ONYX
PHARMACEUTICALS
An Amgen subsidiary

650 266 0000
249 East Grand Avenue · South San Francisco California 94080

Date: 24 June, 2014

Dear Investigator:

Re: Carfilzomib – Important Safety Information Regarding Myelodysplastic Syndrome and Acute Myeloid Leukemia

Onyx, an Amgen subsidiary, would like to inform you of important new safety information with regards to subjects enrolled in clinical trials involving carfilzomib. This letter is being sent to all investigators participating in studies being conducted with carfilzomib.

Carfilzomib is a proteasome inhibitor being evaluated for the treatment of patients with multiple myeloma (MM) or other hematologic / solid tumors. There is an inherent increased risk of developing secondary malignancies in MM patients, including Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML) independent of therapy.

As part of Onyx's continuous evaluation of product safety information, 9 cases (4 MDS and 5 AML) were reported in subjects who received carfilzomib in clinical trials. Of the 9 cases, 4 (2 MDS and 2 AML) were reported by the investigator as related to carfilzomib. Of the 9 cases, 7 are from company-sponsored clinical trials and 2 are from investigator-sponsored trials (ISTs). A total of 2387 subjects have received at least one dose of carfilzomib in company-sponsored clinical trials and 1771 subjects have enrolled in ISTs.

A medical review of the 9 cases revealed that all of the events of MDS/AML were reported in the setting of underlying relapsed/refractory MM in subjects previously treated with multiple chemotherapy regimens and radiation. A meaningful causality assessment could not be made due to prior history of MDS and pretreatment with other chemotherapy agents including melphalan, lenalidamide and thalidomide. MDS and AML are documented in the labeling for these agents

Actions for Onyx

- Update the Informed Consent Form (ICF) (in the core Risk and Discomforts section)
- Update the Investigator's Brochure (IB)

Actions for the Investigator

- The revised ICF will be sent to you shortly. Please submit to your Ethics Committee/ Institutional Review Board as per your usual procedures and re-consent your subjects within 30 days after the ICF is approved.
- Until the updated consent form is received:
  - Amgen requests that investigators communicate, by phone or in-person, the safety findings described above to study subjects receiving investigational product within 30 days of receiving this letter.
  - For subjects who are not currently receiving study drug, but are still participating in the study, investigators are requested to communicate the safety findings at the next regularly scheduled contact with the subject.
  - Please ensure these communications to study subjects are documented in the source medical records for the subject.

Actions for the Investigator, continued

- Please file a copy of this letter in your trial file and submit a copy to your Ethics Committee or Institutional Review Board, if appropriate

If you have any questions regarding this letter, please contact Sanjay Aggarwal MB BChir (Cantab) at 650 266.1459 (office) or saggarwal@onyx com

Sincerely,

Barbara Klencke MD

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