Simplified Annual Safety Report

Title of study	Goal-directed fluid removal with furosemide in intensive care patients with fluid overload: a randomised, blinded, placebo-controlled trial (GODIF)
Investigational Medicinal Product(s) (active substance – brand name – ATC code)	Furosemide, ACT C03CA01
☒ I confirm the IMP(s) is/are authorized and the SmPC is used as RSI.	
ASR Number	5
Period covered	01.01.2025 to 31.12.2025
Name Sponsor	Morten Bestle
Address	Nordsjaellands Hospital, Dyrehavevej, 29, 3400 Hilleroed, Denmark
Date of the report	30.01.2026
Relevant study (EU CT number and internal number)	2024-512186-14-00
Note: - This ASR contains safety information about one active substance belonging to two investigational medicinal products (IMPs) from an investigator-initiated clinical trial. The principal investigator has no access to information from other sponsors conducting trials with the same IMPs. - This ASR Report contains confidential information - This report includes unblinded adverse event data, if applicable.	

Abbreviations

AxMP	Auxiliary Medicinal Product
AKI	Acute Kidney Injury
ASR	Annual safety report
CA	Competent Authority
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
IMP	Investigational Medicinal Product
MedDRA	Medical Dictionary for Regulatory Activities
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics

Executive Summary

This ASR contains safety information about furosemide from an investigator-initiated, blinded, placebo-controlled clinical trial. The Sponsor is not the marketing authorisation holder and thus has no access to information on manufacturing issues, non-clinical data, the marketing status, or any aspects of the IMP's development beyond the clinical trial covered in this ASR.

The GODIF trial was transitioned to CTIS in November 2024. This is the fifth ASR, and this is the first time this ASR template has been applied. The trial is multinational, and the following countries were active in 2025: Denmark, the Netherlands, Switzerland, and Australia. Sweden has approved the trial, but it was never initiated and ended/terminated as a member state in 2025. The Czech Republic and Lithuania approved the trial in 2025, but they did not start the recruitment in 2025.

The first ASR covered the period from 17th August 2020 to 31st December 2020, and the following ASRs covered the whole year from 1st January to 31st December.

In the GODIF trial, **furosemide 10 mg/ml is the investigational drug**. It is a blinded trial, and half of the patients receive furosemide, and the other half receive a placebo (saline). The drug is administered as an infusion and titrated to effect and protocolised goal for daily fluid removal. The infusion is titrated within the interval of 0 mg/h to max 40 mg/h (equal to 0-4 ml/h). When a neutral fluid status is achieved, the trial drug is paused/stopped. It is only administered during ICU stay.

Initially, the trial was approved with a trial drug produced by The Capital Region Pharmacy in Denmark. The pharmacy has a license to produce and distribute trial drugs. The pharmacy does not produce furosemide or saline for the market and does not have its own SmPCs. The trial was approved with SmPC from Accord both in Denmark and the Netherlands. The trial has been approved without an SmPC for saline. A simplified IMPD for both placebo and furosemide with a certificate of compliance and release, and a certificate of analysis of the produced furosemide were approved, and GMP documents were provided and approved. Denmark and the Netherlands conduct the trial using the trial drug manufactured and distributed in Denmark. The trial was also conducted in Norway, Iceland, and Finland with the Danish-produced trial drug; however, these countries were terminated before the transition to CTIS.

An amendment to the protocol from 14th April 2024 allowed new countries to participate in the trial with their own furosemide and saline with marketing authorisation and perform the blinding on-site. Following, all new additional member states have used their own medicine with ACT codes (Switzerland and Australia, and it will apply to Lithuania and the Czech Republic too).

ACT code for furosemide: C03CA01

In this report, we will only report data for patients randomised in the trial in 2025. We refer to the former ASR for data from the previous years.

In 2025, 162 participants were enrolled, 7 in Australia, 16 in the Netherlands, 24 in Switzerland and 115 in Denmark.

The trial is blinded with an allocation ratio of 1:1 to furosemide and placebo, so we expect that approximately 81 participants have received furosemide and 81 placebo. We are not able to provide data on the cumulative dose due to blinding of the trial design and titration of the trial drug to effect. These data will be available after unblinding of the trial.

Summary of the overall safety assessment:

According to the approved protocol, a predefined list of potential suspected adverse reactions (SARs) to the trial drug (furosemide) must be documented for all patients on all trial days. If any listed SAR is observed, the event has been reported to the sponsor, even when the treating clinician assessed that there is no causal or possible relationship between the trial drug and the observed event. This approach was chosen to minimise the risk of underreporting SARs. According to the mandatory ASR template, only SARs assessed as related or possibly related to the intervention must be reported. Applying this requirement represents a change in our reporting practice for this trial and will result in fewer reported events.

Four SARs with possible relation to the intervention had been reported and all have been resolved.

We have observed no new safety issues.

No SUSARS have been reported during the conduct of the trial.

Summary of important risk:

We have identified no new risks.

No actions have been taken for safety reasons.

Conclusion: The reported SARs did not give rise to any new safety concerns; all events were resolved. Risk and benefits for the patients are considered unchanged.

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1. Introduction

ASR number: 5

Reporting period: 01.01.2025 to 31.12.2025

Trial intervention: Furosemide 10 mg/ml administered as an IV infusion in a titratable dose of 0-40 mg/h. The drug is titrated according to effect and goal for daily fluid balance in ICU patients with fluid overload.

The GODIF trial is an investigator-initiated, randomised, blinded trial investigating goal-directed fluid removal in adult ICU patients with at least 5% of fluid accumulation in the body. Fluid accumulation/fluid overload is associated with increased morbidity and mortality.

The trial investigates whether early goal-directed fluid removal (1 ml/kg of body weight/h) with furosemide versus placebo until a neutral fluid status is achieved will improve patient-important outcomes. The intervention is conducted during admission to the ICU.

ACT code for furosemide: C03CA01 used in Switzerland and Australia. Furosemide, used in Denmark and the Netherlands, is produced by the Pharmacy of the Capital Region of Denmark. Reference SmPC from Accord. The comparator is saline (NaCl 0.9%), used as a placebo.

2. Worldwide marketing approval status

Not applicable.

3. Actions taken in the reporting period for safety reasons

We have taken no actions for safety reasons during the reporting period of this ASR and have received no requests that place limitations on our study.

4. Changes to reference safety information

As reference safety information (RSI), the Summary of Product Characteristics (SmPC) is used, which was in effect at the beginning of the reporting period. The English version of the SmPC dated 20th of July 2020 is provided with the submission.

5. Inventory of clinical trials ongoing and completed during the reporting period

Overview of the ongoing Study Furosemide

EU CT number	**Internal protocol number**	**Country**	**Study design (including randomisation ratio)**	**Study population**	**Start date**	**Planned enrolment**	**Subject exposure ****
2024-512186-14-00	GODIF trial	Denmark, the Netherlands, Australia and Switzerland. Sweden has never started and ended in 2025 as an MSC.	A controlled, double-blinded, parallel trial. 1:1 allocation to furosemide and placebo (saline)	Adult ICU patients (>18 years of age), acutely admitted, clinically stable and with fluid overload of at least 5% of ideal body weight.	DK: 02.06.2021 NL: 30.08.2023 CH: 02.10.2023 AU: 06.06.2025 SE: NA	500 will receive furosemide, and 500 will receive a placebo (saline)	778 participants have been enrolled since initiation of the trial. In 2025, 162 patients were enrolled. Participants included per country in 2025: DK: 115 NL: 16 CH: 24 AU: 7 SE: 0 As it is a blinded trial, we do not have the exact numbers. We expect that 50% received furosemide and 50% placebo (saline)
******Based upon total number of patients recruited as of 31.12.2025 and applied randomisation schemes							

The trial has not been completed during the reporting period.

6. Estimated cumulative exposure

6.1. Cumulative subject exposure in the study(ies)

Treatment	Number of subjects
Drug (furosemide)	An estimate of 81 in 2025. For the entire trial period until 31.12.2025 the estimate is 389 participants
Comparator	
Placebo	An estimate of 81 in 2025. For the entire trial period until 31.12.2025 the estimate is 389 participants

The numbers are estimated, as it is a blinded trial.

6.2. Patient exposure from marketing experience

Not applicable. The study drug is not marketed by the sponsor.

7. Data in line listings and summary tabulations

7.1. Reference information

The Medical Dictionary for Regulatory Activities (MedDRA) was used for the coding of adverse events.

Please refer to section 4 with respect to information on the RSI.

7.2. Line listings of serious adverse reactions during the reporting period

SARs reported from 1st January to 31st December 2025, at least possibly related to IMP

Case ID/ Subject number*	Country Gender Age	Serious adverse drug reactions (SARs)	Expected/unex-pected	Date of onset** Time to onset**	Outcome	Suspect Drug	Daily dose Route Formulation	Dates of treatment Treatment duration	Comments

