

REQUEST FOR AUTHORISATION OF A CLINICAL TRIAL ON A MEDICINAL PRODUCT FOR HUMAN USE TO THE COMPETENT AUTHORITIES AND FOR OPINION OF THE ETHICS COMMITTEES IN THE COMMUNITY
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To be filled in by the applicant

The questions in this form for the request for authorisation from the Competent Authority are also relevant for the opinion from an Ethics Committee (it represents module 1 of the form for applying to an ethics committee) and can be used as part of that application. Please indicate the relevant purpose in a box below.

REQUEST FOR AUTHORISATION TO THE COMPETENT AUTHORITY: No •
REQUEST FOR OPINION OF THE ETHICS COMMITTEE: Yes •

A. TRIAL IDENTIFICATION

A.1	Member State in which the submission is being made:	Denmark - DHMA
A.2	EudraCT number:	2019-004292-40
A.3	Full title of the trial: English	Goal directed fluid removal with furosemide in intensive care patients with fluid overload - A randomised, blinded, placebo-controlled trial (GODIF).
A.3.1	Title of the trial for lay people, in easily understood, i.e. non-technical, language: English	Goal directed fluid removal in critically ill patients with fluid overload.
	Danish	Måltrettet behandling af væskeophobning hos patienter på intensiv afdeling.
A.3.2	Name or abbreviated title of the trial where available: English	GODIF trial
A.4	Sponsor's protocol code number, version and date ¹ :	
A.4.1	Sponsor's protocol code number:	GODIF
A.4.2	Sponsor's protocol version:	2.6
A.4.3	Sponsor's protocol date:	2021-02-22
A.5	Additional international study identifiers (e.g. WHO, ISRCTN ² , US NCT Number ³) if available	
A.5.1	ISRCTN number:	
A.5.2	US NCT number:	NCT04180397
A.5.3	WHO Universal Trial Number (UTN):	
A.5.4	Other Identifier:	
A.6	Is this a resubmission? If 'Yes', indicate the resubmission letter ⁴ :	No • First Submission
A.7	Is the trial part of an agreed Paediatric Investigation Plan?	No •
A.8	EMA Decision number of Paediatric Investigation Plan:	

B. IDENTIFICATION OF THE SPONSOR RESPONSIBLE FOR THE REQUEST

B.1	SPONSOR
B.1.1	Name of organisation: Department of Anesthesia and Intensive Care Medicine, Nordsjællands hospital
B.1.2	Name of the person to contact:
B.1.2.1	Given name Morten
B.1.2.2	Middle name Heiberg
B.1.2.3	Family name Bestle
B.1.3	Address:
B.1.3.1	Street address Dyrehavevej 29
B.1.3.2	Town/city Hillerød
B.1.3.3	Post code 3400
B.1.3.4	Country Denmark
B.1.4	Telephone number: +45 41951195
B.1.5	Fax number:
B.1.6	E-mail: morten.bestle@regionh.dk
B.2	LEGAL REPRESENTATIVE⁵ OF THE SPONSOR IN THE COMMUNITY FOR THE PURPOSE OF THIS TRIAL (if different from the sponsor)
B.2.1	Name of organisation:
B.2.2	Name of person to contact:
B.2.2.1	Given name
B.2.2.2	Middle name
B.2.2.3	Family name
B.2.3	Address:
B.2.3.1	Street address
B.2.3.2	Town/city
B.2.3.3	Post code
B.2.3.4	Country
B.2.4	Telephone number:
B.2.5	Fax number:
B.2.6	E-mail:
B.3	STATUS OF THE SPONSOR:
B.3.1	Commercial: No •
B.3.2	Non commercial: Yes •
B.4	Source(s) of Monetary or Material Support for the clinical trial (repeat as necessary):
B.4.1	Name of organisation: Novo Nordisk Foundation
B.4.2	Country: Denmark
B.4	Source(s) of Monetary or Material Support for the clinical trial (repeat as necessary):
B.4.1	Name of organisation: Jakob Madsens and Hustru Olga Madsens foundation
B.4.2	Country: Denmark
B.5	Contact point⁶ designated by the sponsor for further information on the trial
B.5.1	Name of organisation: Department of Anesthesia and Intensive Care Medicine, Nordsjællands hospital
B.5.2	Functional name of contact point (e.g. "Clinical Trial Information Desk"): Morten Bestle
B.5.3	Address:
B.5.3.1	Street address Dyrehavevej 29
B.5.3.2	Town/city Hillerød
B.5.3.3	Post code 3400

B.5.3.4	Country	Denmark
B.5.4	Telephone number:	+45 48292017
B.5.5	Fax number:	
B.5.6	E-mail: (use a functional e-mail address rather than a personal one)	morten.bestle@regionh.dk

C. APPLICANT IDENTIFICATION, (please tick the appropriate box)

C.2	REQUEST FOR THE ETHICS COMMITTEE
C.2.1	Sponsor
C.2.2	Legal Representative of the Sponsor
C.2.3	Person or organisation authorised by the sponsor to make the application
C.2.4	Investigator in charge of the application if applicable ⁸ : Co-ordinating investigator (for multicentre trial) Principal investigator (for single centre trial)
C.2.5	Complete the details of the applicant below even if they are provided elsewhere on the form:
C.2.5.1	Organisation:
C.2.5.2	Name of contact person:
C.2.5.2.1	Given name
C.2.5.2.2	Middle name
C.2.5.2.3	Family name
C.2.5.3	Address:
C.2.5.3.1	Street address
C.2.5.3.2	Town/city
C.2.5.3.3	Post code
C.2.5.3.4	Country
C.2.5.4	Telephone number:
C. 2.5.5	Fax number:
C. 2.5.6	E-mail:

D. INFORMATION ON EACH IMP

Information on each 'bulk product' before trial-specific operations (blinding, trial specific packaging and labelling) should be provided in this section for each investigational medicinal product (IMP) being tested including each comparator and each placebo, if applicable. **For placebo go directly to D.8.** If the trial is performed with several products use extra pages and give each product a sequential number in D.1.1. If the product is a combination product, information should be given for each active substance.

