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Quick Pulse

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FDA Advisory Committee Recommends Against Approval of New Prostate Cancer Therapy

Bethesda, MD
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The FDA's Oncologic Drugs Advisory Committee (ODAC) gave thumbs down to Abbott Laboratories' Xinlay (atrasentan) for the treatment of metastatic hormone refractory prostate cancer, saying that the company failed to show that Xinlay is effective against prostate cancer. The pivotal study missed its primary endpoint and four out of five secondary endpoints, and the panel also pointed to serious cardiovascular safety issues with the drug. Panel members said that while they had high hopes for the drug, it did not reach its goals.

Xinlay is a potent selective ET delta receptor antagonist, which is orally bioavailable at once-daily dosing. Abbott was seeking FDA approval to market Xinlay for treatment of men with hormone refractory prostate cancer with metastases to bone.

FDA Opening Remarks

An FDA staff member outlined the reasons the drug was taken to an advisory panel, "First, is there a persuasive, clinically convincing effect on an endpoint? The level of evidence on the endpoints should be the same. You have to have convincing, persuasive findings on that endpoint…I think what people have to understand is that when we talk about the uncertainty with accelerated approval, we're not talking about the effect of the therapeutic effect on that endpoint…The ambiguity in relationship is between that endpoint and it being reasonably able to predict effect."

Two randomized clinical trials were conducted in patients with metastatic hormone refractory prostate cancer. Study 211 compared Xinlay 10 mg with placebo in 809 patients, and Study 594 compared Xinlay 10 mg, Xinlay 2.5 mg, and placebo in 288 patients. FDA staff said that an important background fact is the recent approval of Sanofi-Aventis' Taxotere (docetaxel) for this patient population, based on improved survival.

The FDA officials said that Study 211 was stopped because it failed to meet its primary endpoint of time-to-disease progression (TTP) by an intent-to-treat analysis. The trial also failed four out of five secondary endpoints which were: overall survival (OS), change in bone scan index, time to PSA progression, and progression-free survival (PFS). The fifth secondary endpoint, mean change in bone alkaline phosphatase, reached statistical significance, though a mean change of 22 ng/mL had 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 (KPS), and mean change from baseline in PSA.

Toxicity with Xinlay in Study 211

Adverse event	Xinlay	Placebo
Grade 3/4 CHF	3%	0.75%
Cardiac toxicity (MI, angina, revascularization)	2%	0.5%
Cardiac arrhythmia	2%	N/A
Peripheral edema	40%	13%
Deaths	8 patients	2 patients

The FDA said that in Study 211, Xinlay had more deaths from cardiovascular (CV) causes than placebo. It is known to cause congestive heart failure (CHF) from previously performed Phase II trials.

The FDA staff said that it did not believe Study 594 was a well-designed and well-conducted trial with a satisfactory protocol. Disease progression was not adequately defined, and about 50% of patients had protocol violations. Fewer than half the patients had paired bone scans available for examination, and fewer than half had paired CT scans available for examination.

The FDA staff said that 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 were not bioequivalent by FDA standards. Furthermore, the FDA does not believe that Study 594 had a satisfactory protocol or was well conducted.

FDA speakers blasted Abbott's data and said that Xinlay is not superior to placebo in terms of progression to disease, survival, or quality of life. They also pointed out several safety concerns. Among the other points FDA reviewers made were:

- The Phase II study was unacceptable.
- In the Phase III study:
  - Four out of five secondary endpoints were not met, and the fifth was not clinically meaningful and of questionable value.
  - Bone markers and quality of life endpoints that were pre-specified in the secondary and tertiary analyses failed.
  - Marginal improvement was of questionable clinical relevance and reliability in all three populations presented.
  - Multiple post hoc analyses warrant further study.

THE COMPANY PERSPECTIVE

Abbott speakers argued that although Xinlay did not meet its primary endpoints, there was still benefit, saying that the drug delayed the progression of bone metastases. An Abbott vice president told the panel, "There was consistent benefit in patients with bone metastases…There is a large unmet need in this group of men." Another Abbott speaker said, "There is a clear need for more treatment options in this area."

