

Summary Minutes of the Arthritis Advisory Committee Meeting December 20, 2012

The following is the final report of the Arthritis Advisory Committee (AAC) meeting held on December 20, 2012. A verbatim transcript will be available in approximately six weeks, sent to the Division of Pulmonary, Allergy, and Rheumatology Products and posted on the FDA website at:

<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/ucm286552.htm>

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

The Arthritis Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on December 20, 2012 at the FDA White Oak Campus, Building 31, The Great Room (Rm. 1503), White Oak Conference Center, Silver Spring, Maryland. Prior to the meeting, members and temporary voting members were provided copies of the background materials from the FDA and Hemispherx Biopharma, Inc. The meeting was called to order by Lenore Buckley, MD, MPH (Acting Chairperson); the conflict of interest statement was read into the record by Yvette Waples, PharmD (Acting Designated Federal Officer). There were approximately 150 persons in attendance. There were 30 Open Public Hearing speakers.

Issue: The committee discussed new drug application (NDA) 22151, rintatolimod injection (proposed trade name AMPLIGEN) submitted by Hemispherx Biopharma, Inc. for the treatment of patients with chronic fatigue syndrome.

Attendance:

AAC Members Present (Voting): Lisa Gualtieri, PhD, ScM (Consumer Representative); Robert Lahita, MD, PhD; Irwin J. Russell, MD, PhD

AAC Members Not Present (Voting): Tuhina Neogi, MD, PhD; Peter I. Peduzzi, PhD;

AAC Member Present (Non-Voting): Brian L. Kotzin, MD (Industry Representative)

Temporary Members (Voting): Larry Borish, MD; Lenore Buckley, MD, MPH (Acting Chairperson); Ralph B. D'Agostino, Sr., PhD; Jacqueline Gardner, MPH, PhD; Sean Hennessy, PharmD, PhD; Anthony Komaroff, MD, MA; Gailen D. Marshall, Jr., MD, PhD; Elaine Perry, MPH (Patient Representative); Matthew Rudorfer, MD; Elizabeth Unger, PhD, MD; James H. Ware, PhD

FDA Participants (Non-Voting): Robert Temple, MD; Christine P. Nguyen, MD; Badrul Chowdhury, MD, PhD; Theresa Michele, MD; Janet Maynard, MD, MHS; David Hoberman, PhD

Acting Designated Federal Officer (Non-Voting): Yvette Waples, PharmD

Open Public Hearing Speakers: Alexander and Matthew Lopez-Majano (statement read by Denise Lopez-Majano); Anita Kathryn Patton; Bille Moore (New Jersey Chronic Fatigue Syndrome Association, Inc.); Cheryl Marshall; Cort Johnson; Courtney Alexander; Daniel and Alex Miller; David Marshall; Denise Lopez-Majano; Ed Burmeister (statement read by Billie Moore); Janet E. Smith, MD; Jeannette Burmeister; Joan Grobstein, MD (statement read by Mindy Kitei); Joe Landson; K. Kimberly McCleary (The CFIDS Association of America); Karl Baty; Konstance Knox, PhD (Wisconsin Viral Research Group); Laurel Wright-Feighery; Lori Chapo-Kroger (Patient Alliance for Neuro-endocrine-immune Disorder Organization for Research and Advocacy, Inc. [PANDORA]); Mary Dimmock (statement read by Denise Lopez-Majano); Mary M. Schweitzer, PhD; Matina Nicholson; Matthew Lazell-Fairman (statement read by Cort Johnson); Michael Walzer; Michelle Backus Walzer, MD; Mindy Kitei; Patricia LaRosa, RN, MSN (statement read by Nancy McGrory); Sidney Wolfe, MD (Public Citizen Health Research Group); Steven G. Chilinski, MD; Tina Tidmore (PANDORA)

The agenda proceeded as follows:

Call to Order and Introduction of Committee	Lenore Buckley, MD Acting Chairperson, AAC
Conflict of Interest Statement	Yvette Waples, PharmD Acting Designated Federal Officer, AAC
FDA Introductory Remarks	Theresa Michele, MD Clinical Team Leader Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) Office of Drug Evaluation II (ODE-II) Office of New Drugs (OND), CDER, FDA
SPONSOR PRESENTATIONS	Hemispherx Biopharma, Inc.
Ampligen® for the Treatment of Chronic Fatigue Syndrome rintatolimod (Poly I: Poly C ₁₂ U) NDA 22-151	William Carter, MD CEO Hemispherx Biopharma, Inc. Philadelphia, PA
	David Strayer, MD Medical Director Hemispherx Biopharma, Inc. Philadelphia, PA
	Bruce Stouch, PhD Director Biostatistics and Clinical Epidemiology The Philadelphia College of Osteopathic Medicine Philadelphia, PA
	Richard P. Chiacchierini, PhD President and CEO R.P. Chiacchierini & Associates Rockville, MD

SPONSOR PRESENTATIONS (CONT.)

Lucinda Bateman, MD
Director of the Fatigue Consultation Clinic
Salt Lake City, UT

Christopher Snell, PhD
Professor, Health, Exercise, and Sport Sciences
The University of the Pacific
Stockton, CA

Mr. Robert Miller
CFS Patient and Advocate
Reno, NV

Clarifying Questions to the Sponsor

BREAK

FDA PRESENTATIONS

Overview of the Clinical Program

Janet Maynard, MD, MHS
Clinical Reviewer
DPARP, ODE-II, OND, CDER, FDA

Statistical Review of Efficacy

David Hoberman, PhD
Statistical Reviewer
Division of Biometrics II (DB-II)
Office of Biostatistics (OB)
Office of Translational Sciences (OTS), CDER, FDA

Clinical Review of Efficacy, Safety and
Risk/Benefit

Janet Maynard, MD, MHS

Clarifying Questions to the FDA

LUNCH

Open Public Hearing Session

BREAK

Concluding Remarks/Charge to the
Committee

Theresa Michele, MD

Questions to the Committee/Committee
Discussion

ADJOURNMENT

Questions to the Committee:

- 1) **DISCUSSION:** Discuss the efficacy data for Ampligen considering the following:
 - a. Karnofsky performance scale (KPS)
 - b. Exercise tolerance testing (ETT)
 - c. Other analyses (e.g. quality of life, concomitant medication use)

***Committee Discussion:** The majority of the committee members were concerned with the integrity, strength and reliability of the efficacy data for Ampligen. Committee members were concerned that the sponsor was unable to inform the committee whether the efficacy data from the trial (AMP-516) were unblinded prior to the sponsor's decision to perform the primary efficacy analysis based on untransformed data instead of transformed data as prespecified in the trial's statistical analysis plan. In regards to the initial trial (AMP-502), many members were also concerned about the exclusion of data from several patients who were evaluated using the original ETT protocol, which was later modified because the original protocol proved to be too strenuous for most study subjects. Most of the members agreed that the KPS and ETT showed inconsistencies in the two studies presented (AMP-502 and AMP-516). Furthermore, most members agreed that the analysis for quality of life measures showed insignificant p-values and that these endpoints did not support efficacy. In addition, some of the members were concerned that the data on concomitant medication use was not collected in a prespecified systematic manner, rendering the results on concomitant medication use uninterpretable. While stating that there were some interesting trends in the data suggesting efficacy, the majority of the committee agreed that the data for Ampligen did not clearly show efficacy and additional data are needed. Please see the transcript for details of the committee discussion.*

- 2) **DISCUSSION:** Discuss the safety data for Ampligen.

Due to time limitations, question #2 was skipped. The committee members addressed their safety concerns during the discussions of question #4 and #5.

- 3) **VOTE:** Considering the totality of the data, is there substantial evidence of efficacy for Ampligen for the treatment of patients with chronic fatigue syndrome (CFS)?

Vote: **Yes = 4** **No = 9** **Abstain = 0** **No Voting = 1**

***Committee Discussion:** The majority of the committee (9 of 13 members who voted) did not agree that the data provided substantial evidence of efficacy for Ampligen for the treatment of patients with CFS and did not agree that the data met the FDA standard for substantial evidence. However, some committee members opined that the data showed some "signals" of efficacy. The committee members who voted "Yes" stated that there is enough of an efficacy signal to make Ampligen available to CFS patients now, and proposed that the applicant conduct post-marketing studies to collect more efficacy data. One committee*

member left the meeting early and thus there was one “No Voting”. Please see the transcript for details of the committee discussion.

