**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**

# FDA CLINICAL BRIEFING DOCUMENT FOR THE ONCOLOGIC DRUG ADVISORY COMMITTEE SEPTEMBER 13, 2005 MEETING

| | |
|---|---|
| NDA NUMBER: | **21-491** |
| DRUG NAME: | **Xinlay® (atrasentan)** |
| INDICATION: | **Metastatic Hormone-Refractory Prostate Cancer** |
| APPLICANT: | **Abbott Laboratories** |
| CLINICAL REVIEWER: | **Amna Ibrahim, M.D**. |
| CLINICAL TEAM LEADER: | **John Johnson M.D.** |

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**Executive Summary**

# EXECUTIVE SUMMARY

This briefing document provides the Oncology Drug Advisory Committee (ODAC) with findings from the FDA clinical review of atrasentan. On September 13th 2005, FDA will present their findings to ODAC and seek their advice. Some additional findings may be presented at the meeting because the review of the NDA is ongoing.

Abbott Laboratories has submitted a New Drug Application for the following indication

*XINLAY is indicated for the treatment of men with metastatic hormone-refractory prostate cancer*.

More than half way into the review process, the applicant has changed the patient population to men with confirmed bone metastases.

## Recommendation

Recommendation is deferred pending advice of ODAC. Of particular interest is the issue whether there is convincing evidence of efficacy of atrasentan for this indication, and if the risk-benefit ratio justifies its possible approval.

## Brief Overview of the Clinical Program

This document discusses the FDA's review of the design, efficacy and safety of two randomized studies of atrasentan for men with metastatic, hormone-refractory prostate cancer. One of these studies is a phase III study (M00-211) and the other is a phase II study (M96-54). Although time to disease progression is the primary endpoint for both studies, the two studies differ in the treatment population, design and definition of disease progression. The formulations used in the two studies are not bioequivalent by FDA standards. Furthermore, the design of the phase II study is not acceptable for a registration study. The results of these studies cannot be pooled together. First the design and efficacy results of the phase III study will be presented, followed by the design and conduct issues of the phase II study. The safety of the two trials will be presented in tandem to corroborate the signals observed in the phase III trials.

## Phase III study (M00-211)

Population and Primary endpoint:
The phase III study, M00-211 is a well-designed, prospectively randomized, double blind study in patients with hormone-refractory prostate cancer with rising PSAs. The primary endpoint is time to disease progression defined as time from randomization to first event of disease progression. Disease progression is a composite end point, comprised of radiographic progression, pain (intervention with one of opioid, corticosteroid, radiation, radionuclide therapy

or chemotherapy), events requiring intervention due to metastatic prostate cancer and skeletal event. These events are clinically relevant, except for the definition of pain. Ten of 14 consecutive days requiring oral or transdermal opioids constituted disease progression, but a single injection of opioid (for example, a single injection of Demerol) could define disease progression. Evidence of prostate cancer was required at site of pain. Central review by an independent oncologist blinded to serum PSA values was conducted on patients identified by the investigator as having disease progression by the protocol definition. The time and event of disease progression for primary analysis was identified by this independent reviewer. All imaging studies were read by independent radiologists who were given specific criteria for identifying tumor progression on bone scans and CT scans.

Study Design:
Eight hundred and nine patients without a history prior treatment for prostate cancer were randomized to one of two arms; placebo (N=401) and 10 mg of atrasentan (N=408). The patients ingested the study drug daily until tumor progression, or toxicity. Bone scans were performed at baseline and every 12 weeks to evaluate skeletal metastases. CT scans were performed at baseline to evaluate soft-tissue metastases. If baseline soft-tissue metastases were identified, CT scans were repeated every 12 weeks. PSA was performed every 4 weeks for the first 12 weeks, and then every 12 weeks. Patients who completed the study or who had premature discontinuation had a final assessment visit. Those who completed the study were eligible for participating in other extension studies. Survival follow-up was performed every 3 months. Qol questionnaires were administered, but these were tertiary endpoints without a well-defined pre-specified statistical plan.

Efficacy Analysis:
The phase III study was discontinued early because of futility. The applicant defined a "per-protocol" population prior to breaking the blind. According to the applicant, 17% of patients who violated major enrollment criteria were excluded from this per-protocol population. According to the FDA analysis, 15% violated major enrollment criteria.

The study failed its primary endpoint of intent-to-treat analysis of time to disease progression. It also failed 4 of 5 secondary endpoints which were overall survival, change in bone scan index, time to PSA progression and progression-free survival. The 5$^{th}$ endpoint, mean change in ALP reached statistical significance. However, a mean change of 20 ng/mL has questionable clinical relevance. The study also failed many of its tertiary endpoints. These failed tertiary endpoints were Quality of Life adjusted time to disease progression (QATTP), Karnofsky performance status and mean change from baseline in PSA.

About 75% of patients had any event of disease progression. Of all disease progression events, 75% were radiographic. Twenty percent events were pain-related. Less than 5% each were from events requiring intervention or SREs. Radiographic progressions drove the results of the study.

Six months into the NDA review, the applicant changed the population for consideration of approval to patients with bone metastases at baseline. This population was one of many on which retrospective analysis were performed. It was not protocol-specified in the primary, secondary or

tertiary endpoints. The number of patients in this subgroup changed by 6 patients from the time of submission of NDA in December 2004 to June 2005 because of a change in the definition of this subgroup.

**Figure 1: Time-to-Disease Progression- ITT**

Applicant Analysis

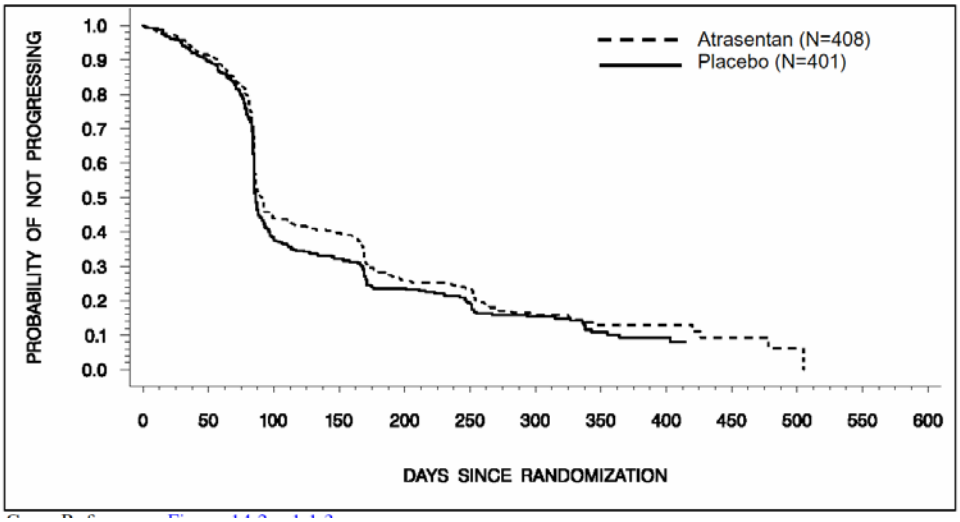



**Table 1: Time to disease Progression- ITT and Two Subpopulations**

Based on Applicant Analyses

| | N | Events | 25th | Median | 75th (95% CI) |
|---|---|---|---|---|---|
| **ITT** | | | | | |
| Placebo | (N=401) | 311(77.6%) | 79 days | 86 days | 171 days (168,246) |
| Atrasentan | (N=408) | 299(73.3%) | 82 days | 91 days | 233 days (173,254) |
| **Per-Protocol** | | | | | |
| Placebo | (N=329) | 271(82.4%) | 79 Days | 85 Days | 169 Days (134,201) |
| Atrasentan | (N=342) | 256(74.9%) | 83 Days | 89 Days | 197 Days (171,261) |
| **Patients with bone metastases at baseline** | | | | | |
| Placebo | (N=332) | 262(78.9%) | 77 Days | 85 Days | 169 Days (144,230) |
| Atrasentan | (N=352) | 259(73.6%) | 83 Days | 92 Days | 237 Days (176,264) |

Confidence intervals calculated by FDA Statistical Reviewer

**Table 2: Analysis of Time to Disease Progression- ITT and Two Subpopulations**

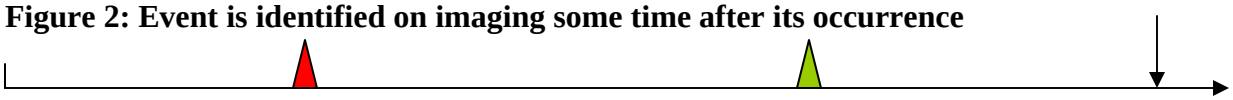
Based on applicant's analyses

| Population | Hazard ratio | 95% CI | Log Rank P value |
|---|---|---|---|
| ITT | 0.885 | 0.755,1.037 | 0.123 |
| Per-Protocol | 0.794 | 0.669, 0.942 | 0.007* |
| Patients with bone metastases at baseline | 0.805 | 0.678, 0.956 | 0.011* |

*No statistical adjustment was made for multiple analyses

The observation of radiographic progression (on imaging) occurs at some time after the actual event of progression. In order for the difference in time to radiographic progression to be reliable, the time to progression should be longer than intervals between imaging. The difference in the time to disease progression in the two arms in this study is too small to be reliable. See table 1 above for differences in time to disease progression in the ITT and two subpopulations.

**Figure 2: Event is identified on imaging some time after its occurrence**



**Randomization** **Event on Arm A** **Event on Arm B** **Imaging study detects event**

- The clinical relevance of the improvement in time to disease progression in any of the given population can be questioned. The difference in time to progression between the two arms is very short. At later time points when the difference appears to be greater, the confidence intervals are wide and overlapping.
- The difference in time to disease progression is too short when compared with intervals between imaging, for detection of any improvement to be reliable.

In addition to the failed results, 15% to 17% major enrollment violations reflect poorly on the conduct of this study. The multiple post hoc analyses performed by the applicant without statistical adjustment should be considered exploratory and hypothesis generating. The results and conduct of phase III study do not provide convincing evidence of efficacy.

**Design and Conduct of the Phase II trial (M96-594)**

The phase II trial was a randomized study in men with hormone refractory prostate cancer. Several major amendments were made over time. Overall design, incorporating all amendments will be described. Two hundred and eighty eight men with rising PSA were enrolled to one of three arms: placebo (n= 104), 2.5 mg of atrasentan (N=95) and 10 mg of atrasentan (N=89). Almost all patients in the phase II study had a history of prior therapies as opposed to the phase III study which specified that no prior therapy other than hormonal therapy should have been administered previously. Patients on the placebo arm were more heavily pretreated than on the atrasentan arms (All prior therapies: 257 on placebo arm, and 214 on atrasentan 10 mg arm; any prior chemotherapy: 25% on placebo arm and 18% on atrasentan 10 mg arm).

The primary endpoint was time to disease progression. Disease progression was a composite endpoint with a definition substantially different from that in the phase III study. Disease progression consisted of intervention for any prostate cancer-related event such as chemotherapy, radiation, surgery and "other" interventions, new bone or visceral pain requiring opioids, new bone or soft –tissue lesions, new symptoms related to tumor growth and other investigator-defined measures of disease progression (PSA rise alone, pain, death, weakness, use of steroids, urinary symptoms and "deterioration". Pain, urinary symptoms, weakness and general deterioration may due to other co-morbid conditions in an elderly population. No duration of opioids was required to define disease progression, and a single dose of opioids could define disease progression. Additionally, no association with evidence of prostate cancer was required at site of pain as in the phase III study. Unlike the phase III study, the results were not based on a blinded, independent review.

Protocol violations in this phase II study were even greater than in the phase III study. An excessive number of protocol violations were observed. According to the applicant's analysis, about 50% patients had protocol violations, which were greater on the atrasentan arms (58% on atrasentan 10 mg, vs. 38% on the placebo arm). Per applicant, less than half (46%) of subjects (132/288) had paired bone scans available for analysis. Less than half patients had paired CT scans available. Radiographic progressions are progression-defining events. In the phase III study, about 75% of the progressions were identified on imaging. The number of missing scans in this phase II study makes disease progression results unreliable.

As with the phase III study, this phase II study failed its primary objective of time to disease progression. This phase II study does not provide substantial evidence of efficacy and is not supportive of approval because of its weak study design, conduct and results.

**Safety:**
Four hundred and four patients who received atrasentan 10 mg were evaluable for safety on the phase III study. The 48 patients on the 10 mg atrasentan arm of the phase II study are not combined with the patients on the phase III study because of questionable bioequivalence of the formulations used. The AUC was the same for formulations in both studies but Cmax was increased in the formulation used in the phase III study. Both AUC and Cmax should be similar for bioequivalence by FDA standards.

In the order of decreasing frequency, the common AE (any grade and greater than 10% in frequency) observed on the phase III study are bone pain, peripheral edema, rhinitis, pain, headache, constipation, asthenia, infection, nausea, anemia, anorexia, back pain and dyspnea. The incidence of pain, bone pain, constipation, nausea, anorexia and asthenia were similar on the atrasentan and placebo arms. In the phase II study the common AEs >10% in frequency are anemia, constipation, anorexia, asthenia, abdominal pain, headache and rhinitis.

Numerically, there were more deaths on the Atrasentan arm (N=166, 41%), compared to the placebo arm (N=158, 39%) on the phase III study. This arm also had more deaths from cardiovascular causes (Atrasentan N=8; placebo N=2). Atrasentan is known to cause CHF from previously performed Phase II trials. In this phase III study an increase in number of arrhythmias

and cardiovascular events (MI, Angina pectoris and stent placements) was observed on the Atrasentan arm in addition to an increase in CHF (atrasentan 40%, placebo 13%). Twenty patients on the Atrasentan arm experienced 24 arrhythmia events, and 5 patients on the placebo arm were reported to have 5 events of arrhythmias. Six patients on the Atrasentan arm had grade 3 or 4 CAD toxicity (MI, angina pectoris or stent placement) as opposed to 2 patients on the placebo arm with grade 3 or 4 toxicity. This finding was also seen in the Phase II study. Ten patients on the atrasentan 10 mg arm and 2 patients on the placebo arm had at least one incidence recorded of CAD. Eleven patients on the atrasentan 10 mg arm and 8 on the placebo arm had arrhythmias.

**Conclusion:** There are some serious cardiovascular safety issues observed in both major randomized trials. Atrasentan does not demonstrate any clear evidence of clinical efficacy in men with hormone refractory prostate cancer in the only major trial of design adequate for a registration study.

# REVIEW OF INDIVIDUAL STUDY REPORTS

Two pivotal trials have been submitted for demonstration of clinical efficacy and safety. They are

- M00-211 (Randomized, double blind, multicenter phase III trial)
- M96-594 (Randomized, double blind, multicenter phase II trial)

These studies have been reviewed in detail below. Although M00-211 (phase III study) design is acceptable as a registration study, M96-594 (phase II study) is not acceptable because of several major design and conduct issues.

**Protocol M00-211**

M00-211 is a well-designed, prospectively randomized, double blind study in patients with hormone-refractory prostate cancer with the primary endpoint of time to disease progression. Disease progression is a composite end point, and for the most part clinically relevant, with some exceptions pointed out later in the review. The applicant employed independent reviewers, and blinded them to PSA values so that bias related to PSA increases may not affect results. This protocol was not reviewed by the FDA prior to the NDA submission.

The DSMB stopped the study early due to futility reasons. Fifteen to 17% of the patients did not meet the enrollment criteria. Atrasentan failed in the primary ITT analysis of time-to-disease progression. Additionally, it failed 4 of 5 secondary endpoints. One of the tertiary analyses on the "per protocol" population and a few other analyses were submitted as a basis for efficacy of atrasentan in this study. At no point in time before breaking blind was the statistical plan adjusted for these analyses. After the submission of the NDA, the treatment population for consideration for labeling purposes was changed to hormone refractory prostate cancer patients with bone metastases at baseline. The population was not pre-specified for primary, secondary or tertiary analyses.

The original protocol and major amendments are given below, mostly verbatim as submitted by the applicant. The amendments are given in italics.

**Title "A Phase III, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of 10 mg Atrasentan in Men with Metastatic, Hormone-Refractory Prostate Cancer"**

Date of Original Protocol: 19 April 2001
Date of Amendment #1: 14 March 2002
Date of Amendment #2: 17 January 2003

**Objectives:**

**"Primary Objective:**
The primary objectives of this study are to evaluate safety and efficacy as measured by time-to-disease progression."

**"Secondary Objective:**
The secondary objectives of this study are to evaluate the effect of 10 mg atrasentan on:

- PSA progression
- Biochemical bone markers
- Bone scan index
- Survival"

"Other objectives include evaluating the effect of 10 mg atrasentan on quality of life and performance status. In addition, population pharmacokinetic analysis will be performed."

**Definitions:**
Disease Progression:
"The primary efficacy assessment of time-to-disease progression will be determined by the time to onset of the earliest of one of the following events:"

- "Pain due to prostate cancer requiring one or more of the following palliative interventions, defined as:
  o opioid therapy:
  – intravenous opioid therapy
  – opioid analgesic use for 10 out of 14 consecutive days
  o glucocorticoid therapy:
  – initiation of > 5 mg oral prednisone (or equivalent) for 10 out of 14 consecutive days (for subjects not currently on oral steroids)
  – doubling of the subject's current chronic steroid therapy for 10 out of 14 consecutive days (for subjects on a stable dose of oral steroids)
  o radionuclide therapy
  o radiation therapy
  o chemotherapy"

"Evidence of disease at the site of pain is required. Pain requiring only non-opioid analgesics will not be considered disease progression."

- "A skeletal related event – a pathologic or vertebral compression fracture not related to trauma, prophylactic radiation or surgery for an impending fracture, or spinal cord compression. Evidence of disease at the site is required."

- "An event due to metastatic prostate cancer requiring intervention, e.g., urinary tract obstruction, malignant pleural effusion, brain metastases, or other similar events. Evidence of disease at the site is required. An increase in PSA is not considered an event of disease progression."

- "One bone scan subsequent to baseline demonstration two or more new skeletal lesions. Refer to Appendix B (of protocol), Bone Scan Lesion Classification Criteria, for specific classification criteria. An increase in size or intensity of known skeletal lesions will not be considered progression."

- "One CT or MRI scan subsequent to baseline demonstrating evidence of extra-skeletal disease progression according to a modified RECIST criteria.
  – an increase in the sum of the longest diameters of target lesions (measuring $\geq$ 2 cm in longest diameter on the baseline scan) by $\geq$ 20% when compared to the smallest sum of the longest diameters of these target lesions

– an increase in size of a solitary sub-target lesion (measuring ≥ 1.5 cm but <2.0 cm in longest diameter on the baseline scan) to > 2.4 cm in longest
– unequivocal progression of existing lesions not identified as target lesions as determined by an independent reviewer
– the appearance of one or more new extra-skeletal lesions (≥ 1.5 cm) in diameter"

"Disease progression will be determined only by comparing images of like imaging technique. All events and date of progression must be reviewed and confirmed by an independent reviewer. These confirmed events and corresponding dates will be used as the primary endpoints."

**Reviewer's comment:**
Bone scans were performed for skeletal lesions. CT scans and MRIs were used to follow non-skeletal lesions. According to the charter, if CT scans or MRIs were negative at baseline, the protocol did not require them to be repeated. Disease progression at a new extra-skeletal site would not be recorded.

**Overall Study Design and Plan:**

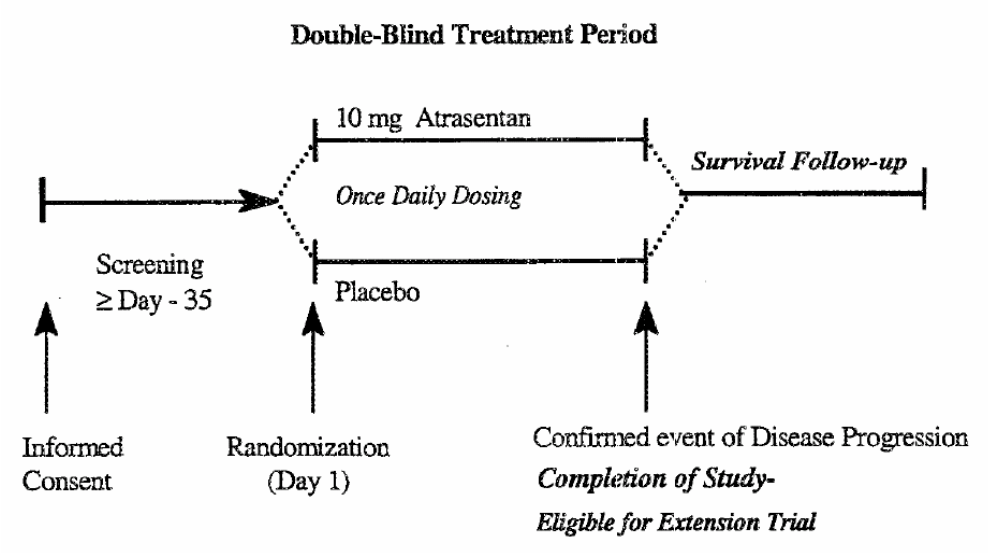
Description

"This is a Phase III, randomized, double-blind, placebo-controlled, multi-center, multi-national study of 10 mg atrasentan. The men participating in this study will have been diagnosed with hormone-refractory prostate cancer that has been treated with surgical and/or chemical castration and is now escaping androgen suppression as demonstrated by a rising PSA. These men must have evidence of distant metastases."

"Approximately 900-1000 male subjects will be enrolled at approximately 200 investigative sites selected by Abbott Laboratories or its designee and will be randomized to receive either atrasentan or placebo. Additional sites and subjects will be added if necessary. Sites will be selected based on their ability to adequately manage study-related requirements and activities, and to enroll eligible subjects."

**Figure 3: A schema of the study design of Protocol M00-211**

Applicant's figure




"During the course of treatment, the subjects will visit the study site on Day 14 and Weeks 4, 8 and 12, and every 6 weeks thereafter. At each visit, subjects will be assessed for safety, clinical evidence of disease progression, and will be dispensed study medication (except Day 14). Every 12 weeks, subjects will be evaluated for disease progression by radiographic imaging. If a subject experiences symptoms suspected to be related to disease progression, an appropriate radiographic study may be performed prior to the scheduled every 12 week radiographic study.

A subject will be considered to have completed the study if he has experienced an event of disease progression that has been confirmed by an independent reviewer or is active in the trial when the double-blind treatment period ends. Subjects who do not complete the study will be classified as having prematurely discontinued from the study and will not be eligible to participate in the extension study. Subjects will have a final assessment (Final Visit) upon study completion or premature discontinuation from the study. Subjects who complete the study will be eligible to participate in an open-label extension study."

"The double-blind treatment period for this study will end when 650 subjects have experienced confirmed events of disease progression."

Discontinuation from Study Drug Treatment:

"Subjects who elect to discontinue study drug prior to having an event of disease progression will remain in the study following a similar schedule of assessments, regardless of subsequent therapies, in order to access subjects for disease progression."

Safety Follow-up:

"Subjects who do not enter the extension study will return for a safety evaluation 30 days after their Final Visit."

Survival Follow-up:

"Subjects will be assessed for post-treatment survival at 3-month intervals after the last study visit."

**Enrollment Criteria**

**Inclusion Criteria**

1. Prior to the performance of any study specific procedure, the subject or his legal representative has signed and dated an informed consent form, approved by an Independent Ethics Committee (IEC) or Institutional Review Board (IRB), after the nature of the study has been explained and the subject or subject's legally authorized representative has had the opportunity to ask questions.

2. Subject is ≥ 19 years of age.

3. Subject has histologically documented diagnosis of prostate adenocarcinorna (PCa).

4. Subject was surgically castrated at least 3 months prior to Screening or has been pharmacologically castrated for a minimum of 3 months prior to Screening. Castration must be verified by a screening testosterone value of < 50 ng/dL (1.73 nm/UL). Any subject pharmacologically castrated must be maintained on androgen suppression therapy for the duration of the study.

5. Subject must meet one of the following PSA criteria:

   a. A PSA level of ≥ 20 ng/ml that is verified by the central laboratory screening PSA level of ≥ 20 ng/ml.

   b. A rising PSA defined by two sequential increases in PSA values. The following data are required: an initial value (#1) followed by a PSA value demonstrating an increase (#2). The increase must be confirmed by another rise in PSA (#3) (3 >2 >1). All measures must be a minimum of 2 weeks apart and obtained within 20 weeks prior to randomization. The central laboratory screening PSA value must be ≥ 5.0 ng/mL (pg/L) but cannot serve as one of the required qualifying measurements.

   Note: For a subject who has withdrawn from anti-androgen therapy, one post-withdrawal measurement must be higher than the last pre-withdrawal measurement. If the subject's

PSA decreased after anti-androgen withdrawal then he can still qualify if two increases (as described in b above) are documented after the post-withdrawal nadir.

*[Criteria # 5 was changed in amendment #1 to following:*
*Subject must meet one of the following PSA criteria:*

*a. A PSA value of ≥ 20 ng/ml (μg/L) obtained within 12 months prior to randomization. The PSA value of ≥ 20 ng/mL (μ/L) must be confirmed by the central laboratory during the 35-day screening period,* ***OR***
*b. A 50% rise in PSA va1ues within 6 months prior to randomization. A central laboratory screening value > 5.0 ng/mL (μg/L) is also required and cannot serve as one of the values necessary to demonstrate the 50% rise,* ***OR***
*c. A rising PSA defined by two sequential increases in PSA values. The following data are required: an initial value (#1) followed by a PSA value demonstrating an increase (#2). The increase must be confirmed by another rise in PSA (#3) (3 >2 >1). All measures must be obtained within 12 months prior to randomization. There must be at least 2 weeks between each qualifying PSA value. A central laboratory screening PSA of ≥ 5 mg/mL (μg/L) is required and this screening value cannot be used as one of the 3 required qualifying PSA values.]*

6. Subject who has received anti-androgen therapy must have a documented withdrawal period prior to randomization: flutamide requires a minimum 4 weeks withdrawal, and nilutamide and bicalutamide require a minimum 6 weeks withdrawal.

*[Following was added to Criteria # 6 in amendment #1 to:*
*For a subject who has withdrawn from anti-androgen therapy LESS than 6 months prior to randomization, one of the following criteria is ALSO required for eligibility:*

*a. Following the completion of the anti-androgen wit4drawal period, one post-withdrawal PSA value must be higher than the last pre-withdrawal PSA value,* ***OR***
*b. Following the completion of the anti-androgen withdrawal period, if the subject's PSA value decreased, then he can still qualify if two increases in PSA values (as described in 5c above) are documented after post-withdrawal nadir.*]

7. Subject has evidence of distant metastases as verified by screening bone scan or CT scan (a MRI scan maybe substituted for a CT scan as described in Section 5.7.4).

*[section 5.7.4 Confirmation of Disease Progression*
*Upon determination by the investigator that a potential event of disease progression has occurred, supporting data will be sent, per the instruction provided in the Disease Progression Packet, to an independent reviewer who will document whether a study- defined event of disease progression has been reached. The primary efficacy analysis will be based on the date of disease progression as determined by an independent reviewer. The independent reviewer will determine the date of progression based on data presented for review for the event of disease progression. A manual instructing the site on the process for confirming an event of disease progression will be supplied by Abbott Laboratories or their designee. There will be no direct communication*

*between the site and the independent reviewer. Abbott Laboratories or their designee will act as an intermediary between the site and the independent reviewer.]*

- To qualify as skeletal metastases, bone scan lesions must meet criteria described in Appendix B, Bone Scan Lesion Classification Criteria. As detailed on these criteria, some findings may require further study to ensure they are consistent with metastatic disease.

*[Appendix B Bone Scan Lesion Classification Criteria*

*Consistent with Metastatic Disease: The following findings on bone scan will be considered evidence of metastatic disease.*

- *Fusiform/expansile lesion (expansile=beyond boundaries of bone) in the ribs.*
- *Uptake involving a large segment of a rib.*
- *Hot spot in the pelvis not consistent with Paget's disease. Focus of uptake in the scapula (except at acromioclavicular joint).*

*Not Consistent with Metastatic Disease: The following findings on bone scan will not be considered evidence of metastatic disease.*

- *Focus of uptake in the anterior rib/costochondral junction.*
- *Focal spot in location consistent with benign condition (specially in the extremities distal to the mid-humerus and mid-femur). e Hot spot in the pelvis consistent with Paget's disease.*

*Require Further Study: The following findings on bone scan are likely due to another etiology but further study (x-ray, CT, cm be utilized. To meet inclusion criteria in M00-211 or to qualify for radiographic progression these lesions require further study to confirm that the etiology is metastatic prostate cancer.*

- *Focus of uptake in the spine.*
- *Hot spot in the skull.*
- *Foci of uptake consistent with stress fractures*
- *Single hot spot in proximal femur or proximal humerus.*
- *Focus of uptake in the sternum (except at sternoclavicular joint and costo-sternal junctions) - CT acquisition preferred.*
- *Hot spot in the clavicle (except at sterno and acromio-clavicular joints)]*

- To qualify as extra-skeletal metastases, CT/MRI lesions must be at least 1.5 cm. in longest diameter. Regional lymph node disease (pelvic, hypogastric, obturator, iliac, periprostatic, sacral) is considered local disease and does not define distant metastases.

8. Subject has had no other malignancies within the previous 5 years with the exception of non-melanoma skin cancer.

9. Subject has a score >70 on the Karnofsky Performance Scale (see Appendix H).

10. Subject has, in the opinion of the investigator, a life expectancy greater than 6 months.

11. Subject has adequate hematologic function defined as:

- A white blood cell count $\geq$3.0 x $10^9$/L (3000/$mm^3$),
- An absolute neutrophil count >1.5 x $10^9$/L (1500/$mm^3$).
- A platelet count $\geq$100 x $10^9$/L (100,000/$mm^3$)
- A hemoglobin concentration $\geq$11 g/dL (6.8 mmol/L).

12. Subject has adequate liver function defined as:

- Total bilirubin <25.65 μmol/L (1.5 mg/dL).
- AST and ALT $\leq$1.5 times the upper limit of normal.

13. Subject has a creatinine clearance $\geq$40 mL/min (ns calculated by the central laboratory using a. serum creatinine value and the Cockcroft and Gault formula),

14. Subject agrees to use a latex condom during and for 8 weeks after his last dose of study medication. If his partner is fertile, another effective contraceptive method (e.g,, birth control pill, vasectomy) must be used during and for 8 weeks after his last dose of study medication.

15. Subject understands that an increase in PSA is not considered disease progression and that discontinuing the trial due to a rise in PSA will make him ineligible for the open-label extension trial.

**Exclusion Criteria**
A subject will be ineligible for study participation if any of the following criteria are met:

1. Subject has a PSA value < 5.0 ng/ (μ/L) at screening as calculated by the central laboratory.

2. Subject has previously received palliative therapy for metastatic, hormone-refractory PCa, e.g., opioid analgesics, radiation therapy, steroids, radionuclides (such as rhenium, strontium, or sumarium), or cytotoxic chemotherapy. However, radiation therapy, brachytherapy or cryotherapy as primary prostate cancer therapy is allowed.

*[In amendment #1, this was changed to:*
*2a. Subjects having previously received therapy [including radiation, steroids, radionuclides (such as rhenium, strontium, or samarium), cryotherapy or cytotoxic chemotherapy] for prostate cancer are ineligible as defined below:*

- *Subjects who received previous cytotoxic chemotherapy or radionuclide therapies are ineligible.*
- *Subjects who received therapy to the prostatic bed (external beam radiotherapy, brachytherapy or cryotherapy) within 6 months prior to randomization are ineligible.*

- *Subjects who received radiation therapy to any lesion outside the prostatic bed more than 6 months after castration or hormone initiation are ineligible.*

*NOTE: Subjects who received intermittent hormonal therapy are considered to have initiated hormone therapy with the first course of treatment.*

*Subjects who received steroids for the treatment of prostate cancer within 6 months prior to randomization are ineligible.*

*NOTE: Subjects who received low dose steroid in conjunction with ketoconazole are eligible.*

*2b. Subjects have received opioid analgesic therapy as defined below:*

- *Subjects who received opioid analgesic therapy for prostate cancer within 6 months prior to randomization are ineligible.*
- *Subjects who received opioid analgesic therapy for a concurrent condition not related to hormone refractory prostate cancer may qualify if taking a low dosage (< 1-2 doses per week). These subjects MUST be discussed on a case- by-case basis with the Abbott medical monitor.]*

3. Subject has received any of the following within 4 weeks of randomization:

- cyproterone acetate, ketoconazole, finasteride, PC-SPES, or other hormonally active therapies (with the exception of GnRH agonists or antagonists).
- intravenous or oral bisphosphonates, e.g., Aredia., Fosamax, Ostac.
- an investigational product.

4. Subject has a known history of cardiovascular disability status of New York Heart Association Class $\geq$2. Class 2 is defined as cardiac disease in which patients are comfortable at rest but ordinary physical activity results in fatigue, palpitations, dyspnea or anginal pain.

5. Subject with significant pulmonary disease has received chronic or pulse steroid therapy within the last 3 months prior to randomization. Steroid therapy for non-pulmonary, non-oncologic conditions is allowed if subject has been on a chronic, steady-dose regimen for a minimum of 2 months prior to randomization.

6. Subject is receiving antiretroviral therapy for HIV.

7. Subject has received previous or current treatment with an endothelin antagonist.

8. Subject has received a blood transfusion within 8 weeks of randomization.

9. Subject has known central nervous system metastases.

10. Subject has a clinically significant, unstable, uncontrolled disease that could be adversely affected by study population.

11. Subject is, in the opinion of the investigator, unable to comply with the requirements of the study protocol or is unsuitable for the study for any reason.

**Prior and Concomitant Medications**

For each subject who is randomized into the study, any medication, including over-the- counter medicines, e.g., aspirin, antacids, vitamins, mineral supplements or herbal therapies taken within 4 weeks prior to randomization or received during the study, must be recorded on the appropriate CRF along with the date(s) of administration, reason for use, dosage, and frequency. Each vaccine administered to the subject should be listed as a concurrent medication.

Anti-cancer therapy with steroids, chemotherapy, radiation therapy, or other agents must not be received during treatment with study drug.

Hormonal treatment, e.g., LHRH agonist, GnRH agonist/antagonist, that is required to suppress serum testosterone level to < 50 ng/ (1.73 nmol/L) must be continued throughout the study period.

Subjects may not initiate chronic steroid therapy, bisphosphonates, or other investigational agents during treatment with study drug.

## Study Visits and Procedures

## Table 3: Schedule of Assessments in original protocol

Applicant table 5.3.a of Original Protocol

| | Screening Period | Double-Blind Treatment Period | | | | | | | | Survival Follow-Up |
|---|---|---|---|---|---|---|---|---|---|---|
| Procedure | ≥ Day -35 | Day 1 | Day 14 | Week 4 | Week 8 | Week 12 and every 12 weeks (24, 36, 48, etc) | Week 18 and every 12 weeks (30, 42, etc) | Final Visit | Safety[1] Follow-Up | Every 3 Months |
| Clinic visits | X | X | X | X | X | X | X | X | X | |
| Informed consent | X | | | | | | | | | |
| Medical/Oncological history | X | | | | | | | | | |
| Physical examination | X | X | X | X | X | X | X | X | X | |
| 12-lead ECG | X | | | | | | | | | |
| Randomize subject | | X | | | | | | | | |
| Testosterone | X | | | | | | | | | |
| Vital signs, including weight, height, and temperature.[2] | X | X | X | X | X | X | X | X | X | |
| Chemistry | X | X | X | X | X | X | | X | X | |
| Hematology | X | X | X | X | X | X | | X | X | |
| Coagulation | X | | | X | | | | X | | |
| Urinalysis | X | | | X | | X | | X | | |
| PSA | X | X | | X | X | X | | X | X | |
| Bone Markers | | X | | X | X | X | | X | X | |
| Plasma for atrasentan assay (trough level) | | | | X | | X (Wk 12 only) | | | | |
| Bone Scan | X | | | | | X | | X[3] | | |
| CT Scan (Chest, Abdomen & Pelvis)/MRI Scan | X | | | | | X[4] | | X[3,4] | | |
| Performance Status (Karnofsky) | X | X | X | X | X | X | X | X | X | |
| QoL (FACT-P and EORTC QLQ C-30) | | X | | X | | X | | X | X[5] | |
| Disease Progression Assessment | | | X | X | X | X | X | X | X[6] | |
| Subject Diary Assessment | | X | X | X | X | X | X | X | X[6] | |
| Adverse Event Assessment | | X | X | X | X | X | X | X | X | |
| Prior and Concomitant Medications Assessment | X | X | X | X | X | X | X | X | X | |
| Collect unused study drug | | | | X | X | X | X | X | | |
| Dispense study drug | | X | | X | X | X | X | | | |
| Survival Assessment | | | | | | | | | | X |

[1] Subjects who enroll in the extension study do not require a Safety Follow-Up visit.