DK01338 Rigshospi-talet	Denmark, Male, 44 years	Low potassium of 2.1 mmol/L (metabo-lism and nutrition disorders)	expected	16.01.2025 eight days after initiating the trial drug	Resolved Substitu-ted with potassium chloride and the potassium level normali-sed.	Furose mide	No fixed daily dose. The medicine is titrated to effect. At the day of the event (24 h) the patient received 19.9 ml trial drug. If it were furose-mide, it would equal 199 mg	08.01 to 16.01 2025	The patient was known to have a tendency to low potassium and had experienced potassium down to 2.1 mmol/L before entering the trial. The patient experienced no clinical symptoms from the low potassium
CH01110 Bern University Hospital	Switzer-land, Female, 66 years	Circulatory collapse leading to cardiac arrest (cardiac disorders)	expected	23.01.2025 eleven days after initiating the trial	Resolved	Furose mide	No fixed daily dose. The medicine is titrated to effect. On the day of the event (24 h), the patient did not receive the trial drug, but the patient received trial drug the day before	13.01 to 22.01 2025	The patient had severe hypotension and sinus arrest. Seven litres of ascites had been removed, and thiazides and spironolac-tone were also administered that day. The trial drug was stopped the day before. It was assessed that the trial drug probably contributed to the event. The patient survived.

DK04105 Aalborg University Hospital	Denmark, Female, 77 years	Low chloride <90 mmol/L (asymptomatic) (metabolism and nutrition disorders)	expected	30.05 to 02.06 Four days with low chloride	Resolved	Furosemide	No fixed daily dose. The medicine is titrated to effect. The average dose on the 4 trial days with low chloride was 94 ml. If it were furosemide, it would equal 940 mg	05.05 to	Develops low chloride after 7 days of treatment with the trial drug and 6 days with thiazides. Trial drug and thiazides were then paused. After 4 days, the trial drug, extra escape furosemide, were administered for several days due to fluid overload and respiratory failure. The trial drug was assessed to contribute to the low chloride in the blood.
DK05036 Regionshospitalet Randers	Denmark, Female 66 years	Low chloride <90 mmol/L (asymptomatic) (metabolism and nutrition disorders)	Expected	04.11 to 08.11 Five days with low chloride	Resolved	Furosemide	No fixed daily dose. The medicine is titrated to effect. The doses administered over the 5 days were between 3 to 26 ml which equals 30 to 260 mg of furosemide	04.11 to 11.11 2025	Chloride drops below 90 and down to 82 during the first 5 trial days. The trial drug is assessed to contribute to the low chloride
*Study/Center/subject **Primary SAR only									

7.3. Cumulative summary tabulations of serious adverse events

The table below shows the cumulative number of SAEs reported during this clinical trial, irrespective of whether they were considered causally related to the intervention or not. Organised by system organ class.

System organ Class		
Preferred term	Study drug (furosemide or placebo)	Code unbroken
Cardiac disorders		
- New onset atrial fibrillation	39	0

- Acute myocardial ischemia	1	0
Renal and urinary disorders - New episode of AKI stage 3	16	0
Nervous system disorders - Cerebral ischemia	10	0
Gastrointestinal disorders - Intestinal ischemia	8	0
Vascular disorders - Limb ischemia	3	0
Total number on the 31.12.2025	77	0

8. Significant findings from clinical trials during the reporting period

8.1. Completed clinical trials

Not applicable.

8.2. Ongoing clinical trials

This ASR contains safety information from this investigator-initiated clinical trial only, and it is ongoing. No further updates available

8.3. Long-term follow-up

Not applicable.

8.4. Other therapeutic use of investigational drug

Not applicable.

8.5. New safety data related to combination therapies

Not applicable.

9. Safety findings from non-interventional studies

Not applicable.

10. Other clinical trial/study safety information

Not applicable

11. Safety findings from marketing experience

Not applicable

12. Non-clinical data

Not applicable

13. Literature

A review of the scientific, peer-reviewed literature was conducted during the duration of the current reporting period. In the searches performed, we identified no new relevant safety findings for furosemide.

14. Other DSURs

Not applicable

15. Lack of efficacy

Not applicable

16. Region-specific information

a. Cumulative summary tabulation of serious adverse reactions:

The trial has been active since 2020 and was transferred to CTIS in November 2024. In previous annual safety reports, data on ten predefined SARs were reported irrespective of whether a causal relationship to the trial drug was assessed as possible. In accordance with the requirements of the current ASR template, only events considered probably related to the trial drug must be reported. These events are presented in the table below; consequently, the number of reported events differs from that in previous reports.

A total of 14 events were classified as SARs with a possible causal relationship to the trial drug. Thirteen events occurred in Denmark and one in Switzerland.

Eight events involved severe electrolyte disturbances and were assessed as possibly related to the trial drug (furosemide/placebo). In all eight cases, the patients were asymptomatic.

Three patients experienced a circulatory collapse leading to cardiac arrest during the trial in the ICU. The intervention is fluid removal (furosemide/placebo), and in these three cases, there was a probability that the intervention contributed to the event. One patient survived.

Three patients experienced impaired hearing in conjunction with the ICU admission, and a possible relation to the trial drug was assessed possible.

