Davidson, Mark

From: Davidson, Mark
Sent: Friday, March 20, 2015 5:02 PM
To: 'Pernice, Michelle'
Subject: Amgen BLA 125518 Clinical/Statistical/Safety 3.20.15

Importance: High

Dear Michelle,

We have revised the Information Request that eliminated questions 4 and 5. Hopefully, now you all will not have to use your entire weekend to respond. Please see the request below concerning safety data that we need to complete our review. If all possible, please try to respond by Sunday 6 PM!

Thank You

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Please try to respond by Sunday 6 PM

Information Request/ Questions:

1. In reviewing the safety data, we have concerns about the compliance with the observation plan to obtain safety data per protocol after the cessation of study treatment in either arm. We note that CSR Table 12-1. provides a Summary of Study Treatment Exposure by treatment arm.

   In an exploratory FDA analysis of the SV dataset we have derived the mean and median end of study visits by days as follows:

Label	GM-CSF	T-VEC
Mean	134	262
Median	86	203.5

We subsequently arrived at the following comparison between the exposure and last visit day – showing that the last visit day was later than the treatment exposure.

Please confirm if this analysis of last visit week reflects the durations of safety follow-up:

Study Treatment Exposure vs last visit day

	Last visit (SVENDY) (as weeks) from SV dataset		**Table 12-1 Study Treatment Exposure**	
Label	**GM-CSF**	**T-Vec**	**GM-CSF**	**T-Vec**
Mean (weeks)	**19.1**	**37.4**	**15.76**	**26.8**
Median (weeks)	**12.2**	**29**	**10**	**23**

If not, please provide an analysis of mean and median treatment exposure times in weeks vs. safety follow-up.

2. In reviewing the safety data, we have concerns about the compliance with the observation plan to obtain safety data per protocol after the cessation of study treatment in either arm. Please provide an excel spreadsheet that includes the following information for all subjects on the trial 005/05 who were eligible for safety assessment (n= 419):

    - Unique patient number
    - Randomization date
    - Treatment assignment
    - Last date of study treatment
    - Last date when any safety assessment was done for toxicity
    - Date of the end of treatment visit (30 days +/-7 days after last injection).
    - Last date for any type of follow-up information

3. Regarding your efficacy analysis, we note that Table 10-4 provides a summary of Objective Response Rate by EAC and Investigators and includes a best overall CR rate of 43 (14.6) by investigators and 32 (10.8%) by EAC. Have you performed analysis of DURABLE CR rates by treatment arm?