Velcade (PS-341)

**Background**
- A first-in-class inhibitor of the 20S segment of the proteasome, the cellular component that regulates the degradation of many cell cycle control proteins.

**In Vitro Studies**
- Velcade® is rapidly cleared when administered i.v. and is unmeasurable in the bloodstream 20 minutes after administration.
- This formulation consists of 2.5 mg drug and 25 mg of mannitol, a commonly used pharmaceutical excipient. This formulation can be easily reconstituted into an aqueous solution at the time of administration.

**Pharmacokinetic (PK) and Pharmacodynamic (PD) Studies**
- The lyophilized product was stored at 5°C, ambient temperature, 37°C, and 50°C. Stability was monitored for approximately 18 months. Over this time period, there was no loss of drug in the lyophilized product stored at any temperature and no evidence of degradation product peaks in the HPLC chromatograms.
- Dose-related inhibition of the proteasome was observed at 1 hour.
- Graph shows results for 137 treated patients.

**Toxicology Studies**
- Clinical data.
- Maximum proteasome inhibition is 72%.

**Formulation and Clinical Batch Preparation**
- Precipic, Inc., the sponsor, provided NCI with a liquid formulation.
- When stored at 2–8°C, the liquid formulation was stable for longer than 6 months.

**Clinical Trial Experience**
- Based on toxicity studies, the starting dose for phase I trials was 0.13 mg/m2/dose (1/6 the maximum safe dose in primates).
- The goals of use of the 20S proteasome measurements are to:
  - Confirm inhibition of the biological target.
  - Use the pharmacodynamic (PD) end point in lieu of blood drug levels;
  - Confirm inhibition of the biological target;
  - Evaluate relationship of 20S inhibition with toxicity, PK, and activity.

**Graph**
- Graph shows results for 137 treated patients.

**Clinical data**
- Major response observed in multiple myeloma (as of 2004).

---

**NSC 681239**
**RECEIVED JULY 1995**
**DN2A JANUARY 1997**
**DN2B/III JUNE 1998**
**CLINICAL TRIAL JULY 1999**
**NDA MAY 2004**

---

**In Vivo Studies**
- Velcade® is rapidly cleared when administered i.v. and is unmeasurable in the bloodstream 20 minutes after administration.
- Velcade® exhibits a dose-dependent and reversible inhibition.

**Hollow Fiber (HF) Testing**
- All compounds met or exceeded criteria for activity.
- Analogs that exhibited potency in the DTP cell line screen were evaluated in the HF assay.
- The goals of use of the 20S proteasome measurements are to:
  - Confirm inhibition of the biological target.
  - Use the pharmacodynamic (PD) end point in lieu of blood drug levels;
  - Confirm inhibition of the biological target;
  - Evaluate relationship of 20S inhibition with toxicity, PK, and activity.

**Hollow Fiber (HF) Testing**
- Dose range 6.0 x 10-8 M to 4 x 10-7 M.
- Highest dose tested for each compound was 4 x 10-6 M.
- No other clinical signs of toxicity noted.

**HF Results**
- Dose range 6.0 x 10-8 M to 4 x 10-7 M.
- Highest dose tested for each compound was 4 x 10-6 M.
- No other clinical signs of toxicity noted.

**Radiolabeled DCI Studies**
- Rat Studies
  - Determination of 20S proteasome activity
  - 1 hour post-treatment at 1.96 mg/m2 showed a 70% decrease in activity

**Hollow Fiber (HF) Testing**
- No other clinical signs of toxicity noted.

**NCI Developmental Therapeutics Program**
- Clinical data.