Annual Safety report GODIF trial

EudraCT number	**2019-004292-40**
Clinical Trial Title	**Goal directed fluid removal with furosemide in intensive care patients with fluid overload – A randomised, blinded, placebo-controlled trial (GODIF).**
Sponsor	**Morten Bestle**
Designated reporter	**Sine Wichmann**
Danish Medicines Agency Journal Number	**2019121067**
Ethics Committees case number	**H-19080597**
Date of the initial authorisation	**February 29, 2020**

Period of reporting: January 1, 2022 to December 31, 2022.

SAR in the period of reporting: 158 included patients. Number of SARs: 14.
Number of patients with SARs: 6

SUSAR in the period of reporting: 158 included patients, 0 SUSAR.

Conclusions on observed SAR/SUSAR:
The number of patients with one or more of the following SARS:

11	Severe electrolyte disturbance (p-K < 2.5 mmol/L, p-Na < 120 mmol/L, p-Cl < 90 mmol/L)
0	Aplastic anaemia
0	Agranulocytosis
0	Pancreatitis
3	Circulatory collapse leading to cardiac arrest
0	Seizures because of furosemide-induced low calcium or magnesium
0	Steven Johnsons syndrome
0	Toxic epidermal necrolysis
0	Hearing impairment/loss
0	Anaphylaxis

Three participants experienced low plasma chloride. One participant had plasma chloride ranging between 80-87 mmol/L for 5 days (counting as five SARs). The clinicians assessed that the treatment of severe fluid accumulation had to continue. The intervention continued and the electrolytes were monitored closely without intervention. One participant experienced plasma chloride of 80-84 mmol/L for two following days (counting as two SARs). The clinicians chose to observe closely without treatment. They did not relate the low plasma chloride to the intervention. A third participant experienced low plasma chloride of 86-89 mmol/L for 4 days (counting as 4 SARs). The participant was not responding to the trial drug and continued

to accumulate fluid on a maximum infusion of the trial drug (4 ml/h of furosemide 10 mg/ml or placebo (saline)). For that reason, the clinicians did not relate the low chloride to the intervention and monitored the condition closely. Eventually, the patient was withdrawn from the study because the clinicians found it necessary to treat the increasing fluid overload. They wanted to treat with open-label furosemide. None of the participants, with low plasma chloride, were affected by it.

Three participants experienced circulatory collapse leading to cardiac arrest.
After enrolment in the trial one participant developed septic shock, severe gastrointestinal bleeding, and during placement of a central line the patient developed bradycardia resulting in cardiac arrest. The participant got resuscitated and transfused with 4.7 litres of blood products. After stabilisation, the GODIF intervention was restarted. Four days later the cardiac arrest the active treatment was stopped due to anoxic brain damage visualised on MR-C and EEG. Further treatment could not save the patient and was stopped. The patient died.
The second participant experienced circulatory collapse leading to cardiac arrest due to the development of cardiac tamponade. The participant was resuscitated and operated on. The cardiac arrest was not due to the trial drug or the intervention of the trial.
The third participant had an unexplained cardiac arrest. The participant was resuscitated and stabilized and afterwards, the treating physicians assessed it to be safe to continue in the GODIF trial.

The listed SARs to the trial drug (furosemide/placebo) are documented each day for all patients without the clinicians deciding on a causal relationship between the trial drug and SARs observed.

Benefit-risk evaluation:
The reported cases did not give rise to any new safety concerns as all patients are closely monitored in the Intensive Care department. Risks and benefits for the patients are considered unchanged.

Implication for the clinical trial population:

Change in /amendment to protocol	☐ YES	☒ NO
Change in study procedures	☐ YES	☒ NO
Change in patient information	☐ YES	☒ NO
Change in informed consent form	☐ YES	☒ NO

Date: January 10th, 2023 **Signature**: