

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

**Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee
Meeting
December 11, 2013**

Location: FDA White Oak Campus, Building 31, The Great Room (Rm. 1503), White Oak Conference Center, 10903 New Hampshire Avenue, Silver Spring, Maryland

Issue: The committee discussed the safety and efficacy of biologic licensing application (BLA) 125390, metreleptin for injection, sponsored by Amylin Pharmaceuticals, LLC, a wholly owned subsidiary of Bristol Myers Squibb. The proposed indication for metreleptin is the treatment of metabolic disorders associated with lipodystrophy, including diabetes mellitus and/or hypertriglyceridemia (elevated triglyceride levels in the blood) in pediatric and adult patients with inherited or acquired lipodystrophy. (Lipodystrophies are rare medical conditions of abnormal loss of the body's fatty tissues.)

These summary minutes for the December 11, 2013 Endocrinologic and Metabolic Drugs Advisory Committee meeting were approved on January 17, 2014.

I certify that I attended the December 11, 2013 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee meeting and that these minutes accurately reflect what transpired.

_____/S/_____
Karen Abraham-Burrell, PharmD
Designated Federal Officer, AVDAC

_____/S/_____
Robert J. Smith, MD
Acting Chairperson, EMDAC

The Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) meeting of the Food and Drug Administration, Center for Drug Evaluation and Research met on December 11, 2013 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 briefing materials from the FDA and Amylin Pharmaceuticals, LLC, a wholly owned subsidiary of Bristol Myers Squibb. The meeting was called to order by Robert J. Smith, MD (Acting Chairperson); the conflict of interest statement was read into the record by Karen Abraham-Burrell, PharmD (Designated Federal Officer). There were approximately 150 persons in attendance. There were six Open Public Hearing speakers.

Issue: The committee discussed the safety and efficacy of biologic licensing application (BLA) 125390, metreleptin for injection, sponsored by Amylin Pharmaceuticals, LLC, a wholly owned subsidiary of Bristol Myers Squibb. The proposed indication for metreleptin is the treatment of metabolic disorders associated with lipodystrophy, including diabetes mellitus and/or hypertriglyceridemia (elevated triglyceride levels in the blood) in pediatric and adult patients with inherited or acquired lipodystrophy. (Lipodystrophies are rare medical conditions of abnormal loss of the body's fatty tissues.)

Attendance:

EMDAC Members Present (Voting): Erica Brittain, PhD; Edward Gregg, PhD; Diana Hallare, MPH (Consumer Representative); Ed Hendricks, MD; Robert Smith, MD (Acting Chairperson); Charles Stanley, MD

EMDAC Members Not Present (Voting): Vera Bittner, MD, MSPH; David Cooke, MD; William Hiatt, MD, FACP; Ellen Seely, MD

EMDAC Member Present (Non-Voting): Mads Rasmussen, MD, PhD (Industry Representative)

Temporary Members (Voting): Joel Lavine, MD, PhD; John O'Shea, MD; Dennis R. Ownby, MD; Bruce Smackey, PhD (Patient Representative); Miriam Vos, MD MSPH; Wyndham Wilson, MD

FDA Participants (Non-Voting): Mary H. Park, MD; Eric C. Colman, MD; Julie K. Golden, MD; James P. Smith, MD, MS; Suzanne Berkman Robottom, PharmD

Designated Federal Officer (Non-Voting): Karen Abraham-Burrell, PharmD

Open Public Hearing Speakers:

Claire Johnson-Walker, Leanne Tavares, Andra Stratton (Lipodystrophy United), Robert Ratner, MD, FACP, FACE (American Diabetes Association), Jason and Troy Fryer, Jilandre Linton

The agenda proceeded as follows:

Call to Order and Introduction of
Committee

Robert J. Smith, MD
Acting Chairperson, EMDAC

Conflict of Interest Statement

Karen Abraham-Burrell, PharmD
Designated Federal Officer, EMDAC

FDA Introductory Remarks

Eric C. Colman, MD
Deputy Director
Division of Metabolism and Endocrinology
Products (DMEP)
Office of Drug Evaluation (ODE) II
Office of New Drugs (OND), CDER, FDA