[2] Height and temperature on Day 1 only.

[3] If a bone, CT or MRI scan is conducted within 6 weeks prior to the Final Visit, then a similar Final Visit scan is not required.

[4] If extra-skeletal disease is documented at baseline on CT or MRI scan (per Section 5.2.1, *Inclusion Criteria*).

[5] All subjects must complete the QoL questionnaires. Subjects enrolling in the extension study must still complete the QoL questionnaires within 30 days of their Final Visit in M00-211.

[6] Required for subjects who have not experienced a confirmed event of disease progression.

The schedule of assessment was changed to below per amendment #1

**Table 4: Schedule of Assessments after amendment #1**

| | Screening Period | Double-Blind Treatment Period | | | | | | | | Survival Follow-Up |
|---|---|---|---|---|---|---|---|---|---|---|
| Procedure[1] | ≥ Day -35 | Day 1 | Day 14 | Week 4 | Week 8 | Week 12 and every 12 weeks (24, 36, 48, etc) | Week 18 and every 12 weeks (30, 42, etc) | Final Visit | Safety[2] Follow-Up | Every 3 Months |
| Clinic visits | X | X | X | X | X | X | X | X | X | |
| Medical/Oncological history | X | | | | | | | | | |
| Physical examination | X | X | X | X | X | X | X | X | X | |
| 12-lead ECG | X | | | | | | | | | |
| Randomize subject | | X[3] | | | | | | | | |
| Testosterone | X | | | | | | | | | |
| Vital signs, including weight, height, and temperature.[4] | X | X | X | X | X | X | X | X | X | |
| Chemistry | X | X | X | X | X | X | | X | X | |
| Hematology | X | X | X | X | X | X | | X | X | |
| Coagulation | X | | | X | | | | X | | |
| Urinalysis | X | | | X | | X | | X | | |
| PSA | X | X | | X | X | X | | X | X | |
| Bone Markers | | X | | X | X | X | | X | X | |
| Plasma for atrasentan assay (trough level) | | | | X | | X (Wk 12 only) | | | | |
| Bone Scan | X[3] | | | | | X | | X[5] | | |
| CT Scan (Chest, Abdomen & Pelvis)/MRI Scan | X[3] | | | | | X[6] | | X[5,6] | | |
| Performance Status (Karnofsky) | X | X | X | X | X | X | X | X | X | |
| QoL (FACT-P and EORTC QLQ C-30) | | X | | X | | X | | X | X[7] | |
| Disease Progression Assessment | | | X | X | X | X | X | X | X[8] | |
| Dispense Diaries | | X | X | X | X | X | X | | | |
| Subject Diary Assessment | | | X | X | X | X | X | X | X[8] | |
| Adverse Event Assessment | | X | X | X | X | X | X | X | X | |
| Prior and Concomitant Medications Assessment | X | X | X | X | X | X | X | X | X | |
| Collect unused study drug | | | | X | X | X | X | X | | |
| Dispense study drug | | X | | X | X | X | X | | | |
| Survival Assessment | | | | | | | | | | X |

1 An M00-211 Informed Consent must be signed and dated prior to conducting any study related procedures.
2 Subjects who enroll in the extension study do not require a Safety Follow-Up visit.
3 Prior to randomization on Day 1, sites MUST receive written confirmation from WorldCare Clinical Inc. that baseline scans were technically adequate.
4 Height and temperature on Day 1 only.
5 If a bone, CT or MRI scan is conducted within 6 weeks prior to the Final Visit, then a similar Final Visit scan is not required.
6 If extra-skeletal disease is documented at baseline on CT or MRI scan (per Section 5.2.1, *Inclusion Criteria*).
7 All subjects must complete the QoL questionnaires. Subjects enrolling in the extension study must still complete the QoL questionnaires within 30 days of their Final Visit in M00-211.
8 Required for subjects who have not experienced a confirmed event of disease progression.

**Table 5: Schedule of Assessments – Following Discontinuation of Study Drug**

Applicant table 5.5.a of original protocol

| Procedure | Disease Progression Follow-Up Period | | | Safety[2] Follow-Up | Survival Follow-Up |
|---|---|---|---|---|---|
| | Drug Cessation Visit | Regularly Scheduled Visit[1] | Final Visit | | Every 3 Months |
| Clinic visits | X | X | X | X | |
| Physical examination | X | X | X | X | |
| Vital signs, including weight | X | X | X | X | |
| Chemistry | X | X[3] | X | X | |
| Hematology | X | X[3] | X | X | |
| Coagulation | X | | X | | |
| Urinalysis | X | | X | | |
| PSA | X | X (q 12 Wks) | X | X | |
| Bone Markers | X | X (q 12 Wks) | X | X | |
| Bone Scan | X[4] | X (q 12 Wks) | X[5] | | |
| CT Scan (Chest, Abdomen & Pelvis)/MRI Scan | X[4,6] | X[6] (q 12 Wks) | X[5,6] | | |
| Performance Status (Karnofsky) | X | X | X | X | |
| QoL (FACT-P and EORTC QLQ C-30) | X | X (q 12 weeks) | X | X | |
| Disease Progression Assessment | X | X | X | X[7] | |
| Subject Diary Assessment | X | X | X | X[7] | X |
| Adverse Event Assessment | X | X | X | X | |
| Prior and Concomitant Medications Assessment | X | X | X | X | |
| Collect unused study drug | X | | | | |
| Survival Assessment | | | | | X |

1 Subjects should maintain their regularly scheduled visit based on their enrollment date. If the next visit is scheduled to occur within 2 weeks of the Drug Cessation Visit, that visit should be skipped and the subject should return for the following scheduled visit.

2 Subjects who enroll in the extension study do not require a Safety Follow-Up visit.

3 Only required at the first visit following the Drug Cessation Visit.

4 If a bone, CT or MRI scan is conducted within 6 weeks prior to the Drug Cessation Visit, then a Drug Cessation Visit scan is not required.

5 If a bone, CT or MRI scan is conducted within 6 weeks prior to the Final Visit, then a Final Visit scan is not required.

6 If extra-skeletal disease is documented at baseline on CT or MRI scan (per Section 5.2.1, *Inclusion Criteria*).

7 Required for subjects who have not experienced a confirmed event of disease progression.

CT/MRI Scan

A CT scan with contrast of the chest, abdomen and pelvis will be performed. If a CT scan cannot be performed for medical reasons, a MRI scan will be accepted. If an extra- skeletal lesion (≥1.5 cm, unidimensional) is documented via CT or MRI scan at Screening, subsequent, like CT/MRI scans will additionally be performed during the study. Only the same type scan will be used for purposes of documenting disease progression. Unscheduled scans performed during the study will be collected. All scan imaging reports will be collected.

The Central Imaging Center, Perceptives Informatics, will qualitatively review all baseline CT/MRI scans to ensure they arc adequate to serve as baseline images. Sites will be notified in the event the images cannot be used for a baseline scan. In such cases, a new image will need to be obtained prior to subject randomization. If a subject has already been randomized, a replacement image must be obtained within 2 weeks of study drug initiation.

All CT/MRI scans will be sent to a Central Imaging Center within two days of collection. Specific instructions for preparation of images and shipment will be provided by the Central Imaging Center.

Bone Scan

A whole body bone scan will be performed. Unscheduled scans performed during the study will be collected. All scan imaging reports will be collected. All bone scans will be sent to the Central Imaging Center within two days of co].lection. Specific instructions for preparation of images and shipment will be provided by the Central Imaging Center.

Quality of Life (QoL) Assessment

The subject's QoL will be assessed through the Functional Assessment of Cancer Therapy for Subjects with PCa (FACT-P) questionnaire (Appendix F of protocol) and the EGRTC QLQ C-30 (Appendix J of Protocol). The QoL assessment must be completed 30 days after the Final Visit. Subjects who enroll in the extension trial must also complete the QoL assessment 30 days after their Final Visit.

The subject may complete these questionnaires directly on the CRFs containing them. Site personnel will need to check the form returned by the subject for completeness before the subject leaves the clinic.

Disease Progression Assessment

The investigator will assess the subject for evidence of disease progression. This assessment should include, but is not limited to potential pain at a metastatic site, other cancer-related symptoms any review of any scan data. Once the investigator determines a potential event of disease progression has occurred a Disease Progression Packet must be completed and submitted

with supporting documents as instructed in the Disease Progression Manual. Subjects should continue dosing until confirmation from an independent reviewer has been received indicating that an event of disease progression has occurred. Confirmation should be provided to the investigator within 14 days of receipt of a complete Disease Progression Packet.

Extension Study

Any subject who has a confirmed event of disease progression as determined by an independent reviewer will be eligible to participate in an open label extension study. When the double-blind treatment period of this study ends, the blind will be broken and all remaining active subjects will be eligible to participate in the extension study.

Method of Assigning Subjects to Treatment Groups

All subjects will be randomized using an Interactivc Voice Response System supplied by ClinPhone, Inc. Before the study is initiated, the telephone number and call-in directions for the IVRS will be provided to each investigational site.

The investigational site will contact the IVRS on the subject's study Day 1 and a unique 4-digit randomization or subject number will be provided. The subject numbers will assign subjects to either 10 mg atrasentan or placebo via a. randomization schedule. Randomization will be equally balanced between treatment groups within each participating site. Subject number randomization schedules will be generated for each site. In addition to subject number randomization, a bottle number randomization will be generated in a similar fashion to that of subject numbers except that the bottle number randomization will be done centrally, instead of for each site, These randomization schedules will be computer generated by the Clinical Statistics Department nt Abbott oratories, Abbott Park, IL prior to the start of the study. A copy of all randomization schedules will be kept by the Clinical Statistics Department at Abbott Laboratories and a copy will be forwarded to a ClinPhone, Inc.

Independent Data Monitoring Committee (IDMC)

An IDMC will review and interpret safety and efficacy data from the study on a regular basis. The IDMC membership and responsibilities wil1 be documented in a charter that will be prepared and forwarded to the sponsor before data is released to the IDMC. The IDMC will receive interim summaries, divided by treatment group, that include enrollment characteristics, safety and efficacy. After each review, the IDMC will communicate its recommendations to Abbott Laboratories on continuing, modifying, or terminating the study. Abbott clinical and statistical personnel directly responsible for the conduct of the study will not have access to either the treatment codes or interim summaries prepared for the IDMC,

Interim statistical analyses and summaries for presentation to the IDMC will be prepared by an independent CRG. Requests for additional analyses by the IDMC will be directed to the CRO. A minimum number of Abbott personnel will be designated access to the treatment codes in the event that the CRO or lDMC requests Abbott assistance. These individuals will otherwise not be involved in any decisions regarding the conduct or primary statistical analyses for this study.

## Statistical Methods

Determination of Sample Size

The population targeted in M00-211 is similar to the population in M96-594. Simulations based on the M96-594 study were performed in order to determine the power for the primary analysis at the two-sided 0.05 level of significance. The simulations indicate that 650 events of disease progression yield approximately 90% power. It is anticipated that between 900 and 1000 subjects will need to be enrolled in order to achieve 650 events of disease progression.

Statistical and Analytical Plans

Unless otherwise noted, for all statistical analyses, statistical significance will be determined by a two-sided p-value $\leq 0.05$. The date of randomization for a subject is defined as the date the subject was first dispensed study medication. All statistical analyses will include only subjects that were randomized. Subjects who were assigned a subject randomization number through S but were not dispensed study medication, will not be considered to have been randomized.

Primary Efficacy Endpoint

The primary efficacy analysis will be a comparison of the time to disease progression distributions between the 10 mg atrasentan and placebo treatment groups using the weighted log rank statistic, G, developed by Fleming et. al..

Secondary Efficacy Endpoints

Secondary efficacy analyses comparing the effects of 10 mg atrasentan versus placebo on the following set of endpoints will also be performed: mean change from 4aseline to final value in bone alkaline phosphatase, time to onset of PSA progression, mean rate of change from baseline to final value in total bone scan index, and survival.

Tertiary Efficacy Endpoints

In addition to the primary and secondary efficacy analyses, tertiary efficacy analyses comparing the effects of 10 mg atrasentan versus placebo on the following set of endpoints will be performed: time to disease progression, progression-free survival, survival, Quality of Life (QoL) adjusted time to disease progression, time to onset of PSA progression, time to onset of bone alkaline phosphatase progression, and changes and/or percent changes from baseline in PSA, bone markers, Karnofsky performance status, FACT-P (by domain), and EORTC QLQ-C30 (by domain).

Timing of Efficacy Analyses and Safety Evaluations

Following the collection and adjudication of all data for all randomized subjects up to and including the date of the 650 confirmed event of disease progression, the study blind will be broken. The date of the 650 confirmed event of disease progression will be the primary data "cutoff" date used for all statistical analyses.

The date the study blind is broken may be used as a secondary cutoff date for additional analyses, following the collection and adjudication of data for all randomized subjects through this date.

After all subjects have been followed for survival (have either died or become lost to follow-up), a "Final Survival Analysis" will be performed. This analysis will not use a data cutoff date.

**Statistical Analyses of Efficacy**

Primary Analysis of Efficacy

For or a given subject, time to disease progression will be defined as the number of days from the day the subject was randomized to the day the subject experiences a confirmed event of disease progression. All events of disease progression, as confirmed by the independent reviewer, will be included, regardless of whether the event occurred while the subject was still taking study drug or had previously discontinued study drug. If the subject does not have a confirmed event of disease progression, the subject's data will be censored at the date of the subject's last available evaluation. This date will be the date of the last available vital sign measurement, performance status assessment, or physical exam. An exception to this rule may occur if the subject has an unconfirmed event of disease progression (Disease Progression Packet submitted but an event of disease progression was not confirmed by independent reviewer). In this case, the last available date of evaluation will be the date of disease progression determined by the investigator for the unconfirmed event or the date of the last available vital sign measurement, performance status assessment, or physical exam, whichever is last.

The distribution of time to disease progression will be estimated for each treatment group using Kaplan-Meier methodology. A weighted log rank statistic will be used to test the null hypothesis that the distribution of the time to disease progression for the placebo and the 10 mg atrasentan treatment groups are the same. The weighted log rank test statistic, G, is a member of the class of weighted log rank statistics, G. The G class of statistics also includes the standard log rank (G) and Prentice-Wilcoxon (G1) statistics,

Secondary Analyses of Efficacy

If the primary efficacy analysis (time to disease progression using the G test) is statistically significant at the ($\alpha$=0.05 Level, then p-values for the second analyses will be subject to multiple comparison adjustments using the step-down rule, with analyses performed in the following order: (1) mean change from baseline to formal value in bone alkaline phosphatase, (2} time to

onset of PSA progression, (3) mean rate of change from baseline to final value in total bone scan index, and (4) survival. If any of these secondary analyses does not achieve statistical significance at the $\alpha$=0.05 level, then statistical significance will not be declared for the subsequent secondary analyses, regardless of the observed p-values. If the primary efficacy analysis is not statistically significant at the $\alpha$=0.05 level then statistical significance will not be declared for any of these secondary analyses, regardless of the observed p values.

Survival

Time to death for a given subject will be defined as the number of days from the day the subject was randomized to the date of the subject's death. All events of death will be included, regardless of whether the event occurred while the subject was still taking study drug, or r the subject discontinued study drug. If a subject has not died, then his data will be censored according to the following rule: if the subject was lost to follow-up, then data will be censored at the last study visit, or the last contact date, or the date the subject was last known to be alive, whichever is last; if the subject was not lost to follow-up, then data will be censored at the last study visit or the last contact date, whichever is last. The date the subject was last known to be alive and the last contact date will be collected via the VFRS survival follow-up assessment. The date of the last study visit will be determined by selecting the last available of the following study procedures for a subject: physical examination, vital signs assessment, blood chemistry and hematology collection, urinalysis and coagulant collection, PSA and bone marker collection, bone scan, CT scan, Karnofsky performance status, and QoL questionnaire completion.

The distribution of the time to death will be estimated for each treatment group using Kaplan-Meier methodology. The G test will be used to compare the time to death between 10 mg atrasentan and placebo.

Tertiary Analyses of Efficacy

In addition to the primary and secondary efficacy analyses, tertiary efficacy analyses comparing the effects of 10 mg atrasentan versus placebo on the following set of endpoints will be performed: time to disease progression, progression-free survival, survival, Quality of Life (QoL) adjusted time to disease progression, time to onset of PSA progression, Time to onset of bone alkaline phosphatase progression, and changes and/or percent changes from baseline in PSA, hone markers, Karnofsky performance status, FACT-P (by domain), and EORTC QLQ-C30 (by domain). Details describing the methodology to be used for these analyses are found in Appendix K of protocol.

Evaluable Subject Analyses

Prior to breaking the blind for this study, all randomized subjects will be classified by members of the Abbott medical team as to whether they met all of the inclusion and none of the exclusion criteria, as listed in Sections 5.2 1 and 5.2.2 of the protocol. Subjects who met all of the inclusion and none of the exclusion criteria will be classified as "evaluable". If there exist some randomized subjects who are not considered "evaluable", then some of the analyses of efficacy

described above (primary, secondary and. tertiary) will be performed including only the "evaluable" subjects. However, these analyses will be considered tertiary, and statistical significance will not be declared, regardless of the observed p-values.

**Amendments**

Amendment 1 (14 March, 2002)

1. Modified the threshold of opioid use for the primary endpoint to include intramuscular, subcutaneous and transdermal routes of administration.

RATIONALE: One dose parenterally is a sufficient threshold of opioid administration to determine that an endpoint has been reached. Transdermal dosing should be of the same duration as oral dosing.

Change:
o opioid therapy:
– intravenous opioid therapy
– opioid analgesic use for 10 out of 14 consecutive days

To Read:
o opioid therapy:
– intravenous, intramuscular or subcutaneous opioid therapy administered as a single dose
– oral or transdermal opioid analgesic use administered for 10 out of 14 consecutive days

2. Expanded eligibility criteria regarding required PSA values and definitive timeframes. RATIONALE: These modifications are being instituted to allow investigators more leeway in identifying patients using historical PSA values. Patients who meet the new criteria would still be considered hormone refractory.

3. Added distinctive timeframes for palliative therapies to better determine subject eligibility. RATIONALE: The term palliative therapy has been subject to varied interpretation. Distinct timeframes for the therapies will allow more uniform assessment by the investigators.

4. Added imaging approval must be obtained prior to randomization.

5. Added real-time review of scans for the purpose of monitoring for radiographic events of disease progression.

6. Deleted the following statements in Section 8.1, Statistical and Analytical Plans. The date of randomization for a subject is defined as the date the subject was first dispensed study medication. Subjects who were assigned a subject randomization number through IVRS but were not dispensed study medication, will not be considered to have been randomized.
RATIONALE: All subjects who receive a randomization number will be considered to be randomized.

7. The primary analysis of efficacy was changed from an unstratified G test to the G test stratified by region (US sites vs. non-US sites).

8. The definition of PSA progression was modified for subjects with a baseline PSA less than or equal to 10 ng/mL. RATIONALE: Patients who enter the trial with very (low PSA values could have premature determination of PSA progression due to small fluctuations. Determination of PSA progression should not be influenced by these small changes.

Amendment No.2: 17 January 2003

As discussed with the European Committee for Proprietary Medicinal Products (CPMP), the following changes have been made to the statistical analyses for Europe:
Change the definition of progression-free survival to be disease progression plus deaths or hypercalcemia. Include progression-free survival as a second primary endpoint.

Section 8.0, Statistical Methods and Determination of Sample Size, has been changed in order to clarify how to define the time-to-disease progression for the following subjects: Subjects randomized into Study M00-211 and Transferred to Study M00-244 due to lack of evidence of metastatic disease Subjects with disease progression prior to randomization Subjects with more than one disease progression packet Subjects that had the study blind broken.

**Sponsor Charters**

Abbott Laboratory Charters and the Independent review charters are briefly reviewed below.

**Abbott Laboratories Charter:**

The Abbott Laboratories Charter version 3, dated March 29, 2002 was submitted.

For pain or SRE treated with radiation, the decision to utilize radiation therapy will be considered adequate evidence if radiographic documentation of disease is not available. The date of progression will be the day of initiation of therapy e.g. the first of 10 of 14 days of opioid therapy.

Two or more new skeletal lesions on a bone scan when compared to baseline will be considered disease progression. One or more new extra-skeletal lesions $\geq$ 15 mm in diameter, visible on any single CT/MRI scan subsequent to baseline, is disease progression. The date of radiographic progression will be the date of the first study demonstrating progression consistent with endpoint definitions.

If more than one event occurs on the earliest date of progression, the oncology reviewer will assign the primary event in order of:

1. Skeletal Event
2. Event Due to Metastatic Prostate Cancer Requiring Intervention
3. Pain
4. Radiographic progression

**Definition of Lesions**

According to the Abbot Charter, tumor lesions will be categorized as follows:

Skeletal lesions identified on bone scans will be categorized as non-measurable lesions.
Extra-skeletal lesions identified at baseline on CT or MRI scans will be categorized as follows:

A measurable lesion is an extra-skeletal lesion having a longest diameter of > 20 mm.

A non-measurable lesion is any extra-skeletal lesion less than 20 mm in longest diameter or leptomeningeal disease, ascites, pleural/pericardial effusion, lymphangitis cutis/pulmonitis, and cystic lesions.

A target lesion is a measurable lesion chosen at baseline.

A sub-target lesion can be any non-measurable, extra-skeletal lesion measuring 15 to < 20 mm in longest diameter.

Any lesion not identified as a target lesion is a non-target lesion. Non-target lesions can include any measurable lesion not specified as a target lesion, or any lesion identified as a sub-target lesion at baseline. Non-target lesions can also include any non-measurable skeletal lesions.

**Changes made to the charter**:

According to version 1,

> Extra-skeletal lesions identified at baseline on CT or MRI scans will be categorized as follows:
> A measurable lesion is an extra-skeletal lesion having a longest diameter of ≥ 2 cm.
> A non-measurable lesion is any extra-skeletal lesion less than 2 cm in longest diameter or leptomeningeal disease, ascites, pleural/pericardial effusion, lymphangitis cutis/pulmonitis, and cystic lesions.
> A target lesion is a measurable lesion chosen at baseline.
> A sub-target lesion can be any non-measurable, extra-skeletal lesion measuring 1.5 to < 2 cm in longest diameter.

Changes in version2:

- Skeletal lesions identified on bone scans were categorized as non-measurable (and not non-target) (version 2).
- Any lesion not identified as a target lesion is a non-target (version 1). Non-target lesions can also include any non-measurable skeletal lesions (version 2).

Changes in version 3:

- Single dose of intramuscular or subcutaneous opioid, or 10 of 14 days of oral or transdermal opioid was added in the 3rd version of the charter.
- The number of total radiologists was increased to seven from five. Instead of a single radiologists determining presence of baseline extra-skeletal metastases, two reviewers were to read all scans. Should the radiologists disagree, an independent evaluation of the case study by a third radiologist reviewer will be scheduled and used as the "tiebreaker" reading.
- Distant lymph node involvement was clarified as metastatic disease.
- Non-target disease could be used for disease progression if they doubled in size.

**Independent Review:**

World Care Clinical Inc provided the independent reviewer for this trial. Their charter was requested. There are 5 versions submitted. They are:

**Table 6: Versions of Charter**

| VERSION | DATE OF VERSION | OBSOLETE | |
|---|---|---|---|
| 1 | 5-8-02 | 11-1-02 | |
| 2 | 6-25-02 | 11-1-02 | Documents approval of the site imaging process for each site |
| 3 | 11-07-02 | 4-10-03 | Updated to reflect the new process of using Part 11 compliant Abbott database tracker application. |
| 4 | 3-08-03 | 6-02-03 | Updated to reflect current process using database application. |
| 5 | 6-02-03 | | Updated to reflect changes in the data transfer procedure. |

A group of sub-specialist radiologists from MGH that analyze imaging data and associated documentation for study M00-211. All radiologists will be trained on SSP-504 (Abbott Radiologist Training and Testing Procedures) for the Abbott Clinical Trial and documented using Form 2008 (Abbott Radiologist Training and Testing Form). To maintain objectivity in evaluations, all radiologists will be blinded to the study treatment arm. A group of sub-specialist oncologists that confirm disease progression based on both clinical and radiographic evidence.

Two radiologists would read the radiological studies. If there is discordance, a third tiebreaker read was mandated.

All subjects were to be followed with regularly scheduled bone scans. If distant extraskeletal disease was found on CT scan at baseline, subjects were to be followed with regularly scheduled CT scans. Otherwise CT scans/MRIs were not mandated in the protocol. Multiple visits were received and could have been read during one standing radiological review, because vendors were changed.

According to the applicant, "*The case was forwarded to one of the two primary oncologist reviewers for endpoint evaluation. The determination of whether an individual case met the protocol- defined endpoint criteria was based upon the evaluation of the WorldCare Clinical radiology review report and the site- generated disease progression packet. If necessary, the oncologist reviewer could review study images and request additional clinical information. The endpoint assessment of the oncologist reviewer was documented on Abbott Laboratories case report form pages 650EP, 651EP and 652EP."*

*"Abbott Laboratories notified the site that radiographic progression had been confirmed based on independent radiology review and requested that a disease progression packet be submitted for the subject. If the Investigator did not agree with this assessment, a dialog was established between Abbott Laboratories and the Investigator."*

**Post Hoc Changes**

**Reviewer's Comments:**
A study synopsis was submitted to the FDA for an EOP2 meeting. No protocol or details were submitted. The trial endpoint is composite and unusual. The FDA had accepted the general idea of a composite endpoint in the EOP2 meetings. The endpoint was prospectively defined for a prospectively randomized, double-blind trial and the trial result was based on an independent review instead of the investigator report. This endpoint will need to be captured well in the CRF and the SAS database for verification purposes, and could be a major problem. The independent reviewers were blinded to the PSA results. Except for imaging studies, the investigator would need to identify the event of disease progression before forwarding it to the independent reviewer.

The trial was blinded but the results of PSA were known to the physician and patient. A rise in PSA may have led to treatment decisions, and had an impact on the endpoint. At the EOP2 meeting dated 10/4/2000, the sponsor was informed that approval would require a clinically significant delay in TTP in the ITT population.

**Results**

There were several important changes made during the study. A chronology for these changes is given below. A review of disposition, protocol violations followed by efficacy and then safety results are presented.

**Table 7: Important Study Dates**

| | |
|---|---|
| Abbott Charter version 1 (Original version for 1st independent review vendor | May 7th, 2001 |
| Date first patient randomized: | June 25th, 2001 |
| Abbott Charter version 2 (Revised version for 1st independent review vendor) | August 7th, 2001 |
| Date last patient randomized: | Nov 25th, 2002 |
| Independent Review vendor changed | Feb 22nd, 2002 |
| Amendment 1 | March 14th, 2002 |
| Scans started to be sent to 2nd vendor | |
| Abbott Charter version 3 (Prepared for 2nd independent review vendor)<br>2nd vendor read all scans done again (possibly different from 1st vendor) | March 29th, 2002 |
| Amendment No.2: (PFS added as primary endpoint for EAMA) | Jan 17th, 2003 |
| IDMC recommended that study be stopped because of futility based on primary endpoint: | Jan 24th, 2003 |
| Date of last dose of last patient: | March 19th, 2003 |
| Criteria for "per-protocol" population identified | May 8th, 2003 |
| Blind broken for Study M00-211: | May 16th, 2003 |

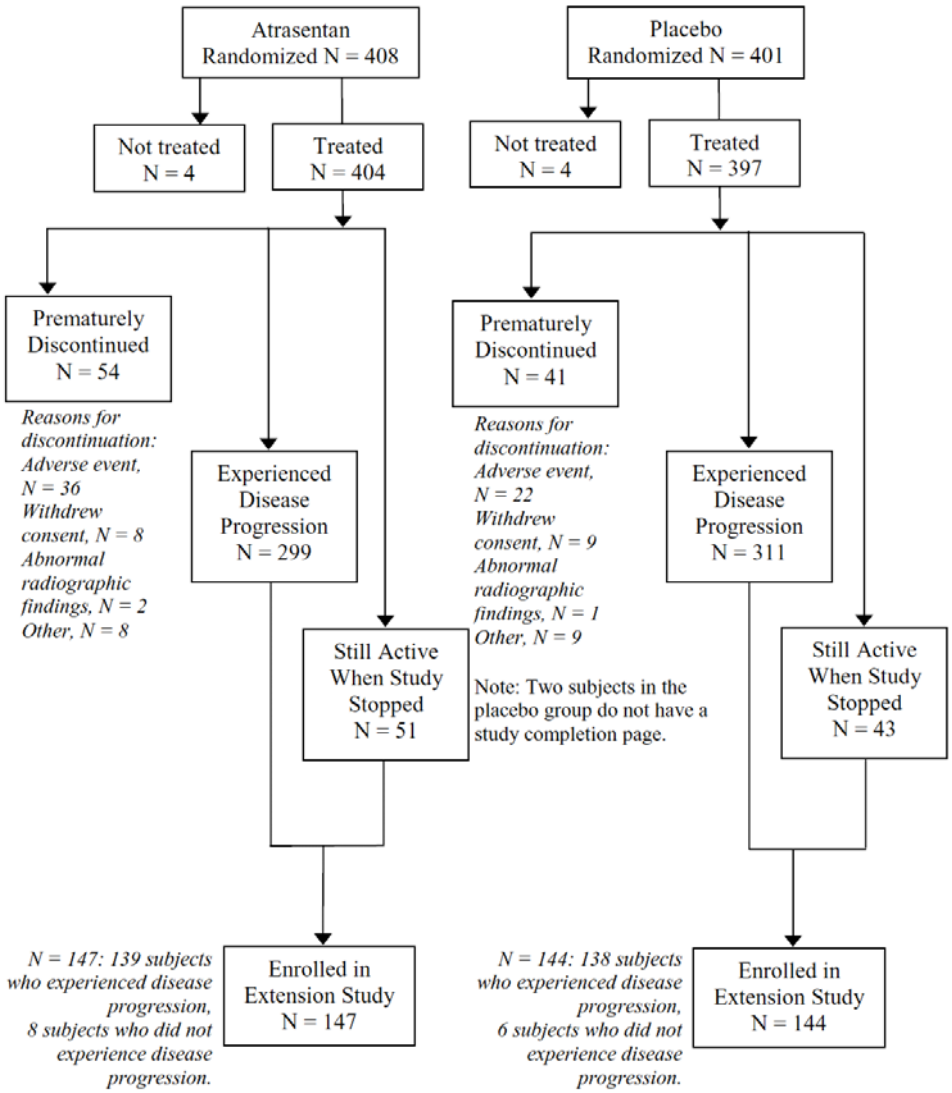
**Reviewer's Comment:**
The classification plan to define the "per protocol population" was made before the blind was broken, but after the study was closed by IDMC for futility. It can not be considered an uninformed analysis.

## Disposition

Four hundred and four patients were randomized to the atrasentan arm and 401 patients were randomized to the placebo arm. Four patients from each arm was not treated. Six hundred and ten patients (75%) experienced progression, 73% on the atrasentan arm, and 78% on the placebo arm.

## Figure 4: Subject Disposition

Applicant figure 6 (CSR)



***Demographics***

All patients were male, ranging in age from 45 to 93 years. A total of 770 subjects (95%) were Caucasian; 26 (3%) were Black. There were no statistically significant differences in demographics between the two treatment groups.

**Table 8: Demographic Characteristics**

Applicant table 6 from CSR

| Variable | Treatment Group Number of Subjects | | Total (N = 809) | P-value[b] |
|---|---|---|---|---|
| | Placebo (n=401) | Atrasentan 10 mg (n=408) | | |
| **Age (years)** | **N = 401** | **N = 408)** | **N = 809** | |
| Mean (SE[a]) | 71.3 (0.41) | 72.3 (0.40 | 71.8 (0.29) | **0.080** |
| Median | 72.0 | 73.0 | 72.0 | |
| Range | 45.0 – 92.0 | 45.0 – 93.0 | 45.0 – 93.0 | |
| **Race** | **N = 401** | **N = 408** | **N = 809** | |
| Caucasian | 386 (96%) | 384 (94%) | 770 (95%) | 0.254 |
| Black | 8 (2%) | 18 (4%) | 26 (3%) | |
| Asian | 4 (1%) | 4 (1%) | 8 (1%) | |
| Other | 3 (1%) | 2 (0%) | 5 (1%) | |
| **Weight (kg)** | **N = 399** | **N = 408** | **N = 807** | |
| Mean (SE) | 85.2 (0.78) | 83.9 (0.71) | 84.5 (0.53) | 0.196 |
| Median | 83.0 | 81.2 | 82.1 | |
| Range | 47.0 – 154.2 | 53.5 – 176.9 | 47.0 – 176.9 | |
| **Height (cm)** | **N = 394** | **N = 400** | **N = 794** | |
| Mean (SE) | 174.7 (0.38) | 174.4 (0.38) | 174.6 (0.27) | 0.606 |
| Median | 175.0 | 175.0 | 175.0 | |
| Range | 152.4 – 195.0 | 152.0 – 198.1 | 152.0 – 198.1 | |

a Standard error
b P- values are from the F- test of equality of the means between treatment groups or from Fisher's exact test.

***Baseline Disease Characteristics***

The results of the comparison of baseline characteristics demonstrate that the two treatment groups were not statistically different for any characteristic except LDH and Bone Scan Index. The mean LDH value at baseline was slightly higher for subjects in the placebo group compared with the atrasentan treatment group, although the medians were not clinically relevant.

## Table 9: Selected Baseline Characteristics

| Variable | Treatment Group Number of Subjects: Placebo (N = 401) | 10 mg Atrasentan (N = 408) | Total (N = 809) | P-value |
|---|---|---|---|---|
| **Hemoglobin (g/dL)** | N = 393 | N = 400 | N = 793 | |
| Mean (SE[a]) | 13.1 (0.065) | 13.3 (0.061) | 13.2 (0.045) | 0.128 |
| Median | 13.2 | 13.4 | 13.3 | |
| Range | 9.1 – 18.1 | 9.3 – 17.4 | 9.1 – 18.1 | |
| **LDH (IU/L)** | N = 394 | N = 402 | N = 796 | |
| Mean (SE) | 221.9 (8.61) | 200.7 (4.28) | 211.2 (4.79) | 0.027* |
| Median | 188.0 | 186.0 | 186.0 | |
| Range | 108.0 – 2365.0 | 97.0 – 1318.0 | 97.0 – 2365.0 | |
| **Total alkaline phosphatase (IU/L)** | N = 397 | N = 407 | N = 804 | |
| Mean (SE) | 208.2 (17.27) | 196.8 (20.68) | 202.4 (13.49) | 0.673 |
| Median | 112.0 | 110.0 | 110.0 | |
| Range | 41.0 – 3774.0 | 36.0 – 5482.0 | 36.0 – 5482.0 | |
| **Bone alkaline phosphatase (ng/mL)** | N = 382 | N = 387 | N = 769 | |
| Mean (SE) | 59.7 (6.27) | 58.6 (7.70) | 59.1 (4.97) | 0.909 |
| Median | 24.8 | 25.5 | 25.2 | |
| Range | 2.0 – 1599.0 | 2.0 – 1903.8 | 2.0 – 1903.8 | |
| **PSA (ng/mL)** | N = 396 | N = 407 | N = 803 | |
| Mean (SE[a]) | 218.1 (21.3) | 212.2 (24.0) | 215.1 (16.1) | 0.855 |
| Median | 79.6 | 69.8 | 72.9 | |
| Range | 2.2 – 5424.8 | 1.7 – 5784.0 | 1.7 – 5784.0 | |
| **Screening testosterone (ng/dL)** | N = 396 | N = 406 | N = 802 | |
| Mean (SE) | 12.7 (0.36) | 12.7 (0.35) | 12.7 (0.25) | 0.951 |
| Median | 11.3 | 11.5 | 11.5 | |
| Range | 2.9 – 46.0 | 2.9 – 57.7 | 2.9 – 57.7 | |
| **Total Gleason Score** | N = 315 | N = 317 | N = 632 | |
| Mean (SE) | 7.3 (0.09) | 7.2 (0.08) | 7.3 (0.06) | 0.412 |
| Median | 7.0 | 7.0 | 7.0 | |
| Range | 2.0 – 10.0 | 3.0 – 10.0 | 2.0 – 10.0 | |
| **Bone Scan Index** | N = 355 | N = 377 | N = 732 | |
| Mean (SE) | 5.5 (0.46) | 4.3 (0.37) | 4.9 (0.29) | 0.032* |
| Median | 1.8 | 1.4 | 1.5 | |
| Range | 0.0 – 44.5 | 0.0 – 47.9 | 0.0 – 47.9 | |
| **Time since diagnosis (yrs)** | N = 401 | N = 408 | N = 809 | |
| Mean (SE) | 5.5 (0.18) | 5.8 (0.19) | 5.7 (0.13) | 0.212 |
| Median | 4.8 | 5.0 | 4.9 | |
| Range | 0.1 – 23.2 | 0.3 – 23.7 | 0.1 – 23.7 | |

a Standard error

b P-values are from the F-test of the equality of the means between treatment groups or from Fisher's exact test.

