Supplemental Online Content

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Supplement 1. Trial protocol and statistical analysis plan

This supplemental material has been provided by the authors to give readers additional information about their work.

Protocol: **Effect of high-dose baclofen on agitation-related events among patients with unhealthy alcohol use receiving mechanical ventilation: a randomized clinical trial**

Protocol for the Manuscript Entitled:

Effect of high-dose baclofen on agitation-related events among patients with unhealthy alcohol use receiving mechanical ventilation: a randomized clinical trial

This supplement contains the following items:

CONTENTS

SUMMARY

TITLE	*BACLO-REA Protocol – Prevention of agitation in ICU patients who present unhealthy alcohol use.* Baclofen versus placebo. A randomized controlled trial.
PROMOTOR	Nantes University Hospital
COORDINATING INVESTIGATOR	Professor Karim Asehnoune
JUSTIFICATION/ CONTEXT	In general hospitals, 25% to 35% of men and 5% to 10% of women hospitalized are chronic alcoholics. In intensive care, up to 28% of admissions are directly related to excessive alcohol consumption. According to the National Institute on Alcohol Abuse and Alcoholism (NIAAA), a patient is considered as an at-risk consumer if his or her consumption exceeds: • For a male: consumption of >14 glasses/week in the year prior to hospitalization; • For a male >65 years or a female: consumption of >7 glasses/week in the year prior to hospitalization. The two principal consequences of alcoholism in intensive care are withdrawal syndrome and agitation. They are the sources of serious adverse events such as self-extubation, self-ablation of medical devices, falls, or heavy sedation causing delayed awakening. All of these elements increase morbidity and mortality in the ICU. Baclofen is a centrally acting muscle relaxant. Two randomized studies have reported its effectiveness in the treatment of alcohol withdrawal syndrome and two others in the reduction of alcohol consumption. We therefore propose this multicenter, randomized, placebo-controlled baclofen trial. Our objective is to evaluate the efficacy of baclofen in reducing adverse events related to agitation by ICU patients who present unhealthy alcohol use.
PRINCIPAL OBJECTIVE	To evaluate the efficacy of baclofen compared with placebo in reducing agitation-related adverse events in non-brain injured patients admitted to intensive care and classified as at-risk alcohol consumers according to NIAAA criteria and requiring mechanical ventilation for at least 48 hours.
SECONDARY OBJECTIVES	To evaluate the impact of baclofen on morbidity and mortality in the hospital and the ICU in patients who present unhealthy alcohol use.
PRINCIPAL JUDGEMENT CRITERIA	*The occurrence of at least 1 adverse event in the ICU among:* • Self-extubation. • Patient ablation of a medical device (urinary catheter, central catheter, arterial catheter, surgical drain). • Falling out of bed. • Self-aggressive or hetero-aggressive act. • ICU Runaway • Removal of restraints. The primary criterion is measured from D1 (day of inclusion) to discontinuation of treatment. The recording of events related to agitation will be interrupted in cases of intensive care discharge
SECONDARY JUDGEMENT CRITERIA	• The occurrence of at least 1 adverse event related to agitation from D1 to D28. • The number of adverse events per ICU patient from D1 to D28. • Agitation requiring rapid intravenous or intramuscular administration of a hypnotic or neuroleptic (bolus). • Extubation failure defined by reintubation <48 hours after extubation • Need for tracheotomy for ventilation weaning.

	• Reintubation by D28 • ICU-acquired infection(s): urinary tract infections, catheter infections, bacteremia, nosocomial pneumonia. • Cumulative doses of psychotropic drugs in the ICU (benzodiazepine, neuroleptics, morphinics) from D1 to D28. • SAS agitation score from D1 (day of inclusion) to D28. • Alcohol withdrawal score: CIWA-Ar from the day of extubation/tracheo until 7 days after extubation (calculation of the interrupted score in case of recovery before D7). • Duration of ICU stay. • Duration of hospital stay. • ICU mortality. • Hospital mortality. • Mortality from D28 to D90. • Agitation and mortality in the ICU by D28. • Duration of mechanical ventilation. • Number of days alive without mechanical ventilation during the first 28 days (Ventilator-free days)
METHODOLOGY/ TRIAL DESIGN	Phase III therapeutic study • Prospective • Multicenter • Randomized • Controlled • Versus placebo
CRITERIA FOR PATIENT INCLUSION	Patients admitted to the ICU with: • Consumption of alcohol qualified "at risk" (for males: consumption >14 drinks/week in the month prior to hospitalization; for males >65 years and females: consumption >7 drinks/week in the month prior to hospitalization). • AND intubated, on mechanical ventilation intended for more than 48 hours. • AND 18 to 70 years old.
CRITERIA FOR PATIENT NON-INCLUSION	• Patient receiving baclofen treatment prior to ICU admission regardless of the indication. • Pregnancy. • Porphyria. • Patient admitted for burns. • Ongoing treatment by GHB (Alcover®/Xyrem®). • Patient with brain injury/damage: brain imaging for recent stroke (ischemic or hemorrhagic), or meningeal hemorrhage and recent traumatic injury(ies). • Recent or former quadriplegic or paraplegic patient. • Cardiac arrest with manual cardiac massage on admission. • Administration of enteral treatment impossible or contraindicated for the duration of >48h. • Patient who does not benefit from French health insurance or who is under the state medical aid system. • Known hypersensitivity to baclofen. • Known celiac disease. • History of epilepsy resistant to treatments or epileptic seizure within 6 months of inclusion (seizures during alcohol withdrawal or balanced epilepsies will not be excluded).

	• Dementia or schizophrenia or bipolar/monopolar disease or severe depression. • Parkinson's disease. • Implementation of procedure of "limitation of active therapeutics". • Patient tracheostomized on ICU admission.
TREATMENTS/ STRATEGIES/ PROCEDURES	Randomized, double-blind, multicenter, placebo-controlled trial. 18 participating ICU's. Inclusion for 42 months and 90-day follow-up. • *Administration of treatment*: After inclusion, patients will be randomized to either the treatment group (baclofen) or the placebo group. Patients will receive either 150mg baclofen (adapted dosage in case of renal insufficiency) or 150mg placebo via the nasogastric tube on the day of inclusion. Patients will then receive the treatment or placebo daily for the duration of mechanical ventilation (dosage adapted to renal function). • *Gradual interruption:* After extubation/tracheotomy or after the 15th day of treatment if the patient has not been extubated/tracheotomized. • *On ICU discharge:* ❖ Questioning of the patient on his/her consumption, search for misuse (Questionnaire in Appendix 3) ❖ Propose, if necessary, specialized care through an addictology consultation.
NUMBER OF PATIENTS	314 patients The sample size may be adjusted during interim analysis if the prevalence of agitation observed in our population was greater than the data used to calculate the number of patients to be included. It will allow us to re-estimate, if necessary, the number of patients to be included in the trial in order to maintain the power of the trial.
DURATION OF THE TRIAL	Duration of the inclusion period: 42 months. Duration of participation for each patient: 90 days. Total duration of the trial: 45 months.
EXPECTED RETURNS	Administration of baclofen during the period of mechanical ventilation to prevent episodes of agitation could: • Facilitate the ventilatory weaning period, limit the duration of ventilation and nosocomial pneumonia. • Limit the use of psychotropic drugs. • Decrease morbidity and mortality and the neuropsychiatric consequences of agitation and delirium in the ICU.

1. Trial objectives

1.1 Principal objective

In a population of "at-risk alcohol consuming" patients admitted to intensive care and requiring mechanical ventilation, **evaluate the efficacy** of baclofen compared with placebo in reducing agitation-related adverse events.

1.2 Secondary objectives

Evaluate the impact of baclofen use on ICU morbidity and mortality in patients who present alcohol abuse.

2. Trial design

2.1 Precise statement of primary and secondary evaluation criteria.

2.1.1 Principal evaluation criteria

Occurrence of <u>at least 1</u> adverse event related to agitation in the ICU among:

- Self-extubation.
- Patient ablation of a medical device (i.e. urinary catheter, central catheter, arterial catheter, surgical drain).
- Falling out of bed.
- Flight.
- Removal of restraints.
- Self-aggressive or hetero-aggressive act.

Patients will therefore be classified into 2 groups:

- Patients who do not experience an adverse event.
- Patients with at least 1 adverse event.

<u>Collection method</u>: Since the principal criterion is strictly clinical, the data will be collected at patient bedside by the trial physician.

<u>Collection schedule</u>: The primary criterion is measured from D1 (day of inclusion) to cessation of treatment.

2.1.2 Secondary evaluation criteria

ICU morbidity-mortality:

- Occurrence of at least 1 adverse event related to agitation from D1 to D28.
- Number of adverse event(s) per ICU patient from D1 to D28.
- Agitation requiring rapid intravenous or intramuscular administration of a hypnotic or neuroleptic (bolus).
- Extubation failure defined by reintubation <48 hours after extubation.
- Need for tracheotomy for ventilation weaning.
- Reintubation by D28.
- ICU-acquired infection(s): urinary tract infections, catheter infections, bacteremia, nosocomial pneumonia.
- Cumulative doses of psychotropic drugs in the ICU (benzodiazepine, neuroleptics, morphinics) from D1 to D28.
- SAS agitation score from D1 (day of inclusion) to D28 (or until ICU discharge if before D28).
- Alcohol withdrawal score: CIWA-Ar from the day of extubation/tracheo until 7 days after

extubation (calculation of the interrupted score in case of recovery before D7).

- Duration of ICU stay.
- Duration of hospital stay.
- ICU mortality.
- Hospital mortality.
- Mortality from D28 to D90.
- Agitation and mortality in the ICU by D28.
- Duration of mechanical ventilation.
- Number of days alive without mechanical ventilation during the first 28 days.

Collection schedule

- Infections acquired in the ICU will be collected throughout the patient's hospitalization in the ICU.
- Cumulative doses of psychotropic drugs will be collected from D1 to D28.
- Agitation and withdrawal scores will be evaluated.
    - For the SAS agitation score: the worst score over the day, evaluated each day from D1 (inclusion) to D28 (or until the ICU discharge if before D28).
    - For the CIWA-Ar score: calculated each day at 8 a.m., from the day of extubation until D7 after extubation. Stopped on ICU discharge in case of discharge before D7.

2.2 Description of trial methodology, accompanied by its schematic presentation specifying, in particular, scheduled consultations and examinations.

2.2.1 Experimental plan

Statement of the selected design and justification:

- Phase III drug trial.
- Interregional multicenter trial.
- Comparative.
- Randomized.
- Controlled.
- Group control: placebo.
- Of superiority.
- Double-blind (patients and investigators).
- Comparison of 2 parallel groups

Baclofen Group: administration 3 times a day at a dosage adapted to renal function.
Placebo group (same procedure)

The efficacy of baclofen will be compared with that of placebo in terms of reducing the occurrence of adverse events related to agitation in the ICU.

Distribution of patients in the groups according to a ratio (1:1).

2.2.2 Conduct of the trial

2.2.2.1 Inclusion

- Verification of inclusion and exclusion criteria

- Information and signature of consent: After completing the interview and informing the family or support person (if designated), written informed consent to participate will be obtained by the investigator from the patient or the patient's representative, as appropriate. Whenever the patient is admitted to the ICU without intubation and his/her state of health permits, consent to participate in

the trial will be sought from the patient prior to intubation. In all cases, consent to proceed will be sought after clinical improvement and extubation. Prior written and signed informed consent must be obtained prior to the first administration of baclofen/placebo.

- Emergency consent: The protocol also provides for the possibility of emergency consent. Indeed, this protocol is aimed at a category of patients who are fragile and often socially isolated because of their dependence on alcohol. If we exclude all patients for whom there is no family member to sign consent within 24 hours, we risk creating a selection bias in our population, namely the exclusion of the most isolated patients suffering from severe addiction. Moreover, some patients will have short ventilatory durations, so we will need to start treatment very early so that the effect is optimized at the time of extubation. Emergency consent is therefore necessary for the successful completion of this trial.

2.2.2.2 Patient follow-up

A daily consultation by the investigator is planned for:

- Investigations specific to the trial:
  - **Clinical investigations**:
    - SAS Score Evaluation = highest score of the day (each day from D1 (inclusion) to D28 (or until ICU discharge if before D28).
    - Evaluation of the CIWA-Ar score (after extubation) = once a day at 8 a.m. (each day from the day of extubation to D+7)
    - Record of adverse events related to agitation during the entire ICU stay.
  - **Paraclinical investigations**: Plasma triglyceride levels will not be monitored because hypertriglyceridemia under treatment is observed for prolonged periods of treatment. In this trial, the maximum duration of treatment will be 15 days at the maximum dose followed by a maximum of 7 days of tapering.
  - **Blinded monitoring of the investigator**: Baclofen plasma levels at D3 and D10 of treatment in 3 participating centers – Surgical Intensive Care Unit, Nantes University Hospital, Medical Intensive Care Unit, Nantes University Hospital, Medical Intensive Care Unit, Rennes University Hospital – (details in paragraph 2.4.4).

- Investigations not specific to the trial:

  - **Clinical investigations**: Standard daily clinical examination of the ICU patient.
  - **Paraclinical investigations**: Detection of ICU-acquired infections is also part of routine ICU care. Intubated and ventilated ICU patients will benefit from extensive daily biological assessments as part of their management. In all cases, bioassessment will include at least 1 daily evaluation of blood glucose and complete CBC, plasma creatinine clearance, ionogram and urea, as well as 1 weekly hepatic check-up in order to adapt trial doses and ensure patient safety. These exams are part of standard ICU practice and are not protocol-specific exams.

2.3 Description of the measures taken to reduce and avoid bias

2.3.1 Drawing of lots

Randomization will be:

- Double-blind.
- Stratified on the trial center.
- Carried out in a 1:1 ratio and in blocks of 4.

Randomization will be carried out via Clinsight software by connecting to: **https://www.dirc-hugo-online.org/csonline/.** The connection will be via a login, a password and a trial number, provided by a data-manager from the Research Promotion Department at Nantes University Hospital.

The following information must be provided:

- The first letter of the family name.
- The first letter of the first name.
- Date of birth.
- Compliance with inclusion and non-inclusion criteria (yes/no).
- Signature of informed consent (yes/no).
- Stratification variable (trial center).

Randomization will be performed by the trial practitioner or the clinical research associate (CRA) of each center.

A randomization number will be assigned automatically during randomization. An e-mail confirmation will be sent to the person who made the randomization and to all concerned. The statistician responsible for randomization and the pharmacist will receive this information as well as the randomization group by e-mail.

2.3.2 Blinding methods

The Nantes University Hospital Pharmacy will prepare 10, 20 and 50 mg baclofen capsules and placebo capsules in such a way that they are indistinguishable in order to comply with double-blinding and then deliver them to the various trial centers.

In Nantes University Hospital Pharmacy, the baclofen or placebo capsules will be prepared and delivered by the central pharmacy of each trial center.

The two preparations will be indistinguishable: same aspect, same labelling, same smell, same color. They will have a batch number, a randomization number, dosage information, patient identification and the expiration date of the product.

2.4 Description of dosage and administration methods of the trial drug. Description of unit form, packaging and labelling of the trial drug.

2.4.1 Dosage and methods of administration

After inclusion, patients will be randomized to either the treatment group (baclofen) or the placebo group. Patients will receive either 150 mg baclofen (or an adapted dosage in case of renal insufficiency) or 150 mg placebo (or an adapted dosage in case of renal insufficiency) via nasogastric tube in a single dose from the day of inclusion (D1).

Patients will then receive the treatment or placebo daily for the duration of mechanical ventilation (dosage adapted to renal function) in 3 administrations.

Estimated eGFR	Day 1 = Loading dose	From day 2, until day 15 (or extubation/tracheostomy if it occurs before)
≥ 90	150 mg	50–50–50
89–60	100 mg	30–30–50

30–59	70 mg	20–20–30
<30 or continuous hemodialysis	50 mg	20–10–20
Sequential hemodialysis	50 mg	50 mg before each session
<15 with hemodialysis	50 mg	No administration

Breakdown of dosages according to creatinine clearance after D1:

- Clearance ≥90ml/min/1.73m^2: 150 mg/24h,
- Clearance 89–60 ml/min/1.73m^2: 100mg/24h,
- Clearance 30–59 ml/min/1.73m^2: 70 mg/24h,
- Clearance <30 ml/min/1.73m^2 or continuous hemodialysis: 50 mg/24h,
- Clearance <15 ml/min/1.73m^2 without substitution treatment: temporary cessation until kidney function improves,
- Intermittent hemodialysis: 50mg before each session.

Treatment decrease will begin either:

- The day after extubation/tracheotomy,
- After the 15th day of treatment if the patient is not extubated/tracheotomized.

The latter will last for a maximum of 7 days until the treatment is discontinued. Treatment decrease schedule:

Dosage on day of extubation/tracheotomy/D15	150 mg	100 mg	70 mg	50 mg	IHD 50mg
D+1	100mg (20-30-50)	70mg (20-20-30)	50mg (10-20-20)	30mg (10-10-10)	30mg before the session (nothing if no dialysis)
D+2	70mg (20-20-30)	50mg (10-20-20)	30mg (10-10-10)	20mg (10-0-10)	30mg before the session (nothing if no dialysis)
D+3	50mg (10-20-20)	30mg (10-10-10)	20mg (10-0-10)	10mg (10-0-0)	10mg before the session (nothing if no dialysis)
D+4	30mg (10-10-10)	20mg (10-0-10)	10mg (10-0-0)	STOP	STOP
D+5	20mg (10-0-10)	10mg (10-0-0)	STOP		
D+6	10mg (10-0-0)	STOP			
D+7	STOP				

2.5 Expected duration of patient participation and description of the chronology and duration of all trial periods

On inclusion, the promoter will promptly inform the Competent Authority and the REB of the effective starting date of the trial (effective starting date = date of signature of consent by the first trial patient).
The trial completion date will be transmitted by the promoter to ANSM (French Agency for the Safety of Health Products) and REB within 90 days. The end date of the trial will correspond to the end of the participation of the last patient who participates in the trial, or if applicable, **to the term defined in the protocol**.

Total duration of trial participation for each patient: **90 days**.
Total duration of the trial: **45 months.**

2.6 Description of the rules for final or temporary discontinuation

2.6.1 Cessation of a patient's participation in the trial

There are 3 situations that can lead to the termination of a patient's participation in the trial:

- Withdrawal of consent: at the request of a patient or his or her legal representative/trusted person, a patient's participation may be discontinued. "Legally authorized representative" means any person or authority with legal power or authority to legally consent to the patient's participation in trial procedures on the patient's behalf. If consent is withdrawn, the investigator will discontinue treatment. The investigator will notify the promoter, via the eCRF of the trial, of the premature termination of the trial for a patient and continue the collection of safety data.
- Death

- At the request of the promoter

Exception: The investigator may temporarily or permanently discontinue a patient's therapy for any reason that would be in the best interest of the patient, particularly in the event of serious adverse events. The patient's follow-up data should be retrieved during the patient's hospitalization in the ICU and, if possible, until the D90 consultation.
In the event of a patient lost to follow-up, the investigator will make every effort to regain contact with the patient.

2.6.2 Discontinuation of a part or all of the trial

The trial may be terminated prematurely in the event of unexpected serious adverse events requiring a review of the safety profile of the drug.
Similarly, unanticipated events or new information relating to the drug, which is unlikely to achieve the objectives of the trial or clinical program, may cause the promoter to terminate the trial prematurely.
Nantes University Hospital reserves the right to interrupt the trial, at any time, if the inclusion objectives are not met. The trial's Independent Monitoring Committee will be asked after the inclusion of the 100th and 200th patient to decide on continuation of the trial.
In the event of an early termination of the trial, the information will be transmitted by the promoter within 15 days to the ANSM and the REB.

Included patients will not be able to participate in any other intervention trials before D90 following inclusion.

2.7 PROVISIONS IMPLEMENTED FOR THE MAINTENANCE OF BLINDING AND PROCEDURES FOR LIFTING OF BLINDING

Randomization lists will be known only to the statistician, the clinical trial pharmacist, the promoter and the manager of the trial-specific eCRF. Investigators will not have access to these lists.

The trial drug and its placebo will be strictly identical in appearance.

3. Selection and exclusion of patients from the trial

3.1 CRITERIA FOR INCLUSION OF TRIAL PATIENTS

- "at-risk" drinking will be defined as consumption of >14 drinks/week for males in the month prior to hospitalization or >7 drinks/week in the month prior to hospitalization for males >65 years and females.
- **AND** intubated, ventilated with an expected mechanical ventilation time of at least 48 hours
- **AND** 18 to 70 years of age

3.2 CRITERIA FOR NON-INCLUSION OF PATIENTS

- Patient receiving baclofen treatment prior to ICU admission regardless of indication
- Pregnancy.
- Porphyria.

- Patient admitted for burns.
- Ongoing treatment by GHB (Alcover®/Xyrem®).
- Brain injured patient: brain imaging for a recent stroke (ischemic or hemorrhagic), or meningeal hemorrhage and recent traumatic injury(ies).
- Quadriplegic or paraplegic.
- Cardiac arrest with manual cardiac massage on admission.
- Administration of impossible or contraindicated enteral treatment for a duration of >48h.
- Patient who does not benefit from French health insurance or who is under the state medical aid system.
- Known hypersensitivity to baclofen.
- Known celiac disease.
- History of epilepsy resistant to treatments or epileptic seizure within 6 months of inclusion (seizures during alcohol withdrawal or balanced epilepsies will not be excluded).
- Dementia or schizophrenia or bipolar/monopolar disease or severe depression.
- Parkinson's disease.
- Implementation of procedure of "limitation of active therapeutics".
- Patient tracheostomized on ICU admission.
- Patient under legal protection.

  Since alcohol addiction affects populations of protected adults and the benefit of baclofen treatment may also be significant in this type of population, patients under guardianship or curatorship may be included with the agreement of their guardian/curator, or failing that, by emergency consent.

3.3 Procedure for early termination of treatment with the experimental drug and procedure for exclusion from the trial and follow-up of a patient within the framework of the trial

3.3.1 Criteria and methods for premature termination of treatment or exclusion of a patient from the trial

The situations that should lead to temporary or permanent discontinuation of treatment are as follows:

- Renal insufficiency with creatinine clearance assessed <15 ml/min/1.73m2 without replacement therapy: temporary discontinuation.
- Cytolysis >20 N: Temporary discontinuation until cytolysis <20N.
- Erythema or unexplained allergic manifestation: permanent discontinuation.

- Bradycardia <35/min with no other cause found, whatever the tolerance: permanent discontinuation.

- Bradycardia <50/min with poor hemodynamic tolerance with no other cause found: temporary discontinuation.

- Unilateral or bilateral areactive mydriasis: permanent discontinuation.

- Seizure in the ICU: permanent discontinuation.

- Ischemic or hemorrhagic stroke or cardiac arrest in the ICU (diagnosis by CT scan or MRI): permanent discontinuation.

- Delayed awakening defined by failure to open eyes to noise or pain 72 hours after complete cessation of sedation (morphinic, hypnotic): permanent discontinuation.

There are two situations that can lead to the exclusion of a patient from the trial:

- Withdrawal of consent: at the request of a patient or his or her legal representative/trusted person, a patient's participation may be discontinued. Legally authorized representative means any person or authority with legal power or authority to legally consent to the patient's participation in trial procedures on the patient's behalf.
- At the request of the promoter.

The investigator can temporarily or permanently discontinue a patient's therapy for any reason that would be in the best interest of the patient, particularly in the event of serious adverse events.
In the event of a patient lost to follow-up, the investigator will make every effort to regain contact with the patient.

3.3.2 Methods and timeframe for collecting data

Data concerning exclusions and early termination will be communicated to the promoter within a maximum of 7 days or 24 hours in case of serious adverse event(s). This declaration will be made via the eCRF and must include: the day of the termination of the protocol in relation to the inclusion, the reasons for the termination of the protocol.

The investigator will also complete the data collection notebook including the section concerning deviations from the protocol in which he or she will justify the termination or exclusion of the patient. The data collection notebooks will be regularly monitored by the trial's clinical research associate.

3.3.3 Arrangements for the replacement of patients, if applicable

Patients who discontinued the trial early will be retained in the intent-to-treat analysis and will not be replaced. These patients will be those:

- who present a treatment-related adverse event requiring discontinuation.
- who are lost to follow-up.
- for whom the trial was stopped at the request of the promoter.

If a patient dies before he or she is able to sign the consent to proceed or does not regain the ability to give consent, the data will be retained and analyzed in consideration of the initial consent of the patient's representative.

3.3.4 Patient follow-up methods

If participation is discontinued before the end of expected follow-up, the investigator will provide clinical and biological follow-up of the patient until regression of the possible side effects of the treatment. If the patient is discharged from the hospital, the investigator will use all of the means at his or her disposal (mail, telephone) to ensure that no side effects occur within 7 days of the last medication.

A patient's discharge from the trial will in no way change the management of his or her disease. In case of adverse event(s), serious or not, precise follow-up can be performed depending on the seriousness of the adverse event. The Supervisory Committee will specify monitoring procedures on a case-by-case basis.

4. Treatments administered to trial patients

4.1 Description of the treatments required to perform the trial

4.1.1 Experimental drug

4.1.1.1 Identification of the drug

Baclofen:

- INN: baclofen
- Galenic formulation: capsules dosed at 50 mg, 20 mg and 10 mg
- Composition:
    - Active ingredient: baclofen
    - Excipient: lactose

4.1.1.2 Packaging and labelling

The different dosages of baclofen will be packaged in PVC/aluminum anti-UV blisters.
Trial products will be packaged and labelled in accordance with current clinical trial regulations and good manufacturing practices by the Hôtel-Dieu Hospital Pharmacy, Nantes University Hospital, authorized to make preparations for biomedical research.

4.1.1.3 Manufacturing and distribution of the drug

Beforehand, baclofen capsules of different dosages and corresponding placebo capsules will have been manufactured by the Hôtel-Dieu Hospital Pharmacy, Nantes University Hospital, authorized to make preparations within the framework of biomedical research. The capsules will be made from powdered pharmaceutical grade baclofen.
In addition, the Nantes University Hospital Pharmacy will be the coordinating pharmacy for this trial and will ensure the distribution of the therapeutic units (verum and placebo) to the pharmacies of the trial centers. Shipments will be sent at the appropriate temperature via a rapid Chronopost-type carrier.

4.1.1.4 Administration

After inclusion, patients will be randomized into the treatment group (baclofen) or the placebo group. They will receive double-blind either 150mg baclofen (or an adapted dosage in case of renal insufficiency) or 150mg placebo (or an adapted dosage in case of renal insufficiency) through a nasogastric tube in 1 single time, from the day of inclusion (D1).

Patients will then receive the treatment or placebo in 3 doses during the following days. Administration of the treatments will be performed on medical prescription by a blinded registered nurse from the treatment group. For the duration of mechanical ventilation, administration will be performed via nasogastric tube. After extubation, if the patient swallows properly, treatment will be administered orally, if not, a nasogastric tube will be used.

4.1.2 Non-experimental drug: Placebo

4.1.2.1 Identification of the drug

- Galenic formulation: capsules
- Composition: excipient lactose

4.1.2.2 Packaging and labelling

The placebo capsules will be packaged in anti-UV PVC/aluminum blisters in order to be indistinguishable from the baclofen capsules.
They will be packaged and labelled in accordance with current clinical trial regulations and good manufacturing practices by the Hôtel-Dieu Hospital Pharmacy, Nantes University Hospital, authorized to make preparations for biomedical research.

4.1.2.3 Preparation and distribution of the drug

The placebo capsules will be prepared by the Hôtel-Dieu Hospital Pharmacy, Nantes University Hospital, authorized to make preparations for biomedical research. Preparation will be carried out with pharmaceutical grade raw materials.

The Hôtel-Dieu Hospital Pharmacy, Nantes University Hospital will be the coordinating pharmacy for this trial and will ensure the distribution of the therapeutic units (verum and placebo) to the pharmacies of the trial centers. Shipments will be sent at the appropriate temperature via a rapid Chronopost-type carrier.

4.1.2.4 Administration

Since the trial is double-blind, placebo-controlled, administration regimens will be identical.

4.1.3 Blinded investigator monitoring of plasma concentrations

Plasma concentrations will be monitored at 3 participating centers – Surgical Intensive Care Unit (Nantes University Hospital), Medical Intensive Care Unit (Nantes University Hospital), Medical Intensive Care Unit (Rennes University Hospital), with an expected number of patients of 80/314 and a theoretical number of patients treated with baclofen of 40/80.

The rate of the plasma dosages performed has been established with the referring pharmacologist of the trial, Professor E. Dailly. The purpose of the dosages is to verify the equilibrium of the plasma concentrations just before administration. Dosages will therefore be performed before morning administration on D3 and D10 of the treatment for patients still receiving treatment on these dates (excluding the decreasing period).

This will provide us with early data after the initiation of treatment and an evolution of plasma concentrations in situations of prolonged intensive care. I**n order to keep this double-blind, randomized trial blinded, while ensuring patient safety, the results of the assays will be sent blinded to the independent trial monitoring committee after the 20th, 40th, 60th and 80th patients are included. Samples will all be centralized at the Nantes University Hospital and prepared in Professor Dailly's pharmacology laboratory.**

This population of 40 treated patients/80 patients will be comparable to the number of patients in the only currently published trial (n=37 patients) on the pharmacokinetics of baclofen in alcohol-dependent patients.

After discussion with Pr. Dailly, we agreed to perform the first dosages 48 hours after the first administration because:

- Since the elimination half-life of baclofen is 4.5 to 6.8 hours, the stability of plasma concentrations is theoretically expected after a minimum of 5 ½ lives, i.e. 34 hours. Therefore, at D+1 (24 hours), the equilibrium of plasma concentrations would not be reached.
- For patients with renal insufficiency who will require an adaptation of the dosage, plasma half-lives will be longer.

Thus, taking pharmacokinetic samples on D3, i.e. 48 hours after the first dose, will make it possible to target a period during which plasma concentrations will be at an equilibrium for most of the patients in the trial.

4.2 Authorized and unauthorized drugs and treatment within the framework of the protocol, including rescue drugs

4.2.1 Authorized treatments

Patients admitted to the ICU will present life-threatening distress. All medications will be authorized in this situation. In particular, since this is a double-blind, placebo-controlled trial, the intensivist in charge of the patient will be authorized to prescribe the treatments he or she wishes within the context of the prevention of withdrawal syndrome.

4.2.2 Non-authorized treatments

The protocol does not set any treatment restrictions except for treatments included in the contraindicated combinations of acamprosate, naltrexone, disulfiram, nalmefen, lithium, antiparkinsonian drugs and baclofen.

5. Safety evaluation

5.1 Description of safety evaluation parameters

The safety of the trial will be evaluated:

- On biological criteria from ICU work-ups performed in current practice, in particular, detection of cytolysis.
- On clinical criteria (see list of adverse events [AEs] and serious adverse events [SAEs])

5.2 Methods and schedule for measuring, collecting and analyzing safety evaluation parameters

Methods:

- Collection of clinical AEs will take place during daily physical examinations in the ICU.
- Biological monitoring will be performed through regular reviews of current ICU practices.

The collection of safety parameters will begin with the first administration of treatment and will end one week after the last administration of baclofen.

5.3 Procedures in place for the registration and notification of adverse events.

Notification of adverse events will be made via the eCRF. These notifications will be transmitted to the promoter and registered in the vigilance database. Regular analyses will be carried out with the updating of databases.

5.3.1 Role of the investigator

5.3.1.1 Notification of serious adverse events

5.3.1.1.1 Information to be transmitted to the promoter

Each SAE will be described on the form to this effect ("Initial Declaration of Serious Adverse Event" or "Follow-up Declaration of Serious Adverse Event") with attention to be as complete as possible. The information to be transmitted will be as follows:

- patient identification (number, code, date of birth, date of inclusion, gender, weight, height),
- severity of AE,
- dates of the onset and end of AE,
- clear and detailed description of AE (diagnosis, symptoms, intensity, chronology, actions taken and results),
- evolution of AE,
- current illnesses or relevant patient history,
- treatments received by the patient,
- causal relationship of the AE to the trial drug, comparator(s), possible associated treatments, research or other criteria.

The investigator should also attach to the SAE report, whenever possible:

- a copy of the report of hospitalization or extension of hospitalization,
- if applicable, a copy of the autopsy report,
- a copy of all the results of further examinations, including any relevant negative results, together with normal laboratory values,
- any other document deemed useful and relevant.

These documents will be anonymous and will bear the patient's identification number.

5.3.1.1.2 How to notify the promoter

Any SAE, regardless of its causal relationship with trial treatment or research (with the exception of those identified in the protocol as not requiring an immediate declaration), must be declared by fax at 02 53 48 28 36 to the promotion department.

5.3.1.1.3 Time limit to notify the promoter

The investigator must immediately notify the trial promoter as soon as he or she becomes aware of any SAE.
The initial declaration may be followed by additional relevant information within **8 days** in the case of a fatal or life-threatening event and within **15 days** in other cases.

5.3.1.1.4 Promoter notification period

It is the investigator's responsibility to record and report all SAE occurring throughout the trial:
- from the date consent is signed,
- for the duration of the patient's follow-up,
- and up to 4 weeks (or >4 weeks taking into account the pharmacological characteristics of the experimental drug) after the end of the patient's follow-up.

5.3.1.1.5 Protocol specifics

- List of known and expected side effects:

Known and expected adverse effects in an ICU:

Infectious complications: on medical devices, nosocomial pneumonia

Neurological complications:
- Confusion and somnolence of medicinal origin: hypnotic used for sedation in ICU, powerful morphinics, antalgics, or nefopam,
- Confusion related to hospitalization itself (sleep disorders),
- ICU polyneuromyopathy,Convulsions or confusion after abrupt withdrawal from hypnotic drugs,
- Delayed awakening after administration of hypnotic or morphine treatments,
- Stroke under sedation or after extubation.

Cardiovascular complications: hypotension related to hypnotics (used for sedation in the ICU) and morphinic analgesics,

Respiratory complications: Delayed extubation, respiratory depression linked to hypnotics used for sedation in the ICU and morphinic analgesics. Need for reintubation and tracheotomy,

Digestive complications: gastric or duodenal ulcer, vomiting, occlusive syndrome,

Renal complications: renal insufficiency,

Liver complications: liver failure owing to drug toxicity,

Death in the ICU.

N.B. An exhaustive list of complications in the ICU is not feasible owing to the diversity of the pathologies treated.

Known and expected adverse effects within the framework of the pathology in the trial:
- Infectious: Increased susceptibility to infection,

- Neurological: Convulsions on alcohol or hypnotic withdrawal used for sedation in the ICU, agitation, deficiency encephalopathy (Gayet Wernicke's Syndrome),
- Digestive: Increased susceptibility to gastric or duodenal ulcers, digestive hemorrhage on rupture of esophageal varices,
- Biological: Liver failure with underlying liver disease, acute renal failure with hepatorenal syndrome.

Known and expected adverse effects within the framework of copathologies:

- Infectious complications: Implantable device infections, nosocomial pneumonia,
- Neurological complications:
- Drowsiness, confusion, convulsions, delayed awakening, stroke including hemorrhagic,
- Alcohol withdrawal syndrome and agitation,
- Digestive complications: Digestive hemorrhage, rupture of esophageal varices, gastric ulcer,
- Renal complications: Hepatorenal syndrome, renal insufficiency,
- Liver complications: Liver failure.

Known and expected adverse effects to trial treatment (baclofen) and its placebo:

The adverse events are presented below in descending order of frequency using the following categories: very common (³ 1/10), common (³ 1/100 and <1/10), infrequent (³ 1/1,000 and <1/100), rare (³ 1/10,000 and <1/1,000), very rare (<1/10,000), unknown (cannot be estimated based on available data).

Nervous system disorders	
Very frequent:	sedation, drowsiness, especially at the beginning of treatment
Frequent:	confusion, dizziness, headaches, insomnia, ataxia, tremors
Rare:	paresthesia, dysarthria, dysgeusia, tinnitus
Frequency undetermined:	lowering of the epileptogenic threshold in epileptics, paradoxical increase in spasticity in some patients
Psychiatric disorders	
Frequent:	euphoric state, depression, hallucinations
Ocular disorders	
Frequent:	accommodative dysfunction
Musculoskeletal and systemic disorders	
Rare:	muscular hypotonia that can be corrected by decreasing the daytime dose and possibly increasing the evening dose
Cardiac disorders	
Rare:	bradycardia
Respiratory disorders	
Frequent:	respiratory depression
Vascular disorders	
Frequent:	hypotension
Gastrointestinal disorders	
Very frequent:	nausea
Frequent:	vomiting, constipation, diarrhea, dry mouth
Rare:	abdominal pain, anorexia
Hepatobiliary disorders	
Rare:	abnormal liver function (increased alkaline phosphatases and transaminases)
Skin and subcutaneous tissue disorders	

Frequent:	hyperhidrosis, rash
Frequency undetermined:	hives
Kidney and urinary tract disorders	
Frequent:	aggravation of pre-existing dysuria
General disorders and anomalies at the administration site	
Very frequent:	asthenia
Very rare:	dose-dependent hypothermia
Investigations	
Frequency undetermined:	increased blood sugar levels

Post-weaning syndrome: discontinuation of treatment, especially if abrupt, can induce a post-weaning syndrome that is sometimes lethal. The most frequently reported reactions (by analogy with what has been observed via intrathecal administration) are: neuromuscular disorders (spasticity, dyskinesias, rhabdomyolysis, paresthesia, convulsions or even epileptic seizures), pruritus, dysautonomia (hyperthermia, hypotension), consciousness and behavioral disorders (confused state, anxiety, manic or paranoid psychotic state) and coagulopathy.

- Non-serious adverse events subject to immediate reporting:

All non-serious adverse events and/or abnormal test results defined below as critical to the assessment of the safety of trial patients must be reported to the promoter by the investigator in accordance with the reporting requirements for SAE:

  - *major hyperglycemia (grade 3 and above)*
  - *major hyperleukocytosis (grade 3 and above).*

- SAE that do not require reporting:

Certain circumstances requiring hospitalization do not fall under the "hospitalization or extension of hospitalization" severity criteria and should not be declared as SAE:

- hospitalization predefined by the protocol,
- admission for social or administrative reasons,
- outpatient care,
- hospitalization for routine treatment or monitoring of a pathology not associated with a deterioration of the patient's condition,
- hospitalization for medical or surgical treatment scheduled before the start of the trial.

In addition, the following SAE will not require (in agreement with the health authorities) an im57 statement:

- Death before administration of the medication,
- Adverse events occurring 7 days after the definitive discontinuation of baclofen and corresponding to the origin of the underlying pathologies,
- Traumatic pathology/complication related to ICU management.

5.3.2 Role of the promoter

5.3.2.1 Analysis of serious adverse events

The promoter must assess:

- the causality of the SAE (all adverse events, for which the investigator or promoter believes that a causal relationship with the trial drug can reasonably be considered as being linked suspected adverse events. In the event of a different assessment by the promoter and the investigator, both opinions will be noted in the notification to the Competent Authority if such notification is necessary),
- and their expected or unexpected nature, using the current reference document (Investigator's Brochure or SPC).

5.3.2.2 Accountability assessment

In accordance with the ICH recommendations on the Management of Adverse Events in Clinical Trials - ICH E2B(R3), version of May 12, 2005 – an accountability assessment will be performed for any reported adverse drug reaction (ADR).
Adverse events with a minimally questionable relationship to the trial drug or its placebo will be considered as reasonably related to it/them. If they are unexpected, they will be qualified as unexpected serious adverse drug reactions (USADRs) and must be reported by the promoter.

5.3.2.3 Reporting USADRs

The promoter will report all serious and unexpected adverse events (SAEs) to Eudravigilance (European Pharmacovigilance Database), the French Health Authorities (ANSM) and the Research Ethics Board (REB) and to the investigators.
The statutory declaration shall be made within a maximum period of:
- **7 calendar days** for serious unexpected fatal or life-threatening adverse effects. In these cases, additional relevant information must be sought and transmitted within a further **8 days**.
- **15 calendar days** for all other serious and unexpected adverse effects. Similarly, additional relevant information must be sought and transmitted within a further **8 days**.
In the case of blinded trials, as a general rule, the promoter will report the serious unexpected adverse reaction to the health authorities and the REB after unblinding the trial drug.
In exceptional cases, and with the agreement of the ANSM requested by the promoter at the time of the application for authorization of the clinical trial, the procedures for unblinding and reporting of suspected adverse reactions may be adjusted. These procedures will be precisely defined in the trial protocol.
Detailed records of all adverse events reported by the investigators may be provided to the ANSM on request.

5.3.2.4 Transmission of annual safety reports

On the anniversary date of trial authorization issued by the Health Authorities, the promoter will prepare a safety report that includes:
- a list of serious adverse events that could be related to the trial drug including unexpected and expected serious adverse effects,
- a concise and critical analysis of patient safety that could be used for research.
This report may be submitted to the coordinating investigator for approval. It will be sent to the Competent Authorities (ANSM) and the REB within 60 days of the anniversary date of trial authorization.

5.3.2.5 Transmission of half-yearly safety reports

Every six months, the promoter will send the REB, with a copy to the ANSM, a list of the USADRs that have occurred in trials outside of the national territory, as well as the USADRs that have occurred in other trials with the same trial drug. When the promoter has an investigational drug in development, the list will also include other USADRs on that drug that the promoter is aware of (publication or pharmaceutical company). The list will be accompanied by a summary.

5.3.3 Monitoring Committee

The mission of the Independent Monitoring Committee will be to monitor the clinical and biological tolerability of the trial drug. It will be responsible for informing the Scientific Committee of its decisions to amend or discontinue the trial. It will be formed at the beginning of the trial and will include at least three members not directly involved in the trial.
The Monitoring Committee will transmit its recommendations to the Scientific Committee which will decide whether or not to stop the trial. The decision to stop the trial may be taken earlier if it appears

contrary to the rules to continue it (the occurrence of serious adverse events, publication of the results of a trial providing the answer to a given question, etc.).
The Independent Monitoring Committee will have the authority to make recommendations for the termination of the trial based on evaluation of the results.

Since the trial is double-blind, the Independent Monitoring Committee will only evaluate the raw data, with no unblinding (i.e. without attribution). If the frequency of adverse events in one of the two groups turns out to be higher than expected and then leads to suspicion of a higher frequency for the trial drug, the Independent Monitoring Committee may then request unblinding and a halt to inclusions in order to verify the frequency in each treatment group.

At the request of the ANSM, baclofen plasma concentrations will be blinded by the investigator at 3 participating centers and reported to the Independent Monitoring Committee which will verify the absence of overdose with the trial's dosing regimen.

6. Statistics

Names and contact details of the persons in charge of the analysis:
Dr. Fanny Feuillet and Dr. Véronique Sébille, Biometrics Platform – Nantes University Hospital & EA 4275 "Biostatistics, Pharmacoepidemiology and Subjective Measures in Health" – UFR of the University of Nantes Pharmacy.

Statistics software:
The statistical analysis will be performed using SAS 9.3 software.

6.1 Description of the planned statistical methods, including the schedule of planned interim analyses

The final statistical analysis will be performed via intent-to-treat (ITT) and will be completed as soon as the trial has ended.

An intermediary analysis will be carried out which will make it possible to re-estimate, if necessary, the number of patients to be included in the trial in order to maintain the power of the trial. It will be performed after inclusion of half of the total number of patients (i.e. 157 patients). The global probability of the event will be estimated from all of the data (groups of treatments combined) in order to preserve blinding. The method proposed by Friede and Kieser (47,48) will make it possible to maintain the initial clinical hypothesis (15-point decrease in the agitation rate) and to preserve the initial Type 1 error of 5%.

All analyses will be adjusted at trial centers (stratified randomization on this factor).

In order to meet the main objective, a logistic regression model will be applied to compare the proportions of agitation between the two groups.
The need to adjust for cirrhosis will be evaluated for all criteria by testing the significance of this variable and its possible interaction with the treatment in the models.
In order to account for mortality, two sensitivity analyses will be performed: 1) all patients who died without an agitation-related adverse event will be considered to have had at least 1 adverse event, 2) all patients who died without an agitation-related adverse event will be considered to have had no adverse events.

An additional per protocol analysis will be performed to enable exclusion from the analysis of patients who were wrongly included, non-observing patients or patients having received the treatment of the other group.

In order to meet secondary objectives:
- a Poisson regression model will be applied to compare the number of adverse events related to ICU agitation between the two groups of patients,
- survival models (Kaplan-Meier estimator) will be applied to compare length of stay and duration of mechanical ventilation between the two groups of patients.
- logistic regression models will be applied in order to compare binary qualitative criteria between the two groups of patients (reintubation, extubation failure, ICU-acquired infections, mortality ...).

No subgroup analysis is planned.

6.2 Anticipated number of people to be included in the trial and anticipated number of patients at each trial site with statistical justification

A preliminary trial (MD thesis, University of Nantes, 2013) indicated an ICU agitation rate of 42% (corresponding to the occurrence of at least one agitation-related adverse event). The hypothesis of a 15-point decrease in this agitation rate in the baclofen group appears to be clinically relevant, i.e. 27% agitation. The number of patients required for the trial for a potency (1-β) of 80% and a risk (α) of 5% is 157 patients per group, i.e. a total of 314 patients.

6.3 Expected degree of statistical significance

The expected degree of significance is set at 5% or less

6.4 Statistical criteria for stopping the trial

Not applicable.

6.5 Method for taking into account missing, unused or invalid data

Patients cannot be lost to follow-up as long as they are in the ICU.
Since the main criterion is measured during ICU stay, missing data will be rare or non-existent. The only possibility for a patient to be lost to follow-up is to flee the ICU: this event would correspond to an adverse event related to agitation (flight).

In all cases, patients lost to follow-up will not be replaced but will be included in the intention-to-treat analysis.

Data from early exclusions will be retained in the intent-to-treat analysis.

Missing data will be described in terms of numbers and corresponding percentages per group. Patients will not be replaced. The presence of possible imbalances in terms of the proportion of missing data between treatment groups will be assessed according to their cause by tests of comparisons of observed proportions (tests from $\chi 2$, Fisher exact tests or logistic regression models in case of adjustment).

6.6 Management of changes to the initial strategy analysis plan

The trial may be stopped early at the decision of the promoter if the frequency of baclofen-related SAEs reported by the trial pharmacovigilance administrator is high.

6.7 Selection of patients to be included in the trial

The analysis will focus on the intent-to-treat (ITT) population. All included patients will be included in the primary endpoint analysis. The time between inclusion and the start of treatment in the trial will

be very short. No included patient will be lost to follow-up between inclusion and the administration of the treatment. It will therefore be unlikely that data will be missing for the main criterion.

7. Right of access to source data and documents

7.1 Access to data

In accordance with GCP:
- the promoter will be responsible for obtaining the agreement of all parties involved in the trial in order to guarantee direct access to all trial locations, source data, source documents and reports for the purpose of quality control and audit by the promoter,
- the investigators will make available to the persons responsible for monitoring, quality control or auditing biomedical research, the documents and individual data strictly necessary for this control, in accordance with the legislative and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the Public Health Code).

The source documents for the trial will be:

- The handwritten trial observation notebook,
- Patient medical records with the medical observation and nursing surveillance sheets.

7.2 Data privacy

In accordance with the provisions concerning the confidentiality of the data to which the persons in charge of quality control of biomedical research have access (article L.1121-3 of the Public Health Code), in accordance with the provisions relating to the confidentiality of information concerning, in particular, the nature of experimental medicinal products, the trials, the persons involved and the results obtained (Article R. 5121-13 of the Public Health Code), persons with direct access shall take all necessary precautions to ensure the confidentiality of information relating to trial medicinal products, the trials, the patients participating in them and, in particular, with regard to their identity and the results obtained.
These persons, in the same way as the investigators themselves, will be subject to professional secrecy (according to the conditions defined by articles 226-13 and 226-14 of the penal code).
During or at the conclusion of the trial, the data collected on patients and transmitted to the promoter by the investigators (or other specialized stakeholders) will be made anonymous.
Under no circumstances should the names of patients or their addresses appear.
Only the first letter of the patient's family name and the first letter of the patient's first name will be recorded, accompanied by a coded number specific to the trial indicating the order of inclusion of the patients.
The promoter will ensure that each patient who participates in the trial has given his or her written consent for access to patient data concerning him or her that is strictly necessary for quality control of the trial.

8. Trial Monitoring

Monitoring will be performed by the promotion department of the Research Directorate. A Clinical Research Associate (CRA) will make regular visits to each site (investigator's department and pharmacy) in order to carry out quality control of the data reported in the case report forms.
The protocol has been classified according to the estimated level of risk to the patient.
It will be classified as follows:
Risk C: high predictable risk

On-site monitoring visits will be organized after an appointment with the investigator.
CRAs will need to be able to consult on each site:
- patient data collection notebooks,
- patient medical and nursing records,

- the investigator's notebook

During these visits, the following items will be reviewed:

- Informed consent,
- Verification of inclusion and non-inclusion criteria,
- Conformity of the visit dates on the theoretical calendar,
- Verification of the main evaluation criterion,
- Verification of secondary evaluation criteria,
- The search for unreported SAEs and related treatments, new developments,
- Product management

On the other hand, the investigators will undertake to accept quality assurance audits performed by the promoter as well as inspections performed by the competent authorities. All data, documents and reports can be subject to regulatory audits and inspections without being subject to medical secrecy.

9. Ethical considerations

9.1 Research Ethics Board (REB)

The protocol, the information form and the certificate of consent for the trial were submitted for opinion to the Angers REB and received a favorable opinion on July 6, 2015.
Notification of the REB's favorable opinion was forwarded to the trial promoter and the Competent Authority. An authorization was sent by the promoter to ANSM.

9.2 Substantial modifications

If the investigator makes a substantial change to the protocol, it must be approved by the promoter. The latter will have to obtain, prior to its implementation, a favorable opinion from the REB and an authorization from ANSM within the framework of their respective competences. New consent from trial participants will have to be obtained if deemed necessary.

9.3 Patient information and written informed consent form

Patients and patient representatives will be fully and fairly informed, in understandable terms, of the objectives and constraints of the trial, the possible risks involved, the necessary monitoring and safety measures, their rights to refuse to participate in the trial or to withdraw from the trial at any time.
All this information will appear on an information and consent form given to the patient. The patient's free, informed and written consent will be obtained by the investigator or a physician representing the patient prior to final inclusion in the trial. A copy of the consent form signed by both parties will be given to the patient, the investigator will keep the original.

❖ **For patients on mechanical ventilation on arrival in the ICU (the most frequent cases):**
The patient will not be able to sign the informed consent himself/herself. The protocol provides informed information and a consent form for patient representative. The investigator undertakes to inform this person in a clear and fair manner and to ask him or her for written informed consent. The investigator must also sign and date the consent form. These two documents will be provided on paper with a minimum of 2 copies so that the patient's representative and the investigator can each keep one copy. The investigator's original will be filed in the investigator's binder.
As soon as the patient's condition permits, the investigator will undertake to inform the patient in a clear and fair manner and to provide him or her with an information letter and to ask for written informed consent to continue the trial if he or she is competent.
In an emergency situation, the consent form will be signed by a patient representative other than a guardian/curator/family member/trusted person and by an investigator. Patient consent will be sought as soon as the patient's condition permits.

❖ **For non-intubated patients admitted to the ICU:**

If the patient is competent, he or she will be informed by an information letter and his or her consent will be sought before intubation. Otherwise the emergency consent procedure may be used.

9.4 Definition of the exclusion period

The defined exclusion period for this trial is 90 days, during which time the patient may not participate in another **interventional** clinical research protocol after the end of the trial or after early termination of the trial.

9.5 Trial-related support

Management of the patients included in this trial was modelled on the management that is usually recommended.

Except for the administration of the treatments in this trial, ICU management will not differ from its standard management.

Biological monitoring on inclusion and as long as baclofen is administered will concern, complete CBC and blood glucose levels daily, renal function per 24 hours (calculation of creatinine clearance). Liver function will be evaluated once a week from inclusion to one week after baclofen/placebo discontinuation.

9.6 Patient compensation

No compensation will be provided.

10. Insurance

The promoter will subscribe to an insurance policy for the entire duration of the trial to cover the promoter's own civil liability as well as that of any physician involved in the trial (Article L 1121-10). The promoter will also ensure full compensation for possible harmful consequences of the trial for a patient who agrees to participate in the trial and his or her heirs, unless it can be proven that the damage is not attributable to the promoter or to that of any party involved, without being able to oppose the fact of a third party or the voluntary withdrawal of the person who initially agreed to participate in the trial.

11. Publication conditions

A copy of the publication will be given to the Nantes University Hospital, promoter of the trial which will necessarily be cited. The authors will be prorated based on the number of patients included. The coordinating investigator will draw up the list of authors.

The signatories, Mickael Vourc'h (MD) as first author, Pierre-Joachim Mahé (MD) as penultimate author, and Karim Asehnoune (MD, PhD) as last author, and 1 investigator per participating center (in order of the number of inclusions provided that the center has included at least 10 patients over the duration of the trial) and the statistician-methodologist. A second investigator per center may be co-signatory in centers with 30 or more patients. Finally, all investigators who have included patients will be listed in the BACLO-REA trial group at the end of the publication in alphabetical order.

The rules of publication will follow international recommendations (N Engl J Med, 1997; 336:309-315).

The trial will be registered on an open access website (Clinical trial) prior to inclusion of the first patient in this trial.

CONTENTS

SUMMARY

TITLE	*BACLO-REA Protocol – Prevention of agitation in ICU patients who present unhealthy alcohol use.* Baclofen versus placebo. A randomized controlled trial.
PROMOTOR	Nantes University Hospital
COORDINATING INVESTIGATOR	Professor Karim Asehnoune
JUSTIFICATION/ CONTEXT	In general hospitals, 25% to 35% of men and 5% to 10% of women hospitalized are chronic alcoholics. In intensive care, up to 28% of admissions are directly related to excessive alcohol consumption. According to the National Institute on Alcohol Abuse and Alcoholism (NIAAA), a patient is considered as an at-risk consumer if his or her consumption exceeds: • For a male: consumption of >14 glasses/week in the year prior to hospitalization; • For a male >65 years or a female: consumption of >7 glasses/week in the year prior to hospitalization. The two principal consequences of alcoholism in intensive care are withdrawal syndrome and agitation. They are the sources of serious adverse events such as self-extubation, self-ablation of medical devices, falls, or heavy sedation causing delayed awakening. All of these elements increase morbidity and mortality in the ICU. Baclofen is a centrally acting muscle relaxant. Two randomized studies have reported its effectiveness in the treatment of alcohol withdrawal syndrome and two others in the reduction of alcohol consumption. We therefore propose this multicenter, randomized, placebo-controlled baclofen trial. Our objective is to evaluate the efficacy of baclofen in reducing adverse events related to agitation by ICU patients who present unhealthy alcohol use.
PRINCIPAL OBJECTIVE	To evaluate the efficacy of baclofen compared with placebo in reducing agitation-related adverse events in non-brain injured patients admitted to intensive care and classified as at-risk alcohol consumers according to NIAAA criteria and requiring mechanical ventilation for at least 48 hours.
SECONDARY OBJECTIVES	To evaluate the impact of baclofen on morbidity and mortality in the hospital and the ICU in patients who present unhealthy alcohol use.
PRINCIPAL JUDGEMENT CRITERIA	*The occurrence of at least 1 adverse event in the ICU among:* • Self-extubation. • Patient ablation of a medical device (urinary catheter, central catheter, arterial catheter, surgical drain). • Falling out of bed. • Self-aggressive or hetero-aggressive act. • ICU Runaway • Removal of restraints. The primary criterion is measured from D1 (day of inclusion) to discontinuation of treatment. The recording of events related to agitation will be interrupted in cases of intensive care discharge
SECONDARY JUDGEMENT CRITERIA	• The occurrence of at least 1 adverse event related to agitation from D1 to D28. • The number of adverse events per ICU patient from D1 to D28. • The occurrence of at least 1 agitation-related adverse event during treatment or mortality by D28. • Agitation requiring rapid intravenous or intramuscular administration of a hypnotic or neuroleptic (bolus).

	• Extubation failure defined by reintubation <48 hours after extubation • Need for tracheotomy for ventilation weaning. • Reintubation by D28 • ICU-acquired infection(s): urinary tract infections, catheter infections, bacteremia, nosocomial pneumonia. • Cumulative doses of psychotropic drugs in the ICU (benzodiazepine, neuroleptics, morphinics) from D1 to D28. • SAS agitation score from D1 (day of inclusion) to D28. • Alcohol withdrawal score: CIWA-Ar from the day of extubation/tracheo until 7 days after extubation (calculation of the interrupted score in case of recovery before D7). • Duration of ICU stay. • Duration of hospital stay. • ICU mortality. • Hospital mortality. • Mortality from D28 to D90. • Agitation and mortality in the ICU by D28. • Duration of mechanical ventilation. • Number of days alive without mechanical ventilation during the first 28 days (Ventilator-free days)
METHODOLOGY/ TRIAL DESIGN	Phase III therapeutic study • Prospective • Multicenter • Randomized • Controlled • Versus placebo
CRITERIA FOR PATIENT INCLUSION	Patients admitted to the ICU with: • Consumption of alcohol qualified "at risk" (for males: consumption >14 drinks/week in the month prior to hospitalization; for males >65 years and females: consumption >7 drinks/week in the month prior to hospitalization). • AND intubated, on mechanical ventilation intended for more than 24 hours. • AND 18 to 80 years old.
CRITERIA FOR PATIENT NON-INCLUSION	• Patient receiving baclofen treatment prior to ICU admission regardless of the indication. • Hospitalization >7 days (current episode). • Pregnancy. • Porphyria. • Patient admitted for burns. • Ongoing treatment by GHB (Alcover®/Xyrem®). • Patient with brain injury/damage: brain imaging for recent stroke (ischemic or hemorrhagic), or meningeal hemorrhage and recent traumatic injury(ies). • Recent or former quadriplegic or paraplegic patient. • Cardiac arrest with manual cardiac massage on admission. • Administration of enteral treatment impossible or contraindicated for the duration of >48h. • Patient who does not benefit from French health insurance or who is under the state medical aid system. • Known hypersensitivity to baclofen. • Known celiac disease.

	• History of epilepsy resistant to treatments or epileptic seizure within 6 months of inclusion (seizures during alcohol withdrawal or balanced epilepsies will not be excluded). • Dementia or schizophrenia or bipolar/monopolar disease or severe depression. • Parkinson's disease. • Implementation of procedure of "limitation of active therapeutics". • Patient tracheostomized on ICU admission. • Patient participating in other drug intervention trial(s).
TREATMENTS/ STRATEGIES/ PROCEDURES	Randomized, double-blind, multicenter, placebo-controlled trial. 18 participating ICU's. Inclusion for 42 months and 90-day follow-up. • *Administration of treatment*: After inclusion, patients will be randomized to either the treatment group (baclofen) or the placebo group. Patients will receive either 150mg baclofen (adapted dosage in case of renal insufficiency) or 150mg placebo via the nasogastric tube on the day of inclusion. Patients will then receive the treatment or placebo daily for the duration of mechanical ventilation (dosage adapted to renal function). • *Gradual interruption:* After extubation/tracheotomy or after the 15th day of treatment if the patient has not been extubated/tracheotomized. • *On ICU discharge:* ❖ Questioning of the patient on his/her consumption, search for misuse (Questionnaire in Appendix 3) ❖ Propose, if necessary, specialized care through an addictology consultation.
NUMBER OF PATIENTS	314 patients The sample size may be adjusted during interim analysis if the prevalence of agitation observed in our population was greater than the data used to calculate the number of patients to be included. It will allow us to re-estimate, if necessary, the number of patients to be included in the trial in order to maintain the power of the trial.
DURATION OF THE TRIAL	Duration of the inclusion period: 42 months. Duration of participation for each patient: 90 days. Total duration of the trial: 45 months.
EXPECTED RETURNS	Administration of baclofen during the period of mechanical ventilation to prevent episodes of agitation could: • Facilitate the ventilatory weaning period, limit the duration of ventilation and nosocomial pneumonia. • Limit the use of psychotropic drugs. • Decrease morbidity and mortality and the neuropsychiatric consequences of agitation and delirium in the ICU.

1. Trial objectives

1.1 Principal objective

In a population of "at-risk alcohol consuming" patients admitted to intensive care and requiring mechanical ventilation, **evaluate the efficacy** of baclofen compared with placebo in reducing agitation-related adverse events.

1.2 Secondary objectives

Evaluate the impact of baclofen use on ICU morbidity and mortality in patients who present alcohol abuse.

2. Trial design

2.1 Precise statement of primary and secondary evaluation criteria.

2.1.1 Principal evaluation criteria

Occurrence of <u>at least 1</u> adverse event related to agitation in the ICU among:

- Self-extubation.
- Patient ablation of a medical device (i.e. urinary catheter, central catheter, arterial catheter, surgical drain).
- Falling out of bed.
- Flight.
- Removal of restraints.
- Self-aggressive or hetero-aggressive act.

Patients will therefore be classified into 2 groups:

- Patients who do not experience an adverse event.
- Patients with at least 1 adverse event.

<u>Collection method</u>: Since the principal criterion is strictly clinical, the data will be collected at patient bedside by the trial physician.

<u>Collection schedule</u>: The primary criterion is measured from D1 (day of inclusion) to cessation of treatment.

2.1.2 Secondary evaluation criteria

ICU morbidity-mortality:

- Occurrence of at least 1 agitation-related adverse event during treatment or mortality by D28.
- Occurrence of at least 1 adverse event related to agitation from D1 to D28.
- Number of adverse event(s) per ICU patient from D1 to D28.
- Agitation requiring rapid intravenous or intramuscular administration of a hypnotic or neuroleptic (bolus).
- Extubation failure defined by reintubation <48 hours after extubation.
- Need for tracheotomy for ventilation weaning.
- Reintubation by D28.
- ICU-acquired infection(s): urinary tract infections, catheter infections, bacteremia, nosocomial pneumonia.
- Cumulative doses of psychotropic drugs in the ICU (benzodiazepine, neuroleptics, morphinics) from D1 to D28.
- SAS agitation score from D1 (day of inclusion) to D28 (or until ICU discharge if before D28).

- Alcohol withdrawal score: CIWA-Ar from the day of extubation/tracheo until 7 days after extubation (calculation of the interrupted score in case of recovery before D7).
- Duration of ICU stay.
- Duration of hospital stay.
- ICU mortality.
- Hospital mortality.
- Mortality from D28 to D90.
- Agitation and mortality in the ICU by D28.
- Duration of mechanical ventilation.
- Number of days alive without mechanical ventilation during the first 28 days.

Collection schedule

- Infections acquired in the ICU will be collected throughout the patient's hospitalization in the ICU.
- Cumulative doses of psychotropic drugs will be collected from D1 to D28.
- Agitation and withdrawal scores will be evaluated.
    - For the SAS agitation score: the worst score over the day, evaluated each day from D1 (inclusion) to D28 (or until the ICU discharge if before D28).
    - For the CIWA-Ar score: calculated each day at 8 a.m., from the day of extubation until D7 after extubation. Stopped on ICU discharge in case of discharge before D7.

2.2 Description of trial methodology, accompanied by its schematic presentation specifying, in particular, scheduled consultations and examinations.

2.2.1 Experimental plan

Statement of the selected design and justification:

- Phase III drug trial.
- Interregional multicenter trial.
- Comparative.
- Randomized.
- Controlled.
- Group control: placebo.
- Of superiority.
- Double-blind (patients and investigators).
- Comparison of 2 parallel groups

Baclofen Group: administration 3 times a day at a dosage adapted to renal function.
Placebo group (same procedure)

The efficacy of baclofen will be compared with that of placebo in terms of reducing the occurrence of adverse events related to agitation in the ICU.

Distribution of patients in the groups according to a ratio (1:1).

2.2.2 Conduct of the trial

2.2.2.1 Inclusion

- Verification of inclusion and exclusion criteria

- Information and signature of consent: After completing the interview and informing the family or support person (if designated), written informed consent to participate will be obtained by the investigator from the patient or the patient's representative, as appropriate. Whenever the patient is

admitted to the ICU without intubation and his/her state of health permits, consent to participate in the trial will be sought from the patient prior to intubation. In all cases, consent to proceed will be sought after clinical improvement and extubation. Prior written and signed informed consent must be obtained prior to the first administration of baclofen/placebo.

- Emergency consent: The protocol also provides for the possibility of emergency consent. Indeed, this protocol is aimed at a category of patients who are fragile and often socially isolated because of their dependence on alcohol. If we exclude all patients for whom there is no family member to sign consent within 24 hours, we risk creating a selection bias in our population, namely the exclusion of the most isolated patients suffering from severe addiction. Moreover, some patients will have short ventilatory durations, so we will need to start treatment very early so that the effect is optimized at the time of extubation. Emergency consent is therefore necessary for the successful completion of this trial.

2.2.2.2 Patient follow-up

A daily consultation by the investigator is planned for:

- Investigations specific to the trial:

- **Clinical investigations**:
  - SAS Score Evaluation = highest score of the day (each day from D1 (inclusion) to D28 (or until ICU discharge if before D28).
  - Evaluation of the CIWA-Ar score (after extubation) = once a day at 8 a.m. (each day from the day of extubation to D+7)
  - Record of adverse events related to agitation during the entire ICU stay.
- **Paraclinical investigations**: Plasma triglyceride levels will not be monitored because hypertriglyceridemia under treatment is observed for prolonged periods of treatment. In this trial, the maximum duration of treatment will be 15 days at the maximum dose followed by a maximum of 7 days of tapering.
- **Blinded monitoring of the investigator**: Baclofen plasma levels at D3 and D10 of treatment in 3 participating centers – Surgical Intensive Care Unit, Nantes University Hospital, Medical Intensive Care Unit, Nantes University Hospital, Medical Intensive Care Unit, Rennes University Hospital – (details in paragraph 2.4.4).

- Investigations not specific to the trial:

- **Clinical investigations**: Standard daily clinical examination of the ICU patient.
- **Paraclinical investigations**: Detection of ICU-acquired infections is also part of routine ICU care. Intubated and ventilated ICU patients will benefit from extensive daily biological assessments as part of their management. In all cases, bioassessment will include at least 1 daily evaluation of blood glucose and complete CBC, plasma creatinine clearance, ionogram and urea, as well as 1 weekly hepatic check-up in order to adapt trial doses and ensure patient safety. These exams are part of standard ICU practice and are not protocol-specific exams.

2.3 Description of the measures taken to reduce and avoid bias

2.3.1 Drawing of lots

Randomization will be:

- Double-blind.
- Stratified on the trial center.
- Carried out in a 1:1 ratio and in blocks of 4.

Randomization will be carried out via Clinsight software by connecting to: **https://www.dirc-hugo-online.org/csonline/.** The connection will be via a login, a password and a trial number, provided by a data-manager from the Research Promotion Department at Nantes University Hospital.

The following information must be provided:

- The first letter of the family name.
- The first letter of the first name.
- Date of birth.
- Compliance with inclusion and non-inclusion criteria (yes/no).
- Signature of informed consent (yes/no).
- Stratification variable (trial center).

Randomization will be performed by the trial practitioner or the clinical research associate (CRA) of each center.

A randomization number will be assigned automatically during randomization. An e-mail confirmation will be sent to the person who made the randomization and to all concerned. The statistician responsible for randomization and the pharmacist will receive this information as well as the randomization group by e-mail.

2.3.2 Blinding methods

The Nantes University Hospital Pharmacy will prepare 10, 20 and 50 mg baclofen capsules and placebo capsules in such a way that they are indistinguishable in order to comply with double-blinding and then deliver them to the various trial centers.

In Nantes University Hospital Pharmacy, the baclofen or placebo capsules will be prepared and delivered by the central pharmacy of each trial center.

The two preparations will be indistinguishable: same aspect, same labelling, same smell, same color. They will have a batch number, a randomization number, dosage information, patient identification and the expiration date of the product.

2.4 Description of dosage and administration methods of the trial drug. Description of unit form, packaging and labelling of the trial drug.

2.4.1 Dosage and methods of administration

After inclusion, patients will be randomized to either the treatment group (baclofen) or the placebo group. Patients will receive either 150 mg baclofen (or an adapted dosage in case of renal insufficiency) or 150 mg placebo (or an adapted dosage in case of renal insufficiency) via nasogastric tube in a single dose from the day of inclusion (D1).

Patients will then receive the treatment or placebo daily for the duration of mechanical ventilation (dosage adapted to renal function) in 3 administrations.

Estimated eGFR	Day 1 = Loading dose	From day 2, until day 15 (or extubation/tracheostomy if it occurs before)
≥ 90	150 mg	50–50–50
89–60	100 mg	30–30–50

30–59	70 mg	20–20–30
<30 or continuous hemodialysis	50 mg	20–10–20
Sequential hemodialysis	50 mg	50 mg before each session
<15 with hemodialysis	50 mg	No administration

Breakdown of dosages according to creatinine clearance after D1:

- Clearance ≥90ml/min/1.73m^2: 150 mg/24h,
- Clearance 89–60 ml/min/1.73m^2: 100mg/24h,
- Clearance 30–59 ml/min/1.73m^2: 70 mg/24h,
- Clearance <30 ml/min/1.73m^2 or continuous hemodialysis: 50 mg/24h,
- Clearance <15 ml/min/1.73m^2 without substitution treatment: temporary cessation until kidney function improves,
- Intermittent hemodialysis: 50mg before each session.

Treatment decrease will begin either:

- The day after extubation/tracheotomy,
- After the 15th day of treatment if the patient is not extubated/tracheotomized.

The latter will last for a maximum of 7 days until the treatment is discontinued. Treatment decrease schedule:

Dosage on day of extubation/tracheotomy/D15	150 mg	100 mg	70 mg	50 mg	IHD 50mg
D+1	100mg (20-30-50)	70mg (20-20-30)	50mg (10-20-20)	30mg (10-10-10)	30mg before the session (nothing if no dialysis)
D+2	70mg (20-20-30)	50mg (10-20-20)	30mg (10-10-10)	20mg (10-0-10)	30mg before the session (nothing if no dialysis)
D+3	50mg (10-20-20)	30mg (10-10-10)	20mg (10-0-10)	10mg (10-0-0)	10mg before the session (nothing if no dialysis)
D+4	30mg (10-10-10)	20mg (10-0-10)	10mg (10-0-0)	STOP	STOP
D+5	20mg (10-0-10)	10mg (10-0-0)	STOP		
D+6	10mg (10-0-0)	STOP			
D+7	STOP				

2.5 Expected duration of patient participation and description of the chronology and duration of all trial periods

On inclusion, the promoter will promptly inform the Competent Authority and the REB of the effective starting date of the trial (effective starting date = date of signature of consent by the first trial patient).
The trial completion date will be transmitted by the promoter to ANSM (French Agency for the Safety of Health Products) and REB within 90 days. The end date of the trial will correspond to the end of the participation of the last patient who participates in the trial, or if applicable, **to the term defined in the protocol**.

Total duration of trial participation for each patient: **90 days**.
Total duration of the trial: **45 months.**

2.6 Description of the rules for final or temporary discontinuation

2.6.1 Cessation of a patient's participation in the trial

There are 3 situations that can lead to the termination of a patient's participation in the trial:

- Withdrawal of consent: at the request of a patient or his or her legal representative/trusted person, a patient's participation may be discontinued. "Legally authorized representative" means any person or authority with legal power or authority to legally consent to the patient's participation in trial procedures on the patient's behalf. If consent is withdrawn, the investigator will discontinue treatment. The investigator will notify the promoter, via the eCRF of the trial, of the premature termination of the trial for a patient and continue the collection of safety data.
- Death

- At the request of the promoter

Exception: The investigator may temporarily or permanently discontinue a patient's therapy for any reason that would be in the best interest of the patient, particularly in the event of serious adverse events. The patient's follow-up data should be retrieved during the patient's hospitalization in the ICU and, if possible, until the D90 consultation.
In the event of a patient lost to follow-up, the investigator will make every effort to regain contact with the patient.

2.6.2 Discontinuation of a part or all of the trial

The trial may be terminated prematurely in the event of unexpected serious adverse events requiring a review of the safety profile of the drug.
Similarly, unanticipated events or new information relating to the drug, which is unlikely to achieve the objectives of the trial or clinical program, may cause the promoter to terminate the trial prematurely.
Nantes University Hospital reserves the right to interrupt the trial, at any time, if the inclusion objectives are not met. The trial's Independent Monitoring Committee will be asked after the inclusion of the 100th and 200th patient to decide on continuation of the trial.
In the event of an early termination of the trial, the information will be transmitted by the promoter within 15 days to the ANSM and the REB.

Included patients will not be able to participate in any other intervention trials before D90 following inclusion.

2.7 PROVISIONS IMPLEMENTED FOR THE MAINTENANCE OF BLINDING AND PROCEDURES FOR LIFTING OF BLINDING

Randomization lists will be known only to the statistician, the clinical trial pharmacist, the promoter and the manager of the trial-specific eCRF. Investigators will not have access to these lists.

The trial drug and its placebo will be strictly identical in appearance.

3. Selection and exclusion of patients from the trial

3.1 CRITERIA FOR INCLUSION OF TRIAL PATIENTS

- "at-risk" drinking will be defined as consumption of >14 drinks/week for males in the month prior to hospitalization or >7 drinks/week in the month prior to hospitalization for males >65 years and females.
- **AND** intubated, ventilated with an expected mechanical ventilation time of at least 24 hours
- **AND** 18 to 80 years of age

3.2 CRITERIA FOR NON-INCLUSION OF PATIENTS

- Patient receiving baclofen treatment prior to ICU admission regardless of indication
- Hospitalization >7 days (current episode).
- Pregnancy.

- Porphyria.
- Patient admitted for burns.
- Ongoing treatment by GHB (Alcover®/Xyrem®).
- Brain injured patient: brain imaging for a recent stroke (ischemic or hemorrhagic), or meningeal hemorrhage and recent traumatic injury(ies).
- Quadriplegic or paraplegic.
- Cardiac arrest with manual cardiac massage on admission.
- Administration of impossible or contraindicated enteral treatment for a duration of >48h.
- Patient who does not benefit from French health insurance or who is under the state medical aid system.
- Known hypersensitivity to baclofen.
- Known celiac disease.
- History of epilepsy resistant to treatments or epileptic seizure within 6 months of inclusion (seizures during alcohol withdrawal or balanced epilepsies will not be excluded).
- Dementia or schizophrenia or bipolar/monopolar disease or severe depression.
- Parkinson's disease.
- Implementation of procedure of "limitation of active therapeutics".
- Patient tracheostomized on ICU admission.
- Patient participating in another drug-type intervention trial.
- Patient under legal protection.

  Since alcohol addiction affects populations of protected adults and the benefit of baclofen treatment may also be significant in this type of population, patients under guardianship or curatorship may be included with the agreement of their guardian/curator, or failing that, by emergency consent.

3.3 Procedure for early termination of treatment with the experimental drug and procedure for exclusion from the trial and follow-up of a patient within the framework of the trial

3.3.1 Criteria and methods for premature termination of treatment or exclusion of a patient from the trial

The situations that should lead to temporary or permanent discontinuation of treatment are as follows:

- Renal insufficiency with creatinine clearance assessed <15 ml/min/1.73m2 without replacement therapy: temporary discontinuation.

- Cytolysis >20 N: Temporary discontinuation until cytolysis <20N.
- Erythema or unexplained allergic manifestation: permanent discontinuation.
- Bradycardia <35/min with no other cause found, whatever the tolerance: permanent discontinuation.
- Bradycardia <50/min with poor hemodynamic tolerance with no other cause found: temporary discontinuation.
- Unilateral or bilateral areactive mydriasis: permanent discontinuation.
- Seizure in the ICU: permanent discontinuation.
- Ischemic or hemorrhagic stroke or cardiac arrest in the ICU (diagnosis by CT scan or MRI): permanent discontinuation.
- Delayed awakening defined by failure to open eyes to noise or pain 72 hours after complete cessation of sedation (morphinic, hypnotic): permanent discontinuation.

There are two situations that can lead to the exclusion of a patient from the trial:

- Withdrawal of consent: at the request of a patient or his or her legal representative/trusted person, a patient's participation may be discontinued. Legally authorized representative means any person or authority with legal power or authority to legally consent to the patient's participation in trial procedures on the patient's behalf.
- At the request of the promoter.

The investigator can temporarily or permanently discontinue a patient's therapy for any reason that would be in the best interest of the patient, particularly in the event of serious adverse events.
In the event of a patient lost to follow-up, the investigator will make every effort to regain contact with the patient.

3.3.2 Methods and timeframe for collecting data

Data concerning exclusions and early termination will be communicated to the promoter within a maximum of 7 days or 24 hours in case of serious adverse event(s). This declaration will be made via the eCRF and must include: the day of the termination of the protocol in relation to the inclusion, the reasons for the termination of the protocol.

The investigator will also complete the data collection notebook including the section concerning deviations from the protocol in which he or she will justify the termination or exclusion of the patient. The data collection notebooks will be regularly monitored by the trial's clinical research associate.

3.3.3 Arrangements for the replacement of patients, if applicable

Patients who discontinued the trial early will be retained in the intent-to-treat analysis and will not be replaced. These patients will be those:

- who present a treatment-related adverse event requiring discontinuation.
- who are lost to follow-up.
- for whom the trial was stopped at the request of the promoter.

If a patient dies before he or she is able to sign the consent to proceed or does not regain the ability to give consent, the data will be retained and analyzed in consideration of the initial consent of the patient's representative.

3.3.4 Patient follow-up methods

If participation is discontinued before the end of expected follow-up, the investigator will provide clinical and biological follow-up of the patient until regression of the possible side effects of the treatment. If the patient is discharged from the hospital, the investigator will use all of the means at his or her disposal (mail, telephone) to ensure that no side effects occur within 7 days of the last medication.

A patient's discharge from the trial will in no way change the management of his or her disease. In case of adverse event(s), serious or not, precise follow-up can be performed depending on the seriousness of the adverse event. The Supervisory Committee will specify monitoring procedures on a case-by-case basis.

4. Treatments administered to trial patients

4.1 Description of the treatments required to perform the trial

4.1.1 Experimental drug

4.1.1.1 Identification of the drug

Baclofen:

- INN: baclofen
- Galenic formulation: capsules dosed at 50 mg, 20 mg and 10 mg
- Composition:
    - Active ingredient: baclofen
    - Excipient: lactose

4.1.1.2 Packaging and labelling

The different dosages of baclofen will be packaged in PVC/aluminum anti-UV blisters.
Trial products will be packaged and labelled in accordance with current clinical trial regulations and good manufacturing practices by the Hôtel-Dieu Hospital Pharmacy, Nantes University Hospital, authorized to make preparations for biomedical research.

4.1.1.3 Manufacturing and distribution of the drug

Beforehand, baclofen capsules of different dosages and corresponding placebo capsules will have been manufactured by the Hôtel-Dieu Hospital Pharmacy, Nantes University Hospital, authorized to make preparations within the framework of biomedical research. The capsules will be made from powdered pharmaceutical grade baclofen.
In addition, the Nantes University Hospital Pharmacy will be the coordinating pharmacy for this trial and will ensure the distribution of the therapeutic units (verum and placebo) to the pharmacies of the trial centers. Shipments will be sent at the appropriate temperature via a rapid Chronopost-type carrier.

4.1.1.4 Administration

After inclusion, patients will be randomized into the treatment group (baclofen) or the placebo group. They will receive double-blind either 150mg baclofen (or an adapted dosage in case of renal insufficiency) or 150mg placebo (or an adapted dosage in case of renal insufficiency) through a nasogastric tube in 1 single time, from the day of inclusion (D1).

Patients will then receive the treatment or placebo in 3 doses during the following days. Administration of the treatments will be performed on medical prescription by a blinded registered nurse from the treatment group. For the duration of mechanical ventilation, administration will be

performed via nasogastric tube. After extubation, if the patient swallows properly, treatment will be administered orally, if not, a nasogastric tube will be used.

4.1.2 Non-experimental drug: Placebo

4.1.2.1 Identification of the drug

- Galenic formulation: capsules
- Composition: excipient lactose

4.1.2.2 Packaging and labelling

The placebo capsules will be packaged in anti-UV PVC/aluminum blisters in order to be indistinguishable from the baclofen capsules.
They will be packaged and labelled in accordance with current clinical trial regulations and good manufacturing practices by the Hôtel-Dieu Hospital Pharmacy, Nantes University Hospital, authorized to make preparations for biomedical research.

4.1.2.3 Preparation and distribution of the drug

The placebo capsules will be prepared by the Hôtel-Dieu Hospital Pharmacy, Nantes University Hospital, authorized to make preparations for biomedical research. Preparation will be carried out with pharmaceutical grade raw materials.

The Hôtel-Dieu Hospital Pharmacy, Nantes University Hospital will be the coordinating pharmacy for this trial and will ensure the distribution of the therapeutic units (verum and placebo) to the pharmacies of the trial centers. Shipments will be sent at the appropriate temperature via a rapid Chronopost-type carrier.

4.1.2.4 Administration

Since the trial is double-blind, placebo-controlled, administration regimens will be identical.

4.1.3 Blinded investigator monitoring of plasma concentrations

Plasma concentrations will be monitored at 3 participating centers – Surgical Intensive Care Unit (Nantes University Hospital), Medical Intensive Care Unit (Nantes University Hospital), Medical Intensive Care Unit (Rennes University Hospital), with an expected number of patients of 80/314 and a theoretical number of patients treated with baclofen of 40/80.

The rate of the plasma dosages performed has been established with the referring pharmacologist of the trial, Professor E. Dailly. The purpose of the dosages is to verify the equilibrium of the plasma concentrations just before administration. Dosages will therefore be performed before morning administration on D3 and D10 of the treatment for patients still receiving treatment on these dates (excluding the decreasing period).

This will provide us with early data after the initiation of treatment and an evolution of plasma concentrations in situations of prolonged intensive care. I**n order to keep this double-blind, randomized trial blinded, while ensuring patient safety, the results of the assays will be sent blinded to the independent trial monitoring committee after the 20th, 40th, 60th and 80th patients are included. Samples will all be centralized at the Nantes University Hospital and prepared in Professor Dailly's pharmacology laboratory.**

This population of 40 treated patients/80 patients will be comparable to the number of patients in the only currently published trial (n=37 patients) on the pharmacokinetics of baclofen in alcohol-dependent patients.

After discussion with Pr. Dailly, we agreed to perform the first dosages 48 hours after the first administration because:

- Since the elimination half-life of baclofen is 4.5 to 6.8 hours, the stability of plasma concentrations is theoretically expected after a minimum of 5 ½ lives, i.e. 34 hours. Therefore, at D+1 (24 hours), the equilibrium of plasma concentrations would not be reached.
- For patients with renal insufficiency who will require an adaptation of the dosage, plasma half-lives will be longer.

Thus, taking pharmacokinetic samples on D3, i.e. 48 hours after the first dose, will make it possible to target a period during which plasma concentrations will be at an equilibrium for most of the patients in the trial.

4.2 Authorized and unauthorized drugs and treatment within the framework of the protocol, including rescue drugs

4.2.1 Authorized treatments

Patients admitted to the ICU will present life-threatening distress. All medications will be authorized in this situation. In particular, since this is a double-blind, placebo-controlled trial, the intensivist in charge of the patient will be authorized to prescribe the treatments he or she wishes within the context of the prevention of withdrawal syndrome.

4.2.2 Non-authorized treatments

The protocol does not set any treatment restrictions except for treatments included in the contraindicated combinations of acamprosate, naltrexone, disulfiram, nalmefen, lithium, antiparkinsonian drugs and baclofen.

5. Safety evaluation

5.1 Description of safety evaluation parameters

The safety of the trial will be evaluated:

- On biological criteria from ICU work-ups performed in current practice, in particular, detection of cytolysis.
- On clinical criteria (see list of adverse events [AEs] and serious adverse events [SAEs])

5.2 Methods and schedule for measuring, collecting and analyzing safety evaluation parameters

Methods:

- Collection of clinical AEs will take place during daily physical examinations in the ICU.
- Biological monitoring will be performed through regular reviews of current ICU practices.

The collection of safety parameters will begin with the first administration of treatment and will end one week after the last administration of baclofen.

5.3 Procedures in place for the registration and notification of adverse events.

Notification of adverse events will be made via the eCRF. These notifications will be transmitted to the promoter and registered in the vigilance database. Regular analyses will be carried out with the updating of databases.

5.3.1 Role of the investigator

5.3.1.1 Notification of serious adverse events

5.3.1.1.1 Information to be transmitted to the promoter

Each SAE will be described on the form to this effect ("Initial Declaration of Serious Adverse Event" or "Follow-up Declaration of Serious Adverse Event") with attention to be as complete as possible. The information to be transmitted will be as follows:

- patient identification (number, code, date of birth, date of inclusion, gender, weight, height),
- severity of AE,
- dates of the onset and end of AE,
- clear and detailed description of AE (diagnosis, symptoms, intensity, chronology, actions taken and results),
- evolution of AE,
- current illnesses or relevant patient history,
- treatments received by the patient,
- causal relationship of the AE to the trial drug, comparator(s), possible associated treatments, research or other criteria.

The investigator should also attach to the SAE report, whenever possible:

- a copy of the report of hospitalization or extension of hospitalization,
- if applicable, a copy of the autopsy report,
- a copy of all the results of further examinations, including any relevant negative results, together with normal laboratory values,
- any other document deemed useful and relevant.

These documents will be anonymous and will bear the patient's identification number.

5.3.1.1.2 How to notify the promoter

Any SAE, regardless of its causal relationship with trial treatment or research (with the exception of those identified in the protocol as not requiring an immediate declaration), must be declared by fax at 02 53 48 28 36 to the promotion department.

5.3.1.1.3 Time limit to notify the promoter

The investigator must immediately notify the trial promoter as soon as he or she becomes aware of any SAE.
The initial declaration may be followed by additional relevant information within **8 days** in the case of a fatal or life-threatening event and within **15 days** in other cases.

5.3.1.1.4 Promoter notification period

It is the investigator's responsibility to record and report all SAE occurring throughout the trial:
- from the date consent is signed,
- for the duration of the patient's follow-up,
- and up to 4 weeks (or >4 weeks taking into account the pharmacological characteristics of the experimental drug) after the end of the patient's follow-up.

5.3.1.1.5 Protocol specifics

- List of known and expected side effects:

Known and expected adverse effects in an ICU:

Infectious complications: on medical devices, nosocomial pneumonia

Neurological complications:
- Confusion and somnolence of medicinal origin: hypnotic used for sedation in ICU, powerful morphinics, antalgics, or nefopam,
- Confusion related to hospitalization itself (sleep disorders),
- ICU polyneuromyopathy,Convulsions or confusion after abrupt withdrawal from hypnotic drugs,
- Delayed awakening after administration of hypnotic or morphine treatments,
- Stroke under sedation or after extubation.

Cardiovascular complications: hypotension related to hypnotics (used for sedation in the ICU) and morphinic analgesics,

Respiratory complications: Delayed extubation, respiratory depression linked to hypnotics used for sedation in the ICU and morphinic analgesics. Need for reintubation and tracheotomy,

Digestive complications: gastric or duodenal ulcer, vomiting, occlusive syndrome,

Renal complications: renal insufficiency,

Liver complications: liver failure owing to drug toxicity,

Death in the ICU.

N.B. An exhaustive list of complications in the ICU is not feasible owing to the diversity of the pathologies treated.

Known and expected adverse effects within the framework of the pathology in the trial:
- Infectious: Increased susceptibility to infection,

- Neurological: Convulsions on alcohol or hypnotic withdrawal used for sedation in the ICU, agitation, deficiency encephalopathy (Gayet Wernicke's Syndrome),
- Digestive: Increased susceptibility to gastric or duodenal ulcers, digestive hemorrhage on rupture of esophageal varices,
- Biological: Liver failure with underlying liver disease, acute renal failure with hepatorenal syndrome.

Known and expected adverse effects within the framework of copathologies:

- Infectious complications: Implantable device infections, nosocomial pneumonia,
- Neurological complications:
- Drowsiness, confusion, convulsions, delayed awakening, stroke including hemorrhagic,
- Alcohol withdrawal syndrome and agitation,
- Digestive complications: Digestive hemorrhage, rupture of esophageal varices, gastric ulcer,
- Renal complications: Hepatorenal syndrome, renal insufficiency,
- Liver complications: Liver failure.

Known and expected adverse effects to trial treatment (baclofen) and its placebo:

The adverse events are presented below in descending order of frequency using the following categories: very common (³ 1/10), common (³ 1/100 and <1/10), infrequent (³ 1/1,000 and <1/100), rare (³ 1/10,000 and <1/1,000), very rare (<1/10,000), unknown (cannot be estimated based on available data).

Nervous system disorders	
Very frequent:	sedation, drowsiness, especially at the beginning of treatment
Frequent:	confusion, dizziness, headaches, insomnia, ataxia, tremors
Rare:	paresthesia, dysarthria, dysgeusia, tinnitus
Frequency undetermined:	lowering of the epileptogenic threshold in epileptics, paradoxical increase in spasticity in some patients
Psychiatric disorders	
Frequent:	euphoric state, depression, hallucinations
Ocular disorders	
Frequent:	accommodative dysfunction
Musculoskeletal and systemic disorders	
Rare:	muscular hypotonia that can be corrected by decreasing the daytime dose and possibly increasing the evening dose
Cardiac disorders	
Rare:	bradycardia
Respiratory disorders	
Frequent:	respiratory depression
Vascular disorders	
Frequent:	hypotension
Gastrointestinal disorders	
Very frequent:	nausea
Frequent:	vomiting, constipation, diarrhea, dry mouth
Rare:	abdominal pain, anorexia
Hepatobiliary disorders	
Rare:	abnormal liver function (increased alkaline phosphatases and transaminases)
Skin and subcutaneous tissue disorders	

Frequent:	hyperhidrosis, rash
Frequency undetermined:	hives
Kidney and urinary tract disorders	
Frequent:	aggravation of pre-existing dysuria
General disorders and anomalies at the administration site	
Very frequent:	asthenia
Very rare:	dose-dependent hypothermia
Investigations	
Frequency undetermined:	increased blood sugar levels

Post-weaning syndrome: discontinuation of treatment, especially if abrupt, can induce a post-weaning syndrome that is sometimes lethal. The most frequently reported reactions (by analogy with what has been observed via intrathecal administration) are: neuromuscular disorders (spasticity, dyskinesias, rhabdomyolysis, paresthesia, convulsions or even epileptic seizures), pruritus, dysautonomia (hyperthermia, hypotension), consciousness and behavioral disorders (confused state, anxiety, manic or paranoid psychotic state) and coagulopathy.

- Non-serious adverse events subject to immediate reporting:

All non-serious adverse events and/or abnormal test results defined below as critical to the assessment of the safety of trial patients must be reported to the promoter by the investigator in accordance with the reporting requirements for SAE:

  - *major hyperglycemia (grade 3 and above)*
  - *major hyperleukocytosis (grade 3 and above).*

- SAE that do not require reporting:

Certain circumstances requiring hospitalization do not fall under the "hospitalization or extension of hospitalization" severity criteria and should not be declared as SAE:

- hospitalization predefined by the protocol,
- admission for social or administrative reasons,
- outpatient care,
- hospitalization for routine treatment or monitoring of a pathology not associated with a deterioration of the patient's condition,
- hospitalization for medical or surgical treatment scheduled before the start of the trial.

In addition, the following SAE will not require (in agreement with the health authorities) an im57 statement:

- Death before administration of the medication,
- Adverse events occurring 7 days after the definitive discontinuation of baclofen and corresponding to the origin of the underlying pathologies,
- Traumatic pathology/complication related to ICU management.

5.3.2 Role of the promoter

5.3.2.1 Analysis of serious adverse events

The promoter must assess:

- the causality of the SAE (all adverse events, for which the investigator or promoter believes that a causal relationship with the trial drug can reasonably be considered as being linked suspected adverse events. In the event of a different assessment by the promoter and the investigator, both opinions will be noted in the notification to the Competent Authority if such notification is necessary),
- and their expected or unexpected nature, using the current reference document (Investigator's Brochure or SPC).

5.3.2.2 Accountability assessment

In accordance with the ICH recommendations on the Management of Adverse Events in Clinical Trials - ICH E2B(R3), version of May 12, 2005 – an accountability assessment will be performed for any reported adverse drug reaction (ADR).
Adverse events with a minimally questionable relationship to the trial drug or its placebo will be considered as reasonably related to it/them. If they are unexpected, they will be qualified as unexpected serious adverse drug reactions (USADRs) and must be reported by the promoter.

5.3.2.3 Reporting USADRs

The promoter will report all serious and unexpected adverse events (SAEs) to Eudravigilance (European Pharmacovigilance Database), the French Health Authorities (ANSM) and the Research Ethics Board (REB) and to the investigators.
The statutory declaration shall be made within a maximum period of:
- **7 calendar days** for serious unexpected fatal or life-threatening adverse effects. In these cases, additional relevant information must be sought and transmitted within a further **8 days**.
- **15 calendar days** for all other serious and unexpected adverse effects. Similarly, additional relevant information must be sought and transmitted within a further **8 days**.
In the case of blinded trials, as a general rule, the promoter will report the serious unexpected adverse reaction to the health authorities and the REB after unblinding the trial drug.
In exceptional cases, and with the agreement of the ANSM requested by the promoter at the time of the application for authorization of the clinical trial, the procedures for unblinding and reporting of suspected adverse reactions may be adjusted. These procedures will be precisely defined in the trial protocol.
Detailed records of all adverse events reported by the investigators may be provided to the ANSM on request.

5.3.2.4 Transmission of annual safety reports

On the anniversary date of trial authorization issued by the Health Authorities, the promoter will prepare a safety report that includes:
- a list of serious adverse events that could be related to the trial drug including unexpected and expected serious adverse effects,
- a concise and critical analysis of patient safety that could be used for research.
This report may be submitted to the coordinating investigator for approval. It will be sent to the Competent Authorities (ANSM) and the REB within 60 days of the anniversary date of trial authorization.

5.3.2.5 Transmission of half-yearly safety reports

Every six months, the promoter will send the REB, with a copy to the ANSM, a list of the USADRs that have occurred in trials outside of the national territory, as well as the USADRs that have occurred in other trials with the same trial drug. When the promoter has an investigational drug in development, the list will also include other USADRs on that drug that the promoter is aware of (publication or pharmaceutical company). The list will be accompanied by a summary.

5.3.3 Monitoring Committee

The mission of the Independent Monitoring Committee will be to monitor the clinical and biological tolerability of the trial drug. It will be responsible for informing the Scientific Committee of its decisions to amend or discontinue the trial. It will be formed at the beginning of the trial and will include at least three members not directly involved in the trial.
The Monitoring Committee will transmit its recommendations to the Scientific Committee which will decide whether or not to stop the trial. The decision to stop the trial may be taken earlier if it appears

contrary to the rules to continue it (the occurrence of serious adverse events, publication of the results of a trial providing the answer to a given question, etc.).
The Independent Monitoring Committee will have the authority to make recommendations for the termination of the trial based on evaluation of the results.

Since the trial is double-blind, the Independent Monitoring Committee will only evaluate the raw data, with no unblinding (i.e. without attribution). If the frequency of adverse events in one of the two groups turns out to be higher than expected and then leads to suspicion of a higher frequency for the trial drug, the Independent Monitoring Committee may then request unblinding and a halt to inclusions in order to verify the frequency in each treatment group.

At the request of the ANSM, baclofen plasma concentrations will be blinded by the investigator at 3 participating centers and reported to the Independent Monitoring Committee which will verify the absence of overdose with the trial's dosing regimen.

6. Statistics

Names and contact details of the persons in charge of the analysis:
Dr. Fanny Feuillet and Dr. Véronique Sébille, Biometrics Platform – Nantes University Hospital & EA 4275 "Biostatistics, Pharmacoepidemiology and Subjective Measures in Health" – UFR of the University of Nantes Pharmacy.

Statistics software:
The statistical analysis will be performed using SAS 9.3 software.

6.1 Description of the planned statistical methods, including the schedule of planned interim analyses

The final statistical analysis will be performed via intent-to-treat (ITT) and will be completed as soon as the trial has ended.

An intermediary analysis will be carried out which will make it possible to re-estimate, if necessary, the number of patients to be included in the trial in order to maintain the power of the trial. It will be performed after inclusion of half of the total number of patients (i.e. 157 patients). The global probability of the event will be estimated from all of the data (groups of treatments combined) in order to preserve blinding. The method proposed by Friede and Kieser (47,48) will make it possible to maintain the initial clinical hypothesis (15-point decrease in the agitation rate) and to preserve the initial Type 1 error of 5%.

All analyses will be adjusted at trial centers (stratified randomization on this factor).

In order to meet the main objective, a logistic regression model will be applied to compare the proportions of agitation between the two groups.
The need to adjust for cirrhosis will be evaluated for all criteria by testing the significance of this variable and its possible interaction with the treatment in the models.
In order to account for mortality, two sensitivity analyses will be performed: 1) all patients who died without an agitation-related adverse event will be considered to have had at least 1 adverse event, 2) all patients who died without an agitation-related adverse event will be considered to have had no adverse events.

An additional per protocol analysis will be performed to enable exclusion from the analysis of patients who were wrongly included, non-observing patients or patients having received the treatment of the other group.

In order to meet secondary objectives:
- a Poisson regression model will be applied to compare the number of adverse events related to ICU agitation between the two groups of patients,
- survival models (Kaplan-Meier estimator) will be applied to compare length of stay and duration of mechanical ventilation between the two groups of patients.
- logistic regression models will be applied in order to compare binary qualitative criteria between the two groups of patients (reintubation, extubation failure, ICU-acquired infections, mortality ...).

No subgroup analysis is planned.

6.2 Anticipated number of people to be included in the trial and anticipated number of patients at each trial site with statistical justification

A preliminary trial (MD thesis, University of Nantes, 2013) indicated an ICU agitation rate of 42% (corresponding to the occurrence of at least one agitation-related adverse event). The hypothesis of a 15-point decrease in this agitation rate in the baclofen group appears to be clinically relevant, i.e. 27% agitation. The number of patients required for the trial for a potency (1-β) of 80% and a risk (α) of 5% is 157 patients per group, i.e. a total of 314 patients.

6.3 Expected degree of statistical significance

The expected degree of significance is set at 5% or less

6.4 Statistical criteria for stopping the trial

Not applicable.

6.5 Method for taking into account missing, unused or invalid data

Patients cannot be lost to follow-up as long as they are in the ICU.
Since the main criterion is measured during ICU stay, missing data will be rare or non-existent. The only possibility for a patient to be lost to follow-up is to flee the ICU: this event would correspond to an adverse event related to agitation (flight).

In all cases, patients lost to follow-up will not be replaced but will be included in the intention-to-treat analysis.

Data from early exclusions will be retained in the intent-to-treat analysis.

Missing data will be described in terms of numbers and corresponding percentages per group. Patients will not be replaced. The presence of possible imbalances in terms of the proportion of missing data between treatment groups will be assessed according to their cause by tests of comparisons of observed proportions (tests from $\chi 2$, Fisher exact tests or logistic regression models in case of adjustment).

6.6 Management of changes to the initial strategy analysis plan

The trial may be stopped early at the decision of the promoter if the frequency of baclofen-related SAEs reported by the trial pharmacovigilance administrator is high.

6.7 Selection of patients to be included in the trial

The analysis will focus on the intent-to-treat (ITT) population. All included patients will be included in the primary endpoint analysis. The time between inclusion and the start of treatment in the trial will

be very short. No included patient will be lost to follow-up between inclusion and the administration of the treatment. It will therefore be unlikely that data will be missing for the main criterion.

7. Right of access to source data and documents

7.1 Access to data

In accordance with GCP:
- the promoter will be responsible for obtaining the agreement of all parties involved in the trial in order to guarantee direct access to all trial locations, source data, source documents and reports for the purpose of quality control and audit by the promoter,
- the investigators will make available to the persons responsible for monitoring, quality control or auditing biomedical research, the documents and individual data strictly necessary for this control, in accordance with the legislative and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the Public Health Code).

The source documents for the trial will be:

- The handwritten trial observation notebook,
- Patient medical records with the medical observation and nursing surveillance sheets.

7.2 Data privacy

In accordance with the provisions concerning the confidentiality of the data to which the persons in charge of quality control of biomedical research have access (article L.1121-3 of the Public Health Code), in accordance with the provisions relating to the confidentiality of information concerning, in particular, the nature of experimental medicinal products, the trials, the persons involved and the results obtained (Article R. 5121-13 of the Public Health Code), persons with direct access shall take all necessary precautions to ensure the confidentiality of information relating to trial medicinal products, the trials, the patients participating in them and, in particular, with regard to their identity and the results obtained.
These persons, in the same way as the investigators themselves, will be subject to professional secrecy (according to the conditions defined by articles 226-13 and 226-14 of the penal code).
During or at the conclusion of the trial, the data collected on patients and transmitted to the promoter by the investigators (or other specialized stakeholders) will be made anonymous.
Under no circumstances should the names of patients or their addresses appear.
Only the first letter of the patient's family name and the first letter of the patient's first name will be recorded, accompanied by a coded number specific to the trial indicating the order of inclusion of the patients.
The promoter will ensure that each patient who participates in the trial has given his or her written consent for access to patient data concerning him or her that is strictly necessary for quality control of the trial.

8. Trial Monitoring

Monitoring will be performed by the promotion department of the Research Directorate. A Clinical Research Associate (CRA) will make regular visits to each site (investigator's department and pharmacy) in order to carry out quality control of the data reported in the case report forms.
The protocol has been classified according to the estimated level of risk to the patient.
It will be classified as follows:
Risk C: high predictable risk

On-site monitoring visits will be organized after an appointment with the investigator.
CRAs will need to be able to consult on each site:
- patient data collection notebooks,
- patient medical and nursing records,

- the investigator's notebook

During these visits, the following items will be reviewed:

- Informed consent,
- Verification of inclusion and non-inclusion criteria,
- Conformity of the visit dates on the theoretical calendar,
- Verification of the main evaluation criterion,
- Verification of secondary evaluation criteria,
- The search for unreported SAEs and related treatments, new developments,
- Product management

On the other hand, the investigators will undertake to accept quality assurance audits performed by the promoter as well as inspections performed by the competent authorities. All data, documents and reports can be subject to regulatory audits and inspections without being subject to medical secrecy.

9. Ethical considerations

9.1 Research Ethics Board (REB)

The protocol, the information form and the certificate of consent for the trial were submitted for opinion to the Angers REB and received a favorable opinion on July 6, 2015.
Notification of the REB's favorable opinion was forwarded to the trial promoter and the Competent Authority. An authorization was sent by the promoter to ANSM.

9.2 Substantial modifications

If the investigator makes a substantial change to the protocol, it must be approved by the promoter. The latter will have to obtain, prior to its implementation, a favorable opinion from the REB and an authorization from ANSM within the framework of their respective competences. New consent from trial participants will have to be obtained if deemed necessary.

9.3 Patient information and written informed consent form

Patients and patient representatives will be fully and fairly informed, in understandable terms, of the objectives and constraints of the trial, the possible risks involved, the necessary monitoring and safety measures, their rights to refuse to participate in the trial or to withdraw from the trial at any time.
All this information will appear on an information and consent form given to the patient. The patient's free, informed and written consent will be obtained by the investigator or a physician representing the patient prior to final inclusion in the trial. A copy of the consent form signed by both parties will be given to the patient, the investigator will keep the original.

❖ **For patients on mechanical ventilation on arrival in the ICU (the most frequent cases):**
The patient will not be able to sign the informed consent himself/herself. The protocol provides informed information and a consent form for patient representative. The investigator undertakes to inform this person in a clear and fair manner and to ask him or her for written informed consent. The investigator must also sign and date the consent form. These two documents will be provided on paper with a minimum of 2 copies so that the patient's representative and the investigator can each keep one copy. The investigator's original will be filed in the investigator's binder.
As soon as the patient's condition permits, the investigator will undertake to inform the patient in a clear and fair manner and to provide him or her with an information letter and to ask for written informed consent to continue the trial if he or she is competent.
In an emergency situation, the consent form will be signed by a patient representative other than a guardian/curator/family member/trusted person and by an investigator. Patient consent will be sought as soon as the patient's condition permits.

❖ **For non-intubated patients admitted to the ICU:**

If the patient is competent, he or she will be informed by an information letter and his or her consent will be sought before intubation. Otherwise the emergency consent procedure may be used.

9.4 Definition of the exclusion period

The defined exclusion period for this trial is 90 days, during which time the patient may not participate in another **interventional** clinical research protocol after the end of the trial or after early termination of the trial.

9.5 Trial-related support

Management of the patients included in this trial was modelled on the management that is usually recommended.

Except for the administration of the treatments in this trial, ICU management will not differ from its standard management.

Biological monitoring on inclusion and as long as baclofen is administered will concern, complete CBC and blood glucose levels daily, renal function per 24 hours (calculation of creatinine clearance). Liver function will be evaluated once a week from inclusion to one week after baclofen/placebo discontinuation.

9.6 Patient compensation

No compensation will be provided.

10. Insurance

The promoter will subscribe to an insurance policy for the entire duration of the trial to cover the promoter's own civil liability as well as that of any physician involved in the trial (Article L 1121-10). The promoter will also ensure full compensation for possible harmful consequences of the trial for a patient who agrees to participate in the trial and his or her heirs, unless it can be proven that the damage is not attributable to the promoter or to that of any party involved, without being able to oppose the fact of a third party or the voluntary withdrawal of the person who initially agreed to participate in the trial.

11. Publication conditions

A copy of the publication will be given to the Nantes University Hospital, promoter of the trial which will necessarily be cited. The authors will be prorated based on the number of patients included. The coordinating investigator will draw up the list of authors.

The signatories, Mickael Vourc'h (MD) as first author, Pierre-Joachim Mahé (MD) as penultimate author, and Karim Asehnoune (MD, PhD) as last author, and 1 investigator per participating center (in order of the number of inclusions provided that the center has included at least 10 patients over the duration of the trial) and the statistician-methodologist. A second investigator per center may be co-signatory in centers with 30 or more patients. Finally, all investigators who have included patients will be listed in the BACLO-REA trial group at the end of the publication in alphabetical order.

The rules of publication will follow international recommendations (N Engl J Med, 1997; 336:309-315).

The trial will be registered on an open access website (Clinical trial) prior to inclusion of the first patient in this trial.

SUMMARY OF CHANGES

Summary of changes of the protocol	Time line	Time from the beginning of the study	Number of inclusions from the beginning of the study
	First Clinical Trial registration March 2016		
	Protocol submission in *Trials journal* April 19, 2016		
	First inclusion June 27, 2016		
Modification of 2 screening criteria: * Patient with expected ventilation duration of 24 hours can be included (instead of 48 hours in the initial version) * Patient up to 80 years old can be included (instead of 70 years old in the initial version) **Addition of 2 non-inclusion criteria:** * Patient with 7 days hospitalization before ICU admission * Patient already included in a randomized clinical trial testing the effect of a drug **Addition of 1 secondary outcome:** (composite) Occurrence (yes or no) of agitation during treatment or death at day 28 **Participating center:** Suppression of Medical Intensive Care Unit of Angers University Hospital. This center has never been opened due to Principal Investigator change of mind for participation. **Change of principal investigator:** *University Hospital of Poitiers: Dr. Dahyot-Fizelier Claire instead of Pr. Mimoz Olivier *University Hospital of Nantes, Medical Intensive Care Unit: Dr. Garret Charlotte instead of Dr.Guitton Christophe	Submitted July 18, 2016	20 days	5 patients
Participating center: *New participating centre: University Hospital of Montpellier, Medical intensive care Unit, Dr. Jung Boris as a principal investigator	Submitted October 6, 2016	3 months, 8 days	13 patients

SUMMARY OF CHANGES

<u>Participating center:</u> *New participating centre: University Hospital of Tours, Medical intensive care Unit, Pr. Ehrmann Stephan as a principal investigator *New participating centre: University Hospital of Brest, Surgical intensive care Unit, Dr. Huet Olivier as a principal investigator *New participating centre: University Hospital of Brest, Medical intensive care Unit, Dr. L'Her Erwann as a principal investigator	Submitted February 8, 2017	7 months, 10 days	47 patients
<u>Participating center:</u> *New participating centre: University Hospital of Caen, Medical intensive care Unit, Pr. Du Cheyron Damien, as a principal investigator *New participating centre: District Hospital of Le Mans, Medical intensive care Unit, Dr. Guitton Christophe as a principal investigator *New participating centre: District Hospital of Lorient, Medical intensive care Unit, Dr. Smonig Roland as a principal investigator **<u>Extension of the duration of the study</u>:** for 18 additional months.	Submitted March 28, 2018	1 year, 8 months	203 patients
	End of the follow-up of the last participant May 2019		
Summary of changes of the statistical analysis plan	**Time line**	**Time from the beginning of the study**	**Number of inclusion from the beginning of the study**
NONE	-	-	-