FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Oncologic Drugs Advisory Committee (ODAC) Meeting
FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503)
10903 New Hampshire Avenue, Silver Spring, Maryland 20993
July 13, 2017

DRAFT QUESTIONS

BLA 761028

ABP215, a proposed biosimilar to Avastin (bevacizumab)

Applicant: Amgen, Inc.

Proposed Indications:

- 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.

Background:

The PHS Act defines the terms "biosimilar" or "biosimilarity" to mean that "the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product." A 351(k) application must contain, among other things, information demonstrating that the proposed product is biosimilar to a reference product based upon data derived from analytical studies, animal studies, and a clinical study or studies, unless FDA determines, in its discretion, that certain studies are unnecessary in a 351(k) application (see section 351(k)(2) of the PHS Act).

The Applicant used a non-US-licensed comparator (EU-approved bevacizumab) in the comparative clinical study intended to support a demonstration of no clinically meaningful differences from US-licensed Avastin. Accordingly, the Applicant provided scientific justification for the relevance of that data by establishing an adequate scientific bridge between EU-approved bevacizumab, US-licensed Avastin, and ABP215. Review of an extensive battery of test results provided by the Applicant confirmed the adequacy of the scientific bridge and hence the relevance of comparative clinical data obtained with EU-approved bevacizumab to support a demonstration of biosimilarity to US-licensed Avastin. This battery of tests included both analytical studies and a comparative PK study in humans.

In considering the totality of the evidence, the data submitted by the Applicant support a demonstration that ABP215 is highly similar to US-licensed Avastin, notwithstanding minor differences in clinically inactive components, and support a demonstration that there are no clinically meaningful differences between ABP215 and US-licensed Avastin in terms of the safety, purity, and potency of the product.

Chemistry, Manufacturing, and Controls:

The Applicant utilized an array of analytical methods to assess the primary and higher order structure, physicochemical properties, and biological functions of ABP215 in comparison to US-licensed Avastin and EU-approved bevacizumab. The comparison to EU-approved bevacizumab was performed to provide the analytical portion of the scientific bridge to justify the use of clinical data generated using EU-approved bevacizumab as the comparator. The results of the analytical similarity assessment showed that each pairwise comparison between products met the pre-specified acceptance criteria for analytical similarity that also included statistical equivalency criteria for the potency bioassay (inhibition of endothelial cell proliferation assay) and for binding to the target antigen, vascular endothelial growth factor A. These results support a demonstration that ABP215 is highly similar to US-licensed Avastin. Minor differences in glycosylation profile, charge variant profile, levels of aggregates, levels of fragments and FcγRIIIa (158V) binding were observed. In each case, the differences did not preclude a demonstration that ABP215 is highly similar to US-licensed Avastin, as the differences were evaluated and not found to have clinical impact.

The results of the analytical similarity assessment which consisted of three pair-wise analytical comparisons of ABP215 to US-licensed Avastin, ABP215 to EU-approved bevacizumab, and EU-approved bevacizumab to US-licensed Avastin, provide an adequate analytical portion of the scientific bridge between EU-approved bevacizumab, US-licensed Avastin, and ABP215 to justify the relevance of the comparative clinical data generated using EU-approved bevacizumab.

Pharmacology/Toxicology:
To support the initial clinical study with ABP215, the Applicant conducted a comparative toxicity study in which monkeys received ABP215 or US-licensed Avastin, twice per week, for 1 month. No biologically significant differences in toxicity or toxicokinetics were noted between ABP215 and US-licensed Avastin. Additional pharmacology studies and a single-dose pharmacokinetic study in rats further support the similarity between ABP215 and US-licensed Avastin. These studies were not designed to demonstrate statistical significance for similarity.

Clinical Pharmacology:
The objective of the clinical pharmacology program was to evaluate the pharmacokinetic similarity between ABP215 and US-licensed Avastin and to support the scientific bridge between ABP215, US-licensed Avastin and EU-approved bevacizumab.

Overall, Study 20110216 supports a demonstration of PK similarity between ABP215 and US-licensed Avastin, as well as the scientific bridge between ABP215, US-licensed Avastin and EU-approved bevacizumab.

Efficacy and Safety:
Study 20120265 was a randomized, double-blind, multicenter study comparing ABP215 to EU-approved bevacizumab (15 mg/kg IV every three weeks) in 642 patients with advanced non-small cell lung cancer (NSCLC). Trough concentrations of ABP215 or EU-approved bevacizumab were collected on Cycle 1 through Cycle 4, and Cycle 6 pre-dose.

No new safety signals were identified in the ABP215 arm compared to the known toxicity profile of US-licensed Avastin. Overall, there were no meaningful differences in adverse events (AEs), serious adverse events (SAEs), deaths up to 30-days after the last treatment dose, or treatment discontinuations.

QUESTIONS:

1. **DISCUSSION**: Please discuss whether the evidence supports a demonstration that ABP215 is highly similar to US-licensed Avastin, notwithstanding minor differences in clinically inactive components.
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.
3. **DISCUSSION**: Please discuss whether there is adequate scientific justification to support licensure for all of the proposed indications.

DRAFT QUESTIONS (cont.)

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.