D.1 IMP IDENTIFICATION		
Indicate which of the following is described below, then repeat as necessary for each of the numbered IMPs to be used in the trial (assign numbers from 1-n):		
D.1.1	This refers to the IMP number:	PR1
D.1.2	IMP being tested	Yes •
D.1.3	IMP used as a comparator	No •
D.2 STATUS OF THE IMP		
D.2.1	Has the IMP to be used in the trial a marketing authorisation? No • If the IMP has a marketing authorisation in the Member State concerned by this application, but the trade name and marketing authorisation holder are not fixed in the protocol, go to section D.2.2.	
D.2.1.1	If 'Yes', specify the product to be used in the clinical trial:	
D.2.1.1.1	Trade name	
D.2.1.1.1.1	EV Product Code (where applicable)	
D.2.1.1.2	Name of the Marketing Authorisation Holder:	
D.2.1.1.3	Marketing Authorisation number (if Marketing Authorisation granted by a Member State):	
D.2.1.1.4	Is the IMP modified in relation to its Marketing Authorisation? No •	
D.2.1.1.4.1	If 'Yes', please specify:	
D.2.1.2	The country that granted the Marketing Authorisation	
D.2.1.2.1	Is this the Member State concerned with this application? No •	
D.2.2	Situations where an IMP to be used in the CT has a Marketing Authorisation in the Member State concerned, but the protocol allows that any brand of the IMP with a Marketing Authorisation in that Member State be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start	
D.2.2.1	In the protocol, is treatment defined only by active substance? Not Answered •	
D.2.2.1.1	If 'Yes', give active substance in D.3.8 or D.3.9	
D.2.2.2	In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS? Not Answered •	
D.2.2.2.1	If 'Yes', give active substance in D.3.8 or D.3.9	
D.2.2.3	The products to be administered as IMPs are defined as belonging to an ATC group ⁹ Not Answered •	
D.2.2.3.1	If 'Yes', give the ATC group of the applicable authorised codes in the ATC code field (level 3 or the level that can be defined) in D.3.3	
D.2.2.4	Other: Not Answered •	
D.2.2.4.1	If 'Yes', please specify:	
D.2.3	IMPD submitted:	
D.2.3.1	Full IMPD: No •	
D.2.3.2	Simplified IMPD: Yes •	
D.2.3.3	Summary of product characteristics (SmPC) only: No •	
D.2.4	Has the use of the IMP been previously authorised in a No •	

D.2.4.1	clinical trial conducted by the sponsor in the Community? If 'Yes' specify which Member States:	
D.2.5	Has the IMP been designated in this indication as an orphan drug in the Community?	No •
D.2.5.1	If 'Yes', give the orphan drug designation number ¹⁰ :	

D.2.6	Has the IMP been the subject of scientific advice related to this clinical trial?	No •
D.2.6.1	If 'Yes' to D.2.6, please indicate source of advice and provide a copy in the CTA request:	
D.2.6.1.1	CHMP ¹¹ ?	No •
D.2.6.1.2	National Competent Authority?	No •

D.3	DESCRIPTION OF THE IMP	
D.3.1	Product name where applicable ¹² :	Furosemide
D.3.2	Product code where applicable ¹³ :	
D.3.3	ATC codes, if officially registered ¹⁴ :	C03CA01
D.3.4	Pharmaceutical form (use standard terms):	Infusion
D.3.4.1	Is this a specific paediatric formulation?	No •
D.3.5	Maximum duration of treatment of a subject according to the protocol: Maximum 90 days	
D.3.6	Dose allowed:	
D.3.6.1	For first trial only: Specify per day or total Specify total dose (number and unit): Route of administration (relevant to the first dose):	Not Answered •
D.3.6.2	For all trials Specify per day or total Specify total dose (number and unit): Route of administration (relevant to the maximum dose):	Per day • Maximum dose 1500 mg milligram(s) Intravenous use
D.3.7	Routes of administration (use standard terms):	Intravenous use

D.3.8	Name of each active substance (INN or proposed INN if available): FUROSEMIDE	
D.3.9	Other available name for each active substance (provide all available):	
D.3.9.1	CAS ¹⁵ number	
D.3.9.2	Current sponsor code	
D.3.9.3	Other descriptive name loop diuretics	
D.3.9.4	EV Substance code	SUB07849MIG
D.3.9.5	Full Molecular formula	
D.3.9.6	Chemical/biological description of the Active Substance	
D.3.10	Strength (specify all strengths to be used):	
D.3.10.1	Concentration unit:	mg/ml milligram(s)/millilitre
D.3.10.2	Concentration type ("exact number", "range", "more than" or "up to"):	equal
D.3.10.3	Concentration (number).	10

D.3.11	Type of IMP	
Does the IMP contain an active substance:		
D.3.11.1	Of chemical origin?	Yes •
D.3.11.2	Of biological / biotechnological origin (other than Advanced Therapy IMP (ATIMP))?	No •
Is this a:		