* Indicates a statistically significant difference between treatment groups at P = 0.05.

**Protocol Violations:**

The blind was broken early for 8 patients (7 on Atrasentan and 1 on placebo). All except 1 patient were evaluable. The reason for breaking the blind is not clear. These numbers are few, and would not likely affect the analysis.

Certain protocol violation criteria were identified by the applicant after the study was closed due to futility by the DSMB, but before the blind was broken. Per sponsor, a total of 183 (22.6%) subjects did not meet at least one inclusion or exclusion criteria. Some of these were major and some were minor. One hundred and thirty eight (17%) patients did not meet the sponsor's criteria because of major violations. These are given below in tabular form.

**Table 10: Reasons for Exclusion from Per- Protocol Analysis**

Applicant table 10 (CSR)

| | Number (%) of subjects excluded[a] | | |
|---|---|---|---|
| **Reason for Exclusion** | **Placebo N = 73** | **Atrasentan N = 66** | **Total N = 139** |
| **No definitive evidence of metastatic HRPCa** | | | |
| No distant metastatic diagnosis based in independent radiological review | 14 (19.2%) | 8 (12.1%) | 22 (15.8%) |
| No histopathologic or cytologic evidence of PCa | 9 (12.3%) | 13 (19.7%) | 22 (15.8%) |
| **Incomplete evidence of a hormone-refractory state** | | | |
| Cannot rule out anti-androgen withdrawal effect | 13 (17.8%) | 9 (13.6%) | 22 (15.8%) |
| Lack of confirmatory evidence of castration | 5 (6.8%) | 3 (4.5%) | 8 (5.8%) |
| PSA values do not support a hormone-refractory state | 4 (5.5%) | 4 (6.1%) | 8 (5.8%) |
| No PSA value > 5 within the screening period | 4 (5.5%) | 3 (4.5%) | 7 (5.0%) |
| Insufficient anti-androgen withdrawal | 2 (2.7%) | 0 (0.0%) | 2 (1.4%) |
| **Potential use of a confounding medication** | | | |
| Opioid use as therapy ≤ 6 months prior to start of study drug | 23 (31.5%) | 23 (34.8%) | 46 (33.1%) |
| Received exclusionary medication during study drug administration | 7 (9.6%) | 5 (7.6%) | 12 (8.6%) |
| Study drug duration (never received drug, n = 8; dosed < 7 days, n = 1) | 5 (6.8%) | 4 (6.1%) | 9 (6.5%) |
| Steroid use as cancer therapy within 6 months | 2 (2.7%) | 2 (3.0%) | 4 (2.9%) |
| Received exclusionary medication within 4 weeks prior to study | 1 (1.4%) | 1 (1.5%) | 2 (1.4%) |
| **Other** | | | |
| Admission criteria[b] | 13 (17.8%) | 8 (12.1%) | 21 (15.1%) |

Note: One subject was censored at the time that he began taking exclusionary medications.
a Subjects may have been counted in more than one category
b Admission criteria exclusions varied and included Karnofsky score < 70, malignancy < 5 years prior to study initiation, and prior cytotoxic or radiation therapy.

This reviewer attempted to duplicate the exclusions due to the use of opioids using only the SAS datasets. There were many dissimilarities in the applicants' and this reviewers calculations. For example, in the FDA reviewer analysis there were 16 patients in the atrasentan arm and 10 on the placebo arm that had used at least 2 doses of an opioid in the 6 months (168 days) prior to randomization. According to the applicant table above, 23 patients on each arm used opioids in the 6 months before randomization.

Major Protocol violations (FDA Reviewer):
Violations considered major by the FDA were chosen according to the proposed indication "for hormone-refractory, metastatic prostate cancer". FDA clinical team identified violations involving inclusion criteria numbers 3-7 and exclusion criteria 3 as major. Additionally, a short time interval between antiandrogen therapy and randomization was included in these major violation criteria to avoid confounding response from antiandrogen withdrawal. Prior cytotoxic therapy, radiation, use of opioids or steroids or other concomitant medications poor KPS, a malignancy in the past 5 years were not counted as major protocol violations. The FDA major enrollment criteria are summarized below:

- Histological diagnosis of prostate adenocarcinoma (PCa).
- Surgical or pharmacological castration at least 3 months prior.
- Subject must meet pre-specified PSA criteria:
- A documented withdrawal period after antiandrogen therapy prior to randomization.
- Evidence of distant metastases as verified by screening bone scan or CT scan.

There were 57 (14%) patients with at least 1 major violation on the Atrasentan arm, and 63 (15.7%) on the placebo arm. Fourteen patients on the atrasentan arm had no histological diagnosis and 12 on the placebo arm. Twenty six patients did not have pathological diagnosis (Atrasentan: 14, placebo: 12). At least 3 of these patients had cytological evidence of prostate cancer (1 on Atrasentan and 2 on placebo). For the others, diagnosis was made on "clinical evidence", a remote diagnosis of prostate cancer, or a bone scan and high PSA levels. Thirteen patients had non-metastatic disease. (Atrasentan Arm: 1, Placebo: 8, No treatment administered: 1, Moved to protocol 0024: 3). Some of these deviations were approved by the applicant.

**Table 11: Major Protocol Violations (FDA Analysis)**

| INCLUSION/EXCLUSION CRITERIA | ATRASENTAN | | PLACEBO | |
|---|---|---|---|---|
| | N=408 | % | N=401 | % |
| Informed consent | 2 | 0.5 | 3 | 0.7 |
| Histological Diagnosis | 14 | 3.4 | 12 | 3.0 |
| 3 months of castration and testosterone level <50ng/dl | 1 | 0.2 | 2 | 0.5 |
| Anti-androgen therapy with appropriate intervening interval | 14 | 3.4 | 6 | 1.5 |
| PSA criteria | 30 | 7.4 | 38 | 9.5 |
| Documentation of metastatic disease | 3 | 0.7 | 10 | 2.5 |
| H/o malignant disease not < 5 years from randomization | 0 | 0.0 | 1 | 0.2 |
| KPS ≥ 70 | 1 | 0.2 | 2 | 0.5 |
| Life expectancy > 6 months | 8 | 2.0 | 9 | 2.2 |
| Adequate hematological function | 3 | 0.7 | 8 | 2.0 |
| Adequate liver function | 10 | 2.5 | 10 | 2.5 |
| Active drug administered within 4 weeks of randomization | 3 | 0.7 | 1 | 0.2 |

Datasets: AD and PT
The major violations (FDA criteria) are shaded rows

***Reviewer's Comment:***
*FDA chose the major eligibility criteria according to the proposed indication. Approximately 15% patients enrolled violated the criteria in line with the proposed indication by the FDA. This number increased to 17% for all per-protocol exclusions as submitted by the applicant. This high rate of protocol violations reflects on the conduct of the study. These violations were divided equally in the two arms.*

*The applicant chose the major violations after the study was closed by the DSMB based on futility.*

***Efficacy***

In this section, the efficacy of atrasentan in the phase III trial will be discussed. The study failed its only primary endpoint (time to disease progression) and 4 of 5 of its secondary endpoints.

Per applicant:

*"A total of 809 men with metastatic HRPC were enrolled in study M00- 211; the target enrollment was 900 to 1000. Upon the recommendation of the independent data monitoring committee (IDMC) (27 September 2002), enrollment was stopped at 809 subjects because the committee felt that a sufficient number of subjects were enrolled to achieve the prespecified number of 650 endpoints. Following the next meeting with the IDMC on 24 January 2003 the committee recommended that the study be stopped on 10 February 2003 because the results of the primary analysis were not likely to achieve statistical significance at the end of the trial. This decision was based on 343 events from the 809 subjects enrolled. Once all subjects had completed the final study visits and had undergone final imaging procedures, there were 610 disease progression events for study M00- 211."* The prespecified number of 650 progressions was calculated to yield a 90% power to the study.

According to the original SAP, the analyses of evaluable patients would be considered tertiary and statistical significance will not be declared, regardless of the observed p-values.

**Primary Endpoint**

Time to Disease Progression:

Time to disease progression was the primary endpoint of the study. Disease progression was counted from the day of first administration of study drug to the first one of several events. The definition of this composite event is given in the original protocol, in the Appendix.

If the investigator identified a disease progression event, a prompt for an independent review was sent. Based on independent review, progression or lack of there of and date was assigned. In the mean time, the patient was to be continued on the study drug. All imaging studies underwent independent review. If more than one event occurs on the earliest date of progression, the oncology reviewer was to assign the primary event in order of:

1. Skeletal Event
2. Event Due to Metastatic Prostate Cancer Requiring Intervention
3. Pain (intervention with one of opioid, corticosteroid, radiation, radionuclide therapy or chemotherapy)
4. Radiographic progression

Radiologic Progression

By far, the most common progression event was radiologic progression. Please see table below. Bone scans were used to evaluate progression of skeletal lesions, and CT scans/MRI were used

for extra-skeletal lesions. All patients per-protocol were to have bone scans at baseline and then at 2 month intervals, but follow-up CT scans/MRI were not required if there were no soft tissue lesions at baseline. Progression due to new soft-tissue lesions would not be recognized by this method, and impact on the definition and clinical impact of the primary endpoint of time-to-disease progression.

Pain and intervention with opioids:
Pain due to prostate cancer requiring one or more palliative interventions (opioids 10 of 14 days of transdermal (Amendment 1, 14 March, 2002) or oral, or single dose of intravenous (original protocol) or intramuscular or subcutaneous injection (Amendment 1, 14 March, 2002) constituted disease progression. Fourteen to 17% patients progressed by this definition.

Other Events:
There were few SREs or other events requiring intervention. This may be because no time was pre-specified for assessing these two categories.

**Table 12: Summary Of Reasons For Disease Progression (All Randomized Subjects)**

Adapted from CSR table 14.2_1.1.5

| **Treatment Group** | **N** | **Number Of Subjects Reaching Disease Progression Event #** | | | | | |
|---|---|---|---|---|---|---|---|
| | | **A** | **B** | **C** | **D** | **E** | **TOTAL** |
| **Placebo** | 401 | 68 (17) | 9 (2) | 6 (2) | 181 (45) | 47 (11) | 311 (77%) |
| **Atrasentan** | 408 | 56 (14) | 9 (2) | 9 (2) | 177 (43) | 48 (12) | 299 (73%) |

A= pain due to prostate cancer requiring palliative intervention;
B= skeletal related event;
C= event due to metastatic prostate cancer requiring intervention;
D= one bone scan subsequent to baseline demonstrating two or more new skeletal lesions;
E= one CT or MRI scan subsequent to baseline demonstrating evidence of extra- skeletal disease progression according to modified RECIST criteria.
The tables below from the applicant's CSR have been audited for accuracy.

**Table 13: Applicant's assessment of proportion of events leading to disease progression**

Section 11.4.1.1.1.1 of CSR

| **EVENT OF DP** | **BOTH TREATMENT ARMS (%)** |
|---|---|
| SRE | 2 |
| Event Requiring Intervention | 3 |
| Pain | 20 |
| Radiographic progression | 74 |

Blinding to PSA:
An attempt was made to blind the independent reviewer from the PSA values. According to the applicant (email dated 4/19/2005) *"In order to control for potential PSA bias, the independent radiologists and oncologists did not have access to the serum PSA results. Investigators were instructed in the Event of Disease Progression Confirmation Instructions not to include any reference to PSA results in their narratives. Additionally, each Disease Progression Packet was screened at Abbott Laboratories and if a reference to PSA had been included in the narrative, this information was obscured before it was sent to the Independent Oncology Reviewer to ensure that the endpoint confirmations were not influenced by PSA results."*
On March 14, 2002, after changing of independent review vendors, and 10 months after enrollment of the first patient, definition of disease progression due to administration of opioids due to pain was changed. A single dose of intramuscular or subcutaneous opioid injection or 10 of 14 days of transdermal opioid now was also included in the definition f disease progression.

Methodology of Investigator/Independent Review:
Prompt of disease progression was sent from site to independent reviewer (an oncologist). Study drug was continued by site until confirmation by Independent reviewer was received at the site. Based on radiographic progression noted at WorldCare (independent reviewer), request could be made to the site to submit further information on the patient. There was a turnaround time of 10-14 days for the independent reviewer to send final assessment to the sponsor. There was no time pre-specified for investigator's review and assessment for progression by SRE's or intervention for prostate cancer complications.

Study drug was administered until progression assessment was made by the IR (Independent Reviewer), and not discontinued based on the investigator's assessment. Twenty eight patients had PD according to the investigators without concurrence from the independent review. Twelve of these patients were on the Atrasentan arm and 16 were on the placebo arm. Only 6-7 patients discontinued study drug before assessment by the IR and they were equally divided in the two treatment arms.

According to the definition of the primary event, opioid administration could be part of Event requiring intervention, or Pain. Corticosteroid administration could be part of intervention and pain. Radiation could be part of SRE, pain or interventional event. The final classification of the disease progression event was at the discretion of the reviewer.

In 14 patients, disease progression occurred before 14 days from randomization and was equally distributed between the two dose groups. Eight were on the atrasentan arm and five were on the placebo arm.

**Table 14: Occurrence of event of Disease Progression in less than 14 days from randomization**

| TREATMENT ARM | PATIENT ID | EVENT OF DP | DATE OF RANDOMIZATION | DATE OF DP | TDP |
|---|---|---|---|---|---|
| Atrasentan N=9 | 1137 | Pain | 12/19/2001 | 12/12/2001 | -7 |
| | 1782 | Pain | 02/18/2002 | 02/18/2002 | 0 |
| | 1903 | Pain | 02/21/2002 | 02/22/2002 | 1 |
| | 2178 | Pain | 05/15/2002 | 05/16/2002 | 1 |
| | 3030 | Pain | 08/15/2002 | 08/22/2002 | 7 |
| | 1142 | Intervention | 08/07/2002 | 08/15/2002 | 8 |
| | 1145 | Pain | 08/31/2001 | 09/12/2001 | 12 |
| | 1242 | Intervention | 04/09/2002 | 04/21/2002 | 12 |
| | 1310 | Pain | 05/31/2002 | 06/12/2002 | 12 |
| Placebo N=5 | 1138 | Pain | 01/22/2002 | 01/22/2002 | 0 |
| | 2268 | Pain | 07/17/2002 | 07/18/2002 | 1 |
| | 1511 | Pain | 07/11/2002 | 07/14/2002 | 3 |
| | 1688 | Pain | 08/09/2002 | 08/19/2002 | 10 |
| | 1966 | Intervention | 08/23/2002 | 09/02/2002 | 10 |

**Reviewer's comment:**
In an EOP2 meeting, FDA accepted the idea of a composite endpoint of disease progression (DP), with the caveat that it should be clinically meaningful and not driven by PSA. Overall, the final protocol was well-designed. There was a major weakness in the primary endpoint. Only one opioid injection constituted disease progression, whereas protracted ingestion/transdermal application was required for disease progression. The clinical relevance of pain captured by this methodology and its validity as a component of disease progression is questioned. For example, a single injection of demerol could determine DP (as in patient ID 1014), vs. 9 days of oral MSO4 would not qualify as DP per rules of the protocol. Twenty percent of the progressions were due to initiation of opioids.

Additionally, instances of radiologic progression on CT scans could have been missed. Bone scans were performed every 12 weeks throughout the trial, but if there were no metastases at baseline, the CT scan/MRI did not need to be repeated. Some investigators do not obtain CT scans if negative at baseline in their clinical practice because of questionable clinical relevance of enlarging abdominal lymph nodes. However, probably most if not all of them will change therapy if progression was noted on CT scans.

**Time-to-disease progression:**

Applicant Analysis:

The assessment of disease progression was made by the independent reviewer (i.e. by an oncologist), based on a prompt by the investigator and on review of independent radiologist. However, in absence of such a prompt, the disease assessment was made only by the investigator. No actual date was recorded for the investigator assessment. The date of the last measurement of vital signs, performance status or physical examination was used by the applicant as the date of disease assessment. According to the statistical plan, *"If the subject does not have a confirmed event of disease progression, the subject's data will be censored at the date of the subject's last available evaluation. This date will be the date of the last available vital sign measurement, performance status assessment, or physical exam. An exception to this rule may occur if the subject has an unconfirmed event of disease progression (Disease Progression Packet submitted but an event of disease progression was not confirmed by independent reviewer). In this case, the last available date of evaluation will be the date of disease progression determined by the investigator for the unconfirmed event or the date of the last available vital sign measurement, performance status assessment, or physical exam, whichever is last."*

Per applicant *"The G[1,1] analysis of time to disease progression demonstrated no statistically significant differences between results for the two groups ( P = 0.136). The hazard ratio was 0.89 (P = 0.131)."*

**Table 15: Time-to-Disease Progression**

Applicant Analysis

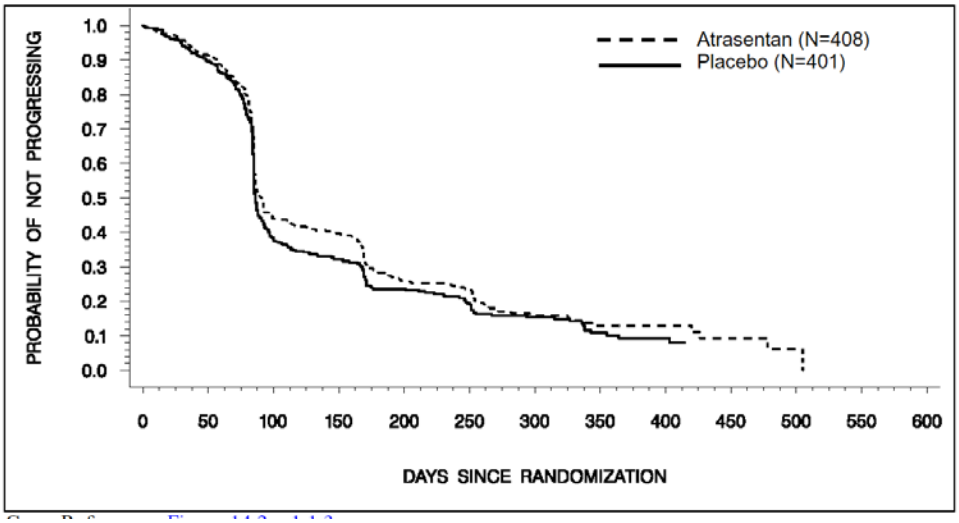


**Table 16: Analysis of Time to disease progression-ITT**

Applicant table 14.2_1.1.3 from CSR

| | **Placebo (N=401)** | **Atrasentan (N=408)** |
|---|---|---|
| Events | 311(77.6%) | 299(73.3%) |
| **Quartiles** | | |
| 25th | 79 days | 82 days |
| Median | 86 days | 91 days |
| 75th | 171 days | 233 days |

**Table 17:Treatment comparison: placebo vs. Atrasentan**

Applicant table 14.2_1.1.3 from CSR

| **Kaplan-Meier method:** | | |
|---|---|---|
| **Test** | **Chi-square** | **P-value** |
| G(1,1) | 2.22 | 0.136 |
| Log-rank | 2.38 | 0.123 |
| Wilcoxon | 2.97 | 0.085+ |

FDA Analysis:

Because no time is given in the CRF when the investigator actually made assessment, FDA performed an exploratory analysis on time to disease progression (TDP) using dates where actual assessment of disease progression took place. Radiological assessment dates and pain assessment dates were used to censor patients who did not progress. As noted earlier in the review, only 5 % patients had any other progression events.

Seventeen non-progressing patients had no assessment after randomization. Ten of the17 patients were treated for 2-16 days, and 7 patients did not receive medication. These 17 patients were censored at randomization. The median time-to-disease progression was similar in both arms.

**Figure 5: Kaplan-Meier Curve for Time to disease progression**

FDA exploratory analysis

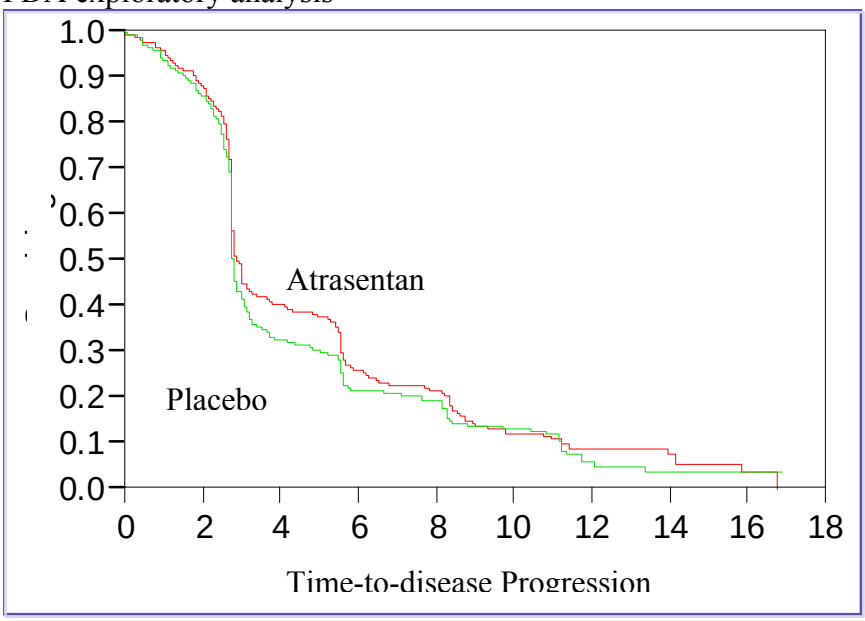



**Table 18: FDA Analysis of Time to Disease Progression**

| Treatment Arms | Progressed (N) | Censored (N) |
|---|---|---|
| Atrasentan | 298 | 109 |
| Placebo | 311 | 90 |

| Treatment Arms | Median Time (days) | Lower 95% | Upper 95% | 25% Failures | 75% Failures |
|---|---|---|---|---|---|
| Atrasentan | 88 | 85 | 95 | 81 | 196 |
| Placebo | 85 | 84 | 87 | 78 | 170 |

| Test | P value |
|---|---|
| Log-Rank | 0.22 |
| Wilcoxon | 0.13 |

**Reviewer Comments:**

1 - In a hypothetical situation, if all progressions on arm A occurred at 2 weeks after randomization and on arm B eight weeks after randomization, time to disease progression will be 12 weeks for both arms, if all imaging was performed at exactly 12 weeks. The difference in time to disease progression would be reliably detected only if the difference was greater than one imaging cycle or if imaging was not the leading event of disease progression.


**Figure:** Time to Disease Progression: Time of actual event vs. Time when event is detected

In this study, the difference of 3 to 5 days in the medians identifies the time when imaging detects disease progression was performed and not for the actual event of progression. The actual event on either arm could have occurred anywhere from date of randomization to the time of radiographic imaging. The radiographic imaging was scheduled for every 3 months. Disease progression detected on imaging constituted 75% of the progression events drove the results of the study. Any difference less than one imaging cycle (12 weeks) would not be reliable.

2 - Using an analogy of patients' treatment and medical records, "*if it was not recorded, it did not happen,"* lack of date of clinical assessment of disease progression (pain, some components of SRE and other prostate cancer-related interventions) is a serious deficiency impacting the primary endpoint of the trial. Just because a patient had a physical exam, performance status evaluation or vital sign, it can not be assumed that he was assessed for disease progression at that visit. Without dates of disease assessment for censoring patients who have not progressed, accurate assessment of time to disease progression is not possible.

For an exploratory analysis, the FDA clinical review team chose to censor at the date of last radiology exam (datasets RA. BS01 and BS02) or last pain assessment (dataset C4), whichever came first. The FDA method of censoring would not catch events due to SREs or interventions for prostate cancer-related complications. Events due to SRE and interventions for prostate cancer-related complications were relatively few in patient who did progress. One argument could be that SREs and other interventions were few (or fewer than the actual number) *because* they may have been missed due to lack of assessment.

A difference of less than a week in the median TDP can not be reliably identified in this study. The median TDP was 3 – 5 days by the applicant analysis and FDA reviewer analysis.

**Secondary Endpoints**

According to the statistical analysis plan, the secondary endpoints were:
(1) Mean change from baseline to final value in bone alkaline phosphatase,
(2} time to onset of PSA progression,
(3) Mean rate of change from baseline to final value in total bone scan index, and
(4) Survival.

Progression-free survival will be a 5th secondary endpoint for the FDA Analysis. This was a co-primary endpoint requested by the European regulators.

**Reviewer's Comments on Secondary Endpoints Results:**

Atrasentan failed 3 of the 4 pre-specified secondary endpoints. These were time to onset of PSA progression, mean rate of change from baseline to final value in total bone scan index and survival. Missing data in the analysis of the 4th endpoint (mean change in ALP) prevented it from being reliable and the difference in mean change in ALP of 20 ng/ml in the two arms can not be considered clinically meaningful.

The 5th endpoint, progression-free survival, also failed.

Data collection for survival was not robust. Twenty one percent patients were lost to follow-up. (This includes (3%) patients alive and not "lost to follow-up" per applicant, for whom no updated info was submitted for 6 to 15 months before the cut-off date. Survival was to be updated every 3 months). Survival data updated to July 1st, 2005 has been requested by the FDA on patients alive at last follow-up.

These secondary endpoints should not be interpreted as being supportive of atrasentan's efficacy because the study failed its primary endpoint. According to the Statistical Analysis Plan (SAP), *"If the primary efficacy analysis (time-to-disease progression using the stratified $G^{1,1}$ test) is statistically significant at the n=0.05 level, then p-values for the secondary analyses will be subject to multiple comparison adjustments using the step-down rule, with analyses performed in the following order: (1) mean change from baseline to final value in bone alkaline phosphatase, (2) time to onset of PSA progression, (3) mean rate of change from baseline to final value in total bone scan index, and (4) survival."* And *"if any of these secondary analyses does not achieve statistical significance at the $\alpha$=0.05 level, then statistical significance will not be declared for the subsequent secondary analyses, regardless of the observed p-values. If the primary efficacy analysis is not statistically significant at the $\alpha$=0.05 level then statistical significance will not be declared for any of these secondary analyses, regardless of the observed p values".*

Contrary to the SAP, the applicant has chosen to use the secondary endpoints to support the efficacy of atrasentan. A more detailed analysis of the secondary endpoints is given below.

**Secondary Endpoint #1: Mean change from baseline to final value in bone alkaline phosphatase**

Per SAP, *"Mean change from baseline to final value in bone alkaline phosphatase will be calculated for each treatment group and compared using an analysis of covariance (ANCOVA) with treatment group and baseline bone alkaline phosphatase value as the factors. If more than one measurement exists for a subject on a particular day, then an arithmetic average will be calculated. This average will be considered to be that subject's measurement of bone alkaline phosphatase for that day. Baseline will be defined as the measurement collected prior to and closest to the first dose of study drug. The final value will be defined as the last available post-baseline measurement within seven days of the last dose of study drug. Subjects lacking either a baseline or a final value for bone alkaline phosphatase will not be included in this analysis."*

Applicant Analysis:

Change in baseline to final value of alkaline phosphatase was measured as a marker for osteoblastic activity,. Alkaline phosphatase was analyzed by the applicant using ANCOVA. The mean increase to final value was lower for subjects treated with atrasentan (13.19 ng/ mL) than for subjects who received placebo (33.86 ng/ mL) (P = 0.001). The difference in the Alkaline Phosphatase from baseline to final value for the placebo group was an increased by 33 units and for atrasentan was an increase by 14 units. The increase was less for the atrasentan group but the actual difference between groups was too small to be clinically meaningful.

It should be noted that this is not an ITT analysis. Sixty-six (9%) patients were excluded. The difference in mean change of ALP is 20 ng/mL and is not clinically meaningful.

**Table 19: Mean Change in alkaline phosphatase**

**Applicant Analysis**

| Treatment Group | N | Baseline | Final visit | Change from baseline | | | Between group comparison 10 mg vs. Placebo | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Mean | Mean | Mean | (se) | P-value | Mean | (se) | P-value |
| Placebo | 374 | 57.75 | 91.34 | 33.86 | (4.478) | <0.001 | -20.66 | (6.378) | 0.001 |
| Atrasentan | 364 | 52.45 | 65.91 | 13.19 | (4.540) | 0.004 | | | |

FDA analysis:
The analysis of change from randomization to last visit was attempted by this reviewer. The baseline ALP was the first ALP measurement within 30 days prior to randomization. For both groups, mean baseline measurement was 12.8 days and median was 14 days prior to randomization, (range was 29 before randomization to 14 days after randomization). For 15

patients the first date of ALP measurement was 1 to14 days after randomization (atrasentan n=8, placebo n=7).

However, 169 (20%) patients had ALP measurements > 7 days prior to drug discontinuation (atrasentan n =72; placebo n=97) and 76 (9%) patients had ALP values drawn > 30 days prior to drug discontinuation. For the 169 patients, the mean time of measurement was approximately 30 days prior to last dose administration (30 days for atrasentan and 34 days for placebo) and up to about 85 days before last drug administration (87 days for atrasentan and 84 days for placebo). It should be recalled that the median time to disease progression was about 3 months. The ALP measurements of these patients will be close to the first day of treatment. With such wide variation, and missing data close to the last measurement of ALP, there can be little confidence in the values obtained for change from baseline in ALP.

**Reviewer's comments:**
- Approximately 20% patients had their final measurement of ALP greater than +/- 7 days of discontinuing the drug, and the range was wide (mean of 30 days). The median TDP was 3 months (12 weeks). A difference of 30 days would be significant in this patient population.

- Data on 9% patients was missing. On another 9-20%, last measurement of ALP was not close to end of treatment (data was from greater than 7days to over 30 days from end of treatment). With almost 20-30% patients with inadequate data collection, this analysis of mean change in ALP cannot be considered reliable.

- A mean change difference of 20 ng/mL in ALP between the two arms as calculated by the applicant although statistically significant, is not clinical meaningful.

**Secondary Endpoint #2: Time to onset of PSA progression**
The results of the $G^{1,1}$ analysis of time to onset of PSA progression among the ITT subject population demonstrated no difference between the two treatment groups (P = 0.344). The hazard ratio was 0.84 (P = 0.064). It is noted that about 11% of patients are not included in the applicant's ITT analysis which should have 809 patients. The difference in median time to progression of PSA was 3 days.

**Figure 6: Kaplan-Meier Curve of Time to PSA Progression**

N = 720
Applicant figure 8 from the CSR

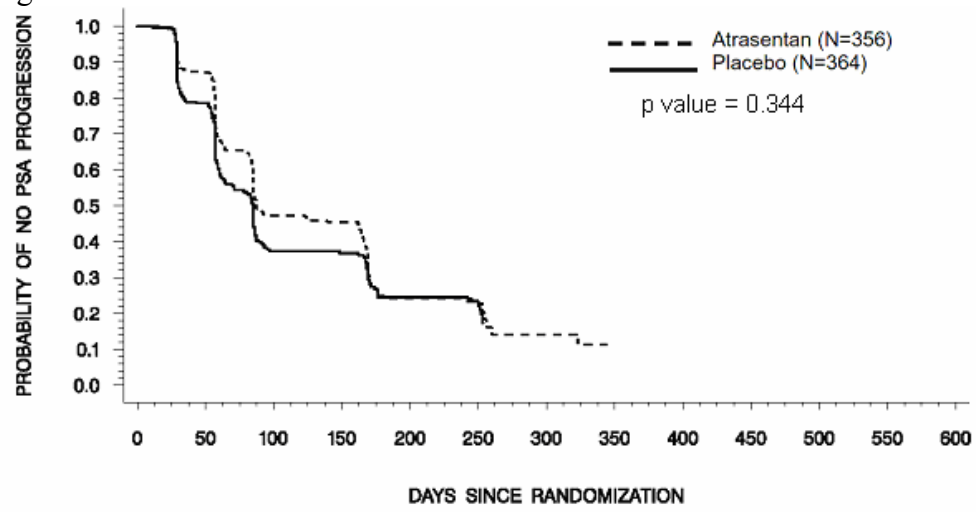



**Table 20: Analysis of Time to PSA Progression**

FDA Analysis

| | **Placebo (N=306)** | **Atrasentan (N=304)** |
|---|---|---|
| **Events** | 199(65.0%) | 191(62.8%) |
| **Quartiles** | | |
| 25th | 55 Days | 57 Days |
| Median | 84 Days | 87 Days |
| 75th | 170 Days | 176 Days |

**Secondary Endpoint #3: Mean Rate of Change from Baseline to Final Value in Total Bone Scan Index**

Bone scans were obtained at baseline, at 12- week intervals, and at study completion. Per applicant, quantitative analyses were performed on all available bone scans from individual subjects using the experimental Bone Scan Index (BSI). Axial, appendicular, and total bone scan indices were calculated for baseline bone scans and for subsequent scans. The mean rate of change from baseline to final value in BSI was calculated. Mean BSI values were similar for the two treatment groups. Atrasentan conferred no advantage to mean rate of change in BSI compared with placebo (P = 0.844).

**Secondary Endpoint #4: Survival:**

Per Applicant, *"Survival information was collected at 3- month intervals following the final visit for an assessment of post- treatment survival. Data were included through 17 November 2003. Given the limited number of deaths to date ( N = 324 [ 40%]; 166 among atrasentan recipients*

*and 158 among placebo recipients) and the short duration of study drug exposure, the results of the G1,1 analysis demonstrated no difference between the two treatment groups (P = 0.982). The hazard ratio was 1.01 (P = 0.944)."*

The number of deaths were greater on the atrasentan arm (atrasentan N=166, 57.3%; and placebo N=158, 56.6%) and the median survival was greater by 7 days in the Atrasentan arm. A cut-off date of April 30, 2004 was used for this analysis by FDA.

Fifty-two (18%) patients were lost to follow-up. For 10 (3%) patients alive and not "lost to follow-up", no updated info was given for 6 – 15 months before the cut-off date. Because survival was to be updated up to every 3 months, these 3 % patients could be counted as "lost-to-follow-up" for the survival analysis, bring up the "lost-to-follow-up" percentage to 21%. The FDA analysis which follows the applicant's analysis censored 18% of patients.

