

**Food and Drug Administration  
Center for Drug Evaluation and Research**

**Final Summary Minutes of the Endocrinologic and Metabolic Drugs  
Advisory Committee Meeting  
May 10, 2018**

Location: Tommy Douglas Conference Center, The Ballroom, 10000 New Hampshire Avenue, Silver Spring, Maryland.

Topic: The committee discussed the safety and efficacy of new drug application (NDA) 210645, for volanesorsen solution for subcutaneous injection, submitted by Akcea Therapeutics, Inc. The proposed indication is as an adjunct to diet for the treatment of patients with familial chylomicronemia syndrome.

These summary minutes for the May 10, 2018 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration were approved on June 12, 2018.

I certify that I attended the May 10, 2018, meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

\_\_\_\_\_/s/  
LaToya Bonner, PharmD  
*Designated Federal Officer, EMDAC*

\_\_\_\_\_/s/  
Peter Wilson, MD  
*Chairperson, EMDAC*

**Summary Minutes of the Endocrinologic and Metabolic Drugs  
Advisory Committee Meeting  
May 10, 2018**

The Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on May 10, 2018, at the Tommy Douglas Conference Center, The Ballroom, 10000 New Hampshire Avenue, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Akcea Therapeutics, Inc. The meeting was called to order by Peter Wilson, MD (Chairperson). The conflict of interest statement was read into the record by LaToya Bonner, PharmD (Designated Federal Officer). There were approximately 175 people in attendance. There were 13 Open Public Hearing (OPH) speaker presentations.

A verbatim transcript will be available, in most instances, at approximately ten to twelve weeks following the meeting date.

**Agenda:** The committee discussed the safety and efficacy of new drug application (NDA) 210645, for volanesorsen solution for subcutaneous injection, submitted by Akcea Therapeutics, Inc. The proposed indication is as an adjunct to diet for the treatment of patients with familial chylomicronemia syndrome.

**Attendance:**

**EMDAC Members Present (Voting):** Daniel Budnitz, MD, MPH; Brendan M. Everett, MD, MPH; Kenneth D. Burman, MD; Cecilia C. Low Wang, MD, FACP; James D. Neaton, PhD; Thomas J. Weber, MD; Peter W.F. Wilson, MD (*Chairperson*); Susan Z. Yanovski, MD

**EMDAC Members Not Present (Voting):** Michael Blaha, MD, MPH; Susan R. Heckbert, MD, PhD

**EMDAC Member Present (Non-Voting):** Reshma Kewalramani, MD (*Industry Representative*)

**Temporary Members (Voting):** Nichole Cuaresma (*Patient Representative*); Michael S. Epstein, MD, FACG, AGAF; Robert Kane, MD, PA; Anna McCollister-Slipp (Acting Consumer Representative); Elaine H. Morrato, DrPH, MPH; Connie B. Newman, MD, FACP, FAHA, FAMWA; Thomas L. Ortel, MD, PhD; Jean-Pierre Raufman, MD; Maghan Rowcliffe PharmD, BCPS, BCPPS; Robert Shamburek, MD; Susan M. Sinclair, PhD, MPH, RN; David F. Stroncek, MD

**FDA Participants (Non-Voting):** Mary T. Thanh Hai, MD; James P. Smith, MD, MS; John Sharretts, MD; Mary D. Roberts, MD; Cynthia LaCivita, PharmD

**Designated Federal Officer (Non-Voting):** LaToya Bonner, PharmD, NCPS

**Open Public Hearing Speakers:** Lori Alexander (Foundation of National Lipid Association); Mark Childers and Yeun Kim (Akcea); Russ Cross; David Davidson, MD (FCS Patients); Melissa Goetz (Familial Chylomicronemia Syndrome Foundation); Lindsey Sutton; Mary Harmon; Nicole McCoy; Lindsey Sutton (on behalf of Rebecca McFalls); Frederick F. Saremi;

Lynn Saremi; Joseph Titlebaum (National Pancreas Foundation); Farhad Zangeneh, MD  
(American Association of Clinical Endocrinologists)

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***The agenda was as follows:***