D.3.11.3	Advanced Therapy IMP (ATIMP)?	No •
D.3.11.3.1	Somatic cell therapy medicinal product ¹⁶ ?	No •
D.3.11.3.2	Gene therapy medicinal product ¹⁷ ?	No •
D.3.11.3.3	Tissue Engineered Product ¹⁸ ?	No •
D.3.11.3.4	Combination ATIMP (i.e. one involving a medical device ¹⁹)?	No •
D.3.11.3.5	Has the Committee on Advanced Therapies issued a classification for this product?	No •
D.3.11.3.5.1	If 'Yes' please provide that classification and its reference number:	
D.3.11.4	Combination product that includes a device, but does not involve an Advanced Therapy?	No •
D.3.11.5	Radiopharmaceutical medicinal product?	No •
D.3.11.6	Immunological medicinal product (such as vaccine, allergen, immune serum)?	No •
D.3.11.7	Plasma derived medicinal product?	No •
D.3.11.8	Extractive medicinal product?	No •
D.3.11.9	Recombinant medicinal product?	No •
D.3.11.10	Medicinal product containing genetically modified organisms?	No •
D.3.11.10.1	Has the authorisation for contained use or release been granted?	No •
D.3.11.10.2	Is it pending?	No •
D.3.11.11	Herbal medicinal product?	No •
D.3.11.12	Homeopathic medicinal product?	No •
D.3.11.13	Another type of medicinal product?	No •
D.3.11.13.1	If 'another type of medicinal product' specify the type of medicinal product:	
D.3.12	Mode of action (<i>free text</i> ²⁰) Our trial drug is the well known furosemide. It is produced by the Hospital Pharmacy of the Capital Region of Denmark who doesn't have a marketing authorisation for this drug. We want the pharmacy to produce the trial drug because they can produce it in the same vials we want to use for our placebo medicine. In that way the clinical staff administering the trial drug will remain blinded during the trial.	
D.3.13	Is it an IMP to be used in a first-in-human clinical trial?	No •
D.3.13.1	If 'Yes', are there risk factors identified, according to the guidance FIH? ²¹	

D.4 SOMATIC CELL THERAPY INVESTIGATIONAL MEDICINAL PRODUCT (NO GENETIC MODIFICATION)

D.4.1	Origin of cells	
D.4.1.1	Autologous	No •
D.4.1.2	Allogeneic	No •
D.4.1.3	Xenogeneic	No •
D.4.1.3.1	If 'Yes', specify the species of origin:	
D.4.2	Type of cells	
D.4.2.1	Stem cells	No •
D.4.2.2	Differentiated cells	No •
D.4.2.2.1	If 'Yes', specify the type (e.g. keratinocytes, fibroblasts, chondrocytes...):	
D.4.2.3	Others:	No •
D.4.2.3.1	If others, specify:	

D.5 GENE THERAPY INVESTIGATIONAL MEDICINAL PRODUCTS

D.5.1	Gene(s) of interest:	
D.5.2	In vivo gene therapy:	No •
D.5.3	Ex vivo gene therapy:	No •
D.5.4	Type of gene transfer product	

D.5.4.1	Nucleic acid (e.g. plasmid): If 'Yes', specify if:	No •
D.5.4.1.1	Naked:	No •
D.5.4.1.2	Complexed	No •
D.5.4.2	Viral vector:	No •
D.5.4.2.1	If 'Yes', specify the type: adenovirus, retrovirus, AAV, ...:	
D.5.4.3	Others	No •
D.5.4.3.1	If others, specify:	
D.5.5	Genetically modified somatic cells: If 'Yes', specify the origin of the cells:	No •
D.5.5.1	Autologous:	No •
D.5.5.2	Allogeneic:	No •
D.5.5.3	Xenogeneic:	No •
D.5.5.3.1	If 'Yes', specify the species of origin:	
D.5.5.4	Specify type of cells (hematopoietic stem cells...):	

D.6 TISSUE ENGINEERED PRODUCT
The indication which determines that this is a Tissue Engineered Product as opposed to a Cell Therapy product is given in section E.1.1.

D.6.1	Origin of cells	
D.6.1.1	Autologous	No •
D.6.1.2	Allogeneic	No •
D.6.1.3	Xenogeneic	No •
D.6.1.3.1	If 'Yes', specify the species of origin:	
D.6.2	Type of cells	
D.6.2.1	Stem cells	No •
D.6.2.2	Differentiated cells	No •
D.6.2.2.1	If 'Yes', specify the type of cells(e.g. keratinocytes, fibroblasts, chondrocytes, ...):	
D.6.2.3	Others:	No •
D.6.2.3.1	If others, specify:	

D.7 PRODUCTS CONTAINING DEVICES (i.e. MEDICAL DEVICES, SCAFFOLDS ETC.)

D.7.1	Give a brief description of the device:	
D.7.2	What is the name of the device?	
D.7.3	Is the device implantable?	No •
D.7.4	Does this product contain:	
D.7.4.1	A medical device?	No •
D.7.4.1.1	Does this medical device have a CE mark?	No •
D.7.4.1.1.1	The notified body is:	
D.7.4.2	Bio-materials?	No •
D.7.4.3	Scaffolds?	No •
D.7.4.4	Matrices?	No •
D.7.4.5	Other?	No •
D.7.4.5.1	If other, specify:	

D.8 INFORMATION ON PLACEBO (if relevant; repeat as necessary)

D.8.1	Is there a placebo:	Yes •
D.8.2	This refers to placebo number:	PL1
D.8.3	Pharmaceutical form:	Injection
D.8.4	Route of administration:	Intravenous use
D.8.5	Which IMP is it a placebo for? Specify IMP Number(s) from D.1.1	PR1
D.8.5.1	Composition, apart from the active substance(s):	
D.8.5.2	Is it otherwise identical to the IMP?	Yes •
D.8.5.2.1	If not, specify major ingredients:	

D.9 SITE(S) WHERE THE QUALIFIED PERSON CERTIFIES BATCH RELEASE²²

This section is dedicated to **finished** IMPs, i.e. medicinal products randomised, packaged, labelled and certified for use in the clinical trial. If there is more than one site or more than one IMP is certified, use extra pages and give each IMP its number from section D.1.1 or D.8.2 In the case of multiple sites indicate the product certified by each site