The company's oncology global project head said that the 10 mg dose was found to slow time-to-progression (TTP) of disease better and more effectively than placebo. He said, "This trial did not meet the primary endpoint, but what you can see is the 'radiographic' curve. More than 50% of patients progressed at the first bone scan in both treatment groups, and discounting the treatment effect of atrasentan on those patients who go through the first bone scan is not descriptive of the effect…There is a clear scientific rationale to evaluate atrasentan in light of the progression of bone metastases. Furthermore, the majority of outpatients have metastatic disease of bone confirmed at baseline – 690 out of 809 patients. We then looked at the treatment of atrasentan in this population…There was a treatment effect with atrasentan in patients with metastatic disease in their bone. There was a 19% reduction in risk of disease progression." He noted that Xinlay attenuates the mean change in bone alkaline phosphatase compared to placebo in patients with bone metastases, adding, "This confirms that atrasentan delays the progression of disease in patients with bone metastases." He also pointed out that patients receiving Xinlay had a >2 month delay in quality of life deterioration associated with the disease.

The Abbott speaker insisted that Xinlay significantly delays disease progression, which was the protocol-specified primary endpoint of the study, with a 19% reduction in delay of disease progression. He said the results of both studies showed a consistency of treatment effect, and he concluded that the data "provide compelling evidence that patients with hormone refractory metastatic cancer with metastases to bone will derive significant benefit from treatment with atrasentan."

Safety

An Abbott speaker said that most of the adverse events in the trial were mild and resolved spontaneously or with treatment. Total number of adverse events in both groups was high. Serious adverse events or severe adverse events and discontinuations due to adverse events were similar between the groups.

Bone pain was an exceedingly common adverse event and was more common in placebo patients, according to the speaker. Other adverse events included peripheral edema, rhinitis, headache, anemia, infection, and dyspnea.

More patients on Xinlay had CV events compared to those on placebo. An Abbott expert said, "Our experience with CV

Statistically Significant Adverse Events ≥ 10%

Adverse event	Any adverse event		Grade 3/4 adverse events	
	Placebo n=544	Xinlay 10 mg n=541	Placebo n=544	Xinlay 10 mg n=541
Bone Pain	51%	44%	14%	9%
Peripheral edema	14%	38% *	1%	1%
Rhinitis	13%	34% *	0	0
Headache	14%	22% *	0.4%	0.7%
Anemia	9%	14% *	3%	4%
Infection	7%	11% *	0	0.6%
Dyspnea	4%	10% *	0.6%	1%

* p<.05

events included arrhythmias, which resulted in no deaths, heart failure, and MI. Many of these events are manageable, and there are identifiable risk factors for these individuals… There are CV safety recommendations for the use of this drug as with other vasoactive compounds in the elderly...The safety experience is large, the overall safety profile when one considers Grade 3/4 events, discontinuations, and deaths, is similar between placebo and atrasentan, and serious CV events are infrequent and, with monitoring, can be managed. There were no drug interactions warranting dose adjustments, and there were no significant hepatic, renal, or marrow toxicities noted.

An Abbott prostate cancer program co-leader said that more options are needed for patients with hormone refractory prostate cancer (HRPC) and bone metastases who suffer debilitating pain. He commented, "Patients who may benefit can be easily identified. For them, atrasentan offers a unique option…with convenient, once-daily, outpatient dosing…The potential toxicities are predictable and manageable… Atrasentan should be made available for use, so there are more options for patients…to have more good days."

FDA Presentation

The FD said that there have been two approvals for HRPC in the past two years – mitoxantrone + prednisone (approved in 1996) and Taxotere + prednisone (approved in 2004). The primary endpoint for mitoxantrone + prednisone was confirmed improvement in pain, using an interpretable pain severity scale, with a pre-specified analysis plan for pain evaluation, and improved time-to-progression. The primary endpoint for the second drug was overall survival. The FDA staffer said that the results for these were clinically and statistically persuasive.

