Randomized trial of the efficacy of acetazolamide in patients with COPD developing metabolic alkalosis during invasive mechanical ventilation

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NB: This version corresponds to the text of the protocol and appendices sent to the IRB and the competent authority, respectively, for expert opinion and to request authorization.

If a new version is subsequently produced following modifications, signatures must be obtained again, to ensure that the active protocol is always updated.
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LIST OF ABBREVIATIONS

ARDS: acute respiratory distress syndrome
BAL: bronchoalveolar lavage
BF: blood formula
COPD: chronic obstructive pulmonary disease
FEV₁: forced expiratory volume in 1 second
FiO₂: fraction of inspired oxygen
LVEF: left ventricular ejection fraction
NIV: non-invasive ventilation
PEEP: positive end-expiratory pressure
PR: prothrombin ratio
RR: respiration rate
RV: residual volume
SAE: serious adverse event
SAPS II: Simplified Acute Physiology Score II
SOFA: Sequential Organ Failure Assessment
SpO₂: oxygen saturation on pulse oximetry
TLC: total lung capacity
TSH: thyroid stimulating hormone
VAP: ventilator-associated pneumonia
VC: vital capacity
# SUMMARY

## Scientific justification of the study

Metabolic alkalosis is frequent in intensive care and is often inevitable, particularly in patients with chronic obstructive pulmonary disease (COPD) leading to respiratory insufficiency. The contribution of metabolic alkalosis in difficulties weaning patients off artificial ventilation has been described in several studies. Acetazolamide is a carbonic anhydrase inhibitor that is often prescribed to patients with COPD and metabolic alkalosis. This drug has been shown to modify ventilatory parameters in patients with COPD, causing an increase in PaO₂, and decreases in PaCO₂, serum bicarbonate concentration and pH. These effects result from the stimulation of central and peripheral chemoreceptors. It has been clearly demonstrated that invasive mechanical ventilation is associated with a risk of complications, such as ventilator-associated pneumonia, and that this risk increases with the duration of respiratory assistance. In addition to their impact on morbidity and mortality, these complications increase the duration of the patient’s stay in intensive care, considerably increasing costs. We hypothesize that, in this population of patients, the metabolic modifications triggered by this drug may affect the duration of artificial ventilation, including in particular the time taken to wean the patient off respiratory assistance, thereby decreasing the risk of complications, the duration of hospital stay, economic costs and death rates in intensive care.

## Objectives

The primary objective of this study is to investigate the effect of acetazolamide on the total duration of invasive mechanical ventilation in patients with COPD. We expect the treatment to decrease the total duration of invasive mechanical ventilation by approximately 15%.

The secondary objectives include the assessment of treatment safety and an evaluation of the effects of acetazolamide on the duration of invasive mechanical ventilation, weaning success, the number of unplanned extubations, the need for noninvasive ventilation after extubation, the number of ventilator-associated pneumonia, the length of stay in intensive care unit and death rate in intensive care unit.

## Selection criteria

### Inclusion criteria:
- Patients with COPD, whatever their respiratory status at home (no respiratory assistance, O₂, NIV, tracheotomy, or ventilation with tracheotomy). COPD was defined according to the criteria of the ATS (American Thoracic Society).
- Age ≥18 years.
- Affiliated to or a beneficiary of social security.
- Hospitalized in the intensive care department for respiratory insufficiency, including postoperative cases.
- Ventilated in an invasive manner (by intubation or via a tracheotomy cannula)< 24 hours.
- Initial medical examination adapted for the study.
- Informed consent obtained from members of the patients’ family or trusted friends if present, and from the patients themselves as soon as possible.

### Exclusion criteria:
- History of allergy to acetazolamide.
- History of allergy to sulfamides.
- Contraindication for acetazolamide: history of nephritic colic, pregnant, breast-feeding, hepatocellular insufficiency (bilirubin concentration >150 μmol/L and ASAT activity >50 IU), with a prothrombin ratio <50 %, adrenal insufficiency without substitution by oopherapy, chronic renal insufficiency, with creatinemia >250 μmol/L and/or long-term extrarenal dialysis, uncontrolled dysthyroidism, concomitant prescription of quinidine-based drugs (quinindines and hydroquinidines) or carbamazepine.
- Patients with cystic fibrosis or bronchial dilatation.
- Moribund patients (life expectancy < 3 weeks)
- Patient already included in another interventional clinical trial, unless authorization is granted by the coordinating investigator on behalf of the steering committee.
- Pregnant or breast-feeding women.
- Prisoners and institutionalized patients.
- Legally incompetent adults.

## Methodology: Experimental plan

Randomized controlled, double-blind multicenter study (at least 10 centers): acetazolamide (Diamox®) versus placebo.
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1 SCIENTIFIC JUSTIFICATION OF THE STUDY

1.1 Summary of the available results for non-clinical and clinical trials relevant to the biomedical research study concerned.

COPD is defined as a limitation of expiratory air flow. The bronchial obstruction is progressive, linked to the progression of chronic bronchitis or emphysema, and smoking is the principal risk factor. The prevalence of this disease in France has been estimated at 5% [1], qualifying COPD as a major public health problem, given the high levels of associated morbidity and mortality. In the United States, COPD is the fourth leading cause of morbidity and mortality [1]. COPD is one of the most frequent reasons for emergency room consultation and hospitalization in intensive care unit [2, 3]. The use of invasive mechanical ventilation is required in 26 to 77% of COPD patients treated in intensive care unit, depending on the author and the series considered [2, 3, 4], and the mortality rates are high, at between 20 and 82% of cases, depending on the severity of the respiratory attack and the underlying context [5, 6]. There is a high risk of prolonged ventilation (more than 21 days) in 10% of COPD patients undergoing invasive ventilation [7], associated with a high risk of failure to wean the patients off of invasive ventilation (55 to 78%). Prolonged invasive ventilation is thus a prognostic factor predictive of death in hospital [8, 9]. In published studies [7, 9], several mechanisms, generally quite complicated in nature, have been implicated in the difficulties weaning COPD patients off of invasive mechanical ventilation:

- Advanced age.
- Severity of the initial clinical presentation.
- Associated comorbid conditions, such as left cardiac dysfunction in particular.
- Metabolic problems, including hypokalemia, hypomagnesemia, hypophosphoremia.
- Critical illness polyneuromyopathy.
- Ventilator-associated pneumonia (VAP). VAP and sepsis have been identified as factors predictive of prolonged mechanical ventilation in COPD patients [7].
- Metabolic alkalosis, a condition frequently observed in intensive care unit, has been identified as a factor limiting weaning off of invasive ventilation in patients hospitalized in intensive care, including those with COPD in particular [10, 11].

Acid/base homeostasis is essentially dependent on the lungs and kidneys. Disturbances in the acid/base balance may result from changes in respiratory function causing respiratory acidosis or alkalosis due to hypo- or hyperventilation, or acid or alkali loading...
causing metabolic acidosis or alkalosis [12, 13]. Respiratory acidosis and metabolic alkalosis are the principal acid/base disequilibrium problems observed in COPD patients with decompensation. Nevertheless, mixed acid/base disorders may also be observed. Respiratory acidosis results from hypercapnia generating $H^+$ ions following alveolar hypoventilation, according to the following equation: $CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$. It may be acute or chronic, depending on renal adaptation capacity. In COPD patients with acute respiratory decompensation, hypercapnia triggers acid loading in the extracellular medium (in most cases buffered by intracellular solutions), a decrease in pH and excess bicarbonate with an increase in intracellular buffers, with no base excess. If the hypercapnia persists, it results in a state of hypercarbonatemia and hypochloremia (posthypercapnic metabolic alkalosis), which may be normalized, once the hypoventilation is corrected, by the administration of acetazolamide or chlorine salts (KCl, NaCl) [12, 14]. Metabolic alkalosis is frequently observed in intensive care patients and is often associated with other metabolic disorders (hypokalemia, hypomagnesemia, hypophosphoremia) [15, 16]. Metabolic alkalosis has depressive effects on the cardiovascular system, decreasing cardiac output, and on the respiratory system, limiting the activity of respiratory nerve centers [17, 18]. Metabolic alkalosis inhibits the dissociation of oxyhemoglobin and maintains hypokalemia and hypophosphoremia [17, 18]. Several studies have suggested that this condition is involved in the problems weaning patients off of invasive mechanical ventilation, and in the high rates of morbidity and mortality in patients hospitalized in intensive care units, particularly those with COPD [10, 11, 19]. In intensive care unit, metabolic alkalosis is often of iatrogenic origin, secondary to the supply of excessive amounts of bicarbonate, the administration of diuretics and/or corticosteroids, permissive hypercapnia due to the mechanical ventilation technique used in cases of ARDS and possible digestive problems (vomiting) [20]. The correction of metabolic alkalosis increases respiratory minute volume and oxygenation (PaO$_2$), facilitating weaning off of invasive mechanical ventilation [21, 22].

1.2 Summary of the benefits, if appropriate, and of the predictable and known risks for persons taking part in the research study

Acetazolamide is a carbonic anhydrase inhibitor. Carbonic anhydrase is an enzyme that is found throughout the body and has several functions: alveolar/capillary transport of CO$_2$, regulation of the hydroelectrolytic acid/base equilibrium and ventilation control [23]. Acetazolamide has been proposed for use as a respiratory stimulant in COPD patients and in
patients with sleep apnea [23], and as a preventive treatment for acute altitude sickness [23, 24]. The adverse effects of therapeutic doses of acetazolamide are well known and are rare or exceptional (see Appendix 1).

Acetazolamide, when administered at doses of 250 to 500 mg (equivalent to 3.5 to 7 mg/kg), causes:
- A 10 to 20% increase in respiratory minute ventilation, both at rest and on effort, in normal subjects [25].
- An increase in the O2 saturation of hemoglobin from 3 to 6 % in hypoxemic subjects at high elevations, or at sea level in cases of hypoxemia linked to damage to the pulmonary parenchyma [18, 23].

The principal effect of acetazolamide is the induction of metabolic acidosis, the principal stimulant of peripheral and central chemoreceptors, through inhibition, in the kidney, of proximal bicarbonate reabsorption in the proximal convoluted tubule and the distal secretion of H+ ions. This is followed by alkaline diuresis, with a loss of bicarbonates in the urine, peaking after 24 h at about 4 to 6 mmol/L. This results in the blood pH decreasing by 0.05 to 0.1 units. The secondary ventilatory response leads to a decrease of 0.7 to 0.8 kPa (5-6 mmHg) in PaCO2 [23]. According to Stewart et al. [26], the effect of acetazolamide is mediated by an increase in the renal secretion of strong cations (with bicarbonates), chlorine retention and, thus, a decrease in the difference in concentration of strong ions defined as follows: ([Na+] + [K+] + [Mg++]) + [Ca++] − ([Cl−] + [lactates]). This difference in the concentrations of strong ions is one of the factors governing the dissociation of water and, thus, the concentration of H+ ions and acidic/basic state. Indeed, Stewart identified three factors influencing the concentration of H+ ions: the total concentration of weak acids with low levels of dissociation (phosphates, proteins), PaCO2 and the difference in strong ion concentrations.

Vos et al. [27] showed that the administration of acetazolamide to COPD patients led to an improvement in blood gas concentrations with no significant improvement in respiratory minute ventilation. This effect is thought to be due to the spontaneous voluntary hyperventilation observed in a large proportion (90%) of patients with COPD. By contrast, the studies of Swenson [23] and Teppema [28] showed that acetazolamide increased respiratory minute ventilation by decreasing the base excess. However, it has also been reported that patients not responding to acetazolamide treatment (decrease in PaCO2 < 0.7 kPa) display more severe bronchial obstruction (FEV1 24% of the predicted value) than patients responding to treatment (FEV1 42 % of the predicted value) [29], but the correlation
between FEV$_1$ and the strength of the response to acetazolamide has not been clearly established. One randomized multicenter study initiated in 2002 in Norway aimed to evaluate the benefits of orally administered acetazolamide during respiratory decompensation in COPD patients requiring hospitalization, but the results of this study (particularly those concerning the effect of acetazolamide on the need for intubation and invasive respiratory assistance) are not yet available (http://clinicaltrials.gov/ct2/show/NCT00222534).

1.3 Description and justification of the route of administration, dose, dose schedule and duration of treatment

Mazur et al. [30] evaluated the effects of two dose schedules for acetazolamide (a single dose of 500 mg/day versus four doses of 250 mg/day) on changes in bicarbonate levels in 38 intubated and ventilated COPD patients with metabolic alkalosis in intensive care, over a period of 72 hours. A sustained, significant decrease in bicarbonate levels was reported for both these acetazolamide regimens. This suggests that the duration of the pharmacological effect of acetazolamide exceeds its half-life in the plasma (5 hours). Indeed, during acetazolamide administration, 30% of the filtered bicarbonates are eliminated in the urine, and the transepithelial transport of bicarbonates decreases by 70 to 100% [31, 32]. Another study [33], in surgical intensive care unit, evaluated the effect of acetazolamide administered at a dose of 500 mg/day and reported similar results. In a randomized, double-blind trial, acetazolamide administered twice daily, at a dose of 250 mg (2 × 250 mg/day), improved PaO$_2$ in hypoxemic COPD patients with metabolic alkalosis, in the short term (between D3 and D6) [34]. Despite the frequent use of acetazolamide in cases of metabolic alkalosis and in the absence of associated metabolic problems, few studies have considered the recommended dose. Some [30, 33] recommend a single dose of 250 to 500 mg/day, whereas others [21, 35] recommend multiple doses of 250 to 500 mg administered at six- to eight-hour intervals. In the English-speaking world [36, 37], multiple doses of acetazolamide are generally recommended for the correction of metabolic alkalosis. We recently published a study showing that acetazolamide administered at a dose of 500 mg/day to COPD patients with metabolic alkalosis while they were being weaned off of mechanical ventilation significantly decreased bicarbonate levels and increased the PaO$_2$/FiO$_2$ ratio without affecting PaCO$_2$ or respiratory parameters such as respiratory minute ventilation or respiratory rate [38]. We also observed a spontaneous decrease in bicarbonate levels in the control group, resulting in there being no difference in terms of the decrease in bicarbonate levels between the control group
and the group of patients treated with 500 mg acetazolamide/day. This finding raises questions about the efficacy of 500 mg/day acetazolamide for decreasing bicarbonate levels to any great extent in patients. The statistically significant but clinically irrelevant decrease in bicarbonate concentration (< 4 mmol/L) in the treated patients in this study may account for the absence of an effect on PaCO₂ and respiratory parameters. Furthermore, no pharmacodynamics results are available describing the effect of acetazolamide on bicarbonate levels in COPD patients on mechanical ventilation. We therefore carried out another preliminary study based on the analysis of the medical dossiers of 506 COPD patients treated by invasive ventilation methods, with the aim of identifying factors likely to influence the pharmacodynamics of acetazolamide in intubated and mechanically ventilated COPD patients (Appendix 2). In this second preliminary study, we modeled the pharmacodynamics of acetazolamide in this situation: the pharmacodynamics model indicated that in cases of high chloremia (>110 mmol/L), oral corticosteroid prescription and, particularly, furosemide coprescription (effect on the constant of elimination kₜ of the model), larger unit doses of acetazolamide were required to obtain an effective decrease in bicarbonate levels in COPD patients with metabolic alkalosis. The action of furosemide (effect on kₜ) was the factor with the strongest influence on acetazolamide pharmacodynamics. The prescription of oral corticosteroids is rare in this context (as indeed is chloremia >110 mmol/L). Our first preliminary study [38] also revealed that more than 40% of the mechanically ventilated COPD patients had been prescribed furosemide, particularly during the period of weaning off of mechanical ventilation.

The drug will be administered intravenously in this study, because this is the only route of administration guaranteeing the administration of 100% of the dose prescribed. Furthermore, intubated and ventilated patients in intensive care display highly variable levels of digestive absorption and the oral route is not always feasible in such patients (stomach emptying and intestinal transit problems aggravated by the use of sedatives or vasoconstrictors). The dose schedule used corresponds to that in the AMM (the authorization for market release in France), the references cited above and recent studies carried out by our group [38, Appendix 2]: 500 mg twice daily or, in cases of coprescription of furosemide or a loop diuretic, 1 g twice daily (see above). The administration schedule will depend on whether the patient has pure or mixed (bicarbonates >26 mmol/L) alkalosis, which will be checked daily by blood gas analyses while the patient is on invasive mechanical ventilation. The treatment will be administered throughout the duration of invasive artificial ventilation (acetazolamide treatment will be stopped on extubation or when mechanical ventilation is
stopped in patients with a tracheotomy or on the return to usual ventilation methods for patients with tracheotomies routinely ventilated at home).

2 OBJECTIVES OF THE STUDY

2.1 Principal objective

The principal objective will be to assess the effect of acetazolamide on the duration of invasive mechanical ventilation in intensive care in intubated or tracheotomized COPD patients. We expect to see a decrease of the order of 15% in the duration of invasive mechanical ventilation (due particularly to a decrease in the duration of weaning off of invasive mechanical ventilation), together with a decrease in the frequency of complications linked to invasive mechanical ventilation.

2.2 Secondary objectives

The secondary objectives include assessing the safety of treatment and evaluating the effect of acetazolamide on:
- The duration of weaning off of mechanical ventilation.
- Weaning success.
- The number of unplanned extubations.
- The need for noninvasive ventilation (NIV) after extubation.
- The number of VAP.
- Duration of hospitalizations in intensive care unit.
- Mortality in intensive care unit.

3 METHODOLOGY

3.1 Experimental plan

We will carry out a randomized, placebo-controlled, double-blind multicenter study, including two parallel groups of COPD patients undergoing invasive mechanical ventilation for acute respiratory decompensation and at risk of prolonged mechanical ventilation and difficulties being weaned off of respiratory assistance (superiority study).
3.2 Study population

The study population consists of COPD patients:

- Requiring invasive mechanical ventilation in intensive care unit (via intubation or a tracheotomy cannula) for acute respiratory decompensation (including postoperative decompensation),
- At risk of developing metabolic alkalosis during the course of invasive mechanical ventilation (a frequent situation in intensive care unit), and therefore at risk of prolonged mechanical ventilation and difficult weaning off of respiratory assistance.

Metabolic alkalosis is extremely frequent in COPD patients requiring respiratory assistance, due, in particular, to the reventilation effect, which rapidly lowers hypercapnic acidosis. Metabolic alkalosis is not an inclusion criterion, but it is a parameter used to monitor treatment administration (acetazolamide or placebo) in this study.

COPD patients have a chronic respiratory handicap, the severity of which differs between patients. At home, their respiration may require:

- No assistance
- Oxygen supplementation
- Noninvasive ventilation (NIV)
- Tracheotomy
- Tracheotomy and respiratory assistance.

Morbidity and mortality in this population are non-negligible, due, in particular, to the duration of invasive mechanical ventilation in intensive care unit (mean of 12 days in our first preliminary study [38] carried out at Georges Pompidou European Hospital) and the complications associated with such prolonged ventilation. The expected benefits of acetazolamide treatment in terms of the duration of invasive ventilation and/or weaning off of respiratory assistance and the rates of complications associated with prolonged invasive ventilation make this population ideal for studies of the efficacy of acetazolamide for this indication.

3.3 Eligibility criteria for participation in this study

3.3.1 Inclusion criteria

All patients:
- COPD, regardless of respiratory status at home (no respiratory assistance, O₂ supplementation, NIV, tracheotomy or ventilation + tracheotomy). The criteria defining COPD are those of the ATS (American Thoracic Society. Standards for the diagnosis and care of patients with COPD. Am J Respir Crit Care Med 1995; 152:S77-S120).
- Age ≥18 years.
- Social security cover.
- Hospitalized in intensive care for respiratory insufficiency (including postoperative respiratory insufficiency).
- Invasive ventilation (by intubation or with a tracheotomy cannula)< 24 hours.
- Prior medical examination appropriate for the study.
- Informed consent obtained from family members or trusted friends if present, and from the patient himself/herself as soon as possible.

3.3.2 Exclusion criteria
- History of allergy to acetazolamide.
- History of allergy to sulfamides.
- Contraindication of acetazolamide: history of nephritic colic, pregnant, breast-feeding, hepatocellular insufficiency (bilirubin concentration >150 μmol/L and ASAT activity >500 IU) with a PR <50 %, adrenal insufficiency without opotherapy substitution, chronic renal insufficiency with creatinemia >250 μmol/L and/or long-term extrarenal dialysis, uncontrolled dysthyroidism and concomitant prescription of quinidines/hydroquinidines or cabamazepine.
- Cystic fibrosis or bronchial dilatation.
- Moribund patient (life expectancy <3 weeks).
- Patient already included in another interventional clinical trial protocol, apart from exceptions authorized by the coordinating investigator representing the steering committee.
- Pregnant or breastfeeding women.
- Prisoners and institutionalized patients.
- Legally incompetent adults.
3.4 Duration of the study and of the participation of individual patients

The total duration of the study is three years. The duration of the inclusion period is fixed at 35 months. The duration of participation for individual patients is limited to the duration of invasive mechanical ventilation (which may be initiated before admission to the intensive care unit) and will not exceed 28 consecutive days (Figure 1). The administration of acetazolamide or placebo will continue until extubation or the cessation of mechanical ventilation in tracheotomized patients or until the return to usual ventilation in tracheotomized patients ventilated at home. The maximum duration of participation is fixed at 28 consecutive days of invasive mechanical ventilation.

4 JUDGMENT CRITERIA

4.1 Principal judgment criterion

The principal judgment criterion is the duration (in hours) of invasive mechanical ventilation.

- For patients without respiratory assistance at home, or with oxygen supplementation or NIV at home, measurement will begin with intubation (not necessarily in intensive care) and will end at extubation in intensive care unit.

- For patients who were already tracheotomized, measurement will begin with the initiation of invasive ventilation and will end when this invasive ventilation is completely stopped.

- For tracheotomized patients on respiratory assistance at home, measurement will begin at the initiation of a type of invasive ventilation different from that routinely used at home via the tracheotomy cannula and will end with the return to usual ventilation methods.

4.2 Secondary judgment criteria

4.2.1 List of criteria

Secondary judgment criteria relating to the safety of acetazolamide
- Tolerance of acetazolamide and possible occurrence of adverse effects.

Secondary judgment criteria relating to the efficacy of acetazolamide
- Decrease in metabolic alkalosis (pH, bicarbonate concentration), PaO₂, PaCO₂, PaO₂/FiO₂, base excess, minute ventilation, respiratory rate, and tidal volume on invasive mechanical ventilation. These parameters can be used to evaluate the effect of acetazolamide on the acid/base balance and repercussions for the ventilator parameters of the patients.
- Duration (in hours) of weaning off of invasive mechanical ventilation*.
- Weaning success**.
- Need for noninvasive ventilation (NIV, calculated in hours) after extubation.
- Number of unplanned extubations in intensive care unit.
- Number of cases of VAP*** in intensive care unit.
- Duration (in days) of the patient’s stay in intensive care unit.
- Mortality in intensive care unit.

* See §4.2.2
** See §4.2.2
*** VAP is defined as the presence of at least three criteria (Chastre J, Fagon JY. Ventilator-associated pneumonia. Am J Resp Crit Care Med 2002;165: 867-903):
- Systemic signs of infection.
- Appearance of infiltrate on recent X rays or the aggravation of infiltrates already visible on lung X rays.
- Positive findings for bacteriological tests on samples (BAL and/or protected brush or distal samples).

### 4.2.2 Definitions linked to weaning (duration and success)

*The duration of weaning off of ventilation is defined as the period from the point at which the patient first satisfies the criteria for initiating weaning and the end of invasive mechanical ventilation, as defined in §4.1 (extubation, or the end of invasive ventilation in tracheotomized patients or the return to usual ventilation for tracheotomized patients ventilated at home). The criteria for initiating weaning are:
- Resolution of the factor triggering the acute respiratory insufficiency,
- No sedation and a Glasgow score >12,
- Absence of excessive tracheal/bronchial blockage and an effective cough reflex,
- Body temperature <38.5°C,
- Hemodynamic stability (no vasoconstrictors, heart rate (HR) <120 beats/min),
- Systolic arterial blood pressure between 90 and 160 mm Hg,
- Absence of major dysnatremia or dyskalemia,
- Hemoglobin concentration >8 g/dL,
- RR ≤35/min,
- PEEP ≤8 cm H₂O,
- FiO₂ ≤50 %,

The mode of ventilation used during weaning will be volume-assisted ventilation, with sessions of spontaneous ventilation with a T-piece of steadily increasing duration or pressure support with a steady decrease in the pressure of the inspiratory assistance. The choice of method will be left to the clinicians managing the patients. An external PEEP (usually 4-6 cm H₂O) may be used to counterbalance possible auto-PEEP.

A test of suitability for weaning, involving the performance of at least one test of spontaneous ventilation with a T-piece, for one hour, with a FiO₂ equal to that administered during mechanical ventilation, will be carried out as soon as the patient satisfies the criteria for weaning listed above. At the end of this test, a decision will be taken as to whether to extubate the patient (or to stop mechanical ventilation in tracheotomized patients), which would lead to the cessation of acetazolamide administration, or whether to continue mechanical ventilation and therefore the acetazolamide administration protocol. The criteria defining failure in the T-piece test for weaning suitability are as follows (Conférence de Consensus de la Société de Réanimation de Langue Française, October 2001; Boles JM et al. Weaning from mechanical ventilation. Eur Respir J 2007; 29: 1033-1056):

- Sweating and/or agitation.
- Somnolence.
- RR >35 cycles/min during the test.
- Decrease in SpO₂ >5 % on pulse oximetry during the test.
- Increase in HR or systolic arterial blood pressure >20 % during the test.
- PaO₂/FiO₂ <150, increase in PaCO₂ >10 mm Hg and decrease in arterial pH >0.1 in the blood gas analyses carried out at the end of the T-piece test before reconnection to the ventilator.

Patients adjudged suitable for weaning in this test will be extubated and oxygen will be administered via a nasal tube to achieve a SpO₂ ≥90 %.
For intubated patients failing the weaning suitability test, indications for tracheotomy and the way in which this procedure should be performed will be left to the discretion of the doctors managing the patients.

**Successful weaning is defined as an absence of need for invasive mechanical ventilation during the 48 hours following planned extubation or the complete cessation of invasive mechanical ventilation in tracheotomized patients (Brochard L et al. Am J Respir Crit Care Med 1994; 150: 896-903).**

The criteria for considering re-intubation or the use of NIV after planned extubation or unplanned extubation are:

- Agitation or signs of respiratory encephalopathy,
- RR >35/min, tachycardia >120/min, marked and persistent arterial hypertension or hypotension,
- Bronchial blockage and ineffective cough,
- Laryngeal dyspnea,
- Increase in PaCO₂ >10 mm Hg,
- Decrease in arterial pH ≥0.1, decrease in PaO₂ <60 mm Hg or in SaO₂ <90 % with a FiO₂ >50 %.

The decision as to whether to repeat blood gas analyses after extubation will be left to the discretion of the doctors managing the patients.

5 **RUNNING OF THE TRIAL**

5.1 **Course of the trial for an individual patient (Figure 1)**
COPD (with or without respiratory assistance at home)
Need for invasive ventilation (by intubation or with a tracheotomy cannula) <24 hours before admission to intensive care or during a stay in intensive care

Randomization
(Before 24 hours of invasive mechanical ventilation)

Acetazolamide
Placebo

Daily evaluation from randomization onwards:
bicarbonate concentration >26 mmol/L and pH ≥7.35?

YES

NO

Temporary contraindication of acetazolamide?

YES

NO

Acetazolamide or placebo
Temporary cessation

Daily evaluation of the criteria for weaning, from randomization onwards
Test of suitability for weaning if weaning criteria present:
Continuation of invasive mechanical ventilation?

YES

NO

Success in suitability for weaning test?
Restoration of usual ventilation method in patients ventilated at home?

NO

Invasive ventilation > 28 days?

End of protocol

YES

D0

D1 to D28

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5.2 Scheduled visits and examinations

5.2.1 Measurements made on inclusion (D0):

- SOFA score (Appendix 3)
- SAPS II (Appendix 4)

5.2.2 Measurements made from D0 to the day of extubation (or the day on which mechanical ventilation is stopped in tracheotomized patients or the day of return to usual ventilation on tracheotomized patients ventilated at home):

- Analysis of blood gases sampled on mechanical ventilation, blood ionogram, glycemia
- Calcemia, BF, PR, hepatocellular evaluation on D0 and then every 5 days thereafter
- Uricemia, TSH on inclusion and then in case of symptoms (gout, kidney stones, signs suggestive of dysthyroidism)
- Chest X-ray, in bed, on D0 and then in cases of suspected pneumonia acquired on mechanical ventilation
- Criteria for initiating weaning off invasive mechanical ventilation (daily)
- Transthoracic echocardiography, in bed, to estimate left ventricular ejection fraction at the time of weaning off of mechanical ventilation, on artificial ventilation and specifying the use or non-use of positive inotropic drugs
- Criteria for weaning suitability (daily, once weaning becomes possible).

5.2.3 Measurements made on the day of extubation (or the day on which mechanical ventilation is stopped in tracheotomized patients or the day of return to usual ventilation in tracheotomized patients ventilated at home) or on D28 for patients not weaned off of mechanical ventilation:

- Number of days of metabolic alkalosis
- Number of days of acetazolamide (or placebo) administration
- Duration of mechanical ventilation (in hours)
- Duration of weaning off invasive mechanical ventilation (in hours)
- Number of cases of VAP
- Number of unplanned extubations.
5.2.4 **Measurements carried out at the end of intensive care stay or on D28 for patients not weaned off of invasive mechanical ventilation:**

- Duration of stay in intensive care unit unit (in days)
- Total duration (in hours) of invasive mechanical ventilation
- Mortality in intensive care unit unit

5.3 **List of variables to be recorded in the observation notebook**

See Appendix 5.

5.4 **Timetable for data collection**

The parameters recorded to evaluate efficacy are shown in italic, bold typeface.

<table>
<thead>
<tr>
<th>Data to be recorded</th>
<th>Mechanical ventilation (D0)</th>
<th>Mechanical ventilation (D1-D28)</th>
<th>Extubation or cessation of invasive ventilation in tracheotomized patients</th>
<th>End of stay in the ICU or D28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>X</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Weight</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking habits</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFT results (if available)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of oral corticosteroids, diuretics or β2-agonists for &gt; 8 weeks</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygenotherapy and/or NIV at home</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOFA score</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAPS II</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cause of COPD decompensation</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Arterial blood gases</strong></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Chest X ray (in bed)</td>
<td>X</td>
<td>If necessary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mode of ventilation</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ventilation parameters (FR, VM, Vt, FiO2)</strong></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Administration of drugs favoring metabolic alkalosis</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Criteria for initiating weaning off invasive ventilation</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Criteria for extubating the patient</td>
<td></td>
<td>As soon as weaning becomes possible</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Presence of metabolic alkalosis</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Administration of Diamox® (or placebo)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of nosocomial infection</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>LVEF estimated on echocardiography</td>
<td></td>
<td>Once during weaning</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Duration of invasive mechanical ventilation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Duration of weaning</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unplanned extubation</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>Ventilator-associated pneumonia</strong></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Success/failure of weaning</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Cause of weaning failure</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>Need for tracheotomy</strong></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
5.5 Description of the dose schedule and mode of administration of the treatments

In this double-blind biomedical research study, the intensive care staff will administer acetazolamide or placebo to the patient, twice daily from randomization onwards: 1000 mg (2 x 500 mg)/day or 2000 mg (2 x 1000 mg)/day in case of coprescription of furosemide or loop diuretics. The placebo is identical in appearance to acetazolamide.

The decision to administer acetazolamide or placebo intravenously will be taken daily, according to the presence or absence of metabolic alkalosis (bicarbonate >26 mmol/L) as determined by the blood gas analysis carried out each morning on patients on artificial ventilation (Figure 1).

The lower pH limit for the administration of acetazolamide is fixed at 7.35, based on the frequency of hypercapnic acidosis in mechanically ventilated COPD patients (“mixed” or “complex” alkalosis), due to the aggravation of this acidosis by acetazolamide. If the pH is less than 7.35 or there are temporary contraindications to the use of acetazolamide, then the patient will receive no injection of acetazolamide or placebo on the day concerned.

5.6 Rules for definitively or temporarily stopping treatment

In cases of a pH <7.35 or the appearance of temporary contraindications to the use of acetazolamide, no injection (of acetazolamide or placebo) is administered to the patients (temporary cessation, see Figure 1, §5.1). The patient will be checked for temporary contraindications to treatment daily, during the course of the study (see Figure 1, §5.1). If the temporary contraindication is no longer present the next day but the patient still has metabolic alkalosis, the treatment (acetazolamide or placebo) is restarted. The risks of treatment are those linked to the use of acetazolamide. These risks are well known and are avoidable if the contraindications for acetazolamide use (Appendix 2) are respected, particularly in the intensive care setting.

The temporary contraindications to acetazolamide use that may occur during the patient’s stay in intensive care are:
- pH <7.35,
- Hepatocellular insufficiency (bilirubin concentration >150 µmol/L and ASAT activity > 500 IU) with a PR <50 %,
- Adrenal insufficiency without substitution by opotherapy,
- Severe renal insufficiency with creatinemia >250 μmol/L and/or extrarenal dialysis,
- Concomitant prescription of quinidines/hydroquinidines or carbamazepine.

The cut-off values indicated above correspond to the contraindications to acetazolamide (the definition of hepatocellular insufficiency as established by the Société Française d'Hépato-Gastroentérologie).

Treatment may be definitively stopped for the following reasons:

- Anaphylactic shock: sudden appearance, during the minutes following the injection of the study treatment, of cardiovascular signs (severe arterial hypotension, tachycardia or bradycardia, cardiac arrest), cutaneous/mucosal signs (erythema or enanthema) or respiratory signs (bronchospasm), these signs being potentially associated with various degrees of severity.
- Arterial hypotension or heart rate problems refractory to the usual treatments during perfusion of the test product. Refractory hypotension is considered to correspond to a mean arterial blood pressure below 70 mm Hg despite vascular filling with two boluses of 250 mL of saline and the injection of at least one vasoconstrictor or inotrope. Arrhythmia is considered refractory if it persists despite the administration of at least one anti-arrhythmia drug and the performance of defibrillation.

The reasons for definitively stopping treatment during the administration period are the administration of at least one anti-arrhythmia drug and the performance of defibrillation.

6 MEASURES TAKEN TO DECREASE BIAS

6.1 Randomization

After checking the inclusion and exclusion criteria and obtaining the informed consent of the patient (if he or she is able to give such consent) or of the members of the patient’s family or close friends if present, the patient will be assigned to a treatment group (acetazolamide or placebo) within 24 hours of intubation. Patients will be randomized with the centralized randomization system of Cleanweb software, according to a pre-established randomization list. The single randomization list will be programmed in advance by the study statistician and will be generated and edited by another statistician independent of the study from the clinical research unit of HEGP.
The investigator will be notified of each randomization by a confirmation e-mail attributing a treatment number from which it is not possible to identify the treatment arm. The pharmacy or PUI of the participating center will be informed of each randomization by an e-mail and a fax attributing a treatment number and the treatment arm (acetazolamide or placebo).

One-for-one randomization will be carried out, with stratification for:

- The respiratory status of the patients before hospitalization:
  - No respiratory assistance at home.
  - Respiratory assistance at home, whatever its nature (O₂ supplementation, NIV, tracheotomy, tracheotomy + ventilation).
- Center
- The seriousness of the patient’s condition on admission to intensive care, defined by SAPS II score <50 or ≥50 (a SAPS II score of 50 or more on admission to intensive care could potentially influence the pharmacodynamics of acetazolamide in COPD patients on artificial ventilation, according to the results of our second preliminary study: see Appendix 2).

The list will be balanced by blocks of different sizes alternated in a random manner.

### 6.2 Blinding methods

This study will be a double-blind biomedical research study. The intensive care staff will administer acetazolamide (500 mg, or 1 g, i.v.) or placebo, twice daily, after randomization. The placebo is identical in appearance to acetazolamide.

