

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

**Summary Minutes of the Dermatologic and Ophthalmic Drugs Advisory Committee Meeting
July 26, 2012**

Topic: During the morning session, the committee discussed a supplement to biologics license application (BLA) 125156 for LUCENTIS (ranibizumab injection) by Genentech, Inc., for the treatment of diabetic macular edema (DME). Ranibizumab injection is currently approved for the treatment of neovascular (wet) age-related macular degeneration (AMD) and macular edema following retinal vein occlusion (RVO). During the afternoon session, the committee discussed new biologics license application (BLA) 125422, ocriplasmin intravitreal injection (proposed tradename, Jetrea) by ThromboGenics, Inc., indicated for the treatment of symptomatic vitreomacular adhesions (sVMA) including macular hole.

These summary minutes for the July 26, 2012 Dermatologic and Ophthalmic Drugs Advisory Committee meeting were approved on September 10, 2012.

I certify that I attended the July 26, 2012 Dermatologic and Ophthalmic Drugs Advisory Committee meeting and that these minutes accurately reflect what transpired.

_____/s/
Yvette Waples, Pharm.D.
(Designated Federal Officer)

_____/s/
Michael X. Repka, M.D.
(Chair)

Summary Minutes of the Dermatologic and Ophthalmic Drugs Advisory Committee Meeting July 26, 2012

The following is the final report of the Dermatologic and Ophthalmic Drugs Advisory Committee meeting held on July 26, 2012. A verbatim transcript will be available in approximately four weeks, sent to the Division of Transplant and Ophthalmology Products and posted on the FDA website at <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DermatologicandOphthalmicDrugsAdvisoryCommittee/ucm280522.htm>

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

The Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on July 26, 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, Genentech, Inc., and ThromboGenics, Inc.. The meeting was called to order by Michael Repka, M.D. (Chairperson). The conflict of interest statement was read into the record by Yvette Waples, Pharm.D. (Designated Federal Officer). There were approximately 120 people in attendance for the morning session and 100 people in attendance for the afternoon session. There were thirteen (13) Open Public Hearing speakers for the morning session and five (5) for the afternoon session

Issue: During the morning session, the committee discussed a supplement to biologics license application (BLA) 125156 for LUCENTIS (ranibizumab injection) by Genentech, Inc., for the treatment of diabetic macular edema (DME). Ranibizumab injection is currently approved for the treatment of neovascular (wet) age-related macular degeneration (AMD) and macular edema following retinal vein occlusion (RVO). During the afternoon session, the committee discussed new biologics license application (BLA) 125422, ocriplasmin intravitreal injection (proposed tradename, Jetrea) by ThromboGenics, Inc., indicated for the treatment of symptomatic vitreomacular adhesions (sVMA) including macular hole.

Attendance:

DODAC Members Present (Voting): Lynn K. Gordon, M.D., Ph.D.; Susan M. MacDonald, M.D.; Michael X. Repka, M.D. (Chairperson); Allan R. Rutzen, M.D.

DODAC Members Not Present (Voting): Jean L. Bolognia, M.D.; Lynn A. Drake, M.D.; Sancy A. Leachman, M.D., Ph.D.; Paul F. Lizzul, M.D., Ph.D., M.P.H., M.B.A; Mary E. Maloney, M.D.; Robert F. Melendez, M.D., M.B.A (Consumer Representative); Ronald P. Rapini, M.D.; Peter Zloty, M.D.

DODAC Member Present (Non-Voting): Gavin R. Corcoran, M.D., FACP (Industry Representative)

Temporary Members (Voting): Marcia D. Carney, M.D.; Stephen S. Feman, M.D., M.P.H., FACS; Philip T. Lavin, Ph.D., FASA, FRAPS; Jo-Ellen DeLuca (Patient Representative); Michele J. Orza, Sc.D. (Acting Consumer Representative); William B. Phillips, II, M.D.

FDA Participants (Non-Voting): Edward M. Cox, M.D., M.P.H.; Renata Albrecht, M.D.; Wiley Chambers, M.D.; Rhea Lloyd, M.D. (morning session only); Jennifer Harris, M.D. (afternoon session only)

Designated Federal Officer: Yvette Waples, Pharm.D.

