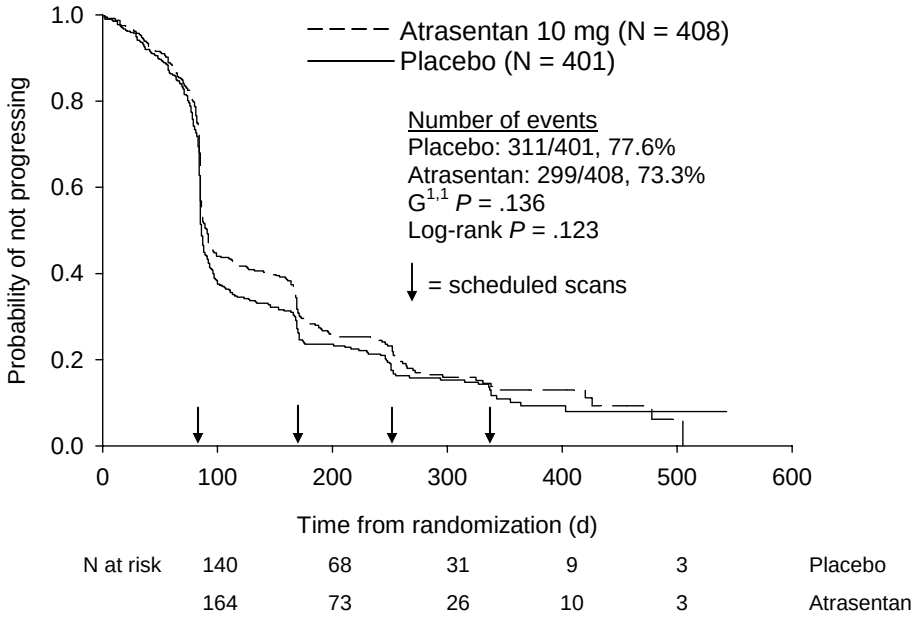
4.2.3.1 Primary Endpoint: Time to Disease Progression

For a given patient, time to disease progression was defined as the number of days from the date of randomization to the date of the first independently confirmed event of disease progression, regardless of whether it occurred while the patient was still taking study drug or had previously discontinued study drug, but remained in the study. Patients who died and those who discontinued from the study were censored.

The treatment effect of atrasentan in the intent-to-treat population, suggesting an 11% reduction in the risk of disease progression, did not reach statistical significance

($G^{1,1}$ *P* = .136) (HR = .885, 95% CI = [.755, 1.037]) (Figure 10). Figure 10 shows the impact of scheduled radiographic scans on the analysis of time to disease progression. The 12-weekly scheduling of radiographic evaluations had important consequences. Due to the large number of radiographic events at the first scan, the observed difference in median time to disease progression does not fully characterize the true treatment effect of atrasentan. Theoretically, if scans had been scheduled more frequently than defined in the protocol (although not clinically feasible), a larger treatment effect in the overall time to progression may have been detected. In addition, because radiographic progressions were a component of the composite endpoint along with events that represent true clinical progression, the high proportion of radiographic events may have diluted the true effect of the drug on clinical progression of the disease.

Figure 10. Time to Disease Progression: M00-211 Intent-to-Treat Population



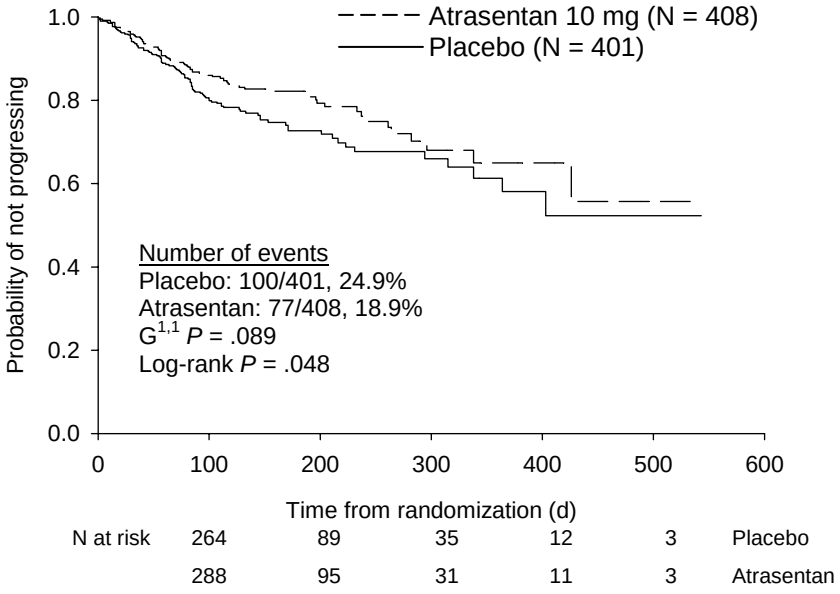
Disaggregation of Composite Endpoint

As described earlier (section 4.2.1), the primary endpoint consisted of 2 distinct major components, radiographic and clinical events. According to the protocol-defined

endpoint, patients could either experience disease progression due to radiographic events, based on evaluations of scheduled bone or CT scans, or due to clinical events, including pain due to metastatic disease, clinically overt skeletal-related events, or other clinical manifestations of prostate cancer requiring intervention. Most patients who experienced clinical events experienced more than one simultaneously. The incidence of radiographic disease progression was similar for the 2 treatment groups (251/401 [62.6%] for placebo and 247/408 [60.5%] for atrasentan), whereas the incidence of clinical disease progression was lower in atrasentan-treated patients than in those receiving placebo (77/408 [18.9%] versus 100/401 [24.9%]).

Separate analyses of radiographic and clinical disease progression were performed to elucidate the nature of the benefit of atrasentan in the intent-to-treat population. The evaluation of time to radiographic disease progression did not demonstrate a difference between treatment groups (HR = .904, 95% CI = [.758, 1.078]). In contrast, the evaluation of time to clinical disease progression demonstrated significant delay in patients receiving atrasentan (Figure 11). Atrasentan reduced the risk of experiencing a clinical event of disease progression by 26% compared with placebo (HR = .742, 95% CI = [.551, .999]) and the estimated probability of remaining clinically progression-free at 6 months was 82.2% for patients receiving atrasentan compared with 72.7% for those receiving placebo. While the median time to clinical progression was not reached for patients in either treatment arm, a 90-day delay was recorded with atrasentan (153 days versus 243 days) in the 25th percentile of the Kaplan-Meier curve.

Figure 11. Time to Disease Progression Due to a Clinical Event: M00-211 Intent-to-Treat Population



The majority of the disease progression events were due to the development of 2 or more new lesions on bone scan. Nearly 87% (433/498) of radiographic progression events occurred in the absence of any clinical progression event. Of the 177 patients who progressed due to a clinical event, 65 of these progressed with simultaneous radiographic event. Fifty-two had a concurrent positive bone scan and 23 had a concurrent positive CT scan (10 patients had both positive bone scans and CT scans as well as clinical progression). The remaining 112 patients progressed by clinical measures alone.

Radiographic evaluations were scheduled every 12 weeks in study M00-211 with the intention of avoiding the potential effect rising PSA values may have on triggering an investigator to request scans in the absence of any clinical indication (as seen in the phase 2 study). This routine scheduling of scans differs from standard clinical practice where scans are obtained only when clinically indicated. This is particularly true for patients with positive baseline bone scans, as was the case for most patients in this study. Clinical events, on the other hand, usually prompt a change in therapy (eg, initiation of opiates,

radiopharmaceuticals, chemotherapy), and are of greater clinical importance than asymptomatic radiographic events. Disease progression due to a clinical event was rigorously and clearly defined in the protocol, requiring that a central oncology reviewer independently adjudicate and confirm that these events had *documented evidence of disease at the site* and that they *required substantial therapeutic intervention* according to the protocol.

An unanticipated consequence of the scheduled scans was that most patients progressed with radiographic changes without any clinical progression event. These results show that the effect of the 12-week radiographic evaluations substantially depleted the number of patients available for analysis of clinical progression.

Sensitivity Analyses Using Data Through the First Scheduled Scan

The fact that more than half of the patients progressed at the first radiographic evaluation (and most did not experience a concurrent clinical event) limited the opportunity to observe the benefit of atrasentan on clinical disease progression. To address this concern, analyses were conducted using all data for all patients through the first scheduled radiographic evaluation.

Time-to-event analyses conducted on data accrued through the first scheduled radiographic scan showed that atrasentan delayed the time to a clinical event (HR = .691, 95% CI = [.480, .996]). The proportion of patients who had an event of clinical progression by the time of the first scheduled scan was 12.0% for atrasentan compared with 17.5% for placebo. These results suggest the significant effects observed in the overall analysis of clinical progression is representative of the true treatment effect of atrasentan, presenting evidence for the clinical benefit of atrasentan in patients with metastatic HRPC.

Metastatic and Evaluable Patient Populations

In an analysis of time to disease progression in the large population with baseline metastases confirmed by an independent radiological reviewer, representing more than

97% of patients (N = 787), the hazard ratio in favor of atrasentan was .823 (95% CI = [.701, .966]).[a] In this population, as in the intent-to-treat population, atrasentan showed a stronger effect on delaying time to clinical disease progression (HR = .680, 95% CI = [.503, .918]). Additionally, in a protocol-specified evaluable population (N = 670),[b] the results of the time to disease progression analysis were significant in favor of atrasentan. In this population, atrasentan significantly delayed time to disease progression ($G^{1,1}$ P = .009), suggesting that atrasentan may reduce the risk of disease progression by as much as 21% relative to placebo (HR = .794, 95% CI = [.669, .942]).

Patients with Bone Metastases

During the course of the study, a body of compelling data emerged highlighting and confirming the pivotal role of the endothelin axis in the interaction between cancer cells and osteoblasts in the bone microenvironment, the site of most metastases in this disease. ET_A receptor antagonism with atrasentan in vivo abrogates the effects of ET-1 binding by the ET_A receptor (see Figure 1).[22,25] These findings suggested that ET_A receptor antagonism might also play an important role in a clinical setting in the treatment of men with prostate cancer that has metastasized to bone, ie, the majority of metastatic HRPC patients. Based on these observations, Abbott analyzed the benefit of atrasentan in the large population of patients (85% of those enrolled) whose HRPC had metastasized to bone.

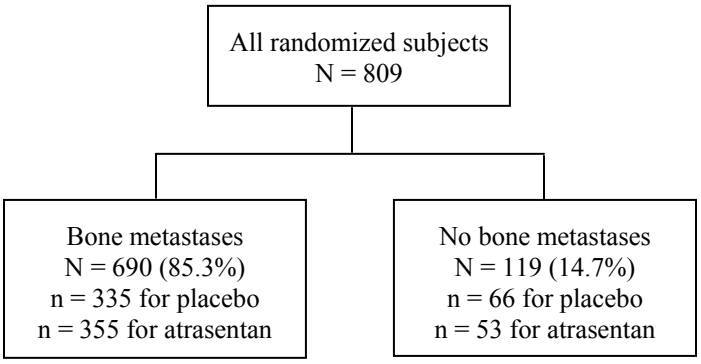
In study M00-211, a central radiologic reviewer independently confirmed the presence and location of metastases at baseline. Of the 809 patients randomized into the study, 690 had independently confirmed metastatic disease in bone at baseline. This is consistent with the incidence of bony metastatic disease among the general population of men with HRPC.

a Results for the patients with confirmed metastases at baseline in study M00-211 are presented in Appendix A.

b The definition of the evaluable population and the results of the primary analysis for each study are presented Appendix B.

The distribution of patients by metastatic status is shown in Figure 12.

Figure 12. Distribution of Patients in Study M00-211 by Bone Metastatic Status



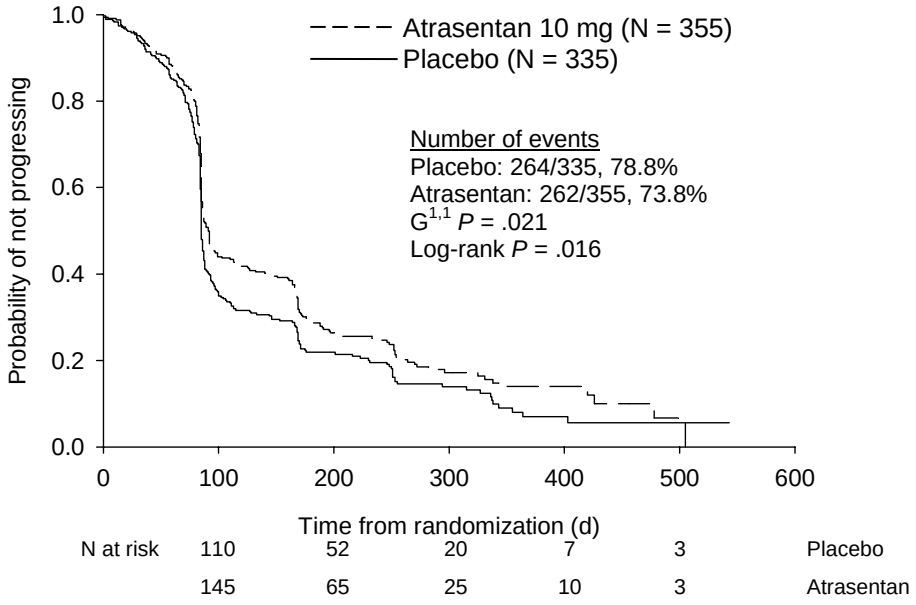
The proportion of patients with bone metastases at baseline was similar between the placebo (335/401, 83.5%) and atrasentan (355/408, 87.0%) treatment arms. Baseline characteristics were similar between the 2 groups (Table 4).

Table 4. Baseline Characteristics: M00-211 Bone Metastatic Population (N = 690)

	Placebo N = 335		Atrasentan N = 355	
Variable	**Median**	**Range**	**Median**	**Range**
Age, y	72.0	(45.0 – 92.0)	73.0	(45.0 – 93.0)
Hemoglobin, g/dL	13.2	(9.1 – 17.1)	13.4	(9.3 – 17.4)
LDH, IU/L	193	(108 – 2365)	186	(97 – 1318)
Bone alkaline phosphatase, ng/mL	31.8	(2.0 – 1599.0)	27.6	(2.0 – 1903.8)
PSA, ng/mL	87.9	(3.1 – 5424.8)	72.8	(1.7 – 5784.0)
Total Gleason score	7.0	(2.0 – 10.0)	7.0	(3.0 – 10.0)
Time since diagnosis, y	4.7	(0.1 – 23.2)	4.8	(0.3 – 23.7)
Karnofsky performance status ≥90	291/335 (86.9%)		309/355 (87.0%)	

In this population of patients with HRPC that had metastasized to bone, atrasentan significantly delayed time to disease progression ($G^{1,1}$ P = .021) and reduced the risk of disease progression on study by 19% (HR = .813, 95% CI = [.685, .965]) (Figure 13). The estimated probability of remaining progression-free at 6 months was 28.7% for patients treated with atrasentan compared with 21.9% for those treated with placebo.

Figure 13. Time to Disease Progression: M00-211 Bone Metastatic Population



Even though the results in this population are also affected by the 12-weekly scheduled scans, the more pronounced treatment effect relative to the intent-to-treat population is consistent with the role of atrasentan in blocking the stimulation of osteoblasts by ET-1 in the bone microenvironment.

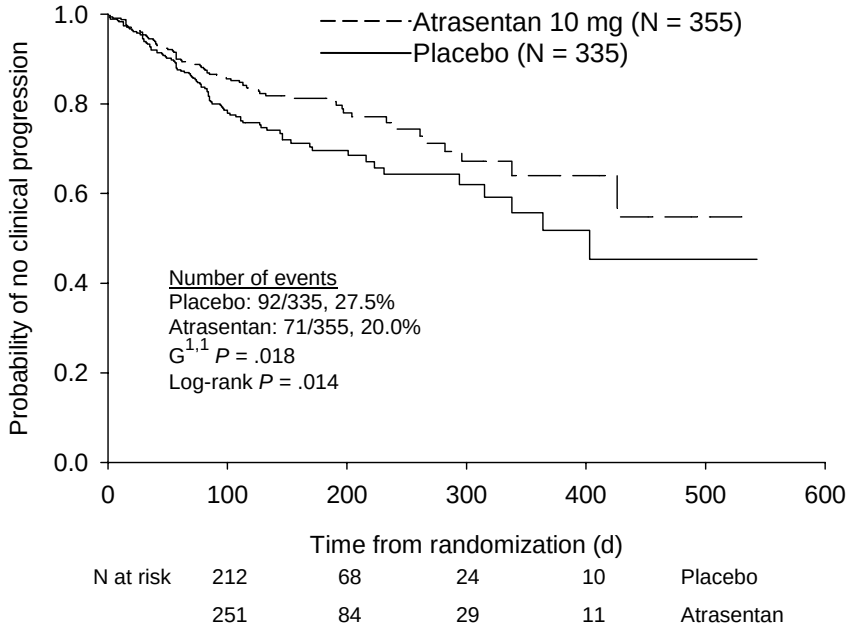
As in the intent-to-treat population, the incidence of radiographic disease progression was similar for the 2 treatment groups (212/355 [59.7%] for atrasentan and 206/335 [61.5%] for placebo). The incidence of clinical events of disease progression was lower in

patients with bone metastases treated with atrasentan than in those treated with placebo (71/355 [20.0%] versus 92/335 [27.5%]).

In the analysis of time to radiographic disease progression in the bone metastatic population, atrasentan therapy resulted in a 15% reduction in the risk of radiographic progression and a modest 37-day delay with atrasentan on the median time to onset of radiographic progression events (HR = .846, 95% CI = [.698, 1.025]). Interestingly, in patients with bone metastases, atrasentan delayed the time to disease progression by bone scan specifically, even with the scans scheduled every 12 weeks (HR = .815, 95% CI = [.667, .996]). Atrasentan delayed the median time to progression by bone scan by 75 days relative to placebo (166 days versus 91 days).

As in the intent-to-treat population, atrasentan resulted in a significant delay in time to clinical disease progression in the bone metastatic population. Atrasentan decreased the risk of clinical progression by 32% (HR = .680, 95% CI = [.499, .927]) (Figure 14).

Figure 14. Time to Disease Progression Due to Clinical Event: M00-211 Bone Metastatic Population



The median time to clinical progression was 403 days with placebo, but was not reached in patients receiving atrasentan. The estimated probability of remaining clinical progression free at 6 months was 81.2% for atrasentan compared with 69.6% for placebo.

Sensitivity Analyses Using Data Through the First Scheduled Scan

In the analyses using data through the first scheduled radiographic scan, atrasentan had a significant effect on disease progression in the bone metastatic population (HR = .791, 95% CI = [.646, .969]). In addition, there was a significantly positive delay on time to clinical disease progression through the first scan, with a 38% reduction in the risk of developing clinical progression in this period (HR = .624, 95% CI = [.425, .915]).