D.9.1	Do not fill in section D.9.2 for an IMP that: <i>Has a MA in the EU and</i> <i>Is sourced from the EU market and</i> <i>Is used in the trial without modification(e.g. not overencapsulated) and</i> <i>The packaging and labelling is carried out for local use only as per article 9.2. of the Directive 2005/28/EC (GCP Directive)</i> If all these conditions are met tick • and list the number(s) of each IMP including placebo from sections D.1.1 and D.8.2 to which this applies
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D.9.2	Who is responsible in the Community for the certification of the finished IMPs?
	This site is responsible for certification of (list the number(s) of each IMP including placebo from sections D.1.1 and D.8.2): PR1
	please tick the appropriate box: PL1
D.9.2.1	Manufacturer Yes •
D.9.2.2	Importer No •
D.9.2.3	Name of the organisation: Hospital Pharmacy of the Capital Region of Denmark
D.9.2.4	Address:
D.9.2.4.1	Street Address Marielundsvej 25
D.9.2.4.2	Town/City Herlev
D.9.2.4.3	Post Code 2730
D.9.2.4.4	Country Denmark
D.9.2.5	Give the manufacturing authorisation number:
D.9.2.5.1	If No authorisation, give the reasons: This is a hospital pharmacy and they have no authorisation number.
<i>Where the product does not have a MA in the EU, but is supplied in bulk and final packaging and labelling for local use is carried out in accordance with article 9.2 of Directive 2005/28/EC (GCP Directive) then enter the site where the product was finally certified for release by the Qualified Person for use in the clinical trial at D.9.2 above.</i>	

E. GENERAL INFORMATION ON THE TRIAL

This section should be used to provide information about the aims, scope and design of the trial. When the protocol includes a sub-study in the MS concerned section E.2.3 should be completed providing information about the sub-study. To identify it check the sub-study box in the 'Objective of the trial' question below.

E.1 MEDICAL CONDITION OR DISEASE UNDER INVESTIGATION																																				
E.1.1	Specify the medical condition(s) to be investigated ²³ (free text): English Treatment of fluid overload in critically ill adult patients in intensive care unit.																																			
E.1.1.1	Medical condition in easily understood language English Treatment of excess fluid in the body in critically ill adults admitted to an intensive care unit.																																			
E.1.1.2	Therapeutic area Not possible to specify																																			
E.1.2	MedDRA version, system organ class, level, term and classification code ²⁴ :																																			
	<table border="1"> <thead> <tr> <th>Version</th> <th>System Organ Class</th> <th>Classification Code</th> <th>Term</th> <th>Level</th> </tr> </thead> <tbody> <tr> <td>22.1</td> <td>100000004861</td> <td>10015766</td> <td>Extracellular fluid increased</td> <td>LLT</td> </tr> <tr> <td>20.0</td> <td>100000004861</td> <td>10016808</td> <td>Fluid retention in tissues</td> <td>LLT</td> </tr> <tr> <td>24.0</td> <td>100000004861</td> <td>10022608</td> <td>Interstitial fluid increased</td> <td>LLT</td> </tr> <tr> <td>24.1</td> <td>100000004861</td> <td>10033303</td> <td>Overhydration</td> <td>LLT</td> </tr> <tr> <td>20.0</td> <td>100000004867</td> <td>10030102</td> <td>Oedema generalised</td> <td>LLT</td> </tr> <tr> <td>20.1</td> <td>100000004867</td> <td>10034611</td> <td>Peripheral oedema</td> <td>LLT</td> </tr> </tbody> </table>	Version	System Organ Class	Classification Code	Term	Level	22.1	100000004861	10015766	Extracellular fluid increased	LLT	20.0	100000004861	10016808	Fluid retention in tissues	LLT	24.0	100000004861	10022608	Interstitial fluid increased	LLT	24.1	100000004861	10033303	Overhydration	LLT	20.0	100000004867	10030102	Oedema generalised	LLT	20.1	100000004867	10034611	Peripheral oedema	LLT
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E.1.3	Is any of the conditions being studied a rare disease ²⁵ ? No •																																			

E.2 OBJECTIVE OF THE TRIAL	
E.2.1	Main objective: English To assess benefits and harms of goal directed fluid removal with furosemide versus placebo on patient-important outcome measures in adult ICU patients with moderate to severe fluid overload. The primary objective is to determine, if forced fluid removal with furosemide compared to placebo (spontaneous fluid excretion) will increase the number of days alive and out of hospital at 90 days.
E.2.2	Secondary objectives: English To investigate if goal directed fluid removal compared to placebo in adult ICU patients with fluid overload will change the: 1. <input type="checkbox"/> All-cause mortality at day 90 after randomization. 2. <input type="checkbox"/> Days alive at day 90 without life support (vasopressor/inotropic support, invasive mechanical ventilation or renal replacement therapy). 3. <input type="checkbox"/> All-cause mortality at 1-year after randomization. 4. <input type="checkbox"/> Number of participants with one or more serious adverse events (SAEs) and serious adverse reactions (SARs) to furosemide. Explorative outcomes: 1. <input type="checkbox"/> Health related quality of life 1-year after randomization measured using the EuroQoL (EQ)-5D-5L and EQ-VAS scores. 2. Participants subjective assessment of their quality of life since the treatment in the ICU (unacceptable/neutral/acceptable) compared to (EQ)-5D-5L and EQ-VAS scores. 3. <input type="checkbox"/> Cognitive function 1-year after randomization assessed by the

Montreal Cognitive Assessment (MoCa) score.

E.2.3 Is there a sub-study? **No •**
E.2.3.1 If 'Yes', give the full title, date and version of each sub-study and their related objectives:

E.3 PRINCIPAL INCLUSION CRITERIA (list the most important)

English **All of the parameters must be met:**

- Acute admission to the ICU.
- Age \geq 18 years of age.
- Fluid accumulation estimated according to daily fluid charts, the cumulative fluid balance, development in body weight, and clinical examination corresponding \geq 5% of ideal body weight.
- Clinical stable assessed by the clinicians (minimum criteria: MAP > 50 mmHg and maximum infusion of 20 microgram/kg/minute of noradrenaline and lactate < 4,0 mmol/L).

E.4 PRINCIPAL EXCLUSION CRITERIA (list the most important)

English

- Known allergy to furosemide or sulphonamides.
- Known pre-hospitalization advanced chronic kidney disease (eGFR < 30 mL/minute/1.73 m² or chronic renal replacement therapy).
- Ongoing renal replacement therapy
- Anuria for \geq 6 hours
- Rhabdomyolysis with indication for forced diuresis
- Ongoing life-threatening bleeding.
- Acute burn injury of more than 10 % of the body surface area.
- Severe dysnatremia (p-Na < 120 mmol/L or > 155 mmol/l).
- Severe hepatic failure as per the clinical team.
- Patients undergoing forced treatment.
- Fertile women (women < 50 years) with positive urine human chorionic gonadotropin (hCG) or plasma-hCG.
- Consent not obtainable as per the model approved for the specific trial site.

