Monitoring Plan

”Stress Ulcer Prophylaxis with proton pump inhibitor (pantoprazole) in adult critically ill patients in the Intensive Care Unit: A randomized, blinded, placebo-controlled trial”, EudraCT no. 2015-000318-24

Prerequisites of the monitoring plan

This monitoring plan has been issued based on protocol version 3.0 and risk assessment of the trial performed in cooperation with sponsor according to SOP I02-16 Monitoring Plan of the GCP units.

Extent of the monitoring plan

This monitoring plan describes solely the quality control/monitoring that is done by the GCP units.

It may be necessary to carry out quality assurance/quality control of other procedures or parameters; this should be described and documented by sponsor.

Monitoring visits

Initiation of each site will be carried out. When the prerequisite to include trial subjects at a site has been fulfilled, this will be documented by the GCP units with written approval for trial start.

The first monitoring at each site will be scheduled immediately after the first trial subject is discharged from the Intensive Care Unit (ICU), or has completed 5 days of hospitalization at ICU, whichever comes first.

The GCP unit will hereafter carry out monitoring visits at each site in consideration of the agreed-upon monitoring level, inclusion rate and the needs of the site. The monitoring frequency is expected to be more frequent in the inclusion period. The GCP unit will be in contact with each site once annually as a minimum.

The Source Data Verification (SDV) will end at sponsor’s site, when data from all trial subjects has been entered at the 90 days follow-up registration in the CRF. The last monitoring visit at sponsor’s site will be scheduled, when the authorities have been informed off end of trial.

The monitoring will be completed at other sites, when data from the 90 days follow-up has been entered in CRF.

Monitoring of general protocol compliance and data quality

To verify that the site has implemented procedures to ensure good protocol compliance, it will be checked to extend possible for the GCP coordinator, that protocol specific procedures have been carried out as outlined in the protocol.

To verify that the site has implemented procedures to ensure good data quality, it will be verified, that all data are correctly registered in the CRF. Furthermore, it will be controlled, that the CRF data registration is complete and that corrections have been done correctly according to GCP.

The above will be done for the 3 first included trial subjects, hospitalized for a minimum of 4 days at each site and hereafter for randomly selected trial subjects until approximately 10% in total have been checked.

Since there is no added quality in monitoring all “Day Forms” for each trial subject with long stay in the

ITA, data monitored on day forms will be limited to the first 4 days of hospitalization. Remaining CRF pages will be monitored fully.

It will be evaluated, in cooperation with sponsor, if replacement of a primary project staff member should result in the selection of one new trial subject for 100% monitoring.

Monitoring of selected trial data

The monitoring strategy below is based on a risk assessment of the trial.

Project organisation

- It will be controlled on a regular basis, that project staff carrying out protocol-specific tasks have been delegated these tasks, and were relevant and adequate qualified at the time of delegation of these tasks
- It will be controlled on a regular basis that sponsor are distributing relevant documents and revised documents to participating sites

Data handling

- Source data verification of the primary effect parameter will be carried out for all included trial subjects
- For trial subjects with registered "Yes" on bleeding form in CRF, data registered and follow up actions according to protocol will be verified in the medical records
- It will be controlled on a regular basis, that Trial Master File contains updated documents, and current project documents are being used

Trial subjects' rights and general safety

- At each monitoring visit, the screening list will be controlled and it will be assessed if it is complete
- It will be verified for all trial subjects, that no protocol-specific actions have been performed prior to informed consent
- It will be verified for all trial subjects, that informed consent has been obtained by persons delegated this task
- It will be controlled for all trial subjects, that given oral and written information as well as the trial subject's consent, has been recorded correctly in the medical journal
- It will be controlled for all trial subjects, if consent from trial guardian, surrogate consent and consent of the trial subject if this persons regains his/her legal capacity, has been obtained

The following in- and exclusion criteria will be verified in the medical records and electronic patient systems for all trial subjects:

- Inclusion criteria:
  A minimum of one risk factor as defined in the protocol section 4.1 must be fulfilled

- Exclusion criteria:
  Contraindications to PPI
  Current daily treatment with PPI / H2RA
  GI bleeding during current hospitalization at ITA
  Diagnosed with ulcers during the current hospitalization at ITA
  Organ transplantation during the current hospitalization at ITA
  Note in medical record containing wording of withdrawal from active therapy or brain death
  Fertile woman with positive pregnancy test in urine human chorionic gonadotropin (hCG) or plasma-hCG

- It will be controlled on a regular basis that the inclusion of trial subjects is performed by qualified persons delegated this task
- For all trial subjects a review of the medical records will take place to ensure that fulfilment of selected withdrawal criteria during hospitalization at ICU, including withdrawal of consent, unacceptable side effects to the experimental treatment, SAR, and bleeding causing need of treatment with PPI or H2RA, has resulted in withdrawal from the trial

Examinations

No protocol-specific examinations are carried out in this trial.

Analyses

No protocol-specific analyses are carried out in this trial.

Trial medication

At initiation of the trial, the following will be controlled:

- Whether distribution of trial medication is documented and trial medication accountability is registered. This is done by verifying that shipment papers and delivery receipts correspond with listed trial medication in the SUP ICU medicine module, and the physical storage inventory.
- That documentation for the handling of trial medication, including the reception and preparation of study medication, is present at site
- That trial medication is stored correctly

At monitoring visits, the following will be controlled:

- If the first 3 trial subjects have received treatment in accordance with randomization and protocol. This is done by verifying that administration of trial medicine is signed for in the SUP-ICU's medicine module throughout the trial subject's stay at the ICU, as well as inconsistencies and deviations from the administration, are registered and explained correctly in the system. For these 3 the amount of dispensed medicine in the medicine module is compared with the inventory at each site.
- For every 20 trial subject per site, data in the medicine module is compared to data of the patient medical record, in order to verify correct administration of trial medication

Safety handling

Events and adverse reactions

- For trial subjects with registered "Yes" on SAR form in the CRF, data registered and follow up actions according to protocol will be verified in the medical records. This will be performed from inclusion up to 24 hours following last trial medication administration, or discharge from ICU, in order to verify that registration and reporting of SAR is complete and performed in a timely manner
- It will be verified that all SAR and SUSAR have been reported in a timely manner to Danish Health and Medicines Authority and Ethics Committee, and subsequently to investigators

Concomitant and contra-indicated medication

- It will be verified in the medical records for all trial subjects, if contraindicated medication, e.g. PPI, has been administered from inclusion to discharge from ICU, if the administration has been correctly entered in the CRF, and whether trial subjects has been withdrawn from the trial according to protocol

Monitoring of other departments

Monitoring of other departments is estimated to be irrelevant as they only carry out routine tasks.

Monitoring of CRF accountability

Study data is captured in eCRF, and CRF accountability is not relevant.

Monitoring of database

Sponsor has not requested the GCP unit to be involved in monitoring of the database.

Effective date

This monitoring plan becomes effective from the date of sponsor's acceptance of the monitoring plan.

Evaluation of the monitoring plan

The monitoring plan will be evaluated at as needed.

Furthermore, issues like e.g., protocol amendments, critical non-compliance, insufficient data quality and considerable changes of the project staff will lead to evaluation and potential revision of the monitoring plan.

All changes to the monitoring plan will be in writing.