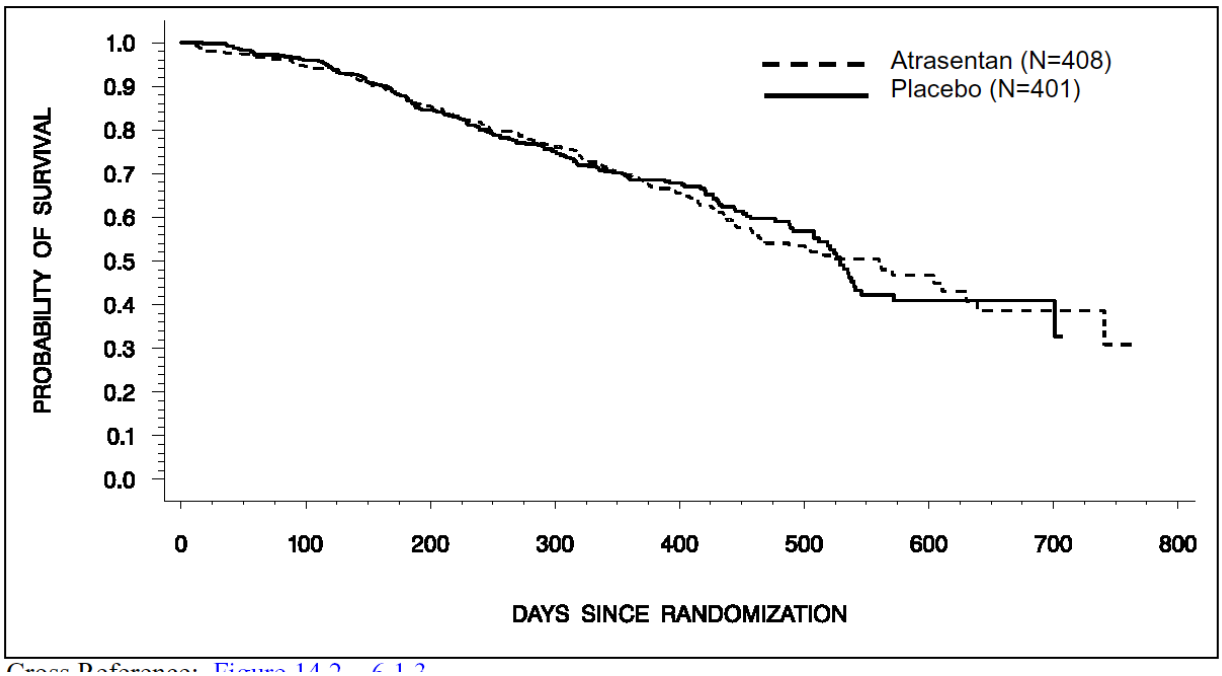
**Table 21: Applicant's Analysis of Time to death- ITT (cut-off date November 17th, 2003)**

CSR Table 14.2_6.1.3

| | **Placebo (N=401)** | **Atrasentan (N=408)** |
|---|---|---|
| **Events** | 158(39.4%) | 166(40.7%) |
| **Quartiles** | | |
| 25th | 301 Days | 317 Days |
| Median | 529 Days | 560 Days |
| 75th | NA | NA |

**Figure 7: Kaplan- Meier Curve of Survival: ITT Subject Population, N = 809**

Applicant's Analysis




Cross Reference: Figure 14.2_6.1.3

**Table 22: Treatment Comparison: Placebo Vs Atrasentan**

CSR Table 14.2_6.1.3

| Test | Chi-square | P-value |
|---|---|---|
| G(1,1) | 0.00 | 0.982 |
| Log-rank | 0.00 | 0.944 |
| Wilcoxon | 0.03 | 0.860 |

Cox Proportional Hazard Model:

| |
|---|
| Hazard ratio: 1.008, p = 0.944 |
| (95% CI: 0.810, 1.253) |

**Figure 8: Kaplan-Meier Curve for Survival**

FDA Analysis

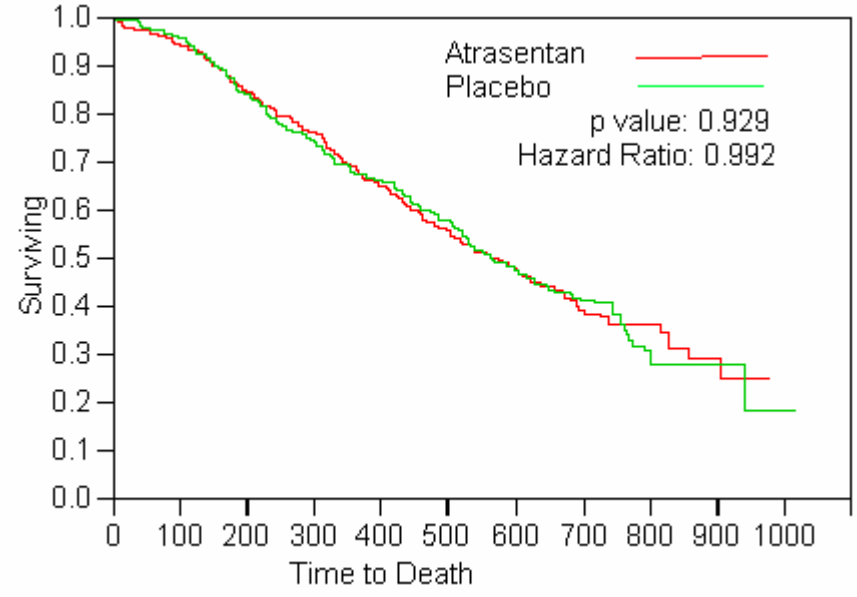



**Table 23: Summary**

| Arm | Number of Deaths N (%) | Censored N |
|---|---|---|
| Atrasentan | 234 (57.3%) | 174 |
| Placebo | 227 (56.6%) | 174 |
| Total | 809 | 348 |

**Quantiles**

| Group | Median Time | 95% CI | 25% Failures | 75% Failures |
|---|---|---|---|---|
| Atrasentan | 574 | 505, 638 | 316 | . |
| Placebo | 567 | 525, 631 | 296 | 944 |

P value 0.9290
HR=0.992, 95% CI (0.826, 1.190)
P values and Hazard Ratio provide by Dr Shengui Tang, statistical reviewer

**Reviewer's Comment:**
There were 8 (1%) more deaths in the atrasentan arm than in the placebo arm. This did not reach statistical significance, but would be of particular concern when treating a large number of patients in with a drug providing questionable benefit. This would be of particular concern in patients with early disease when the survival is relatively longer. Other ongoing studies may help with sorting out a possible adverse survival with atrasentan.

**Tertiary Analysis**

Tertiary analyses should be considered exploratory only. According to the SAP, tertiary analyses comparing the effects of 10 mg atrasentan vs. placebo on the following set of endpoints will be performed. Of note, analysis on patients with bone metastasis at baseline was not one of them.

- time to disease progression,
- progression-free survival,
- survival,
- Quality of Life (QoL) adjusted time to disease progression,
- time to onset of PSA progression,
- time to onset of bone alkaline phosphatase progression, and
- changes and/or percent changes from baseline in PSA, bone markers,
- Karnofsky performance status,
- FACT-P (by domain), and EORTC QLQ-C30 (by domain).

Per study report "*Tertiary analyses included quality-of-life assessments, time to onset of bone alkaline phosphatase progression, and longitudinal analyses of PSA and bone markers. Additional tertiary analyses were performed on both time to disease progression and progression-free survival. As with the secondary analyses, P-values will be considered exploratory for the tertiary analyses."*

**Table 24: Results of Selected Tertiary Endpoints**

| TERTIARY ENDPOINT | UNADJUSTED P < 0.05 | FDA COMMENTS |
|---|---|---|
| Quality of Life (QoL) adjusted time to disease progression,<br>time to onset of PSA progression, | No | |
| time to onset of bone alkaline phosphatase progression, | Yes | 15% missing data |
| Mean changes from baseline in PSA, | No | |
| Bone markers | | Markers and methods of analyses not identified clearly |
| Karnofsky performance status, | No | |
| FACT-P (by domain), | Yes/No | <0.05 in 1 of 6 domains |
| EORTC QLQ-C30 (by domain) | Yes/No | <0.05 for some analyses |

Selected tertiary endpoints will be reviewed below.

**Tertiary endpoint #1: QoL and QATTP** (Quality of Life (QoL) adjusted time to disease progression)

Two types of analyses on QoL were described in the SAP as tertiary endpoints. They were "QoL adjusted time-to-disease progression" and the "quality of life comparison before and after disease progression using appropriate methods". These methods for comparison of QoL were not described in the SAP.

QoL comparison
Per applicant, "Quality of life was assessed during this study using two validated scales: the Functional Assessment of Cancer Therapy – Prostate (FACT- P) 32 and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ- C30). 36 The mean change from baseline to final assessment was analyzed using ANCOVA."

FACT-P:
Per applicant, the FACT-P version 4 is tailored to explore issues specific to prostate cancer. The ITT analysis demonstrated a trend in favor of atrasentan in this tertiary analysis (p= 0.032). Further exploratory analysis on the pain-related domain was in favor of atrasentan (p= 0.015, applicant analysis)

**Table 25: Mean Change from Baseline to Final Assessment for FACT- P: ITT Subject Population**

Applicant table 8 from CSR

| | Mean Change from Baseline at Final Assessment | | Treatment Difference | | |
|---|---|---|---|---|---|
| **Scale (Range)** | **Placebo** | **Atrasentan** | **Mean** | **SE** | **P-value** |
| FACT-P Grand Total (0–156) | –9.34 | –7.95 | 1.40 | 1.222 | 0.253 |
| FACT-G Total (0–108) | –6.11 | –5.54 | 0.58 | 0.874 | 0.510 |
| Prostate Cancer Subscore (0–48) | –3.36 | –2.34 | 1.02 | 0.476 | 0.032* |
| Composite (0–104) | –8.54 | –7.76 | 0.78 | 0.986 | 0.430 |
| Physical well-being (0–28) | –2.71 | –2.73 | –0.02 | 0.343 | 0.946 |
| Social/family well-being (0–28) | –0.17 | 0.26 | 0.44 | 0.278 | 0.115 |
| Emotional well-being (0–24) | –0.70 | –0.49 | 0.21 | 0.265 | 0.438 |
| Functional well-being (0–28) | –2.59 | –2.57 | 0.02 | 0.358 | 0.956 |

*Represents a statistically significant difference between treatment groups at P = 0.05.

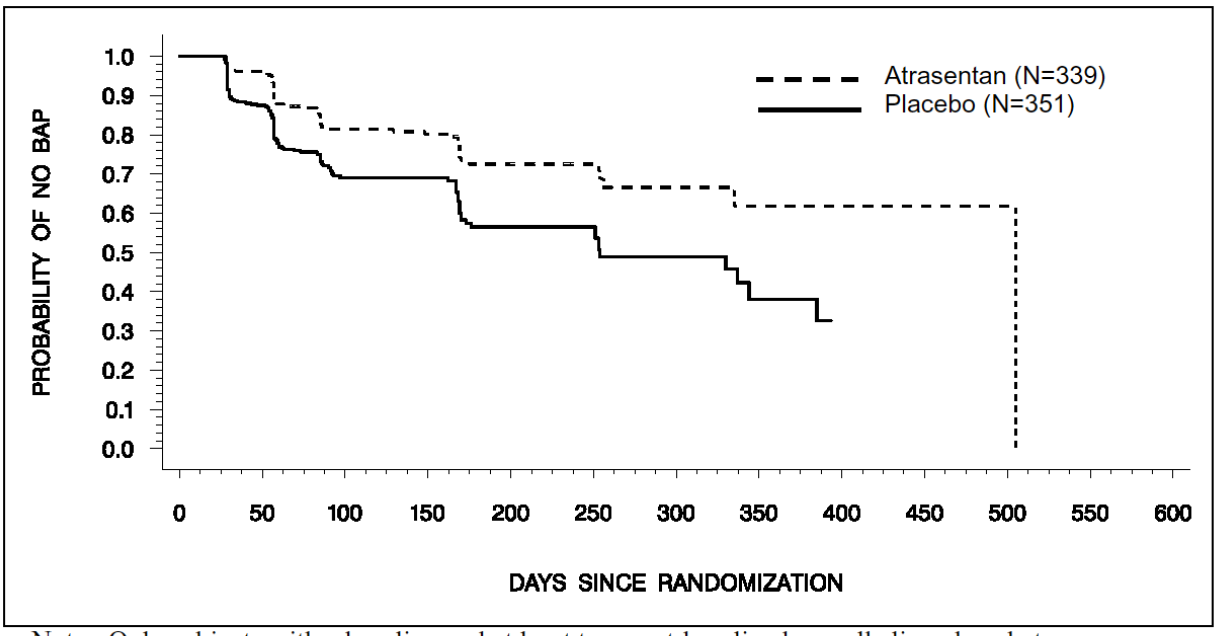
EORTC QLQ- C30:
The applicant analysis suggests that *"Analysis of the EORTC QLQ- C30 questionnaire demonstrated that placebo treatment resulted in deterioration in the social functioning domain compared with atrasentan treatment (mean change from baseline to final – 8.04 and – 11.96 for atrasentan and placebo, respectively; P = 0.027). There was also a trend toward treatment benefit with atrasentan in the pain symptom domain (mean change from baseline to final 10.94 and 14.20 for atrasentan and placebo, respectively, P = 0.090)."*

*QoL Adjusted TTP*
Per applicant, *"To further quantify overall drug benefit for subjects undergoing experimental therapy, a measure was used that integrates efficacy (delay in disease progression) with side effect profile: quality of life– adjusted time to progression (QATTP). This approach adjusts the conventional time to progression variable using a QoL quantitative factor, in this case, the FACT- P. Only the FACT- P grand total score, the FACT- G total score, and the prostate cancer subscale were used. In the ITT subject population QATTP analysis with adjustment using the FACT- P, the median QATTP was longer for the atrasentan group compared with placebo; however, the difference was not statistically significant."*

**Reviewer's Comments:**
The QoL analyses were tertiary analyses and did not demonstrate consistency in all domains. A prespecified detailed SAP for QoL comparison was not submitted. These analyses should be considered exploratory, and not supportive of claim for efficacy.

**Tertiary endpoint #2: Time-to-Onset of Bone Alkaline Phosphatase Progression**
Per Applicant *"Bone alkaline phosphatase progression was defined as the number of days from the day the subject was randomized to the first of two consecutive post- baseline and post- nadir measurements at least 14 days apart that represented increases = 50% of the nadir. The distribution of time to onset of bone alkaline phosphatase progression was estimated for each group using Kaplan-Meier methodology. The analysis of time to onset of bone alkaline phosphatase progression showed that subjects treated with atrasentan had a 44% lower risk of experiencing bone alkaline phosphatase progression than subjects who received placebo (hazard ratio = 0.56 [ P < 0.001 by Cox proportional hazards model])."*

**Figure 9: Kaplan-Meier Curve of Time to Bone Alkaline Phosphatase Progression:**




Note: Only subjects with a baseline and at least two post-baseline bone alkaline phosphatase values were included.

**Reviewer's Comments:**
This analysis excluded 119 patients from analysis (15%), and is not reliable due to missing data.

**Tertiary endpoint #3:**

**Time-to disease progression – per protocol analysis:**
According to the Clinical Study Report, TDP had a median of 85 days on the placebo arm, increasing by only 4 days to 89 days on the atrasentan arm (log-rank p-value: 0.007. HR: 0.79, 95% CI 0.669-0.942)

**Figure 10: Kaplan-Meier Curve of Time to Disease Progression: Per- Protocol Subset**

Applicant figure 13 from the CSR

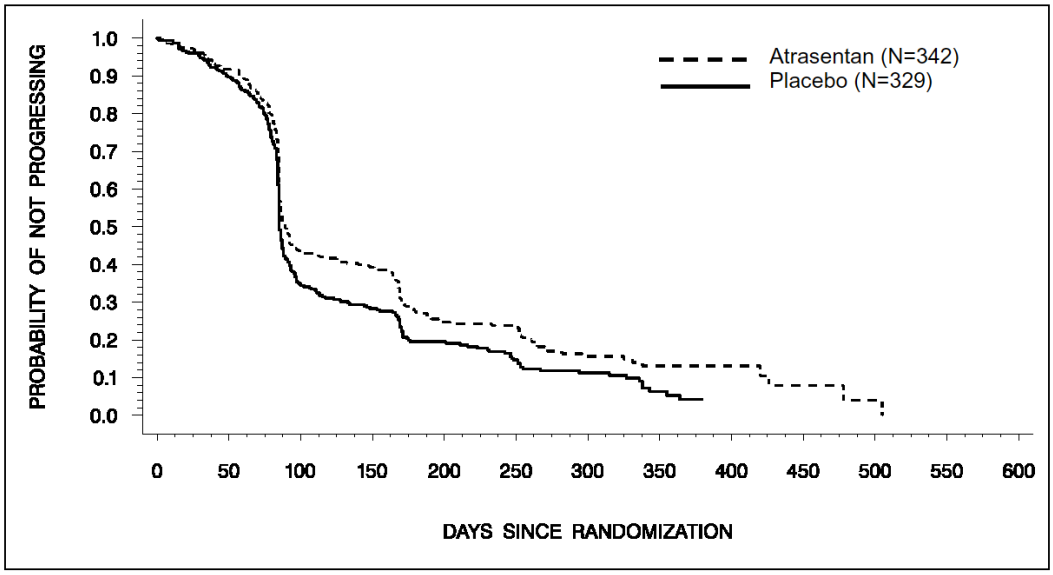



**Table 26: Analysis of Time to Disease Progression (per-protocol analysis)**

Applicant table 14.2__ 1.2.3 from CSR

| | **Placebo (N=329)** | **Atrasentan (N=342)** |
|---|---|---|
| **Events** | 271(82.4%) | 256(74.9%) |
| **Quartiles** | | |
| 25th | 79 Days | 83 Days |
| Median | 85 Days | 89 Days |
| 75th | 169 Days | 197 Days |

Treatment comparison: Kaplan-Meier method:

| **Test** | **Chi-Square** | **P-Value** |
|---|---|---|
| G(1,1) | 6.75 | 0.009 |
| Log-Rank | 7.34 | 0.007 |
| Wilcoxon | 5.82 | 0.016 |

HR: 0.794, 95% C.I.: 0.669, 0.942)

**Reviewer's Comments:**
The per-protocol analysis appears to reach statistical significance. However, there are major weaknesses in this analysis and its results.

- This analysis per protocol was to be tertiary and exploratory only. The statistical significance of this analysis was not going to be claimed, even if it reached significance. No change was made to the SAP to make this a primary endpoint.

- The difference in the TDP can not be considered clinically meaningful.

- Almost 75% of events were due to radiologic disease progression, which records DP at some point after the actual occurrence of DP. The median TDP is slightly less than 12 weeks, which is the time point that the first radiological evaluation was performed. It only means is that the event occurred some time between randomization and the first (12th week) radiological exam, at which time the event was detected. Measuring improvement of only a few days may in reality not be possible.

**Tertiary endpoint #4:**

**PSA**
According to the applicant's analysis, mean change in PSA over time was analyzed using ANCOVA on observed cases. Mean baseline PSA values were slightly higher for placebo subjects than for atrasentan subjects, although not significantly different. (p=0.082)

**Table 27: Median Change from Baseline to Final Value in PSA:ITT**

Applicant table 25 ISE

| Treatment Group | n | Baseline (ng/mL) | Median (ng/mL) | Atrasentan vs. Placebo *P* value[a] |
|---|---|---|---|---|
| Placebo | 387 | 76.7 | 88.7 | .082 |
| Atrasentan | 384 | 66.3 | 68.8 | |

[a] P value based on Wilcoxon rank sum test

**Other Retrospective Subgroup Analyses**
Many subsets were analyzed by the applicant retrospectively. The applicant has changed the efficacy population from the ITT analysis to patients with bone metastases at baseline more than half way through the review of this NDA. This may have been based on the multiple analyses that were performed. These analyses should be considered exploratory and hypothesis generating.

**Table 28: Summary of Time to Disease Progression Analysis in All Subject Populations**

Applicant table 12 from CSR

| Group/Subgroup | G[1,1]P-value | Hazard Ratio | Hazard Ratio P-value |
|---|---|---|---|
| **Intent-to-treat (N = 809)** | **0.136** | **0.89** | **0.131** |
| Per-protocol (N = 671) | 0.009 | 0.79 | 0.008 |
| Bone metastases at baseline (N = 684) | 0.019 | 0.81 | 0.013 |
| No bone metastases at baseline (N = 119) | 0.218 | 1.39 | 0.142 |
| Soft-tissue metastases at baseline (N = 307) | 0.766 | 1.06 | 0.642 |
| No soft-tissue metastases at baseline (N = 496) | 0.208 | 0.81 | 0.041 |
| Bone and soft-tissue metastases at baseline (N = 210) | 0.765 | 1.13 | 0.442 |
| Bone but no soft-tissue metastases at baseline (N = 474) | 0.021 | 0.72 | 0.002 |
| Soft-tissue but no bone metastases at baseline (N = 97) | 0.804 | 0.95 | 0.807 |
| No metastases at baseline (N = 22) | 0.005 | 9.21 | 0.012 |

No adjustment of alpha for multiple analyses was performed.

**Reviewer's Comments:**
The applicant performed multiple analyses, some of which showed atrasentan as better than placebo. Retrospective analysis on a subgroup of patients with bone metastases was identified by the applicant as the primary basis of efficacy for atrasentan 6 months into the review of the NDA.

**Primary Basis of Efficacy Per Applicant:**
The primary basis of efficacy was not evident from the submitted Integrated Summary of Efficacy. In an email sent six months into the review clarifying this primary basis of efficacy, the applicant indicated that the population for primary consideration of efficacy of atrasentan should be patients with bone metastases at baseline. Patients with soft tissue metastases at baseline were

not included, even though they were included in the intended population of the protocol. Additionally, the applicant wanted to change the proposed indication based on this retrospective analysis that was not pre-specified. The relevant parts of this email dated 6/24/2005 are given below.

*"The efficacy analysis we would like you to consider as the critical evidence in support of the clinical benefit of atrasentan is the analysis of the population of patients with baseline metastatic disease to bone in Study M00-211. This group of patients (690/809) represents 85% of all patients included in the study. In the emerging paradigm of personalised medicines, we believe the patients with metastastic disease to bone are the patients likely to receive the optimal benefit from treatment with atrasentan. It is important to note that the presence of metastases to bone in Study M00-211 was determined by an independent, external radiologist prior to enrollment into the study. The treatment effect for the primary endpoint of time to disease progression in this patient population provided a favorable effect for atrasentan (hazard ratio = 0.813, 95% CI = 0.685 - 0.965; p-value = 0.016). This positive effect is further supported by the benefit observed in the secondary and other endpoints: biomarkers, QoL and metastatic pain."*

It is interesting to note that the number of patients with bone metastases at baseline in the email (N=690) is more than that submitted in the Integrated Summary of Efficacy in December 2004 (N=684). The applicant provided clarification about the discrepancy in these numbers as follows: *"In the M00-211 CSR, there are 684 subjects presenting with bone metastases at baseline, where the baseline scans were performed prior to study drug adminsitration. Subsequently, the definition of baseline was changed to include bone and CT scans up to 21 days after the start of study drug to account for subjects whose baseline scans were performed after the start of study drug. As a result, six additional patients (1038, 1039, 1354, 2693, 1013, and 2899) were added to this cohort for a total of 690 patients with bone metastases at baseline."*

**Patients with bone metastases at baseline**

The applicant performed a retrospective review of the 684 patients with bone metastases at base line (that is, 85% of all patients enrolled). The time to disease progression was improved by a median of 7 days with a p value of 0.019, and a hazard ratio of 0.81. This difference does not appear to be clinically significant. The applicant's Kaplan-Meier curve and analyses are given below.

**Figure 11: Time to Disease Progression: Bone Metastasis Population in Study M00- 211**

Applicant figure 14 from CSR

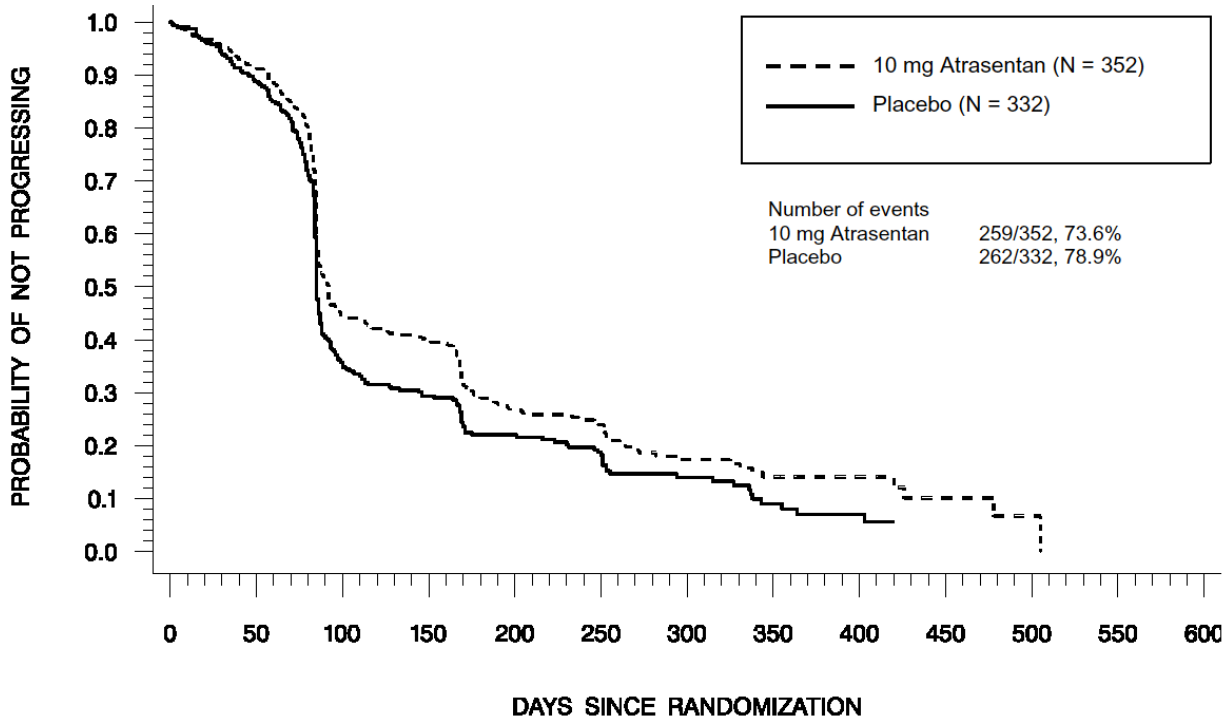



**Table 29Time to Disease progression in patients with bone metastases at baseline (N= 684)**

Applicant analysis
Table 14.2_1.3.1 of CSR

| | **Placebo (N=332)** | **Atrasentan (N=352)** |
|---|---|---|
| Events | 262(78.9%) | 259(73.6%) |
| Quartiles | | |
| 25th | 77 Days | 83 Days |
| Median | 85 Days | 92 Days |
| 75th | 169 Days | 237 Days |

Log rank p:0.011; Hazard ratio 0.805 (95% CI 0.678,0.956)

The applicant submitted many further analyses on this retrospective subgroup which will not be discussed in this review, because the study failed in its primary endpoint, most of the secondary endpoints, and many tertiary endpoints.

**Additional Exploratory Analysis:**
**Time-to-disease Progression in excluded patients**
As noted above, the ITT analysis of patients did not show any difference in the time-to-disease-progression. However, after excluding 139 (17%) patients to come up with the per-protocol population, the TDP becomes significant. An exploratory analysis was performed to evaluate time-to-disease progression in the excluded patients in greater detail.

Forty three of 66 (65%) patients on the Atrasentan arm and 44 of 73 (60%) patients on the placebo arm progressed, with a median of 3.3 months. Although not reaching statistical significance, the placebo patients trend towards a better TDP, particularly after the initial period. The p value for this analysis does not reach statistical significance probably because of the small sample size.

**Figure 12: K-M curve for time to disease progression in patients excluded from the per-protocol population.**

FDA Analysis

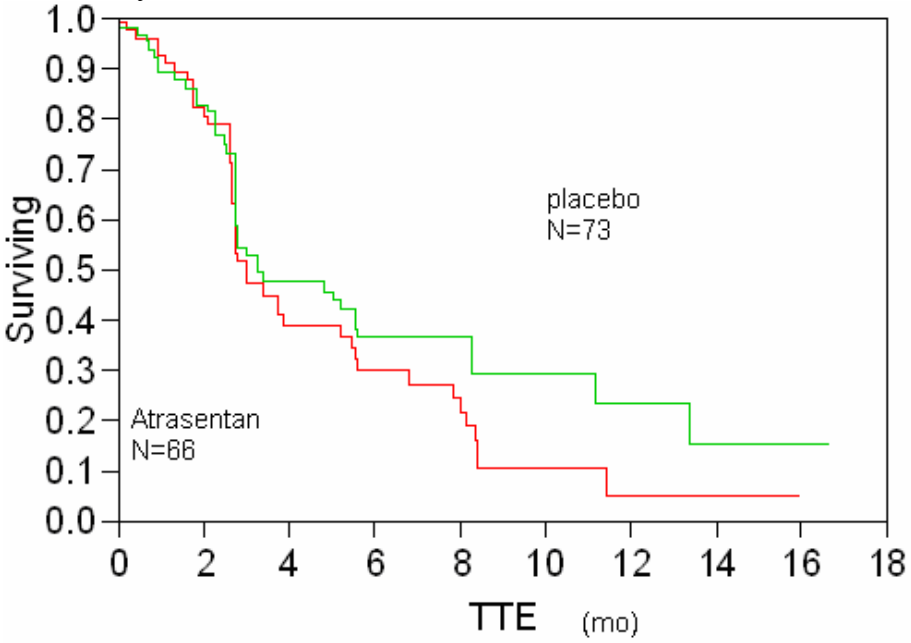



**Table 30: Summary**

| Arm | N Failed | N Censored |
|---|---|---|
| Atrasentan | 43 | 21 |
| Placebo | 44 | 28 |

**Quantiles**

| Arm | Median Time In months | 95% CI | Log Rank P value |
|---|---|---|---|
| Atrasentan | 3.0 | 2.7, 5.5 | 0.19 |
| Placebo | 3.3 | 2.8, 5.7 | |

**Survival in excluded patients**

On the same patients, that were excluded from the per protocol analysis, there was a trend towards poorer survival on the atrasentan arm. This is an exploratory analysis like the one on patients with only bone metastases at baseline. This analysis could raise concern regarding the safety of atrasentan.

**Figure 13: Kaplan-Meier Curve for Survival in Patients excluded from Per-Protocol Analysis**

FDA Reviewer Analysis

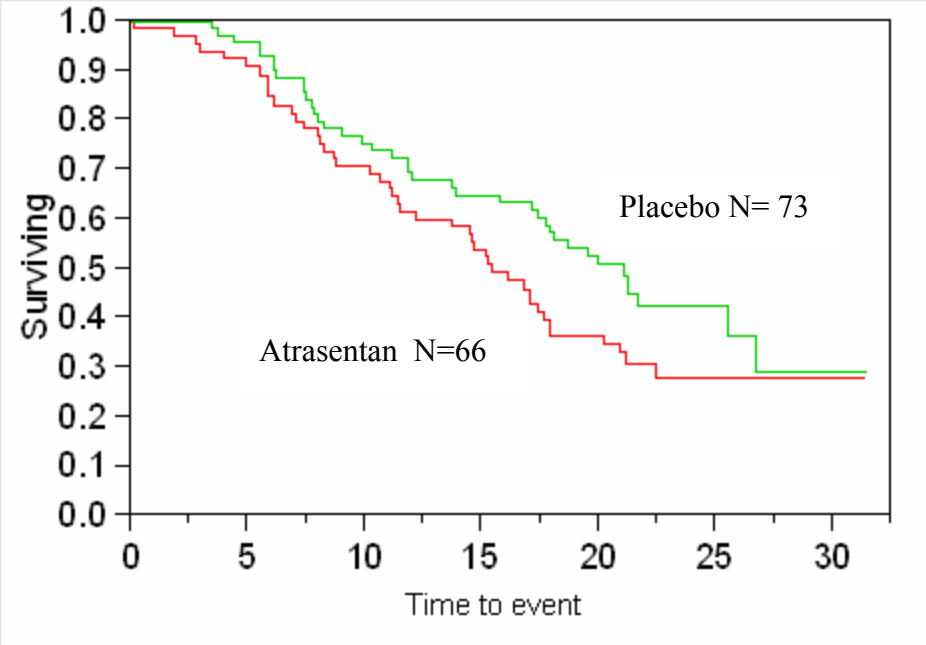



**Table 31: Number of deaths and time to death in excluded patients.**

| Arm | Events | Median Time | 95% CI for time to event |
|---|---|---|---|
| **Atrasentan N=66** | 45 | 15.4 | 11.6-17.933 |
| **Placebo N=73** | 39 | 21.1 | 17.3-26.8 |

Log rank p value 0.0947

**Time to Disease Progression in Patients with No Bone Metastases at Baseline**

As with patients excluded from the per-protocol population, patients with no bone metastases at baseline, also show a trend towards poorer time to disease progression was observed on the atrasentan arm (log rank p vale 0.134).

**Figure 14: K-M curve for time to disease progression in patients with no bone metastases at baseline**

Sponsor Figure

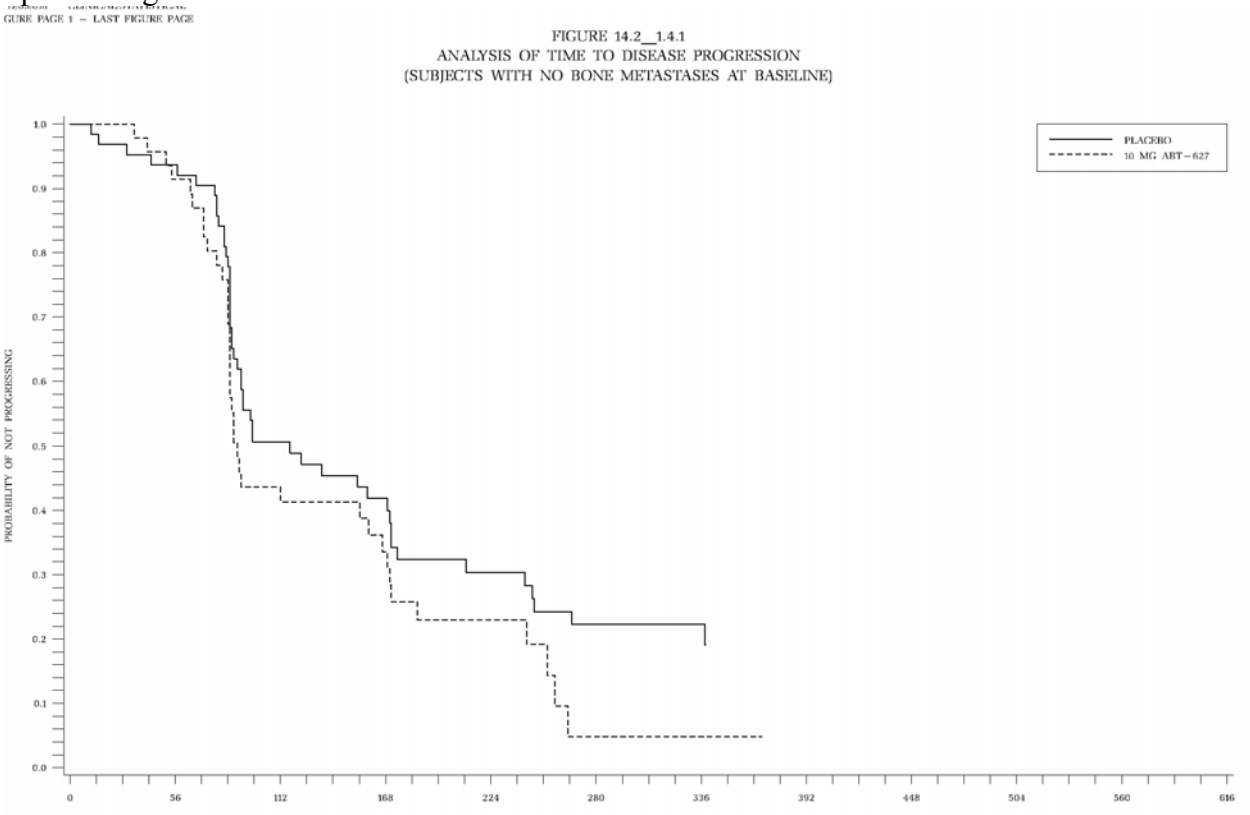


**Table 32Applicant table from CSR**

TABLE 14.2__1.4.1

ANALYSIS OF TIME TO DISEASE PROGRESSION
(SUBJECTS WITH NO BONE METASTASES AT BASELINE)

| | PLACEBO (N=66) | 10 MG ABT-627 (N=53) |
|---|---|---|
| EVENTS | 47(71.2%) | 37(69.8%) |
| QUARTILES | | |
| 25TH | 85 Days | 84 Days |
| MEDIAN | 117 Days | 89 Days |
| 75TH | 247 Days | 185 Days |

TREATMENT COMPARISON: PLACEBO vs 10 MG ABT-627

KAPLAN-MEIER METHOD:

| TEST | CHI-SQUARE | P-VALUE |
|---|---|---|
| G(1,1) | 1.52 | 0.218 |
| LOG-RANK | 2.24 | 0.134 |
| WILCOXON | 1.52 | 0.218 |

COX PROPORTIONAL HAZARD MODEL:
HAZARD RATIO: 1.386, p = 0.142
(95% C.I.: 0.897, 2.142)
(BETA = 0.33, SE = 0.222)

**Survival in patients without bone metastases**

The definition of "baseline" was changed by sponsor to include bone scans performed 21 days after starting the study drugs. The numbers of patients in this survival analysis is based on the updated datasets. The survival was similar in both arms.

