GODIF

Amendment to protocol

Trial drug for the GODIF trial

The trial drug for the GODIF trial is currently produced by The Capital Region Pharmacy in Herlev, Denmark. The pharmacy has a license to produce and distribute medicine for clinical trials from the Danish Medicine Agency.

The trial drug furosemide is produced at a concentration of 10 mg/ml, identical to the furosemide on the commercial market. The trial drug placebo is isotonic saline (NaCl 0.9%) identical to NaCl 0.9% for intravenous infusions on the commercial market.

The trial drug is produced in identical vials of 50 ml to ensure blinding and easy handling (section 3.3 of the protocol). The trial drug is distributed from The Capital Region Pharmacy to the sites at Sponsor's expense.

The GODIF trial is currently approved in Denmark, Norway, Finland, Iceland, and The Netherlands. More countries are expected to seek approval.

In case the trial drug from The Capital Region Pharmacy cannot be approved by legal authorities in other countries, the management committee will allow participation with the use of shelf medication.

In this case, the blinding will be maintained by the following procedure: a dedicated team of unblinded trial site staff. They will have a personal login to the GODIF database with only access to the allocated treatment. The unblinded team will be responsible for preparing the trial drug from furosemide 10 mg/ml or NaCl 0.9% from shelf medication. The trial drug must be prepared in 50 ml syringes for an infusion pump or similar device according to the common practice at the site. The preparation must look identical for both furosemide and placebo to maintain blinding and it must be delivered to the participant ready to infuse. The unblinded team cannot be involved in the treatment or care of the participant, entry of outcome data in the database, statistical analyses, or other aspects of the trial. The Sponsor will not provide the drugs but pay an extra fee of 75 euros in compensation for the medicine for every included participant.

The method with an unblinded third party to prepare and deliver the trial drug in a blinded form to the participants is widely used and we consider it appropriate for the GODIF trial too. The aim to allow this change is to be able to include more countries and sites in the trial which will deliver data from a broader population of critically ill patients and results with a broader relevance.

It can be speculated that the change in the blinding procedure can affect the outcome of the trial. For that reason, we will perform a subgroup analysis of the primary outcome to assess heterogeneity between countries. It will be made clear which blinding procedure the countries have been using. It will be published in the primary paper of the trial.