SPONSOR PRESENTATIONS

Amylin Pharmaceuticals, LLC (subsidiary of
Bristol-Myers Squibb)

Introduction

Joy Koda, PhD
Executive Director
Development Lead – Metreleptin
Bristol-Myers Squibb

Disease Background

David B. Savage, MBChB, MD, FRCP
Wellcome Trust Senior Clinical Fellow
University of Cambridge; UK
Honorary Consultant at Addenbrooke's Hospital
Cambridge University Hospital NHS Foundation
Trust

Clinical Program and Efficacy

Jean L. Chan, MD
Medical Director
Clinical Lead – Metreleptin
Bristol-Myers Squibb

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Safety

Peter Öhman, MD, PhD,
Executive Director, Medical Development
AstraZeneca

Clinical Experience

David B. Savage, MBChB, MD, FRCP

Benefit /Risk Assessment
& Conclusions

Fred Fiedorek, MD
Senior Vice President
Head of Development – Cardiovascular and
Metabolics
Bristol-Myers Squibb

Clarifying Questions

BREAK

NIH PRESENTATION

Pathophysiology, Diagnosis, Complications,
and Management of Lipodystrophy

Rebecca J. Brown, MD, MHSc
Assistant Clinical Investigator
Diabetes, Endocrinology, and Obesity Branch
National Institute of Diabetes and Digestive
Diseases
National Institutes of Health

Clarifying Questions

FDA PRESENTATIONS

Clinical Review of Efficacy and Safety

Julie K. Golden, MD
Medical Officer
DMEP, ODE-II, OND, CDER, FDA

Efficacy Review: Liver-Specific Parameters

Lauren Weintraub, MD
Medical Officer
Division of Gastroenterology and Inborn Errors
Products
ODE-III, OND, CDER, FDA

LUNCH

FDA PRESENTATIONS

Immunogenicity Risk

Laura Salazar-Fontana, PhD
Biologist
Division of Therapeutic Proteins
Office of Biotechnology Products
Office of Pharmaceutical Science
CDER, FDA

Risk Evaluation and Mitigation Strategies

Suzanne Berkman Robottom, PharmD
Division of Risk Management
Office of Medication Error Prevention and Risk
Management
Office of Surveillance and Epidemiology
CDER, FDA

Clarifying Questions

Open Public Hearing

Questions to the Committee/Committee Discussion

BREAK

Questions to the Committee/Committee Discussion (cont.)

ADJOURNMENT

Questions to the Committee:

- 1) **DISCUSSION:** The indicated populations proposed by the applicant include treatment of pediatric and adult patients with (1) generalized lipodystrophy or (2) metabolic disorders associated with partial lipodystrophy, including hypertriglyceridemia and/or diabetes mellitus inadequately controlled on a current therapy, and/or evidence of hepatic steatosis. Discuss whether you believe the applicant has demonstrated substantial evidence for efficacy with regard to glycemic control and hypertriglyceridemia in patients, or a subset of patients, with generalized and/or partial lipodystrophy. At a minimum, discuss the populations that the applicant has proposed, but your thoughts regarding any criteria (e.g., leptin levels, severity of baseline abnormalities, etc.) that you believe important to identify patients for whom metreleptin appears effective are welcome.

In your discussion consider the following:

- a. Patients with generalized lipodystrophy (proposed indication).
- b. Patients with metabolic disorders associated with partial lipodystrophy, including hypertriglyceridemia and/or diabetes mellitus inadequately controlled on a current therapy, and/or evidence of hepatic steatosis (proposed indication).
- c. Patients with generalized lipodystrophy, “low” leptin levels, and inadequately controlled diabetes and/or severe hypertriglyceridemia.
- d. Other subsets of lipodystrophy patients.

In your discussion, please comment on the extent to which various limitations of the metreleptin development program (open-label, single-arm design; modifications to eligibility criteria over time; changes in concomitant medications; missing data; etc.) had on your interpretation of the data.