E.5 END POINT(S):

E.5.1 Primary End Point (repeat as necessary)²⁶
English **Days alive and out of hospital at day 90 after randomisation.**

E.5.1.1 Timepoint(s) of evaluation of this end point
English **90 days post-randomisation.**

E.5.2 Secondary End Point (repeat as necessary)
English

1. All-cause mortality at day 90 after randomization.
2. Days alive at day 90 without life support (vasopressor/inotropic support, invasive mechanical ventilation or renal replacement therapy).
3. All-cause mortality at 1-year after randomization.
4. Number of participants with one or more serious adverse events (SAEs) and serious adverse reactions (SARs) to furosemide.
5. Health related quality of life 1-year after randomization measured using the EuroQoL (EQ)-5D-5L and EQ-VAS scores.
6. Participants subjective assessment of their quality of life since the treatment in the ICU (unacceptable/neutral/acceptable) compared to

(EQ)-5D-**5L and EQ-VAS scores.****7. Cognitive function 1-year after randomization assessed by the Montreal Cognitive Assessment (MoCa) score.**

E.5.2.1 Timepoint(s) of evaluation of this end point
English **Endpoint number 1,2,4,: 90 days post-randomisation**
Endpoint number: 3,5,6: 1 year post-randomisation

E.6 SCOPE OF THE TRIAL – Tick all boxes where applicable

E.6.1	Diagnosis	No •
E.6.2	Prophylaxis	No •
E.6.3	Therapy	Yes •
E.6.4	Safety	Yes •
E.6.5	Efficacy	Yes •
E.6.6	Pharmacokinetic	No •
E.6.7	Pharmacodynamic	No •
E.6.8	Bioequivalence	No •
E.6.9	Dose Response	No •
E.6.10	Pharmacogenetic	No •
E.6.11	Pharmacogenomic	No •
E.6.12	Pharmacoeconomic	No •
E.6.13	Others	No •
E.6.13.1	If others, specify:	

E.7 TRIAL TYPE AND PHASE²⁷

E.7.1	Human pharmacology (Phase I)	No •
Is it:		
E.7.1.1	First administration to humans	No •
E.7.1.2	Bioequivalence study	No •
E.7.1.3	Other:	No •
E.7.1.3.1	If other, please specify:	
E.7.2	Therapeutic exploratory (Phase II)	No •
E.7.3	Therapeutic confirmatory (Phase III)	No •
E.7.4	Therapeutic use(Phase IV)	Yes •

E.8 DESIGN OF THE TRIAL

E.8.1	Controlled	Yes •
	If 'Yes', specify:	
E.8.1.1	Randomised:	Yes •
E.8.1.2	Open:	No •
E.8.1.3	Single blind:	No •
E.8.1.4	Double blind:	Yes •
E.8.1.5	Parallel group:	Yes •
E.8.1.6	Cross over:	No •
E.8.1.7	Other:	No •
E.8.1.7.1	If other specify:	
E.8.2	If controlled, specify the comparator:	
E.8.2.1	Other medicinal product(s)	No •
E.8.2.2	Placebo	Yes •
E.8.2.3	Other	No •
E.8.2.3.1	If 'Yes' to other, specify :	
E.8.2.4	Number of treatment arms in the trial	2

E.8.3	Single site in the Member State concerned (see also section G):	No •
E.8.4	Multiple sites in the Member State concerned(see also section G):	Yes •
E.8.4.1	Number of sites anticipated in Member State concerned	11
E.8.5	Multiple Member States:	Yes •
E.8.5.1	Number of sites anticipated in the EEA:	8
E.8.6	Trial involving sites outside the EEA:	
E.8.6.1	Trial being conducted both within and outside the EEA:	No •
E.8.6.2	Trial being conducted completely outside of the EEA:	No •
E.8.6.3	If E.8.6.1 or E.8.6.2 are Yes, specify the regions in which trial sites are planned: Denmark Finland Germany Italy Netherlands Norway United Kingdom	
E.8.6.4	If E.8.6.1 or E.8.6.2 are Yes, specify the number of sites anticipated outside of the EEA:	
E.8.7	Trial having an independent data monitoring committee:	Yes •
E.8.8	Definition of the end of trial: If it is the last visit of the last subject, please enter "LVLS". If it is not LVLS provide the definition: English 1 year and 3 months post-randomisation of the last included patient in the trial.	
E.8.9	Initial estimate of the duration of the trial ²⁸ (years, months and days)	
E.8.9.1	In the Member State concerned	5 years 7 months days
E.8.9.2	In all countries concerned by the trial	5 years 7 months days
E.8.10	Proposed date of start of recruitment	
E.8.10.1	In the Member State concerned	2020-08-17
E.8.10.2	In any country	