**Figure 15: Kaplan-Meier Curve for patients without bone metastases**

FDA Analysis

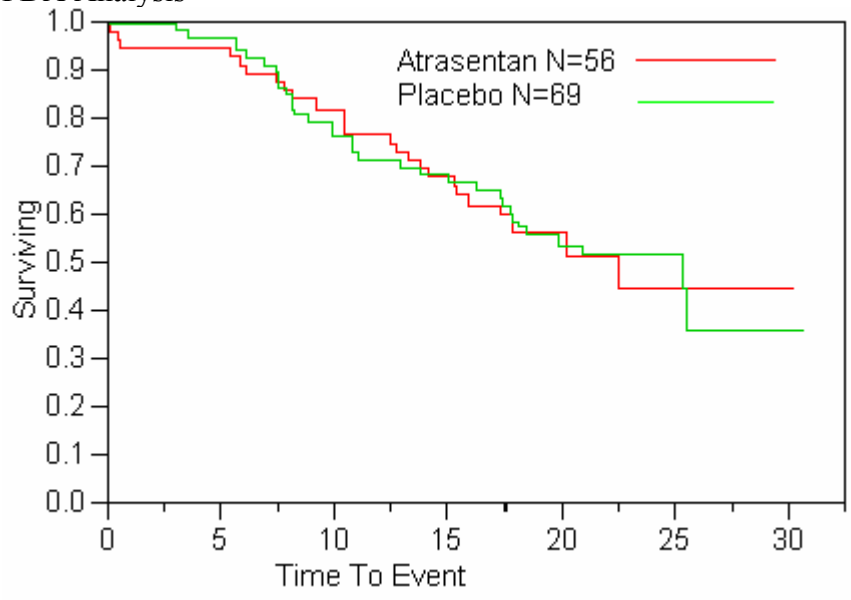


**Table 33: Summary**

| Treatment Arm | Deaths N | Censored |
|---|---|---|
| Atrasentan N=56 | 28 | 28 |
| Placebo N=69 | 33 | 34 |

**Quantiles**

| Treatment Arm | Median Time In weeks |
|---|---|
| Atrasentan | 22.5 |
| Placebo | 25.4 |

**Tests Between Groups**

| Test | Prob>ChiSq |
|---|---|
| Log-Rank | 0.9175 |
| Wilcoxon | 0.9147 |

**Audit of timing of radiology assessments:**

An event occurs sometime before the assessment for the event. Large numbers of missing data, or skewed timing of assessment of these assessments would make the time-to event analyses invalid. Because the most common event in this study was progression due to increase in bone scan lesions, data on bone scans is reviewed for missing data and for skewed timing. Numbers of bone scans performed or missed at scheduled time intervals were similar in both arms.

Six hundred and fifty five of the 809 (80%) patients have documentation of a bone scan at 12 weeks, 327 in the atrasentan arm and 328 in the placebo arm. The time of the "12 week scan" ranged from 35 days to 167 days after randomization. Only 52% of all patients had their 12-week bone scans performed on 90 days after randomization $\pm$ 7 days (Atrasentan: 204 patients; placebo: 215 patients; total 419). One rationale for not performing the bone scan would be if the patient had progressed by some other criteria. However, 69 patients (Atrasentan: 41 and placebo 28, 10% of total number of patients) did not have the 12-week bone scan though they had not progressed. At the next bone scan at 24 weeks, about 70% of patients did not have a bone scan. The numbers of missing scans make evaluations on them pointless, except for the observation that the numbers of scans performed were similar across the two arms.

Most of the patients with missing scans discontinued drug before the first bone scan and did not have a bone scan before study discontinuation. However, 10 % missing data at the first time assessment in an imprecisely determined endpoint of time-to-disease progression when the median TDP is 12 weeks (time for first radiological assessment), adds further questions regarding the validity of the study results.

**Table 34: Number of bone scans performed or missed at scheduled time intervals**

| | Bone scans performed | | Missing bone scans | |
|---|---|---|---|---|
| | **Atrasentan N=408 (%)** | **Placebo N=401 (%)** | **Atrasentan N=408 (%)** | **Placebo N=401 (%)** |
| Week 12 | 327 (80) | 328 (82) | 81 (20) | 73 (18) |
| Week 24 | 135 (33) | 107 (27) | 273 (67) | 294 (73) |
| Week 36 | 49 (12) | 54 (13) | 359 (88) | 347 (87) |
| Week 48 | 21 (5) | 20 (5) | 387 (95) | 381 (95) |
| Week 60 | 6 (1) | 7(2) | 402 (99) | 394 (98) |
| Week 72 | 2 (<1) | 1 (<1) | 406 (>99) | 400 (>99) |

The mean and standard deviation of time to bone scan from randomization was analyzed by the statistical reviewer Dr Shenghui Tang Ph.D. The standard deviations for each time to scheduled bone scan were about 1 week. See table 35. One should question difference in TDP at the median and 25$^{th}$ percentile timepoints between the two arms.

**Table 35: Mean and SD (in weeks) of Time To Bone Scan From Randomization**

| Time from randomization to Bone Scan | # (%) | | Mean (SD) | |
|---|---|---|---|---|
| | **Atrasentan N= 408** | **Placebo N=401** | **Atrasentan N= 408** | **Placebo N=401** |
| Week 12 | 327 | 328 | 11.9 (1.3) | 11.9 (1.4) |
| Week 24 | 135 | 107 | 24.2 (1.3) | 23.8 (0.9) |
| Week 36 | 49 | 54 | 35.6 (1.9) | 36.0 (1.7) |
| Week 48 | 21 | 20 | 47.8 (0.8) | 47.7 (1.0) |
| Week 60 | 6 | 7 | 60.4 (0.8) | 59.5 (2.5) |
| Week 72 | 2 | 1 | 70.4 (2.3) | 71.4 (-) |

**Table 36: Time to disease Progression- ITT and Two Subpopulations**

Based on Applicant Analyses

| | N | Events | 25th | Median | 75th (95% CI) |
|---|---|---|---|---|---|
| **ITT** | | | | | |
| Placebo | (N=401) | 311(77.6%) | 79 days | 86 days | 171 days (168,246) |
| Atrasentan | (N=408) | 299(73.3%) | 82 days | 91 days | 233 days (173,254) |
| **Per-Protocol** | | | | | |
| Placebo | (N=329) | 271(82.4%) | 79 Days | 85 Days | 169 Days (134,201) |
| Atrasentan | (N=342) | 256(74.9%) | 83 Days | 89 Days | 197 Days (171,261) |
| **Patients with bone metastases at baseline** | | | | | |
| Placebo | (N=332) | 262(78.9%) | 77 Days | 85 Days | 169 Days (144,230) |
| Atrasentan | (N=352) | 259(73.6%) | 83 Days | 92 Days | 237 Days (176,264) |

***Safety***

**Compliance:**

The CRF captured the investigator's opinion regarding patients' compliance, as measured by whether the patients took drug ≥ 80% of the time. Treatment compliance was determined prior to dispensing new medication to any study subject. Subjects whose compliance fell below 80% were required to undergo counseling conducted by site personnel. The percentage of subjects who were less than 80% compliant at any visit during which study drug administration was recorded was 10.6% for the placebo group (42 subjects) and 14.9% for the 10 mg atrasentan group (60 subjects).

**Table 37: Treatment compliance**

Applicant table 14.1_1.3

| | **PLACEBO (N=397)** | | **ATRASENTAN (N=404)** | |
|---|---|---|---|---|
| Subjects was 80% compliant | | | | |
| Yes | 355 | (89.4%) | 344 | (85.1%) |
| No | 42 | (10.6%) | 60 | (14.9%) |

**Drug exposure:**

Extent of Subject Exposure to Study Drug was evaluated by the applicant. The exposure was similar in both treatment groups.

**Table 38: Drug Exposure**

Applicant Table 14.1__ 1.4 from CSR

| STUDY DRUG EXPOSURE | PLACEBO (N=401) | 10 MG ABT-627 (N=408) |
|---|---|---|
| 0 DAYS | 4 ( 1.0%) | 4 ( 1.0%) |
| 1-27 DAYS | 12 ( 3.0%) | 27 ( 6.7%) |
| >27 - 55 DAYS | 26 ( 6.5%) | 23 ( 5.7%) |
| >55 - 83 DAYS | 38 ( 9.6%) | 32 ( 7.9%) |
| >83 - 111 DAYS | 101 (25.4%) | 89 (22.0%) |
| >111 - 132 DAYS | 65 (16.4%) | 67 (16.6%) |
| >132 - 167 DAYS | 38 ( 9.6%) | 33 ( 8.2%) |
| >167 - 195 DAYS | 28 ( 7.1%) | 33 ( 8.2%) |
| >195 - 223 DAYS | 25 ( 6.3%) | 37 ( 9.2%) |
| >223 - 251 DAYS | 9 ( 2.3%) | 10 ( 2.5%) |
| >251 - 279 DAYS | 11 ( 2.8%) | 15 ( 3.7%) |
| >279 - 307 DAYS | 14 ( 3.5%) | 17 ( 4.2%) |
| >307 - 335 DAYS | 5 ( 1.3%) | 2 ( 0.5%) |
| >335 - 363 DAYS | 7 ( 1.8%) | 7 ( 1.7%) |
| >363 - 391 DAYS | 6 ( 1.5%) | 5 ( 1.2%) |
| >391 - 419 DAYS | 6 ( 1.5%) | 1 ( 0.2%) |
| >419 - 447 DAYS | 1 ( 0.3%) | 2 ( 0.5%) |
| >447 - 475 DAYS | 2 ( 0.5%) | 1 ( 0.2%) |
| >475 - 503 DAYS | 1 ( 0.3%) | 2 ( 0.5%) |
| >503 DAYS | 2 ( 0.5%) | 1 ( 0.2%) |
| MEAN | 147 DAYS | 144 DAYS |
| STD | 95 DAYS | 91 DAYS |
| MED | 116 DAYS | 119 DAYS |
| RANGE | ( 1, 541) | ( 2, 532) |

Average subject exposure to study drug was shorter in study M00- 211 than in study M96- 594. This could be largely driven by the change in the scheduling of the first bone scan at week 12 in study M00- 211, while the first follow- up bone scan in study M96-594 was performed only at the investigator's discretion or at final visit.

**Table 39: Summary of Subject Exposure to Atrasentan and Placebo in the two randomized trials**

Table 11 ISE

| | M00-211[a] | | M96-594 | | |
|---|---|---|---|---|---|
| **Number of Dosing Days** | **Placebo (N = 397)** | **10 mg Atrasentan (N = 404)** | **Placebo (N = 104)** | **2.5 mg Atrasentan (N = 95)** | **10 mg Atrasentan (N = 89)** |
| Mean | 146 | 143 | 172 | 183 | 182 |
| Median | 116 | 119 | 126 | 139 | 150 |
| Range | 1 – 541 | 2 – 509 | 1 – 521 | 1 – 594 | 14 – 539 |

**Table 40: Number of patients in the safety arms**

| SAFETY ARM | N |
|---|---|
| Atrasentan | 404 |
| Placebo | 397 |
| Not treated | 5 |
| Randomized to M00211 and moved to M00-244 | 3 |

Three hundred and ninety three (97.2%) patients had any AE on the Atrasentan arm and 384 (96.7%) on the placebo arm.

**Adverse Event Severity:**
According to the original protocol, the severity of each adverse event was to be according to the National Cancer Institute (NCI) Common Toxicity Criteria (CTC), version 2.0. If the event was not listed in the NCI CTC, the following Grade (Severity) rating guideline will be used:

- Grade 1 The adverse event is transient and easily tolerated by the subject. (Mild)
- Grade 2 The adverse event causes the subject discomfort and interrupts the subject's usual activities. (Moderate)
- Grade 3/4: The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening. (Severe)

**Table 41:AE By Body System**

AE ≥ 10% for any grade or ≥ 1% for grade 3 or 4 toxicity on Atrasentan Arm

| BODY SYSTEM | COSTART TERM DESCRIPTION | ATRASENTAN ALL GRADES % | ATRASENTAN GRADE 3 & 4 % | PLACEBO ALL GRADES % | PLACEBO GRADE 3 & 4 % |
|---|---|---|---|---|---|
| Body As A Whole | Pain | 24 | 2 | 26 | 2 |
| | Headache | 22 | 1 | 14 | 0 |
| | Asthenia | 16 | 1 | 18 | 2 |
| | Infection | 13 | 1 | 8 | 0 |
| | Back Pain | 10 | 1 | 11 | 1 |
| | Sepsis | 1 | 1 | 1 | 1 |
| Cardiovascular System | Heart Failure | 4 | 3 | 1 | <1 |
| | Myocardial Infarct | 2 | 2 | 1 | 1 |
| | Deep Thrombophlebitis | 1 | 1 | 1 | 0 |
| Digestive System | Constipation | 20 | 1 | 18 | 1 |
| | Nausea | 13 | 1 | 14 | 1 |
| | Anorexia | 12 | 0 | 13 | 1 |
| Hemic And Lymphatic System | Anemia | 13 | 4 | 9 | 4 |
| Metabolic And Nutritional Disorders | Peripheral Edema | 40 | 1 | 13 | 1 |
| | Hyperuricemia | 2 | 1 | 3 | 3 |
| Musculoskeletal System | Bone Pain | 50 | 10 | 55 | 16 |
| | Pathological Fracture | 2 | 1 | 2 | 1 |
| Nervous System | Urinary Retention | 3 | 1 | 6 | 3 |
| | Paraplegia | 2 | 2 | 3 | 2 |
| Respiratory System | Rhinitis | 37 | 0 | 14 | 0 |
| | Dyspnea | 10 | 2 | 4 | 1 |
| | Pneumonia | 3 | 2 | 1 | 0 |
| | Apnea | 1 | 1 | 0 | 0 |
| Urogenital System | Prostatic Carcinoma | 12 | 6 | 16 | 7 |
| | Hematuria | 7 | 2 | 7 | 3 |
| | Urinary Tract Disorder | 3 | 1 | 2 | 1 |
| | Bladder Stenosis | 2 | 1 | 1 | 0 |

1 episode each of PVD (grade 2), Thromboembolism (grade 3) and heart failure (grade 2) occurred on day 31, all on atrasentan arm and were not included in the table above.

**CVS**

*Cerebro*vascular events and pallor were removed by the FDA from the applicant database using Costart Terms for AEs involving cardiovascular system. Eighty one (20%) patients are listed as having had at least one cardiovascular AE in the atrasentan arm and 66 (17%) in the placebo arm.

**Table 42: AE involving Cardiovascular System**

| AE | ATRASENTAN N=404 | PLACEBO N=397 |
|---|---|---|
| Arrhythmia[1] | 20 | 5 |
| Vasodilatation[2] | 16 | 19 |
| Heart Failure | 17 | 4 |
| CAD[3] | 16 | 5 |
| Hypotension[4] | 13 | 10 |
| PVD[5] | 12 | 7 |
| CVD[6] | 4 | 6 |
| Hypertension | 4 | 9 |
| Thromboembolism[7] | 3 | 0 |
| Cardiomegaly | 1 | 1 |
| Endocarditis | 1 | 0 |
| Syncope | 0 | 7 |

1. Arrhythmias includes palpitations and extrasystoles
2. Vasodilatation has been selected for flushing
3. CAD included Angina pectoris and MIs
4. Hypotension includes postural hypotension
5. PVD includes peripheral thrombophlebitis, varicose veins and telangactasia
6. CVD is mostly due to murmurs
7. Thromboembolism included 2 PEs and 1 retinal artery occlusion

Deaths from Cardiovascular Events

There were 10 deathswere due to cardiovascular events in these patients during treatment or within 30 days of discontinuation, 8 on the atrasentan arm and 2 in the placebo arm. Causes of death in these patients are given in the table below.

**Table 43: Deaths of patients with cardiovascular AE**

| DEATH DURING RX OR WITH 30 DAYS OF RX DISCONTINUATION COSTART TERM FOR AE | ATRASENTAN N=404 | PLACEBO N=397 |
|---|---|---|
| Heart Failure | 4 | 0 |
| Left Heart Failure | 2 | 1 |
| Myocardial Infarct | 2 | 1 |

Arrhythmias

Twenty patients on the Atrasentan arm experienced 24 arrhythmia events, and 5 patients on the placebo arm were reported to have 5 events of arrhythmias.

**Table 44: Arrhythmias by number of patients and number of events**

FDA Analysis

| ARRHYTHMIA EVENT | GRADE | ATRASENTAN N=404 | PLACEBO N=397 |
|---|---|---|---|
| Arrhythmia | 3 | 0 | 1 |
| | 1 | 2 | 0 |
| Atrial fibrillation | 4 | 0 | 1 |
| | 3 | 4 | 1 |
| | 2 | 1 | 0 |
| | 1 | 1 | 0 |
| Atrial flutter | 2 | 1 | 0 |
| | 1 | 1 | 0 |
| Bradycardia | 3 | 1 | 0 |
| Extrasystoles | 1 | 1 | 0 |
| Palpitation | 2 | 1 | 0 |
| | 1 | 2 | 1 |
| Supraventricular extrasystoles | 1 | 1 | 0 |
| Supraventricular tachycardia | 3 | 1 | 0 |
| Tachycardia | 1 | 7 | 0 |
| Ventricular extrasystoles | 2 | 0 | 1 |
| **Total Events** | | **24** | **5** |
| **Number of patients** | | **20** | **5** |

CAD
Patients with "cardiovascular disorders" and "coronary artery disease" were included because of the vague Costart Term**.**

**Table 45: Number of CAD Events**

| COSTART TERM | ATRASENTAN N=404 | PLACEBO N=397 |
|---|---|---|
| Myocardial Infarct | 9 | 2 |
| Angina Pectoris | 5 | 3 |
| Coronary Artery Disorder | 2 | 0 |
| **MI + AP +CAD events** | **16** | **5** |
| **Number of patients with MI + AP +CAD** | **13** | **5** |
| **Pts with grade 3 or 4 CAD events** | **8** | **2** |

Eighteen patients experienced 21 AE related to CAD. Sixteen events (3.9%) in 13 patients occurred on the atrasentan arm. Eight patients had grade 3 or 4 toxicity. Five (1.3%) events in 5 patients occurred on the placebo arm and 2 of these patients had grade 3 or 4 toxicity.

All 3 patients under the Costart term "coronary artery disease" were in the atrasentan arm, during or within 30 days of discontinuation of dosing (patient IDs 1253, 1207, and 2634). One patient had unstable angina and 1 required stent placement. The patient with angina pectoris was moved to the appropriate Costart term in the table above.

CHF:
Seventeen patients with CHF on the Atrasentan Arm and 4 patients on the placebo arm. Eleven patients on the atrasentan arm had grade 3 or 4 events. Three patients on the placebo arm had grade 3 or 4 events.

Peripheral edema was classified in metabolic and nutritional disorders in the electronic dataset AE. This term is not listed as such in the NCI criteria version 2 or 3. Edema in NCI toxicity criteria is listed in cardiovascular section. A general classification for default when a term was not found in the NCI CTC was included in the original protocol. There was no differentiation provided between grade 3 or 4 toxicity. Most of peripheral edema events involved bilateral ankle edema, and were likely due to CHF. The incidence of grade 3/4 peripheral edema was low on both arms (1% in each arm).

**Table 46: NCI CTC (v2) for edema**

| Toxicity | Grade 0 | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|---|
| Edema | none | asymptomatic, not requiring therapy | symptomatic, requiring therapy | symptomatic edema limiting function and unresponsive to therapy or requiring drug discontinuation | anasarca (severe generalized edema |

**Table 47: CHF as an AE by treatment arm and severity**

| GRADE | ATRASENTAN N=404 | PLACEBO N=397 | ATRASENTAN % | PLACEBO % |
|---|---|---|---|---|
| 1 | 2 | 1 | 0 | 0 |
| 2 | 4 | 0 | 1 | 0 |
| 3 | 5 | 1 | 1 | 0 |
| 4 | 6 | 2 | 1 | 1 |
| **All grades** | **17** | **4** | **4** | **1** |
| **Grade 3 or 4** | **11** | **6** | **3** | **<1** |

Includes congestive heart failure, heart failure, left heart failure and lung edema.

**Table 48: Peripheral edema by treatment arm and severity**

| GRADE | ATRASENTAN N=404 | PLACEBO N=397 | ATRASENTAN % | PLACEBO % |
|---|---|---|---|---|
| 1 | 96 | 27 | 24 | 7 |
| 2 | 61 | 18 | 15 | 5 |
| 3 | 5 | 5 | 1 | 1 |
| **All grades** | **162** | **50** | **40** | **13** |
| **Grade 3 or 4** | **5** | **5** | **1** | **1** |

Most cases are of bilateral ankle edema

One hundred and seventy (42%) patients on the atrasentan arm had at least one event listed as heart failure, left heart failure, lung edema, or peripheral edema on the atrasentan arm compared to 53 (13%) on the placebo arm. This does not include edema as an event. Twenty patients on the atrasentan arm had edema as an AE compared to 9 patients on placebo.

Cardiovascular Disorder:
Most of the 13 patients under Costart term "cardiovascular disorders had a valvular disorder, with murmurs. One patient had Raynaud's and one had dermatitis related to venous insufficiency.

**Reviewers Comments**
An increase in CHF has been noted with atrasentan use in the phase 2 studies. In this study, there appears to an increase in CAD, heart failures and arrhythmias. There was also an increase in deaths from cardiovascular cause in the atrasentan arm.

**Bleeding**

Bleeding events were listed under various body systems. An attempt has been made below to evaluate them as a group (see table below). Forty six patients on the atrasentan arm had 51 bleeding events, and 44 patients on the placebo arm had 46 bleeding events. The bleeding events were similar in both arms.

**Table 49: Bleeding Events**

| COSTART TERM | ATRASENTAN N=404 | PLACEBO N=397 |
|---|---|---|
| Epistaxis | 13 | 5 |
| Hematuria | 28 | 29 |
| Hemoptysis | 0 | 1 |
| Hemorrhage | 3 | 2 |
| Purpura | 0 | 1 |
| Purpuric Rash | 0 | 1 |
| Rectal Hemorrhage | 6 | 5 |
| Subdural Hematoma | 1 | 2 |
| **Total events** | **51** | **46** |

**Thromboembolism**

There were no data entries for Thromboembolism or thromboses. Several different terms were used to evaluate the incidence of thromboembolism in this study. Cerebral infarct, Cerebral ischemia, Cerebrovascular accident, Coronary artery disorder, Deep thrombophlebitis, Myocardial infarct, Retinal artery occlusion, Thrombophlebitis were evaluated further. Peripheral vascular disease was not included.

There does not appear to be an increase in thromboembolic phenomenon. This does not rule out atherosclerosis leading to CAD and MI.

**Table 50: Thromboembolism Events**

| COSTART TERM | ATRASENTAN N=404 | PLACEBO N=397 |
|---|---|---|
| Cerebral Infarct | 0 | 1 |
| Cerebral Ischemia | 4 | 2 |
| Cerebrovascular Accident | 3 | 3 |
| Coronary Artery Disorder | 3 | 0 |
| Deep Thrombophlebitis | 5 | 2 |
| Myocardial Infarct | 9 | 2 |
| Retinal Artery Occlusion | 1 | 0 |
| Thrombophlebitis | 0 | 1 |

**Gastrointestinal System**

The gastrointestinal AEs were similar on both arms. Constipation occurred most frequently, approximately 20% in each arm, followed by a 13 % incidence of nausea and anorexia.

**Table 51: Selected GI AEs**

| COSTART TERM | ATRASENTAN ALL GRADES % | ATRASENTAN GRADE 3&4 % | PLACEBO ALL GRADES % | PLACEBO GRADE 3&4 % |
|---|---|---|---|---|
| Anorexia | 12 | 0 | 13 | 1 |
| Constipation | 20 | 1 | 18 | 1 |
| Diarrhea | 8 | 0 | 9 | 1 |
| Dry mouth | 6 | 0 | 2 | 0 |
| Dyspepsia | 4 | 0 | 6 | 0 |
| Nausea | 13 | 1 | 14 | 1 |
| Nausea and vomiting | 5 | 0 | 4 | 0 |
| Vomiting | 3 | 1 | 4 | 1 |

**Hemic and Lymphatic System**

Other than the incidence of anemia, all other AEs in the "hemic and lymphatic system" were few.

**Metabolism and nutrition**

The incidence of peripheral edema and edema were higher in the atrasentan arm (40% vs. 12%), probably related to CHF.

**Table 52: Metabolic and nutritional AEs involving at least 1% of patients on the atrasentan arm**

| COSTART TERM | ATRASENTAN ALL GRADES % | PLACEBO ALL GRADES % |
|---|---|---|
| Peripheral edema | 40 | 12 |
| Edema | 5 | 2 |
| Weight loss | 5 | 4 |
| Lactic dehydrogenase increased | 2 | 3 |
| Hyperuricemia | 2 | 3 |
| Weight gain | 1 | 0 |
| Gout | 1 | 1 |
| Hypokalemia | 1 | 0 |
| Alkaline phosphatase increased | 1 | 3 |
| SGOT increased | 1 | 1 |
| Hyperglycemia | 1 | 2 |
| SGPT increased | 1 | 0 |
| Hypoglycemia | 1 | 0 |
| Hyponatremia | 1 | 0 |

**Musculoskeletal system**

Musculoskeletal AEs were similar on both arms, with the most frequently reported AE being bone pain in half the population.

**Table 53: Musculoskeletal AEs involving at least 1% of patients on the atrasentan arm**

| COSTART TERM | ATRASENTAN ALL GRADES % | PLACEBO ALL GRADES % |
|---|---|---|
| Bone pain | 50 | 55 |
| Myalgia | 8 | 6 |
| Arthralgia | 4 | 3 |
| Arthritis | 4 | 2 |
| Leg cramps | 2 | 1 |
| Pathological fracture | 2 | 2 |
| Myasthenia | 1 | 1 |
| Bursitis | 1 | 1 |

**Nervous System**

Nervous system AEs were relatively few. Cerebrovascular ischemia and CVA were recorded in the cardiovascular system, and were few.

**Table 54: Nervous system AEs involving at least 1% of patients on the atrasentan arm**

| COSTART TERM | ATRASENTAN ALL GRADES % | PLACEBO ALL GRADES % |
|---|---|---|
| Dizziness | 8 | 6 |
| Insomnia | 8 | 5 |
| Paresthesia | 4 | 4 |
| Urinary retention | 3 | 6 |
| Somnolence | 3 | 3 |
| Depression | 2 | 3 |
| Paraplegia | 2 | 3 |
| Anxiety | 2 | 2 |
| Hypertonia | 1 | 2 |
| Abnormal gait | 1 | 0 |
| Ataxia | 1 | 0 |
| Emotional lability | 1 | 0 |
| Hallucinations | 1 | 0 |
| Hypesthesia | 1 | 0 |
| Neuropathy | 1 | 0 |

**Respiratory System**

Rhinitis and Dyspnea were higher on the Atrasentan arm. The higher incidence of dyspnea is likely related to CHF. Pneumonia cases were also more on the atrasentan arm, but the difference between arms was small.

**Table 55: Respiratory system AEs involving at least 1% of patients on the atrasentan arm**

| COSTART TERM | ATRASENTAN ALL GRADES % | PLACEBO ALL GRADES % |
|---|---|---|
| Rhinitis | 37 | 14 |
| Dyspnea | 10 | 4 |
| Pharyngitis | 7 | 6 |
| Cough increased | 5 | 5 |
| Pneumonia | 3 | 1 |
| Epistaxis | 3 | 1 |
| Lung disorder | 3 | 1 |
| Bronchitis | 2 | 1 |
| Pleural effusion | 2 | 2 |
| Apnea | 1 | 0 |
| Lung edema | 1 | 0 |
| Atelectasis | 1 | 0 |
| Sinusitis | 1 | 1 |

**Skin**

There was a slightly higher incidence of rash on the experimental arm. 2 of 404 patients had a grade 3 or 4 rash on this arm.

**Table 56: Skin and appendages AEs involving at least 1% of patients on the atrasentan arm**

| COSTART TERM | ATRASENTAN ALL GRADES % | PLACEBO ALL GRADES % |
|---|---|---|
| Rash | 7 | 4 |
| Skin carcinoma | 1 | 1 |
| Dry skin | 1 | 1 |
| Herpes zoster | 1 | 0 |
| Skin disorder | 1 | 0 |
| Skin ulcer | 1 | 1 |
| Sweating | 1 | 2 |

**Special senses**

The AE had a higher trend in the atrasentan arm.

**Table 57: Special senses AEs involving at least 1% of patients on the atrasentan arm**

| COSTART TERM | ATRASENTAN ALL GRADES % | PLACEBO ALL GRADES % |
|---|---|---|
| Conjunctivitis | 3 | 1 |
| Taste perversion | 2 | 0 |
| Deafness | 2 | 0 |
| Amblyopia | 1 | 1 |
| Lacrimation disorder | 1 | 0 |
| Eye disorder | 1 | 1 |
| Cataract specified | 1 | 1 |

**Urogenital system**

The AE in the urogenital system were similar on the two treatment arms. Interestingly, this included prostate cancer, which is the population for this trial, and certainly more than 12-16 % patients had prostate cancer.

**Table 58: AEs involving the urogenital system**

| COSTART TERM | ATRASENTAN ALL GRADES % | PLACEBO ALL GRADES % |
|---|---|---|
| Prostatic carcinoma | 12 | 16 |
| Hematuria | 7 | 7 |
| Urinary tract infection | 5 | 6 |
| Dysuria | 4 | 5 |
| Urinary frequency | 4 | 4 |
| Urinary tract disorder | 3 | 2 |
| Nocturia | 2 | 3 |
| Bladder stenosis | 2 | 1 |
| Hydronephrosis | 2 | 4 |
| Genital edema | 1 | 1 |
| Urinary incontinence | 1 | 1 |
| Urination impaired | 1 | 1 |
| Bladder calculus | 1 | 0 |
| Kidney failure | 1 | 1 |
| Polyuria | 1 | 1 |
| Scrotal edema | 1 | 1 |

**Reviewer's comments regarding safety assessment on M00211:**

The main toxicity of concern is cardiovascular, and CHF is a known AE previously observed in phase II trials. Forty two % patients on atrasentan had CHF vs. 13% on placebo. There were increased numbers of MI in the atrasentan arm (CAD events 16 on atrasentan arm vs 5 on placebo arm). Six patients had grade 3 or 4 arrhythmias on the atrasentan arm when compared to 2 on placebo. The number of deaths due to cardiovascular AEs was greater in the atrasentan arm (N = 8 vs N= 2).

**Conclusions**

M00-211 is a well-designed, prospectively randomized, double blind study in patients with hormone-refractory prostate cancer with the primary endpoint of time to disease progression. This Phase III study and a phase II (M96-594)study have been submitted as the major studies to support the following indication:

*XINLAY is indicated for the treatment of men with metastatic hormone-refractory prostate cancer*.

The phase III study (M00-211) was stopped early by the DSMB due to futility.

Strengths of the study

- This was a well-designed prospectively randomized, double blind study except for a few and relatively minor weaknesses in the primary endpoint definition and its analysis plan.

- The events of disease progression (DP) were progression in skeletal metastases identified by bone scans, soft tissue metastases identified on CT scans, Pain (intervention with one of opioid, corticosteroid, radiation, radionuclide therapy or chemotherapy), interventions for events related to prostate cancer and skeletal related events. These events are clinically relevant, except for those noted later in this section.

- An independent radiologist reviewed all scans. An independent oncologist reviewed all the radiology results and all other events if prompted by the investigator. This oncologist was blinded to the PSA values to prevent any bias related to the PSA values.

Weaknesses in the design of study

- The events defining DP were clinically relevant, except for use of opioids for pain. Ten of fourteen consecutive days of oral or transdermal treatment were required for disease progression, but only one single injection of an opioid (such as Demerol) could qualify a patient for disease progression. Twenty percent of events of disease progression were

related to the use of opioids. Events due to single injections of opioids were likely not enough to impact the study results.

- Follow-up CT scans were not required by the protocol if no soft tissue metastases were identified at baseline. Some progressions due to new soft tissue lesions would have been missed.

- There was no specified time allotted for investigators review of events due to SRE and interventions for prostate cancer related complications. This may have resulted in identification of fewer of these events for disease progression.

Weakness in the analysis and results of study

- According to the statistical analysis plan, the ITT analysis of TDP was the primary endpoint. If this failed, there would be no claims based on the secondary analysis. Tertiary analyses would only be exploratory, and would not be used to make claims. The applicant did not adhere to this SAP for this NDA.

- The study failed to meet its primary endpoint of an ITT analysis of TDP.

- The study failed to meet 4 of 5 secondary endpoints (OS, change in bone scan index, time to PSA progression and progression-free survival). The difference in two arms in the mean change in ALP of 20 ng/ml noted on the fifth endpoint was statistically significant, but not clinically meaningful.

- No one or two analyses were identified as basis of efficacy of atrasentan at the time of submission. Instead many analyses that appear to be in favor of atrasentan were submitted in the ISE to support the efficacy of the NDA.

- After study closure for futility, the applicant defined per-protocol exclusion prior to unblinding, and submitted this and other pre-specified tertiary analyses to support the efficacy of atrasentan. It is to be noted that the SAP was not altered. The difference in the TDP in the “per protocol population” can not be considered clinically meaningful.

- Many retrospective analyses were performed, some of which were in favor of atrasentan and some were not. Atrasentan appears to have adversely affected the TDP of patients with no bone metastases at baseline, soft tissue metastases at baseline, bone and soft-tissue metastases at baseline, and particularly those with no metastases at baseline.

**Table 59: Summary of Time to Disease Progression Analysis in All Subject Populations**

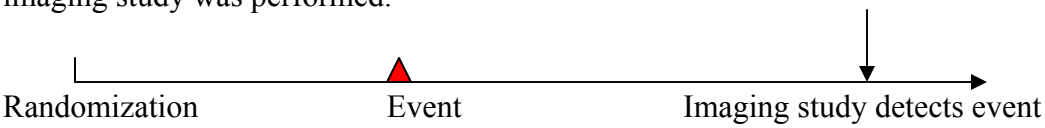
Applicant table 12 from CSR

| SUBGROUP | G[1,1]P-VALUE | HAZARD RATIO | HAZARD RATIO P-VALUE |
|---|---|---|---|
| **Intent-to-treat (N = 809)** | **0.136** | **0.89** | **0.131** |
| Per-protocol (N = 671) | 0.009 | 0.79 | 0.008 |
| Bone metastases at baseline (N = 684) | 0.019 | 0.81 | 0.013 |
| No bone metastases at baseline (N = 119) | 0.218 | 1.39 | 0.142 |
| Soft-tissue metastases at baseline (N = 307) | 0.766 | 1.06 | 0.642 |
| No soft-tissue metastases at baseline (N = 496) | 0.208 | 0.81 | 0.041 |
| Bone and soft-tissue metastases at baseline (N = 210) | 0.765 | 1.13 | 0.442 |
| Bone but no soft-tissue metastases at baseline (N = 474) | 0.021 | 0.72 | 0.002 |
| Soft-tissue but no bone metastases at baseline (N = 97) | 0.804 | 0.95 | 0.807 |
| No metastases at baseline (N = 22) | 0.005 | 9.21 | 0.012 |

No adjustment for alpha for multiple analyses was performed.