Open Public Hearing Speakers for the Morning Session: Jeff Todd (Prevent Blindness America); Michael J. Elman, M.D. (Diabetic Retinopathy Clinical Research Network); Narinder Sharma, BSc. Hons., M.B.A., PGDL (AMD Alliance International); Helen D. Nickerson, Ph.D. (JDRF); Victor H. Gonzalez, M.D. (American Diabetes Association); Patricia Corirossi; Sallie Cartwright; Katherine Tomlinson; Norton Strickland; Donna Strickland; Robert E. Ratner, M.D. (American Diabetes Association); Mary Osgood; Raymond Paxton

Open Public Hearing Speakers for the Afternoon Session: Jeff Todd (Prevent Blindness America); Elias Reichel, M.D.; Maureen Kearney; Leonard Feiner, M.D., Ph.D.; Mark Humayun, M.D., Ph.D.

The agenda proceeded as follows:

Morning Session

Call to Order and Introduction of Committee

Michael X. Repka, M.D.
Chairperson, DODAC

Conflict of Interest Statement

Yvette Waples, Pharm.D.
Designated Federal Officer, DODAC

FDA Introductory Remarks

Wiley Chambers, M.D.
Deputy Director, Division of Transplant and Ophthalmology Products (DTOP)
Office of Antimicrobial Products (OAP)
Office of New Drugs (OND), CDER, FDA

SPONSOR PRESENTATIONS

Genentech, Inc.

Therapeutic Rationale

Anthony P. Adamis, M.D.
Vice President, Global Head of Ophthalmology
Genentech, Inc.

Diabetic Macular Edema – An Unmet Medical Need

Donald J. D'Amico, M.D.
Professor and Chairman
Department of Ophthalmology
The Betty Neuwirth Lee and Chilly Professor
Weill Cornell Medical College
Ophthalmologist-in-Chief
New York-Presbyterian Hospital

RIDE/RISE Study Design and Efficacy Outcomes

Jason S. Ehrlich, M.D., Ph.D
Medical Director, Ophthalmology
Genentech, Inc.

Safety and Benefit/Risk

Anthony P. Adamis, M.D.

Clarifying Questions from Committee

FDA PRESENTATION

BLA 125156 for Lucentis (ranibizumab injection)

Rhea Lloyd, M.D.
Medical Officer
DTOP, OAP, OND, CDER, FDA

Clarifying Questions from Committee

BREAK

Open Public Hearing

Questions to the Committee and Committee Discussion

LUNCH

Afternoon Session

Call to Order and Introduction of Committee

Michael X. Repka, M.D.
Chairperson, DODAC

Conflict of Interest Statement

Yvette Waples, Pharm.D.
Designated Federal Officer, DODAC

FDA Introductory Remarks

Wiley Chambers, M.D.
Deputy Director, Division of Transplant and Ophthalmology Products (DTOP)
Office of Antimicrobial Products (OAP)
Office of New Drugs (OND), CDER, FDA

SPONSOR PRESENTATIONS

ThromboGenics, Inc.

Introduction

Kim Brazzell, Ph.D.
Head, U.S. Clinical Development
ThromboGenics, Inc.

Therapeutic Rationale

Peter Kaiser, M.D.
Professor of Ophthalmology
Cleveland Clinic
Lerner College of Medicine, Cole Eye Institute

Clinical Program

Kim Brazzell, Ph.D.

Efficacy

Kim Brazzell, Ph.D.

Safety

Michael Klepper, M.D.
Drug Safety Consultant
ThromboGenics, Inc.

Benefit/ Risk

Julia Haller, M.D.
Ophthalmologist-in-Chief, Wills Eye Institute
Chair, Department of Ophthalmology
Thomas Jefferson University

Clarifying Questions from Committee

FDA PRESENTATION

BLA 125422 for Jetrea (ocriplasmin) intravitreal injection

Clarifying Questions from Committee

BREAK

Open Public Hearing

Questions to the Committee and Committee Discussion

ADJOURNMENT

Questions to the Committee (Morning Session):

**BLA 125156
Lucentis (ranibizumab injection)**

APPLICANT: Genentech, Inc.

