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

## Summary Minutes of the Oncologic Drugs Advisory Committee
## July 13, 2017

Location: FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Rm. 1503), Silver Spring, Maryland

Topic: During the morning session, the committee discussed biologics license application (BLA) 761028 for ABP 215, a proposed biosimilar to Genentech/Roche's US-licensed AVASTIN (bevacizumab), submitted by Amgen Inc. The proposed indications (uses) for this product are (1) for the first- or second-line treatment of patients with metastatic carcinoma of the colon or rectum in combination with intravenous 5-fluorouracil-based chemotherapy, (2) in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy, for the second-line treatment of patients with metastatic colorectal cancer who have progressed on a first-line bevacizumab product-containing regimen, (3) for the first-line treatment of unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer in combination with carboplatin and paclitaxel, (4) for the treatment of glioblastoma with progressive disease in adult patients following prior therapy as a single agent, (5) for the treatment of metastatic renal cell carcinoma in combination with interferon alfa, and (6) in combination with paclitaxel and cisplatin or paclitaxel and topotecan for the treatment of persistent, recurrent, or metastatic carcinoma of the cervix.

During the afternoon session, the committee discussed biologics license application (BLA) 761074 for MYL-1401O, a proposed biosimilar to Genentech Inc.'s HERCEPTIN (trastuzumab), submitted by Mylan GmbH. The proposed indications (uses) for this product are: (1) for adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature) breast cancer (a) as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel; (b) with docetaxel and carboplatin; or (c) as a single agent following multi-modality anthracycline based therapy; (2) in combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer; (3) as a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease; and, (4) in combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease.

These summary minutes for the July 13, 2017 meeting of the Oncologic Drugs Advisory Committee of the Food and Drug Administration were approved on August 30, 2017.

I certify that I attended the July 13, 2017, meeting of the Oncologic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

**/s/**
Jay R. Fajiculay, PharmD
*Acting Designated Federal Officer, ODAC*

**/s/**
Bruce J. Roth, MD
*Chairperson, ODAC*

***Quick Minutes***
**Oncologic Drugs Advisory Committee Meeting**
**July 13, 2017**

The following is the final report of the Oncologic Drugs Advisory Committee (ODAC) meeting held on July 13, 2017. A verbatim transcript will be available in approximately six weeks, sent to the Office of Hematology and Oncology Products and posted on the FDA website at: https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/ucm547155.htm.

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

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The Oncologic Drugs Advisory Committee (ODAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on July 13, 2017 at the FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), Silver Spring, Maryland. Prior to the meeting, members and temporary voting members were provided copies of the briefing materials from the FDA, Amgen Inc., and Mylan GmbH. The meeting was called to order by Bruce J. Roth, MD, (Chairperson). The conflict of interest statement was read into the record by Jay R. Fajiculay, PharmD, (Acting Designated Federal Officer). There were approximately 175 people in attendance. There were six Open Public Hearing (OPH) speakers for the morning session. There were eleven OPH speakers for the afternoon session.

**Issue:** During the morning session, the committee discussed biologics license application (BLA) 761028 for ABP 215, a proposed biosimilar to Genentech/Roche's US-licensed AVASTIN (bevacizumab), submitted by Amgen Inc. The proposed indications (uses) for this product are (1) for the first- or second-line treatment of patients with metastatic carcinoma of the colon or rectum in combination with intravenous 5-fluorouracil-based chemotherapy, (2) in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy, for the second-line treatment of patients with metastatic colorectal cancer who have progressed on a first-line bevacizumab product-containing regimen, (3) for the first-line treatment of unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer in combination with carboplatin and paclitaxel, (4) for the treatment of glioblastoma with progressive disease in adult patients following prior therapy as a single agent, (5) for the treatment of metastatic renal cell carcinoma in combination with interferon alfa, and (6) in combination with paclitaxel and cisplatin or paclitaxel and topotecan for the treatment of persistent, recurrent, or metastatic carcinoma of the cervix.

During the afternoon session, the committee discussed biologics license application (BLA) 761074 for MYL-1401O, a proposed biosimilar to Genentech Inc.'s HERCEPTIN (trastuzumab), submitted by Mylan GmbH. The proposed indications (uses) for this product are: (1) for adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature) breast cancer (a) as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel; (b) with docetaxel and carboplatin; or (c) as a single agent following multi-modality anthracycline based therapy; (2) in combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer; (3) as a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease; and, (4) in combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease.

**Attendance:**
**ODAC Members Present (Voting):** Grzegorz S. Nowakowski, MD; Courtney J. Preusse, MA (Consumer Representative); Gregory J. Riely, MD, PhD (participation in morning session only); Brian I. Rini, MD, FACP (participation in afternoon session only); Bruce J. Roth, MD (Chairperson); Thomas S. Uldrick, MD, MS

**ODAC Members Not Present (Voting):** Harold J. Burstein, MD, PhD; Philip C. Hoffman, MD; Heidi D. Klepin, MD, MS; Vassilliki A. Papadimitrakopoulou, MD; Alberto S. Pappo, MD; Alice T. Shaw, MD, PhD

**ODAC Member Not Present (Non-Voting)**: Phuong Khanh (P.K.) Morrow, MD, FACP

**Temporary Members (Voting):** Deborah K. Armstrong, MD; Cynthia Chauhan (Patient Representative); Shein-Chung Chow, PhD; Bernard F. Cole, PhD; Craig W. Hendrix, MD; Adel H. Karara, PhD, FCP; Donald E. Mager, PharmD, PhD; Antonio R. Moreira, PhD; Diane L. Reidy-Lagunes, MD (participation in morning session only); John E. Schiel, PhD; Deborah Schrag, MD, MPH (participation in morning session only); Andrew D. Seidman, MD (participation in afternoon session only); Scott A. Waldman, MD, PhD, FCP, FAHA

**Acting Industry Representative to the Committee (Non- Voting):** Gary Gordon, MD, PhD

**FDA Participants** (**Non-Voting):** Laleh Amiri-Kordestani, MD (participation in afternoon session only); Julia Beaver, MD (participation in afternoon session only); Leah Christl, PhD; Patricia Keegan, MD (participation in morning session only); Steven Lemery, MD (participation in morning session only); Steven Kozlowski, MD; Richard Pazdur, MD (participation in afternoon session only)

**Acting Designated Federal Officer (Non-Voting):** Jay R. Fajiculay, PharmD

**Open Public Hearing Speakers:**
**Morning Session:** Thair Phillips (RetireSafe); Andrew Spiegel, Esq. (Global Colon Cancer Association); Tiffany L. McCaslin (National Business Group on Health); Dennis Cryer, MD (Alliance for Safe Biologic Medicines); Fouad Atouf, PhD (United States Pharmacopeia); Harry L. Gewanter, MD (Alliance for Safe Biologic Medicines);

**Afternoon Session:** Angie L. Cramer, BSN, RN, ONN-CG (The Johns Hopkins Breast Center); Christine Simmon (The Biosimilars Council); Sally Greenberg (National Consumers League); Thair Phillips (RetireSafe); Tiffany L. McCaslin (National Business Group on Health); Dennis Cryer, MD (Alliance for Safe Biologic Medicines); Larry McNeely (National Coalition on Health Care); Elizabeth Miller (United States Pharmacopeia); Edward Li, PharmD, MPH, BCOP (University of New England College of Pharmacy); Adrian van den Hoven (Medicines for Europe)

***The Agenda proceeded as follows:***

***Morning Session:* ABP 215 – Amgen, Inc.**

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| Call to Order and Introduction of Committee | **Bruce Roth, MD**<br>Chairperson, Oncologic Drugs Advisory Committee (ODAC) |
| Conflict of Interest Statement | **Jay Fajiculay, PharmD**<br>Designated Federal Officer<br>Division of Advisory Committee and Consultant Management (DACCM), CDER, FDA |
| Overview of the Regulatory Framework and FDA's Guidance for the Development and Approval of Biosimilar Products in the US | **Sue Lim, MD**<br>Team Leader<br>Office of New Drugs (OND), Therapeutic Biologics and Biosimilars Staff (TBBS) CDER, FDA |
| **INDUSTRY PRESENTATION** | **Amgen, Inc.** |
| Introduction to Bevacizumab Amgen, Inc. – Biosimilar to Genentech/Roche's Avastin® | **Richard Markus, MD, PhD**<br>Global Development, Amgen |
| Analytical Similarity | **Simon Hotchin**<br>Regulatory Affairs, Amgen |
| Non-Clinical and Clinical Similarity and Extrapolation to All Indications | **Richard Markus, MD, PhD**<br>Global Development, Amgen |
| Conclusion | **Lisa Bollinger, MD**<br>Regulatory Affairs and Safety, Amgen |

**FDA Presentations**

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| Product Quality Review | **Jee Chung, PhD**<br>Product Quality Reviewer<br>Division of Biotechnology Review and Research IV<br>Office of Biotechnology Products (OBP)<br>Office of Pharmaceutical Quality (OPQ), CDER, FDA |
| Statistical Equivalence Testing for Tier 1 Quality Attributes | **Tianhua Wang, PhD**<br>Product Quality Statistical Reviewer<br>Division of Biometrics VI (DBVI),<br>Office of Biostatistics (OB)<br>Office of Translational Sciences (OTS), CDER, FDA |
| Clinical Pharmacology | **Edwin C. Y. Chow, PhD**<br>Clinical Pharmacology Reviewer<br>Division of Clinical Pharmacology V<br>Office of Clinical Pharmacology, OTS, CDER, FDA |

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| Comparative Clinical Study | **Weishi (Vivian) Yuan, PhD**<br>Statistical Reviewer<br>Division of Biometrics V (DBV)<br>OB, OTS, CDER, FDA |
| Summary of Safety<br>Extrapolation<br>Summary of FDA Analysis of Similarity | **Sandra Casak, MD**<br>Clinical Reviewer<br>Gastrointestinal Cancer Team<br>Division of Oncology Products 2 (DOP2)<br>Office of Hematology and Oncology Products (OHOP)<br>OND, CDER, FDA |

Clarifying Questions to Presenters

**BREAK**

**OPEN PUBLIC HEARING**

Questions to the Committee and Committee Discussion

**LUNCH**

***Afternoon Session:*** **MYL:-1401O – Mylan GmbH**

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| Call to Order and<br>Introduction of Committee | **Bruce Roth, MD**<br>Chairperson, Oncologic Drugs Advisory Committee (ODAC) |
| Conflict of Interest Statement | **Jay Fajiculay, PharmD**<br>Designated Federal Officer,<br>Division of Advisory Committee and Consultant Management (DACCM), CDER, FDA |
| Opening Remarks | **Laleh Amiri-Kordestani, MD**<br>Medical Officer Team Leader, Breast Cancer Team<br>Division of Oncology Products 1 (DOP1)<br>Office of Hematology and Oncology Products (OHOP)<br>OND, CDER, FDA |
| **INDUSTRY PRESENTATION** | **Mylan GmbH.** |
| Introduction | **Arnd Annweiler, PhD**<br>Head of Research and Development, Mylan |
| Analytical and Nonclinical Demonstration of Similarity | **Patrick T. Vallano, PhD**<br>Head of Global Biologics Scientific Affairs, Mylan |
| Confirmatory Clinical Efficacy and Safety | **Abhijit Barve, MD, PhD**<br>Head of Global Clinical Research, Mylan |

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| Clinical Perspective | **Hope S. Rugo, MD**<br>Professor of Medicine, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA |
| Totality of the Evidence and Concluding Remarks | **Arnd Annweiler, PhD**<br>Head of Research and Development, Mylan |