The Abbott Phase III study was a double-blinded randomized study. Quality of life was a tertiary endpoint without a detailed analysis plan. There was no mention of a specific measurement of pain submitted. Radiographic progression drove results of the study. The protocol-specified primary endpoint was time-to-disease progression by intent-to-treat (ITT) analysis, which it failed. The study also failed 4 of the 5 secondary endpoints, including time to PSA progression, change in bone scan index, overall survival, and PFS. The only secondary endpoint that was statistically significant was a mean change in ALP, but a difference of only 22 ng/mL was described as of questionable significance. The study also failed several tertiary endpoints, including quality of life-adjusted TTP (QATTP), KPS, and mean change in PSA.

An FDA reviewer said that clinical disease progression analysis was not pre-specified, not adjusted for multiple comparisons, and more than 75% were censored for progression. He added that the analyses violated established principles for clinical trials. There were additional problems with subgroup analyses, he said, including:

- High false positive or false negative rates.
- False positive finding increases with number of significant tests.
- Not pre-specified, post hoc analysis.
- Primary failed, and p-value not interpretable.

Efficacy in Phase II and III *(by ITT Analysis)*

Measurement	Phase III n=809	Phase II n=193
Median time-to-disease progression		
Xinlay 10 mg	91 days	183 days
Placebo	86 days	137 days
p-value, log-rank	0.123	0.132
Hazard ratio	0.88	0.77

He concluded that the subgroup analyses were not interpretable because the primary endpoints failed, so subgroup analyses would be exploratory and useful for hypothesis-formulating, not testing. Furthermore, he pointed out that the pooled analysis of Phase II and Phase III studies was not acceptable because of many reasons, including:

- Neither trial individually showed a statistically significant difference.
- The studies had different definitions of TTP.
- The studies had different patient populations.
- The Xinlay formulations were not bioequivalent.
- No independent review of progression evaluation was conducted in the Phase II study.
- Pooling data causes imbalance in randomization.
- Type 1 error was not controlled.

Quality of life (QoL) was a tertiary endpoint, but there were no hypotheses for QoL analysis and no adjustment for multiple comparisons. Other problems with QoL analysis included:

- Recall bias.

- Clinical significance of the PCS (prostate cancer sub-score) mean change of 1.02 on a scale of 0-48 makes it difficult to interpret.
- PCS doesn't capture all the patient perceived impact of Xinlay treatment.
- Missing data.

Unlike the mitoxantrone study, pain was not a primary endpoint for Xinlay studies. The mean change in pain-related scores in PCS were:

- Not designed or validated for such use.
- Clinical significance of the prostate cancer pain score mean change of 0.7 on a scale of 0 to 16.
- Each pain item measures a different attribute of pain.
- 7-day recall period.
- Questions were not specific to bone pain.
- Questions do not adequately measure pain.

An FDA official talked about the safety aspect of the two studies, concluding that:

- Primary endpoint failed.
- Pre-specified statistical plan: If primary endpoint fails, study fails.
- Most secondary endpoints failed (including time to PSA change, PFS, and OS).
- Many tertiary endpoints failed (including bone markers and QoL-related endpoints).
- Pain-related endpoints not pre-specified.

Phase III Study Events

Measurement	Xinlay n=404	Placebo n=397
MI	9	2
Angina pectoris	5	3
Coronary artery disorder	2	0
Number of patients – all CAD events	13	5
Patients with Grade 3/4 events	8	2
Deaths	2	1
Arrhythmias	5	1
All-cause mortality	41	39
Total CV causes	2	0.5

Phase III Xinlay Study

Adverse event	Xinlay n=404	Placebo n=397
Deaths – any cause	41%	39%
Deaths – CV causes	2%	0.5%
CAD Grade 3/4 events	2%	0.5%
CHF Grade 3/4 events	3%	0.75%
Arrhythmias	5%	1%
Pneumonia Grade 3/4	1%	0

- Safety concerns (CAD, CHF, arrhythmias).
- Xinlay compared to placebo and not active control.

Arrhythmias included atrial fibrillation, atrial flutter, brady-cardia, extrasystoles, palpitation, supraventricular extrasysto-les, supraventricular tachycardia, tachycardia, and ventricular extrasystoles.

