Amendment to the previously approved protocol entitled 'Stress ulcer prophylaxis with proton pump inhibitor (pantoprazole) in adult critically ill patients in the intensive care unit: A randomised, blinded, placebo-controlled trial', version 3.0, October 20th 2015. EudraCT 2015-000318-24.

This amendment replaces Appendix 3 in the above mentioned protocol.

Appendix 3.1 Charter for the independent Data Monitoring and Safety Committee (DMSC)

Amendment June 23, 2017

Cancelation of the second interim analysis (2500/3350 included patients).

Due to the high inclusion rate, the SUP-ICU trial Steering Committee and Data Monitoring and Safety Committee (DMSC) has decided to cancel the second interim analysis as the results (incl. 90-day follow-up) will not be available until the trial has been completed.

The statement paper from the DMSC following the first interim analysis (1675/3350 included patients) supports this decision. The wording in the trial protocol, including appendix 3 has not been revised.

ClinicalTrials.gov Identifier: NCT02467621

Research ethical committee no: H-15003141

Introduction

The DMSC will constitute its own plan of monitoring and meetings. However, this charter will define the minimum of obligations and primary responsibilities of the DMSC as perceived of the steering committee (SC), its relationship with other trial components, its membership, and the purpose and timing of its meetings. The charter will also outline the procedures for ensuring confidentiality and proper communication, the statistical monitoring guidelines to be implemented by the DMSC, and an outline of the content of the open and closed reports which will be provided to the DMSC.

Primary responsibilities of the DMSC

The DMSC will be responsible for safeguarding the interests of trial patients, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. The DMSC will provide recommendations about stopping or continuing the trial to the SC of the SUP-ICU trial. To contribute to enhancing the integrity of the trial, the DMSC may also formulate recommendations relating to the selection/recruitment/retention of patients, their management, improving adherence to protocol-specified regimens and retention of patients, and the procedures for data management and quality control.

The DMSC will be advisory to the SC. The SC will be responsible for promptly reviewing the DMSC recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in trial conduct are required.

The DMSC is planned by protocol to meet physically in order to evaluate the planned interim analyses of the SUP-ICU trial. The interim analyses will be performed by an independent statistician selected by the members of the DMSC (to be announced). The DMSC may additionally meet whenever they decide or contact each other by telephone or e-mail in order to discuss the safety for trial participants. The sponsor has the responsibility to report the overall number of Serious Adverse Reactions (SARs) yearly to the DMSC. The DMSC can, at any time during the trial, request the distribution of events, including outcome measures and SARs according to intervention groups. Further, the DMSC can request unblinding of the interventions if suggested by the data, see section on 'closed sessions'. The recommendations of the DMSC regarding stopping, continuing or changing the design of the trial should be communicated without delay to the SC of the SUP-ICU trial. As fast as possible, and no later than 48 hours, the SC has the responsibility to inform all investigators of the trial and all the sites including patients in the trial, about the recommendation of the DMSC and the SC decision hereof.

Members of the DMSC

The DMSC is an independent multidisciplinary group consisting of clinicians and a biostatistician that, collectively, has experience in the management of ICU patients and in the conduct, monitoring and analysis of randomised clinical trials.

DMSC Members

Anders Åneman, MD PhD
Tim Walsh, professor, MD, PhD

DMSC Biostatistician

Aksel Karl Georg Jensen, Section of Biostatistics, University of Copenhagen

Conflicts of interest

DMSC members will fill in and sign a declaration of conflicts of interests see *appendix* 13. DMSC membership has been restricted to individuals free of conflicts of interest. The source of these conflicts may be financial, scientific, or regulatory in nature. Thus, neither trial investigators nor

individuals employed by the sponsor, nor individuals who might have regulatory responsibilities for the trial products, are members of the DMSC. The DMSC members do not own stock in the companies having products being evaluated by the SUP-ICU trial.
The DMSC members will disclose to fellow members any consulting agreements or financial interests they have with the sponsor of the trial, with the contract research organisation (CRO) for the trial (if any), or with other sponsors having products that are being evaluated or having products that are competitive with those being evaluated in the trial.
The DMSC will be responsible for deciding whether these consulting agreements or financial interests materially impact their objectivity.
The DMSC members will be responsible for advising fellow members of any changes in these consulting agreements and financial interests that occur during the course of the trial. Any DMSC members who develop significant conflicts of interest during the course of the trial should resign from the DMSC.
DMSC membership is to be for the duration of the clinical trial. If any members leave the DMSC during the course of the trial, the SC will appoint the replacement(s).

Formal interim analyses meeting

Two formal interim analysis meetings will be held to review data relating to treatment efficacy, patient safety, and quality of trial conduct. The three members of the DMSC will meet when 90-day follow-up data of 1650 (approximately 50% of sample size estimation) and 2500 (approximately 75% of sample size estimation) patients have been obtained.

Proper communication

To enhance the integrity and credibility of the trial, procedures will be implemented to ensure the DMSC has sole access to evolving information from the clinical trial regarding comparative results of efficacy and safety data, aggregated by treatment group. An exception will be made to permit access to an independent statistician who will be responsible for serving as a liaison between the database and the DMSC.
At the same time, procedures will be implemented to ensure that proper communication is achieved between the DMSC and the trial investigators. To provide a forum for exchange of information among various parties who share responsibility for the successful conduct of the trial, a format for open sessions and closed sessions will be implemented. The intent of this format is to enable the DMSC to preserve confidentiality of the comparative efficacy results while at the same time providing opportunities for interaction between the DMSC and others who have valuable insights into trial-related issues.

