Questions

Vernakalant
December 11, 2007

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Cardio-Renal Advisory Committee

The Advisory Committee is asked to opine on the use of vernakalant to effect conversion of atrial fibrillation (AF) to normal sinus rhythm.

There is no question that vernakalant is effective in converting AF to normal sinus rhythm. This was demonstrated in two studies wherein patients (mean age 63, 68% male, 96% Caucasian, 15% with history of heart failure) in AF for 3 hours to 45 days (7 days for the primary end point) were randomized to study drug or placebo, and conversion was assessed within 90 minutes of the start of infusion. Although the end point only required maintenance of normal sinus rhythm for one minute, the durability of conversion was clearly longer than the lifetime of the drug in the blood.

Given time, the rate of spontaneous conversion of atrial fibrillation is highest among the very patients in whom vernakalant is most effective (those in atrial fibrillation of short duration), so the question becomes how long one should wait for spontaneous conversion before resorting to a drug, and that is a function of the risks of waiting and the risks associated with the drug. The challenge to the Committee is whether the available demonstration of activity and characterization of safety suffice to identify a population with a compelling case for net benefit.

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?
    - Reduction in hemorrhagic events (reduced need for warfarin)?
    - Reduction in the need for hospitalization?
    - Reduction in symptoms attributable to atrial fibrillation?
    - Avoidance of electrical cardioversion?
    - Others?
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?

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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?
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.
    - How well characterized is the relationship between time in atrial fibrillation and conversion on vernakalant?
    - What length of time in atrial fibrillation is clinically meaningful?
    - For patients who have been in atrial fibrillation for what duration is the time savings attributable to vernakalant clinically meaningful?
5. What effect does unsuccessful conversion with vernakalant have upon subsequent attempts at electrical conversion?
6. How is atrial hemodynamic function affected by vernakalant? Does this matter?
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?
    - 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?
8. How much of a safety concern is bradycardia?
9. How much of a safety concern are thromboembolic events, including strokes?
10. Are there other safety concerns?
11. Is the risk management plan proposed by the sponsor appropriate for the safety concerns?

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

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

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

    - … to what range of durations of atrial fibrillation should approval apply?
    - … should use extend to patients with recent MI or heart failure?
    - … should the claim 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?