BLA 125518 Amgen

December 19, 2014

We have the following clinical information requests:

1. In your safety reviews, you indicate that in the Primary Melanoma Analysis Set that there were 18 incidents of cellulitis in the talimogene laherparepvec arm and 2 in the GM-CSF arm. Please provide:
    a. The preferred term(s) that were used to establish these incidents
    b. The subject ID numbers for these incidents of cellulitis.
    c. The date of diagnosis of cellulitis.
    d. Clarification that the Primary Melanoma Analysis Set includes incidents of cellulitis if they occurred in 005/05E.
    e. The incidents of cellulitis for the Supportive Melanoma Analysis Set and the Program-Wide Analysis Set excluding the cases from 005/05.
    f. For all incidents of cellulitis- please provide timing with respect to the most recent treatment with either talimogene laherparepvec or GM-CSF.
    g. For all incidents of cellulitis – please provide its location with respect to the site of the injection of either talimogene laherparepvec or cellulitis.
    h. Best overall response for subjects with cellulitis.
    i. Please confirm if any subjects who achieved a durable response per protocol definition experienced cellulitis with their therapy.
    j. Information to determine if therapy was stopped for any subject with cellulitis.
    k. Information on whether or not the pattern of lesion injection was modified due to cellulitis for any of the subjects.

2. In the Program-Wide Analysis Set for safety, in study 005/04, subject (b) (6) initiated therapy on 7.12.2007, finished therapy on 9.21.2008 and died of respiratory failure on (b) (6) . Please clarify this apparent discrepancy.

3. On pg. 30 (Table of Contents – list of appendices) – Table 16.2 Patient Data Listings 16.2.1 Discontinued Subjects (Not Applicable) was not included. Please provide this information or confirm that it was provided in Table 14-1.1: Subject Disposition with Discontinuation Reason. Also see Figure IAS-1.1 - End of Treatment Reason by Treatment Duration (Integrated Summary of Safety Page 36) Please provide a tablular listing of subject discontinuations by reason for the same time periods listed in Figure IAS-1.1

4. Please provide for the Primary Melanoma Analysis Set, a safety evaluation to include: most common adverse events, serious adverse events, adverse events of interest, deaths, exposure, and progressive disease by cycle. This should include subjects in both arms not just the GM-CSF arm.

5. We note that in the Table 14-4.1.10. (Analysis of Subject Best Overall Response Based on Investigator <Intent to Treat Population>) on page 187 of the BLA Submission Clinical Study Report 005/05: response assessment based on investigator was not done for 19 of 141 subjects in the GM-CSF arm, and 8 of 295 subjects in the talimogene laherparepvec arm. We also note that in the Figure 9-1. (Subject Disposition) on page 65 of the BLA Submission Clinical Study Report 005/05: fourteen (14) subjects who

never received investigational product in the GM-CSF arm, and 4 subjects who never received investigational product in the talimogene laherparepvec arm. Please provide information regarding why response assessments based on investigator was not done for the 27 subjects.

6. We note from the Table 14-4.1.1 (Analysis of Subject Best Overall Response Based on EAC Assessment < Intent to Treat Population>>) on page 179 of the BLA Submission Clinical Study Report 005/05: response assessments were not reviewed by EAC for 122 of 141 subjects in the GM-CSF arm, and 171 of 295 subjects in the talimogene laherparepvec arm. Please provide information regarding where information is contained in the BLA regarding why these subjects' responses were not reviewed by the EAC or provide summary tabular information.

7. We note from the Table 14-4.1.10. (Analysis of Subject Best Overall Response Based on Investigator <Intent to Treat Population>) on page 187 of the BLA Submission Clinical Study Report 005/05: response assessment based on investigator was done for only 122 of 141 subjects in the GM-CSF arm, and 287 of 295 subjects in the talimogene laherparepvec arm. Please provide information regarding the reasons for these 27 missing investigator assessments.

8. We also note that in the Figure 14-4.1.3 (Best Tumor Response for Each Patient per Investigator <Intent to Treat Population>) on page 349 of the BLA Submission Clinical Study Report 005/05: 88 subjects in the GM-CSF arm and 208 subjects in the talimogene laherparepvec arm were assessed for tumor response. Please provide information regarding the discrepancy of the subject numbers in the Table 14-4.1.10 and Figure 14-4.1.3.

9. We note that in the Table 14-4.1.1 (Analysis of Subject Best Overall Response Based on EAC Assessment < Intent to Treat Population>) on page 179 of the BLA Submission Clinical Study Report 005/05: response assessment was reviews by EAC for 19 of 141 subjects in the GM-CSF arm, and 124 of 295 subjects in the talimogene laherparepvec arm. We also note that in the Figure 14-4.1.1 (Best Tumor Response for Each Patient per EAC <Intent to Treat Population>) on page 348 of the BLA Submission Clinical Study Report 005/05: 18 subjects in the GM-CSF arm and 122 subjects in the talimogene laherparepvec arm were assessed for tumor response. Please provide information regarding the discrepancy of the subject numbers in the Table 14-4.1.1 and Figure 14-4.1.1.

