Food and Drug Administration
Center for Drug Evaluation and Research
Hilton College Park, 4095 Powder Mill Road, Beltsville, Maryland.

Meeting Minutes of the Cardiovascular and Renal Drugs Advisory Committee meeting on December 11, 2007.

On December 11, 2007, the committee discussed new drug application (NDA) 22-034, vernakalant hydrochloride injection, 20 milligrams per milliliter, Astellas Pharma U.S., Incorporated, for the proposed indication of use for conversion of atrial fibrillation to normal sinus rhythm

These summary minutes for the December 11, 2007 meeting of the Cardiovascular and Renal Drugs Advisory Committee were approved on Monday, December 17, 2007.

I certify that I attended the December 11, 2007 meeting of the Cardiovascular and Renal Drugs Advisory Committee and that these minutes accurately reflect what transpired.

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Cathy A. Miller, M.P.H., R.N.	William R. Hiatt, M.D.	Date
Designated Federal Official	Committee Chair	

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

The Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on December 11, 2007 at the Sheraton College Park, 4095 Powder Mill Road, Beltsville, Maryland. Prior to the meeting, the members and the invited consultants had been provided the background material from Astellas Pharma US, Inc. The meeting was called to order by William Hiatt, M.D. (Committee Chair); the conflict of interest statement was read into the record by Cathy A. Miller, M.P.H. (Designated Federal Official). There were approximately 125 persons in attendance. There were no Open Public Hearing speakers for this session.

Issue: The committee discussed new drug application (NDA) 22-034, vernakalant hydrochloride injection, 20 milligrams per milliliter, Astellas Pharma U.S., Incorporated, for the proposed indication of use for conversion of atrial fibrillation to normal sinus rhythm.

Attendance:

Cardiovascular and Renal Drugs Advisory Committee Members Present (Voting):
Steven D. Findlay, M.P.H.; William Hiatt, M.D. (Chair); Frederick J. Kaskel, M.D. Robert A. Harrington, M.D., F.A.C.C.; Abraham Michael Lincoff, M.D., F.A.C.C.

Special and Federal Government Employee Consultants (Voting):
Richard Cannon, M.D.; Barry M. Massie, M.D.; Thomas Simon (Patient Representative)

Cardiovascular and Renal Drugs Advisory Committee Members Not Present:
Henry Black, M.D.; John M. Flack, M.D.; Lynn Warner Stevenson, M.D.; Emil Paganini, M.D.; Jonathan Fox, M.D.; John Teerlink, M.D.; James Neaton, Ph.D

Guest Speaker (Non-Voting):
Christopher B. Granger, M.D.

FDA Participants (Non-Voting):
Norman Stockbridge, Ph.D., M.D.
Ellis Unger, M.D.

Designated Federal Official:
Cathy A. Miller, M.P.H., R.N.

Open Public Hearing Speakers:
None Registered

The agenda was as follows:

Call to Order and Introductions	**William R. Hiatt, M.D.** Committee Chair Cardiovascular and Renal Drugs Advisory Committee
Conflict of Interest Statement	**LCDR Cathy A. Miller, M.P.H., R.N.** Designated Federal Official Cardiovascular and Renal Drugs Advisory Committee
Introduction and Background	**Norman Stockbridge, M.D., Ph.D.** Director, Division of Cardiovascular and Renal Products FDA Center for Drug Evaluation and Research

FDA Guest Speaker Presentation:

Cardioversion for Atrial Fibrillation	**Christopher B. Granger, M.D.** Cardiologist Duke University School of Medicine Durham, North Carolina
	Questions to the Committee Part 1 **General Considerations - Atrial Fibrillation**

Astellas Pharma US, Inc. Presentation:

Introduction	**Donald L. Raineri, Pharm.D.** Senior Director, Regulatory Affairs Astellas Pharma US, Inc. Deerfield, Illinois
Clinical Overview of Atrial Fibrillation	**Edward L.C. Pritchett, M.D.** Consulting Professor of Medicine Duke University Medical Center Durham, North Carolina
Mechanism of Action	**Greg Beatch, Ph.D.** Vice President, Scientific Affairs Cardiome Pharma Corp. Vancouver, B.C., Canada
Toxicology & Clinical Pharmacology	**James Keirns, Ph.D.** Senior Director, Biopharmaceutical Sciences Astellas Pharma US, Inc. Deerfield, Illinois
Clinical Efficacy and Safety	**Therese M. Kitt, M.D.** Senior Director, Medical Sciences Astellas Pharma US, Inc. Deerfield, Illinois
Risk/Benefit Summary	**Jeremy N. Ruskin, M.D.** Director, Cardiac Arrhythmia Services Massachusetts General Hospital Boston, Massachusetts
	Question/Discussion from the Committee
	Break

FDA Division of Cardiovascular and Renal Products Presentation:

Vernakalant for Conversion of Atrial Fibrillation	**Ellis Unger, M.D.** Deputy Director Division of Cardiovascular and Renal Products CDER, FDA
	Questions/Discussion from the Committee
	Lunch

Open Public Hearing

Questions to the Committee Part 2

Adjournment

Questions to the Committee [PART 1]:

1. Before considering drugs to effect conversion of AF (and AFL) to normal sinus rhythm, the AC is asked to consider:

   - How well characterized is the time course for spontaneous conversion?

   The Committee generally agreed that the time course for spontaneous conversion is reasonably well known but with a considerable range over certain intervals (early versus late). We know quite a bit about drug and placebo comparison endpoints over a 2-hour window from the two development programs to be discussed, but have less certainty in later time periods (24 hrs, 7 days). The committee noted that spontaneous conversion rates were quite high early after the onset of atrial fibrillation and that those rates decreased the longer atrial fibrillation continued.

   - How well characterized are the harms of being in AF?

   The Committee touched on the harm issue of being in atrial fibrillation, citing symptoms in some patients, the thromboembolic risk in all patients and the bleeding risks from chronic anticoagulation. A potential additional harm was the need for electrical cardioversion which required sedation and was unpleasant for patients.

   - How well characterized is the time course for successful electrical conversion?

   This was felt to be initially successful in the vast majority of patients.

   (See transcripts for detailed discussion)

2. What are the disadvantages to waiting for spontaneous conversion?

   - Symptoms?

   The Committee commented that the urgency for cardioversion depends on hemodynamic instability and symptoms. Stable patients who are asymptomatic would not need urgent cardioversion and could wait for spontaneous conversion over a 24- to 48-hour interval.

   - Risk of being on anticoagulant therapy?

   The Committee agreed that there were substantial risks of chronic anticoagulation. The committee also felt that, anticoagulant therapy is not necessarily avoided in patients for whom a rhythm control strategy is employed.

   - Reduction in the success rate for conversion?

   The Committee agreed that waiting for spontaneous conversion would not alter the response to electrical conversion in the short-term.

   - Poorer hemodynamic outcome?

   The Committee commented that hemodynamics with multiple rate control drugs can be an issue (i.e. particularly post operative patients.) Hemodynamics may be an issue for this population.

   - Shorter duration of normal sinus rhythm?

   The Committee was unsure of the benefits of obtaining normal sinus rhythm with a drug a few hours in advance of spontaneous conversion.

- Other?

(See transcripts for detailed discussion)

3. Can you describe the magnitude and durability of any of these disadvantages?

(See transcripts for detailed discussion)

4. What is the right interval to integrate the success of spontaneous conversion? If someone were very likely to convert spontaneously within the next hour, would it make sense to consider treatment options? Within the next day? Within the next week?

The Committee emphasized the need to see data that illustrates a time-dependent risk-benefit analysis. The Committee agreed that the risks and benefits vary at different time points. There was also some discussion of different subgroups of patients in atrial fibrillation and not all atrial fibrillation is the same.