PANEL DISCUSSION

The committee chair asked the company to summarize ongoing studies. An Abbott speaker said that there is an ongoing study in men with cancer that is not metastatic to bone. He said that Abbott has two pilot studies looking at Xinlay in combination with Novartis's Zometa (zoledronic acid), and the company is in discussions with the Southwest Oncology Group (SWOG) and the FDA regarding a large study of atrasentan with Sanofi-Aventis' Taxotere (docetaxel). Patient population will be HRPC with metastases.

A panel member asked about the company's concerns relative to the use of other vasoactive compounds in patients. A company speaker responded, "We have not seen any increase in adverse events, i.e., patients on Coumadin (warfarin)… We'll have more specific recommendations (re CV problems) in the clinical trials with regard to patient education." Another Abbott speaker talked about the two pilot studies. He said that survival would be one endpoint, but they were still working on endpoints for pain. The chair asked what the primary endpoint would be in ongoing studies, but an official said that has not been completely resolved yet.

PUBLIC DISCUSSION

Several patients and doctors spoke, including:

- Joe Waldenfels, a prostate cancer patient, spoke in favor of Xinlay. He said that approval of the drug would help men with HRPC who are running out of options.
- Bill Blair, chairman of Scientific Support Network, said that there are few treatment options for men with advanced prostate cancer with skeletal metastases and HRPC.
- Dr. J. Kuntz, a clinical investigator for Xinlay, who treats patients with prostate cancer, said, "It's not about statistics. It's about the individual patient…The fact is that if it might work, it's an effective drug…I'm not the sharpest tool in the drawer – I'm a urologist." He also said that it's a safe drug, adding that his patients want as many options as possible.

The committee chair said, "There's a general assumption that somehow those of us sitting here don't actually take care of patients…That is not the case. There are many of us on this committee who do nothing but see patients day in and day out …who understand the day-to-day practicalities of taking care of patients with cancer."

COMMITTEE DISCUSSION

Expanded access

A panel member asked if the drug would still be available in the expanded access program. An Abbott speaker said there is no intent to change the expanded access program. He said that if the drug is not approved, the program would continue until the FDA decides to discontinue it.

The Abbott official insisted that Xinlay does benefit some men with HRPC. As for ending the study early, he said it seemed inappropriate to modify the plan when the company was told to stop the study. An Abbott biostatistician said that the ITT population was pre-specified and documented and added that some secondary endpoints were biologic rather than clinical. He also claimed that the quality of life results were significant. The Abbott vice president said that the primary composite endpoint was met in the group of men with bone metastases, and he said that was the basis of the discussion.

Stopping the trial early

An FDA panel member said that one of the panel's concerns was the recommendation of the independent data monitoring committee (IDMC) to halt the study. He asked if Abbott was unable to convince its own committee that it should fight to keep the study going. An Abbott statistical consultant said that when the IDMC saw the 344 confirmed events and stopped the study, the end result was that between the 75th percentile and the 40th percentile occurred at the first bone scan.

Any benefit?

An oncologist on the committee said that one concern was that a subset of patients probably does get benefit from the drug (those with bone metastases), but the question is what endpoint should be used in the study. She suggested that time-to-progression should perhaps have been a secondary endpoint and asked, "Are we actually able to salvage this to get to the main question?" A biostatistician on the panel said, "Even when you have a full set of data, the data we're looking at still isn't statistically significant…I think it's going to be a great test case, example in text books, but to say that we're comfortable pulling a subgroup…is very questionable."

Another panel member started this dialogue:

Panel member #1: "I hate subsets…If this drug is approved right now, we tell these honorable men from Abbott that they can sell it to all men with prostate cancer, and that takes away the incentive for them to find that 15% of the population that should be taking the drug. So, what are you actually doing to find the subset that actually responds to the drug?"

Abbott official: "We already have a group of men who are more likely to respond to this drug than others. We are saying it is that group of men who have metastatic disease involving bone – out of all men with HRPC."

Panel chair: "But that could encompass every person with prostate cancer..."

Abbott speaker: "The indication we are looking for is that group of men with documented bone disease…Of the men who are asymptomatic, they will become symptomatic, and this drug is for them."

Panel chair: "How are we going to deal with patients who are not asymptomatic if this drug is indicated for men whose symptoms are asymptomatic?"

