Food and Drug Administration
Center for Drug Evaluation and Research

Advisory Committee Conference Room, Rm. 1066, 5630 Fishers Lane, Rockville, MD.

Summary Minutes of the Cardiovascular and Renal Drugs Advisory Committee Meeting February 24, 2005.

The committee discussed supplemental applications (sNDAs) S-022, S-024 and S-025 to approved new drug application (NDA) 20-838, ATACAND® (candesartan cilexetil) Tablets (4 mg, 8 mg, 16 mg and 32 mg), AstraZeneca, for the use in the treatment of patients with congestive heart failure.

Attendance:

Cardiovascular and Renal Drugs Advisory Committee Members Present (voting):
Steven Nissen, MD (Committee Chair)
Blasé Carabello, MD
Susanna Cunningham, PhD
William Hiatt, MD
Frederick Kaskel MD, PhD
Thomas Pickering, MD, DPhil
Ronald Portman, MD
John Teerlink, MD

Cardio-Renal Advisory Committee Members Absent:
Beverly Lorell, MD
David Demets, PhD
Lynn Warner Stevenson, MD

Cardiovascular and Renal Drugs Advisory Committee Consultants (voting):
Jonathan Sackner-Bernstein, MD
Ralph D'Agostino, PhD

Patient Representative (voting):
None Present

Industry Representative (non-voting):
John Neylan, MD

FDA Participants:
Robert Temple, MD
Norman Stockbridge, MD

Executive Secretary:
Cathy A. Groupe, RN, BSN

These summary minutes for the February 24, 2005 meeting of the Cardiovascular and Renal Drugs Advisory Committee were approved on March 1, 2005.

I certify that I attended the February 24, 2005 meeting of the Cardiovascular and Renal Drugs Advisory Committee and that these minutes accurately reflect what transpired.

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Cathy A. Groupe, R.N., B.S.N.
Executive Secretary

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Steven E. Nissen, M.D.
Chair

Open Public Hearing Speakers:
There were no registered speakers for the open public hearing.

Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA and from the sponsors. The meeting was called to order by Steven Nissen, M.D. (Committee chair); the conflict of interest statement was read into the record by Cathy Groupe, RN, BSN (Executive Secretary). There were approximately 65 persons in attendance. There were no speakers for the Open Public Hearing sessions.

Issue: The committee discussed supplemental new drug applications (sNDAs) S-022, S-024, S-025 to approved new drug application (NDA) 20-838, ATACAND® (candesartan cilexetil) Tablets (4 mg, 8 mg, 16 mg, and 32 mg), AstraZeneca LP, for the use in the treatment of patients with congestive heart failure.

The agenda was as follows:

Call to Order and Introductions	**Steven E. Nissen, M.D. (Chair)**
Conflict of Interest Statement	**LT Cathy Groupe, B.S.N.** Executive Secretary Cardiovascular and Renal Drugs Advisory Committee
Welcome and Comments	**Norman Stockbridge, M.D., Acting Director** Division of Cardiovascular and Renal Drug Products
Sponsor Presentation	
Regulatory Overview	**Cindy Lancaster, M.S., M.B.A, J.D.** AstraZeneca LP
Sponsor Presentation (continued)	
Background and Rationale	**James B. Young, M.D.** Cleveland Clinic Foundation
	John J.V. McMurray, M.D. University of Glasgow
Efficacy	**Mark A. Pfeffer, M.D., Ph.D** Brigham and Women's Hospital Boston
Safety	**James Hainer, M.D., M.P.H.** AstraZeneca LP
Benefit/Risk Summary	**James B. Young, M.D.** Cleveland Clinic Foundation
Discussion	**Marc A. Pfeffer, M.D., Ph.D.** Brigham and Women's Hospital Boston
Break	
Questions from the Committee	
Lunch	
Open Public Hearing	

Agenda (continued):

Committee Discussion and Questions

Break

Committee Discussion and Questions (continued)

Adjournment

Questions to the Committee:

The Cardiovascular and Renal Drugs Advisory Committee is asked to opine on the candesartan development program in heart failure, a series of three studies enrolling a total of 7601 subjects.

The Division expects to approve use of candesartan in patients with heart failure who are not, for whatever reason, taking an ACE inhibitor. CHARM-Alternative shows candesartan is effective in patients intolerant of ACE inhibitors and, at least, CHARM-Added is supportive of this use. The question for the Advisory Committee is whether CHARM-Added provides compelling evidence that candesartan should, under some circumstances, be recommended for use in patients on an ACE inhibitor.

The questions address three possible bases for approval. Once there is general agreement on a possible basis for approval, the Committee is invited to skip directly to question 7 and address the strength of evidence for this claim.