- One of the retrospectively identified subsets with favorable results, i.e., patients with no bone metastases at baseline was chosen by the applicant as the primary basis for efficacy six months into the review of this NDA. At this time, the proposed indication for the NDA also changed. The number of patients in this subgroup changed by 6 patients from the time of submission of NDA in December 2004 to June 2005 because of a change in the definition of this subgroup. Any analysis other than the ITT analysis should be considered exploratory and hypothesis-generating.

- With the median time to disease progression at approximately 3 months, most progressions occurred some time between randomization and detected when the first imaging study was performed.




That means the time to disease progression will not reliably identify differences in the time of actual progression, when difference in the two arms is less than 3 months (one imaging cycle). The TDP is similar in the ITT populations, the per-protocol sub-population and the sub-population of patients with bone metastases at baseline, and the difference at various time points is consistently less than 3 months. See table below

**Table 60:Time to disease Progression- ITT and Two Subpopulations**

Based on Applicant Analyses

| | N | EVENTS | 25TH | MEDIAN | 75TH |
|---|---|---|---|---|---|
| **ITT** | | | | | |
| Placebo | (N=401) | 311(77.6%) | 79 days | 86 days | 171 days |
| Atrasentan | (N=408) | 299(73.3%) | 82 days | 91 days | 233 days |
| **Per-Protocol** | | | | | |
| Placebo | (N=329) | 271(82.4%) | 85 Days | 85 Days | 169 Days |
| Atrasentan | (N=342) | 256(74.9%) | 89 Days | 89 Days | 197 Days |
| **Patients with bone metastases at baseline** | | | | | |
| Placebo | (N=332) | 262(78.9%) | 85 Days | 85 Days | 169 Days |
| Atrasentan | (N=352) | 259(73.6%) | 92 Days | 92 Days | 237 Days |

- The standard deviations for time to scheduled bone scan were about 1 week. **See table X** The difference in TDP in the various subpopulations between the two arms is mostly within this standard deviation.

- QoL was defined as a tertiary analysis. The statistical plan was never amended to include QoL as primary efficacy analysis. No statistical adjustment was made for the multiple analyses, and the p values are not interpretable. Internal consistency in efficacy was not observed in the QoL analyses.

Weakness in the conduct of the study

- According to the applicant's analysis, 17% of patients had major protocol deviations (15% by the FDA analysis).

- There were substantial missing data from some secondary endpoints. 18% of patients were lost to follow-up in the survival analysis, and an additional 3% had a most recent follow-up of 6-15 months. This would bring actual percentage of patients lost to follow-up to 21%. There was inadequate data on ALP. Almost 20 to 30% patients had data on ALP either missing or too early to be a final value in a study in which the median time on-study for patients was only approximately 3 months.

Safety Issues

Numerically, there were more deaths on the Atrasentan arm, compared to the placebo arm. This arm also had more deaths from cardiovascular causes. Atrasentan is known to cause CHF in previous Phase II trials. In this study an increase in number of arrhythmias and cardiovascular events such as MI, Angina pectoris and stent placements on the Atrasentan arm was observed. This finding was also seen in the Phase II study which will be discussed next.

Applicant's basis of efficacy:
As noted earlier, several analyses were submitted by the applicant as the basis of efficacy at the time of submission of the NDA. No adjustments in alpha were made for multiple analyses. After several discussions between the FDA and the applicant, a clarifying email was received six months into the review. Patients with baseline metastatic disease to the bone were submitted as the primary population, (as opposed to the ITT population, or the "per protocol" population which were more prominent in the Integrated Summary of Efficacy) and Biomarkers, QoL and metastatic pain were to provide support to this retrospectively defined sub-population.

Conclusion: There are some serious safety issues observed in both major randomized trials and atrasentan does not demonstrate any clear evidence of clinical efficacy in the only major trial a design adequate for a registration study.

**Protocol M96-594**

The original protocol and major amendments (in italics) are given verbatim, as submitted by the applicant. This protocol was not submitted to the FDA prior to the NDA.

**Title "A Phase II, Double-Blind Comparison of the Safety and efficacy of ABT-627 Versus Placebo in Subjects with Asymptomatic Hormone Refractory Prostate Cancer"**

| | |
|---|---|
| Date of Original Protocol: | July 1997 |
| Date of Amendment #1: | November 19th, 1997 |
| Date of Amendment #2: | January 15th, 1999 |
| Date of Amendment #3: | April 20th, 1999 |
| Date of Amendment #4: | September 10th, 1999 |
| Date of Amendment #5: | June 4th, 2001 |
| | |
| Date first dose administered: | February 26th, 1998 |
| Date last patient enrolled: | February 15th, 1999 |
| Date last dose given: | June 30th, 2002 |

Excerpts from the original protocol followed by pertinent amendments are given below.

**Original Protocol:**

Primary and secondary objectives are given below. These objectives were changed in amendments 1 and 5, as will be noted.

**Objectives:**

*"**The primary objective** of this dose ranging study is to assess the safety and efficacy of ABT – 627 combined with supportive treatment, as compared to placebo combined with supportive treatment, in asymptomatic subjects diagnosed with advanced prostate cancer, which is refractory to hormone ablation therapy. Efficacy will be assessed using the primary endpoint of the time to disease progression. The primary measurement of disease progression will be determined by a rise in PSA by $\geq$ 50% on two consecutive occasions evaluated at least four weeks apart."*

***"Secondary efficacy measures** of disease progression include:*

*• Response (decline) of PSA at least 60 days after the baseline measurement maintained for two consecutive determinations at least two weeks apart.*
*• Either progression of or new appearance of skeletal metastatic disease.*
*• Appearance of bone pain.*
*• Either progression of or new appearance of extra – skeletal metastatic disease.*
*• A new symptom related to tumor growth or a significant change in existing symptoms.*
*• Changes in bone markers."*

*"Secondary objectives will include:*

*• Quality of life.*
*• Symptom collection (pain)."*

*"In addition, data will be collected to assess safety and survival following the termination of the study."*

**Study Design:**
*"This is a Phase II, randomized, double – blind, placebo – controlled, parallel group, multicenter study of ABT – 627. This study will consist of a 14 day Screening Period, and a 168 Day Double – Blind Period. Up to 120 male subjects diagnosed with hormone refractory prostate cancer will be enrolled.. Subjects will be equally randomized to receive either ABT-627 or matching placebo. The study will include three treatment arms each consisting of 40 subjects. The determination of the power of this study and the rationale for the number of subjects, is provided in Section 10.1, Efficacy Assessments. Subjects will be randomized to receive either 10 mg or 2.5 mg of ABT – 627 or placebo, Subjects will enter the study only if the investigator determines that supportive treatment is the appropriate therapy for the subject at the time of enrollment."*

*"Within 14 days prior to Day 1, subjects will receive a full explanation of the study design and study procedures, provide a written inform consent, and undergo the following screening procedures: a medical history including an oncologic history, measurement of vital signs, routine clinical laboratory evaluations, a Hepatitis A, B, and C screen, a serum prostate – specific antigen (PSA) and a testosterone determination, a 12 – lead electrocardiogram (ECG), and a chest x – ray. A Bone Scan and a CT scan of the abdomen and pelvis will be obtained. The Eastern Cooperative Oncology Group Performance Status Scale (ECOG) will also be completed during the screening period. A central laboratory will be used to analyze sample results, see Section 6.9, Laboratory Analysis."*

*"Subjects who meet the enrollment criteria described in Section 5.0 will undergo the following procedures on Day 1: a complete physical examination (including height and weight) and the measurement of vital signs. Blood and urine samples will be collected for routine clinical laboratory evaluations, serum PSA, chromogranin, IL – 6, and bone markers. Plasma samples for study drug concentration and an endothelin assay (iET) will be drawn at selected sites. The Functional Assessment of Cancer Therapy (FACT), with a subsection designed for prostate cancer (FACT – P), EUROQOL and the EORTC QLQ – C30 will be administered to assess the subject's quality of life."*

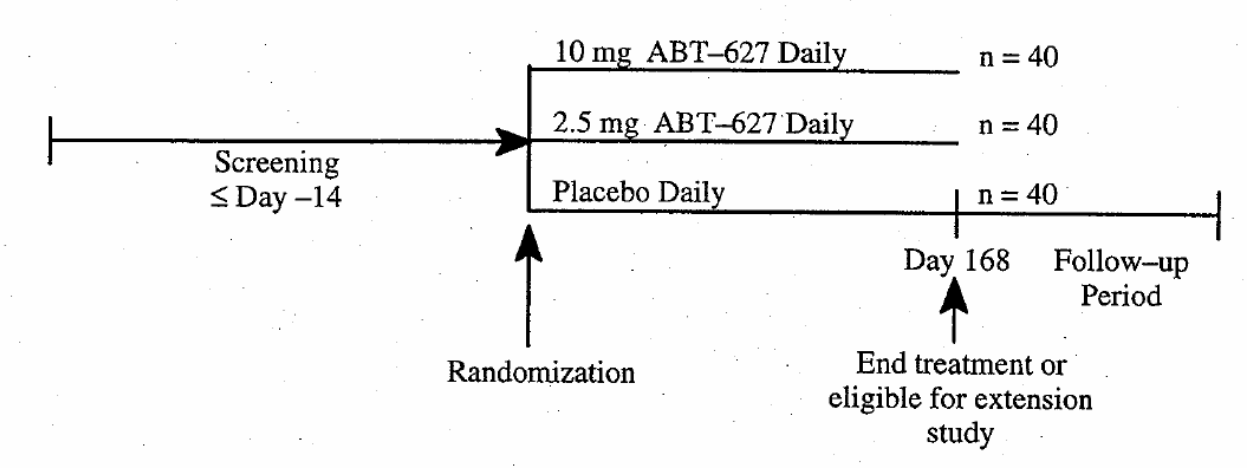



**Figure 16: Schema of Study Design in the Original Protocol**

(Applicant figure)

*"Subjects who experience progression of this disease which require treatment may remain in the trial if felt desirable by subject and the investigator concurs. Assessments of tolerance of multiple therapies will be made at each study-visit. However, failure of drug will be entered on the day any of the criteria for disease progression are first met."*

*"Completion of the study will occur on Day 168. Specific study procedures for Day 168 are listed in Table 2. Day 168 procedures are to be performed if a subject prematurely discontinues from the study. Subjects completing the 6 month study without dose reduction will be offered enrollment in M97 – 739, an open labeled randomized safety and efficacy study of ABT – 627."*

*"Subjects will be contacted at three month intervals after the termination of the trial to assess potential effects of the study drug on survival for two years following enrollment. Subjects who have successfully completed this study will be offered the opportunity to enroll into an extension study. Subjects who do not continue in the extension study will return for a follow – up visit four weeks following study completion."*

**Reviewer's Comments:**
The title of the study, primary objective, sample size and duration of treatment changed in amendments to the protocol. With amendment 1 (prior to enrollment of any patient), the primary objective was changed to time of onset of the first clinical event requiring medical intervention. The definition of the clinical event continued to evolve until after all patients were enrolled. With this amendment, sample size was increased to 204 males with hormone refractory cancer. According to amendment 4, if at least 180 subjects have completed the study before October 31, 1999 the primary analysis cutoff date will be October 31, 1999. If less than 180 subjects have completed the study by October 31, 1999 the primary analysis cutoff date will be the date when the 180th subject completes the study.

**Safety Assessment**

*"If a subject experiences a grade three or higher drug – related toxicity (see Appendix A, NCI Common Toxicity Criteria) or if elevations in liver transaminases (ALT or AST) exceed three times the upper limit of normal or five times the baseline value on Day 1, whichever is lower, treatment will be withheld until the toxicity resolves to within NCI grade 1 criteria or normal limits. When the toxicity has resolved the subject may resume study drug at a reduced dose level. The first dose reduction will be to 1 mg or placebo in a blinded fashion that will match the treatment assignment. If after two weeks or longer at the reduced dose level, the subject experiences a grade three or higher drug – related toxicity a further reduction will be allowed. A second dose reduction to 0.2 mg or placebo will be allowed under the same criteria in a blinded fashion."*

**Inclusion Criteria**

*"1. Prior to any study specific procedure, written informed consent must be obtained from each subject after the purpose and nature of the study has been explained. Study specific procedures include titration or withdrawal of medication prior to evaluation of subject eligibility for enrollment.*
*2. The subject must be at least 18 years of age, inclusive.*
*3. The subject must have a histological documented diagnosis of prostate adenocarcinoma (PCa) rated as T3 or T4, N+, Mo or M+. The subject's Gleason score or the European equivalent will be recorded when available.*
*4. The subject has a life expectancy greater than six months.*
*5. The subject must have a score of 0, 1 or 2 on the Eastern Cooperative Oncology Group Performance Status (see Appendix C).*
*6. The subject must have evidence of androgen ablation defined as a testosterone level less than or equal to 1.04 nmol/L (30 mcg/mL) within the screening period.*
*7. The subject must have documented PCa which is clinically refractory to androgen ablation defined as: a Prostate Serum Antigen (PSA) value greater than or equal to 20 ng/mL on two occasions at least four weeks apart within a 3 month period prior to screening and:*

- *The subject must have had a documented treatment with LHRH agonists or must have had an orchiectomy. Subjects may have had treatment with other anti – androgen agents, e.g., flutarnide, biclutamide, or nilutamide.*
- *A subject who has received flutamide must have a documented minimum withdrawal period of 4 weeks with a documented subsequent rise in PSA after withdrawal of the anti – androgen on two consecutive measurements at least one month apart.*
- *A subject who has received biclutamide or nilutamide must have a documented minimum withdrawal period of 8 weeks with a documented subsequent rise in PSA, after withdrawal of the anti-androgen, on two consecutive measurements at least one month apart.*

*8. The subject must have recovered from prior treatment regimens, e.g., surgery, radiation or chemotherapy.*

*9. A subject who is currently taking steroids must have been on a stable dose for at least 4 weeks. Subject must either continue their stable steroid therapy, or not have taken any steroids within the last 4 weeks.*
*10. A subject may enter the study despite a recent history of clinically significant medical disorders, if the disorder is stable and well controlled. Permissible medical disorders include: cardiovascular [e.g., myocardial infarction, stroke (CVA), angina, congestive heart failure (CHF)], respiratory, metabolic (e.g., diabetes), autoimmune, gastrointestinal, and neurologic (e.g., seizures) disorders.*
*11. The subject must have a white blood cell count greater than 2.0 x $10^9$/L (2000/$mm^3$), an absolute neutrophil count (ANC) greater than 1.0 x $10^9$/L (1000/$mm^3$), a platelet count greater than 100 x $10^9$/L (100,000/$mm^3$), and a hemoglobin level greater than 1.395 nmol/L (9 g/dL).*
*12. The subject rnust have a total bilirubin less than 25.65 p,mol/L (1.5 mg/dL) and an AST and ALT $\leq$1.5 x the upper limit of normal.*
*13. The subject must have a calculated creatinine clearance of $\geq$ 0.48 ml/sec/$m^3$ (50 mL/min.).*
*14. The subject must be pain free.*
*15. A subject who is sexually active and their partner must use two reliable barrier forms of contraception, for example condoms and diaphragms, from Day 1 until two months after the subject stops taking medication."*

**Exclusion Criteria**

*"1. A subject who has received strontium or suramin within 12 weeks of Day 1, or who has received rhenium – 186 etidronate within 8 weeks of Day 1.*
*2. A subject who has had surgery, radiotherapy or chemotherapy in the past 28 days, and/or has not fully recovered from any toxicity or side effects related to the treatment(s).*
*3. A subject who has bone pain which requires immediate radiotherapy, or symptoms consistent with spinal cord compression.*
*4. A subject with positive test results for active hepatitis A, B or C.*
*5. A subject who is known to have AIDS or is known to be HIV – positive.*
*6. A subject who has a history of any disturbance with his entero – hepatic circulation which may result in decreased metabolism of the drug.*
*7. A subject who has a history of migraine headaches or a chronic headache syndrome.*
*8. A subject who has a clinically significant abnormal electrocardiogram (ECG).*
*9. A subject who has received an investigational drug within 4 weeks prior to Day l.*
*10. A subject who has central nervous system (CNS) metastases.*
*11. A subject who has liver metastases.*
*12. A subject who, in the opinion of the investigator is unable to comply with the requirements of the study protocol or who is unsuitable for the study for any reason."*

**Reviewer's Comment:**
The enrollment criteria were changed in amendment 1. Patients were now required to have prostate cancer that was metastatic. PSA criteria were given to insure hormone refractoriness of disease. For further details, please read the amendments.

**Pain Assessment**

*At the time the subject reports pain, pain intensity will be assessed by the subject daily using a numeric rating scale. Subjects will be pain free at the start of this study; however, they will still record pain assessment to better document the onset of pain.*

**Pain Scales**

*At bedtime, subjects will complete a Daily Log which will include a numeric rating pain scale (NRS, Appendix E) beginning at screening through completion Day 168. The Daily Log will be collected from the subject at the next study site visit, see Table 2.*

**Analgesic Assessment**

*Subjects who begin to have pain which requires the use of pain medication will record, the type and amount of all opioids and over–the– counter medications taken into the same Daily Log (Appendix E* of protocol*) as noted above. Subjects will record medication data from the beginning of its use through completion Day 168.*

**Table 61: Schedule of Study Activities**

Applicant table

| Procedure | Day ≤–14 | Day 1 | Day 14 | Day 28 | Day 42 | Day 56 | Day 70 | Day 84 | Day 126 | Day 140 | Day 154 | Day 168 | 28 Day Follow Up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Clinic visits | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Informed consent | X | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | |
| Oncologic history | X | | | | | | | | | | | | |
| Physical examination (including weight) | | X[1] | X | | X | | | X | | | | X[1] | X |
| 12–lead ECG | X | | | | X | | | X | | | | X | |
| Chest x–ray[2] | X | | | | | | | | | | | | |
| Hepatitis A, B and C screen | X | | | | | | | | | | | | |
| Randomize subject | | X | | | | | | | | | | | |
| Testosterone | X | | | | | | | | | | | | |
| Vital signs[3] | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Chemistry (fasting) | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Hematology | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Urinalysis | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Tumor Markers | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Bone Markers | | X | | | X | | | X | | | | X | |
| Plasma for ABT–627 and iET assay (predose) | | X | X | X[4] | X | X | X | X | X | X | X | X | X[5] |
| Bone Scan | X | | | | | | | | | | | X | |
| CT Scan (Abdomen & Pelvis) | X | | | | | | | | | | | X | |
| Performance status (ECOG) | X | | X | | X | | X | | | | | X | X |
| QOL | | X | | | X | | | X | | | | X | X |
| Pain Assessment | | X | X | X | X | X | X | X | X | X | X | X | X |
| Adverse event assessment | | | X | X | X | X | X | X | X | X | X | X | X |
| Dispense medication | | X | X | X | X | X | X | X | X | X | X | | |
| Collect unused study drug | | | X | X | X | X | X | X | X | X | X | X | |

1. Height will be obtained.
2. May use a previous chest x–ray if obtained within 12 months prior to Day 1.
3. Including weight.
4. 24–hour study performed at selected sites at 0, 1, 2, 3, 6, 12 and 24 hours post dosing.
5. Sample collection needed for iET only.

**Disease Progression Criteria**

*"An increase of serum PSA of > 50% from the baseline measurement on two occasions at least four weeks apart will constitute disease progression.*

*• Appearance of any new lesions or metastases found on bone scan attributable to metastatic disease."*

*"The following signs and symptoms will also be monitored and evaluated:*

*• An increase of greater than 25% in bidemensionally measurable tumor mass.*
*• Palliative treatment of new bone pain with an opioid.*
*• Palliative radiation (external beam, implants, or strontium) for treatment of new bone pain.*
*• New symptoms related to tumor growth.*
*• A decrease in PSA by > 50% at least 60 days after the onset of drug treatment.. The decrease must be sustained at two consecutive visits at least one week apart.*
*• Significant prostate cancer-related deterioration in body weight, symptoms, or performance status."*

**Reviewer's Comments:**
Criteria for disease progression evolved up until the 5th and last amendment, 4 months after the enrollment of the last patient.

In the 1st amendment, the disease progression criteria were changed to:

"*• Palliative treatment of new bone or visceral pain with an opioid.*
*• Palliative radiation (external beam, implants, strontium, suramin or rhenium) for treatment of new bone pain.*
*• New symptoms related to tumor growth requiring intervention.*
*• Treatment with chemotherapy (such as estramustine, mitoxantrone or any increases in steroid use).*
*• An increase of greater than 25% in bidimensionally measurable tumor mass."*

*"Time-to-disease progression is defined as the time of onset of the first clinical event requiring medical intervention. The clinical event will be described on the adverse event case report form along with the treatment prescribed (e.g., medication, radiotherapy or other).This then constitutes termination from this study and will be noted on the study outcome case report form"*

In the 5th amendment, the following were added:
*"Completion of the study will occur when subjects have a defined onset of a clinical event (i.e., opioid use for pain due to PCa disease; clinical intervention such as chemotherapy, radiotherapy or surgery; new measurable bone or soft tissue lesions; or other investigator-defined measures) as clinical evidence of disease progression."*

*"The following were added to the disease progression criteria:*
*• New measurable bone lesions*
*• New measurable soft tissue lesions*
*• Other investigator-defined measures of disease progression."*

Progression of skeletal or extra-skeletal progression was removed from definition of disease progression.

**Time to Progression**
*Time to progression will be based on the interval from randomization (for comparison of the groups).*

**Statistical Methods**

**Efficacy Assessments**

Per applicant, *"Definitive proof of the efficacy for ABT – 627 in this population will require larger randomized trials. The purpose of the present study is to determine the safety of ABT – 627 as well as to ascertain whether or not efficacy appears to be promising enough to proceed to Phase III randomized trials. The results of this smaller study will be regarded as sufficiently positive to justify proceeding if one of the ABT – 627 groups is superior to the control group at the time of analysis."*

*"The primary efficacy measurement is time to disease progression, which is defined as an increase of serum PSA of greater than or equal to 50% from baseline measurement, see Sections 8.1 and 8.2. The baseline measurement of PSA will be the measurement of PSA at Day 1 visit. The subsequential measurements are scheduled in Table 2, Section 7.0. The distribution of time to progression will be estimated using Kaplan – Meier methodology. Comparison between randomization groups for time to progression will be performed using logrank test and Cox proportional hazards model. All data will be analyzed according to intent – to – treat principle. All of the analysis may be subjected to the adjustment of the baseline characteristics and prognostic factors."*

*"All of the eligible subjects will be recruited within six months. The study procedures will last 168 days. For all subjects who have not progressed at the time of the analysis, tirne to progression will be censored at the time of the last assessment of disease status."*

*"In general, the median disease progression time for late stage PCa subjects is about 3 months. At 6 months, the percentage of the disease progression is 75%. All subjects are enrolled in the trial within 6 months, and each of the subjects will be followed for at least 168 days. Without adjusting for multiple comparisons, using two – sided test, after assuming that 10% of subjects are lost to follow – up, with 120 subjects for three arms, 40 of them being assigned to each of the two ABT – 627 arms and placebo arm, respectively, there is 80% power to detect a difference at least between one of the ABT – 627 groups and control groups at the 0.20 significant level if ABT – 627 increases the time of disease progression by 50% (median time to disease progression 4.5 months and 6 months progression free 40%). If an ABT – 627 group can prolong the median time to progression by 70% (median time to disease progression 5.1 rnonths and 6 months progression free is 44%), then the same sample size will be able to detect this difference with 85% power and 0.10 significant level."*

*"Other secondary efficacy measurements will include the proportion of subjects who have a 50% reduction in PSA after 60 days, quality of life, pain relief, survival, etc. Analysis of QOL and pain will use repeated measurement methodology for the subjects who have 50% reduction in PSA and will be compared among different treatment groups."*

*"All subjects will be followed for survival which will be measured from randomization until death. Survival data for subjects still alive at the time of analysis or lost to follow – up will be censored at the date of last contact. Survival comparisons between groups and estimates of survival distributions will be performed using the same methodologies as are being employed for time to progression. Other endpoints will be analyzed using appropriate methodologies."*

**Reviewer's Comment:**

Changes to the original protocol:

Most of the important parts of the protocol were changed in the amendments. These included the title, primary and secondary objective, sample size, inclusion and exclusion criteria and duration of study.

For the purpose of primary analysis, cut-off was to be 180 subjects completing study or October 31, 1999, whichever comes later. Efficacy analysis was to be the primary analysis dataset (as above) and not the overall dataset that included all of the subjects who completed or discontinued from this study. A central reviewer of CT scans and bone scans was instituted by the 3rd amendment, and after all subjects were enrolled. However, according to the applicant (email clarification dated 7/22/05), the primary analysis of time to disease progression in study M96-594 was based on the investigator's determination of disease progression. The objectives and enrollment criteria also changed with amendments.

Differences in population of phase II and Phase III studies:

Population intended for enrollment in to this protocol was different from that of study M00-211. Patient may have been pretreated, by methods including chemotherapy.

Difference in Disease Progression definition in Phase II and Phase III studies:

The disease progression criteria are different from those of the phase III study (M00211) and are of questionable clinical significance in this study. Increase in tumor size was not included in the definition of disease progression in this study. Criteria for assessment of bone scans for metastatic disease were stringent in the phase III study but not in the phase II study. Central review was not incorporated in the phase II study. The institution of opioids alone was not sufficient to constitute disease progression in M00211, the phase III study. It required a certain duration, route and objective evidence of cancer at the pain site. According to this phase II protocol, codeine for pain unrelated to prostate cancer could define disease progression in patients. "Other investigator-defined measures of disease progression" is a vague term (may include PSA measurement and subjective criteria), as is "symptoms related to disease progression". These are included in the criteria for disease progression in the phase II randomized study and not the phase III study.

**Conclusion:** The primary objective of the original protocol changed. The definition of disease progression continued to evolve until after all patients were enrolled and is itself of questionable clinical significance. The imaging studies were performed only at the beginning and the end. The central review of imaging studies was instituted after all patients had been enrolled. Because of this and a different definition of disease progression from that of the phase III M00-211 study, the results of these two studies can not be considered in one meta-analysis, or included in the efficacy claims with M00-211.

**Amendments**

Amendment No. 1 (July 1997)

The following Amendment has been written to change the primary endpoint, modify the enrollment criteria, update the statistical section, increase the number of subjects per arm, and reduce the number of quality of life questionnaires.

1. The Protocol title has been changed to:
*"Dose Ranging Study Comparing Best Medical Therapy With and Without ABT-627 for the Treatment of Men with Asymptomatic Hormone Refractory Adenocarcinoma of the Prostate"*

2. *"The primary measurement of disease progression will be determined by time to onset of the first disease related clinical event, such as the onset of disease related pain requiring the use of opioids or clinical intervention, such as radiotherapy or chemotherapy. The expected average time to the first occurrence of the event is six to nine months."*

3. "*Secondary efficacy measures of disease progression include:*
*• An increase of serum PSA of > 50% from the baseline measurement (average of Screening Visit plus Day 1 value) on two occasions at least four weeks apart.*
*• Either progression of or new appearance of skeletal metastatic disease.*
*• Either progression of or new appearance of extra-skeletal metastatic disease.*
*• Changes in bone markers from baseline."*

"*Secondary objectives will include:*
*• Quality of life.*
*• Performance status."*

4. *"At least 204 male subjects diagnosed with hormone refractory prostate cancer will be enrolled."*
5. *"Subjects who experience progression of disease which requires treatment may be enrolled into the extension study, M97-739."*
6. Inclusion criterion # 3 has been changed to *"The subject must have a histological/cytological documented diagnosis of prostate adenocarcinoma (PCa) rated as M+. The subject's Gleason score will be recorded if available."*
7. Inclusion criterion #7 was changed to *"The subject must have documented PCa which is clinically refractory to androgen ablation defined as: a Prostate Serum Antigen (PSA) value greater than or equal to 20 ng/mL on two occasions at least four weeks apart within a 3 month period prior to screening or if less than 20 ng/mL a rise in PSA of at least 5 ng/mL and:*
*- The subject must have had a documented treatment with LHRH agonists or must have had an orchiectomy.*
*- The rise in PSA must be with concomitant treatment with LHRH agonists or status post orchiectomy.*

*- Subjects may continue on LHRH agonists at constant dosing throughout the Study Period. Subjects may have had treatment with other anti-androgen agents, e.g., flutamide, biclutamide, or nilutamide."*

8. Inclusion criterion 9 was changed to *"A subject who is currently taking steroids must have been on a stable dose for at least 4 weeks. The subject must either continue their stable steroid therapy (at constant dose throughout study), or not have taken any steroids within the last 4 weeks."*
9. Inclusion criterion #10 was changed to *"A subject may enter the study despite a recent history of clinically significant medical disorders, if the disorder is stable and well controlled. Permissible medical disorders include: cardiovascular [e.g., myocardial infarction, angina, congestive heart failure (CHF)], respiratory, metabolic (e.g, diabetes), autoimmune, gastrointestinal, and neurologic (e.g., stroke (CVA), seizures) disorders."*

10. Study Activities

**Table 62: Schedule of Assessments**

Applicant Table

| Procedure | Day ≤-14 | Day 1 | Day 14 | Day 28 | Day 42 | Day 56 | Day 70 | Day 84 | Day 126 | Day 140 | Day 154 | Day 168 | Every 28 Days With Continued Dosing | Final Visit or Early Termination | 28 Day Follow Up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Clinic visits | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Informed consent | X | | | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | | |
| Oncologic history | X | | | | | | | | | | | | | | |
| Physical examination (including weight) | | X[1] | X | | X | | | X | | | | X[1] | X | X | X |
| 12-lead ECG | X | | | | X | | | X | | | | X | | X | |
| Chest x-ray[2] | X | | | | | | | | | | | | | | |
| Hepatitis A, B and C screen | X | | | | | | | | | | | | | | |
| Randomize subject | | X | | | | | | | | | | | | | |
| Testosterone | X | | | | | | | X | | | | X | | X | |
| Vital signs[3] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Chemistry (fasting) | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Hematology | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Urinalysis | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Tumor Markers | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Bone Markers | | X | | | X | | | X | | | | X | X[4] | X | |
| Plasma for ABT-627 and iET assay (predose) | | X | X | X[5] | X | X | X | X | X | X | X | X | X | X | X[6] |
| Bone Scan | X | | | | | | | | | | | | | X | |
| CT Scan (Abdomen & Pelvis)[7] | X | | | | | | | | | | | | | X | |
| Performance status (ECOG) | X | | X | | X | | | X | | | | X | X | X | X |
| QOL | | X | | | X | | | X | | | | X | X | X | X |
| Adverse event assessment | | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Dispense medication | | X | X | X | X | X | X | X | X | X | X | X[8] | X[8] | | |
| Collect unused study drug | | | X | X | X | X | X | X | X | X | X | X | X | X | |

1. Height will be obtained.
2. May use a previous chest x-ray if obtained within 12 months prior to Day 1.
3. Including weight.
4. Bone markers collected every 8 weeks.
5. 24-hour study performed at selected sites at 0, 1, 2, 3, 6, 12 and 24 hours post dosing.
6. Sample collection needed for iET only.
7. A CT scan of the chest may be done if clinically indicated.
8. If subject continues dosing on study M96-594.

11. *Because PSA may vary with treatment with ABT-627, disease progression will be defined as a clinical event as detailed below. A PSA elevation alone will not be considered a clinical event unless it is present with any of the following. The following shall constitute a clinical event:*
    - *Palliative treatment of new bone or visceral pain with an opioid.*
    - *Palliative radiation (external beam, implants, strontium, suramin or rhenium) for treatment of new bone pain.*
    - *New symptoms related to tumor growth requiring intervention.*

*• Treatment with chemotherapy (such as estramustine, mitoxantrone or any increases in sterioid use).*
*• An increase of greater than 25% in bidimensionally measurable tumor mass.*

*"Secondary efficacy measures of disease progression include:*

*• An increase of serum PSA of 50% from the baseline measurement (average of screening visit plus Day 1 value) on two occasions at least four weeks apart.*
*• Either progression of or new appearance of skeletal metastatic disease.*
*• Either progression of or new appearance of extra-skeletal metastatic disease.*
*• Changes in bone markers from baseline will be analyzed."*

12. *"Time-to-disease progression is defined as the time of onset of the first clinical event requiring medical intervention. The clinical event will be described on the adverse event case report form along with the treatment prescribed (e.g., medication, radiotherapy or other). This then constitutes termination from this study and will be noted on the study outcome case report form; however subjects will be allowed to enter the open label extension trial M97-739."*

13. *"The primary efficacy measurement is time-to-disease progression, which is defined in Sections 8.1 and 8.2. The distribution of time-to-progression will be estimated using Kaplan-Meier methodology. Comparison between randomization groups in time-to-progression will be performed using a log-rank test and Cox proportional hazards model. All data will be analyzed according to intent-to-treat principle. All of the analysis may be subjected to the adjustment of the baseline characteristics and prognostic factors."*

*"The sample size planned for this study is estimated based on the assumption that all of the eligible subjects will be recruited in 6 months, and study duration will be 18 months. Hence, each of the subjects will be followed at least 12 months. For all subjects who have not progressed at the time of the analysis, time-to-progression will be censored at the time of the last assessment of disease status. The median disease progression time for late stage PCa subjects is estimated to be 9 months. Hence, the estimated percentage of disease progression is 60% at 12 months. Without adjusting for multiple comparisons, using a two-sided test, after assuming that 10% of subjects are lost to follow-up, with 204 subjects for three arms, 68 of them being assigned to each; there is 70% power to detect a difference at least between one of the ABT-627 groups and the control group at the 0.20 significance level if ABT-627 increases the time of disease progression by 50% (i.e., median time to disease progression 13.5 months and the percentage of the subjects with disease progression at 12 months is 48%). If the ABT-627 group can prolong the median time to progression by 70% (i.e., median time to disease progression 15.3 months and the percentage of subjects with disease progression at 12 months is 40%), then the same sample size will provide 75% power and 0.10 significance level to detect this difference."*

*"Overall survival, PSA levels, bone markers, QOL, Performance Status, etc. are secondary efficacy variables. All subjects will be followed for survival, which will be*

*measured from the randomization until death. Survival data for subjects still alive at the time of analysis or lost to follow-up will be censored at the date of last contact. Survival comparisons between groups and estimates of survival distributions will be performed using the same methodologies as are being employed for the time-to-progression analysis. PSA levels will be measured as indicated in Table 2 in Section 7.0. The time-to-event of an increase of serum PSA of > 50% from baseline on two occasions at least four weeks apart will be analyzed using the same methodology. The percentage of the subjects who have had 50% or more decrease in PSA during the first 60 days will also be compared using a Cochran-Mantel-Haenszel test or a Generalized Linear Model. In addition, PSA levels will also be analyzed, together with the bone markers, QOL and performances status, using repeated measurement methodology. All other efficacy and safety endpoints will be analyzed as appropriate. Also, all of the analyses may be subjected to adjustment for baseline characteristics and prognostic factors"*

**Amendment #3: (April 1999)**

1. *"Subjects will be contacted at one to three month intervals after the termination of the trial to assess potential effects of the study drug on survival for up to two years following enrollment."*
2. *"An independent Data Monitoring Committee (DMC), comprised of three physicians, one statistician, and one epidemiologist will establish criteria for evaluating safety data from this study and other current Phase II oncology studies utilizing ABT-627."*
3. *"Subject CT scan responses will be compared between treatment arms using a Cochran-Mantel-Haenzel test."*
4. *"The change from baseline in bone scan results will also be examined using appropriate methodology."*

**Reviewer's Comment:**
The following should be noted:
Per applicant (email clarification dated 7/22/2005), "*the primary analysis of time to disease progression in study M96-594 was based on the investigator's determination of disease progression and recorded on the "study outcome" page of the CRF."*
*Additionally, the applicant stated that the central radiographic review for this study was not linked to the endpoint assessment.*

**Amendment #4: September 1999**

1. *Subjects who are considered completers of the study are those subjects who have experienced a disease related clinical event requiring medical intervention as defined in Section 8.0, Disease Progression. Study No. M96-594 will be considered ready for primary analysis on the date when one of the following events occur:*

*a. If at least 180 subjects have completed the study before October 31, 1999 the primary analysis cutoff date will be October 31, 1999.*

*b. If less than 180 subjects have completed the study by October 31, 1999 the primary analysis cutoff date will be the date when the 180th subject completes the study.*

*Therefore, the primary analysis will be performed on data consisting of at least 180 events which will provide power to detect differences in median time to disease progression between one of the two ABT-627 arms and the placebo arm (see Section 10.0 Statistical Methods).*

*Subjects, who have not met the definition of study completer and remain active after the primary analysis date, may continue to receive blinded study medication until the study blind is broken or they discontinue from the study.*

2. *Comparison between randomization groups in time-to-disease progression will be performed primarily using the unadjusted log-rank test. Other tests and models will also be explored for this Phase II study, such as Wilcoxon test and the Cox proportional hazard model.*

3. *Three data sets will be examined for this study. These data sets are described below with the second data set including more data than the first data set and the third data set including more data than the second data set. The efficacy and safety analyses will be performed using each data set. The results of the study are based on the primary analysis, as defined below. Therefore, no type I error adjustment is needed in this Phase II trial.*

*• "Primary Analysis Data Set": includes all subjects' data upon the primary analysis cutoff date, see Section 3.0, Study Design, for the definition of primary analysis cutoff date.*

*• "Blinded Data Set": includes all subjects' data available through the date when the study is unblinded to perform the primary analysis.*

*"Overall Data Set": includes all subjects' data up to the time when all of the subjects complete/discontinue from this study.*

*The total number of subjects planned initially for this study is based on the assumptions that the accrual and duration of the study is 6 and 18 months, respectively, and the median time to disease progression in the placebo treatment group is 9 months. Under this assumption, 204 subjects, 68 per arm, will be able to detect a 50% improvement of time to disease progression in one of the ABT-627 dose groups compared to the placebo group with 0.2 significance level and 70% power. The total number of disease progressions in the 204 subjects during the 18 month study duration is expected to be 125.*

*As of February 1999, 288 subjects enrolled in the study and the total number of disease progressions in the 288 subjects is expected to be approximately 180 to 200 at the time of the primary analysis cutoff date as outlined in Section 3.0, Study Design. Without adjusting for the multiple comparisons using two-sided tests, a total of 180 events will be able to detect a 50% improvement of time to disease progression in one of the ABT-627 groups compared to the placebo group with 0.2 significance level and 80% power. A total of 200 events will be able to detect a 50% improvement to time to disease progression in one of the ABT-627 arms*

*compared to the placebo group with 0.1 significance level and 76% power. Alternatively, if compared to the placebo group the improvement of time to disease progression in one of the ABT-627 arms is 70%, 180 and 200 disease progressions will be able to detect this improvement with significance level 0.05 and power 85% and 87% respectively.*

**Amendment #5: 4 June 2001**

1. *"Objective: The primary measurement of disease progression will be determined by time to onset of the first disease related clinical event, such as the onset of pain requiring the use of opioids; clinical intervention, such as radiotherapy, chemotherapy or surgery; new measurable bone or soft tissue lesions; or other investigator-defined measures of disease progression."*
2. *"Completion of the study will occur when subjects have a defined onset of a clinical event (i.e., opioid use for pain due to PCa disease; clinical intervention such as chemotherapy, radiotherapy or surgery; new measurable bone or soft tissue lesions; or other investigator-defined measures) as clinical evidence of disease progression."*
3. *"The following were added to the disease progression criteria:*
   - *New measurable bone lesions*
   - *New measurable soft tissue lesions*
   - *Other investigator-defined measures of disease progression"*

Note: increase in tumor size is not a component of disease progression.