Corroborative Data from the Bone Metastatic Population in Study M96-594

In order to corroborate the significant benefit observed in the bone metastatic population in study M00-211, results for a similar population in study M96-594 were also analyzed. As in study M00-211, bone and CT scans were performed as protocol-specified screening procedures in study M96-594. Unlike study M00-211, however, in which independent radiologists confirmed the presence of metastases at baseline, the investigator in M96-594 designated on the case report form whether baseline scan results were normal or abnormal. A slightly higher proportion of patients in study M96-594 had abnormal baseline bone scans (261/288, 90.6%), and an analysis of time to disease progression was performed on these patients. Consistent with the M00-211 data, atrasentan had a greater effect on time to disease progression in favor of atrasentan in patients with an abnormal bone scan than was observed in the intent-to-treat population. Atrasentan treatment resulted in a 54-day delay in the median time to disease progression compared with placebo in this cohort (183 days versus 129 days). In the bone metastatic population, atrasentan decreases the risk of disease progression by 27% relative to placebo (HR = .730, 95% CI = [.510, 1.045]) using Cox proportional hazards modeling. In the analysis of time to clinical events of disease progression in the population with abnormal bone scans at baseline in M96-594, the hazard ratio was .819 in favor of atrasentan, (95% CI = [.557, 1.204]).

Across the 2 populations in each of the 2 studies, atrasentan demonstrated clinical benefit by delaying time to disease progression, more markedly in patients with bone metastases. In study M00-211, the analysis of time to clinical progression events more clearly shows the treatment effect because it is not affected by scheduled assessments (although subject to informative censoring). The time to disease progression results in the 2 populations in both studies are summarized below (Table 5). The estimated probability of remaining progression-free at 3 and 6 months was greater for atrasentan-treated patients than for placebo-treated patients.

Table 5. Treatment Benefit of Atrasentan on Disease Progression: M00-211 and M95-594

	Number of Events (%)						Relative Difference in Progression-free Rates	
Population	**Placebo**		**10 mg Atrasentan**		**HR**	**95% CI**	**3 Months**	**6 Months**
M00-211								
Bone metastatic	264/335	(78.8%)	262/355	(73.8%)	.813	.685, .965	25.4%	32.4%
Intent-to-treat	311/401	(77.6%)	299/408	(73.3%)	.885	.755, 1.037	14.1%	19.9%
M96-594								
Abnormal bone scan	75/99	(75.8%)	51/78	(65.4%)	.730	.510, 1.045	3.6%	39.1%
Intent-to-treat	77/104	(74.0%)	58/89	(65.2%)	.769	.545, 1.085	2.8%	34.2%

The estimated probability of remaining free of clinical progression at 3 and 6 months was also greater for atrasentan-treated patients than for placebo-treated patients (Table 6).

Table 6. Treatment Benefit of Atrasentan on Clinical Progression Events: M00-211 and M96-594

	Number of Events (%)						Relative Difference in Progression-free Rates	
Population	**Placebo**		**10 mg Atrasentan**		**HR**	**95% CI**	**3 Months**	**6 Months**
M00-211								
Bone metastatic	92/335	(27.5%)	71/355	(20.0%)	.680	.499, .927	8.3%	16.7%
Intent-to-treat	100/401	(24.9%)	77/408	(18.9%)	.742	.551, .999	5.9%	13.1%
M96-594								
Abnormal bone scan	62/99	(62.6%)	45/78	(57.7%)	.819	.557, 1.204	3.3%	31.3%
Intent-to-treat	64/104	(61.5%)	50/89	(56.2%)	.831	.573, 1.204	4.0%	31.8%

These results highlight the consistency of the effect of atrasentan in metastatic HRPC across studies.

4.2.3.2 Protocol-Specified Secondary Endpoints

Four analyses were prespecified as secondary endpoints in study M00-211:

- Mean change from baseline to final value in bone alkaline phosphatase
- Time to PSA progression
- Mean rate of change in Bone Scan Index (BSI)
- Survival

Bone Alkaline Phosphatase

In prostate cancer, the clinical, radiographic, and biochemical manifestations of disease are reflected in altered bone physiology. Because of the important role that the ET-1/ET_A receptor interaction plays in prostate cancer, ET_A receptor antagonists such as atrasentan should affect measures of bone physiology, primarily osteoblastic changes. Osteoblastic

activity is measured primarily by increases in bone alkaline phosphatase.[41] Atrasentan blocks the interaction between prostate cancer cells and osteoblasts in the bone microenvironment, and one would expect it to slow the increase in bone alkaline phosphatase levels. This is important, given the documented prognostic value of bone alkaline phosphatase in prostate cancer.[42,43]

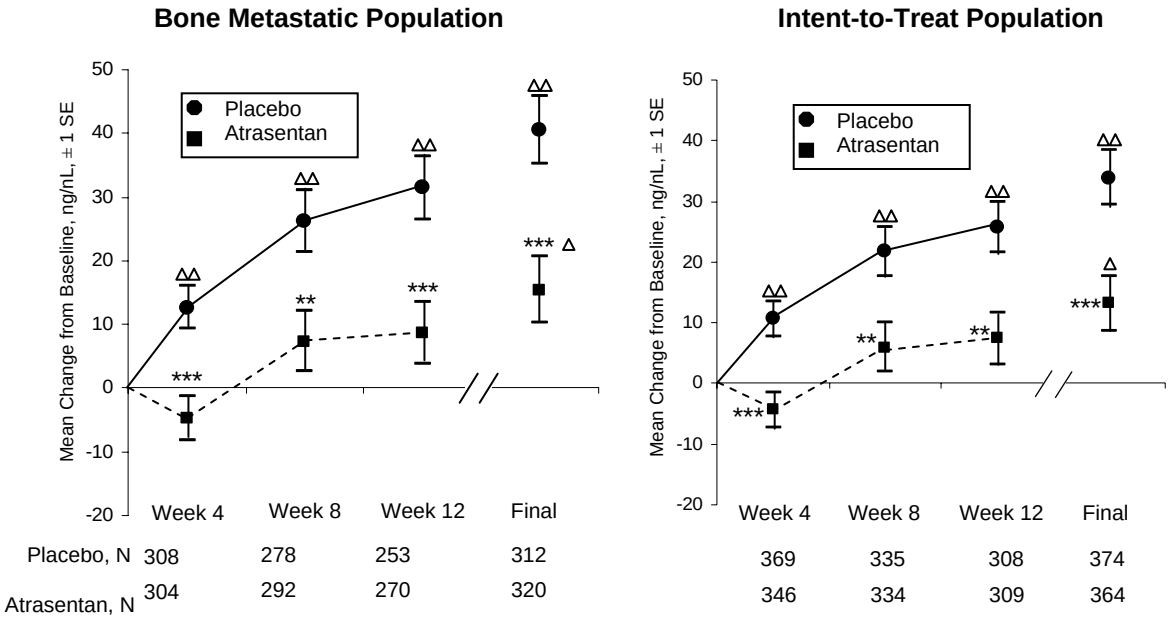
Consistent with the results from study M96-594, the mean increase from baseline to final value was significantly lower with atrasentan than with placebo in study M00-211 (Table 7).

Table 7. Mean Change from Baseline to Final Value in Bone Alkaline Phosphatase, ng/mL: M00-211 Bone Metastatic and Intent-to-Treat Populations

	Placebo		Atrasentan			
Population	**Baseline**	**Mean Change (SE)**	**Baseline**	**Mean Change (SE)**	**Treatment Difference**	***P* value**
Bone metastatic	66.93	40.66 (5.238)	57.15	15.28 (5.172)	25.38	<.001
Intent-to-treat	57.75	33.86 (4.478)	52.45	13.19 (4.540)	20.66	.001

In a supportive longitudinal analysis of mean changes from baseline in both the bone metastatic and intent-to-treat populations, bone alkaline phosphatase did not increase significantly from baseline over the course of the study in those patients receiving atrasentan until the final assessment. In contrast, for patients receiving placebo, bone alkaline phosphatase increased steadily and significantly from baseline as early as week 4 (Figure 15).

Figure 15. Mean Change from Baseline in Bone Alkaline Phosphatase: M00-211 Bone Metastatic and Intent-to-Treat Populations

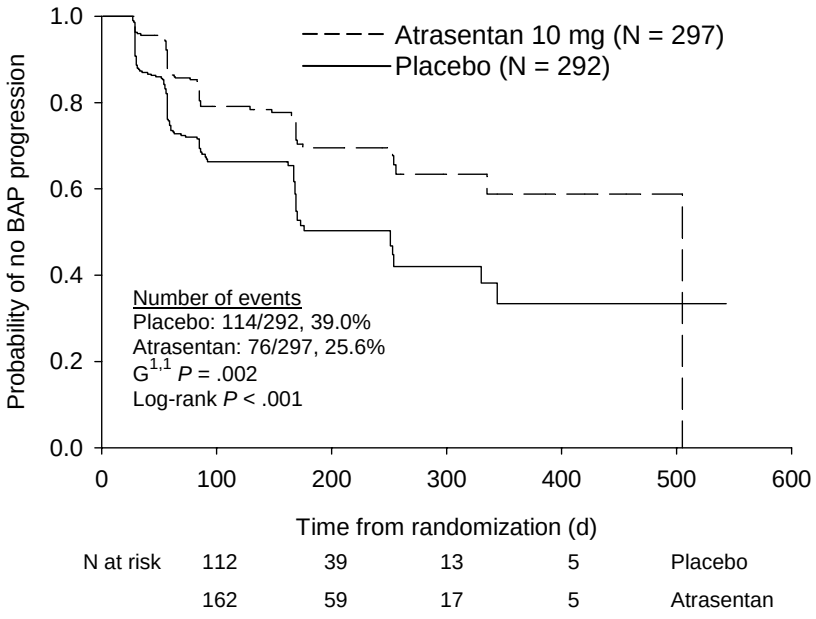


, * *P* < .01 and .001, respectively, for the difference between treatments

Δ ΔΔ *P* < .01 and .001, respectively, for the difference from baseline

In addition to slowing the increase of bone alkaline phosphatase as measured by the longitudinal analysis, atrasentan also delayed the onset of bone alkaline phosphatase progression (the first of 2 consecutive post-baseline measurements at least 2 weeks apart that represent increases ≥50% from nadir). In the bone metastatic population, atrasentan significantly increased the median time to bone alkaline phosphatase progression by 254 days (505 days versus 251 days) and reduced the risk of bone alkaline phosphatase progression by 45% relative to placebo (HR = .548, 95% CI = [.410, .733]) (Figure 16).

Figure 16. Time to Bone Alkaline Phosphatase Progression: M00-211 Bone Metastatic Population



Only patients with both a baseline and at least 2 post-baseline measurements are included in the analysis.

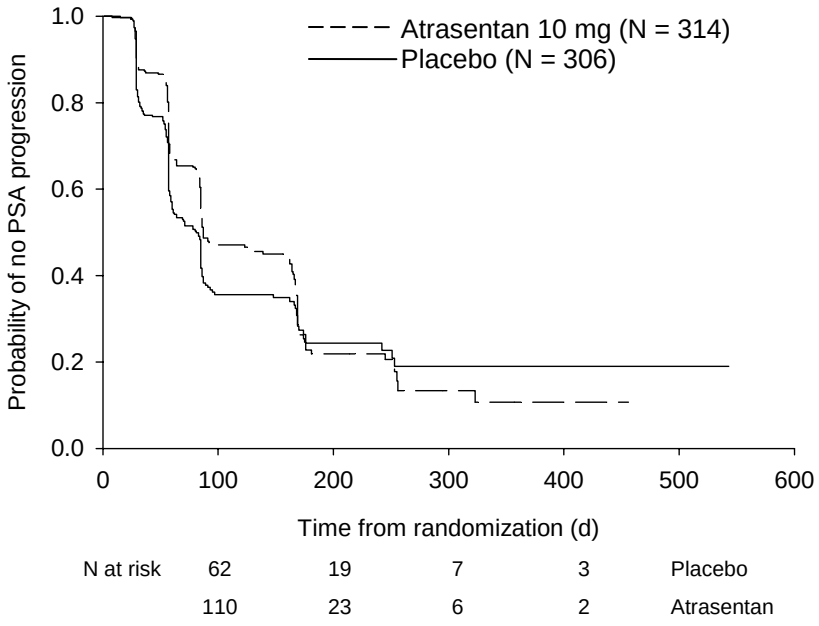
Similar results were observed in the intent-to-treat population with a difference in the median time to bone alkaline phosphatase progression of 251 days (505 days versus 254 days) and a 44% reduction in the risk (HR = .561, 95% CI = [.422, .745]).

PSA

PSA is reportedly an independent marker of prognostic importance in metastatic HRPC.[42] Like bone alkaline phosphatase, PSA increases over time, reflecting increased tumor burden, and the rate at which it rises is predictive of prostate cancer outcome in several stages of the disease. [38,44,45] As atrasentan does not affect PSA secretion in prostate cancer cell lines in vitro,[46] PSA data from atrasentan trials likely reflects the drug effect on tumor burden.

Time to PSA progression, defined as an increase in serum PSA ≥50% from baseline on the first of 2 consecutive occasions at least 2 weeks apart, was a protocol-specified secondary analysis. Atrasentan delayed time to PSA progression compared with placebo in the bone metastatic population (HR = .820, 95% CI = [.673, .999]) (Figure 17).

Figure 17. Time to PSA Progression: M00-211 Bone Metastatic Population



Only patients with both a baseline and at least 2 post-baseline measurements are included in the analysis.

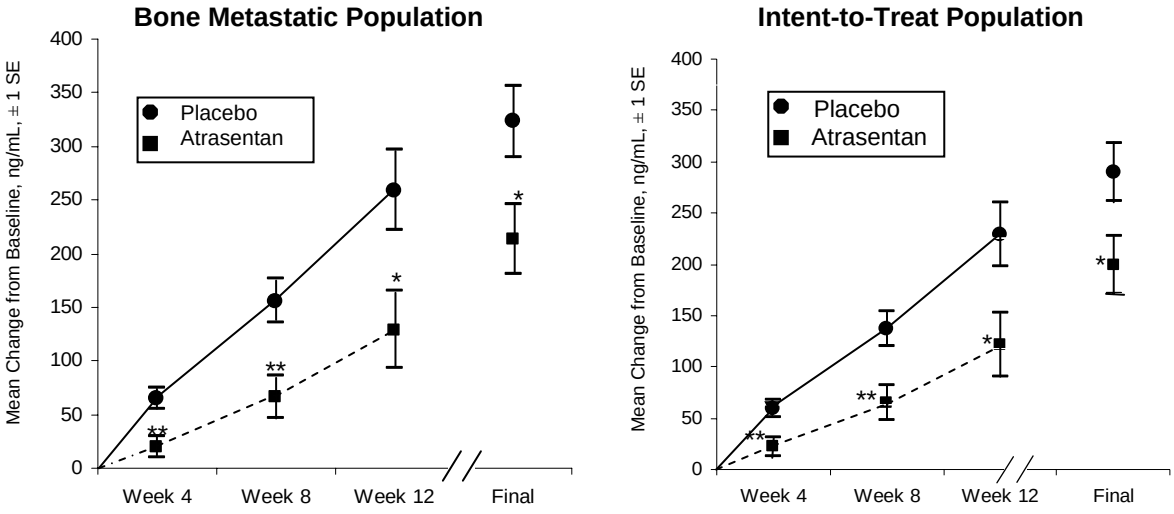
In the intent-to-treat population, the effect of atrasentan on time to PSA progression showed a nonsignificant delay (HR = .844, 95% CI = [.703, 1.014]).

An additional, retrospective analysis of time to the first 50% increase in PSA (whether confirmed or unconfirmed) was performed because a large number of patients experienced radiographic disease progression at week 12 and subsequently were not followed for PSA. Therefore, many patients with a 50% increase in PSA did not have the requisite confirmatory value to be included in the prespecified analysis. An additional 161 patients (75 in the placebo arm and 86 in the atrasentan arm) were included in the

analysis of time to first unconfirmed PSA progression in the intent-to-treat analysis. Atrasentan delayed the time to unconfirmed PSA progression in the intent-to-treat population (HR = .856, 95% CI = [.731, 1.002]) and with a more pronounced effect in patients with bone metastases at baseline (HR = .797, 95% CI = [.673, .944]).

In a supportive longitudinal analysis of mean changes from baseline in PSA, atrasentan significantly slowed the increase of PSA in both the bone metastatic and intent-to-treat populations (Figure 18). At the final visit, the difference between treatments in mean change from baseline was 91.04 ng/mL for the intent-to-treat population and 112.10 ng/mL for the bone metastatic population in favor of atrasentan.

Figure 18. Mean Change from Baseline in PSA: M00-211 Bone Metastatic and Intent-to-Treat Populations



*, ** $P < .05$ and .01, respectively, for the difference between treatments

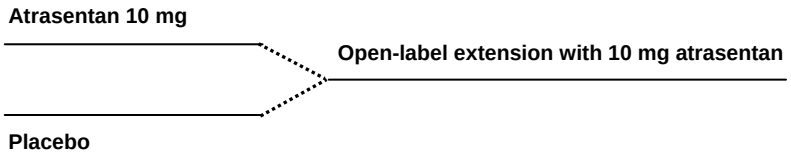
Bone Scan Index

Bone scans are used successfully to diagnose metastatic disease, but their value as a quantitative measure is limited. The Bone Scan Index was developed in an attempt to improve the usefulness of bone scans in assessing the extent of disease in bone, although its utility in assessing progression of bone metastases, especially in patients with existing metastases, has not been established.[47,48] To date, the method has not gained wide acceptance due to technical difficulties in obtaining reproducible results. Thus, the interpretability of results is limited. Bone Scan Index was measured for bone scans obtained at baseline and at study completion, and quantitative analyses were performed using this protocol-specified, but nonvalidated, instrument. No statistically significant difference between treatments was observed in either population using this exploratory method.

Survival

All deaths were included in the survival analysis. After discontinuing from the study, patients were assessed for survival at 3-month intervals using telephone calls received through an interactive voice response system. Median survival was 20.5 months (575 days) for patients initially randomized to receive atrasentan and 20.1 months (564 days) for patients initially randomized to receive placebo. Results were similar for the bone metastatic population.

The study was not designed to analyze survival as a primary endpoint, and the incorporation of an open-label extension study option further limited this analysis.



In the intent-to-treat population, 255 patients from each treatment arm (510/809 or 63% total) elected to take open-label atrasentan in the extension study. Patients may have entered the extension either at the time of progression or when study M00-211 was closed. Mean exposure to atrasentan over the double-blind and open-label periods combined was 305 days (10.9 months) for patients initially randomized to receive atrasentan and 221 days (7.9 months) for patients initially randomized to receive placebo. The difference in the mean exposure to atrasentan for the 2 groups of patients based on initial randomization was 3 months. Given the open-label study design option, it was not expected that a survival difference could be detected.

Notwithstanding the effect of the open-label extension design on an analysis of survival, the observed overall survival with atrasentan in this patient population compares favorably with that recently reported with docetaxel/prednisone (SWOG 99-16 and TAX 327).[7,8] Although such cross-study comparisons should not be overinterpreted, the populations studied in the docetaxel trials and in study M00-211 appear largely similar.

These 3 studies evaluated patients with metastatic HRPC who were progressing and whose baseline characteristics were broadly consistent. The median survival of 20.5 months in study M00-211 for subjects initially randomized to receive atrasentan is comparable to the median survival of 18.0 and 18.9 months reported with docetaxel in combination with estramustine and prednisone, respectively.

4.2.3.3 Protocol-Specified Quality of Life Analyses

Quality of life for late-stage patients in a palliative setting may be as valuable as response rate or even survival.[49] One would expect effective therapy to slow the decline in patient-reported disease-specific quality of life outcomes measures, although a decrease in overall quality of life caused by treatment-related side effects may obscure the benefit. Quality of life instruments weigh the clinical benefit of a therapy against its undesirable side effects as well as detrimental effects of advancing disease.