System organ Class		
Preferred term	Study drug (furosemide or placebo)	Code unbroken

metabolism and nutrition disorders: Severe electrolyte disturbance: K<2.5 mmol/L or Na<120 mmol/L or Cl<90 mmol/L	**Total: 8** Chloride <90 mmol/L: 7 (DK) Potassium < 2.5 mmol/L: 1 (DK) Sodium < 120 mmol/L: 0	No
Cardiac disorders: Circulatory collapse leading to cardiac arrest:	**Total: 3** 2 (DK) 1 (CH)	No
Ear and labyrinth disorders: Hearing impairment/loss:	**Total: 3** 3 (DK)	No
Total number on 31.12.2025	**14 SARSs, 13 in DK and 1 in CH**	No

b. List of subjects who died during the reporting period:

In the table below, trial participants included and died during the reporting period 01.01.2025 to 31.12.2025 are listed. Data on mortality are within the 90-day follow-up period. We do not have data on the cause of death in the majority of cases.

The trial is blinded, so allocation of furosemide/placebo is not available

Case ID/ Subject number*	**Site/country**	**Causality to study drug**	**Cause of death/comments**
DK01343	Rigshospitalet/DK	No	
DK01346	Rigshospitalet/DK	No	
DK01347	Rigshospitalet/DK	No	
DK01360	Rigshospitalet/DK	No	
DK01361	Rigshospitalet/DK	No	
DK01364	Rigshospitalet/DK	No	
DK01372	Rigshospitalet/DK	No	
DK01382	Rigshospitalet/DK	No	
DK01390	Rigshospitalet/DK	No	
DK01402	Rigshospitalet/DK	No	
DK01406	Rigshospitalet/DK	No	
DK04097	Aalborg Universitets Hospital (AUH), DK	No	Septic shock, multiorgan failure, irreversible cerebral ischemia. Active treatment was discontinued as further treatment was considered futile, and the patient died.
DK04103	AUH, DK	No	Respiratory failure due to pneumonia
DK04107	AUH, DK	No	Complications of cardiac surgery
DK04110	AUH, DK	No	
DK04112	AUH, DK	No	
DK05029	Regionshospitalet Randers, DK	No	
DK05034	Regionshospitalet Randers, DK	No	
DK05036	Regionshospitalet Randers, DK	No	
DK08056	Regionshospitalet Viborg, DK	No	
DK11253	Nordsjællands Hospital, DK	No	
DK11258	Nordsjællands Hospital, DK	No	
DK11275	Nordsjællands Hospital, DK	No	
DK11278	Nordsjællands Hospital, DK	No	
DK14071	Sjællands University Hospital Køge, DK	No	
DK14074	Sjællands University Hospital Køge, DK	No	
DK20054	Herlev Hospital, DK	No	
DK20062	Herlev Hospital, DK	No	

DK30075	Odense Universitets Hospital (OUH), DK	No	
DK30080	OUH, DK	No	
DK30084	OUH, DK	No	
DK30085	OUH, DK	No	
DK30088	OUH, DK	No	
DK30089	OUH, DK	No	
DK41037	Regionshospitalet Gødstrup, DK	No	
NL01031	University Medical Center Groningen (UMCG), NL	No	
NL01032	UMCG, NL	No	
NL01033	UMCG, NL	No	
NL01035	UMCG, NL	No	
NL01037	UMCG, NL	No	
CH01217	University Hospital Bern, CH	No	Active therapy was withdrawn as further treatment was considered futile, and the patient died
CH01240	University Hospital Bern, CH	No	Active therapy was withdrawn as further treatment was considered futile, and the patient died

c. List of subjects who dropped out of clinical trials in association with an adverse event during the reporting period:

No trial participants dropped out of the clinical trial due to an adverse event during the reporting period.

Case ID/ Subject number*	Assigned treatment	Causality to the study drug	Adverse event leading to drop out (PT term)	Comments
NA	NA	NA	NA	NA
*Study/Center/subject				

17. Late-breaking information

No events have been identified.

18. Overall safety assessment

Four expected SARs have been identified in the reporting period. All cases are resolved. Based on the information described in this ASR, we do not have any new safety concerns.

18.1. Evaluation of the risks

No new safety concerns and no new information relative to previously identified safety concerns have been identified during the reporting period.

18.2. Benefit-risk considerations

The trial is conducted in critically ill patients in the ICU. The number of SAEs and SARs is expected for this population. There are no changes to the risk-benefit balance since the previous ASR.

19. Summary of important risks

Not applicable

20. Conclusions

We conclude that the information obtained in this reporting period justifies continuation of this blinded investigator-initiated trial without any modification. The benefit-risk balance for participants in the clinical trial is considered to remain unchanged and favourable.