(See transcripts for detailed discussion)

Questions to the Committee [PART 2]:

1. What clinical benefits were *demonstrated* in the development program for vernakalant? For which of them are there beneficial and meaningful trends?

   - Reduction in thromboembolic events?

   The Committee found no evidence for this.

   - Reduction in hemorrhagic events (reduced need for warfarin)?

   The Committee commented that conversion does not necessarily eliminate the need for anticoagulation or reduction in hemorrhagic events. No evidence was presented that vernakalant reduced hemorrhagic events.

   - Reduction in the need for hospitalization?

   The Committee found to assess this. The actual number of days in hospital was not collected by sponsor.

   - Reduction in symptoms attributable to atrial fibrillation?

   The Committee felt this was well demonstrated with a reduction of symptoms at 90 minutes compared with patients randomized to placebo. Some cited methodological flaws in how the symptoms data were collected (unblinding), though there seemed to be a tie between symptoms at sinus rhythm at 90 minutes with the drug.

   - Avoidance of electrical cardioversion?

   The committee agreed that yes, there was a demonstrated avoidance of electrical conversion

   - Others?

(See transcripts for detailed discussion)

2. What clinical benefits do you believe should be *expected* through the use of vernakalant? Compared with what treatment (electrical cardioversion, rate control, or another drug) are these clinical benefits expected?

The Committee felt that the sample size to prove that a shorter time in AF with drug therapy would have a measurable clinical outcome was not feasible. The Committee commented that the avoidance of performing the electrical cardioversion procedure could be perceived as a benefit for use of vernakalant.

3. Cited conversion rates excluded patients who underwent early electrical conversion, those who converted prior to receiving study drug, and those who otherwise did not receive study drug. Are these exclusions reasonable? If not, how should these cases be handled?

Some of the Committee commented that those who spontaneously converted should be in the intent to treat numerator and denominator. The Committee also commented that these exclusions are reasonable as long as we are shown why the patients did not get the treatment. Sensitivity analyses provided by the sponsor confirmed the robustness of the data.

4. In a restricted sense, vernakalant is clearly more effective than is placebo. Among patients who had been in atrial fibrillation for 3 hours to 7 days, the rates of spontaneous conversion on placebo *within a 1.5-h window* were about 4% in ACT I and ACT III, while conversion rates on drug were 51% at proposed doses.

    - How well characterized is the relationship between time in atrial fibrillation and spontaneous conversion? Note that 3% of patients converted spontaneously after randomization but before study drug administration.

    The Committee agreed that spontaneous conversion rates within 24 hours are relatively well known and that additional patients would have converted had the run-in period been 24 hours

    - How well characterized is the relationship between time in atrial fibrillation and conversion on vernakalant?

    The Committee generally agreed that this relationship is relatively well characterized in the first 48 hours. The treatment effect was reduced in patients in AF longer than 48 hours, but still measurable.

    - What length of time in atrial fibrillation is clinically meaningful?

    The Committee cited 48 hours for a decision to electrically convert in patients on adequate anticoagulation (often with TEE guidance as there is a risk of emboli), therefore the majority of benefit from drug therapy would be within that window.

    - For patients who have been in atrial fibrillation for what duration is the time savings attributable to vernakalant clinically meaningful?

    The Committee agreed that within 48 hours drug clearly beats placebo but were unsure how to quantify time-savings, especially given that time was largely driven by the protocol as clinicians needed to wait 90 minutes before giving other therapies. The Committee also recognized that electrical cardioversion takes time to set up (~2 hours).

(See transcripts for detailed discussion)

5. What effect does unsuccessful conversion with vernakalant have upon subsequent attempts at electrical conversion?

The Committee agreed that unsuccessful conversion with vernakalant had no effect on subsequent attempts at electrical conversion.