F. POPULATION OF TRIAL SUBJECTS

F.1 AGE RANGE		
F.1.1	Are the trial subjects under 18? If 'Yes', specify the estimated number of subjects planned in each age range for the whole trial: Approx. No. of patients ²⁹	No •
F.1.1.1	In utero	() No •
F.1.1.2	Preterm newborn infants (up to gestational age < 37 weeks)	() No •
F.1.1.3	Newborns (0-27 days)	() No •
F.1.1.4	Infants and toddlers (28 days - 23 months)	() No •
F.1.1.5	Children (2-11 years)	() No •
F.1.1.6	Adolescents (12-17 years)	() No •
F.1.2	Adults (18-64 years)	(210) Yes •
F.1.3	Elderly (>= 65 years)	(831) Yes •
F.2 GENDER		
F.2.1	Female	Yes •
F.2.2	Male	Yes •
F.3 GROUP OF TRIAL SUBJECTS		
F.3.1	Healthy volunteers	No •
F.3.2	Patients	Yes •
F.3.3	Specific vulnerable populations	Yes •
F.3.3.1	Women of child bearing potential not using contraception	Yes •
F.3.3.2	Women of child bearing potential using contraception	Yes •
F.3.3.3	Pregnant women	No •
F.3.3.4	Nursing women	No •
F.3.3.5	Emergency situation	Yes •
F.3.3.6	Subjects incapable of giving consent personally	Yes •
F.3.3.6.1	If 'Yes', specify: English Patients admitted to an ICU are temporarily incompetent, because of severe illness and the treatment (sedative medicine/opioids). Consent will be obtained according to national law.	
F.3.3.7	Others:	No •
F.3.3.7.1	If 'Yes', specify:	
F.4 PLANNED NUMBER OF SUBJECTS TO BE INCLUDED:		
F.4.1	In the member state	700
F.4.2	For a multinational trial:	
F.4.2.1	In the EEA	1041
F.4.2.2	In the whole clinical trial	1041
F.5 PLANS FOR TREATMENT OR CARE AFTER THE SUBJECT HAS ENDED HIS/HER PARTICIPATION IN THE TRIAL. please specify (free text):		
	English None	

G. CLINICAL TRIAL SITES/INVESTIGATORS IN THE MEMBER STATE CONCERNED BY THIS REQUEST

G.1	CO-ORDINATING INVESTIGATOR (for multicentre trial) and principal investigator (for single centre trial)	
G.1.1	Given name:	Sine
G.1.2	Middle name, if applicable:	
G.1.3	Family name:	Wichmann
G.1.4	Qualification (MD.....)	MD
G.1.5	Professional address:	
G.1.5	Institution name	Nordsjællands hospital
G.1.5	Institution department	Department of Anaesthesiology and Intensive Care medicin
G.1.5.1	Street address	Dyrehavevej 29
G.1.5.2	Town/city	Hillerød
G.1.5.3	Post code	3400
G.1.5.4	Country	Denmark
G.1.6	Telephone number:	+45 26142620
G.1.7	Fax number:	
G.1.8	E-mail:	sine.wichmann@regionh.dk

G.1	CO-ORDINATING INVESTIGATOR (for multicentre trial) and principal investigator (for single centre trial)	
G.1.1	Given name:	Marianne
G.1.2	Middle name, if applicable:	Krogh Lauridsen
G.1.3	Family name:	Vang
G.1.4	Qualification (MD.....)	
G.1.5	Professional address:	
G.1.5	Institution name	Aarhus Universitetshospital
G.1.5	Institution department	Intensiv Nord
G.1.5.1	Street address	Palle Juul-Jensens Boulevard 165
G.1.5.2	Town/city	Århus
G.1.5.3	Post code	8200
G.1.5.4	Country	Denmark
G.1.6	Telephone number:	
G.1.7	Fax number:	
G.1.8	E-mail:	

G.2	PRINCIPAL INVESTIGATORS (for multicentre trial ; where necessary, use additional forms)	
G.2.1	Given name:	Jørgen
G.2.2	Middle name, if applicable:	
G.2.3	Family name:	Wiis
G.2.4	Qualification (MD.....)	MD
G.2.5	Professional address:	
G.2.5	Institution name	Rigshospitalet
G.2.5	Institution department	Department for Intensive Care medicin 4131
G.2.5.1	Street address	Blegdamsvej 9
G.2.5.2	Town/city	Copenhagen
G.2.5.3	Post code	2100
G.2.5.4	Country	Denmark
G.2.6	Telephone number:	
G.2.7	Fax number:	
G.2.8	E-mail:	

G.2	PRINCIPAL INVESTIGATORS (for multicentre trial ; where necessary, use additional forms)	
G.2.1	Given name:	Christoffer
G.2.2	Middle name, if applicable:	Gant
G.2.3	Family name:	Sølling
G.2.4	Qualification (MD.....)	MD, PhD
G.2.5	Professional address:	
G.2.5	Institution name	Regionshospitalet Viborg
G.2.5	Institution department	Department of Anaesthesia and Intensive Care
G.2.5.1	Street address	
G.2.5.2	Town/city	Viborg
G.2.5.3	Post code	8800
G.2.5.4	Country	Denmark
G.2.6	Telephone number:	
G.2.7	Fax number:	
G.2.8	E-mail:	

G.2	PRINCIPAL INVESTIGATORS (for multicentre trial ; where necessary, use additional forms)	
G.2.1	Given name:	Anne
G.2.2	Middle name, if applicable:	Craveiro
G.2.3	Family name:	Brøchner
G.2.4	Qualification (MD.....)	MD, PhD
G.2.5	Professional address:	
G.2.5	Institution name	Sygehus Lillebælt, Kolding
G.2.5	Institution department	Department of Anaesthesia and Intensive Care
G.2.5.1	Street address	
G.2.5.2	Town/city	Kolding
G.2.5.3	Post code	6000
G.2.5.4	Country	Denmark
G.2.6	Telephone number:	
G.2.7	Fax number:	
G.2.8	E-mail:	

G.2	PRINCIPAL INVESTIGATORS (for multicentre trial ; where necessary, use additional forms)	
G.2.1	Given name:	Pawel
G.2.2	Middle name, if applicable:	Stefan
G.2.3	Family name:	Berezowicz
G.2.4	Qualification (MD.....)	MD
G.2.5	Professional address:	
G.2.5	Institution name	Sygehus Lillebælt, Vejle
G.2.5	Institution department	Department of Anaesthesia and Intensive Care
G.2.5.1	Street address	
G.2.5.2	Town/city	Vejle
G.2.5.3	Post code	7100
G.2.5.4	Country	Denmark
G.2.6	Telephone number:	
G.2.7	Fax number:	
G.2.8	E-mail:	

G.2	PRINCIPAL INVESTIGATORS (for multicentre trial ; where necessary, use additional forms)	
G.2.1	Given name:	Meike
G.2.2	Middle name, if applicable:	Tomesch
G.2.3	Family name:	Behzadi

G.2.4	Qualification (MD.....)	MD
G.2.5	Professional address:	
G.2.5	Institution name	Aalborg Universitets Hospital
G.2.5	Institution department	Department of Anaesthesia and Intensive Care
G.2.5.1	Street address	
G.2.5.2	Town/city	Aalborg
G.2.5.3	Post code	9000
G.2.5.4	Country	Denmark
G.2.6	Telephone number:	
G.2.7	Fax number:	
G.2.8	E-mail:	

G.2 PRINCIPAL INVESTIGATORS (for multicentre trial ; where necessary, use additional forms)

G.2.1	Given name:	Thomas
G.2.2	Middle name, if applicable:	
G.2.3	Family name:	Strøm
G.2.4	Qualification (MD.....)	MD, PhD
G.2.5	Professional address:	
G.2.5	Institution name	Sygehus Sønderjylland, Aabenraa
G.2.5	Institution department	Department of Anaesthesia and Intensive Care
G.2.5.1	Street address	
G.2.5.2	Town/city	Aabenraa
G.2.5.3	Post code	6200
G.2.5.4	Country	Denmark
G.2.6	Telephone number:	
G.2.7	Fax number:	
G.2.8	E-mail:	

G.2 PRINCIPAL INVESTIGATORS (for multicentre trial ; where necessary, use additional forms)

G.2.1	Given name:	Louise
G.2.2	Middle name, if applicable:	Gamstrup
G.2.3	Family name:	Nielsen
G.2.4	Qualification (MD.....)	MD
G.2.5	Professional address:	
G.2.5	Institution name	Odense Universitets Hospital
G.2.5	Institution department	Department of Anaesthesia and Intensive Care
G.2.5.1	Street address	
G.2.5.2	Town/city	Odense
G.2.5.3	Post code	5000
G.2.5.4	Country	Denmark
G.2.6	Telephone number:	
G.2.7	Fax number:	
G.2.8	E-mail:	

G.2 PRINCIPAL INVESTIGATORS (for multicentre trial ; where necessary, use additional forms)

G.2.1	Given name:	Thomas
G.2.2	Middle name, if applicable:	
G.2.3	Family name:	Hildebrandt
G.2.4	Qualification (MD.....)	MD
G.2.5	Professional address:	
G.2.5	Institution name	Sjællands Universitets Hospital, Roskilde
G.2.5	Institution department	Department of Anaesthesia and Intensive Care
G.2.5.1	Street address	
G.2.5.2	Town/city	Roskilde

G.2.5.3	Post code	4000
G.2.5.4	Country	Denmark
G.2.6	Telephone number:	
G.2.7	Fax number:	
G.2.8	E-mail:	

G.2 PRINCIPAL INVESTIGATORS (for multicentre trial ; where necessary, use additional forms)

G.2.1	Given name:	Thomas
G.2.2	Middle name, if applicable:	
G.2.3	Family name:	Mohr
G.2.4	Qualification (MD.....)	MD, PhD
G.2.5	Professional address:	
G.2.5	Institution name	Gentofte Hospital
G.2.5	Institution department	Department of Anaesthesia and Intensive Care
G.2.5.1	Street address	
G.2.5.2	Town/city	Hellerup
G.2.5.3	Post code	2900
G.2.5.4	Country	Denmark
G.2.6	Telephone number:	
G.2.7	Fax number:	
G.2.8	E-mail:	

G.2 PRINCIPAL INVESTIGATORS (for multicentre trial ; where necessary, use additional forms)

G.2.1	Given name:	Lars
G.2.2	Middle name, if applicable:	
G.2.3	Family name:	Nebrich
G.2.4	Qualification (MD.....)	MD
G.2.5	Professional address:	
G.2.5	Institution name	Sjællands Universitets Hospital, Køge
G.2.5	Institution department	Department of Anaesthesia and Intensive Care
G.2.5.1	Street address	
G.2.5.2	Town/city	Køge
G.2.5.3	Post code	4600
G.2.5.4	Country	Denmark
G.2.6	Telephone number:	
G.2.7	Fax number:	
G.2.8	E-mail:	

G.2 PRINCIPAL INVESTIGATORS (for multicentre trial ; where necessary, use additional forms)

G.2.1	Given name:	Kjeld
G.2.2	Middle name, if applicable:	Asbjørn Jensen
G.2.3	Family name:	Damgaard
G.2.4	Qualification (MD.....)	MD
G.2.5	Professional address:	
G.2.5	Institution name	Regionshospitalet Nordjylland, Hjørring
G.2.5	Institution department	
G.2.5.1	Street address	
G.2.5.2	Town/city	
G.2.5.3	Post code	
G.2.5.4	Country	Denmark
G.2.6	Telephone number:	
G.2.7	Fax number:	
G.2.8	E-mail:	

G.3 CENTRAL TECHNICAL FACILITIES TO BE USED IN THE CONDUCT OF THE TRIAL		
Laboratory or other technical facility, in which the measurement or assessment of the main evaluation criteria are centralised (repeat as needed for multiple organisations).		
G.3.1	Name of organisation:	
G.3.2	Department	
G.3.3	Name of contact person:	
G.3.3.1	Given name	
G.3.3.2	Middle name	
G.3.3.3	Family name	
G.3.4	Address:	
G.3.4.1	Street address	
G.3.4.2	Town/city	
G.3.4.3	Post code	
G.3.4.4	Country	
G.3.5	Telephone number:	
G.3.6	Fax number:	
G.3.7	E-mail:	
G.3.8	Enter the details of any duties subcontracted to this central technical facility in this trial	
G.3.8.1	Routine clinical pathology testing	No •
G.3.8.2	Clinical chemistry	No •
G.3.8.3	Clinical haematology	No •
G.3.8.4	Clinical microbiology	No •
G.3.8.5	Histopathology	No •
G.3.8.6	Serology/ endocrinology	No •
G.3.8.7	Analytical chemistry	No •
G.3.8.8	ECG analysis/ review	No •
G.3.8.9	Medical image analysis/ review - X-ray, MRI, ultrasound, etc.	No •
G.3.8.10	Primary/ surrogate endpoint test	No •
G.3.8.11	Other Duties subcontracted?	No •
G.3.8.11.1	If 'Yes', specify the other duties	