**FDA Presentations**

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| Product Quality | **Kristen Nickens, PhD**<br>Product Quality Reviewer<br>Division of Biotechnology Review and Research I (DBRRI), Office of Biotechnology Products (OBP)<br>Office of Pharmaceutical Quality (OPQ), CDER, FDA |
| | **Meiyu Shen, PhD**<br>Expert Mathematical Statistician – Team Leader<br>Division of Biometrics VI (DBVI)<br>Office of Biostatistics (OB)<br>Office of Translational Sciences (OTS), CDER, FDA |
| Clinical Pharmacology | **Brian D. Furmanski, PhD**<br>Senior Clinical Pharmacology Reviewer<br>Division of Clinical Pharmacology V (DCPV)<br>Office of Clinical Pharmacology (OCP),<br>OTS, CDER, FDA |
| Clinical Efficacy and Safety | **Jennifer Gao, MD**<br>Medical Officer, Breast Cancer Team<br>DOP1, OHOP, OND, CDER, FDA |
| Summary of FDA Findings | **Jennifer Gao, MD** |

Clarifying Questions to Presenters

**BREAK**

**OPEN PUBLIC HEARING**

Questions to the Committee and Committee Discussion

**ADJOURNMENT**

***Question to the Committee:***

***Morning Session:* ABP 215 – Amgen, Inc.**

1. **DISCUSSION:** Please discuss whether the evidence supports a demonstration that ABP 215 is highly similar to US-licensed Avastin, notwithstanding minor differences in clinically inactive components.

***Committee Discussion:*** The committee members agreed that the analytical profile of ABP 215 was highly similar, nothwithstanding minor differences, to that of the reference product, US-licensed Avastin.

A concern was raised regarding data to support extrapolation, particularly if any of the analytical differences discussed could affect tissue distribution or the ability of the biosimilar product to reach the appropriate compartment, specifically for the glioblastoma multiforme indication. It was noted that the mechanism of action for bevacizumab products occurs in the vascular space, and so tissue penetration should not be a concern. A committee member stated further that even if PK were different between indications, it would not, by itself, preclude extrapolation to GBM. The committee member indicated that the totality of this data supports a judgment that any indication-specific PK differences would be the same for the reference product and for APB215. Please see the transcript for details of the committee discussion.

2. **DISCUSSION:** Please discuss whether the evidence supports a demonstration that there are no clinically meaningful differences between ABP215 and US-licensed Avastin in the studied condition of use.

   ***Committee Discussion:*** The committee members agreed with FDA's conclusion that there were no clinically meaningful differences observed between ABP 215 and the reference product. Please see the transcript for details of the committee discussion.

3. **DISCUSSION:** Please discuss whether there is adequate scientific justification to support licensure for all of the proposed indications.

   ***Committee Discussion:*** The committee members agreed with FDA's conclusion that based on the totality of evidence provided by the Applicant, there is evidence to support licensure for ABP215 for all of the proposed indications. The data showed analytical and clinical similarity; the side effect profile was similar to that of the reference product. The committee held some discussion regarding the strength of the data to support extrapolation to the glioblastoma multiforme indication. The clinical effect of bevacizumab in this cancer type (as with other cancer types) is postulated to be due to binding circulating VEGF. Based on this rationale and other considerations regarding similarity, the committee agreed with the Applicant's proposal regarding extrapolation in all proposed conditions of use. Please see the transcript for details of the committee discussion.

4. **VOTE:** Does the totality of the evidence support licensure of ABP215 as a biosimilar product to US-licensed Avastin for each of the indications for which US-licensed Avastin is currently licensed and for which the Applicant is seeking licensure as listed below:

   - Metastatic colorectal cancer, with intravenous 5-fluorouracil–based chemotherapy for first- or second-line treatment.
   - Metastatic colorectal cancer, with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line Avastin-containing regimen.