Call to Order and Introduction of Committee	<b>Peter Wilson, MD</b> Chairperson, EMDAC
Conflict of Interest Statement	<b>LaToya Bonner, PharmD, NCPS</b> Designated Federal Officer, EMDAC
FDA Introductory Remarks	<b>John Sharretts, MD</b> Clinical Team Lead (acting) Division of Metabolism and Endocrinology Products (DMEP), Office of Drug Evaluation II (ODE-II) Office of New Drugs (OND), CDER, FDA
<b>APPLICANT PRESENTATIONS</b>	<b>Akcea Therapeutics, Inc.</b>
Introduction	<b>Louis St.L. O’Dea, MB BCh BAO. CSPQ. FRCP(C)</b> Chief Medical Officer, Akcea Therapeutics
Unmet Need: Disease Background	<b>Daniel J. Rader, MD</b> Seymour Gray Professor of Molecular Medicine Perelman School of Medicine University of Pennsylvania
Pancreatitis	<b>Steve Freedman, MD, PhD</b> Professor of Medicine, Harvard Medical School Chief, Division of Translational Research Director, The Pancreas Center Beth Israel Deaconess Medical Center
Efficacy	<b>Louis St.L. O’Dea, MB BCh BAO. CSPQ. FRCP(C)</b>
Safety	<b>Walter Singleton, MD</b> Former Chief Medical Officer, Ionis Pharmaceuticals
Risk Management	<b>Michael Stevenson, RPh, PhD</b> Head of Medical Affairs, Akcea Therapeutics
Clinical Perspective	<b>Seth J. Baum, MD, FACC, FACPM, FAHA, FNLA, FASPC</b> President, American Society of Preventive Cardiology Affiliate Clinical Professor of Medicine Schmidt College of Medicine
Clarifying Questions to Applicant	

**BREAK**

**FDA PRESENTATIONS**

Clinical Review Introduction	<b>Mary D. Roberts, MD</b> Clinical Reviewer DMEP, ODE-II, OND, CDER, FDA
Statistical Review of Efficacy	<b>Alexander Cambon, PhD</b> Statistical Reviewer Division of Biometrics II, Office of Biostatistics Office of Translational Sciences (OTS), CDER, FDA
Clinical Review	<b>Mary D. Roberts, MD</b>
Clinical Pharmacology Review	<b>Yunzhao Ren, MD, PhD</b> Clinical Pharmacology Reviewer Division of Clinical Pharmacology II Office of Clinical Pharmacology (OCP) OTS, CDER, FDA
Risk Evaluation and Mitigation Strategy (REMS) Considerations	<b>Ingrid N. Chapman, PharmD, BCPS</b> Risk Management Analyst Division of Risk Management (DRISK) Office of Medication Error and Risk Management (OMEPRM) Office of Surveillance and Epidemiology (OSE) CDER, FDA
Benefit/Risk Summary	<b>Mary D. Roberts, MD</b>
Clarifying Questions to FDA	

**OPEN PUBLIC HEARING**

Questions to the Committee/Committee Discussion

**BREAK**

Questions to the Committee/Committee Discussion

**ADJOURNMENT**

***Questions to the Committee:***

1. **DISCUSSION:** A reduction in fasting triglycerides (TG) has been accepted by FDA as an endpoint that can establish efficacy for several classes of drugs intended to treat patients with severe hypertriglyceridemia (TG >500 mg/dL), since lowering TG in this setting is expected to reduce the risk for acute pancreatitis. In trial CS6, patients with familial chylomicronemia syndrome (FCS) assigned to volanesorsen 300 mg weekly exhibited a 77% reduction in TG at month 3, on average, compared with an 18% increase among those assigned to placebo (p<0.0001).

When efficacy is established via an effect on a surrogate endpoint, however, uncertainty generally remains regarding the magnitude of the drug's effect on clinical benefit (i.e., how patients feel, function, or survive). The expected type and magnitude of clinical benefit(s) are important to consider when making a benefit/risk assessment. Please discuss the efficacy/clinical benefits of volanesorsen in patients with FCS.

- a. Has the applicant adequately characterized the effect of volanesorsen on TG to inform labeling, despite the proposal of a dosing strategy that has not been studied in clinical trials?