- a. If not, what further data should be obtained?

Committee Discussion: *The committee noted that additional trials with adequate sample size and appropriate outcome measures, with replicated results would be needed to provide substantial evidence of efficacy. In addition, the committee agreed that post-marketing studies could address subgroups that may substantially benefit from Ampligen use. Some members suggested that a better characterization of patients prior to the start of the trial, such as time of onset of illness or biologic measures (i.e., T-cells, viral load) would be helpful. Please see the transcript for details of the committee discussion.*

- 4) **VOTE:** Has the safety of Ampligen been adequately assessed and characterized for the treatment of chronic fatigue syndrome (CFS)?

Vote: **Yes = 4** **No = 9** **Abstain = 0** **No Voting = 1**

Committee Discussion: *The majority of the committee did not agree that the safety of Ampligen has been adequately assessed and characterized for the treatment of CFS, based on the limited size of the database and the multiple discrepancies and gaps in the safety data of the Ampligen clinical program. Some members stated that they had no confidence in the veracity of the data and questioned whether the data were deceptive or just shoddy. The committee members who voted “Yes” stated that some of the discrepancies have already been identified and addressed by the FDA and that any hidden serious adverse events would have emerged over the long period of time that Ampligen has been in use. One committee member left the meeting early and thus there was one “No Voting”. Please see the transcript for details of the committee discussion.*

- a. If not, what further data should be obtained?

Committee Discussion: *The committee agreed that a larger study with predefined safety assessments and definitions of adverse events of interest should be conducted to better characterize the safety profile of Ampligen. Please see the transcript for details of the committee discussion.*

- 5) **VOTE:** Is the safety profile of Ampligen adequate for approval for the treatment of CFS?

Vote: **Yes = 8** **No = 5** **Abstain = 0** **No Voting = 1**

Committee Discussion: *While the committee members expressed that the safety profile of Ampligen has not been adequately characterized for approval, many stated that if taken at face value, the profile would be “good enough” for approval. The committee members who voted “Yes” opined that, given the lack of any treatment for CFS, patients would accept a number of safety risks for Ampligen. In addition, the committee members agreed that due to the severity of the illness, patients should be able to make informed decisions of what level of risks they are willing to accept. The committee members who voted “No” stated that the size*

and scope of the database were not adequate and that more safety data are needed before Ampligen is made available to a large diverse population. Some noted concerns over reports of serious clinical adverse outcomes consistent with safety findings in preclinical studies. One committee member left the meeting early and thus there was one “No Voting”. Please see the transcript for details of the committee discussion.

- a. If not, what further data should be obtained?

Committee Discussion: *The committee agreed that well-controlled randomized studies should be conducted. In addition, long term data to identify any unknown risks should be obtained as it would be beneficial to those patients with less severe CFS in making informed decisions regarding risks. Furthermore, some committee members agreed that data on the effects of children and patients with autoimmune conditions should be obtained. Please see the transcript for details of the committee discussion.*

- 6) **VOTE:** Based on the information included in the briefing materials and presentations, has the applicant provided sufficient efficacy and safety data to support marketing of Ampligen for the treatment of chronic fatigue syndrome (CFS)?

Vote: **Yes = 5** **No = 8** **Abstain = 0** **No Voting = 1**

Committee Discussion: *The majority of the committee did not agree that the applicant has provided sufficient efficacy and safety data to support marketing of Ampligen for the treatment of CFS. However, there was a general consensus that Ampligen showed possible signals of efficacy and has potential for the treatment of CFS. The committee members who voted “Yes” noted that there is enough information to make Ampligen available now, but that post-marketing studies should be conducted to obtain additional information. One committee member left the meeting early and thus there was one “No Voting”. Please see the transcript for details of the committee discussion.*

- a. If not, what further data should be obtained?

Committee Discussion: *The committee members who voted “No” recommended that a well designed and appropriately controlled study, with Agency input, is necessary to address the major safety and efficacy gaps in the Ampligen development program. In addition, the committee members stated that the applicant needs to further investigate which selective subgroups, including subgroups based on severity of disease, would respond well to Ampligen. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 5:15 p.m.