Abbott speaker: "The idea is whether adding chemotherapy to atrasentan is beneficial for asymptomatic patients who become symptomatic. But it's important that this drug be given to patients who are asymptomatic…The big question is what happens to those patients who are asymptomatic who then become symptomatic?...We do not have that data."

Panel member #2: "The question is finding those individuals who are going to benefit...Is there a variability to patients who are more blastic…"

Abbott official: "There's no clear-cut indication other than the question of someone being asymptomatic or symptomatic."

Cardiovascular disease

An oncology nurse on the panel asked about cardiovascular disease and asked Abbott to speak to the issue of co-morbidities. An Abbott speaker responded that most men with CHF and MI were older. Another Abbott speaker said that patients with unstable conditions were excluded from one study when they discovered cardiac problems in patients.

Subgroups

The chair's final question to Abbott was, "I want you to summarize what you have demonstrated in that sub-population." An Abbott speaker answered, "I think that what we have shown…We have had a positive effect in reduction of the risk (in developing pain)…You would expect to see changes in the bone scan progression. We see that…On top of that, if you believe these are things that matter to patients, those things in the quality of life measure do in fact change and show benefit to those patients."

COMMENTS, FDA QUESTIONS, AND VOTES

Panel comments included:

- "If we approve this drug now what we're going to do is slow down the approval process for other drugs, so I think it's a disservice to approve this drug."
- "I think it would be a real shame for the company to throw this away. I don't think you gave us the data to approve this, but I'm sad about it, actually."

- "I agree with not voting for approval. This is an interesting compound that does have more than just general effects on the bone…and going forward the idea is going to be to really look carefully at patient selection parameters, but more importantly to think about the types of endpoints that can enhance the quality of life of these patients."
- "It's important to go forward with combination trials carefully…There are ways to combine drugs that are positive, and there are ways that might give you a false negative result…They need to be careful on how they do it and have some rationale for the dose schedule."
- *Panel chair:* "We want to see simple and effective therapy. When you see it and combine it with other therapies that maybe are not so effective or easy to tolerate, then you lose something…So, I'm also concerned that the drug, in and of its own, needs further study without confusing it."
- "I also do not consider this drug to be ready for approval. The toxicity of the drug has been, in my opinion, downplayed significantly. I am from Texas, and the specter of Vioxx (Merck, rofecoxib) looms large over us …I can see patients suffering rather than benefiting."
- "I have hope for this drug, and I hope it continues to be developed…I would like to see prostate cancer patients have options. However, I want them to have legitimate options. Development of this drug would be slowed down if we were to approve it at this time."

Question 1: *In Study 211 in the ITT analysis of TTP 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 un-pre-specified subgroup analysis in HRPC patients with bone metastasis.* ***Are the TTP results in Study 211 in the bone metastasis subgroup statistically persuasive?***
Unanimously NO

Question 2: *In Study 211 the difference in median TTP 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 TTP effect in Study 211 in the ITT, per protocol subgroup or bone metastasis subgroup clinically important?***
No vote taken

One panel member said she thought the time-to-disease progression shouldn't be the question, but that the question should be time-to-symptoms. She said she did not hear any data that time-to-symptoms was accurately, consistently, and reliably measured. Another panel member said, "I think the study was a failure, and I don't think that we want a discussion about clinical significance if the statistical significance isn't there." The chair said, "There are times when there is clinical significance…I think that there is clinical value in what has been presented today. The issue is, do I want to change my behavior based on it?"

Question 3: *There is concern about atrasentan cardiovascular toxicity. In Study 211 atrasentan had more deaths from cardiovascular causes than placebo (atrasentan 8 vs. placebo 2). Atrasentan is known to cause CHF from previously performed Phase II trials. In Study 211 the atrasentan group had an increased incidence of Grade 3 or 4 CHF (atrasentan 3% vs. placebo 0.75%), Grade 3 or 4 CAD toxicity (MI, angina pectoris, or stent placement) was atrasentan 2% vs. placebo 0.5%, cardiac arrhythmias (atrasentan 2% vs. placebo), peripheral edema (atrasentan 40% vs. placebo 13%).* ***Is the risk:benefit ratio for atrasentan favorable?***
No vote taken

Question 4: *Should this NDA be approved?*
Unanimously NO

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