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Protocol ABI-007-PANC-003

A Phase 3, Randomized, Multicenter, Open-Label, Randomized Study of nab®-Paclitaxel Plus Gemcitabine Versus Gemcitabine Alone As Adjuvant Therapy In Subjects With Surgically Resected Pancreatic Adenocarcinoma

PANC-003 Protocol Amendment 2 dated 03Dec2015: Clarification of Abraxane Infusion Time and Data Collection Criteria for a Potential Overdose on an Infusion Rate Basis

This memo provides clarification of Section 8.2.2 of the protocol, Overdose, which currently states: On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate; and on Section 11.1 Monitoring, Recording and Reporting of Adverse Events, which indicates the use of an Overdose CRF page

**Infusion time clarification**

In Protocol section 8.2: the protocol specified rate for nab-paclitaxel infusion is 30-40 minutes.

In clinical practice, from time to time, infusions may be completed faster than 30 minutes. From PK studies for nab-paclitaxel, an infusion completed in less than 25 minutes may increase C\text{max} by approximately 20% which is the threshold for clinical relevancy. Therefore, for infusions completed between 25 and 30 minutes, there is no clinical significance. Section 8.2.2 of the Protocol should have included guidance to reflect clinical practice and ensure that only clinically significant events are reported as overdoses. A nab-paclitaxel infusion completed in less than 25 minutes will meet the infusion rate criterion for an overdose and should be reported as such.

This change poses no risk to patient safety since the change in C\text{max} for the infusions between 25 and 30 minutes is not clinically significant. The overdose criteria specified above for nab-paclitaxel have been adopted as standard text in newer protocols. This change will not impact the conduct of the study, the scope of the study, the analysis of the study endpoints, or the validity of the study.

**Overdose CRF**

Section 11.1 Monitoring, Recording and Reporting of Adverse Events: states overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose CRF. However, the use of an overdose CRF was included in error when Protocol Amendment 1 was issued in June 2014, and the ABI-007-PANC-003 study does not have an
Overdose CRF page. Per the original protocol, an overdose, accidental or intentional, whether or not it is associated with an AE, or abuse, withdrawal, sensitivity, or toxicity to an investigational product should be reported as an AE. If an overdose is associated with an AE, the overdose and AE should be reported as separate events. Furthermore, if an overdose and the AE meet serious criteria, they should be reported to the GDSRM as separate SAEs.

Time for flushing the infusion line should not be counted together with infusion time. Following administration of nab-paclitaxel, the intravenous line should be flushed with sodium chloride 9mg/mL (0.9%) solution for injection to ensure administration of the complete dose, according to local practice.

No formal protocol amendment is planned to clarify the criteria for an overdose on an infusion rate basis.

This memo should be submitted to local IRBs and Ethics Committees, as applicable.

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