Committee Discussion: Many committee members agreed that the best evidence for use has been demonstrated in patients with generalized lipodystrophy. For partial lipodystrophy, most committee members agreed that this group is harder to assess, and substantial evidence for efficacy has not been demonstrated for this group. The heterogeneity of the clinical presentation of patients with partial lipodystrophy and the lack of established criteria to define the disease were additional concerns. Other subsets of lipodystrophy patients were not identified by the committee as showing evidence of efficacy, with the committee citing the limited data. Some committee members expressed concern that attempting to define partial lipodystrophy subgroups that may benefit (e.g., using specific leptin levels) would be arbitrary and could deny the use of metreleptin from others that might derive benefit. The committee also discussed the need for guidelines to manage decision making on the course of therapy, continuation, and discontinuation of metreleptin. Please see the transcript for details of the committee discussion.

- 2) **DISCUSSION:** The applicant has proposed that evidence of hepatic steatosis is an indication for treatment among patients with partial lipodystrophy. Discuss your interpretation of the data regarding the effect of metreleptin on the liver, whether in patients with generalized or partial lipodystrophy, and whether you believe that any observed effects represent clinically meaningful changes.

Committee Discussion: The committee members discussed that, in general, hepatic steatosis alone is not an indication for treatment. In the setting of generalized lipodystrophy, where there are other metabolic abnormalities that would influence decisions on treatment, the committee agreed that hepatic steatosis would not add measurably as a guiding criterion. Most committee members agreed that hepatic steatosis is not a severe enough diagnosis in and of itself to warrant treatment with metreleptin. It was also mentioned that there were no data presented to support the changes observed in liver-related parameters being clinically important, so hepatic steatosis should not be a labeled indication. Overall, the committee was not convinced that there is clear evidence of metreleptin resolving hepatic abnormalities in patients with lipodystrophy. Please see the transcript for details of the committee discussion.

- 3) **DISCUSSION:** Discuss the safety profile of metreleptin. In your discussion, please consider the following, including your level of concern for the contribution of metreleptin to these potential risks:
- a. Lymphoma. Comment on the potential risk to patients with autoimmune forms of lipodystrophy (e.g., acquired generalized lipodystrophy) versus other lipodystrophy populations.

- b. Immunogenicity (i.e., neutralizing antibody). Comment on the potential risk to the lipodystrophy populations and whether concern for risk would vary by pre-treatment leptin concentration.
- c. Any other potential risks

***Committee Discussion:** In context of generalized lipodystrophy, members of the committee acknowledged that there may be an increased occurrence of various malignancies, including lymphomas, although it was agreed that the data are not adequate to truly assess this finding. The potential for metreleptin to promote the process of tumor development was discussed as a concern, but it was stated that the data do not allow definitive conclusions. Some committee members commented that the benefit of using metreleptin in patients with autoimmune forms of lipodystrophy outweighs the risk of lymphomas. Overall, the committee agreed that the risk for lymphoma should not preclude use of metreleptin but that criteria for monitoring should be established.*

Regarding immunogenicity, the committee commented that there is evidence of antibody generation in response to metreleptin use and these antibodies could potentially cause clinical problems in certain patient populations. The committee further elaborated that there could also be other immune responses that are driven by antibody formation that could have adverse effects for patients with lipodystrophy. Some committee members noted that the immunogenicity risk should not be a categorical disqualification for the use of metreleptin, for the degree of antibody generation by metreleptin is less than the immune response of some other drugs that are currently in use. The committee members also discussed the potential of maternal-fetal transfer of antibodies, with one member noting that if maternal-fetal antibody transfer did occur, it would be transient since maternal antibody would be cleared by the newborn in the weeks following birth.

In terms of other potential risks, the committee also gave consideration to the possibility of an altered immune response, secondary to metreleptin use, that could increase susceptibility to infections. The committee recommended consideration of monitoring for severe types of infections that might occur in the presence of immunosuppression or immunodeficiency. Please see the transcript for details of the committee discussion.