**Protocol amendment summary by applicant**

"*Amendment No. 1 was incorporated into the protocol on 19 November 1997. The purpose of this amendment was to change the primary endpoint, modify the enrollment criteria, update the statistical section, increase the number of subjects per arm, reduce the frequency of quality of life questionnaires and to correct minor inconsistencies and typographical errors. This change was mad prior to the enrollment of any subjects in the study."*

*"Amendment No. 2 was incorporated into the protocol on 15 January 1999. The purpose of this amendment was to include the collection of a sample for the possible testing of genetic polymorphism differences and to delete the reference to the Abbott Netherlands affiliate as a contact for serious adverse event reporting. Approximately 282 subjects were enrolled in the study prior to this change."*

*"Amendment No. 3 was incorporated into the protocol on 20 April 1999. The purpose of this amendment was to 1) allow for more frequent follow-up on survival information, 2) address the collection of subject CT and bone scans to be read by a central reader in order to determine response in a standardized manner, and 3) institute an independent DMC to review and evaluate safety outcomes from this study in combination with other ongoing Phase 2 oncology studies using atrasentan. All 288 subjects presented in this report were enrolled in the study prior to thsi s amendment."*

*"Amendment No. 4 was incorporated into the protocol on 10 September 1999. The purpose of this amendment was to 1) clarify that investigational sites in France would not be participating*

*in the optional genetic polymorphism evaluation, 2) establish the primary analysis cutoff date, and 3) update the statistical methods section. All 288 subjects presented in this report were enrolled in the study prior to this amendment."*

*"Amendment No. 5 was incorporated into the protocol on 4 June 2001. The purpose of this amendment was to update the protocol definition of the primary efficacy endpoint of clinical progression to be consistent with the manner in which data were collected in the CRFs. This modification included addition of the following categories: 1) radiographic measures of disease progression, and 2) other investigator-defined measures of progression. PSA elevation alone was not to be considered a clinical event unless it was present with the primary disease related events. In addition, the Abbott Oncology contact information for serious adverse event reporting was updated, and administrative errors discovered from a previous version were corrected. All 288 subjects presented in this report were enrolled in the study prior to this amendment."*

**Post Hoc Changes**

**Results**

There were 74 investigators from 9 countries participating in this study that enrolled 288 patients randomized to the three treatment arms. These countries were United States of America, France, Sweden, Germany, the Netherlands, United Kingdom, Poland, Spain and Belgium.

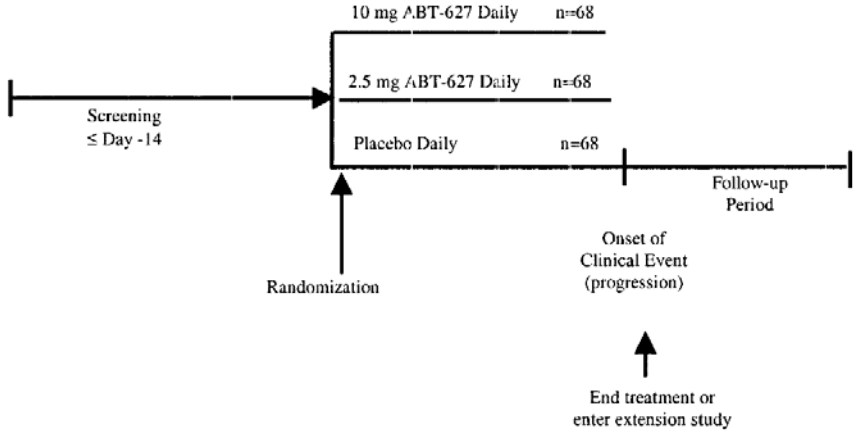
The primary amendments was changed and developed through most of the study as described above. According to the applicant Clinical Study Report (CSR):

*"Disease progression was determined by the time to onset of the first disease-related clinical event including;*
*• Palliative treatment of new bone or visceral pain with an opioid*
*• Palliative radiation (external beam, implants, strontium, suramin, or rhenium$^{186}$)*
*• New symptoms related to tumor growth*
*• Treatment with chemotherapy (such as estramustine, mitoxantrone, or any increases in steroid use)*
*• New measurable bone lesions*
*• New measurable soft tissue lesions*
*• Other investigator-defined measures of disease progression."*

*"Additionally, supporting efficacy measures of disease progression (which alone could not define a clinical event) may have included:*
*• An increase of serum prostate-specific antigen (PSA) of >50% from the baseline measurement (average of screening visit and day 1 values) on two occasions at least 2 weeks apart;*
*• Changes in markers of bone remodeling from baseline; and*
*• An increase of greater than 25% in bidimensionally measurable tumor mass."*

**Figure 17: Study Schematic**

Applicant figure 9.1.a from CSR




*"Secondary objectives included:*
• *Quality of life and*
• *Performance status."*

Subjects were randomized to receive: 10 mg atrasentan, 2.5 mg atrasentan, or placebo daily in a 1:1:1 ratio, in addition to their standard care. A subject was considered to have completed the study after presenting evidence of disease progression (event). Bone scans and CT scans were reviewed by blinded reviewers (Steven Larson MD for bone scans and Lawrence H Schwartz MD for CT scans. Both physicians were from Sloan Kettering Cancer Center). IDMC composed of 3 physicians for monitoring safety events did not make specific recommendations for the study.

Abbott Laboratories supplied atrasentan in two dosage forms:
1) capsules of two strengths, 2.5 and 10 mg, and
2) an oral solution (50% glycerin, 14% alcohol, and water) of 1 mg/mL of atrasentan to be used if a dose reduction was required.

If a subject experienced a National Cancer Institute (NCI) Common Toxicity Criteria (CTC) Grade 3 or 4 drug-related toxicity or if elevations in liver transaminases, alanine transaminase (ALT) or aspartate transaminase (AST), exceeded 3x the upper limit of normal (ULN) or 5 x the day 1 baseline value, whichever was lower, study drug was discontinued until the toxicity resolved to within NCI CTC Grade 1 criteria or normal limits. When the toxicity resolved, the subject could resume study drug at a reduced dose. The first dose reduction was to 1 mg atrasentan or to a matching placebo. If after two weeks or longer at the reduced dose, the subject experienced an N°"I CTC Grade 3 or 4 drug-related toxicity, a second reduction to 0.2 mg atrasentan or matching placebo was allowed under similar criteria. Subjects randomized to active study medication received the active oral solution and those randomized to placebo received placebo oral solution.

According to applicant
"*The primary analysis was performed for all data through the cutoff date of 31 October 1999. A second data set cutoff of 31 January 2000, corresponding to the date the study blind was broken, was analyzed. All available subject data through 31 January 2000 were included in this data set, This analysis was specified prior to breaking the blind.*"

*"Subjects returned previously dispensed drup containers to the site so that drug compliance could be determined. Each subject's compliance was determined by counting retrnied study drug at each visit and questioning the subject about their adherence to the protocol. If a subject's compliance was below 80%, consultation with study site personnel was required. If a subject's compliance was below 80% on two or more occasions, discontinuation of the subject from study participation was considered."*

*"Visits were scheduled every two weeks, with the exception of the six-week interval between Days 84 and 126, which was part of the original study design"*

**Figure 18: Sequence of monitoring**

| Procedure | Day ≤14 | Day 1 | Day 14 | Day 28 | Day 42 | Day 56 | Day 70 | Day 84 | Day 126 | Day 140 | Day 154 | Day 168 | Every 28 Days With Continued Dosing | Final Visit or Early Termination | 28 Day Follow Up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Clinic visits | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Informed consent | X | | | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | | |
| Oncologic history | X | | | | | | | | | | | | | | |
| Physical examination (including weight) | | X[1] | X | | X | | | X | | | | X[1] | X | X | X |
| 12-lead ECG | X | | | | X | | | X | | | | X | | X | |
| Chest x-ray[2] | X | | | | | | | | | | | | | | |
| Hepatitis A, B and C screen | X | | | | | | | | | | | | | | |
| Randomize subject | | X | | | | | | | | | | | | | |
| Testosterone | X | | | | | | | X | | | | X | | X | |
| Vital signs[3] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Chemistry (fasting) | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Hematology | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Urinalysis | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Tumor Markers | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Bone Markers | | X | | | X | | | X | | | | X | X[4] | X | |
| Plasma for ABT-627 and iET assay (predose) | | X | X | X[5] | X | X | X | X | X | X | X | X | X | X | X[6] |
| Genetic Polymorphism Sample | | X[6.1] | | | | | | | | | | | | | |
| Bone Scan | X | | | | | | | | | | | | | X | |
| CT Scan (Abdomen & Pelvis)[7] | X | | | | | | | | | | | | | X | |
| Performance status (ECOG) | X | | X | | X | | | X | | | | X | X | X | X |
| QOL | | X | | | X | | | X | | | | X | X | X | X |
| Adverse event assessment | | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Dispense medication | | X | X | X | X | X | X | X | X | X | X | X[8] | X[8] | | |
| Collect unused study drug | | | X | X | X | X | X | X | X | X | X | X | X | X | |

1. Height will be obtained.
2. May use a previous chest x-ray if obtained within 12 months prior to Day 1.
3. Including weight.
4. Bone markers collected every 8 weeks.
5. 24-hour study performed at selected sites at 0, 1, 2, 3, 6, 12 and 24 hours post dosing.
6. Sample collection needed for iET only.
6.1. Sample may be collected on visit days other than Day 1.
7. A CT scan of the chest may be done if clinically indicated.
8. If subject continues dosing on study M96-594.

**Reviewer's Comment:**
Bone scans and CT scans were performed only at the beginning and end of study, unlike the phase III Study M00-211, where imaging was performed every 12 weeks (CT scans were repeated only if baseline soft tissue metastases were present in the phase III study). This is important because disease progression based on imaging can not be identified until the time when imaging is performed, and can falsely inflate TTP or erase differences in the two treatment arm for shorter TTP. Progression identified on imaging constituted 74% of events in the phase III study.

*"Subjects were contacted at least every 3 months after the blind was broken to assess potential effects of the study drug on survival for two years following enrollment. Subjects who did not continue in the extension study M97-739 returned for a final follow-up visit 4 weeks following study completion"*

*"The clinical event signaling disease„e progression was described on the adverse event CRF along with the treatment prescribed (e.g., medication, radiotherapy). Case report forms for the study provided for the collection of the following data:"*

*"• New measurable lesions*
*• New measurable soft tissue lesions*
*• New intervention of chemotherapy, radiotherapy, surgery, or other*
*• Pain requiring opioids*
*• Other"*

*"For those subjects whose only event was recorded on the CRF as "other", the "other" category specified one of the following: PSA rise alone, pain, death, increases in bone or soft tissue lesions, weakness, use of steroids, "disease progression", urinary symptoms, and "deterioration"."*

*"RECIST Criteria was used for measurable lesion. For bone scans, the reader determined the total bone scan index by determining the fraction of each bone involved in prostate cancer. The central reader also assigned one of the following response descriptions to the final bone scan for each subject: complete response, partial response, stable disease, progressive disease, not evaluable, or incomplete."*

**Reviewer Comment:**
Any new lesion, measurable or immeasurable should qualify as disease progression.

The "Other" category does not characterize clinical benefit. A rise in PSA should not be regarded as a validated component of definition of disease progression for registration studies. Use of steroids in itself is not meaningful, unless it is associated with reduction in events providing clinical benefit. "Urinary symptoms" is too vague a term and has no duration associated, as stated in the CRF. "Deterioration" can be due to any number of reasons, and maybe age-related, or from co-morbid conditions.

**Disposition**

According to the applicant, the patients were randomized to the study the same day they received the first dose. The first dose of study drug was administered on 26 February 1998. A total of 288 subjects were randomized and received study drug as of 31 October 1999. Two hundred subjects completed the study with disease progression. As of 31 October 1999, a total of 49 subjects did not experience disease progression, but discontinued the study for these other reasons: adverse events (13), noncompliance (1), personal reasons (19), death (7), concomitant medications (2), lost to follow-up (1), and other (selection criteria not met or discontinued by physician to seek

other therapy [6]). The remaining 31 subjects were active in the study as of 31 January 2000. A summary of subject disposition is provided in applicant table below.

**Reviewer's Comments:**
There is a slight increase in patients getting off the study early in the placebo arm. 13% on the placebo arm, and 19% on each of the Atrasentan arms discontinued the study drug before disease progression. This difference is mostly due to patients discontinuing because of adverse events.

**Table 63: Patient Disposition**

Applicant table 14.1_1.4

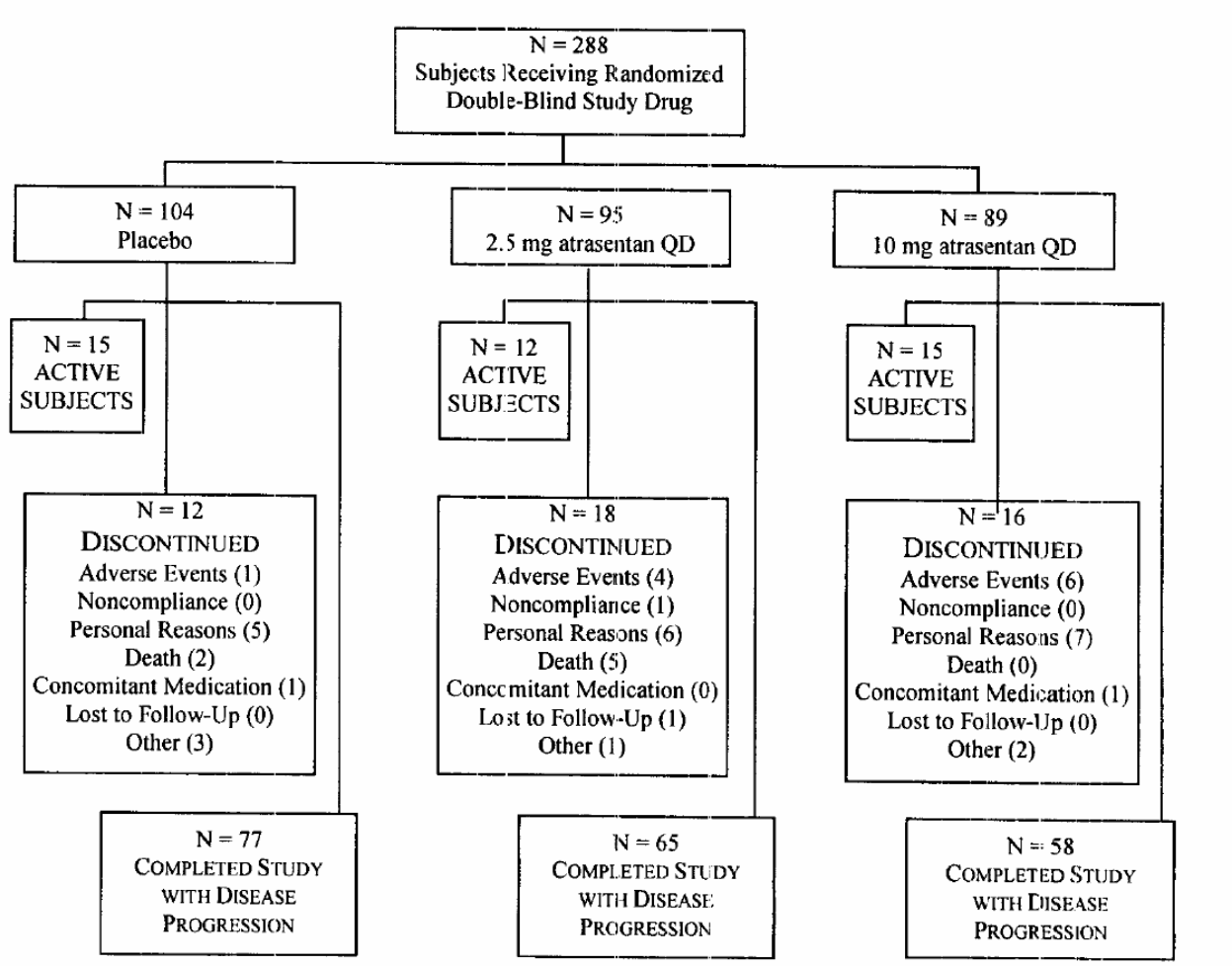
SUMMARY OF SUBJECT ACCOUNTABILITY THROUGH 31JAN2000

| | PLACEBO | 2.5 MG | 10 MG | TOTAL |
|---|---|---|---|---|
| SUBJECTS RANDOMIZED BUT NOT TREATED | 0 | 0 | 0 | 0 |
| SUBJECTS RANDOMIZED AND TREATED | 104 | 95 | 89 | 288 |
| SUBJECTS WHO HAD A DOSE REDUCTION | 0 | 1 | 1 | 2 |
| SUBJECTS NOT EXPERIENCING DISEASE PROGRESSION: | | | | |
| PRIMARY REASON SUBJECTS ENDED STUDY: | | | | |
| ADVERSE EVENTS | 2 | 4 | 7 | 13 |
| NONCOMPLIANCE | 0 | 1 | 0 | 1 |
| PERSONAL REASONS | 6 | 6 | 7 | 19 |
| DEATH | 2 | 5 | 0 | 7 |
| CONCOMITANT MEDICATIONS | 1 | 0 | 1 | 2 |
| LOST TO FOLLOW-UP | 0 | 1 | 0 | 1 |
| ABBOTT TERMINATED STUDY | 0 | 0 | 0 | 0 |
| OTHER | 3 | 1 | 2 | 6 |
| TOTAL | 14 | 18 | 17 | 49 |
| SUBJECTS EXPERIENCING DISEASE PROGRESSION | 79 | 66 | 63 | 208 |
| SUBJECTS ENROLLING IN EXTENSION STUDY | 53 | 46 | 38 | 137 |
| SUBJECTS ACTIVE | 11 | 11 | 9 | 31 |

NOTE: DATA INCLUDED ARE SUBJECT TO A CUTOFF DATE OF 31JAN2000.

**Figure 19: Subject Accountability as of 31 October 1999**

Applicant figure 10.1.a




• Primary Analysis Data Set: includes all subjects' data upon the primary analysis cutoff date (31 October 1999).
• Blinded Data Set: includes all subjects' data available through 31 January 2000, the date when the study was unblinded to perform the primary analyses. This is called the Secondary Data Set in this report.
• Overall Data Set: includes all subjects' data up to the time when all of the subjects completed/discontinued from this study (30 June 2002).

Secondary objectives were QoL and performance status by the time of amendment 5. According to the the SAP of the 5th amendment, OS, PSA levels, bone markers (not specified), QoL, performance status *etc* are secondary efficacy variables. Per Clinical Study Report, overall survival, time-to-PSA progression, bone biology markers, biochemical markers of tumor burden,

bone scan indices, quality of life, and quality adjusted time- to-progression results were secondary efficacy variables.

**Protocol Violations**

There were more protocol deviations on the Atrasentan arms than on placebo, as assigned by the applicant. According to the Applicant analysis, 38% on the placebo arm (n=39) and 58% (n=52) and 55% (n=53) significant violations occurred on the Atrasentan 10 mg and 2.5 mg arms respectively. Please see table 65 below.

Major protocol violation on FDA review were inadequate documentation of metastatic prostate cancer, androgen ablation, refractoriness to hormone therapy, stable dose of steroids or prostate cancer-related pain. These were more on the atrasentan 10 mg arm (45%) vs. on placebo arm (35%). See table 64 below.

For 2 patients on atrasentan 10 mg and 3 patients on the placebo arm, the blind was broken early.

**Table 64: Major Protocol violations as assessed by the FDA**

| | **ATRASENTAN 10 M N=89** | **ATRASENTAN 2.5 MG N=95** | **PLACEBO N=104** |
|---|---|---|---|
| Documentation of Prostate cancer as metastatic disease | 8 | 3 | 1 |
| Evidence of Androgen ablation by testosterone levels | 7 | 9 | 15 |
| Evidence of refractoriness by PSA levels | 6 | 9 | 1 |
| Recovery from prior treatments | 5 | 5 | 1 |
| Stable dose of steroids | 13 | 14 | 16 |
| Freedom from prostate cancer-related pain | 1 | 0 | 2 |
| Surgery, radiation or chemotherapy in the past 28 days, and/or not fully recovered from AE | 1 | 1 | 0 |
| Received strontium, suramin or rhenium within 12 weeks | 0 | 0 | 1 |
| **Total** | **41 (45%)** | **41 (42%)** | **37 (35%)** |

Dataset: AD

## Table 65: Significant Protocol Deviations assessed by the Applicant

Applicant table 10.2.a

| Deviation | Subject Number | | |
|---|---|---|---|
| | Placebo | 2.5 mg | 10 mg |
| Screening labs obtained before appropriate informed consent | 610 | 772 | 601, 611, 46 |
| No histological/cytological documentation of prostate adenocarcinoma | 777 | 842 | 40, 505, 688, 738, 740, 899 |
| Anti-androgen therapy | | 888, 856 | 858, 773 |
| Steroid therapy | 710, 707 | | |
| Non-metastatic disease | | 620, 647 | 40 |
| Testosterone was not ≤1.04 nmol/L | 44, 545, 794, 810, 833, 863, 623 | 91, 536, 670, 699, 809, 820, 850, 866, 647 | 26, 40, 43, 602, 627, 782, 854 |
| PSA criteria not met/inadequate PSA value(s) | 507, 853, 34, 622, 677 | 536, 842, 703, 607, 530, 772, 647 | 658, 854, 843, 543, 36, 624 |
| Inadequate anti-androgen withdrawal | | 513, 678 | |
| Screening & Day 1 were the same day so laboratory results were not available prior to study drug administration | | | 627 |
| Hematology requirements not met | 755, 771 | 657, 855 | 740, 798 |
| Hepatic requirements not met | 749, 67 | | 818, 662 |
| Positive for active hepatitis B | 623 | | |
| Renal requirements not met | 67, 524, 528, 752, 833, 898 | 513, 783, 809, 575, 647, 783, 809 | 531, 753, 854, 867 |
| Screening ECG was clinically significant or performed late | | | 46, 543, 573, 662, 851, 867 |
| History of migraine headaches, last one 12 years ago | | 666 | |
| Not free of pain related to prostate cancer or required medication to be pain free | 550, 771, 614, 895 | 517, 878, 437, 856 | 627, 889, 818 |
| Inadvertently started study <12 weeks after stopping suramin; subject was clinically and biochemically free of suramin side effects. | 504 | | |
| Subject had surgery or chemotherapy <28 days prior to Day 1 | | 673, 856, 678 | 658, 773, 858 |
| Received an investigational drug for Alzheimer's disease within 4 weeks prior to Day 1 and was discontinued from the study after 1 dose of study drug | 785 | | |
| Bone scan was done outside the 35-day screening period | | | 627 |
| Study drug compliance <50%, or subject received drug <20 days | 755, 833, 785 | 39, 510, 619, 714, 737, 741, 830, 620 | 38, 854 |
| Subject not discontinued after receiving excluded medication for pain | 82, 895, 819 | 517, 878, 437, 856 | 889, 818, 627 |
| Total | 39 | 53 | 52 |
| **Total (%)** | **37.5%** | **56%** | **58%** |

**Reviewer's Comment:**
The significant protocol violations (as appropriated by the applicant) in each of the two atrasentan arms are greater than 50%! By the FDA analysis, major protocol violations involving the enrollment criteria are 41%. By any method, the protocol violations are excessive in number.

## Demographics

### Baseline Characteristics

The patients were matched across the 3 treatment arms for baseline characteristics. It should be noted that information was not available for all 288 patients for many variables such as, BSA, Gleason's score, baseline hemoglobin, PSA and ALP.

**Table 66: Demographic and Baseline Characteristics – All Treated Subjects**

Applicant table

**Table 11.2.a Demographic and Baseline Characteristics – All Treated Subjects**

| Variable (units) | Treatment Group: Placebo N = 104[a] | Atrasentan 2.5 mg N = 95[b] | Atrasentan 10 mg N = 89[c] | Total N = 288[d] | P-Value[e] |
|---|---|---|---|---|---|
| Race | | | | | 0.738 |
| Caucasian | 102 (98%) | 91 (96%) | 85 (96%) | 278 (97%) | |
| Black | 1 (1%) | 3 (3%) | 2 (2%) | 6 (2%) | |
| Asian | 0 | 1 (1%) | 1 (1%) | 2 (1%) | |
| Hispanic | 1 (1%) | 0 | 1 (1%) | 2 (1%) | |
| Age (yrs) | | | | | 0.374 |
| Mean (SE[f]) | 71.6 (0.69) | 70.5 (0.81) | 72.1 (0.92) | 71.4 (0.46) | |
| Median | 72.0 | 71.0 | 72.0 | 72.0 | |
| Range | 54 - 88 | 52 - 89 | 43 - 94 | 43 – 94 | |
| Weight (kg) | | | | | 0.227 |
| Mean (SE[f]) | 83.7 (1.19) | 81.1 (1.25) | 84.0 (1.55) | 82.9 (0.77) | |
| Median | 82.0 | 81.5 | 82.5 | 82.0 | |
| Range | 43 - 116 | 58 - 113 | 53 - 119 | 43 - 119 | |
| Height (cm) | | | | | 0.134 |
| Mean (SE[f]) | 175.2 (0.63) | 173.0 (0.86) | 174.5 (0.86) | 174.3 (0.45) | |
| Median | 175.0 | 175.0 | 175.0 | 175.0 | |
| Range | 160 - 191 | 157 - 195 | 157 - 195 | 157 - 195 | |
| Body Surface Area ($m^2$) | | | | | 0.170 |
| Mean (SE[f]) | 2.03 (0.017) | 1.98 (0.019) | 2.02 (0.022) | 2.01 (0.011) | |
| Median | 2.02 | 1.97 | 2.03 | 2.01 | |
| Range | 1.4 - 2.5 | 1.6 - 2.4 | 1.6 - 2.4 | 1.4 - 2.5 | |

[a] N=100 for height and body surface area.
[b] N=92 for height and body surface area.
[c] N=80 for height and body surface area, N=88 for weight.
[d] N=272 for height and body surface area, N=287 for weight.
[e] P-value for racial breakdown is from a Fisher's exact test; remaining P-values are from ANOVA.
[f] Standard error.

Continued on next page

Table: Demographic and Baseline Characteristics – All Treated Subjects (continued from previous page)

| | Treatment Group | | | | |
|---|---|---|---|---|---|
| **Characteristic (units)** | **Placebo N = 104[a]** | **2.5 mg N = 95[b]** | **10 mg N = 89[c]** | **Total N = 288[d]** | **P-Value[e]** |
| Histopathological Stage | | | | | 0.065 |
| G1 | 6 (6%) | 2 (2%) | 3 (3%) | 11 (4%) | |
| G2 | 25 (24%) | 15 (16%) | 17 (19%) | 57 (20%) | |
| G3 | 24 (23%) | 30 (32%) | 22 (25%) | 76 (26%) | |
| G4 | 6 (6%) | 9 (10%) | 4 (5%) | 19 (7%) | |
| GX | 0 | 0 | 1 (1%) | 1 (0%) | |
| U | 43 (41%) | 39 (41%) | 42 (47%) | 124 (43%) | |
| Baseline Hemoglobin (g/dL) | | | | | 0.393 |
| Mean (SE[f]) | 13.0 (0.133) | 13.0 (0.140) | 13.2 (0.138) | 13.1 (0.079) | |
| Median | 13.2 | 13.1 | 13.5 | 13.3 | |
| Range | 8 - 16 | 8 - 15 | 10 - 16 | 8 - 16 | |
| Acid Phosphatase (IU/L) | | | | | 0.527 |
| Mean (SE[f]) | 60.2 (26.00) | 33.0 (12.98) | 36.4 (11.08) | 43.9 (10.88) | |
| Median | 10.1 | 6.4 | 9.6 | 8.8 | |
| Range | 4 - 2496 | 3 - 1160 | 3 - 748 | 3 - 2496 | |
| Alkaline Phosphatase (IU/L) | | | | | 0.591 |
| Mean (SE[f]) | 298.5 (50.98) | 247.9 (33.14) | 314.0 (54.07) | 286.6 (27.11) | |
| Median | 156.0 | 113.0 | 155.0 | 146.0 | |
| Range | 58 - 4640 | 39 - 2096 | 50 - 3892 | 39 - 4640 | |
| Bone Alkaline Phosphatase (IU/L) | | | | | 0.432 |
| Mean (SE[f]) | 107.9 (22.9) | 78.8 (11.7) | 112.2 (22.57) | 99.5 (11.4) | |
| Median | 42.2 | 31.6 | 40.9 | 36.1 | |
| Range | 9 - 1877 | 12 - 676 | 9 – 1369 | 9 - 1877 | |
| Baseline PSA | | | | | 0.877 |
| Mean (SE[f]) | 305.8 (80) | 292.5 (113) | 246.3 (47) | 283.1 (49) | |
| Median | 94.8 | 67.3 | 86.4 | 80.8 | |
| Range | 0 - 7431 | 0 - 9374 | 2 – 2931 | 0 - 9374 | |
| Total Gleason Score | | | | | 0.080 |
| Mean (SE[f]) | 6.9 (0.18) | 7.4 (0.18) | 6.9 (0.22) | 7.1 (0.11) | |
| Median | 7.0 | 7.0 | 7.0 | 7.0 | |
| Range | 4 - 10 | 3 - 10 | 2 – 9 | 2 - 10 | |
| ECOG Performance Score | | | | | 0.872 |
| Mean (SE[f]) | 0.5 (0.05) | 0.5 (0.06) | 0.5 (0.06) | 0.5 (0.03) | |
| Median | 0.0 | 0.0 | 0.0 | 0.0 | |
| Range | 0 - 2 | 0 - 2 | 0 – 2 | 0 - 2 | |

[a] N=52 for total Gleason score, N=94 for bone alkaline phosphatase.
[b] N=55 for total Gleason score, N=94 for acid phosphatase and ECOG performance score, N=91 for baseline PSA, N=89 for alkaline phosphatase.
[c] N=51 for total Gleason score, N=88 for baseline Hgb, N=87 for baseline PSA, N=82 for bone alkaline phosphatase.
[d] N=158 for total Gleason score, N=287 for acid phosphatase, N=287 for ECOG, N=287 for baseline Hgb, N=282 for baseline PSA, N=265 for bone alkaline phosphatase.
[e] The P-value for the histopathological comparison is from a Cochran-Mantel-Haentzel row mean score test. The remaining P-values are from ANOVA test results.
[f] Standard error.

**Table 67: Number of prior cancer treatments***

| TYPE OF PRIOR CANCER THERAPY | ATRASENTAN 10 MG | | ATRASENTAN 2.5 MG | | PLACEBO | |
|---|---|---|---|---|---|---|
| | N=89 | % | N=95 | % | N=104 | % |
| Hormone therapy | 87 | 98 | 86 | 91 | 96 | 92 |
| Surgery | 59 | 66 | 64 | 67 | 78 | 75 |
| Radiation therapy | 37 | 42 | 28 | 29 | 44 | 42 |
| Chemotherapy | 16 | 18 | 20 | 21 | 26 | 25 |
| Steroids | 7 | 8 | 6 | 6 | 6 | 6 |
| Radiopharmaceuticals | 5 | 6 | 3 | 3 | 4 | 4 |
| Biological therapy | 1 | 1 | 5 | 5 | 1 | 1 |
| Bisphosphonates | 1 | 1 | 1 | 1 | 2 | 2 |
| Other | 1 | 1 | 0 | 0 | 0 | 0 |
| **Total number of prior cancer therapies** | **214** | | **213** | | **257** | |

*More than 1 type of therapy may have been administered per patient. Each type of therapy (e.g. hormone therapy, chemotherapy radiation therapy) was counted to a maximum of one per patient.
Per applicant, 3 patients on each of the atrasentan arm received chemotherapy less than 28 days prior to day 1.

## Efficacy

### *Primary Endpoint Analyses*

The applicant assigned a cut-off date of 31st October 1999 for the primary analysis approximately 1 month before this date. Time to Progression on this dataset conducted by the Kaplan-Meier method did not reach statistical significance. As can be noted, the numbers of patients at risk in the treatment arms remain close to each other. The primary endpoint of time to disease progression differed markedly from one study to the other. Regarding imaging and pain endpoint, the applicant clarified in emails as below.