PROPOSED INDICATION: For the treatment of diabetic macular edema (DME)

- 1) **VOTE:** Is there a clinically significant difference in efficacy between the 0.3 and 0.5 mg Lucentis (ranibizumab injection) doses for the treatment of diabetic macular edema?
YES: 0 NO: 10 ABSTAIN: 0

Committee Discussion: The committee unanimously agreed that the efficacy data did not show a clinically significant difference between the 0.3 and 0.5mg Lucentis (ranibizumab injection) doses for the treatment of diabetic macular edema. Please see the transcript for details of the Committee discussion.

- 2) **VOTE:** Is there a clinically significant difference in safety between the 0.3 and 0.5 mg Lucentis (ranibizumab injection) doses for the treatment of diabetic macular edema?
YES: 4 NO: 4 ABSTAIN: 2

Committee Discussion: The committee members who voted “Yes” noted that the safety data showed a trend towards a difference between the 0.3 and 0.5mg Lucentis (ranibizumab injection) doses for the treatment of diabetic macular edema. Those who voted “No” commented that there is not enough data or little evidence of clinical significance. Those who abstained were concerned that the sample size presented by the Sponsor was not sufficient to make a determination. There was a general consensus that additional data is needed to determine if there is a clinically significant difference in safety between the two doses. Please see the transcript for details of the Committee discussion.

- 3) **VOTE:** Has substantial evidence of efficacy been provided to demonstrate that Lucentis (ranibizumab injection) is effective for the treatment of diabetic macular edema?
YES: 10 NO: 0 ABSTAIN: 0

Committee Discussion: The committee unanimously agreed that substantial evidence of efficacy has been provided to demonstrate that Lucentis (ranibizumab injection) is effective for the treatment of diabetic macular edema. Please see the transcript for details of the Committee discussion.

- 4) **VOTE:** Are additional studies needed prior to approval to evaluate the safety of Lucentis (ranibizumab injection)?
YES: 0 NO: 9 ABSTAIN: 1

Committee Discussion: *The majority of the committee agreed that no additional studies are needed prior to approval to evaluate the safety of Lucentis (ranibizumab injection) since this drug product is already on the market with a known safety history.*

a) **DISCUSSION:** If so, what studies?

Committee Discussion: *In summary, although there was a consensus that no additional studies are needed prior to approval, the committee suggested post-marketing studies to be conducted to address the safety of bilateral injections, optimal dosing intervals, and best time to initiate therapy. It was also noted that long-term follow-up of the pivotal trials should continue.*

Please see the transcript for details of the Committee discussion.

5) **VOTE:** Do you recommend for approval, the 0.5 mg dose of Lucentis (ranibizumab injection) administered monthly in the treatment of diabetic macular edema?

YES: 8 NO: 2 ABSTAIN: 0

Committee Discussion: *The majority of the committee recommended for approval, the 0.5 mg dose of Lucentis (ranibizumab injection) administered monthly in the treatment of diabetic macular edema. Some of the committee members who voted “Yes” noted that the safety and efficacy profiles of Lucentis are satisfactory. Those who voted “No” were concerned of the potential increased safety risk with continued use of the 0.5 mg dose. Please see the transcript for details of the Committee discussion.*

6) **VOTE:** Do you recommend for approval, the 0.3 mg dose of Lucentis (ranibizumab injection) administered monthly in the treatment of diabetic macular edema?

YES: 10 NO: 0 ABSTAIN: 0

Committee Discussion: *The committee unanimously recommended for approval, the 0.3 mg dose of Lucentis (ranibizumab injection) administered monthly in the treatment of diabetic macular edema. The committee agreed there is a benefit of the 0.3mg dose of Lucentis in terms of the efficacy and safety endpoints. Please see the transcript for details of the Committee discussion.*

7) **VOTE:** Do you have any suggestions concerning the labeling of the product?

