QUESTIONS FOR THE
ONCOLOGY DRUGS ADVISORY COMMITTEE
SEPTEMBER 13, 2005 MEETING

NDA 21493 Xinlay (atrasentan)

PROPOSED INDICATION For treatment of metastatic hormone refractory prostate cancer. Changed by the Applicant during the FDA review to the following. For treatment of hormone refractory prostate cancer metastatic to bone.

Two RCTS were conducted in patients with metastatic hormone refractory prostate cancer. Study 211 compared atrasentan 10 mg with placebo in 809 patients and study 594 compared atrasentan 10 mg, atrasentan 2.5 mg and placebo in 288 patients. Important background information is the recent FDA approval of docetaxel for this patient population based on improved survival.

The FDA believes study 211 is a well-designed trial with a generally satisfactory protocol. Study 211 was stopped for futility to meet its primary endpoint (TDP), based on the recommendation of the DSMB. 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 5th secondary endpoint, mean change in bone alkaline phosphatase, 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.

Figure 1: Time-to-Disease Progression- ITT

Applicant's Figure

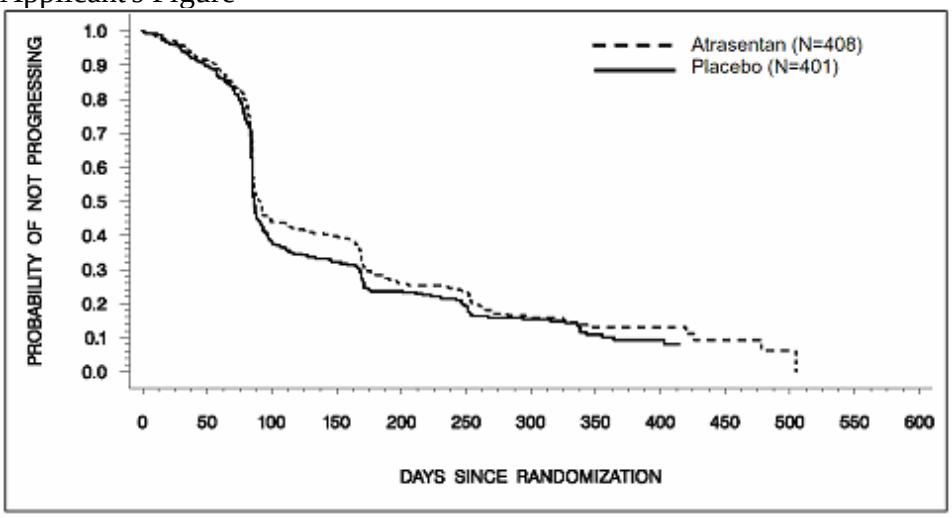

Table 1: Time to disease Progression- ITT and Two Subpopulations

Based on Applicant's 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

In study 211 atrasentan had more deaths from cardiovascular causes than placebo (atrasentan 8 versus placebo 2). Atrasentan is known to cause CHF from previously performed Phase 2 trials. In study 211 the Atrasentan group had in increased incidence of grade 3 or 4 CHF (atrasentan 3% versus placebo 0.75%), grade 3 or 4 CAD toxicity (MI, angina pectoris or stent placement) (atrasentan 2% versus placebo 0.5%), cardiac arrhythmias (atrasentan 5% versus placebo 1%) and peripheral edema (atrasentan 40% versus placebo 13%).

The FDA does not believe study 594 is a well designed and well conducted trial with a satisfactory protocol. Disease progression was not adequately defined, about 50% of patients had protocol violations, less than half of the patients had paired bone scans available for examination and less than half had paired CAT scans available for examination.

The two studies should not be combined for analysis. 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 FDA does not believe study 594 had a satisfactory protocol or was well conducted.

QUESTIONS FOR THE ODAC

1. In study 211 in the ITT analysis of TDP and PFS atrasentan did not show an advantage over placebo. Multiple subgroup analyses were done which the FDA considers exploratory. The Applicant now requests approval based on an unprespecified subgroup analysis in HRPC patients with bone metastasis. Are the TDP results in study 211 in the bone metastasis subgroup statistically persuasive?

2. In study 211 the difference in median TDP between Atrasentan and placebo is 5 days in the ITT population, 4 days in the per protocol subgroup and 7 days in the bone metastasis subgroup. Is the size of the atrasentan TDP effect in study 211 in the ITT, per protocol subgroup or bone metastasis subgroup clinically important?

3. There is concern about atrasentan cardiovascular toxicity. In study 211 atrasentan had more deaths from cardiovascular causes than placebo (atrasentan 8 versus placebo 2). Atrasentan is known to cause CHF from previously performed Phase 2 trials. In study 211 the atrasentan group had in increased incidence of grade 3 or 4 CHF (atrasentan 3% versus placebo 0.75%), grade 3 or 4 CAD toxicity (MI, angina pectoris or stent placement) (atrasentan 2% versus placebo 0.5%), cardiac arrhythmias (atrasentan 5% versus placebo 1%) and peripheral edema (atrasentan 40% versus placebo 13%). Is the risk/benefit ratio for atrasentan favorable?

4. Should this NDA be approved?