**Committee Discussion:** Overall, the committee agreed that the applicant did not adequately characterize the effect of volanesorsen on TG to inform labeling, especially considering that the proposed dosing strategy has not been prospectively studied in clinical trials. The committee members also noted that tolerability of the intended regimen was rather low. However, one committee member expressed that for an orphan disorder with limited patients, the applicant did adequately demonstrate that volanesorsen lowers TG. Please see the transcript for details of the committee discussion.

- b. How does the extent of drug discontinuation after month 3 affect your assessment of the efficacy of volanesorsen, if at all?

**Committee Discussion:** One committee member stated that although tolerability appears quite low, the effect on TG is fairly robust as analyzed by the FDA. Please see the transcript for details of the committee discussion.

- c. Discuss whether the available data provide evidence that volanesorsen reduces the risk of acute pancreatitis.

**Committee Discussion:** Overall, the committee members agreed that the data provided do not show direct evidence that volanesorsen reduces the risk of acute pancreatitis. However, some committee members noted that since it is assumed that elevated TG cause pancreatitis in this condition, the reduction of TG levels demonstrated in the study would be expected to reduce pancreatitis. Please see the transcript for details of the committee discussion.

- d. Discuss whether the available data provide evidence that volanesorsen reduces abdominal pain in patients with FCS.

**Committee Discussion:** Overall, the committee agreed that the available data do not provide evidence that volanesorsen reduces abdominal pain in patients with FCS. One committee member noted that abdominal pain is a very subjective assessment that can only be determined in a placebo-controlled trial and expressed that there may be bias observed from the data presented and from the testimonies heard during the open public hearing session. Please see the transcript for details of the committee discussion.

- e. Considering both the benefits that you expect based on the magnitude of TG lowering as well as what was observed in the development program, how would you characterize the overall magnitude of clinical benefit that results from treatment with volanesorsen?

***Committee Discussion:** Overall, the committee agreed that clinical benefit could be inferred based on the magnitude of TG lowering, but agreed that it was not observed from the available data. Please see the transcript for details of the committee discussion.*

2. **DISCUSSION:** Aside from thrombocytopenia, discuss the tolerability and safety of volanesorsen, such as injection site reactions, immunogenicity, hypersensitivity, liver-related safety, renal-related safety, and any other safety concerns you have identified.

***Committee Discussion:** One committee member noted injection site reactions that included skin discoloration, erythema, pain and itching, and that not all of the reactions resolved. Another committee member added that injection site reactions observed in 87% of the patients treated with volanesorsen was much greater than what would be expected from other biologics seen in other trials, which hovers around 5-8%. One committee member added that aside from injection site reactions, with just under 100 patients, the safety database was too small to understand safety of the other adverse events. One committee member expressed concerns with the presence of antibodies and what role that may play and the immunogenic response that would present over time. Another committee member expressed concerns with renal adverse events that were present and noted that both protein and creatinine elevation rates were higher in the volanesorsen group. Please see the transcript for details of the committee discussion.*

3. **DISCUSSION:** Discuss the risk for thrombocytopenia and bleeding associated with volanesorsen.
  - a. Discuss your level of concern for the risk of thrombocytopenia and bleeding with chronic treatment with volanesorsen.

***Committee Discussion:** Some committee members agreed that the risk of developing Type 1 thrombocytopenia is a slow process so it could be picked up and be monitored unlike Type 2 thrombocytopenia, which seems to be idiosyncratic and of more concern. Overall, the committee members agreed that there was some disconnect between bleeding episodes and platelet count. Please see the transcript for details of the committee discussion.*

- b. The applicant has proposed labeling that recommends intensive platelet monitoring (i.e., a minimum of every 2 weeks for the duration of treatment with this potentially lifelong therapy). Discuss whether the proposed frequency of monitoring adequately addresses the risk of thrombocytopenia and bleeding, as well as whether such monitoring would be feasible in clinical practice. If you disagree with the proposed monitoring scheme, discuss how patients treated with volanesorsen should be monitored for thrombocytopenia/bleeding, if approved.