G.4 NETWORKS TO BE INVOLVED IN THE TRIAL (e.g. Paediatric Networks involved in the trial)		
G.4.1	Name of organisation:	Copenhagen Trial Unit
G.4.2	Name of contact person:	
G.4.2.1	Given name	
G.4.2.2	Middle name	
G.4.2.3	Family name	
G.4.3	Address:	
G.4.3.1	Street address	Blegdamsvej 9
G.4.3.2	Town/city	Copenhagen
G.4.3.3	Post code	2100
G.4.3.4	Country	Denmark
G.4.4	Telephone number:	
G.4.5	Fax number:	
G.4.6	E-mail:	
G.4.7	Activities carried out by the network:	

G.4 NETWORKS TO BE INVOLVED IN THE TRIAL (e.g. Paediatric Networks involved in the trial)		
G.4.1	Name of organisation:	Centre for Research in Intensive Care (CRIC)
G.4.2	Name of contact person:	
G.4.2.1	Given name	Anders
G.4.2.2	Middle name	

G.4.2.3	Family name	Perner
G.4.3	Address:	
G.4.3.1	Street address	Blegdamsvej 6
G.4.3.2	Town/city	Copenhagen
G.4.3.3	Post code	2100
G.4.3.4	Country	Denmark
G.4.4	Telephone number:	
G.4.5	Fax number:	
G.4.6	E-mail:	anders.perner@regionh.dk
G.4.7	Activities carried out by the network:	

G.5 ORGANISATIONS TO WHOM THE SPONSOR HAS TRANSFERRED TRIAL RELATED DUTIES AND FUNCTIONS

G.5.1 **Has the sponsor transferred any major or all the sponsor's trial related duties and functions to another organisation or third party? Yes •**

Repeat as necessary for multiple organisations:

G.5.1.1	Organisation name:	GCP Unit	
G.5.1.2	Organisation department	Copenhagen University Hospital	
G.5.1.3	Name of contact person :		
G.5.1.3.1	Given name	Birgitte	
G.5.1.3.2	Middle name	Vilsbøll	
G.5.1.3.3	Family name	Hansen	
G.5.1.4	Address:		
G.5.1.4.1	Street address	Frederiksberg hospital, Nordre Fasanvej 57	
G.5.1.4.2	Town/city	Frederiksberg	
G.5.1.4.3	Post code	2000	
G.5.1.4.4	Country	Denmark	
G.5.1.5	Telephone number:	+45 38635620	
G.5.1.6	Fax number:		
G.5.1.7	E-mail:		
G.5.1.8	All tasks of the sponsor		Not Answered •
G.5.1.9	Monitoring		Yes •
G.5.1.10	Regulatory (e.g. preparation of applications to CA and ethics committee)		No •
G.5.1.11	Investigator recruitment		No •
G.5.1.12	IVRS ³⁰ – treatment randomisation		Yes •
G.5.1.13	Data management		Yes •
G.5.1.14	E-data capture		Not Answered •
G.5.1.15	SUSAR reporting		No •
G.5.1.16	Quality assurance auditing		No •
G.5.1.17	Statistical analysis		No •
G.5.1.18	Medical writing		No •
G.5.1.19	Other duties subcontracted?		No •
G.5.1.19.1	If 'Yes' to other, please specify:		

H. COMPETENT AUTHORITY / ETHICS COMMITTEE IN THE MEMBER STATE CONCERNED BY THIS REQUEST

H.1 TYPE OF APPLICATION		
If this application is addressed to the Competent Authority, please tick the Ethics Committee box and give information on the Ethics committee concerned. If this application is addressed to the Ethics Committee, please tick the Competent Authority box and give the information on the Competent Authority concerned.		
H.1.1	Competent Authority	Yes ●
H.1.2	Ethics Committee	No ●

H.2 INFORMATION ON COMPETENT AUTHORITY		
H.2.1	Name:	Danish Medicines Agency
H.2.2	Address	
H.2.2.1	Street address	Axel Heides Gade 1
H.2.2.2	Town/city	Copenhagen
H.2.2.3	Post code	2300
H.2.2.4	Country	Denmark
H.2.3	Date of submission:	

H.3 AUTHORISATION		
H.3.1	To be requested	No ●
H.3.2	Pending	No ●
H.3.3	Given	No ●
If 'Given', specify:		
H.3.3.1	Date of authorisation:	
H.3.3.2	Authorisation accepted	No ●
H.3.3.3	Not accepted	No ●
If not accepted, give:		
H.3.3.3.1	The reasons	
H.3.3.3.2	The eventual anticipated date of resubmission:	

I. SIGNATURE OF THE APPLICANT IN THE MEMBER STATE

I.1	I hereby confirm that /confirm on behalf of the sponsor (delete which is not applicable) that: <ul style="list-style-type: none">• the information provided is complete;• the attached documents contain an accurate account of the information available;• the clinical trial will be conducted in accordance with the protocol; and• the clinical trial will be conducted, and SUSARs and result-related information will be reported, in accordance with the applicable legislation.
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I.2	APPLICANT OF THE REQUEST FOR THE COMPETENT AUTHORITY (as stated in section C.1):
------------	---

I.2.1	Date:
-------	-------

I.2.2	Signature ³¹ :
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I.2.3	Print name:
-------	-------------

I.3	APPLICANT OF THE REQUEST FOR THE ETHICS COMMITTEE (as stated in section C.2):
------------	--

I.3.1	Date: <i>28.04.2022</i>
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I.3.2	Signature ³² : <i>Sine Wichmann</i>
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I.3.3	Print name:
-------	-------------

