Amgen Mid-Cycle Communication
January 27, 2015

Application type and number: BLA STN #125518
Product name: talimogene laherparepvec
Proposed Indication: The indication is treatment of injectable regionally or distantly metastatic melanoma.
Applicant: Amgen
Meeting date & time: January 27, 2015 at 12:00pm
Committee Chair: Ramjay Vatsan, PhD
RPM: Mark L. Davidson, RHIA

Attendees:

Ramjay Vatsan
Mark L. Davidson
Peter Bross
Maura O'Leary
Robert Le
Andrew Byrnes
Mike Havert
Rabia Ballica
Yuqun (Abigail) Luo
Ying Huang
Christopher Joneckis
Patrick Zhou

Discussion Summary:

The following is a list of concerns identified to date for the BLA. Many of these concerns may be addressed by providing additional information. Reviewer concerns are listed by review disciplines for clarity. As our review of the BLA proceeds, we may have additional Information Requests.

1. CMC Information:

a. In-process hold time is not validated for the proposed "Acceptable Hold Time".

b. OOS, deviation reports, retest procedures and CAPAs implementation procedures are not fully explained in the BLA.

c. Additional information is needed to review the adequacy of the (b) (4) testing.

d. Revisions to the Environmental Assessment document are required.

e. The adventitious agent tests may lack sufficient sensitivity.

f. Additional clarification is needed on qualification of QC reagents.

g. Shipping validation data are required for [redacted] sample, and for IPC samples shipped at [redacted].

h. An evaluation for extractables and leachables for the DP stored at [redacted] is needed.

i. Additional details are needed on the methods used to calculate overages for 10e6 and 10e8 pfu/mL doses.

j. Additional information is needed on the relationship of the visible particles to product storage.

k. Additional information is needed on stability non-conformance that occurred at the 48 month time point for the previous container closure system. Updated stability information is needed for lots with the new container closure system manufactured after the facility changes in 2013.

l. Additional details are needed on the comparability plan for production scale-up and information included in the BLA may require revision.

2. Clinical Information:

a. Clinical Efficacy:

i. Bias in the conduct of the completed Phase 3 trial (005/05) may have influenced the study results. For example, the discrepancy between the two study arms with regard to early dropouts is suggestive of such bias. Discrepancies between the two arms also may have occurred in other areas, such as outcome assessment and dosing. The existence and effects of bias are difficult to confirm and quantitate, but such discrepancies raise concern that bias in study conduct compromises the internal validity of the trial.

ii. Talimogene laherparepvec administration was highly variable, with investigator discretion in the selection of lesions to be injected, the number of lesions to be injected, the total dose administered, the dose administered into each lesion, and the frequency of injections. This variability in dosing makes it difficult to assess the relationship between specific aspects of dosing and the study efficacy results. In addition, because investigator discretion was a substantial factor in dosing, we are concerned that we do not have sufficient information to reach agreement on a product label that would adequately inform physicians on the safe and effective use of talimogene laherparepvec.

iii. We are uncertain of the reliability of the study results with regard to tumor response.

1.) We have been unable to confirm the study efficacy results, particularly with regard to durable responses. For example, we have not found supporting documents that confirm durable responses for some subjects.

2.) Some lesions that were reported to have a complete or partial response appear to be too small (0.3 cm^2 for example) for reliable measurement.

iv. There is insufficient evidence that your product has a beneficial systemic effect, or to support a mechanism of action by which your product might have a beneficial systemic effect.

1.) It is not clear whether talimogene laherparepvec has a benefit in overall survival.

2.) You submitted some analyses of tumor responses in non-injected lesions and discussion regarding possible systemic effects. However, it is very difficult for us to determine which lesions were injected or not injected. Some lesions reported as non-injected appear to be too small for reliable assessment. Therefore, it is not clear whether these non-injected lesions truly regressed.

3.) No immunologic biomarker correlative studies were submitted to support the existence of systemic effects.

v. It is unclear whether the data are sufficient to define a population for whom your product would be indicated. Although the Phase 3 trial (005/05) enrolled patients who had unresectable melanoma, they had not received prior therapies, such as ipilimumab, that are now available with proven efficacy in the treatment of melanoma. Thus, your study population is not representative of the current US melanoma population, and it is not clear how talimogene laherparepvec would fit in the current treatment for patients with unresectable melanoma, For example, it is not clear whether talimogene laherparepvec would be used as a first-line vs. second-line therapy or as a component of a combinationatorial therapy with other available products. Such an uncertainty regarding intended patient population for talimogene laherparepvec is a significant issue for product labeling.

b. Clinical Safety:

i. At this stage of review, we have not identified significant safety issues. However, further review may reveal safety issues such as exposure-dependent adverse events or shedding-related concerns.

3. Pharmacovigilance Information:

In view of Amgen's Pharmacovigilance Plan, we have concerns regarding the ability of the proposed postmarketing study 20130193 to capture (with qPCR confirmation) cases of talimogene laherparepvec transmission to close contacts (CC)/health care providers (HCP), and cases of talimogene laherparepvec-associated symptomatic infection in the patient, should they occur, due to a multi-step lengthy process of sample collection and laboratory testing. Also of note, additional HCP training may be needed to promote safe handling and product administration in order to minimize occupational exposure of HCP and subsequent potential transmission to other patients.

4. Additional Review Communication:

Regarding facility information, we received your January 16, 2015 amendment in response to our January 6, 2015 information request. The information provided in this amendment is under review and we may have additional information requests when the review is completed.

A. Proposed date(s) for the late-cycle meeting with Amgen

Late Cycle package will be sent to Applicant:	April 2, 2015
Late-Cycle Meeting with Applicant:	April 7, 2015

B. Updates regarding plans for the AC meeting

The advisory committee meeting is scheduled for April 29, 2015

C. Other projected milestone dates for the remainder of the review cycle, including changes to previously communicated dates:

The action due date was changed from July 28, 2015 to October 27, 2015 due to the submission of a major amendment on November 28, 2014.

Site Inspection:	February 9th to 13th, 2015
Labeling Target:	September 27, 2015
PMC Study Target:	September 27, 2015
First Action Due:	October 27, 2015