**Committee Discussion:** *Some committee members stated that although some kind of platelet monitoring is needed, the proposed labeling that recommends intense monitoring of a minimum of every 2 weeks would be challenging in general practice. These committee members added that the proposed intensive monitoring would not prevent a precipitous drop in the platelet count. However, one committee member stated that intensive monitoring would help identify those individuals whose platelet counts drop to 10,000/mm<sup>3</sup> and it would prevent them from staying at that level for long periods of time. The committee suggested that a way to better identify those individuals who are at a higher risk for Type 2 thrombocytopenia needs to be determined but should work to decrease the frequency of monitoring for those individuals that are at high risk. Please see the transcript for details of the committee discussion.*

- c. The applicant has proposed a dosing algorithm that recommends a dosing frequency based on platelet level and body weight. Discuss whether the available data in the clinical development program are adequate to inform dosing recommendations for labeling that would ensure the safe use of volanesorsen.

**Committee Discussion:** *Overall, the committee agreed that a dosing algorithm strategy makes sense conceptually even with the limited data to support what is being proposed, but did not agree that it would ensure the safe use of volanesorsen. One committee member expressed concerns with the concept of recommending treatment with steroids for thrombocytopenia of unknown cause since this could be dangerous if steroid use is not necessary. Please see the transcript for details of the committee discussion.*

4. **DISCUSSION:** Discuss whether “familial chylomicronemia syndrome,” without further definition, sufficiently identifies a patient population for whom volanesorsen may have a favorable benefit/risk profile. If not, please discuss alternatives.

**Committee Discussion:** *This question was skipped, and the committee members were instructed to address this question in their response to question #7, as applicable.*

5. **DISCUSSION:** Discuss whether a risk evaluation and mitigation strategy (REMS) is necessary and would be able to ensure that the benefits of volanesorsen outweigh the potential risk of serious bleeding due to severe thrombocytopenia. If volanesorsen were to be approved with a REMS, discuss whether you would recommend any changes to the REMS presented by FDA.

**Committee Discussion:** *Overall, the committee agreed that a REMS is necessary to ensure that the benefits of volanesorsen outweigh the potential risk of serious bleeding due to severe thrombocytopenia. One committee member stated that because of the potential of serious bleeding due to thrombocytopenia, the drug should be limited only to adults who have had a previous episode of acute pancreatitis and should not be available to pediatric patients or for off-label use. Please see the transcript for details of the committee discussion.*

6. **DISCUSSION:** Familial chylomicronemia syndrome can have the onset of symptoms in childhood, yet no pediatric patients have been studied in the volanesorsen development

program. Discuss your level of concern with respect to the potential use of volanesorsen in this population if approved for adults and any recommendations you may have for future study in the pediatric population.

*Committee Discussion: This question was skipped based on the committee discussions that transpired before this question.*

7. **VOTE:** Based on the information included in the briefing materials and presented today, has the applicant provided sufficient efficacy and safety data to support approval of volanesorsen?

**Vote Result:      Yes: 12                      No: 8                      Abstain: 0**

- a. If yes, provide your rationale and any recommendations regarding the indicated patient population, dosing, clinical monitoring, risk management strategies, and/or post-marketing studies.
- b. If no, provide your rationale and comment on what additional data would be required to support approval.

*Committee Discussion: Twelve members of the committee voted “Yes”, agreeing that based on the information included in the briefing materials and presented, the applicant provided sufficient efficacy and safety data to support approval of volanesorsen. The committee members who voted “Yes” noted that the study met its primary endpoint of decreasing TG. One committee member suggested collecting metabolic data from patients as they are being recruited for studies or registries which would create a comprehensive laboratory database that could be explored and help better define this disease moving forward. The majority of the eight committee members who voted “No” voiced concerns with the data presented by the applicant and agreed that the data did not demonstrate a favorable risk/benefit ratio. One committee member added that one disease (FCS) is essentially being traded for another (thrombocytopenia). Another committee member stated that additional data with patients using the proposed dosing and patient reported outcomes on pain and quality of life would be needed to help to support approval. Another committee member stated that there were some critical missteps, such as not testing additional dosing regimens in the pivotal trial that may have better elucidated the benefits and risks. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 5:34 p.m.