- 4) **VOTE:** Taking into account the proposal to implement a Risk Evaluation and Mitigation Strategy (REMS), has the applicant demonstrated substantial evidence that the benefits of metreleptin exceed the risks for the treatment of “pediatric and adult patients with generalized lipodystrophy”?
 - a. If you voted “Yes”, provide your rationale and comment on what type of additional post-approval safety data, if any, you would recommend.
 - b. If you voted “No”, provide your rationale, especially noting if a modification to the proposed indication would identify a population with a more favorable benefit/risk ratio.

Vote: Yes= 11 No = 1 Abstain = 0

Committee Discussion: *The majority of the committee agreed that, taking into account the proposal to implement a REMS, the applicant has demonstrated substantial evidence that the benefits of metreleptin exceed the risks for the treatment of “pediatric and adult patients with generalized lipodystrophy.” The committee recommended additional studies on adverse events associated with the use of metreleptin. The committee also commented on the need for recommendations regarding when and how to stop the drug when adverse events occur, monitoring for liver and renal disease, and possibly monitoring for cardiovascular events. The one member who voted “No” cited concern with the difficulty of diagnosis and with selecting appropriate patients for treatment. Please see the transcript for details of the committee discussion.*

- 5) **VOTE:** Taking into account the proposal to implement a Risk Evaluation and Mitigation Strategy (REMS), has the applicant demonstrated substantial evidence that the benefits of metreleptin exceed the risks for the treatment of “pediatric and adult patients with metabolic disorders associated with partial lipodystrophy, including hypertriglyceridemia and/or diabetes mellitus inadequately controlled on a current therapy, and/or evidence of hepatic steatosis”?
- a. If you voted “Yes”, provide your rationale and comment on what type of additional post-approval safety data, if any, you would recommend for such a population.
 - b. If you voted “No”, provide your rationale, especially noting if a modification to the proposed indication would identify a population with a more favorable benefit/risk ratio.

Vote: Yes= 2 No = 10 Abstain = 0

Committee Discussion: *The majority of the committee members agreed that, taking into account the proposal to implement a REMS, the applicant has not demonstrated substantial evidence that the benefits of metreleptin exceed the risks for the treatment of “pediatric and adult patients with metabolic disorders associated with partial lipodystrophy, including hypertriglyceridemia and/or diabetes mellitus inadequately controlled on a current therapy, and/or evidence of hepatic steatosis.” Most committee members commented that more effort is needed on how to best identify patients with partial lipodystrophy for whom metreleptin provides benefit. Please see the transcript for details of the committee discussion.*

- 6) **DISCUSSION:** If you believe that additional efficacy and/or safety data for metreleptin should be obtained pre-approval for one or more lipodystrophy populations, please describe the additional study(ies) and population(s).

Committee Discussion: *The committee members commented that it would be helpful to consider pre-approval studies in patients with partial lipodystrophy. Some members suggested that the Applicant improve education of physicians with an informational*

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campaign to identify more patients with partial lipodystrophy. In addition, some committee members suggested that the incorporation of measures of leptin, triglycerides, and indices of glucose control such as HbA1c into the study would help to define inclusion criteria.

The committee also had the following recommendations:

- *Consideration should be given to manage other drugs that patients are taking. Changes in medication(s) would be important factors in the study design.*
- *Additional endpoints to consider would be improvement in patient symptoms, such as hyperphagia.*
- *Consideration should be given to identifying a minimum effective dose in future studies, which may inform a dosing strategy that may provide efficacy but reduce the occurrence of antibody formation.*

In terms of randomization, some members recommended there should be some sort of controlled period, such as an initial randomized controlled phase followed by an extension in which those initially assigned to placebo would be provided metreleptin. Other members discussed the concept of first conducting an exploratory study to better define what subgroups of partial lipodystrophy might benefit, and then use this information in the design of a subsequent study. Please see the transcript for details of the committee discussion.

The meeting was adjourned at approximately 5:04 p.m.