FACT-P and EORTC QLQ-C30

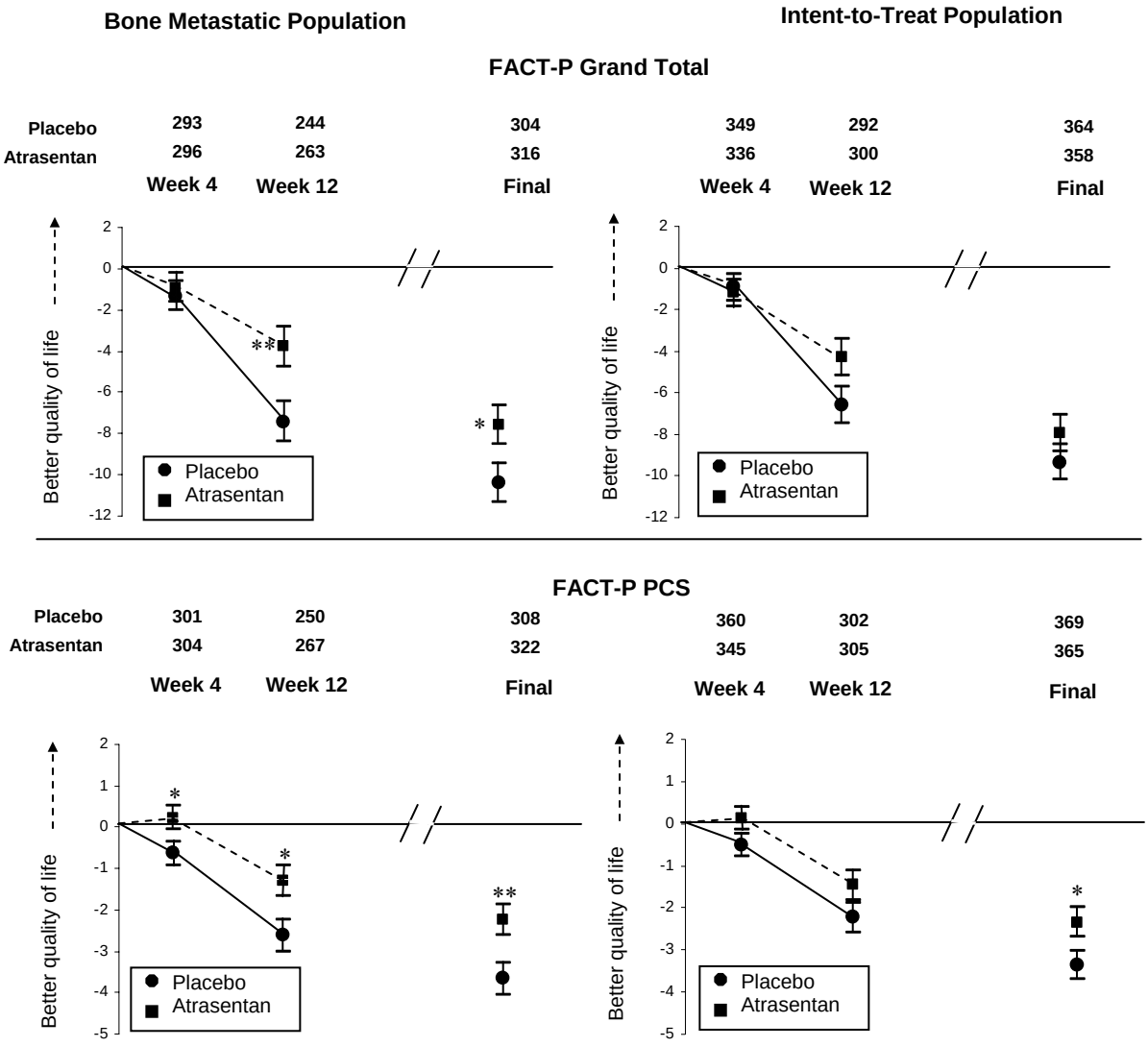
Two protocol-specified, independently validated quality of life instruments were used to measure changes in patient-reported quality of life throughout the study: the Functional Assessment of Cancer Therapy – Prostate (FACT-P)[50] and the European Organisation for Research and Treatment in Cancer (EORTC) QLQ-C30.[51] The 2 instruments are complementary, rather than directly comparable.[52] Each instrument has scores that measure overall quality of life (and specifically the negative impact of a therapy) and disease-specific quality of life (focusing on the pain associated with metastatic prostate cancer). FACT-P measures overall quality of life by the independently validated grand total score and the disease-specific quality of life by the independently validated prostate cancer subscore (PCS).[50] EORTC QLQ-C30 measures overall quality of life by the global health status and disease-specific quality of life by the pain symptoms domain.

The quality of life data captured in study M00-211 were robust for 2 reasons. First, the placebo arm represents one of the largest studies of the natural history of metastatic HRPC, and thus, is an ideal comparator for the relative treatment effect provided by atrasentan. Second, the percentage of scheduled questionnaires answered by patients

during the study was very high (93.2% for FACT-P and 92.7% for EORTC QLQ-C30), providing a thorough data set for analysis.

The data from the placebo arm track the negative impact of advancing disease on patient-reported quality of life outcomes. Atrasentan resulted in consistently smaller mean changes from baseline in both overall and disease-specific quality of life measures in both the bone metastatic and intent-to-treat populations, with significantly less deterioration relative to placebo in the prostate cancer subscore of the FACT-P (Figure 19 and Figure 20).

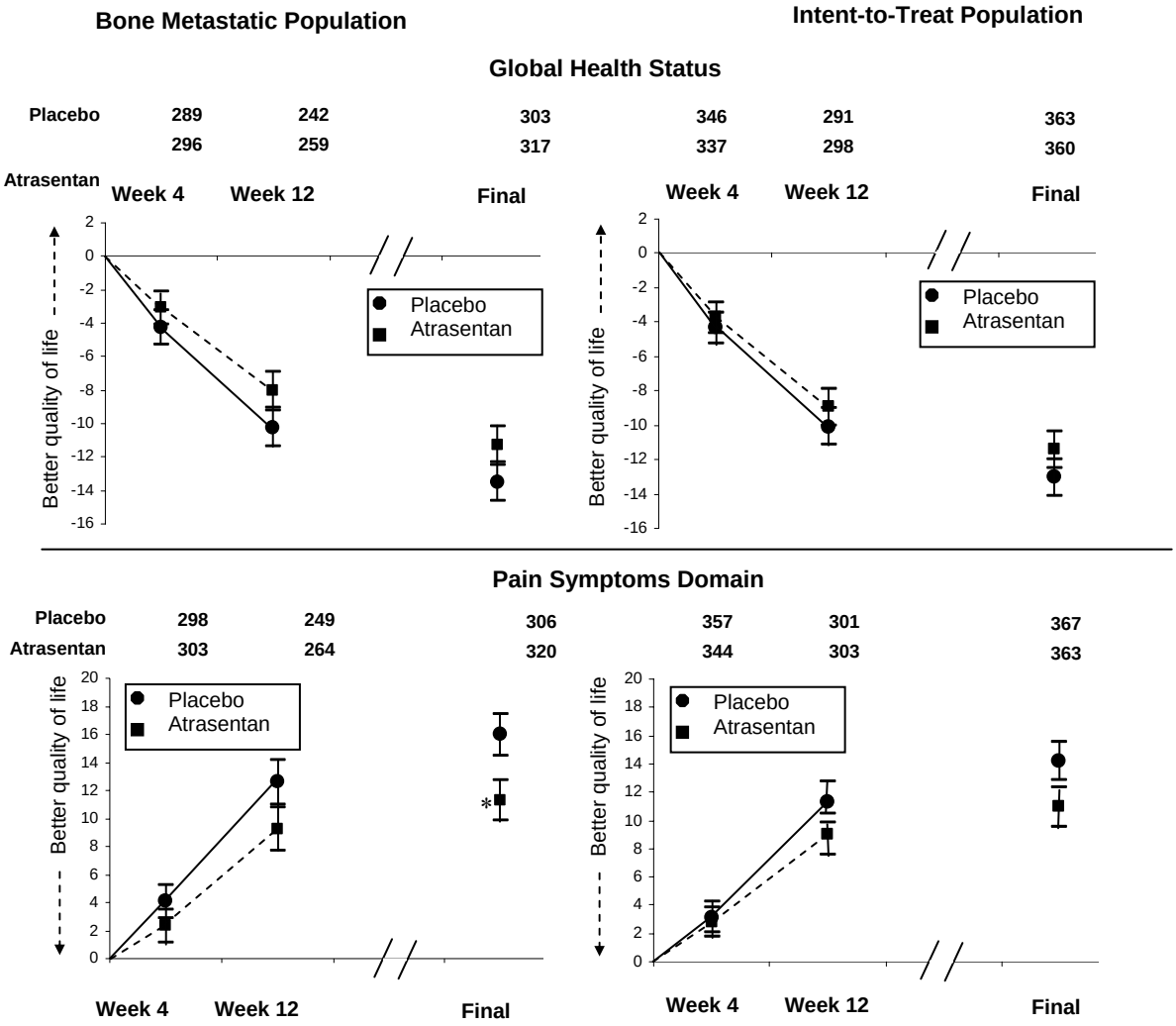
Figure 19. Mean Change from Baseline in FACT-P Scores: M00-211 Bone Metastatic and Intent-to-Treat Populations



Note: Possible scores for the FACT-P grand total range from 0 to 156. Possible scores for the FACT-P PCS range from 0 to 48. Higher scores represent better quality of life.
*, ** $P \leq .05$ and .01 for the difference between treatment arms

The benefit with atrasentan therapy was greater on disease-specific quality of life than on overall quality of life as measured by the FACT-P instrument and it was more pronounced in the bone metastatic population than in the intent-to-treat population.

Figure 20. Mean Change from Baseline in EORTC QLQ-C30 Scores: M00-211 Bone Metastatic and Intent-to-Treat Populations



Note: Possible scores for all domains of the EORTC QLQ-C30 range from 0 to 100. Higher scores represent better quality of life for the global health status whereas lower sores represent better quality of life for the pain symptoms domain.

* $P \leq .05$ for difference between treatment groups.

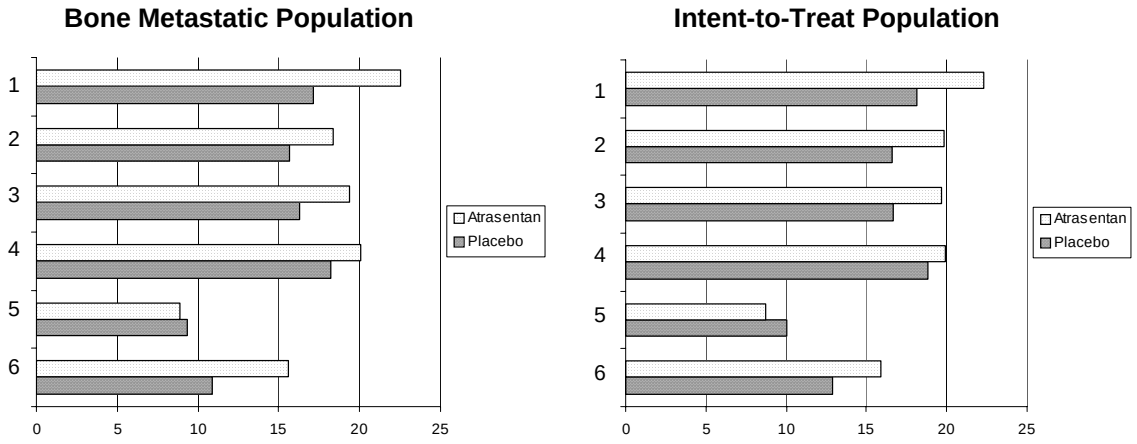
Mean changes from baseline in quality of life as measured by the EORTC QLQ-C30 were smaller for atrasentan recipients than for placebo recipients, indicating less deterioration, although the treatment effect was not as great using this 2-question scale.

The FACT-P prostate cancer subscore (PCS) consists of 12 questions, 8 of which relate to urinary and sexual function and 4 of which relate to pain. These 4 pain-related questions, along with the 2 questions that constitute the EORTC QLQ-C30 pain symptoms domain, track patients' experience of pain as it affects their quality of life.

As described already, prostate cancer is a relentlessly progressive and debilitating disease characterized by the development of painful metastases, most commonly in bone. Atrasentan delays the progression of disease and, thus, slows the deterioration of quality of life.

The proportion of patients who recorded an improvement from baseline to final assessment in the 4 pain-related questions of the FACT-P PCS and the 2 questions of the EORTC QLQ-C30 pain symptoms domain was generally higher for atrasentan than for placebo, while the proportion who recorded a decline was consistently lower (Figure 21 and Figure 22).

Figure 21. Percentage of Patients Recording an Improvement from Baseline at Final Assessment in Pain-Related Quality of Life Scores: M00-211 Bone Metastatic and Intent-to-Treat Populations



Legend: **FACT-P PCS pain questions**

1 = I have aches and pains that bother me.

2 = I have certain areas of my body where I experience significant pain.

3 = My pain keeps me from doing the things I want to do.

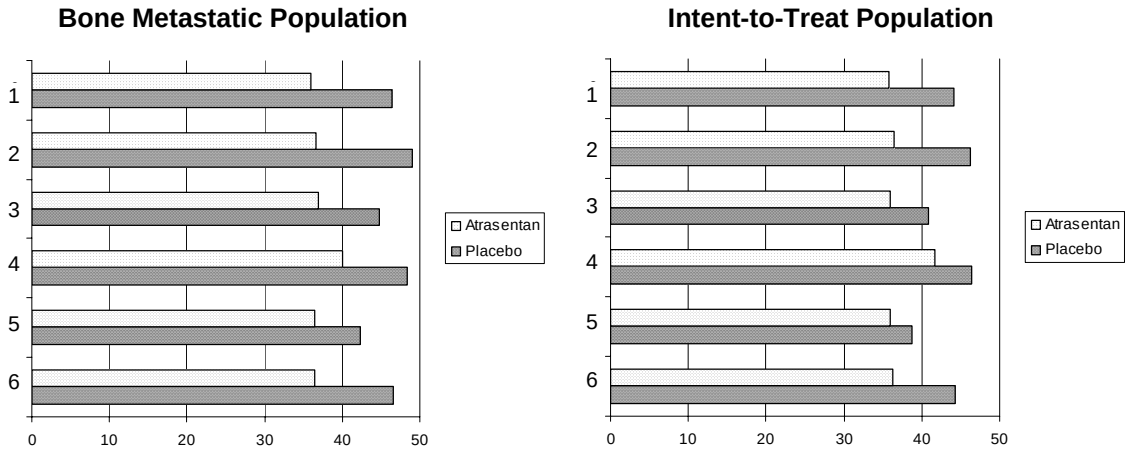
4 = I am satisfied with my present comfort level.

EORTC QLQ-C30 pain symptoms

5 = Did pain interfere with your daily activities?

6 = Have you had pain?

Figure 22. Percentage of Patients Recording a Decline from Baseline at Final Assessment in Pain-Related Quality of Life Scores: M00-211 Bone Metastatic and Intent-to-Treat Populations



Legend: **FACT-P PCS pain questions**

1 = I have aches and pains that bother me.

2 = I have certain areas of my body where I experience significant pain.

3 = My pain keeps me from doing the things I want to do.

4 = I am satisfied with my present comfort level.

EORTC QLQ-C30 pain symptoms

5 = Did pain interfere with your daily activities?

6 = Have you had pain?

4.2.4 Results in Other Patient Populations

In the preceding sections, efficacy results are presented for the intent-to-treat population and a large population of patients with bone metastases at baseline (constituting 85% of the total population); results for the primary endpoint in a population of patients with any metastases are also presented, with more complete details provided in Appendix A. Analysis of the primary endpoint was performed for complementary patient populations: those with no bone metastases (N = 119), and the populations that comprise this group, patients with confirmed soft-tissue metastases only (N = 97) and patients with no metastases at baseline (N = 22). In the analysis of time to disease progression for the 119 patients with no bone metastases, atrasentan did not delay disease progression (HR = 1.386, 95% CI = [.897, 2.142]). In the 97 patients with confirmed metastases to soft tissue only (HR = .945, 95% CI = [.603, 1.483]) and 22 patients with no metastases

(HR = 9.209, 95% CI = [1.645, 51.569]), there was likewise, no treatment benefit with atrasentan. Data interpretation for the 22 non-metastatic patients is difficult due to the low number of patients in this cohort and to the marked imbalance in the number of patients in each arm (14 for placebo versus 8 for atrasentan) as well as in baseline characteristics of particular importance in prostate cancer, bone and total alkaline phosphatase. The effect of atrasentan on men with non-metastatic HRPC is being evaluated in an ongoing phase 3 study of 941 patients. This study began in 18 July 2001 with periodic review by an IDMC, which has recommended that the study continue until completion at the protocol-specified number of disease progression endpoints. Median duration of exposure for the pooled treatment arms is currently 404 days, and 435 endpoints have accrued with a median time to progression of 673 days (1.8 years).

4.2.5 Clinical Benefit of Atrasentan

The clinical benefit of atrasentan is evident in the significant effect on clinical disease progression in both the intent-to-treat and bone metastatic populations, as well as the significant delay in overall time to disease progression in patients with bone metastases. In addition, the treatment effect on clinical progression in the analysis of events through the first scan provides further evidence of clinical benefit. Three additional analyses further support the clinical benefit of atrasentan.

1. Time to 50% decline in pain-related quality of life scores
2. Time to initiation of opioid analgesia
3. Time to first adverse event of bone pain

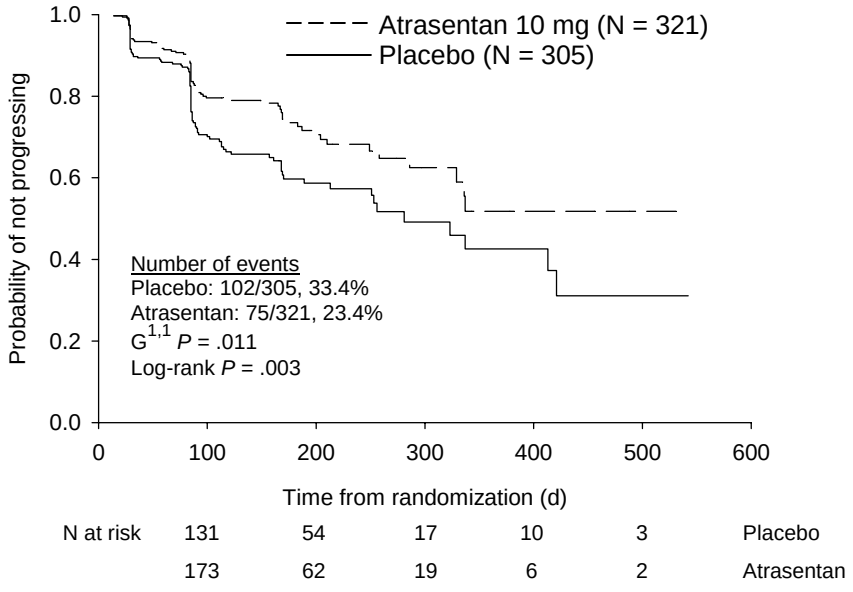
4.2.5.1 50% Decline in Pain-Related Quality of Life Scores

Patients who received placebo consistently recorded a greater deterioration in pain scores as measured by the 4 pain-related questions of the FACT-P PCS and the 2 questions of the EORTC QLQ-C30 pain symptoms domain. Because the clinical interpretation of the absolute change in quality of life is unclear and a minimum clinically important

difference has not been established for the 16-point scale for the pain-related questions of the FACT-P PCS, an analysis of measurable decline in pain-related quality of life scores was performed using a 50% deterioration as the threshold. A decline of 50% in the 16-point pain score of the PCS likely represents a substantial worsening.[53]

A larger proportion of placebo-treated patients in the intent-to-treat population experienced a 50% worsening from baseline in FACT-P PCS pain-related quality of life scores compared with atrasentan-treated patients (30.3% versus 23.1%). Furthermore, atrasentan significantly reduced the risk of 50% worsening in the FACT-P PCS pain-related scores by 25% (HR = .749, 95% CI = [.564, .995]) in the intent-to-treat population and by 36% (HR = .644, 95% CI = [.478, .868]) in the bone metastatic population and significantly delayed the time to 50% deterioration in pain-related quality of life scores (Figure 23).

