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December 16, 2010

Accidental Overdose of POINT Study Drug

Dear POINT Study Team, Investigators and Coordinators

A POINT subject at one of our sites was randomized on December 3, 2010. This subject was given the loading dose of 8 tablets of study drug per protocol and was discharged. At home, the subject proceeded to take 8 tablets per day for the next 12 days. The subject's health is fine. There are no side effects to report.

The site will obtain a chemistry panel and a CBC that includes an assessment of platelet numbers today and again in one week. In the meantime the subject will receive no study drug and aspirin has been discontinued. If all is well after a 7-day treatment hiatus, the subject will resume taking study drug and aspirin. The blind will be maintained.

The Plavix® physician lead at sanofi-aventis informs us they have very few data/reported cases from clinical studies of repeated administration of a high-dose regimen of clopidogrel:

- High-dose regimen studied:

- We have single dose administration up to 900mg as loading dose in ACS patients (e.g. ISAR choice, ALBION),
- We have repeated dose administration up to 150mg (following a loading dose of 600mg) in ACS patients (e.g. CURRENT),
- But no repeated dose administration in patients or healthy volunteers above 150mg,
- Except increased risk of bleeding, no other adverse event has been reported as potentially linked to a high-dose regimen.

Further, no specific recommendations are provided since the physician lead believes this subject was managed adequately:

- With discontinuation and clinical/biological monitoring,
- Resuming treatment after 1 week of discontinuation is consistent with the mechanism of action of clopidogrel and platelet life,
- As usual, in case of bleeding, fresh platelet transfusion may be considered as an option to reverse the effect,
- It is certainly important to continue to monitor the subject closely up to the end of the study.

UCSF Neurology, Box 0114
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We should all learn from this to be especially careful in dispensing and instructing our subjects regarding the study drug. Please make sure you clarify that the daily dose is just one pill a day after the initial load.

Sincerely,

A handwritten signature in black ink, appearing to read "S. Claiborne Johnston". The signature is fluid and cursive, with a prominent initial "S" and a long, sweeping underline.

S. Claiborne Johnston, MD, PhD

A handwritten signature in black ink, appearing to read "J. Donald Easton". The signature is cursive and clearly legible, with a distinct "J" and "E".

J. Donald Easton, MD