Closed sessions

Sessions involving only DMSC membership who generates the closed reports (called closed sessions) will be held to allow discussion of confidential data from the clinical trial, including information about the relative efficacy and safety of interventions. In order to ensure that the DMSC will be fully informed in its primary mission of safeguarding the interest of participating patients, the DMSC will be blinded in its assessment of safety and efficacy data. However, the DMSC can request unblinding from the SC.

Closed reports will include analysis of the primary outcome measure. In addition, analyses of the secondary outcome measures and SARs will also be reported. These closed reports will be prepared by independent biostatistician being a member of the DMSC, with assistance from the trial data manager, in a manner that allow them to remain blinded.

The closed reports should provide information that is accurate, with follow-up on mortality that is complete to within two months of the date of the DMSC meeting.

Open reports

For each DMSC meeting, open reports will be provided available to all who attend the DMSC meeting. The reports will include data on recruitment and baseline characteristics, and pooled data on eligibility violations, completeness of follow-up, and compliance. The independent statistician being a member of the DMSC will prepare these open reports in co-operation with the trial data manager.

The reports should be provided to DMSC members approximately three days prior to the date of the meeting.

Minutes of the DMSC Meetings

The DMSC will prepare minutes of their meetings. The closed minutes will describe the proceedings from all sessions of the DMSC meeting, including the listing of recommendations by the committee. Because it is possible that these minutes may contain unblinded information, it is important that they are not made available to anyone outside the DMSC.

Recommendations to the Steering Committee

After the interim analysis meetings, the DMSC will make a recommendation to the SC to continue, hold or terminate the trial.

Interim analyses will be conducted after patient no. 1650 and 2500 has been followed for 90 days. The DMSC will recommend pausing or stopping the trial if group-difference in the primary outcome measure, SARs or SUSARs are found at the interim analyses with statistical significance levels adjusted according to the LanDeMets group sequential monitoring boundaries based on O'Brien Fleming alfa-spending function [69]. If an analysis of the interim data from 1650/2500 patients fulfils the LanDeMets stopping criterion the inclusion of further patients will be paused and an analysis including patients randomised during the analysis period will be performed. If this second analysis also fulfils the LanDeMets stopping criterion according to the group sequential monitoring boundaries the DMSC will recommend stopping the trial [67]. Furthermore, the DMSC can recommend pausing or stopping the trial if continued conduct of the trial clearly compromises patient safety. However, stopping for futility to show an intervention effect of 15% RRR will not be an option as intervention effects less than 15% RRR of all-cause mortality may be clinically relevant as well.

This recommendation will be based primarily on safety and efficacy considerations and will be guided by statistical monitoring guidelines defined in this charter and the trial protocol.

The SC is jointly responsible with the DMSC for safeguarding the interests of participating patients and for the conduct of the trial. Recommendations to amend the protocol or conduct of the trial made by the DMSC will be considered and accepted or rejected by the SC. The SC will be responsible for deciding whether to continue, hold or stop the trial based on the DMSC recommendations.

The DMSC will be notified of all changes to the trial protocol or conduct. The DMSC concurrence will be sought on all substantive recommendations or changes to the protocol or trial conduct prior to their implementation.

Statistical monitoring guidelines

The outcome parameters are defined in the statistical analyses plan in the protocol. For the two intervention groups, the DMSC will evaluate data on:

<u>The primary outcome measure</u>

Mortality 90 days after randomisation of each patient ("landmark mortality").

The secondary outcome measures

- Proportion of patients with one or more of the following adverse events: clinically important gastrointestinal (GI) bleeding, pneumoni, *clostridium difficile* infection (CDI), and acute myocardial ischemia
- Proportion of patients with clinically important GI bleeding
- 1 year mortality post-randomisation
- The occurrence of SARs in the ICU

The DMSC will be provided with these data from the coordinating centre as:
Number of patients randomised
Number of patients randomised per intervention group
Number of patients stratified pr. stratification variable per intervention group
Number of events, according to the outcomes, in the two groups

Based on evaluations of these outcomes, the DMSC will decide if they want further data from the coordinating centre and when to perform the next analysis of the data.

For analyses, the data will be provided in one file as described below.

DMSC should yearly be informed about SARs occurring in the two groups of the trial.

The DMSC may also be asked to ensure that procedures are properly implemented to adjust trial sample size or duration of follow-up to restore power, if protocol specified event rates are inaccurate. If so, the algorithm for doing this should be clearly specified.

Conditions for transfer of data from the Coordinating Centre to the DMSC
The DMSC will be provided with a file containing the data defined as follows:

Row 1 contains the names of the variables (to be defined below).

Row 2 to N (where N-1 is the number of patients having entered the trial) each contains the data of one patient.

Column 1 to p (where p is the number of variables to be defined below) each contains in row 1 the name of a variable and in the next N rows the values of this variable.

The values of the following variables should be included in the database:

1. screening_id: a number that uniquely identifies the patient

2. rand_code: The randomisation code (group 0 or 1). The DMSC is not to be informed on what intervention the groups received

3. clin_imp_bleed: clinically important GI bleeding (1 if the patient had one or more episodes and 0 if the patient did not)

4. pneumonia: onset of pneumonia in the ICU after randomisation (1 = one or more episodes, 0= no episodes)

5. clostridium: *clostridium difficile* infection (1 = one or more episodes, 0= no episodes)

6. ami: acute myocardial ischemia in the ICU (1 = one or more episodes, 0= no episodes)

7. SAR_indic: SAR indicator (1 = one or more SARs, 0 = no SARs)