Figure 23. Time to 50% Deterioration in FACT-P Pain-Related Quality of Life Scores: M00-211 Bone Metastatic Population



Note: Only patients with a baseline value and at least one post-baseline value and those who could have a measurable 50% worsening from baseline are included.

While the median time to a 50% worsening in FACT-P PCS pain-related scores was 281 days for placebo, it was not reached for atrasentan, as not even 50% of atrasentan-treated patients in the bone metastatic population experienced this degree of decline during the study. Atrasentan reduced the relative risk of experiencing a 50% decline in these pain-related scores by an estimated 14.1% at 3 months and 23.1% at 6 months in the bone metastatic population. The benefit with atrasentan was evident at the time of the first radiographic scan and was maintained throughout the study. The proportion of patients recording a 50% deterioration in pain-related quality of life scores through the first scheduled scan was only 12.9% for atrasentan-treated patients compared with 18.6% for those receiving placebo in the intent-to-treat population and 13.4% compared with 20.1%, respectively, in the patients with bone metastases.

In the sensitivity analysis of time to 50% worsening in FACT-P PCS pain-related scores using all data through the first scheduled scan, results favored atrasentan in the bone metastatic population (HR = .675, 95% CI = [.448, 1.019]), but did not reach statistical significance. In the intent-to-treat population, the benefit with atrasentan was observed as early as the first scheduled scan (HR = .686, 95% CI = [.473, .995]).

Results for the bone metastatic and intent-to-treat populations in the 2 studies are summarized below (Table 8).

Table 8. Treatment Benefit of Atrasentan on 50% Decline in Pain-Related Quality of Life Scores: M00-211 and M96-594

	Number of Events (%)				Relative Difference in Progression-free Rates	
Population	**Placebo**	**10 mg Atrasentan**	**HR**	**95% CI**	**3 Months**	**6 Months**
M00-211						
Bone metastatic	102/305 (33.4%)	75/321 (23.4%)	.644	.478, .868	14.1%	23.1%
Intent-to-treat	111/366 (30.3%)	84/364 (23.1%)	.749	.564, .995	8.9%	15.3%
M96-594						
Abnormal bone scan	33/94 (35.1%)	23/71 (32.4%)	.842	.494, 1.435	7.5%	13.4%
Intent-to-treat	33/99 (33.3%)	28/79 (35.4%)	.979	.591, 1.621	6.6%	9.3%

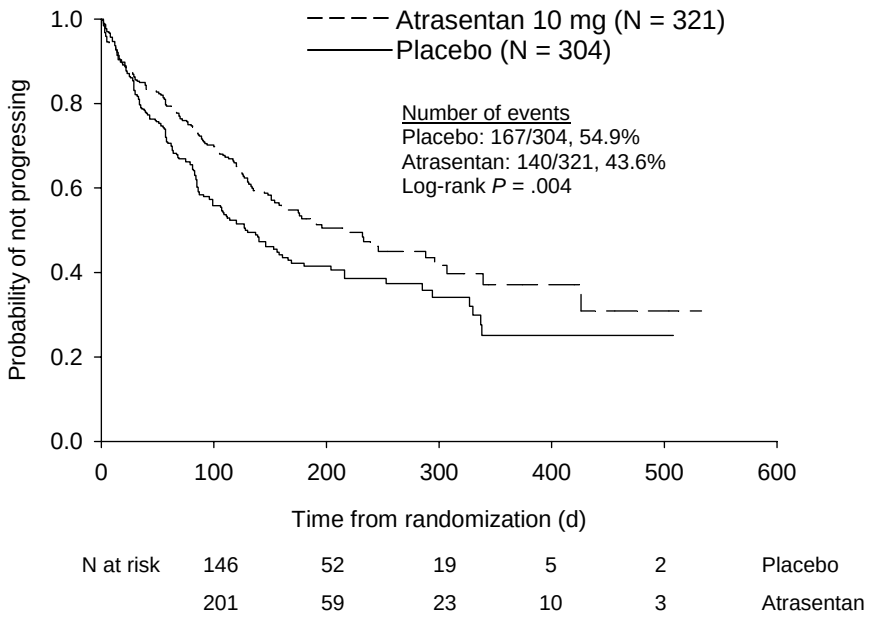
These findings demonstrate that atrasentan treatment is associated with a lesser deterioration in pain-related quality of life scores. Fewer atrasentan-treated patients reach the threshold of 50% deterioration and they reach it later. The consistent treatment effect observed in these quality of life analyses provides additional evidence of the clinical benefit of atrasentan on the pain associated with progressing metastatic HRPC in bone.

4.2.5.2 Opioid Initiation

An additional analysis of time to opioid initiation was performed to determine whether there is a treatment difference in the time to initiation of pain management therapy, combining first use of opiate analgesia with disease progression events due to metastatic pain. This analysis evaluated the experience of increasing pain during the study at levels requiring analgesia more potent than NSAIDs, but not necessarily reaching the threshold qualifying as disease progression. In study M00-211, baseline opioid use and disease progression due to metastatic pain were similar between patients randomized to receive atrasentan and those randomized to receive placebo. Patients treated with opioids at baseline were excluded from the analysis.

In the bone metastatic population, fewer atrasentan-treated patients initiated opiates or experienced disease progression due to metastatic pain, and the difference in the median time to administration of these more severe pain management therapies with atrasentan was 85 days (215 days versus 130 days) (HR = .720, 95% CI = [.575, .902]) (Figure 24).

Figure 24. Time to Opioid Initiation or Disease Progression Due to Metastatic Pain: Study M00-211 Bone Metastatic Population



Note: Patients who were treated with these pain management therapies at baseline were excluded from the analysis.

The time to opioid initiation or disease progression due to metastatic pain was also delayed for intent-to-treat patients who received atrasentan. Atrasentan delayed the median time to initiation of these pain management therapies by 80 days compared with placebo and decreased the hazard associated with having to initiate pain management by 20% relative to placebo (HR = .804, 95% CI = [.649, .996]). These results are consistent with the observation that patients receiving atrasentan had fewer events of metastatic pain than those receiving placebo, and experienced them later.

In the sensitivity analysis of time to opioid initiation using all data through the first scheduled scan, atrasentan demonstrated clinical benefit in the bone metastatic population (HR = .725, 95% CI = [.526, .999]) and in the intent-to-treat population (HR = .744, 95% CI = [.570, .973]).

In study M96-594, although the treatment effect was not as pronounced as in study M00-211, fewer atrasentan-treated patients had to initiate opiate analgesia and the hazard ratios favor atrasentan. Importantly, in both studies, among patients with bone metastases—those most likely to require treatment with opiate analgesia—fewer patients in the atrasentan treatment arms initiated potent pain management (Table 9).

Table 9. Treatment Benefit of Atrasentan on Opioid Initiation

	Number of Events (%)				Relative Difference in Progression-free Rates	
Population	**Placebo**	**10 mg Atrasentan**	**HR**	**95% CI**	**3 Months**	**6 Months**
M00-211						
Bone metastatic	167/304 (54.9%)	140/321 (43.6%)	.720	.575, .902	21.9%	27.0%
Intent-to-treat	184/367 (50.1%)	154/368 (41.8%)	.804	.649, .996	12.9%	17.9%
M96-594						
Abnormal bone scan	37/91 (40.7%)	25/70 (35.7%)	.809	.486, 1.346	–1.5%	10.2%
Intent-to-treat	37/96 (38.5%)	27/81 (33.3%)	.803	.489, 1.321	1.3%	13.1%

4.2.5.3 Adverse Events of Bone Pain

As will be described in the analysis of safety in section 5.3, bone pain was the most common adverse event in both studies. Using data captured for safety monitoring, an analysis was performed on time to the first treatment-emergent adverse event of bone pain. Across studies and populations, atrasentan reduced the incidence of adverse events of bone pain and delayed the time to onset of this pain.

Results of the analysis of time to first adverse event of bone pain are summarized in Table 10.

Table 10. Treatment Benefit of Atrasentan on Bone Pain: M00-211 and M96-594

	Number of Events (%)				Relative Difference in Progression-free Rates	
Population	**Placebo**	**10 mg Atrasentan**	**HR**	**95% CI**	**3 Months**	**6 Months**
M00-211						
Bone metastatic	210/335 (62.7%)	192/355 (54.1%)	.795	.654, .967	22.9%	23.5%
Intent-to-treat	217/401 (54.1%)	198/408 (48.5%)	.876	.722, 1.062	13.7%	9.7%
M96-594						
Abnormal bone scan	55/99 (55.6%)	30/78 (38.5%)	.610	.391, .953	20.1%	36.8%
Intent-to-treat	56/104 (53.8%)	32/89 (36.0%)	.594	.384, .918	21.5%	37.3%

In the analysis of events through the first scheduled scan, atrasentan reduced the risk of an adverse event of bone pain by 23% in the intent-to-treat population (HR = .767, 95% CI = [.616, .955]). The beneficial effect was greater in patients with bone metastases (HR = .706, 95% CI = [.565, .882]), with a 29% reduction in the risk of experiencing bone pain. These data provide further evidence of the clinical benefit of atrasentan.

4.3 Integrated Log-Rank Analysis of Studies M96-594 and M00-211

To further evaluate the treatment effect on time to disease progression in the intent-to-treat population, an integrated log-rank analysis with stratification by study was performed in which data were combined for intent-to-treat patients from studies M00-211 and M96-594 who received either 10 mg atrasentan or placebo (N = 1002). Stratifying by study is an appropriate methodology for this analysis as it maintained the integrity of the individual study designs. The analysis used individual patient data from the 2 studies rather than pooled population results, and each patient was evaluated according to the protocol into which he was enrolled. Atrasentan demonstrated a significant delay in time

to disease progression (HR = .863, 95% CI = [.747, .997], log-rank *P* = .045), providing additional confirmation that atrasentan affords clinical benefit for the population of men with metastatic HRPC.

In secondary analyses of changes in biomarkers, atrasentan significantly slowed the increase of bone alkaline phosphatase and PSA as well as significantly delaying time to biomarker progression (HR = .537, 95% CI = [.414, .695] for bone alkaline phosphatase and HR = .848, 95% CI = [.720, .998] for PSA). Atrasentan treatment provided benefit in slowing the deterioration of quality of life compared with placebo in both overall measures and significantly in disease-specific measures of patient-reported outcomes. Finally, in the supportive analysis of time to bone pain for the integrated data set, atrasentan delayed onset of this adverse event with greatest associated morbidity in metastatic HRPC (HR = .816, 95% CI = [.687, .976]).

4.4 Efficacy Discussion

In the context of late-stage HRPC, the pathophysiologic hallmark of which is extensive osteoblastic metastatic lesions, the results in favor of atrasentan are clinically meaningful, consistent across measures, and similar across studies. The predominant symptom of advanced prostate cancer is pain, typically caused by expanding bone metastases or fractures. Over 90% of patients with metastatic HRPC will die with painful bone metastases requiring substantial opiate analgesia in the final months of life. The clinical benefit of atrasentan in the management of men with metastatic HRPC is observed in the delay in time to disease progression in the bone metastatic population of the pivotal study, M00-211. In this population representing the majority of men with metastatic HRPC, atrasentan reduced the risk of disease progression by 19%.

Of greater relevance, atrasentan significantly reduced the risk of developing confirmed clinical progression events by 32% compared with placebo in this bone metastatic population. Progression defined by pain, skeletal-related events, and other non-radiographic symptomatic events is more clinically relevant to a patient with advanced prostate cancer than radiographic changes observed on serially scheduled

scans. Furthermore, in clinical practice, scans would not be generally obtained without a change in clinical status, and further intervention or a change in therapy would stem from these other causes. The clinical benefit is observed within the first 3 months, as evidenced by the analysis of time to clinical events censored at the first scheduled radiographic scan, ie, before patients discontinued due to radiographic events and without concurrent clinical events, and reflects the overall study results.

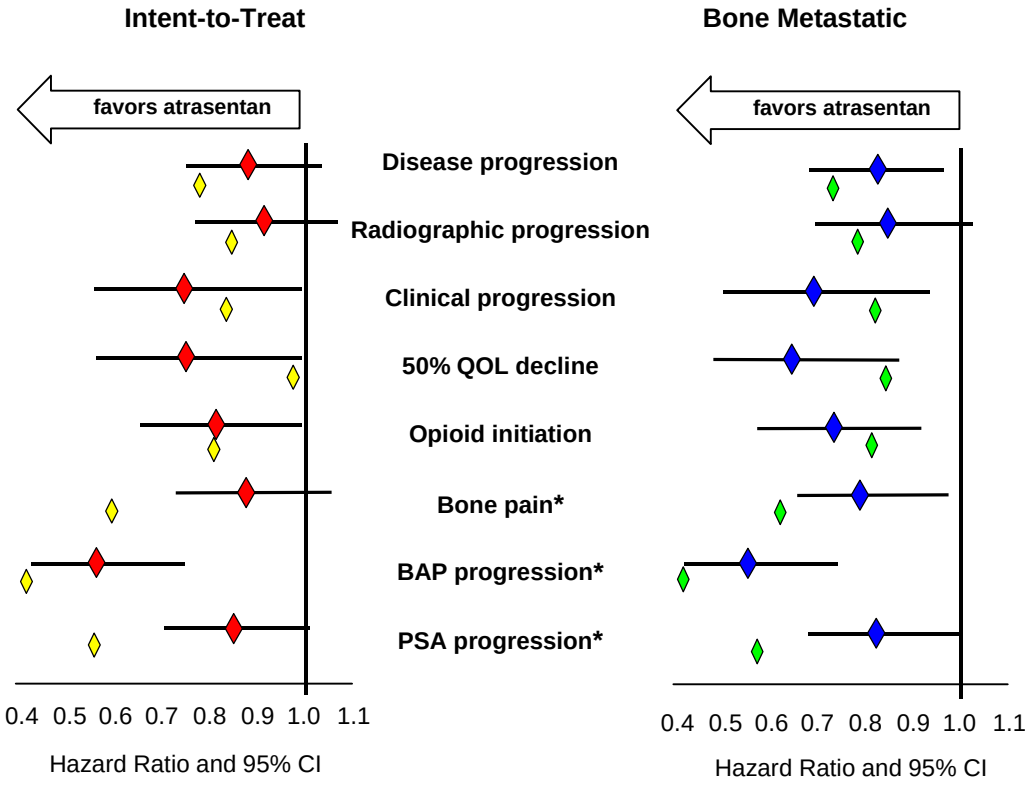
Results of the secondary endpoint analyses in study M00-211, specifically the slower increase of bone alkaline phosphatase and PSA in atrasentan-treated patients compared with those receiving placebo, further support the treatment effect with atrasentan on delaying disease progression. In addition, atrasentan resulted in a significant favorable effect relative to placebo on the prespecified disease-specific quality of life measures, particularly those that measure pain. The exploratory analysis of patient-reported pain-related quality of life scores, in which fewer atrasentan-treated patients reached a clinically meaningful 50% deterioration in these scores, and in which atrasentan delayed the time to that deterioration, corroborates the overall clinical benefit of atrasentan in the population of HRPC patients with bone metastases. Likewise, fewer atrasentan-treated patients experienced an adverse event of bone pain and atrasentan significantly delayed the onset of these events, results that further substantiate the delay in time to disease progression.

The overall body of data presenting compelling evidence for the treatment benefit of atrasentan is represented in Figure 25. For illustrative purposes, hazard ratios for study M96-594, which are consistent with those from the larger study, M00-211, are shown without confidence intervals. All hazard ratios and confidence intervals are provided in the text for study M96-594 for all analyses except those summarized below:

- Time to radiographic progression:
  Intent-to-treat — HR = .841, 95% CI = [.546, 1.296]
  Abnormal baseline bone scan — HR = .786, 95% CI = [.500, 1.238]

- Time to bone alkaline phosphatase progression:
  Intent-to-treat — HR = .409, 95% CI = [.213, .787]
  Abnormal baseline bone scan — HR = .418, 95% CI = [.217, .805]
- Time to PSA progression:
  Abnormal baseline bone scan — HR = .570, 95% CI = [.381, .853]

Figure 25. Treatment Benefit with Atrasentan Across Assessments: Studies M00-211 and M96-594



Legend: ◆ and ◆ = HR for intent-to-treat and bone metastatic patients in study M00-211; ◇ and ◇ = HR for intent-to-treat and bone metastatic patients in study M96-594; QOL = FACT-P PCS pain-related questions; BAP = bone alkaline phosphatase
* The upper 95% confidence limit for study M96-594 did not cross 1.0.

That the population of HRPC patients with metastatic disease in bone would benefit from atrasentan therapy is consistent with the known biology of endothelin and with the preclinical evidence for the activity of atrasentan in the bone microenvironment.

Atrasentan blocks ET_A receptor signaling and inhibits the proliferation of prostate cancer cells and the overproduction of osteoblasts into disorganized and paradoxically weak bone. Atrasentan interrupts the mutually-sustaining and harmful relationship between prostate cancer cells and osteoblasts in bone, and as a result, delays both disease progression and the cascade of negative consequences, including the pain associated with advanced prostate cancer.

5.0 Overview of Safety

Atrasentan is a highly selective antagonist of the ET_A receptor, which mediates the effects of ET-1, a potent endogenous vasoconstrictor. The anticipated clinical effects of atrasentan and blockade of the ET_A receptor include vasodilatation and fluid retention. The most common adverse events observed with atrasentan (peripheral edema, rhinitis, and headache) are consistent with this mechanism of action, and with effects observed with other endothelin receptor antagonists such as bosentan and darusentan.[54,55]

There is considerable safety experience with atrasentan including 1696 patients who have received atrasentan in 35 completed and 6 ongoing Abbott-sponsored clinical trials. This includes 382 subjects in phase 1 studies of normal healthy volunteers, 105 patients (44 with prostate cancer) in phase 1 oncology studies, and 43 patients in studies of unique populations with moderate hepatic insufficiency, diabetic nephropathy, or congestive heart failure, as well as 51 normal healthy volunteers in 4 drug-interaction studies with atrasentan.

The safety profile of atrasentan at the 2.5-mg and 10-mg doses has been studied in randomized, double-blind, placebo-controlled trials involving a total of 1220 patients with metastatic HRPC, 676 of whom received atrasentan (Table 11).