1. When two drugs are presumed to operate by sufficiently distinct mechanisms, one generally does not worry whether therapy with the older one has been optimized before testing the addition of the newer one.
    - 1.1. Should one, in fact, test a new drug against optimized background therapy?
    - 1.2. What are the implications if such optimization is not done?
    - 1.3. Did CHARM-Added have adequate optimization of background therapy with respect to …
        - 1.3.1. …ACE inhibitor use?
        - 1.3.2. …other treatments for heart failure?
        - 1.3.3. Are ACE inhibitors and ARBs sufficiently different that CHARM-Added can support use of candesartan with ACE inhibitors? What clinical data support your view?

Committee Vote on Question 1.4: Yes: 0 No: 10

Committee Discussion: The committee voted unanimously that they did not feel that angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are sufficiently different that the CHARM-Added study supported the use of candesartan with ACE inhibitors. Extensive conversation surrounded what constituted 'optimized' background therapy, and the fact that the measured dose tolerance feature in CHARM-Added relied heavily on investigator-specific clinical decisions in assessing patient dose tolerance. The committee further commented on the potential usefulness of a tool, perhaps in the form of a questionnaire, that could have provided anecdotal information specific to when and why dose titration decisions were made by clinicians. ***(See transcript for detailed discussion)***

If you conclude that ACE inhibitors and ARBs <u>are</u> sufficiently different, skip to question 7. If the mechanisms overlap, then optimization of ACE inhibitors matters more.

2. The protocol for CHARM-Added required subjects to be on an ACE inhibitor and the possible choices were not limited to ones with established claims for heart failure. In designing a trial for an add-on claim, …
   2.1. … should the ACE inhibitors all be ones with an established claim in heart failure?
   2.2. … how does one pick the target regimen for the ACE inhibitors?

Committee Discussion: The committee commented on the selection of the ACE inhibitors used in the trial and hypothesized that an ideal trial protocol might have utilized one specific ACE drug, titrated up to maximum tolerated dose, and then randomized patients into the trial, rather than the current trial design which utilized various ACE Inhibitors. They recognized, however, the sponsor's challenge in successfully executing such a trial design feature, specifically given the limitations of specific authorized drug choices in the various clinical settings, (i.e. the VA System and Health Maintenance Organizations). ***(See transcript for detailed discussion)***

3. The CHARM-Added protocol recommended that subjects be treated on "individualized optimum" doses of ACE inhibitor, based on tolerability and "recommended target doses".
   3.1. What is known about the relationship between dose of ACE inhibitor and clinical benefits and risks in heart failure?
   3.2. Were the choices of ACE inhibitor in CHARM-Added reasonable?
   3.3. Were the target regimens in CHARM-Added reasonable?
   3.4. What features of the CHARM-Added ensured ACE inhibitor optimization?
   3.5. Was optimized usage of ACE inhibitors realized? How do you know?
   3.6. Many subjects in CHARM-Added were never on the target dose of ACE inhibitor. Does one know why?
   3.7. The protocol permitted investigators to lower the dose of other antihypertensive drugs, *including ACE inhibitor*, in order to achieve the target dose of candesartan.
      3.7.1. Was this a potential problem?
      3.7.2. Was it an actual problem?

Committee Discussion: The committee discussed the recommendation included in the CHARM-Added protocol which directed treatment with ACE inhibitors based on an 'individual optimum' dose and patient tolerability. They stated their concern with the lack of consistent dosing decisions made during the trial conduct because of the use of the term "recommended target doses" and its lack of clarity. The committee cited the design of the ATLAS trial (Assessment of Treatment with Lisinopril and Survival), which compared the effectiveness and safety of low doses versus high doses of the ACE inhibitor lisinopril, as a good model of incorporation of ACE inhibitor dose titration. At the same time, they acknowledged that including a dose titration feature in a large clinical trial would present a challenge. This being said, the consensus amongst the committee was that the ACE inhibitor and target regimens selected by the CHARM-Added investigators were reasonable.

There was additional discussion on features of the study that ensured ACE inhibitor optimization, and whether the investigators made reasonable dosing decisions based on the protocol guidelines. Finally, the committee suggested that guidelines could have been incorporated in the study protocol, asking the investigator to provide their rationale for the specific doses used and why further titration was not attempted. They felt that this would have provided additional assurance that the optimal effected dose of ACE inhibitor was used. ***(See transcript for detailed discussion)***

4. A second possible claim would be that candesartan has effects one could not achieve with ACE inhibitors, regardless of dose. What evidence does CHARM-Added provide that candesartan has benefits in patients with full ACE inhibition?

4.1. In analyses of CHARM-Added that factored in ACE inhibitor dose, does it matter that subjects were not randomized to ACE inhibitor dose?
4.2. Compared with full ACE inhibition, what loss of effect with candesartan has been excluded by these analyses?
4.3. Do the results of CHARM-Added support a claim that candesartan has clinical benefits unachievable with ACE inhibitors?