- Non-squamous non-small cell lung cancer, with carboplatin and paclitaxel for first line treatment of unresectable, locally advanced, recurrent or metastatic disease.
- Glioblastoma, as a single agent for adult patients with progressive disease following prior therapy.
- Metastatic renal cell carcinoma with interferon alfa.
- Cervical cancer, in combination with paclitaxel and cisplatin or paclitaxel and topotecan in persistent, recurrent, or metastatic disease.

***YES: 17*** ***NO: 0*** ***ABSTAIN: 0***

***Committee Discussion:*** The committee members unanimously agreed that the totality of the evidence supports licensure of ABP215 as a biosimilar product to US-licensed Avastin for each of the indications for which the Applicant is seeking approval as listed above. The members stated that the analytical package was strong, well laid out, and that the manufacturing process was well controlled and consistent. Comments were made on the uniformity of the pharmacokinetic and clinical results observed in the clinical studies conducted for ABP215. One member identified that the toxicity was near identical in both the ABP 215 and reference product arms which showed both ABP 215 and the reference product may behave similarly in the clinical setting. There was a concern stated by one panel member over the patient population used in the clinical studies, who advocated for expanded efforts to recruit more diverse patients in clinical comparability studies. The same member stated they were concerned that the proposed biosimilar was tested only in men in the PK similarity study. Please see the transcript for details of the committee discussion.

***Afternoon Session:*** **MYL:-1401O – Mylan GmbH**

1. **DISCUSSION:** Please discuss whether the evidence supports a demonstration that "MYL-1301O" is highly similar to US-Herceptin, notwithstanding minor differences in clinically inactive components.

   ***Committee Discussion:*** The committee members commented that the analytical evidence provided by the applicant was appropriate for demonstrating MYL-1401O was highly similar to US-Herceptin. Please see the transcript for details of the committee discussion.

2. **DISCUSSION**: Please discuss whether the evidence supports a demonstration that there are no clinically meaningful differences between "MY:-1401O" and US-Herceptin in the studied condition of use.

   ***Committee Discussion:*** The committee members commented that the clinical evidence provided by the applicant was appropriate for demonstrating MYL-1401O was highly similar to US-Herceptin. Please see the transcript for details of the committee discussion.

3. **DISCUSSION:** Please discuss whether there is adequate scientific justification to support licensure for all of the proposed indications.

***Committee Discussion:*** The committee members stated that there is adequate scientific justification to support licensure for all indications and that the totality of evidence provided by the applicant was appropriate to support licensure of MYL-1401O as a biosimilar to US-licensed Herceptin for the indications for which MYL-1401O is eligible for licensure. Please see the transcript for details of the committee discussion.

4. **VOTE:** Does the totality of the evidence support licensure of "MYL-1401O" as a biosimilar product to US-Herceptin for the following indications for which US-Herceptin is licensed and for which the Applicant is eligible for licensure (HER2 positive breast cancer in the metastatic and adjuvant settings)? Please explain the reasons for your vote.

   ***YES: 16*** ***NO: 0*** ***ABSTAIN: 0***

   ***Committee Discussion:*** The committee members unanimously agreed that the totality of the evidence support licensure of MYL-1401O as a biosimilar product to US-Herceptin for the following indications for which US-Herceptin is licensed and for which the Applicant is eligible for licensure: (1) for adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature) breast cancer (a) as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel; (b) with docetaxel and carboplatin; or (c) as a single agent following multi-modality anthracycline based therapy; (2) in combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer; and (3) as a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease. The committee members stated that based on the totality of evidence, applicant presentations, and FDA presentations, analytical similarity was verified and clinical data was compelling. In addition, it was stated that there were no signals of clinically important differences. There was a recommendation that for assessing the justification for extrapolation, particularly for use of MYL-1401O in the adjuvant setting, careful consideration should be placed on trial design and endpoint selection. Another member noted that in the clinical setting, trastuzumab is traditionally given in conjunction with pertuzumab, and that clinical trials addressing the two used together could be beneficial. Please see the transcript for details of the committee discussion.

The meeting on July 13, 2017 was adjourned at approximately 4:08 p.m.