Table 11. Patient Accountability: Phase 2/3 Placebo-Controlled Studies

	Number of Treated Patients				
	Total Patients		Atrasentan		
Studies		Placebo	2.5 mg	10 mg	Total
M96-500	131	43	40	48	88
M96-594	288	104	95	89	184
M00-211	801	397	0	404	404
All phase 2/3 placebo-controlled	**1220**	**544**	**136**	**541**	**676**

Note: One patient in study M96-594 initially randomized to receive 10 mg atrasentan dose-reduced to 1.0 mg; his data are included with both 2.5 mg atrasentan and 10 mg atrasentan.

In randomized, placebo-controlled phase 2/3 studies, median exposure to atrasentan in the double-blind segment was 111 days, with 214 patients receiving 2.5 mg or 10 mg atrasentan for over 6 months (Table 12).

Table 12. Exposure to Atrasentan in Phase 2/3 Placebo-Controlled Studies

	Exposure (Number of Dosing Days)			
		Atrasentan		
	Placebo N = 544	2.5 mg N = 136	10 mg N = 541	Total N = 676
Mean	144	146	142	143
Median	112	84	112	111
Range	1 – 541	1 – 594	1 – 539	1 – 594

A total of 893 prostate cancer patients have been included in open-label studies of atrasentan not including patients enrolled in study M00-244. Forty-four prostate cancer patients (among 105 cancer patients total) were treated with atrasentan in open-label phase 1 oncology studies with doses ranging from 1 mg to 95 mg. Of the 849 patients receiving atrasentan in the open-label phase 2/3 extension studies, 341 had received

placebo and 410 had received atrasentan in one of the previous phase 2/3 placebo-controlled studies, while 98 patients entered an open-label extension study directly, without having participated in a previous randomized controlled trial of atrasentan. The distribution of patients in open-label studies is presented in Table 13.

Table 13. Patient Distribution in Open-label Studies of Atrasentan

	Number of Treated Patients			
	Atrasentan Dose			
Open-Label Study	**<10 mg[a]**	**10 mg**	**>10 mg[b]**	**Total**
Phase 1 oncology	6	5	33	44
Open-label phase 2/3 extension studies[c]	9	639	217	849

a Includes doses 0.2 mg – 5.0 mg; in open-label phase 2/3 experience, includes 0.2 – 2.5 mg

b Includes doses 20 mg – 95 mg; in phase 2/3 experience, includes only 20 mg and 30 mg.

c M96-594 open-label, M97-739, M01-304, M00-258, excluding patients from study M00-244

The mean duration of treatment with atrasentan in the open-label extension studies was 229 days, with 423 patients treated for at least 6 months. The majority of the safety data were generated with the 10 mg dose of atrasentan, the dose for which approval is being sought. In total, 921 men have received 10 mg atrasentan in clinical trials with a mean exposure of 246 days, and 470 have received 10 mg atrasentan for 6 months or longer. Overall exposure to atrasentan is presented in Table 14 below.

Table 14. Overall Exposure to Atrasentan in Clinical Trials

	Exposure (Number of Dosing Days)			
	<10 mg N = 146	**10 mg N = 921**	**>10 mg N = 250**	**Total N = 1159**
Mean	164	246	162	252
Median	84	169	88	168
Range	1 – 1112	1 – 1934	2 – 1884	1 - 2087

5.1 Safety Experience In Phase 1 Studies with Healthy Volunteers

The most common adverse events observed in phase 1 clinical trials with atrasentan (headache and rhinitis) are consistent with the safety profile of a vasodilatory agent. In phase 1 studies of 382 normal healthy volunteers with doses ranging from 0.2 mg to 139.5 mg (including 105 subjects who received doses of atrasentan greater than 10 mg), rhinitis and headache were the most common adverse events reported with atrasentan, occurring in 12.9% and 45.2% of patients receiving the 10-mg dose in phase 1 multiple-dose studies. A minor mean decrease in hemoglobin of 0.61 g/dL was also observed without evidence of hemolysis, marrow suppression, or blood loss, and was attributed to hemodilution secondary to fluid retention. There were no serious adverse events reported with atrasentan and no other safety issues of concern in these studies.

5.2 Safety Experience in Metastatic HRPC

The study population of the placebo-controlled phase 2/3 studies of atrasentan in metastatic HRPC was elderly (median age 72 years for the 10 mg atrasentan group and 73 years for the placebo group) and included patients with diverse comorbid conditions such as diabetes, hypertension, chronic obstructive pulmonary disease (COPD)/emphysema, and cardiovascular disease, in addition to their underlying metastatic HRPC. These studies provide substantial comparative safety experience with atrasentan in patients with metastatic HRPC. The safety data relating to the experience in patients with metastatic HRPC are presented as an integrated analysis combining data from the 3 placebo-controlled phase 2/3 studies. In addition, results from the pivotal study, M00-211, are also presented. Long-term safety data from the open-label extension studies are presented in section 5.6.

Baseline characteristics were similar between treatment groups (Table 15).

Table 15. Baseline Characteristics: Phase 2/3 Placebo-Controlled Studies

	Placebo N = 544		Atrasentan 2.5 mg N = 136		Atrasentan 10 mg N = 541	
Variable	**Median**	**Range**	**Median**	**Range**	**Median**	**Range**
Age, y	72.0	(45 – 92)	71.0	(46.0 – 89.0)	73.0	(43 – 94)
Weight, kg	83.0	(43.0 – 154.2)	818	(52.4 – 126.1)	82.0	(49.4 – 176.9)
Hemoglobin, g/dL	13.1	(6.7 – 18.1)	12.9	(6.5 – 15.6)	13.3	(9.1 – 17.4)
PSA, ng/mL	83.6	(0.0 – 7431.0)	78.8	(0.1 – 6572.2)	70.8	(1.5 – 5784.0)
LDH, IU/L	188	(95 – 2365)	183	(93 – 807)	186	(74 – 1318)
Bone alkaline phosphatase, U/L	29.0	(2.0 – 1877.1)	38.0	(11.5 – 796.4)	29.0	(2.0 – 1903.8)
Creatinine, mg/dL	1.0	(0.4 – 3.3)	1.0	(0.6 – 10.5)	0.9	(0.4 – 3.8)

5.3 Adverse Events

The overall incidence of adverse events was analyzed for categories of any grade (according to National Cancer Institute Common Toxicity Criteria), grade 3/4 (severe) adverse events, serious adverse events, adverse events leading to discontinuation, and adverse events resulting in death. The overall incidence for most of these categories of events was similar between atrasentan and placebo (Table 16).

Table 16. Comparison of Adverse Events Between Treatment Arms

Category	Number of Patients (%)				
	Phase 2/3			M00-211	
	Placebo N = 544	Atrasentan 2.5 mg N = 136	Atrasentan 10 mg N = 541	Placebo N = 397	Atrasentan 10 mg N = 404
Adverse events of any grade	523 (96.1%)	130 (95.6%)	528 (97.6%)	385 (97.0%)	398 (98.5%)
Grade ¾ adverse events	218 (40.1%)	55 (40.4%)	221 (40.9%)	167 (42.1%)	165 (40.8%)
Serious adverse events	152 (27.9%)	48 (35.3%)	173 (32.0%)	103 (25.9%)	119 (29.5%)
Discontinuations due to adverse event	76 (14.0%)	13 (9.6%)	93 (17.2%)	64 (16.1%)	71 (17.6%)
Deaths due to adverse events	28 (5.1%)	9 (6.6%)	31 (5.7%)	21 (5.3%)	25 (6.2%)

Note: One patient in study M96-594 initially randomized to receive 10 mg atrasentan dose-reduced to 1.0 mg; his data are included with both 2.5 mg atrasentan and 10 mg atrasentan.

The overall incidence of adverse events of any grade reported for at least 10% of patients in any treatment arm is presented in Table 17. The discussion of adverse events focuses on the 10 mg dose, as this is the dose for which approval is sought.

Table 17. Adverse Events Occurring with at Least 10% Incidence

Adverse Event	Number of Patients (%)									
	Phase 2/3								M00-211	
	Placebo N = 544		Atrasentan 2.5 mg N = 136		Atrasentan 10 mg N = 541		Any Atrasentan N = 676		Placebo N = 397		Atrasentan 10 mg N = 404	
Overall	523	(96.1%)	130	(95.6%)	528	(97.6%)	657	(97.2%)	386	(97.2%)	398	(98.5%)
Bone pain	277	(50.9%)*	40	(29.4%)	239	(44.2%)	279	(41.3%)	215	(54.2%)	191	(47.3%)
Peripheral edema	76	(14.0%)	42	(30.9%)	208	(38.4%)	249	(36.8%)*	47	(11.8%)	160	(39.6%)*
Rhinitis	73	(13.4%)	27	(19.9%)	185	(34.2%)	211	(31.2%)*	54	(13.6%)	144	(35.6%)*
Headache	74	(13.6%)	19	(14.0%)	117	(21.6%)	136	(20.1%)*	57	(14.4%)	86	(21.3%)*
Constipation	89	(16.4%)	25	(18.4%)	107	(19.8%)	132	(19.5%)	67	(16.9%)	77	(19.1%)
Pain	118	(21.7%)	15	(11.0%)	113	(20.9%)	128	(18.9%)	102	(25.7%)	94	(23.3%)
Asthenia	98	(18.0%)	20	(14.7%)	97	(17.9%)	117	(17.3%)	69	(17.4%)	63	(15.6%)
Nausea	74	(13.6%)	19	(14.0%)	81	(15.0%)	100	(14.8%)	55	(13.8%)	51	(12.6%)
Anemia	51	(9.4%)	19	(14.0%)	77	(14.2%)	96	(14.2%)*	34	(8.6%)	49	(12.1%)
Infection	39	(7.2%)	16	(11.8%)	61	(11.3%)	77	(11.4%)*	30	(7.6%)	52	(12.9%)*
Anorexia	75	(13.8%)	6	(4.4%)	63	(11.6%)	69	(10.2%)	51	(12.8%)	44	(10.9%)
Back pain	58	(10.7%)	3	(2.2%)	51	(9.4%)	65	(9.6%)	46	(11.6%)	41	(10.2%)
Dyspnea	21	(3.9%)	8	(5.9%)	56	(10.4%)	64	(9.5%)*	16	(4.0%)	37	(9.2%)*
Prostatic carcinoma	70	(12.9%)*	5	(3.7%)	54	(10.0%)	59	(8.7%)	64	(16.1%)	49	(12.1%)

Note: One patient in study M96-594 initially randomized to receive 10 mg atrasentan dose-reduced to 1.0 mg; his data are included with both 2.5 mg atrasentan and 10 mg atrasentan.

* Indicates a statistically significant difference between treatments at $P \leq .05$

The most common adverse event in these studies, bone pain related to metastatic disease, was significantly more common in patients receiving placebo. The COSTART term "bone pain" was utilized for reported events of bone pain that corresponded to a metastatic lesion on bone scan but may not have reached the threshold for a disease progression endpoint. The 2 other adverse events most commonly experienced by placebo-treated patients were pain and asthenia.

Six adverse events with ≥10% incidence were statistically more common with atrasentan in phase 2/3 studies: peripheral edema, rhinitis, headache, anemia, infection, and dyspnea. The 3 most common are discussed below. Anemia, infection, and dyspnea are discussed in section 5.3.4.

Peripheral Edema, Rhinitis, and Headache

The 3 most common adverse events associated with atrasentan are clearly related to its vasodilatory properties and/or resulting fluid retention. Reports of peripheral edema were generally described as swelling of the lower extremities and reports of rhinitis as "nasal congestion" or "stuffy nose." Most events of peripheral edema, rhinitis, and headache were mild to moderate in severity (grade 1 or 2), with incidence of grade 3/4 events generally less than 1% (Table 18).

Table 18. Analysis of Peripheral Edema, Rhinitis, and Headache

Event	Number of Patients (%)					
	Phase 2/3				M00-211	
	Placebo N = 544	Atrasentan 2.5 mg N = 136	Atrasentan 10 mg N = 541	Any Atrasentan N = 676	Placebo N = 397	Atrasentan 10 mg N = 404
Peripheral edema						
All events	76 (14.0%)	42 (30.9%)	208 (38.4%)	249 (36.8%)	48 (12.1%)	160 (39.6%)*
Grade 3/4	8 (1.5%)	1 (0.7%)	7 (1.3%)	8 (1.5%)	5 (1.3%)	5 (1.2%)
Discontinuations	2 (0.4%)	0	5 (0.9%)	5 (0.7%)	2 (0.5%)	4 (1.0%)
Resulted in death	0	0	0	0	0	0
Rhinitis						
All events	73 (13.4%)	27 (19.9%)	185 (34.2%)	211 (31.2%)	55 (13.9%)	147 (36.4%)*
Grade 3/4	0	0	3 (0.6%)	3 (0.4%)	0	0
Discontinuations	0	0	5 (0.9%)	5 (0.7%)	0	4 (1.0%)
Resulted in death	0	0	0	0	0	0
Headache						
All events	74 (13.6%)	19 (14.0%)	117 (21.6%)	136 (20.1%)	57 (14.4%)	86 (21.3%)*
Grade 3/4	2 (0.4%)	1 (0.7%)	4 (0.7%)	5 (0.7%)	0	3 (0.7%)
Discontinuations	0	0	2 (0.4%)	2 (0.3%)	0	2 (0.4%)
Resulted in death	0	0	0	0	0	0

Note: One patient in study M96-594 initially randomized to receive 10 mg atrasentan dose-reduced to 1.0 mg; his data are included with both 2.5 mg atrasentan and 10 mg atrasentan.

* Indicates a statistically significant difference between treatments at $P \leq .05$

These events occurred earlier with 10 mg atrasentan treatment than with placebo, with median times to onset with atrasentan of 15 days, 11 days, and 5 days, respectively, for peripheral edema, rhinitis, and headache. These compare with median times to onset of 32.5 days, 28 days, and 17.5 days, respectively, with placebo.

For peripheral edema, the proportion of patients whose events resolved while on study drug was greater for 10 mg atrasentan (40%) than for placebo (17%). For patients whose peripheral edema resolved, the event resolved without any action taken for 52/84 (62%)

of those treated with 10 mg atrasentan and for 10/13 (77%) of those treated with placebo. The peripheral edema resolved with diuretics for 19 patients treated with 10 mg atrasentan and 1 patient treated with placebo. The peripheral edema resolved after study drug discontinuation for 34 atrasentan-treated patients and 6 placebo-treated patients, while no end date was reported for 81 patients treated with 10 mg atrasentan and 49 patients treated with placebo. Despite the fact that peripheral edema resolved for only 57% of patients experiencing the event, only 5 patients (0.9%) receiving 10 mg atrasentan discontinued study drug due to the event compared with 2 patients (0.4%) receiving placebo.

Rhinitis events were reported as having resolved on treatment for fewer atrasentan-treated patients (24%) than for placebo-treated patients (52%). For patients whose rhinitis resolved, similar proportions in each treatment arm did not require medication (31/44 [70%] for 10 mg atrasentan and 28/38 [74%] for placebo). Thirteen atrasentan recipients and 10 placebo recipients were treated for their rhinitis, typically with over-the-counter medication. Events resolved after study drug discontinuation for 38 atrasentan-treated patients and 5 placebo-treated ones. No end date was reported for rhinitis for 108 patients who received 10 mg atrasentan and for 29 who received placebo. Five atrasentan-treated patients and no placebo-treated patient discontinued from the study due to rhinitis.

The proportion of patients whose headaches resolved during treatment was similar for the 2 treatment arms. For patients experiencing headaches, the events resolved for 79 (68%) atrasentan-treated patients, 43 with medication (54%). Events resolved for 51 (69%) placebo-treated patients, 31 with medication (61%). Those who received medication were treated with over-the-counter preparations. Events resolved after discontinuation of study drug for 5 patients treated with 10 mg atrasentan and 3 patients treated with placebo, and end dates were not reported for headaches for 35 patients who received 10 mg atrasentan and 20 who received placebo. No placebo recipient and only 2 atrasentan recipients discontinued from the study due to headaches.

5.3.1 Severe (Grade 3/4) Adverse Events

Grade 3/4 adverse events occurring in ≥1% of patients in either treatment arm are presented in Table 19. Grade 3/4 adverse events more commonly associated with atrasentan were anemia, heart failure, myocardial infarction, and pneumonia. In contrast, grade 3/4 adverse events of bone pain, urinary retention, hematuria, and prostate cancer were more frequent in placebo-treated patients.

Table 19. Grade 3/4 Adverse Events Reported with at Least 1% Incidence

	Number of Patients (%)									
	Phase 2/3								M00-211	
Category/Event	Placebo N = 544		Atrasentan 2.5 mg N = 136		Atrasentan 10 mg N = 541		Any Atrasentan N = 676		Placebo N = 397	Atrasentan 10 mg N = 404
Overall	218 (40.1%)		55 (40.4%)		221 (40.9%)		276 (40.8%)		167 (42.1%)	165 (40.8%)
Bone pain	75 (13.8%)		9 (6.6%)		49 (9.1%)		58 (8.6%)		61 (15.4%)*	38 (9.4%)
Prostatic carcinoma	35 (6.4%)		4 (2.9%)		28 (5.2%)		32 (4.7%)		28 (7.0%)	23 (5.7%)
Anemia	19 (3.5%)		6 (4.4%)		22 (4.1%)		28 (4.1%)		16 (4.0%)	16 (4.0%)
Heart failure[a]	3 (0.6%)		2 (1.5%)		16 (3.0%)		18 (2.7%)		1 (0.2%)	5 (1.2%)
Paraplegia[b]	13 (2.4%)		4 (2.9%)		12 (2.2%)		16 (2.4%)		9 (2.3%)	8 (2.0%)
Pain	10 (1.8%)		6 (4.4%)		9 (1.7 %)		15 (2.2%)		7 (1.8%)	7 (1.7%)
Urinary retention	17 (3.1%)		5 (3.7%)		8 (1.5%)		13 (1.9%)		12 (3.0%)	6 (1.5%)
Asthenia	7 (1.3%)		3 (2.2%)		10 (1.8%)		13 (1.9%)		6 (1.5%)	5 (1.2%)
Hematuria	11 (2.0%)		2 (1.5%)		8 (1.5%)		10 (1.5%)		10 (2.5%)	7 (1.7%)
Back pain	7 (1.3%)		3 (2.2%)		7 (1.3%)		10 (1.5%)		4 (1.0%)	5 (1.2%)
Pneumonia	1 (0.2%)		3 (2.2%)		7 (1.3%)*		10 (1.5%)		0	6 (1.5%)*
Peripheral edema	8 (1.5%)		1 (0.7%)		7 (1.3%)		8 (1.2%)		5 (1.0%)	5 (1.2%)
Urinary tract disorder	5 (0.9%)		2 (1.5%)		6 (1.1%)		8 (1.2%)		5 (1.3%)	6 (1.5%)
Constipation	3 (0.6%)		1 (0.7%)		7 (1.3%)		8 (1.2%)		2 (0.5%)	5 (1.2%)
Dyspnea	3 (0.6%)		1 (0.7%)		7 (1.3%)		8 (1.2%)		2 (0.5%)	7 (1.7%)
Sepsis	2 (0.4%)		0		7 (1.3%)		7 (1.0%)		2 (0.5%)	5 (1.2%)
Myocardial infarct[c]	2 (0.4%)		0		7 (1.3%)		7 (1.0%)		2 (0.5%)	7 (1.7%)
Bladder stenosis	2 (0.4%)		0		7 (1.3%)		7 (1.0%)		1 (0.2%)	5 (1.2%)
Pathological fracture	5 (0.9%)		0		6 (1.1%)		6 (0.9%)		5 (1.3%)	6 (1.5%)
Hyperuricemia	10 (1.8%)		0		5 (0.9%)		5 (0.7%)		11 (2.8%)	5 (1.2%)
Hydronephrosis	9 (1.7%)		1 (0.7%)		4 (0.7%)		5 (0.7%)		8 (2.0%)	3 (0.7%)
Alkaline phosphatase increased	9 (1.7%)		0		4 (0.7%)		4 (0.6%)		9 (2.3%)	4 (1.0%)
LDH increased	9 (1.7%)		0		4 (0.7%)		4 (0.6%)		9 (2.3%)	4 (1.0%)

Note: One patient in study M96-594 initially randomized to receive 10 mg atrasentan dose-reduced to 1.0 mg; his data are included with both 2.5 mg atrasentan and 10 mg atrasentan.

a Includes COSTART terms of congestive heart failure, left heart failure, heart failure, and lung edema and medical term of shock cardiogenic.

b The term "paraplegia" indicates spinal cord compression.

c MI of any grade was statistically more common with atrasentan.

