**BLA 125518 Amgen**

December 23, 2014

We have the following clinical information requests:

1. From the BLA original data and your response to our request, we made a list of subjects with CRs or PRs with surgery after randomization. (Table 1). Please provide confirmation information regarding the number of subjects and the response assessment in the Table 1 or provide your version of the table. In addition we have specific requests for clarification below.

**Table 1: Subjects with CRs or PRs with Surgery after Randomization.**

| | Subject | Treatment Arm | Response Assessment (investigator) | Response Assessment per EAC | Surgery prior to CR (Y/N)? | Biopsy Result |
|---|---|---|---|---|---|---|
| 1 | BVX00505-053008 | T-VEC | COMPLETE RESPONSE | PARTIAL RESPONSE | Yes (L5) Cycle 7 day 1. All other lesions had responded and were gone. The last remaining lesion could be excised. | BX (+) |
| 2 | BVX00505-053018 | T-VEC | COMPLETE RESPONSE | PARTIAL RESPONSE | Yes But not in the *Listing 16-4.7 | BX (+) |
| 3 | BVX00505-003007 | T-VEC | SD | NR | Y (L1, L2, L3, L4) | BX (+) |
| 4 | BVX00505-021002 | T-VEC | CR | CR-? | Y (L1,L2, N1 | L1 – L2 (+) N1 - |
| 5 | BVX00505-035020 | T-VEC | PR | CR | Y (L1) | Bx (-) |
| 6 | BVX00505-065012 | T-VEC | CR | CR | Y (L1) "therapeutic resection" | Bx (-) |
| 7 | BVX00505-067006 | T-VEC | CR | PR | Y (L1, N9) | Bx (+) L1, N9 |
| 8 | BVX00505-005021 | T-VEC | PR | CR | Y (L1) | Bx (-) |
| 9 | BVX00505-005030 | T-VEC | PR | CR | Y (L1) | Bx (-) |
| 10 | BVX00505-010001 | T-VEC | PR | CR -? | Y (L1, N1) | Bx (+) |

Source: Adapted from BLA eCTD 005-05 Clinical Study Report, CRFs and Imaging Data. *Listing 16-4.7. Listing of Conversion of Disease to Suitable for Resection. BLA datasets (including PR.XPT and ADRSEAC.XPT), and the BLA supplements specified.

2. On your response to FDA request #7 submitted on 12-12-2014, you described two subjects (BVX00505-053008 and BVX00505-053018) who were categorized to have a PR following resection of the tumor, per EAC. However, the BVX00505-053018 who had resection of the tumor was not inside the Listing 16-4.7 that you provided in the original BLA as Listing 16-4.7 in Appendix 16.2.6 of the 005/05 Primary Analysis CSR. Please clarify if the 6 subjects in the Listing 16-4.7 had CR or PR after the surgical procedure. In addition, subjects 021002 and 010001 were listed as CR's by the EAC but had biopsies positive for tumor. Please clarify these apparent discrepancies and provide a complete table of palliative and curative procedures with subject numbers and efficacy data per table 1 and question #1 above.

3. In the original BLA Section 3.2 of the Narrative Summary for Study 005/05, you mentioned that a total of 33 subjects in the talimogene laherparepvec arm underwent 35 surgical resections of melanoma. Please provide a tabular list of all subjects (and ID numbers) that had surgical resections after randomization, and indicate which individual subjects who achieved a CR or PR following resection of the tumor. From the PR.XPT dataset there appeared to be 102 subjects with listings "surgery" in column PRTRT. Please clarify how many of these procedures were palliative, how many were curative, and the nature of the additional surgical procedures.

4. On page 31 of your response to FDA questions submitted on 12-12-2014, you described Subject BVX00505-005006 who had responded in non-injected lesions: the L2 (baseline measure = 3 $cm^2$) and L3 (baseline measure = 3.6 $cm^2$) were -100% reduced from the baseline. However, from the CRF of the subject BVX00505-005006, L2 (measure =0 $cm^2$ at cycle 3) and L3 (measure =0 $cm^2$ at cycle 3) were "MERGED". It appears that the 3 lesions grew together and there was no response. Please confirm. We cannot locate any imaging for this subject in the Imaging Data USB drive you provided to us.

5. In your BLA original submission Supplemental Clinical Study Report: 005/05 Primary Overall Survival and Systemic Effect, you described the Subject 009010 (Narrative – Stage IVM1c Complete Response) with Figure 1: Subject 009010 showed injected skin lesions' response. However, we cannot locate any imaging for this subject BVX00505-005006 in the Imaging Data USB drive you provided to us. Please provide information regarding whether the subject's (009010) tumor response data were evaluated by the EAC.

6. Please clarify whether all the imaging data evaluated by the EAC were submitted to the FDA and if not, what was the basis of excluding the imaging data.

7. The protocol (section 5) states that dosing with either T-Vec or control will continue unless there is a clinically relevant Progression (PDr) after 24 weeks on study. From the DS.XPT dataset there appear to be 174 subjects (98 TVEC and 76 control) who discontinued the study on or before 24 weeks (DSDY $\leq$ 168) due to progression. Please confirm this analysis. Also for these subjects who discontinued prior to 24 weeks, is there any information in the CRF or elsewhere regarding the investigators rationale or justification for determining clinically relevant progression (PDr)?