Committee Vote on Question 4.3: Yes: 0 No: 10

Committee Discussion: The committee considered what evidence, if any, CHARM-Added provided that candesartan has benefits in patients with full dose ACE inhibitor. The consensus was CHARM-Added did not support a claim that candesartan has clinical benefits unachievable with ACE inhibitors. The committee felt that it was difficult to make such a determination given the insufficient data available for full dosing of the ACE inhibitor with candesartan. They stated that a forced titration trial was needed to confirm that the maximum dose of the ACE inhibitor was achieved before the candesartan was added. Further, the committee expressed concern with sub-group and post-hoc analyses performed and relied upon by the sponsor. ***(See transcript for detailed discussion)***

If CHARM-Added supports use of candesartan by virtue of effects unachievable with an ACE inhibitor, skip to question 7.

5. A third possible claim might result if one could not achieve a full effect on a system by one drug, perhaps because of system-independent tolerance problems, but one could achieve a larger effect with the addition of a second agent.
   5.1. Does one need to establish that the original, poorly tolerated therapy is still needed in such a trial?
   5.2. What would be required to obtain such a claim?
   5.3. Does CHARM-Added have these design features?
   5.4. Do the results of CHARM-Added support a claim that candesartan should be used in patients unable to take a full dose of ACE inhibitor?

Committee Discussion: Although Question 5.4 was originally designated a 'vote question', the Division was satisfied, after extensive discussion, that no vote was necessary based on comments surrounding the fact that the trial design did not include a protocol requirement to maximize the ACE inhibitor before starting candesartan therapy for heart failure.

The committee considered trial design features required, when adding a second agent due to the patient's system-independent tolerance problem. Again, discussion surrounded the lack of sufficient data to answer this question as stated. There was general agreement amongst the committee that for future clinical trials, it is important to establish that the original therapy is needed prior to the addition of a second therapy. Most committee members agreed that the CHARM-Added trial did not validate the need for the original therapy nor did the trial address whether candasartan should be used in patients unable to take a full dose of ACE inhibitor. The members discussed various possibilities for this chosen design and offered suggestions to address these issues with additional trials. That being said, the committee concluded that at the doses of ACE inhibition reached, it was evident that the addition of candasartan treatment appeared to reduce the risk of cardiovascular mortality and congestive heart failure hospitalizations enough to support some claim. ***(See transcripts for detailed discussion)***

If CHARM-Added supports a claim for candesartan in patients on some dose of ACE inhibitor, skip to question 7.

6. Is there another possible claim resulting from CHARM-Added?

Committee Discussion: The committee was asked to consider whether there was another possible claim resulting from CHARM-Added. Discussion included comments on labeling for CHARM-Added and the possible extent to which physicians might make decisions about utilizing ACE inhibitors based on CHARM-Added claims. There were various suggestions offered to assist the Agency in describing the population for which candesartan would be useful based on the trial design and outcome. The consensus was that the use statement in the label should reflect the limitations and instructions provided by the protocol as it relates to identifying a target dose of candesartan. ***(See transcripts for detailed discussion)***

7. If you have identified a possible pathway to approve candesartan based on questions 1, 4, 5, or 6, comment on the available strength of evidence.
   - 7.1. What are one's prior expectations based on mechanism of action?
   - 7.2. Are there supportive findings in CHARM-Added? Are these findings covered by the statistical analysis plan?
   - 7.3. Are there other data on the use of candesartan added to ACE inhibitors in the treatment of heart failure? If so, are these data supportive?
   - 7.4. Is it appropriate to consider studies of other angiotensin receptor antagonists in this or some related setting? If so, …
     - 7.4.1. … what are these studies?
     - 7.4.2. … are these data supportive?

Committee Discussion: The committee discussed possible pathways for approval of candesartan discussed in the previous questions and supportive findings presented in CHARM-Added. The committee concluded that the support of evidence for the CHARM-Added trial's hypothesis, is primarily based on past experiences and results from the Valsartan Heart Failure Trial (Val-HeFT) which demonstrated similar benefits. ***(See transcripts for detailed discussion)***

8. Should candesartan be approved for use with an ACE inhibitor in the treatment of heart failure?

Committee Vote on Question 8: Yes: 10 No: 0

Committee Discussion: The committee was asked to consider whether candesartan should be approved for use with an ACE inhibitor in the treatment of heart failure. The committee voted 10-0 in favor of approval. Although there was considerable discussion regarding the trial design in relation to optimization of ACE inhibitor dosing titration and the need to provide data with a clear definition 'optimal therapy', the committee felt that overall the investigators did their best to up-titrate the dosage of the ACE Inhibitors. The committee believed that final doses achieved were substantial and in-line with other trials of ACE inhibitors. The committee complemented the sponsor on a very professionally run and well executed trial, citing the informative nature of combining the three trials together (CHARM-Added, CHARM-Alternative and CHARM-Preserved). Finally, the committee provided additional comments on population selection for future clinical trials to include adequate representation of ethnic groups. ***(See transcripts for detailed discussion)***

The meeting adjourned at approximately 1:30 PM.

See transcript for detailed discussion