* Indicates statistically significant difference between treatments at $P \leq .05$

5.3.2 Adverse Events Leading to Discontinuation

Adverse events led to discontinuation in a similar proportion of patients receiving atrasentan (15.7%) as those receiving placebo (14.0%). Events related to prostate cancer, bone pain and prostatic carcinoma, led to discontinuation for a greater proportion of patients in the placebo arm, and occurred at an incidence of 3.3% and 1.5%, respectively, compared with 1.0% for both events for patients receiving atrasentan. The incidence of asthenia leading to discontinuation was similar between treatment arms. The incidence of heart failure and dyspnea led to discontinuation more commonly in patients receiving atrasentan, and these events are discussed below.

Table 20. Most Common Adverse Events Leading to Discontinuation in at Least 1% of Patients in Phase 2/3 Studies

	Number of Patients (%)					
	Phase 2/3				M00-211	
Event	Placebo N = 544	Atrasentan 2.5 mg N = 136	Atrasentan 10 mg N = 541	Any Atrasentan N = 676	Placebo N = 397	Atrasentan 10 mg N = 404
Overall	76 (14.0%)	13 (9.6%)	93 (17.2%)	106 (15.7%)	64 (16.1%)	71 (17.6%)
Heart failure	2 (0.4%)	3 (2.2%)	10 (1.8%)	13 (1.9%)	2 (0.5%)	9 (2.2%)*
Dyspnea	3 (0.6%)	0	9 (1.7%)	9 (1.3%)	3 (0.7%)	8 (2.0%)
Bone pain	18 (3.3%)*	2 (1.5%)	5 (0.9%)	7 (1.0%)	16 (4.0%)*	5 (1.2%)
Asthenia	5 (0.9%)	0	7 (1.3%)	7 (1.0%)	4 (1.0%)	5 (1.2%)
Prostatic carcinoma	8 (1.5%)	1 (0.7%)	6 (1.1%)	7 (1.0%)	8 (2.0%)	5 (1.2%)

Note: One patient in study M96-594 initially randomized to receive 10 mg atrasentan dose-reduced to 1.0 mg; his data are included with both 2.5 mg atrasentan and 10 mg atrasentan.

5.3.3 Adverse Events of Special Interest

5.3.3.1 Heart Failure

The analysis of heart failure included an integrated analysis of the COSTART terms "heart failure," "congestive heart failure," "left heart failure," and "lung edema," as well as the medical term "cardiogenic shock." The incidence of heart failure was greater in patients receiving atrasentan compared with those receiving placebo in the phase 2/3

studies. A total of 28 atrasentan-treated patients (4.1%) developed heart failure, 23 with the 10 mg dose and 5 with the 2.5 mg dose, compared with 5 placebo-treated patients (0.9%) (Table 21).

Table 21. Analysis of Heart Failure

	Phase 2/3				M00-211	
Outcome	Placebo N = 544	Atrasentan 2.5 mg N = 136	Atrasentan 10 mg N = 541	Atrasentan Any N = 676	Placebo N = 397	Atrasentan 10 mg N = 404
All events	5 (0.9%)	5 (3.7%)	23 (4.3%)*	28* (4.1%)	4 (1.0%)	18 (4.5%)*
Grade 3/4 events	3 (0.6%)	2 (1.5%)	16 (3.0%)*	18* (2.7%)	3 (0.8%)	12 (3.0%)*
Discontinuations	2 (0.4%)	3 (2.2%)	10 (1.8%)*	13 (1.9%)*	2 (0.5%)	8 (2.0%)*
Resulted in death	1 (0.2%)	0	7 (1.3%)*	7 (1.0%)	1 (0.3%)	7 (1.7%)
Median time to onset, d	92.0	not determined	24.0	22.5	48.5	49

Note: One patient in study M96-594 initially randomized to receive 10 mg atrasentan dose-reduced to 1.0 mg; his data are included with both 2.5 mg atrasentan and 10 mg atrasentan.
* Indicates a statistically significant difference from placebo at $P \leq .05$

The majority of heart failure events were grade 3/4 for both atrasentan- and placebo-treated patients. Grade 3/4 heart failure occurred in 16/541 (3.0%) patients treated with 10 mg atrasentan compared with 3/544 (0.6%) of those treated with placebo in all phase 2/3 studies, and in 12/404 (3.0%) and 3/397 (0.7%) of atrasentan- and placebo-treated patients in pivotal study M00-211. Events of heart failure occurred earlier in the course of therapy in patients treated with atrasentan who developed heart failure compared with those treated with placebo (median of 24 days compared to 92 days). Of the atrasentan-related events of heart failure, 54% (15/28) occurred within the first 6 weeks and 75% (21/28) within the first 12 weeks of initiating atrasentan therapy.

Among the atrasentan recipients, 5 patients had concurrent events of myocardial infarction that most likely precipitated the event of heart failure. Three of these patients had recent changes in cardiac medications prior to the events myocardial infarction and heart failure (2 abruptly discontinued beta-blocker therapy and 1 had recently initiated alpha-antagonist therapy), 1 had undergone transurethral surgery complicated by major hemorrhage, and the fifth had myocardial infarction and heart failure with bradycardia.

In another 4 patients, fluid retention from prostate cancer–related obstructive uropathy might have precipitated heart failure. Five additional patients had other adverse events that immediately preceded or were concurrent with heart failure including pathological bone fracture, malignant pleural effusion, lung carcinomatosis, pneumonia, and severe anemia. In total, 6 of the 28 patients had a concurrent or preceding event of pneumonia.

Heart failure was the primary reason for discontinuation from study in 13/28 patients, 10 who received 10 mg atrasentan and 3 who received 2.5 mg atrasentan. Heart failure was recorded as having resolved with continued atrasentan therapy after the initiation of diuretic and/or ACE inhibitor therapy in 9 patients, and upon discontinuation of atrasentan therapy in 7 patients. In 4 cases, heart failure was recorded as ongoing at the final follow-up visit and in the remaining 8 cases, the heart failure was unresolved at the time of death.

One patient with an adverse event of heart failure died from carcinomatosis of the lung. In total, 7 heart failure-related deaths were reported in patients receiving atrasentan. In 3 cases, death was attributed to both congestive heart failure and prostate cancer with visceral metastases. The 4 remaining deaths were attributed solely to heart failure, and 2 of these deaths occurred following abrupt discontinuation of beta-blockers. In addition, 6 of the 7 patients had significant underlying cardiovascular morbidities predating atrasentan therapy including a history of heart failure (n = 3), angina (n = 3), peripheral vascular disease (n = 3), arrhythmia (n = 3), coronary artery disease (n = 1), and valvular disease (n = 2).

Atrasentan-treated patients manifesting heart failure tended to be older than the general patient population and 75% of patients developing heart failure had a history of significant cardiac disease compared with 32% of atrasentan-treated patients without study events of heart failure. In addition, atrasentan recipients with events of heart failure had higher mean PSA, bone alkaline phosphatase, and LDH, lower mean hemoglobin, and higher mean creatinine at baseline compared with atrasentan recipients who did not develop events of heart failure (Table 22).

Table 22. Baseline Characteristics for Total Atrasentan Group with and without Events of Heart Failure: Phase 2/3 Studies

	With Heart Failure N = 28		Without Heart Failure N = 648	
Variable	**Median**	**Range**	**Median**	**Range**
Age, y	78.5	(63.0 – 88.0)	72.0	(43.0 – 94.0)
Weight, kg	77.8	(55.0 – 113.0)	82.0	(49.4 – 176.9)
Hemoglobin, g/dL	12.4	(8.9 – 14.9)	13.2	(6.5 – 17.4)
PSA, ng/mL	267.6	(11.6 – 3624.5)	71.2	(0.1 – 6572.2)
Bone alkaline phosphatase, IU/L	32.6	(4.6 – 1233.2)	21.3	(2.0 – 1903.8)
Total alkaline phosphatase, IU/L	165.5	(51.0 – 3247.0)	121.5	(36.0 – 5482.0)
LDH, IU/L	207	(147 – 807)	184	(74 – 1318)
Creatinine, mg/dL	1.1	(0.7 – 3.8)	0.9	(0.4 – 10.5)
Significant cardiac history[a]	75% (21/28)		32% (206/648)	

a Defined as previous CHF, ischemic heart disease (ie, myocardial infarction, coronary artery disease, and/or angina), cardiac arrhythmia, and/or valvular heart disease

The likeliest cause for most events of heart failure is fluid retention, which precipitated heart failure in patients at increased risk due to preexisting underlying cardiac disease. Other evidence for fluid retention associated with atrasentan therapy includes early weight gain and early decreases in hemoglobin and albumin, as well as development of peripheral edema. Patients with events of heart failure experienced greater mean weight gains (2.56 kg versus 1.05 kg) and mean hemoglobin decrease (1.49 g/dL versus 1.1 g/dL) at week 2 compared with atrasentan-treated patients overall. Early weight gain (more than 2 kg) or hemoglobin decrease (more than 2 g/dL) preceded heart failure in 13/28 (46.4%) cases.

There is no evidence for a negative inotropic effect with atrasentan based on both preclinical and phase 1 clinical studies of atrasentan. Safety pharmacology studies in an in vivo canine model indicate that atrasentan increases cardiac contractility, does not decrease cardiac output, and preserves cardiac function. In a placebo-controlled, phase 1 study of atrasentan in 12 patients with severe symptomatic congestive heart failure, hemodynamic monitoring indicated that short-term administration of atrasentan resulted

in favorable effects on pulmonary capillary wedge pressure, cardiac output, and cardiac index. Although there were limited left ventricular ejection fraction data for subjects from controlled phase 2/3 studies during heart failure events, results were suggestive of normal or near-normal left ventricular contractility. Five patients had echocardiograms or other assessments of ejection fraction during events of heart failure with ejection fraction recorded as 45%, 59%, >60%, "normal," and 56%. These findings are consistent with published literature regarding the hemodynamic effects of other endothelin receptor antagonists, bosentan (a mixed $ET_{A/B}$ receptor antagonist) and darusentan (a selective ET_A receptor antagonist), indicating that these agents increase cardiac output.[56]

An expert cardiologist blinded to treatment assignment conducted an independent adjudication of heart failure and related events, which corroborated the above observations.

5.3.3.2 Pneumonia

Pneumonia was reported in 21/676 (3.1%) of patients treated with atrasentan; 17/541 (3.1%) of patients receiving 10 mg atrasentan and 4/136 (2.9%) of those receiving 2.5 mg atrasentan; compared to 5/544 (0.9%) of patients receiving placebo (Table 23).

Table 23. Analysis of Pneumonia

	Phase 2/3				M00-211	
Outcome	Placebo N = 544	Atrasentan 2.5 mg N = 136	Atrasentan 10 mg N = 541	Atrasentan Any N = 676	Placebo N = 397	Atrasentan 10 mg N = 404
All events	5 (0.9%)	4 (2.9%)	17 (3.1%)*	21* (3.1%)	2 (0.5%)	12 (3.0%)*
Grade 3/4 events	1 (0.2%)	3 (2.2%)	7 (1.3%)*	10* (1.5%)	0	6 (1.5%)
Discontinuations	0	1 (0.7%)	4 (0.7%)	5 (0.7%)	0	3 (0.7%)
Resulted in death	0	1 (0.7%)	3 (0.6%)	4 (0.6%)	0	3 (0.7%)
Median time to onset, d	43	not determined	51	52	22	52

Note: One patient in study M96-594 initially randomized to receive 10 mg atrasentan dose-reduced to 1.0 mg; his data are included with both 2.5 mg atrasentan and 10 mg atrasentan.
* Indicates a statistically significant difference from placebo at $P \leq .05$

In patients receiving atrasentan, 10/21 events of pneumonia were grade 3/4 (7/17 events with the 10 mg dose and 3/4 with the 2.5 mg dose) and 5/21 resulted in discontinuation from the study (4 of which were patients receiving the 10 mg dose). There were 3 pneumonia-related fatalities in patients receiving 10 mg atrasentan, with an additional fatality in a patient receiving the 2.5 mg dose. All pneumonia fatalities were reported as not related or probably not related to atrasentan and all were medically complicated. For one patient with an adverse event of pneumonia, death was attributed to carcinomatosis of the lung and not the pneumonia.

Upon review, of the 21 events of pneumonia in patients receiving atrasentan, 11 had radiological or histological features consistent with a diagnosis of pneumonia. In 5 additional cases, no clear radiological evidence of pneumonia was reported on chest X-ray, and in 5 other cases, no radiological studies were performed to confirm the diagnosis. Five patients treated with 10 mg atrasentan with events of pneumonia had concurrent heart failure and are among the 23 patients discussed previously. All patients received antibiotics as part of their treatment, and 14/21 were hospitalized. In total, 14/21 cases were recorded as having resolved. Among the 7 other patients, 4 died due to pneumonia, 1 died with carcinoma of the larynx as an alternative etiology for his death, and 1 died to due carcinomatosis of the lung. In 1 patient, the pneumonia was not recorded as having been resolved at the time of documented disease progression.

An infectious disease expert blinded to treatment assignment conducted an independent adjudication of all reports of pneumonia, which corroborated the above observations. Of the 26 cases of pneumonia presented for independent adjudication, 7 met the criteria for pneumonia, 3 were adjudicated not to be pneumonia, and 7 were considered unlikely to be pneumonia. Information for 9 cases was insufficient for a definitive determination to be made.

There is no apparent pathophysiologic basis for reports of pneumonia in the atrasentan-treated group. The increased incidence of reported cases of pneumonia with atrasentan

may be due in part to presenting symptoms of heart failure leading to a clinical impression of pneumonia.

5.3.3.3 Myocardial Infarction

Myocardial infarction was reported more frequently in patients treated with 10 mg atrasentan (9/541, 1.7%) compared with placebo (2/544, 0.4%). No cases of myocardial infarction were reported in patients receiving the 2.5-mg dose of atrasentan. Most cases of myocardial infarction were grade 3/4: 7/9 in patients treated with atrasentan and 2/2 in those treated with placebo (Table 24).

Table 24. Analysis of Myocardial Infarction

	Phase 2/3				M00-211	
Outcome	Placebo N = 544	Atrasentan 2.5 mg N = 136	Atrasentan 10 mg N = 541	Atrasentan Any N = 676	Placebo N = 397	Atrasentan 10 mg N = 404
All events	2 (0.4%)	0	9 (1.7%)	9 (1.3%)	2 (0.5%)	9 (2.2%)
Grade 3/4 events	2 (0.4%)	0	7 (1.3%)	7 (1.0%)	2 (0.5%)	7 (1.7%)
Discontinuations	2 (0.4%)	0	4 (0.7%)	4 (0.6%)	2 (0.5%)	4 (1.0%)
Resulted in death	1 (0.2%)	0	2 (0.4%)	2 (0.3%)	1 (0.3%)	2 (0.5%)
Median time to onset, d	84.5	not determined	21.0	21.0	84.5	21.0

Note: One patient in study M96-594 initially randomized to receive 10 mg atrasentan dose-reduced to 1.0 mg; his data are included with both 2.5 mg atrasentan and 10 mg atrasentan.
* Indicates a statistically significant difference from placebo at $P \leq .05$

Eight of the 9 events of myocardial infarction occurring with atrasentan (89%) occurred within the first 4 weeks of therapy and the median time to onset was 21 days compared with onset times of 14 and 155 days in the 2 placebo cases. As discussed above in section 5.3.3.1, 5 of the 9 atrasentan-treated patients with myocardial infarction had concurrent events of heart failure. Another patient had possible endocarditis. Five of the 9 patients had at least 80% stenosis of one of more coronary arteries on coronary angiography.

All patients with an event of myocardial infarction interrupted study drug at the time of the infarct. Two patients resumed atrasentan; however, 1 of these subsequently died of left ventricular failure and renal failure 41 days after resuming study drug (post-treatment day 11). Among the remaining 7 cases, the events of myocardial infarction for 2 atrasentan recipients were considered the direct cause of death. In addition, the patient with a diagnosis of endocarditis and myocardial infarction died from cerebral hemorrhage 6 days after the onset of the other 2 events. Four of these 7 atrasentan recipients recovered, but did not resume study drug.

Patients who developed myocardial infarction were older (mean age of 77.1 years versus 71.7 years) and had higher mean baseline PSA (586.9 ng/mL versus 246.6 ng/mL), bone alkaline phosphatase (256.2 ng/mL versus 47.2 ng/mL), and creatinine (1.3 mg/dL versus 1.0 mg/dL) compared with the overall atrasentan-treated population. Additionally, 78% (7/9) of patients with myocardial infarction had significant cardiovascular disease at the time of study entry including congestive heart failure, ischemic heart disease (MI, coronary artery disease, and/or angina), and/or peripheral arterial disease. Five of the 9 patients were taking concurrent nitrates for angina.

Two expert cardiologists blinded to treatment assignment conducted an independent adjudication of all reports of myocardial infarction and reports of chest pain or sudden death, which corroborated the above observations.

5.3.4 Other Adverse Events More Common with Atrasentan

Three events, although less common than peripheral edema, rhinitis, and headache, occurred with >10% incidence and were significantly more common with atrasentan treatment: anemia, infection, and dyspnea.

5.3.4.1 Anemia

Adverse events of anemia were more common in patients receiving atrasentan compared with those receiving placebo. In patients treated with 10 mg atrasentan, 77/541 (14.2%)

had an adverse event of anemia, as did 19/136 (14.0%) of those receiving the 2.5 mg dose, and 51/544 (9.4%) of those receiving placebo.