10. We note that in the Table 9-1 (Summary of Important Protocol Deviations (ITT Population)) on page 67 of the BLA Submission Clinical Study Report 005/05: there were total 5 subjects missing more than one clinical assessment (no subject in the GM-CSF arm, 5 subjects in the talimogene laherparepvec arm). When analyzed the BLA submission section 5.3.5.1 dataset rs.xpt, we identified 5 subjects missing more than one clinical assessment (2 subjects in the GM-CSF arm, 3 subjects in the talimogene laherparepvec arm – see **Table 1**). Please confirm that the table is correct, and provide information regarding the discrepancy of the treatment groups of subjects who missed more than one clinical assessment. Please also provide summarized tabular listings regarding total number of subjects, number of subjects missing visits, number of subjects missing clinical assessments, and number of subjects missing scans in both groups by treatment arms at each of the study follow-up time-points.

11. We note that in the Figure IAS-1.1. (End of Treatment Reason by Treatment Duration <Safety Population>) on page 36 of the BLA Submission Integrated Summary of Safety: there were higher percentage of subjects in the GM-CSF arm stopped treatment at the first few months of the study than that in the talimogene laherparepvec arm. We calculated number of subjects who continued treatment at evaluation time-points (**Table 2**), and number of subjects with response assessments at evaluation time-points (**Table 3**) based on the BLA data. Please confirm information in the Tables 2 and 3, or provide your corrected revised version of the tables based on your analysis of the data. Also please provide a survival curve comparing the end of study day by treatment arm.

12. We note that there were some dosing variations of talimogene laherparepvec administered to individual subjects. We therefore generated a table of dose exposure between response subgroups (Table 4). Please confirm this analysis information in tabular form based on your own analysis of the data, and provide 2 tables: one listing mean exposure by treatment arm in terms of mean and median viral dose and volume injected, including quartiles, and categorize by investigator response assessments: CR, PR, SD, PD or early withdrawal, and another table listing the same information on exposure by treatment group in terms of durable responses confirmed by the EAC vs no durable response. A graphical analysis of this data would also be helpful.

Table 1: Subjects with Missing Assessments

Subject	Treatment	Response	Assessed by	# Missing Visits
BVX00505-002003	T-VEC	SD	INVESTIGATOR	5
BVX00505-002015	GM-CSF	SD	INDEPENDENT ASSESSOR	6
BVX00505-014004	GM-CSF	SD	INDEPENDENT ASSESSOR	1
BVX00505-014007	T-VEC	PD	INVESTIGATOR	1
BVX00505-014011	GM-CSF	SD	INVESTIGATOR	3
BVX00505-028005	T-VEC	PD	INDEPENDENT ASSESSOR	2
029003	T-VEC	SD	INDEPENDENT ASSESSOR	1
033001	T-VEC	SD	INDEPENDENT ASSESSOR	2

Source: Adapted from BLA eCTD - RS.xpt dataset

Please confirm the following FDA analyses (see previous questions):

Table 2. Number of Subjects Continued Treatment at Evaluation Time-Points

Treat Arm	N at Randomization	At 3-month visit, Continued Treatment	At 6-month visit, Continued Treatment	At 9- month visit, Continued Treatment	At 12-month visit Continued Treatment	At 15-month visit, Continued Treatment	At18-month visit, Continued Treatment
T-Vec	296	210	124	70	30	19	5
G-MCSF	141	62	35	30	17	16	14

Source: Adapted from BLA eCTD Integrated Summary of Safety: Figure IAS-1.1 on Page 36.

Table 3. Number of Subjects with Response Assessments at Evaluation Time-Points

Treatment Arm	N at Randomization	At D36-visit, evaluation	At 2-month visit, C3D1 evaluations	At 3- month visit, C4D1 evaluations	At 6- month visit, C4D1 evaluations	At 9- month visit, C10D1 evaluations	End of study
T-Vec	296	276	260 (D66)	213 (D94)	152 (D179)	108 (D266)	245 (D269)
G-MCSF	141	99	79 (D58)	56 (D85)	27 (D172)	17 (D255)	113 (D135)

Source: Adapted from BLA eCTD RS.xpt dataset

Table 4. Exposure and Response of subjects treated with T-Vec

Response	**N Rows**	**Mean (EXVAMT)**	**Sum (EXVAMT)**	**Sum (EXDOSE) pfu**
No CR	260	2.95 ml	41.2 ml	3.8 x 10e9
CR	32	1.67 ml	33.4 ml	3.1 x 10e9
ALL	292	2.8 (0.3- 4.0)	40.3 (1.8 – 319.5)	3.8 x 10 e9

Source: Adapted from BLA eCTD EX.xpt dataset.

Table 14-1.1. Subject Disposition with Discontinuation Reason (study report p 122) appears to include only those patients who received study drug – we have generated the following table based on the randomized population – please confirm or provide a corrected table:

Table 5: FDA reasons for discontinuation

DSTERM	Total	N(GM-CSF)	N(T-VEC)
Total	434	140	294
ADVERSE EVENT	14	3	11
DEATH	8	3	5
FOLLOWED FOR SURVIVAL STATUS	2	2	0
LOST TO FOLLOW-UP	1	1	0
PATIENT HAS HAD PR OR CR FOR 6 CONTINUOUS MONTHS	42	0	42
PATIENT REACHED MAXIMUM ALLOWED NUMBER OF DOSES WITHOUT ACHIEVING 6 MONTHS OF PR OR CR	35	9	26
PHYSICIAN DECISION	12	5	7
PROGRESSIVE DISEASE	286	94	192
WITHDRAWAL BY SUBJECT	34	23	11

Source: Adapted from BLA eCTD DS.xpt dataset.