GODIF

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, 2023 to December 31, 2023.

SAR in the period of reporting: 405 included patients. Number of SARs: 14.
Number of patients with SARs: 9

SUSAR in the period of reporting: 405 included patients, 0 SUSAR.

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

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

Eight times low plasma chloride was reported in four participants. The measurements were between 79 and 89 mmol/L. The low plasma chloride was monitored closely and spontaneously resolved in all patients. The incidents with low chloride did not affect the trial intervention, which was assessed safe to continue.

Three participants experienced circulatory collapse leading to cardiac arrest. The first patient developed hypotension and agonal respiration during mobilisation. The collapse was resistant to increasing doses of noradrenaline. The patient had a do-not-resuscitate decision in the patient file, so further intervention was

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not done, and the patient died. The patient had not responded to the trial drug, so fluid removal was not a reason for the hypotension and collapse and was not associated with the intervention. The second patient with circulatory collapse leading to cardiac arrest was caused by a medicine administration mistake and not related to the trial drug. The case was handled according to protocol/law for such incidents. The third patient was admitted to the hospital due to severe ischemic cardiac disease and treated with cardiac catheterisation, ECMO, and Impella. On the 8th day of the trial, the patient developed ventricular fibrillation and died. The possible reason for the incident is assessed to be hyperkalaemia and ischemic heart disease which was the reason for the hospital admission.

Two participants reported a degree of hearing impairment. One patient was withdrawn from the study due to possible relation with the trial drug. The second patient reported impaired hearing 44 days after enrolment in the trial. The patient had received the trial drug intermittently and received several other ototoxic medicines during the ICU admission. The trial drug may have affected the patient's hearing.

One patient developed agranulocytosis on study day 79. The patient had received 11 different medicaments which could potentially induce leukopenia during the admission. Ceftazidime was stopped and the trial drug was paused. The leukopenia resolved quickly. It was assessed that ceftazidime was the cause of the agranulocytosis and the trial drug was restarted without affecting the leucocyte count afterwards.

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: 15/1-2024

Signature: Sponsor