Table 25. Analysis of Anemia

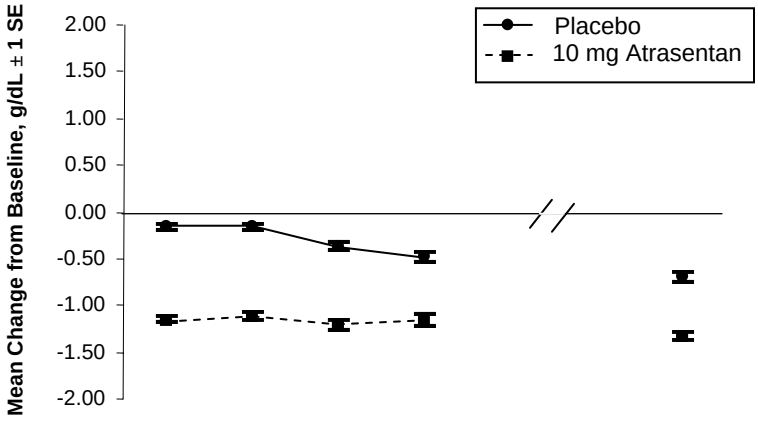
	Phase 2/3				M00-211	
Outcome	Placebo N = 544	Atrasentan 2.5 mg N = 136	Atrasentan 10 mg N = 541	Any Atrasentan N = 676	Placebo N = 397	Atrasentan 10 mg N = 404
All events	51 (9.4%)	19 (14.0%)	77 (14.2%)*	96 (14.2%)*	35 (8.8%)	50 (12.4%)
Grade 3/4 events	19 (3.5%)	6 (4.4%)	22 (4.1%)	28 (4.1%)	16 (4.0%)	16 (4.0%)
Discontinuations	3 (0.6%)	1 (0.7%)	5 (0.9%)	6 (0.9%)	2 (0.5%)	4 (1.0%)
Resulted in death	0	0	0	0	0	0
Median time to onset, d	57.0	not determined	30.0	35.0	not determined	not determined

Note: One patient in study M96-594 initially randomized to receive 10 mg atrasentan dose-reduced to 1.0 mg; his data are included with both 2.5 mg atrasentan and 10 mg atrasentan.
* Indicates a statistically significant difference from placebo at $P \leq .05$

Twenty-eight (28) of the 96 events (29.2%) of anemia in patients treated with any dose of atrasentan were rated as grade 3/4 (22/77 with 10 mg and 6/19 with 2.5 mg) compared with 19/51 (37.3%) events in patients treated with placebo. Events of anemia occurred earlier with atrasentan therapy than with placebo; median time to an event of anemia with atrasentan was 35 days with atrasentan compared with 57 days with placebo. Anemia resulted in study discontinuation in 0.9% of patients treated with atrasentan, with 5 discontinuations due to anemia in patients receiving the 10-mg dose and 1 with the 2.5-mg dose, compared with 3 with placebo (0.6%).

In the phase 2/3 studies, a week 2 mean hemoglobin decrease of 1.16 g/dL was observed in patients who received 10 mg atrasentan compared with a decrease of 0.17 g/dL in those who received placebo. After the initial decrease observed at week 2, the change in mean hemoglobin for atrasentan-treated patients stabilized. The mean hemoglobin decrease from baseline to final value was 1.34 g/dL for patients receiving 10 mg atrasentan compared with 0.70 g/dL for those receiving placebo (Figure 26).

Figure 26. Mean Change from Baseline in Hemoglobin Over Time in Phase 2/3 Studies



Placebo, N	500	502	463	402	534
10 mg Atrasentan, N	497	477	442	399	517

More atrasentan-treated patients than placebo-treated patients received transfusions in study M00-211 (40/401 [10%] versus 28/397 [7%]), with similar total units of red blood cells for the 2 treatment arms (115 units for atrasentan versus 118 units for placebo). In phase 2/3 studies, patients with a week 2 hemoglobin value ≤10 g/dL experienced a higher incidence of heart failure and myocardial infarction (15.8% compared with heart failure incidence of 3.0% in patients with a week 2 hemoglobin value >10 g/dL). Week 2 hemoglobin measurements may be useful in identifying patients at risk for heart failure or myocardial infarction.

The most likely cause for the observed decrease in hemoglobin with atrasentan treatment is hemodilution. The evidence for this is twofold. First, changes in hemoglobin are consistent with other clinical observations suggestive of fluid retention, and second, no preclinical, clinical, or laboratory evidence exists for marrow suppression, hemolysis, or hemorrhage with atrasentan therapy.

Clinical observations consistent with hemodilution include an increase in week 2 mean weight of 1.14 kg and a decrease in week 2 mean albumin of 0.18 g/dL associated with 10 mg atrasentan treatment compared with a 0.02-kg weight decrease and a 0.05-g/dL albumin increase for placebo. In contrast, there was no clinically significant decrease at week 2 in either WBC or platelet counts in patients treated with atrasentan. In patients receiving 10 mg atrasentan, mean WBC decreased from 6.7×10^9/L at baseline to 6.0×10^9/L at week 2, and mean platelet count decreased from 242.3×10^9/L at baseline to 238.7×10^9/L at week 2. A smaller percentage of patients receiving 10 mg atrasentan recorded a decrease in WBC count or platelets to a grade 3/4 low value than the percentage of patients recording a decrease in hemoglobin to a grade 3/4 low value. The WBC count dropped to $<2.0 \times 10^9$/L in only 2/521 patients and platelets dropped to $<50 \times 10^9$/L in 4/514 patients compared with hemoglobin decreasing to <8.0 g/L in 21/526 patients. Adverse events of leukopenia were reported in 5 patients treated with atrasentan, marrow depression in 1 patient, and thrombocytopenia in 6 patients. The comparable rates for placebo were 5 for leukopenia, 1 for marrow depression, and 8 for thrombocytopenia. In addition, 1 placebo recipient experienced pancytopenia. These data support the conclusion that atrasentan therapy does not cause marrow suppression in these patients.

There is a similar lack of evidence that atrasentan predisposes patients to hemorrhagic complications. The cumulative incidence of gastrointestinal bleeding (including COSTART terms gastrointestinal hemorrhage, hematemesis, melena, and rectal hemorrhage) was 15/541 (2.8%) for patients receiving 10 mg atrasentan, 3/136 (2.2%) for those receiving 2.5 mg, compared with 11/544 (2.0%) for those receiving placebo. Hemorrhage was reported in 3 patients (0.6%) receiving 10 mg atrasentan (in none with 2.5 mg) and in 2 patients (0.4%) receiving placebo. Hematuria was reported with similar incidence for the treatment arms: 34/541 (6.3%) for 10 mg, 8/136 (5.9%) for 2.5 mg, and 34/544 (6.3%) for placebo.

5.3.4.2 Infection

The incidence of infection was 11.4% in patients receiving atrasentan (11.3% for 10 mg and 11.8% for 2.5 mg) compared with 7.2% in those receiving placebo. The most common medical term coded as the COSTART term "infection" was "common cold." Reports of common cold accounted for the difference in incidence rates of infection between treatment groups, and were most likely due to symptoms of rhinitis. The incidence of other types of infections (infection, infection respiratory, and infection upper respiratory) was similar between treatment groups.

Table 26. Analysis of Infection

	Number of Patients (%)					
	Phase 2/3				M00-211	
Outcome	Placebo N = 544	Atrasentan 2.5 mg N = 136	Atrasentan 10 mg N = 541	Atrasentan Any N = 676	Placebo N = 397	Atrasentan 10 mg N = 404
All events	39 (7.2%)	16 (11.8%)	61 (11.3%)*	77 (11.4%)*	30 (7.6%)	51 (12.6%)*
Grade 3/4	0	1 (0.7%)	3 (0.6%)	4 (0.6%)	0	3 (0.7%)
Discontinuations	0	0	1 (0.2%)	1 (0.1%)	0	1 (0.2%)
Resulted in death	0	0	0	0	0	0

Note: One patient in study M96-594 initially randomized to receive 10 mg atrasentan dose-reduced to 1.0 mg; his data are included with both 2.5 mg atrasentan and 10 mg atrasentan.
* Indicates a statistically significant difference from placebo at $P \leq .05$

Three events of infection were grade 3/4 with 10 mg atrasentan. Only 1 patient discontinued from the study and no patient died due to infection.

5.3.4.3 Dyspnea

Events of dyspnea were generally described as "dyspnea," "shortness of breath," "shortness of breath on exertion," or "difficulty breathing." Adverse events of dyspnea were reported in 64/676 (9.5%) of patients treated with atrasentan; 56/541 (10.4%) and 8/136 (5.9%) in patients with 10 mg and 2.5 mg atrasentan, respectively, compared with 21/544 (3.9%) in patients treated with placebo (Table 27).

Table 27. Analysis of Dyspnea

Outcome	Phase 2/3				M00-211	
	Placebo N = 544	Atrasentan 2.5 mg N = 136	Atrasentan 10 mg N = 541	Atrasentan Any N = 676	Placebo N = 397	Atrasentan 10 mg N = 404
All events	21 (3.9%)	8 (5.9%)	56 (10.4%)	64 (9.5%)*	17 (4.3%)	38 (9.4%)*
Grade 3/4 events	3 (0.6%)	1 (0.7%)	7 (1.3%)	8 (1.2%)	2 (0.5%)	7 (1.7%)
Discontinuations	3 (0.6%)	0	9 (1.7%)	9 (1.3%)	3 (0.3%)	8 (2.0%)
Resulted in death	0	0	0	0	0	0
Median time to onset, d	47.0	not determined	28.5	32.0	not determined	not determined

Note: One patient in study M96-594 initially randomized to receive 10 mg atrasentan dose-reduced to 1.0 mg; his data are included with both 2.5 mg atrasentan and 10 mg atrasentan.
* Indicates a statistically significant difference from placebo at $P \leq .05$

Few events of dyspnea were grade 3/4 and the percentages were similar in all groups: 8/64 events of dyspnea with atrasentan (7/56 with the 10-mg dose and 1/8 with the 2.5-mg dose) and 3/21 events with placebo. In addition, 9 atrasentan-treated patients discontinued from the study due to dyspnea, all with the 10-mg dose, compared with 3 patients treated with placebo. No deaths attributed to dyspnea were reported. Dyspnea occurred earlier in the course of therapy in patients treated with atrasentan compared with those treated with placebo (median time to onset of 32 days and 47 days, respectively).

Atrasentan recipients with events of dyspnea were generally older (mean: 75 versus 71 years) and weighed more at baseline (mean: 87 versus 83 kg) compared with atrasentan recipients with no reports of dyspnea. Twenty-three of the 64 atrasentan-treated patients reporting dyspnea had a temporally overlapping event of rhinitis (suggestive of nasal congestion). Five patients had concurrent events of heart failure, 8 also had lung disorder, and 1 also had pneumonia.

Four of the 64 patients receiving atrasentan required hospitalization for dyspnea, which they experienced concurrently with other serious adverse events. One patient had concurrent pleural effusions; another patient had back pain, anorexia, and peripheral edema; a third had dyspepsia and dizziness; and a fourth had concurrent anemia,

urosepsis, urinary tract infection, and hypotension. The events resolved with continued atrasentan treatment for 3 patients and upon discontinuation of study drug for the fourth.

5.3.5 Deaths Due to Adverse Events

The overall incidence of adverse events with an outcome of death in phase 2/3 studies was not significantly different between treatment arms (28/544, 5.1% for placebo versus 40/676, 5.9% for atrasentan). The incidence of deaths due to urogenital causes, predominantly prostatic carcinoma, was nearly twice as high for patients receiving placebo than for those receiving atrasentan. More deaths from heart failure and myocardial infarction occurred in the total atrasentan group compared with placebo (8/541, 1.2% versus 2/544, 0.6%), but the overall incidence of cerebrovascular-related deaths (cerebral hemorrhage, cerebrovascular accident, intracranial hemorrhage) was similar. The number of events leading to death by body system is shown in Table 28.

Table 28. Number of Events Leading to Death by Body System

	Phase 2/3								M00-211			
Body System	Placebo N = 544		Atrasentan 2.5 mg N = 136		Atrasentan 10 mg N = 541		Atrasentan Any N = 676		Placebo N = 397		Atrasentan 10 mg N = 404	
Overall	28	(5.1%)	9	(6.6%)	31	(5.7%)	40	(5.9%)	21	(5.3%)	25	(6.2%)
Body as a whole	5	(0.9%)	3	(2.2%)	7	(1.3%)	10	(1.5%)	4	(1.0%)	5	(1.2%)
Cardiovascular	4	(0.7%)	2	(1.5%)	10	(1.8%)	12	(1.8%)	3	(0.8%)	10	(2.5%)
Digestive	0		0		1	(0.2%)	1	(0.1%)	0		1	(0.2%)
Hemic and Lymphatic	1	(0.2%)	0		2	(0.4%)	2	(0.3%)	0		2	(0.5%)
Nervous	1	(0.2%)	0		0		0		1	(0.3%)	0	
Respiratory	2	(0.4%)	1	(0.7%)	6	(1.1%)	7	(1.0%)	1	(0.3%)	6	(1.5%)
Urogenital	22	(4.0%)	3	(2.2%)	11	(2.0%)	14	(2.1%)	17	(4.3%)	7	(1.7%)

Note: Patients could have died due to more than one adverse event.
Note: One patient in study M96-594 initially randomized to receive 10 mg atrasentan dose-reduced to 1.0 mg; his data are included with both 2.5 mg atrasentan and 10 mg atrasentan.

5.3.6 Strategies to Prevent, Mitigate, or Manage Adverse Events

The 3 most common adverse events statistically associated with atrasentan therapy (peripheral edema, rhinitis, and headache) were generally mild to moderate in severity and many cases were reversible either during continued atrasentan therapy or following study drug discontinuation.

Review of study events of heart failure, pneumonia, and myocardial infarction revealed clinical patterns that provide insight into monitoring and management strategies to prevent or detect early events. Patients with heart failure, pneumonia, and/or myocardial infarction were older and were more likely to have a history of significant cardiovascular disease at baseline. Careful monitoring of such subjects, especially during the first 3 months of therapy, for symptoms of dyspnea, angina, excessive weight gain, hemoglobin decrease, and other signs and symptoms of heart failure and/or unstable angina is recommended. Patients who experience concurrent medical illnesses leading to fluid retention and/or anemia should also be closely monitored for signs and symptoms of heart failure and/or angina. Patients who experience signs or symptoms suggestive of heart failure while on atrasentan should be medically evaluated. Interruption of atrasentan may be considered, and appropriate medical management, such as diuretics and/or ACE inhibitors, may be instituted. Changes in the use of other vasoactive drugs should be monitored closely.

Consistent with ET_A receptor blockade, atrasentan may lower blood pressure. In controlled phase 2/3 studies, atrasentan-treated patients experienced small decreases in blood pressure. Within 2 weeks of treatment, the 10-mg dose group experienced a mean systolic blood pressure decreases of 7.21 mm Hg compared with a mean decrease of 1.55 mm Hg for the placebo arm, and a mean diastolic blood pressure decrease of 5.63 mm Hg compared with a mean decrease of 0.92 mm Hg for the placebo arm. The mean decreases from baseline at final visit were slightly greater for both atrasentan (9.23 mm Hg systolic, 7.28 mm Hg diastolic) and placebo treatment (4.16 mm Hg systolic, 2.68 mm Hg diastolic). Subjects who were hypertensive at baseline realized greater reductions in blood pressure than nonhypertensive subjects.

Patients who are on multiple medications with blood pressure–lowering effects, including beta-blockers, diuretics, and nitrates, should be monitored and any dose adjustments of concurrent medications should be made under medical supervision.

5.4 Safety in the Bone Metastatic Population

An analysis of the incidence of adverse events in patients with confirmed baseline bone metastases, the population that derives the greatest clinical benefit from atrasentan therapy, revealed a similar safety profile. The most common adverse events are similar to those observed in the overall population (Table 29).

Table 29. Adverse Events Reported with at Least 10% Incidence: M00-211 Bone Metastatic Population

	Number of Patients (%)[a]			
Category	**Placebo N = 333**		**Atrasentan 10 mg N = 353**	
Overall	325	(97.6%)	349	(98.9%)
Bone pain	209	(62.8%)*	192	(54.4%)
Peripheral edema	38	(11.4%)	141	(39.9%)*
Rhinitis	47	(14.1%)	132	(37.4%)*
Pain	83	(24.9%)	85	(24.1%)
Headache	40	(12.0%)	76	(21.5%)*
Constipation	56	(16.8%)	70	(19.8%)
Asthenia	64	(19.2%)	56	(15.9%)
Nausea	49	(14.7%)	47	(13.3%)
Anemia	30	(9.0%)	47	(13.3%)
Anorexia	46	(13.8%)	44	(12.5%)
Infection	26	(7.8%)	44	(12.5%)
Prostatic carcinoma	51	(15.3%)	43	(12.2%)
Back pain	36	(10.8%)	33	(9.4%)

a Only patients who received study drug are included in these analyses.

* Indicates a statistically significant difference between treatments at $P \leq .05$

The incidence of heart failure, myocardial infarction, dyspnea, and pneumonia in this large group of patients for 10 mg atrasentan was 4.8%, 2.3%, 9.3%, and 3.1%, respectively, compared with 0.9%, 0.6%, 4.8%, and 0.3% for placebo, similar to that observed in the overall population. The difference in the incidence between treatment arms was statistically significant for heart failure, dyspnea, and pneumonia.

5.5 Relevant Laboratory Parameters

Based on laboratory parameters, there is no evidence for an adverse effect with atrasentan on either renal or hepatic function in the phase 2/3 placebo-controlled studies (Table 30).

Table 30. Renal and Hepatic Chemistry: Mean Change from Baseline to Final Value for Phase 2/3 Placebo-Controlled Studies

	Placebo			Any Atrasentan		
Variable	**N**	**Baseline Mean**	**Mean Change from Baseline**	**N**	**Baseline Mean**	**Mean Change from Baseline**
Renal Function						
BUN, mg/dL	538	19.8	1.83	655	19.3	1.66
Creatinine, mg/dL	538	1.0	0.00	654	1.0	0.04
Hepatic Function						
GGT, IU/L	146	47.2	17.27	263	44.8	7.02
LDH, IU/L	535	224.3	56.11	646	201.6	33.05*
AST, IU/L	538	26.6	3.85	654	25.5	1.59*
ALT, IU/L	538	21.3	1.25	654	21.4	–1.12
Total bilirubin, mg/dL	538	0.5	0.00	654	0.5	0.02

* Statistically significantly different from placebo at $P \leq .05$

No significant increase in mean blood urea nitrogen or creatinine was observed in patients receiving atrasentan, and no difference was observed compared with patients receiving placebo. Similarly, no evidence of hepatotoxicity was seen in patients treated with atrasentan. On the contrary, mean increases from baseline to final value in GGT, LDH, AST, and ALT were lower in patients treated with atrasentan compared with those receiving placebo. In addition, there were no differences in the proportion of patients receiving atrasentan or placebo recording a significant increase in any parameter to a

grade 3/4 elevated value, with ≤1% of patients in each treatment group experiencing a grade 3/4 shift for any of the parameters.

5.6 Long-term Safety

The adverse event data from the well-controlled phase 2/3 studies includes substantial experience with long-term exposure, with 214 patients treated with atrasentan for longer than 6 months. An analysis of incidence and prevalence of adverse events over time demonstrated no unexpected drug-related adverse events with long-term exposure. Analyses of additional long-term safety with patients who entered open-label/extension studies include 294 patients treated for longer than 1 year did not identify any unexpected adverse events.

The longer-term safety of 10 mg atrasentan can be evaluated in patients treated in the open label study, M00-258. A total of 570 patients with metastatic HRPC have been enrolled into study M00-258; this includes 254 patients that had received 10 mg atrasentan in the randomized, double-blind, placebo-controlled study, M00-211, and 316 patients previously not exposed to atrasentan (255 from study M00-211 treated with placebo and 61 who entered directly into M00-258 without having been randomized into M00-211).

The data from this open-label study must be understood in the context of the lack of a comparator arm. The most common adverse events reported in study M00-258 were generally the same as those seen with atrasentan in the placebo-controlled study M00-211. No additional safety signals were identified.

5.7 Safety with Concomitant Medications

No safety concerns were identified with atrasentan used in combination with a variety of medications including those most commonly used concomitantly in well-controlled studies of prostate cancer: NSAIDs, LHRH analogs, and opioids.

Four phase 1 pharmacokinetic drug-interaction studies were conducted. The pharmacokinetics of atrasentan were evaluated with a CYP3A inhibitor (ketoconazole) and inducer (rifampin). In addition, the effect of atrasentan on the drug transport of P-glycoprotein (Pgp; fexofenadine was used as a probe Pgp substrate) and the activity of the metabolizing enzyme, CYP3A (midazolam was used as a probe CYP3A substrate) was studied. No drug interaction was identified that warrants dose adjustment.

5.8 Safety in Diverse Populations

In phase 2/3 placebo-controlled studies, analysis of adverse events in patients with various baseline characteristics identified no increased risk for any types of adverse events. Patients with a variety of underlying conditions including hypertension, hepatic impairment, renal impairment, COPD/emphysema, and diabetes did not demonstrate increased incidence of adverse events associated with atrasentan treatment. No dose adjustment is required in subjects with moderate renal or hepatic impairment.

In the phase 2/3 studies, 227/676 patients who were treated with atrasentan (35.6%) had a history of significant cardiac disease (including congestive heart failure, ischemic heart disease [myocardial infarction, coronary artery disease and/or angina], cardiac arrhythmia and /or valvular heart disease). The incidence of both heart failure and myocardial infarction were greater in patients with a history of cardiac disease at baseline, although the vast majority of men with a cardiac history treated with atrasentan did not develop either heart failure or MI. A total of 21/227 (9.2%) of atrasentan-treated patients with a history of cardiac disease had an adverse event of heart failure compared to 7/449 (1.6%) without a history of cardiac disease. Similarly, 7/227 (3.1%) had an adverse event of myocardial infarction compared to 2/449 (0.4%) in patients without a cardiac history. The incidence of other adverse events, including peripheral edema, rhinitis, and headache, was similar in patients who received atrasentan with a cardiac history compared with atrasentan-treated patients without cardiac history. Dyspnea, however, occurred in 37/227 (16.3%) of patients treated with atrasentan with a cardiac history compared with 27/446 (6.0%) of those without a cardiac history. The rates of dyspnea in

the placebo arm for patients with or without a cardiac history were 2.5% and 4.4%, respectively.

These data clearly indicate that patients with a significant history of previous or ongoing cardiac disease are at increased risk for heart failure, dyspnea, and myocardial infarction, but that not all these patients will manifest these adverse events. As with other vasoactive compounds, patients with preexisting cardiac disease who receive atrasentan need to be treated with due caution, in particular, close monitoring for symptoms of heart failure, signs of excessive fluid retention including marked peripheral edema, early rapid weight gain, and anemia. Initiation of appropriate therapy including diuretics may be considered based on clinical judgment.

5.9 Safety Summary

The safety of atrasentan has been tested in 1696 patients in more than 35 studies, from phase 1 studies in healthy volunteers, cancer patients, and special populations, to phase 2/3 studies in metastatic HRPC patients. Long-term safety experience includes data from 214 of these patients who received atrasentan for longer than 6 months in double-blind, placebo-controlled studies and 423 patients who received atrasentan for longer than 6 months in open-label extension studies. The most common adverse events are anticipated based on an understanding of the mechanism of action of atrasentan, and are consistent with those observed with other vasodilatory agents: peripheral edema, rhinitis, and headache. These events were generally mild to moderate and few patients discontinued from the study due to them.

Atrasentan can be administered with other drugs commonly prescribed for prostate cancer patients: LHRH analogs, NSAIDs and opiate analgesics. No dose adjustments are required for patients with moderate hepatic or renal impairment, and laboratory analyses demonstrate that atrasentan causes no hepatic or renal toxicities and no bone marrow suppression.

An increased incidence of heart failure, pneumonia, and myocardial infarction was observed with atrasentan treatment. Heart failure occurs early in the course of therapy and is likely also mechanistically-based. In the elderly population of men with advanced prostate cancer, preexisting cardiac history increases the risk of heart failure, myocardial infarction and possibly dyspnea. As with other vasoactive drugs, patients at increased risk should be monitored closely, and identification of early symptoms and signs of excessive fluid retention early in the course of therapy, with appropriate management based on sound medical judgment, should mitigate most of these events.

For the predominantly elderly population of patients with metastatic HRPC, atrasentan has a manageable safety profile.

6.0 Overall Discussion and Conclusions

Metastatic HRPC is a common, lethal disease with substantial associated morbidity, specifically as a consequence of bone metastases that are the characteristic metastatic lesions occurring in over 85% of patients. Once diagnosed with metastatic hormone-refractory disease, disease progression is typically rapid and most men with metastatic HRPC will likely die within 1 or 2 years in spite of currently available therapies.[7,8] Many of these men will spend their last months being treated for pain with a variety of palliative agents that offer only partial relief. The problem is substantial, with 30,466 men in the United States alone dying from metastatic prostate cancer each year.[1]

Currently the treatment options available for patients with metastatic HRPC include NSAIDs, opioids, systemic radioisotopes, mitoxantrone/prednisone, and localized radiotherapy for palliative relief of pain, as well as zoledronic acid for the prevention of skeletal-related events, many of which are radiographic changes. Unfortunately, once these complications become manifest, the management of affected patients is one of the more arduous challenges facing the physician, the patient, and his caregivers. Response to treatment is inconsistent and variable and the complications of therapy are not inconsequential. Prevention of pain or a delay in the onset of pain and other complications of bone metastases is a fundamental therapeutic goal in the management of

these patients. The only drug proven to increase survival in men with metastatic HRPC is docetaxel in combination with prednisone, which was approved by the FDA for this indication in 2004. Docetaxel is administered intravenously and often results in significant hematologic toxicity, particularly anemia and neutropenia. Importantly, in spite of the proven survival advantage for docetaxel treatment in men with metastatic HRPC, approximately 50% of patients with this disease do not receive cytotoxic chemotherapy of any kind, and of those who do, only 2 out of 3 receive docetaxel.[4] There is, therefore, an indisputable need for additional treatment options for men with metastatic HRPC.

Atrasentan is a novel, once daily orally administered, targeted agent studied for the treatment of metastatic HRPC. Its mechanism of action is to block the interaction of ET-1 with its cognate receptor, ET_A, and substantial preclinical evidence indicates that the ET axis is involved in several oncogenic mechanisms particularly relevant to the interaction between metastatic cancer cells and osteoblasts in the bone microenvironment. Specifically, the axis plays a key role in promoting and driving osteoblastic metastases, thus supporting the examination of atrasentan's therapeutic potential in patients with bone metastases.

Abbott's understanding of the endothelin axis in bone increased after the studies conducted with atrasentan in HRPC were begun. Although the treatment effect of atrasentan on the primary endpoint of disease progression did not reach the .05 level of significance in the intent-to-treat population of the pivotal study M00-211, the overall body of data and the consistency of the treatment effect of atrasentan across endpoints, patient populations, and studies (M00-211 and M96-594), confirm the clinical benefit that atrasentan provides for patients with metastatic HRPC, in particular those with metastatic disease to bone. In these patients, who represent 85% of the total study population, the analysis of the primary endpoint did reach statistical significance.

Several factors need to be considered in evaluating the data of atrasentan in men with metastatic HRPC. Firstly, survival was not the primary endpoint for the studies, and

interpretation of the results is complicated by an extensive crossover of patients onto open label atrasentan treatment upon disease progression or study closure. As a consequence, the mean exposure to study drug in the two treatment arms of the survival analysis of the pivotal M00-211 study is similar (305 days compared with 221 days). It is not surprising therefore that there is no difference in the median survival between the two treatment groups (20.5 and 20.1 months, respectively). Nonetheless, even in the absence of a proven survival advantage, atrasentan provides important clinical benefit.

Secondly, the impact of the scheduled radiographic evaluations which were instituted in an attempt to avoid the potential for PSA to influence the timing of scans was unanticipated and limits the ability to discern the full extent of the treatment benefit with atrasentan on the important, protocol-defined, clinical disease progression events, as the majority of patients discontinued the study as the result of having reached a radiographic endpoint without other evidence of disease progression as defined in the protocol. This notwithstanding, a significant treatment effect on delaying the onset of clinical events of disease progression was observed in the intent-to-treat population where atrasentan reduced the risk of clinical disease progression by 26%. Informative censoring of patients with radiographic changes without clinical disease progression potentially influences this analysis. However the analysis of all patient data through the first scheduled radiographic evaluation demonstrates that the positive effect of atrasentan on clinical disease progression is seen even before the first scan, with a 31% reduction in the risk of clinical disease progression in the intent-to-treat population, mitigating the effect of informative censoring on the time to clinical event analysis.

Furthermore, in the bone metastatic patient population, the treatment effect of atrasentan on the overall primary disease progression endpoint demonstrating a 19% reduction in the risk of disease progression does reach statistical significance. This observation is strong supportive evidence of the beneficial effect of atrasentan and suggests that patients with bone metastases are more likely to derive benefit from atrasentan therapy, which is wholly consistent with the preclinical data.

Additional evidence of the benefit of atrasentan is found in the study-stratified integrated log-rank analysis of disease progression in the intent-to-treat population of the studies M00-211 and M96-594 that demonstrates a 14% reduction in the risk of disease progression.

The clinical benefit of atrasentan is further corroborated by the consistent positive effect of atrasentan on the secondary efficacy variables in the intent-to-treat patient population. Specifically, atrasentan slowed the increase of PSA and bone alkaline phosphatase, both markers of disease burden that have prognostic significance. In addition, the effect of atrasentan on these markers is greater in patients with bone metastases, further supporting the greater benefit observed in these patients.

Importantly, the clinical benefits were not offset by any deterioration in overall quality of life. On the contrary, atrasentan-treated patients experienced significantly less deterioration relative to placebo in validated disease-specific, patient-reported quality of life outcome measures using the FACT-P PCS. In particular, atrasentan-treated patients reported a smaller deterioration in pain-related quality of life scores than those treated with placebo. Significantly fewer atrasentan-treated patients experienced a 50% decline in these scores and a significant delay in the time to this threshold of patient-reported pain scores was observed in patients receiving atrasentan. This positive treatment effect is once again greater in patients with metastatic disease in bone.

In HRPC patients with bone metastases, atrasentan provides these benefits:

- 19% reduction in risk of experiencing disease progression
  - Estimated 25.4% relative difference in progression-free rate at 3 months and 31.1% at 6 months
- 32% reduction in risk of experiencing clinical progression events
- 21% reduction in risk of an adverse event of bone pain
- 36% reduction in risk of experiencing a 50% decline in pain-related quality of life as measured by the FACT-P PCS pain questions

The clinical benefit of atrasentan is enhanced by the fact that it does not require admission to a clinic or hospital for administration, and patients who do not have ready access to specialized oncology centers can be treated with atrasentan. Atrasentan has a manageable safety profile for this progressive disease in this predominantly elderly population of men with metastatic HRPC, and results in no renal or hepatic toxicities and no marrow suppression. The most common adverse effects are associated with the known vasodilatory and fluid retention properties of selective endothelin A receptor antagonists, and are typically low grade and manageable. The most serious adverse event identified is heart failure, which is significant, but also understandable given the fluid retention effects of atrasentan. Incidents of heart failure occurred early in the course of therapy and are recognizable, allowing for appropriate medical management. Patients most at risk are those with preexisting cardiovascular disease, and these patients can be monitored for early signs of fluid retention and symptoms of heart failure, mitigating the risk of developing overt, severe heart failure.

In conclusion, atrasentan provides clinically meaningful benefit for patients with metastatic HRPC in particular by decreasing the risk and delaying the onset of clinical disease progression manifest as severe prostrate cancer-related pain, skeletal-related events, and clinical complications of metastatic disease. Given the relative paucity of treatment options available for these men, specifically non-cytotoxic therapy, atrasentan, if approved, would represent an additional, effective treatment option, particularly for those patients with HRPC metastatic to bone.

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Appendix A

Metastatic Population in Study M00-211

Over 97% of all patients (N = 787) had independently confirmed metastases at baseline in study M00-211. In an analysis of time to disease progression, the hazard ratio in favor of atrasentan was .823 (95% CI = [.701, .966]). In this population, as in the intent-to-treat population, atrasentan showed a stronger effect on delaying time to clinical disease progression (HR = .680, 95% CI = [.503, .918]). Results of all time-to-event analyses showed the beneficial effect of atrasentan therapy in treating patients with metastatic HRPC (Table 31).

Table 31. Summary of Treatment Benefit of Atrasentan for Metastatic Patients

	Number of Events (%)				Relative Difference in Progression-free Rates	
Time to Event	**Placebo**	**10 mg Atrasentan**	**HR**	**95% CI**	**3 Months**	**6 Months**
Disease progression	309/387 (79.8%)	295/400 (73.8%)	.823	.701, .966	19.0%	30.9%
Clinical disease progression	100/387 (25.8%)	74/400 (18.5%)	.680	.503, .918	7.1%	15.2%
50% worsening in pain-related quality of life	110/355 (31.0%)	83/360 (23.1%)	.706	.531, .939	10.3%	17.7%
Opioid initiation	182/354 (51.4%)	151/362 (41.7%)	.759	.612, .942	15.0%	21.8%
Bone pain	216/387 (55.8%)	197/400 (49.3%)	.842	.694, 1.021	15.3%	14.8%

Results of the secondary efficacy analyses showing the benefit of atrasentan in this large population were slightly more marked than what was observed with the intent-to-treat population. Atrasentan significantly slowed the increase of bone alkaline phosphatase and PSA over time, and significantly delayed time to progression for both biomarkers (HR = .533, 95% CI = [.416, .736] for bone alkaline phosphatase and HR = .826, 95% CI = [.686, .994] for PSA). In quality of life analyses, mean changes from baseline were consistently smaller for atrasentan-treated patients than for placebo-treated ones, with a

positive effect of atrasentan on disease-specific quality of life as measured by the FACT-P PCS (*P* = .020).

Appendix B

Evaluable Patient Populations

The M00-211 and M96-594 protocols specified the identification of an evaluable population before the blind break. The patients included in this subpopulation met the requirements of a detailed classification plan and were most strictly representative of the target patient population.

M00-211

In study M00-211, the major reasons for excluding patients were opioid analgesic use within the 6 months preceding study drug initiation, no histological or cytological evidence of prostate cancer, no evidence of distant metastases, and possible androgen-withdrawal effect (Table 32).

Table 32. Number of Patients Not Included in the Evaluable Population in Study M00-211

Reason for exclusion	Number (%) of Patients Not Included[a]		
	Placebo N = 401	Atrasentan N = 408	Total N = 809
Number excluded	73 (18.2%)	66 (16.2%)	139 (17.2%)
No definitive evidence of metastatic HRPC			
No distant metastatic diagnosis based on independent radiological review	14 (3.5%)	8 (2.0%)	22 (2.7%)
No histopathologic or cytologic evidence of PCa	9 (2.2%)	13 (3.2%)	22 (2.7%)
Incomplete evidence of a hormone-refractory state			
Cannot rule out anti-androgen withdrawal effect	13 (3.2%)	9 (2.2%)	22 (2.7%)
Lack of confirmatory evidence of castration	5 (1.2%)	3 (0.7%)	8 (1.0%)
PSA values do not support a hormone-refractory state	4 (1.0%)	4 (1.0%)	8 (1.0%)
No PSA value >5 within the screening period	4 (1.0%)	3 (0.7%)	7 (0.9%)
Insufficient anti-androgen withdrawal	2 (0.5%)	0	2 (0.2%)
Potential use of a confounding medication			
Opioid use as therapy ≤6 months prior to start of study drug	23 (5.7%)	23 (5.6%)	46 (5.7%)
Received exclusionary medication during study drug administration	7 (1.7%)	5 (1.2%)	12 (1.5%)
Study drug duration (never received drug, n = 8; dosed <7 days, n = 1)	5 (1.2%)	4 (1.0%)	9 (1.1%)
Steroid use as cancer therapy within 6 months	2 (0.5%)	2 (0.5%)	4 (0.5%)
Received exclusionary medication within 4 weeks prior to study	1 (0.2%)	1 (0.2%)	2 (0.2%)
Other			
Admission criteria[b]	13 (3.2%)	8 (2.0%)	21 (2.6%)

PCa = prostate cancer

a Patients may have been counted in more than one reason.

b Admission criteria exclusions varied and included Karnofsky score <70, malignancy <5 years prior to study initiation, and prior cytotoxic or radiation therapy.

The difference in time to disease progression was statistically significant in favor of atrasentan in the M00-211 protocol-specified evaluable population ($G^{1,1}$ P = .009),

suggesting that atrasentan may reduce the hazard associated with disease progression by as much as 21% relative to placebo (HR = .794, 95% CI = [.669, .942]).

Atrasentan also showed a favorable effect on slowing the increase of biomarkers and on delaying time to PSA progression (HR = .805, 95% CI = [.660, .982]) and bone alkaline phosphatase progression (HR = .529, 95% CI = [.389, .719]) in the M00-211 evaluable patient population.

M96-594

The number of patients excluded from the evaluable analysis in study M96-594 is shown in Table 33.

Table 33. Number of Patients Not Included in the Evaluable Population in Study M96-594

	Number (%) of Patients Not Included			
Category	**Placebo N = 104**	**2.5 mg Atrasentan N = 95**	**10 mg Atrasentan N = 89**	**Total N = 288**
Number excluded	14 (13.5%)	18 (18.9%)	12 (13.5%)	44 (15.3%)
Pain due to disease at baseline	1 (1.0%)	4 (4.2%)	3 (3.4%)	8 (2.8%)
Hormone manipulation	1 (1.0%)	4 (4.2%)	3 (3.4%)	8 (2.8%)
Confounding medication	2 (1.9%)	0	0	2 (0.7%)
Study drug administration[a]	2 (1.9%)	7 (7.3%)	1 (1.1%)	10 (3.5%)
Admission criteria[b]	8 (7.7%)	3 (3.2%)	5 (5.6%)	16 (5.6%)

a Study drug administration exclusions were for patients whose number of study drug administration days was less than 50% of the total study duration or whose total duration was less than 20 days.

b Admission criteria exclusions varied and included primarily screening testosterone >1.04 nmol/L, prostate cancer not clinically refractory, or PSA <4.9 ng/mL or no evidence of rise.

The analysis of time to disease progression in the M96-594 protocol-defined evaluable population demonstrated a statistically significant delay in time to disease progression in favor of 10 mg atrasentan (HR = .654, 95% CI = [.455, .940], log-rank *P* = .021). The

2.5 mg dose also delayed time to disease progression (HR = .686, 95% CI = [.481, .977], log-rank *P* = .035).

In the evaluable population, results for the longitudinal analyses of biomarkers were similar to those in the intent-to-treat population. Atrasentan significantly delayed both time to PSA progression (HR = .539, 95% CI = [.359, .809]) and time to bone alkaline phosphatase progression (HR = .432, 95% CI = [.223, .837]) compared with placebo.

These results, along with a signal in favor of atrasentan in the intent-to-treat populations of both studies, led to further investigation of the clinical benefit of atrasentan in patients with metastatic HRPC.