6. How is atrial hemodynamic function affected by vernakalant? Does this matter?

The Committee agreed that hemodynamic function could not be assessed given the absence of data from the studies. However the committee was uncertain whether it mattered, though they clarified that for certain patients with stiff hearts, it may.

7. How much of a safety concern is torsade de pointes?

    - Have the rates of torsades been adequately characterized in the patient population and at the doses for which vernakalant should be used?

The Committee agreed that there was a (probably low) risk of the drug inducing torsade, but that the risk was not fully characterized.

- For how long (either hours or QT prolongation) should rhythm be monitored after exposure to vernakalant? Does this time need to be adjusted for 2D6 inhibitors or for poor metabolizer phenotypes?

Many on the Committee agreed that the average practitioner will need to be given guidelines in "X" hours (time) versus QT measurement. In particular the committee was uncomfortable with asking clinicians to accurately monitor QT interval in practice. Therefore a recommend interval of monitoring was felt to be safer. Others added that erring on the side of caution is good, perhaps 3 hours, although they have no data to support this time period. They did feel that we don't know enough from the dataset to limit the time to 2 hours.

(See transcripts for detailed discussion)

8. How much of a safety concern is bradycardia?

The Committee discussed the risks of bradycardia following conversion to sinus rhythm.

(See transcripts for detailed discussion)

9. How much of a safety concern are thromboembolic events, including strokes?

The Committee generally agreed that there was not a signal of thrombolic events from the data provided by the sponsor however, given the small number of patients exposed, this risk was not well quantified.

10. Are there other safety concerns?

Other safety concerns cited by the Committee included hypotension, fatal ventricular fibrillation, risk of direct drug-related events with this compound, as well as the use of this drug in the emergency room versus a controlled clinical setting.

(See transcripts for detailed discussion)

11. Is the risk management plan proposed by the sponsor appropriate for the safety concerns?

The Committee made recommendations including methods for interpreting safety signals (torsades safety registries) and reports of hypotension, bradycardia in pharmacovigilance. They questioned, though, how difficult it will be to find the number of patients necessary to collect meaningful data

(See transcripts for detailed discussion)

12. Is another study necessary to confirm the appropriateness of the dosing recommendations? If so, in what population should it be conducted?

The Committee discussed the particular regimen proposed by the sponsor, which seemed adequate.

(See transcripts for detailed discussion)

13. **VOTE**: Should vernakalant be approved for the conversion of atrial fibrillation?

YES: 6 NO: 2

Those voting 'No' had significant concerns that the actual safety of the drug was not well characterized.

14. If you conclude that vernakalant should be approved, …

- … to what range of durations of atrial fibrillation should approval apply?

The Committee commented that the range should be limited to 3-48 hours, after which the efficacy diminishes. They recommend that this should clearly be stated on the label.

- … should use extend to patients with recent MI or heart failure?

The Committee agreed that the drug should have a narrow indication for approval, should take into consideration stable hemodynamics and should not extend to those with recent MI and questioned use in patients with HF.

- … should the claim extend to atrial flutter?

The Committee agreed that approval should not extend to atrial flutter

- … are any post-marketing commitments appropriate, such as …
    - … to study use with beta-blockers?
    - … to study the effect on ventricular defibrillatory threshold?
    - … to study use in non-Caucasians?
    - … to study use in patients with structural heart disease?
    - … to study use in patients with hepatic impairment?
    - … to study use with inhibitors of P-glycoprotein or other transporters?
    - Others?

    The Committee discussed the sponsor's post-marketing plan. Some agreed that additional data on non-Caucasians would be beneficial. There was considerable discussion about the need for additional studies in heart failure. Though some felt it would be nice to see a controlled HF study, others commented that there are significant efforts in labeling to exclude patients with heart failure. The Committee discussed the questions surrounding drug interactions. We do not know enough about the metabolism and these interactions need to be better defined.

The committee adjourned at approximately 5:00 pm

(See transcript for detailed discussion)