Late-Cycle Review Meeting Minutes
April 7, 2015

Application type and number: BLA STN #125518
Product name: talimogene laherparepvec
Applicant: Amgen
Meeting date & time: April 7, 2015 at 1:00pm

Discussion:

This late-cycle meeting will focus on issues relevant to the joint meeting of the CTGTAC and the ODAC scheduled for April 29, 2015, to include:

1) Any Amgen comments and questions regarding the FDA Briefing Document (BD).

Summary of Discussion: *Amgen requested clarification regarding discrepancies between the Applicants briefing document and FDA's briefing document were noted.*

a. *The FDA briefing document omitted noting that study 005/05 was granted a Special Protocol Assessment (SPA) by FDA on April 17, 2008.This means that FDA agreed that the design and planned analyses of the protocol sufficiently address the study's objectives and that this study is adequately designed to provide the necessary data that, depending upon outcome, could support a license application submission. Additional protocol amendments were reviewed and received concurrence under the SPA agreement, most recently on February 22, 2013.*

b. *A discrepancy was noted regarding the indication contained in the Amgen Advisory Committee Briefing Document, and that contained in the FDA Advisory Committee Briefing Document. Amgen had provided several proposed indication wordings in the BLA submission, and in December of 2014, at FDA's suggestion, Amgen included the term 'injected' in the proposed indication: "Imlygic is an oncolytic immunotherapy indicated for the treatment of injectable regionally or distantly metastatic melanoma." The FDA briefing document added the word "unresectable" to the proposed indication, which was not included in the Applicant's proposed indication.*

Recommendation: *The term "unresectable," be considered for inclusion in any allowed labeling indication due to the fact that surgical resection is considered curative when feasible and that only subjects with unresectable melanoma were included in the study (005/5) that provided efficacy information in support of the BLA. The final allowed indication, if any, will follow public discussion at the Advisory Committee and final determination by FDA*

2) FDA requests for data and analyses relevant to the AC meeting and the two briefing documents.

Summary of Discussion: *Amgen wanted more information regarding Accelerated approval agency pathways or restricted indication. It is topic for the AC meeting will want to discuss. FDA felt this was a topic that might come up. What would be the appropriate population to be studied? You might submit data that support the pathway. We are not suggesting that you should take a certain pathway for the FDA to consider, but it is a topic AC might want to discuss.*

3) Discussion of the proposed indication statement, particularly whether "unresectable" is, or should be, part of the proposed indication statement.

Summary of Discussion: *Please submit your concerns regarding Durable Response Rates. We do want to undertake your concerns. There are two issues- the first is the primary endpoint. The effect size used as evidence we see it as an overall assessment. There is some bias of the evidence which may not be significant. Meaningfulness of the primary endpoint would be a key assessment to accelerated approval and also the cosmetic effect and how do you see this benefit.*

Our thoughts regarding the adding the "unresectable" used in the indication are in alignment with the FDA.

4) CMC issues that may reflect differences in perspective between FDA and Amgen:

a. Amgen states that talimogene laherparepvec exhibits tumor selective replication (pages 9, 23, 24, and 28 of the Amgen BD). However, Amgen has not submitted to the BLA direct evidence of tumor-selective replication or preferential infection of tumor cells.

b. Regarding the shedding data, expression of the data in terms of the number of samples, rather than in terms of the number of individuals tested, may be misleading.

c. Amgen BD refers to talimogene laherparepvec as an immunotherapy. However, no direct evidence of this MOA with tumor specific immune responses in human studies has been provided.

5) Clinical and Statistical issues that may reflect differences in perspective between FDA and Amgen:

a. Subgroup analyses

We intend to make a presentation of the subgroup analysis to the AC committee.

b. Potential bias in the study results

Is there more that Amgen need to present to prevent potential bias robustness regarding overall survival?

c. Available therapies for the proposed indicated population

Summary of Discussion*: FDA noted that surgical oncology experts could have a say into this issue. We have gathered experts who could have certain opinions.*

d. Evidence of a cosmetic benefit

e. Association between durable response (DR) and overall survival (OS). Amgen included similar analyses in the supplemental clinical study report (CSR), using an analysis cut-off date at the primary analysis of DRR (December 21, 2012). It appears that the analyses reported in Amgen's BD (pp.53-54) used a cut-off date based on the final analysis of OS.

i. Please confirm and include the cut-off date used for this set of analyses in the BD.

ii. Please also include a statement whether the analyses in the briefing document give results similar to that included in the CSR.

iii. In your supplemental CSR (p.25 of 310), you state that "The [DR/non-DR] groups are non-randomized and defined by outcomes, therefore bias may be introduced if there are imbalances in prognostic factors, in particular, subjects with earlier disease stage and/or receiving first line therapy which were both shown via multivariate analysis to be independent predictors for achieving a DR." It will be informative if you include analysis to assess how much the confounding factors may contribute to the observed association and include some interpretation of the results.

f. Sensitivity analysis on OS based on updated survival status (p.57). Please clarify whether you used the same analysis cut-off date of March 31, 2014 for this analysis as the primary analysis. What is the p-value for this sensitivity analysis?

g. OS follow-up time. You report (p.48) that "In the primary analysis of OS, at a median follow-up time of 44.4 months …" The median survival in the two study arms were 23.3m and 18.9m, respectively. Therefore, it appears that the follow-up time reported is not the actual follow-up time, calculated as "death/censoring date" – "randomization date" or in a similar way. Please explain how the follow-up time was computed to arrive at a median follow-up of 44.4m.

6) Plan for sharing of draft slide presentations

FDA Attendees

Celia Witten, MD, PhD, Director, OCTGT
Stephanie Simek, PhD, Deputy Director, OCTGT
Mark Davidson, RHIA, RMS, OCTGT
Kimberly Benton, PhD, Deputy Director, DCGT
Ramjay Vatsan, PhD, Biologist, DCGT
Wilson Bryan, MD, Director, DCEPT
Peter Bross, MD, Medical Officer, DCEPT
Robert Le, MD, PhD, Medical Officer, DCEPT
Maura O'Leary, MD, Medical Officer, DCEPT
Estelle Russek-Cohen, PhD, Director, DB/OBE
John Scott, PhD, Deputy Director, DB/OBE
Abigail Luo, PhD, Biostatistics, OBE
Scott Winiecki, MD, Epidemiology, OBE
Meghna Alimchandani, MD, Epidemiology, OBE

Amgen Attendees

Arun Tholudur, PhD, Director, Global Operations Planning
Deborah Arrindell, JD, MD, MPH, Executive Director, Global Patient Safety
Elliott Levy, MD, Senior Vice President, Global Development
Greg Friberg, MD, Executive Director, Global Development
Heba Abdullah, MD, Senior Medical Scientist (acting Global Safety Officer), Global Patient Safety
Jennifer Gansert, MD, PhD, Executive Director, Global Development
Kathy Sugrue-Richards, Senior Manager, Regulatory Affairs CMC

Lisa Shamon, PhD, Director, Global Regulatory Affairs
Mark Taisey, Vice President, Global Regulatory Affairs
Michael Wolf, MS, Director, Biostatistics
Michelle Pernice, PharmD, Manager, Global Regulatory Affairs
Peter Feldman, MBA, Global Product General Manager
Rafael Ponce, PhD, Director, Preclinical Safety
Rhian Thomas, BSc, Executive Director, Global Regulatory Affairs
Steven Galson, MD, MPH, Senior Vice President, Global Regulatory Affairs and Safety