Per applicant *"The central radiology evaluations of the bone scans and CT scans for study M96-594 were performed prior to the completion of the study. The results of these evaluations were entered into the data base prior to the blind break on 31 Jan 2000. The protocol was amended in April 1999 (Amendment 3) to include the central reader. The results of the central review were not provided back to the clinical investigators and therefore were not applied by the investigators to their assessment of time to disease progression."*

And

*"The M96-594 protocol eligibility criteria stated that the subjects must be free of pain related to their prostate cancer. Additionally, subjects who had bone pain requiring immediate radiotherapy, symptoms consistent with spinal cord compression, or a history of migraine headaches/chronic headache syndrome were to be excluded. For M96-594, disease progression due to pain was defined by the onset of a clinical event of pain requiring medical intervention. The interventions specified in the protocol that constituted a clinical event included: palliative treatment of new bone or visceral pain with an opioid, palliative radiation for treatment of new bone pain, or treatment with chemotherapy. The clinical events of pain were collected on the adverse event case report form page. New interventions (chemotherapy, radiotherapy, surgery, other) and pain requiring opioids were collected on the study outcome CRF page. Strict criteria related to duration and route of opioid therapy were not provided in the M96-594 protocol. Objective evidence of disease at the site of pain was not required per the M96-594 protocol."*

A discussion on disease progression events will be presented before the analysis of time to disease progression.

**Events of Disease Progression**

Although the name of the primary objective, i.e., time to disease progression is the same, the definition of disease progression and of its components are different for the phase II and the phase III studies. The differences are presented in the table below.

**Table 68: Comparison of definition of Disease Progression in M00-211 and M96-594**

| EVENTS CONSTITUTING DISEASE PROGRESSION | |
|---|---|
| **Phase III Study (M00-211)** | **Phase II Study (M96-594)** |
| Skeletal Event | |
| Event Due to Metastatic Prostate Cancer Requiring Intervention | Chemotherapy, surgery, radiation or "other" intervention for prostate cancer |
| Pain (intervention with one of opioid, corticosteroid, radiation, radionuclide therapy or chemotherapy). Two week duration of oral opioids and objective evidence of tumor at pain site required). | - New bone pain or visceral pain with opioid. ( no duration or confirmation of tumor at pain site required)<br>- Palliative radiation (external beam, implants, strontium, suramin, or rhenium $^{186}$)<br>- Treatment with chemotherapy. |
| Radiographic progression | Only new bone or soft tissue lesions were counted as progression.<br>Increase in tumor size on a CT scan was not included in the definition of disease progression.* |
| | New *symptoms* related to tumor growth. |
| | Other *investigator-defined* measures of disease progression. These could be:<br><br>PSA rise alone,<br>pain,<br>death,<br>increases in bone or soft tissue lesions,<br>weakness,<br>use of steroids,<br>disease progression<br>urinary symptoms, and<br>deterioration. |

*In addition to a different definition, less than half patients had paired bone scans and CT scans for radiographic assessment.

**Reviewer's Comments:**
The events characterizing disease progression are of a questionable clinical benefit.

- Investigators were not blinded to PSA values, and could introduce bias in the assessment of disease progression

- In the phase III study (M00-211), specific criteria for bone scan reading were used so as to reduce chances of error. No similar criteria were used for this Phase II study.

- Progression of existing lesion on bone scan did not constitute disease progression. Additionally only new "measurable" disease qualified for DP, but new evaluable disease should be recognized as disease progression on bone scans or CT scans.

- Opioids could have been administered just once to qualify for disease progression, and objective evidence of tumor at pain site was not required unlike as in the phase III study M00-211.

- New symptom growth was one of the events leading to disease progression was not captured in the CRF.

- Other "investigator-defined measures" is a mixed basket for terms such as pain, death, increases in bone or soft tissue lesions, weakness, use of steroids, disease progression, urinary symptoms, and deterioration. Many of these are of questionable clinical benefit or of definite relationship to prostate cancer.

**Events of Disease Progression:**

Per Applicant, *"In study M96-594 a single date of disease progression was assigned to a subject. If multiple reasons for disease progression were given for a subject, the CRFs did not capture which event occurred first. In table 1__2.1.3.17 all events of disease progression are given. That is, there was a total of 202 subjects that experienced at least one of the criteria for disease progression or death during the study (77 Placebo, 67 ABT-627 2.5 mg, and 58 ABT-627 10 mg ISE table: 1__2.3.1.1). There were 2 subjects in the 2.5 mg ABT-627 arm that died prior to discontinuing study drug administration and were thus considered to have events of disease progression at the time of their death. Therefore a total of 200 subjects experienced disease progression for a total of 308 reasons for disease progression."*

**Table 69: Summary Of All Events For Disease Progression**

Cutoff 31 Oct 1999 (All Randomized Subjects In The Phase II Study)
Based on Applicant Table 1__ 2.1.3.1.7 (ISE)

| | **Placebo** | **Atrasentan 2.5 mg** | **Atrasentan 10 mg** | **All** | **TOTAL** |
|---|---|---|---|---|---|
| **Treated Subjects** | **104** | **95** | **89** | **184** | **288** |
| Subject Progressions | 77 | 67 | 58 | 125 | 202 |
| All Criteria Met For Progression # | | | | | |
| New Measurable Bone Lesions | 35 | 30 | 23 | 53 | 88 |
| New Intervention | 21 | 22 | 18 | 40 | 61 |
| Pain Requiring Opioids | 23 | 15 | 15 | 30 | 53 |
| New Measurable Soft Tissue Lesions | 12 | 15 | 9 | 24 | 36 |
| Death While On Treatment | 0 | 2 | 0 | 2 | 2 |
| Other | 28 | 22 | 18 | 40 | 68 |
| | | | | **Total Events** | **308** |
| **Number of Patients with events: 200 + 2 Deaths prior to discontinuing study drug** | | | | | |

Note: data included are subject to a cutoff date of 31Oct1999.
# some subjects progressed by more than one criterion.

The most common reasons for "other" were rise in PSA, and increase in pain.

**Radiographic Progressions:**

In the phase III study, the most common events of progression were radiographic progressions (74%) and pain (20%). The analysis of bone scans, CT scans and opioid use will be evaluated before presenting the results of time to disease progression, which was the primary objective of this study.

Bone scans:
According to the sponsor, 46% of subjects (132/288) had paired bone scans available for analysis (equally distributed among treatment groups). Any results from an analysis with greater than 50% missing data cannot be considered reliable.

**Table 70: Subject Disposition- Bone Scan Analyses**

Applicant table 11.4.h from the CSR

| | Number (%) of Subjects | | | | | |
|---|---|---|---|---|---|---|
| | Placebo N=104 | | 2.5 mg N=95 | | 10 mg N=89 | |
| Not Evaluable | 0 | | 1 | (1%) | 0 | |
| Incomplete | 8 | (8%) | 6 | (6%) | 1 | (1%) |
| Missing | 46 | (44%) | 45 | (47%) | 49 | (55%) |
| Total subjects not evaluated | 54 | (52%) | 52 | (55%) | 50 | (56%) |
| Subjects evaluated (qualitative) | 50 | (48%) | 43 | (45%) | 39 | (44%) |

CT scan analysis

About half patients had missing or incomplete CT scans. There were more patients with progression on both the atrasentan arms when compared with placebo.

**Reviewer's Comments:**
Imaging is the most objective method of documentation of progression. The use of bone scans though extremely common for prostate cancer, can be too sensitive, compromising the specificity. The applicant had used certain criteria to increase the specificity of the bone scans for metastatic disease in the phase III study. Similar criteria were not used for this phase II study. Regardless, the absence of greater than half paired bone scans and CT scans points towards the poor conduct of the phase II study. In the phase III study, 74% of progressions were documented by imaging techniques.

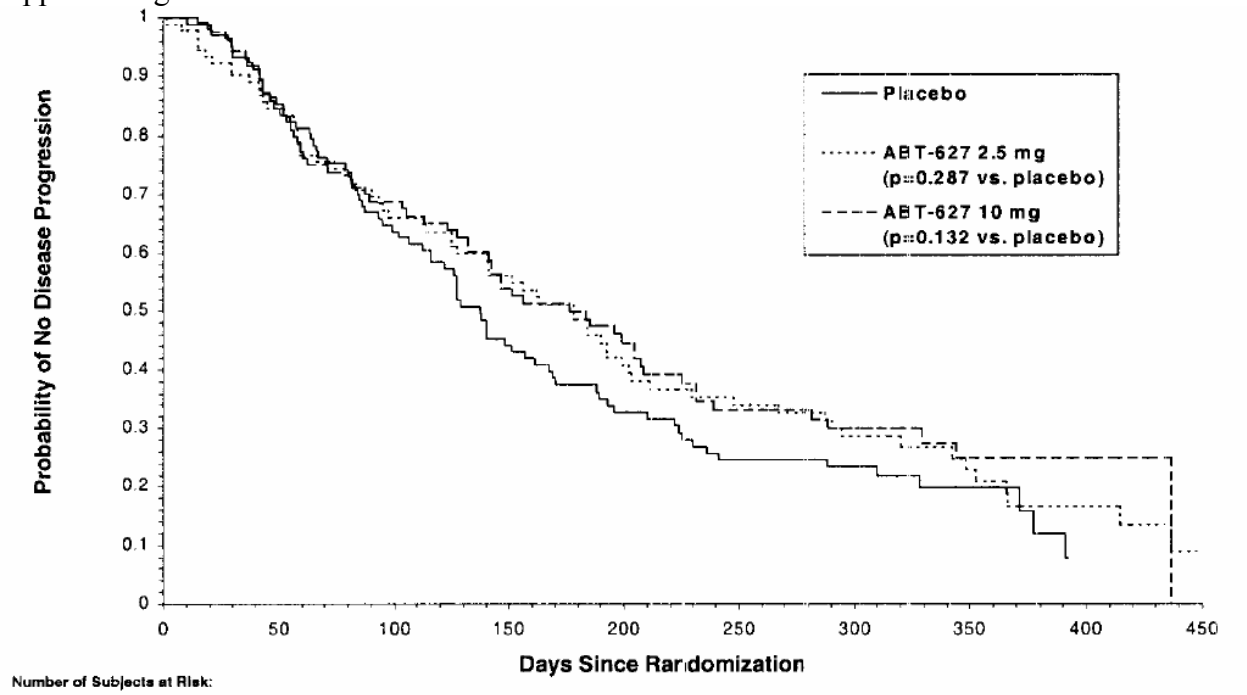
**Use of opioids for pain**

Use of opioids for pain per protocol was one of the components of "disease progression" events. The protocol did not specify duration of use, or that it should be at a site documented to have prostate cancer. Consequently, a single dose of drugs like Codeine or Demerol could be counted as disease progression, even if not related to prostate cancer. The "reason for use" was required to be filled in the CRF. This reason was often terms such as abdominal pain, analgesia, backache, arthritis, intermittent pain, rib pain, thigh pain, tumor pain etc. This component of disease progression, which accounted for 20% disease progressions in the phase III study, is of questionable clinical significance in this phase II study.

**Time To Disease Progression**

**Figure 20: Time to Disease Progression – Analysis of the Primary Data Set (ITT Population)**

Cut-off date October, 31st, 1999
Applicant figure 11.4.a




There was a difference of 8 days in the 25th percentile, 46 days in the median and 103 days in the 75th percentile. As noted above, this difference was not statistically significant.

**Table 71:Time to Disease Progression – Analysis of the Primary Data Set (ITT Population)**

Cut-off date October, 31st, 1999
Applicant table 11.4.a

| Treatment Group | Number (%) of Subjects Progressing | | Time (days) to Progression 25th Percentile | Median | 75th Percentile | 180-Day Progression-Free Rates (%) |
|---|---|---|---|---|---|---|
| Placebo | 77 | (74%) | 79 | 137 | 241 | 37% |
| 2.5 mg | 67 | (71%) | 74 | 178 | 342 | 49% |
| 10 mg | 58 | (65%) | 71 | 183 | 344 | 50% |

**Reviewer's Comments:**
- The ITT analysis did not demonstrate a beneficial effect of atrasentan.
- The definition of disease-progression in this protocol is not acceptable for a registration study because of its questionable clinical significance, as discussed earlier in the section on Primary Endpoint Analysis (see reviewer's comments).
- More than 50% patients had missing paired bone scans and CT scans, making time to disease progression analysis invalid.

***Secondary Endpoints analyses***

According to section 2 of the protocol, secondary objectives included

- QOL
- Performance status

By the time of amendment 5, the SAP had the following statement; *"Overall survival, PSA levels, bone markers, QOL, Performance Status, etc. are secondary efficacy variables."* Considering that the use of word "etc" could introduce any number of secondary efficacy variables, only QoL and Performance status will be analyzed as secondary objective. It should be noted that the bone markers and the methods for their analyses were not identified.

**QoL:**

The quality of life for hormone refractory cancer subjects in this study was evaluated by two instruments - FACT-P and EORTC QLQ-C30. The evaluation of quality of life, from both a general and prostate cancer specific perspective, did not demonstrate consistent statistically significant differences between either atrasentan dose groups and the placebo group for any of the domains, with the exception of the "relationship with doctor" domain, according to the applicant's analysis.

**Performance status**

Per applicant, *"There were no statistically significant differences between treatment groups. Results of the ITT Secondary Data Set Analysis were similar to the ITT Primary Data Set*

*Analysis. Results of the Per-protocol Primary and Secondary Data Set Analyses were also similar to results of the ITT Primary Data Set Analysis."*

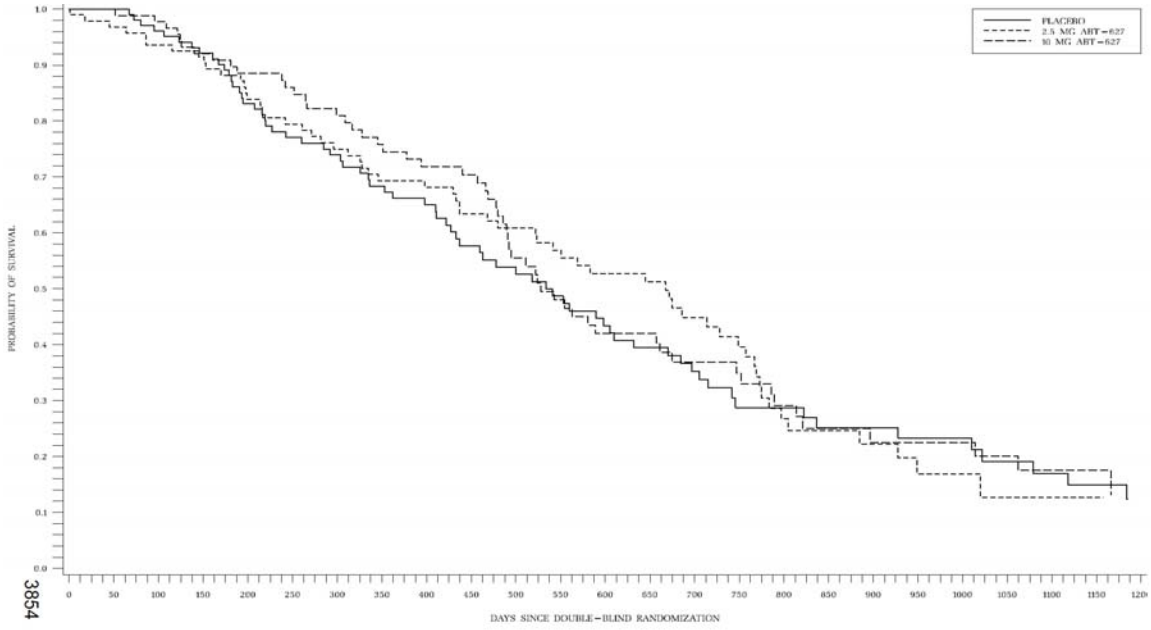
***Tertiary Analyses***

**Survival**

Final database closure occurred on 30 June 2002. This was also the date of administration of the last dose of study drug on this protocol. As of this date, the number of confirmed deaths had increased to 70/104 (67%), 61/95 (64%), and 57/89 (64%) for the placebo, 2.5 mg atrasentan, and 10 mg atrasentan groups, respectively. There were no statistically significant differences in survival between either of the atrasentan treatment groups and the placebo group (P=0.581 for 10 mg vs. placebo and P=0.596 for 2.5 mg vs. placebo).

**Figure 21: Analysis of Survival without cut-off (ITT)**

Applicant figure 1_2.8.3.1.1 from ISE




Analyses of survival for the per-protocol criteria subset demonstrated similar results.

Per applicant," *Analysis of survival is complicated by the crossover of placebo-treated subjects to open-label atrasentan treatment. At the time of disease progression in study M96-594 all subjects were eligible to participate in study M97-739, an open-label extension study in which subjects were randomized to receive either 20 or 30 mg atrasentan. In addition, subjects who remained in Study M96-594 when the blind was broken (31 January 2000) were eligible to receive open-label drug (2.5 mg or 10 mg) and continue in the study until disease progression occurred. Overall, approximately 59% of atrasentan subjects in study M96-594 continued to*

*receive atrasentan after disease progression or blind break, while 57% o f subjects treated with placebo ultimately received atrasentan therapy."*

**Per Protocol Analysis**

Per applicant:
*"To evaluate the effects of atrasentan in a subject population most representative of the intended study population, an analysis of a per-protocol subset of subjects was performed. Prior to breaking the blind for this study, criteria for excluding subjects were defined. These criteria included significant deviations from study inclusion and exclusion criteria, as well as significant deviations from protocol-specific procedures such as use of excluded medications or study drug compliance. The specific criteria are listed below.*

*A. Disease Classification – a subject did not meet the protocol definition for metastatic hormone refractory prostate cancer for one of the following reasons.*

*• The subject did not have documented diagnosis of prostate cancer rated as M+.*
*• The subject did not show evidence of androgen ablation, i.e., had measured testosterone >1.04 nrnol/L (30 pg/dL).*
*• The subject's prostate cancer was not clinically refractory to androgen ablation.*
*• The subject had an insufficient rise in PSA, i,e., less than 4.9 ng/mL at screening/Day 1.*

*B. Insufficient anti-androgen withdrawal*
*• The subject did not meet the minimum withdrawal period for an anti- androgen.*

*C. Use of medications excluded at study entry*
*• The subject had pain related to his prostate cancer at the start of the study defined by opioid use for cancer-related pain.*
*• Subject received an investigational drug within 4 weeks of starting Study M96-594.*

*D. Limited administration of study drug*
*• The number of study drug administration days for a subject were less than 50% of the total study duration for that subject.*
*• A subject received study drug for fewer than 20 days. E. Initiation of excluded medications while on study*
*• The subject initiated steroid use >3 weeks prior to the end of the study, or the subject initiated steroid use not prescribed for a reasonable non-cancer related condition or prescribed for cancer treatment.*
*• The subject began using opioids for pain related to his prostate cancer >3 weeks prior to the end of the study and disease progression was not declared by the investigator. (Initiation of opioid therapy prior to investigator- declared disease progression wa,; likely to confound the endpoint),*
*• The subject was taking other possible confounding medications excluded by the protocol.*

*Based on these criteria, 44 randomized patients were excluded from the primary analysis patients.*

**Table 72: Per-Protocol Exclusions by Category**

Applicant table 11.1.a

| Category* | Placebo | 2.5 mg Atrasentan | 10 mg Atrasentan | Total |
|---|---|---|---|---|
| Pain Due to Disease | 1 | 4 | 3 | 8 |
| Hormone Manipulation | 1 | 4 | 3 | 8 |
| Admission Criteria | 8 | 3 | 5 | 16 |
| Confounding Medications | 2 | 0 | 0 | 2 |
| Study Drug Administration | 2 | 7 | 1 | 10 |
| * Subjects with more than one per-protocol exclusion were included in one category only. | | | | |
| **Total** | **14 (13%)** | **18(19%)** | **12 (13%)** | **44 (15%)** |

With the exclusion of only 15% patients, the applicant's analysis of the log-rank test evaluating the distribution of the time to disease progression values in the Per-Protocol population became statistically significant at the $p<0.05$ level if not adjusted for multiple comparisons and analyses ($P=0.021$, 10 mg; and $P=0.035$, 2.5 mg). This analysis was not included in the primary or secondary endpoint. As mentioned earlier, the definition of disease progression is not acceptable. The most common events on the phase III study (radiographic progressions and use of opioids for pain) had either greater than 50% missing data or were of questionable clinical significance in this study.

**Figure 22: Time to Disease Progression – Analysis of the Primary Data Set (Per-Protocol Population)**

Cut-off October 31st, 1999
Applicant figure 11.4.b

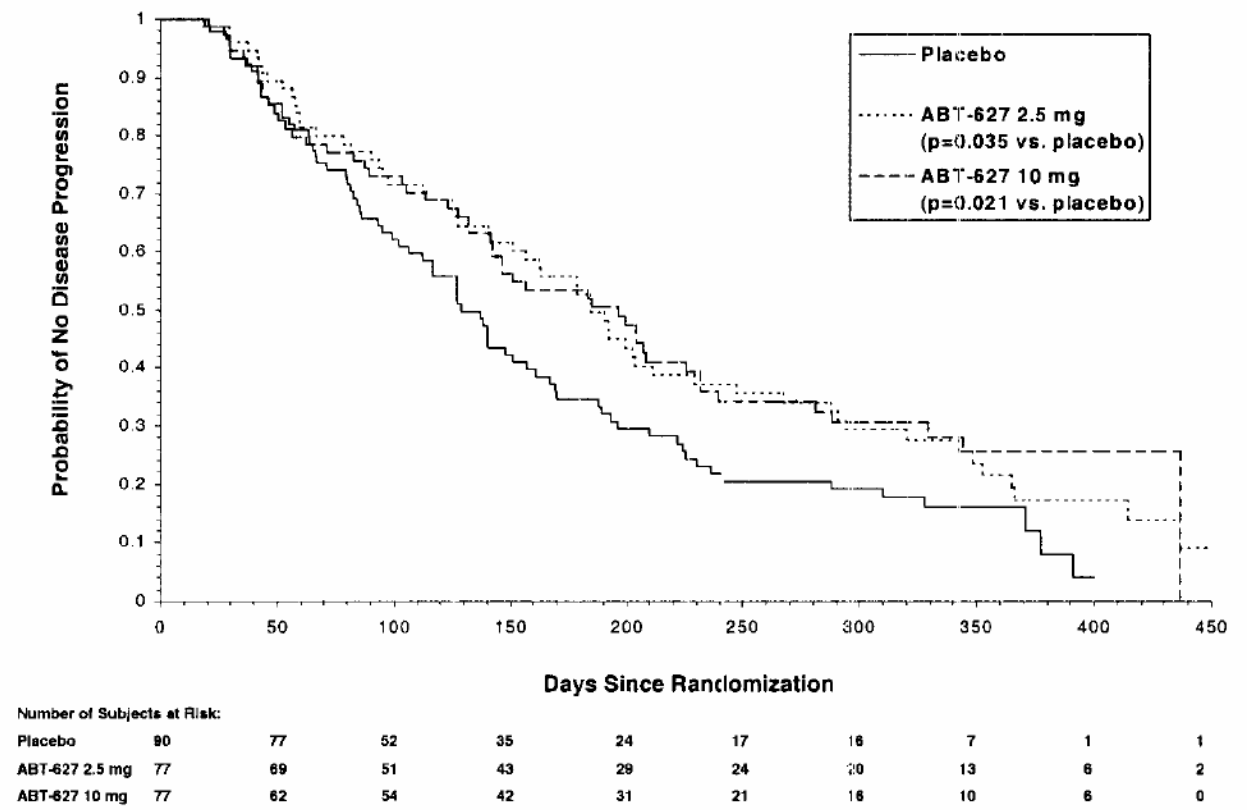



**Table 73:Time to Disease Progression – Analysis of the Primary Data Set (Per-Protocol Population)**

Cut-off October 31st, 1999
Applicant table 14.4.b

| Treatment Group | Number (%) of Subjects Progressing | Time (days) to Progression: 25th Percentile | Median | 75th Percentile | 180-Day Progression-Free Rates (%) |
|---|---|---|---|---|---|
| Placebo | 72 (80%) | 71 | 129 | 225 | 35% |
| 2.5 mg | 57 (74%) | 93 | 184 | 348 | 53% |
| 10 mg | 51 (66%) | 87 | 196 | 436 | 54% |

**Reviewer's Comment:**
It should be noted that only 180 (63%) patients were in the Per-Protocol group. This endpoint was exploratory and the p-value of 0.021 was not adjusted for the various multiple comparisons. The exclusion of 37% patients due to violations speaks of the conduct of this study. When the results were analyzed after an additional 3 months for the secondary dataset, the p-value of even the Per-Protocol analysis became greater than 0.05 (see below).

The Primary (cutoff October 1999) and secondary datasets (cut off January 2000) were analyzed by the applicant for the efficacy endpoints below. The results for selected endpoints given below are all provided by the applicant in the CSR.

• Time to PSA Progression (p=0.002 for ITT population for primary dataset; only 3 more PSA progressions occurred by the secondary cutoff date giving a p-value of 0.003.)
• Changes from baseline in bone markers (alkaline phosphatase, bone alkaline phosphatase, N-terminal cross-linking telopeptide, C-terminal cross-linking telopeptide, and total deoxypyriclinoline)
• Changes from baseline in tumor markers (acid phosphatase, LDH, chromogranin A, interleukin-6)

**Secondary Dataset (31 January 2000 Data Cutoff)**

Per Applicant, 8 more patients progressed by the time of the secondary dataset cutoff. Results of the time to progression analysis for the two populations were similar to those observed with the Primary Data Set; however, in the per-protocol analysis, comparison of the results for the 2.5 mg and 10 mg atrasentan treatment groups with placebo were now greater than 0.05 (P=0.064 and P=0.061, respectively).

**Safety**

The most common (>10%) AE on the 10 mg atrasentan arm were bone pain, peripheral edema, asthenia, rhinitis, nausea, anemia, headache, constipation, dyspnea, pain, back pain, anorexia, rash, abdominal pain, infection, urinary tract infection and paresthesia. Where AE were severe and greater numerically on the atrasentan arm, the AE were anemia, rhinitis, left , heart failure, asthenia, abdominal pain, bladder stenosis, somnolence, headache, constipation, anorexia, hematuria, urinary frequency, dizziness, pleural effusion, pneumonia, pelvic pain, depression, lung disorder, liver function tests abnormal, skin ulcer, neoplasm, congestive heart failure, sepsis, sudden death, tolerance decreased, lung edema, eye disorder, acute kidney failure, and kidney failure.

**Table 74: Severe AE greater on Atrasentan 10 mg arm than on Placebo (%)**

FDA Analysis (continued on next page)

| COSTART TERM | ATRASENTAN 10 MG | | PLACEBO | | ATRASENTAN 2.5 MG | |
|---|---|---|---|---|---|---|
| | ANY GRADE | SEVERE | ANY GRADE | SEVERE | ANY GRADE | SEVERE |
| **Body as a whole** | | | | | | |
| Asthenia | 36 | 2 | 1 | 23 | 16 | 2 |
| Abdominal pain | 12 | 2 | 1 | 8 | 12 | 2 |
| Headache | 22 | 1 | 1 | 11 | 17 | 1 |
| Pelvic pain | 4 | 1 | 0 | 6 | 6 | 0 |
| Neoplasm | 2 | 1 | 0 | 1 | 1 | 0 |
| Sepsis | 1 | 1 | 0 | 0 | 0 | 0 |
| Sudden death | 1 | 1 | 0 | 0 | 2 | 2 |
| Tolerance decreased | 1 | 1 | 1 | 2 | 0 | 0 |
| **Cardiovascular system** | | | | | | |
| Left heart failure | 4 | 3 | 0 | 0 | 2 | 2 |
| Congestive heart failure | 2 | 1 | 0 | 0 | 2 | 0 |
| **Digestive system** | | | | | | |
| Constipation | 22 | 1 | 0 | 13 | 21 | 1 |
| Anorexia | 13 | 1 | 1 | 14 | 6 | 0 |
| Liver function tests abnormal | 3 | 1 | 0 | 3 | 1 | 1 |
| **Hemic and lymphatic system** | | | | | | |
| Anemia | 24 | 6 | 2 | 13 | 16 | 4 |

| COSTART TERM | ATRASENTAN 10 MG | | PLACEBO | | ATRASENTAN 2.5 MG | |
|---|---|---|---|---|---|---|
| | ANY GRADE | SEVERE | ANY GRADE | SEVERE | ANY GRADE | SEVERE |
| **Nervous system** | | | | | | |
| Somnolence | 4 | 2 | 0 | 2 | 6 | 1 |
| Dizziness | 7 | 1 | 0 | 4 | 11 | 0 |
| Depression | 4 | 1 | 0 | 3 | 0 | 0 |
| **Respiratory system** | | | | | | |
| Rhinitis | 33 | 3 | 0 | 15 | 25 | 0 |
| Pleural effusion | 6 | 1 | 0 | 1 | 4 | 1 |
| Pneumonia | 4 | 1 | 1 | 4 | 4 | 3 |
| Lung disorder | 4 | 1 | 0 | 2 | 5 | 1 |
| Lung edema | 1 | 1 | 0 | 0 | 0 | 0 |
| **Skin and appendages** | | | | | | |
| Skin ulcer | 3 | 1 | 0 | 1 | 0 | 0 |
| **Special senses** | | | | | | |
| Eye disorder | 1 | 1 | 0 | 0 | 1 | 0 |
| **Urogenital system** | | | | | | |
| Bladder stenosis | 7 | 2 | 1 | 3 | 2 | 0 |
| Hematuria | 8 | 1 | 1 | 7 | 11 | 3 |
| Urinary frequency | 8 | 1 | 0 | 3 | 3 | 0 |
| Acute kidney failure | 1 | 1 | 0 | 0 | 0 | 0 |
| Kidney failure | 1 | 1 | 1 | 1 | 0 | 0 |

**Cardiovascular System**

Heart Failure is a known AE for atrasentan. However, excess cardiovascular CAD and arrhythmia events were also observed in the phase III study. Cardiovascular system will be reviewed in detail for this phase II study below.

CAD

The terms coronary artery disorder, cardiovascular disorder, angina pectoris, MI and coronary occlusion were evaluated. CAD events, arrhythmias and heart failure events were greater on the atrasentan arms when compared with placebo numerically please see the tables below.

**Table 75: Incidence of Coronary Artery Disorder (by number of patients)**

| COSTART TERM | SEVERITY | ATRASENTAN 10 MG N=89 | ATRASENTAN 2.5 MG N=95 | PLACEBO N=104 |
|---|---|---|---|---|
| Angina Pectoris | severe | 0 | 1 | 0 |
| Angina Pectoris | moderate | 1 | 0 | 0 |
| Angina Pectoris | mild | 1 | 2 | 1 |
| Coronary Artery Disorder | moderate | 3 | 0 | 0 |
| Coronary Occlusion | moderate | 0 | 1 | 0 |
| Myocardial Infarct | mild | 1 | 0 | 0 |
| Cardiovascular Disorder | mild | 4 | 3 | 1 |
| | **Total** | **10** | **7** | **2** |

**Table 76: Incidence of arrhythmia and syncope (by number of patients)**

| COSTART TERM | SEVERITY | ATRASENTAN 10 MG | ATRASENTAN 2.5 MG | PLACEBO |
|---|---|---|---|---|
| AV block | mild | 0 | 1 | 0 |
| Arrhythmia | mild | 1 | 3 | 1 |
| Atrial fibrillation | severe | 0 | 1 | 0 |
| Atrial fibrillation | moderate | 1 | 0 | 1 |
| Atrial fibrillation | mild | 2 | 1 | 0 |
| Bigeminy | mild | 1 | 0 | 0 |
| Electrocardiogram abnormal | mild | 1 | 0 | 0 |
| PR interval prolonged | mild | 0 | 1 | 0 |
| Palpitation | moderate | 1 | 0 | 0 |
| Palpitation | mild | 1 | 1 | 1 |
| Sinus bradycardia | mild | 0 | 0 | 2 |
| Syncope | severe | 0 | 1 | 0 |
| Syncope | moderate | 1 | 1 | 0 |
| Tachycardia | mild | 1 | 2 | 1 |
| Ventricular extrasystoles | moderate | 0 | 0 | 1 |
| Ventricular extrasystoles | mild | 1 | 0 | 1 |
| | **Total** | **11** | **12** | **8** |

**Table 77: Incidence of Heart Failure (by number of patients)**

| COSTART TERM | SEVERITY | ATRASENTAN 10 MG | ATRASENTAN 2.5 MG | PLACEBO |
|---|---|---|---|---|
| Heart failure | 1 | 0 | 0 | 1 |
| Left heart failure | 3 | 3 | 2 | 0 |
| Left heart failure | 2 | 1 | 0 | 0 |
| Lung edema | 3 | 1 | 0 | 0 |
| | **Total** | **5** | **2** | **1** |

**Conclusions**

This randomized phase II study was not reviewed by the FDA prior to its submission in this NDA. It failed in its primary endpoint of time to disease progression in the ITT population. Time to disease progression was defined as the time from randomization to first clinical event requiring an intervention. These clinical events were identified as new lesions on bone scans or CT scans, use of opioids for prostate cancer-related pain, palliative radiation, use of chemotherapy symptoms related to tumor growth and investigator-defined disease progression. This definition of disease progression was different from that in the phase III study (M00-211). This study was a randomized, blinded study, in which survival analysis was included, though not as a primary endpoint.

This section will be divided in two parts; efficacy followed by safety. There are major weaknesses that prevent this phase II study from being acceptable as a registration study. Additionally, the formulation used for the phase II study is different from that used in the phase III study. According to the applicant, because the AUC are similar, these two formulations are bioequivalent. However, by the FDA standards, the formulations would also need to have a similar Cmax. According to the preliminary FDA Clinical Pharmacology analysis, the formulations are not bioequivalent for Cmax; Cmax is 2.1 times greater for the phase III formulation than for the Phase 2 formulation. It is not known whether this difference is of clinical significance or not. The safety information from the phase II study will be considered supportive of the safety information on the phase III study.

Efficacy:

There were several major weaknesses in the design of the study.

a) Most parts of the composite primary endpoint are of questionable clinical significance. Investigators were not blinded to PSA values, and this could introduce bias in the assessment of disease progression. PSA itself is not a validated endpoint for registration studies.

b) In the phase III study (M00-211), several criteria for bone scan reading were used so as to reduce errors and increase specificity for bone metastases. No similar criteria were submitted for this Phase II study.

c) Progression of existing lesion on CT scan did not constitute disease progression. Only new "measurable" disease qualified for DP in this study, but new evaluable disease should also have been recognized as disease progression.

d) Opioids could have been administered just once to qualify for disease progression, and this opioid administration was not required to be for prostate cancer related pain. A single administration of codeine or Demerol would qualify for disease progression

e) Other "investigator-defined measures" is a mixed basket for terms such as pain, death, increases in bone or soft tissue lesions, weakness, use of steroids, disease progression, urinary symptoms, and deterioration. Many of these are too soft as endpoints in a registration study. Pain, urinary symptoms, weakness and general deterioration may due to other co-morbid conditions in an elderly population.

<u>There are major weaknesses in the conduct of the study:</u>

a) The definition of primary endpoint continued to evolve until after all patients were enrolled. According to the applicant, this was done to make the primary objective consistent with the CRF.

b) An excessive number of protocol violations were observed. According to the applicant' analysis, about 50% patients had protocol violations, which were greater on the atrasentan arms (58% on atrasentan 10 mg, vs. 38% on the placebo arm).

c) Per applicant less than half (46%) of subjects (132/288) had paired bone scans available for analysis. Less than half patients had paired CT scans available. Radiographic progressions are progression-defining events. In the phase III study, about 75% of the progressions were identified on imaging. The number of missing scans in this phase II study make disease progression results unreliable

<u>Weaknesses in results of the study</u>

a) The study failed its primary objective.

b) The patients on the placebo arm were more heavily pre-treated than those on the atrasentan arm.

c) The "per protocol" population was not included in the Statistical Analysis Plan (SAP) as a primary objective. Per applicant, the criteria for per protocol population were set prior to breaking the blind, but the SAP was not altered to accommodate this change.