Summary Minutes of the
Cardiovascular and Renal Drugs Advisory Committee
December 10, 2008

Location: Hilton Washington DC/Silver Spring, Maryland Ballroom,
8727 Colesville Road, Silver Spring, MD.

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

These summary minutes for the December 10, 2008 Meeting of the Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration were approved on January 16, 2009

I certify that I attended the December 10, 2008 meeting of the Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

----------/s/----------
Elaine Ferguson M.S., R.Ph.
Designated Federal Official

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Robert A. Harrington, M.D., F.A.C.C..
Acting Committee Chair

Meeting of the Cardiovascular and Renal Drugs Advisory Committee
10 December 2008

The Cardiovascular and Renal Drugs Advisory Committee, Center for Drug Evaluation and Research met on December 10, 2008 at the Hilton Washington DC/Silver Spring, Maryland Ballroom, 8727 Colesville Road, Silver Spring, MD. Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA. This was a voting meeting. There were approximately eighty (80) persons in attendance.

Issue: The committee discussed new drug application (NDA) 22-349, IMAGIFY (perflubutane polymer microspheres) injectable suspension, Acusphere Inc., proposed for use as an ultrasound imaging agent indicated for patients with stable chest pain being evaluated for inducible ischemia for the detection of coronary artery disease based on assessment of myocardial perfusion and wall motion.

Attendance:

Cardiovascular and Renal Drugs Advisory Committee Members Present (Voting):
Robert A. Harrington, M.D. (Acting Chair), John M. Flack, M.D., M.P.H., Michael Lincoff, MD, FACC, James D. Neaton, Ph.D., Emil P. Paganini, M.D., F.A.C.P., F.R.C.P., Steven D. Findlay M.P.H.(Consumer Representative).

Special Government Employee Consultants (Voting):
Professor Ruth S. Day, Frederick J. Kaskel M.D.,Ph.D., John R. Teerlink, M.D., Tal Geva M.D., Mark A Fogel, MD, FACC, FAHA, FAAP, Ruth G. Ramsey, MD, James L. Tatum, M.D., Vanda Sachdev, David DeMets, Thomas Fleming, Robert F. Mattrey, Maya C. Sahajwalla,

Industry Representative Members Present (Non-Voting):
Jonathan C Fox, MD, PhD, FACC

FDA Participants (Non-Voting):
Robert Temple, M.D., Dwaine Rieves, M.D., Alex Gorovets, M.D., Scheldon Kress, M.D., Anthony Mucci, Ph.D.

Acting Designated Federal Official:
Elaine Ferguson, M.S., R.Ph.

Open Public Hearing Speakers: None

Agenda:

8:00 a.m.	Call to Order Introduction of Committee	Robert A. Harrington, MD, FACC Acting Chair, CRDAC
	Conflict of Interest Statement	Elaine Ferguson, MS, RPh Designated Federal Official, CRDAC
8:05 a.m.	FDA Opening Remarks	Rafel (Dwaine) Rieves, MD Director Division of Medical Imaging and Hematology Products, CDER, OND, OODP
8:15 a.m.	<u>Sponsor Presentations</u> Introductory Remarks	Michael R. Slater Acusphere, Inc.
	Use of Ultrasound Contrast for the Detection of Myocardial Ischemia	Michael H. Picard, MD, FACC, FASE Director, Clinical Echocardiography Massachusetts General Hospital
	AI-700 Imaging	Professor R. Senior MD, DM, FRCP, FESC, FACC Consultant Cardiologist & Director of Cardiac Research, Northwick Park Hospital, London
	AI-700 Clinical Efficacy	Richard C. Walovitch, PhD Acusphere, Inc.
	AI-700 Clinical Safety	Howard C. Dittrich, MD, FACC Clinical Professor of Medicine University of California, San Diego
	Innate Immune Response and Complement Activation	John D. Lambris, PhD Dr. Ralph and Sallie Weaver Professor of Research Medicine Department of Pathology & Laboratory Medicine, University of Pennsylvania
	...Continue AI-700 Clinical Safety	Howard C. Dittrich, MD, FAAC
	Concluding Remarks	Richard C. Walovithc, PhD Acusphere, Inc.
10:15 a.m.	<u>Break</u>	
10:30 a.m.	FDA Presentation – Clinical and Statistical review of the application, and FDA introduction to questions	Scheldon Kress, MD Medical Officer Division of Medical Imaging and Hematology Products, CDER, OND, OODP Anthony Mucci, Ph.D Statistical Reviewer Division of Biostatistics, CDER, OB, OTS Alexander Gorovets, MD Team Leader/Medical Officer Division of Medical Imaging and Hematology Products CDER, OND, OODP
11:30 a.m.	Questions to presenters	
12:00 p.m.	Lunch	
1:00 p.m.	Open Public Hearing	
2:00 p.m.	FDA Questions to the committee	
2:30 p.m.	Break	
3:30 p.m.	Discussion of questions to the committee	
4:30 p.m.	Adjourn	

Questions to the Committee

1. Please discuss the extent, to which the phase 3 data provide persuasive evidence of diagnostic efficacy, considering:

a. consistency between the studies

Several members seemed troubled to various degrees by aspects of inconsistency between the studies, such as the variation in diagnostic performance, patient populations and reader training.

b. comparator (SPECT) performance

A few members expressed concern that SPECT may not have been performed or assessed while others were less troubled. Some members questioned the choice of the non-inferiority margin.

c. the added value of AI-700 to non-contrast echocardiography

Most members noted that the data did not sufficiently address the added value of AI-700 to non-contrasted echocardiography.

2. Please discuss the extent, to which the phase 3 data provide persuasive evidence of safety, considering:

a. the rate and nature of acute reactions that necessitated AI-700 discontinuation

The committee was somewhat split as to the meaning and importance of the acute reactions that were presented, with a few members having a low level of concern while a few members were very concerned. The members who had a lower level of concern expressed a perspective that the reactions were not particularly unexpected, that the rates were not concerning and that these reactions could be managed by experienced physicians. Those who were concerned expressed a perspective that the patient population was small and relatively health and the nature of the reactions appeared bothersome.

b. the safety database size and considerations of the single arm study designs as well as the role of the pharmacologic stress agent as a confounder

There was interest in seeing a larger data base particularly including a less healthy population (i.e., potentially more consistent with the market population). The committee suggested that a randomized study design could help clarify the association of the adverse events with AI-700, particularly with respect to the adverse events that could be due to the pharmacological stress agent or additive between AI-700 and the stress agent.

c. the background exploratory biomarker findings of inflammation in association with AI-700

Again, the committee was split as to the meaning and importance of these findings. Some expressed the perspective that these findings were short term reactions that resolved relatively quickly. Others were concerned that there was no information on the long term effects of AI-700.

3. (VOTE) Does contrast enhancement of rest/stress echocardiography with AI-700 provide sufficient diagnostic benefit to justify the risks associated with the product?

1 yes, 16 no, 1 abstain Over all the committee members seemed to agree that the data, based upon the available performance characteristics, did not sufficiently support a benefit.

4. Discuss the need, if any, for additional clinical studies in either the pre-market or post-market setting. If studies are needed, please comment upon the nature of these studies, especially with respect to efficacy, safety and any need for randomized control groups.

The committee made several recommendations/suggestions: 1) better define an evidence based non inferiority margin, 2) clarify the truth standard, 3) randomization, 4) larger safety data base, 5) broader population typical of potential market population, 6) determine the incremental value of perfusion and wall motion with contrast over wall motion alone (with and without contrast), and 7) consider ways to design a study with an enriched population where benefit to risk considerations may more readily be evidenced.