YES: 7 NO: 2 ABSTAIN: 1

Committee Discussion: *The majority of the committee had suggestions concerning the labeling of the product.*

a) **DISCUSSION:** If so, what suggestions?

Committee Discussion: *Some of the committee members suggested having separate labeling for the 0.3 and 0.5mg Lucentis (ranibizumab injection) doses to address the specific adverse events associated with each dose. On the other hand, some committee members suggested the labeling to include both doses. Having different bottle cap color*

designated for each dose was also suggested. Please see the transcript for details of the Committee discussion.

Questions to the Committee (Afternoon Session):

BLA 125422
Ocriplasmin intravitreal injection

APPLICANT: ThromboGenics, Inc.

PROPOSED INDICATION: For the treatment of symptomatic vitreomacular adhesions (sVMA) including macular hole

- 1) **VOTE:** Has substantial evidence been provided to demonstrate that ocriplasmin 125µg is effective for the treatment of vitreomacular adhesions?

YES: 10 NO: 0 ABSTAIN: 0

Committee Discussion: The committee unanimously agreed that substantial evidence has been provided to demonstrate that ocriplasmin 125µg is effective for the treatment of vitreomacular adhesions. However, some of the committee members noted concerns with the secondary efficacy endpoints. In addition, some committee members noted they would like to see a more robust effect size. Please see the transcript for details of the Committee discussion.

- 2) **VOTE:** Has substantial evidence been provided to demonstrate that ocriplasmin 125µg is effective for the treatment of macular holes associated with vitreomacular adhesions?

YES: 7 NO: 3 ABSTAIN: 0

Committee Discussion: The majority of the committee agreed that substantial evidence has been provided to demonstrate that ocriplasmin 125µg is effective for the treatment of macular holes associated with vitreomacular adhesions. The committee members who voted “Yes” noted that the data was favorable. Those who voted “No” were concerned that the sample size of the secondary endpoint presented by the Sponsor was not sufficient to make a determination. Please see the transcript for details of the Committee discussion.

- 3) **VOTE:** Has substantial evidence been provided to demonstrate that ocriplasmin 125µg is effective for the treatment of all macular holes regardless of the presence of adhesions?

YES: 1 NO: 8 ABSTAIN: 1

Committee Discussion: The majority of the committee agreed that substantial evidence has not been provided to demonstrate that ocriplasmin 125µg is effective for the treatment of all macular holes regardless of the presence of adhesions. The committee noted that there was no data presented by the Sponsor regarding this proposed indication. Please see the transcript for details of the Committee discussion.

- 4) **VOTE:** Are additional studies needed prior to approval to evaluate the safety of ocriplasmin's effect on the retina?
YES: 3 NO: 6 ABSTAIN: 1

Committee Discussion: The majority of the committee agreed that additional studies are not needed prior to approval to evaluate the safety of ocriplasmin's effect on the retina.

- a) **DISCUSSION:** If so, what studies?

Committee Discussion: In summary, although the majority agreed that no additional studies are needed prior to approval, the committee suggested post-marketing studies to be conducted to further address the safety of ocriplasmin's effect on the retina, including the need for additional optical coherence tomography (OCT) data.

Please see the transcript for details of the Committee discussion.

- 5) **VOTE:** Do the benefits of administering ocriplasmin for the treatment of vitreomacular adhesions outweigh the potential risks?
YES: 10 NO: 0 ABSTAIN: 0

Committee Discussion: The committee unanimously agreed that the benefits of administering ocriplasmin for the treatment of vitreomacular adhesions outweigh the potential risks. However, some committee members noted the concern that ocriplasmin will benefit a proportion, not the majority, of the population. Please see the transcript for details of the Committee discussion.

- 6) **DISCUSSION:** If this product is approved, are there any suggestions concerning labeling for this product?

Committee Discussion: In summary, the committee suggested the following information to be included in the labeling of ocriplasmin:

- State "for single use in one eye only"
- Include the term "symptomatic" in the indication
- Patient information should accompany the labeling

Please see the transcript for details of the Committee discussion.

The meeting was adjourned at approximately 4:30 p.m.