For the adjustment of treatment administration (daily evaluation of the criteria for administering treatment, Figure 1, page 19), the doctors responsible for evaluating the judgment criteria can decide whether or not treatment (placebo or acetazolamide) should be administered every day, as our first preliminary study showed that a decrease in bicarbonate concentration was not a reliable indicator for distinguishing between patients with and without acetazolamide treatment [38].

### 7 TREATMENTS ADMINISTERED

#### 7.1 Name and description of the treatments

See Appendix 1.
7.2 Drugs and treatments authorized and prohibited in the framework of the protocol, including emergency treatments

Acetazolamide is a drug routinely used in cases of COPD. The usual treatments of patients with COPD in intensive care will not be modified by the protocol. Treatments other than the study treatment will be administered in the same manner in both groups, to make it possible to address correctly the question of the benefit of treating metabolic alkalosis in COPD patients intubated for acute exacerbation. However, given the contraindications for acetazolamide use, the concomitant prescription of quinidines/hydroquinidines or carbamazepine will not be authorized.

7.3 Drug circuit and trial logistics

AGEPS will be responsible for supplying the treatments to the pharmacies of the participating centers. This agency will supply:

- Flasks containing 500 mg of lyophilized acetazolamide (Diamox® 500 mg) and ampules of 10 ml of solvent.
- The ampules of 0.9% NaCl used as the placebo.
- Labeled boxes containing the syringes, obturators and labels required for traceability and a bag for collection of the empty ampules and flasks.

The pharmacies will be responsible for treatment blinding and traceability, through completion of the label during treatment delivery and accounting (Appendix 6: The Drug Circuit, and its appendices).

Acetazolamide (Diamox®)

Diamox® will be supplied as a freeze-dried powder, for storage at room temperature (15 to 30°C) in the pharmacies of each of the participating centers. The solvent (water for injectable preparations) used to reconstitute the lyophilized Diamox® will be supplied and stored at room temperature (15 to 30°C) at the pharmacy. The Diamox® should be reconstituted with 5 ml of solvent at the pharmacy. The reconstituted Diamox® solution is normally a clear, colorless liquid. Reconstituted Diamox® is physically and chemically stable for three days at temperatures of 2 to 8°C. Nevertheless, Diamox® contains no preservatives and the real risk associated with storage is thus potential microbiological contamination.
The reconstituted product will be administered immediately in intensive care, as a slow intravenous injection (3 minutes). Consecutive injections should ideally be separated by an interval of 12 hours. If the pharmacy is unable to reconstitute the product during the weekends and on bank holidays, then the product may be reconstituted by the pharmacy in advance, in controlled and validated aseptic conditions; it may then be stored for up to three days at a temperature of 2 to 8°C before its slow intravenous injection into the patient in intensive care. Alternatively, the pharmacy could prepare the randomized kit for reconstitution on the ward for the weekends and bank holidays. This would require the involvement of a nurse not otherwise involved in the protocol, for reconstitution of the product.

**Placebo (saline, 0.9% NaCl)**

The placebo will be supplied in the form of a solvent (0.9% NaCl) stored at room temperature (15 to 30°C) in the pharmacy. The placebo should normally be clear and colorless. If this is not the case, it should be discarded. The placebo will be packaged, delivered and administered in the same way as Diamox®.

After treatment administration, the ampules and flasks will be collected and returned to the pharmacy, for counting by the clinical research assistant assigned to the study, to ensure compliance with treatment. They will then be destroyed.

### 8 SAFETY EVALUATION

#### 8.1 Description of the parameters used to evaluate safety

- **Adverse events**
  Adverse events are defined as any toxic sign occurring in a person taking part in biomedical research, regardless of whether or not the sign concerned is linked to the study or to the product studied.

- **Adverse effect of an experimental drug**
  All undesirable, toxic reactions to experimental drugs, regardless of the dose administered.

- **Serious adverse events or effects**
  All undesirable events or effects leading to death, or a risk of death of the person taking part in the research, or requiring hospitalization or a prolongation of hospitalization,
causing major or persistent incapacity or disability or involving a congenital abnormality or malformation due to the drug, regardless of the dose administered.

- **Unexpected adverse effects of experimental drugs**
  Any undesirable effect, the nature, severity or progression of which is not consistent with the information provided by the summary of product characteristics issued at the time of market release or in the brochure provided to the investigator for drugs not yet authorized for market release.

- **New findings**
  All new safety findings that could lead to a re-evaluation of the benefit/risk ratio of the study or of the experimental drugs, or that might be considered sufficient to trigger changes in the administration of the experimental drug in the research study.

### 8.2 Evaluation of patients' safety

- Blood ionogram, glycemia, calcemia, BF, PR, hepatocellular evaluation, plasma creatinine and urea concentrations will be determined (Biochemistry Department).
- Uricemia and TSH levels will be determined on the day of inclusion (Biochemistry Department) and these determinations will be repeated in cases of symptoms suggestive of an episode of gout, kidney stones or dysthyroidism.
- A daily clinical examination will be carried out, to check for adverse events imputable to the treatment (signs of allergy and ENT, neurological and hematological signs in particular).

<table>
<thead>
<tr>
<th>Data to be recorded</th>
<th>Mechanical ventilation (D0)</th>
<th>Mechanical ventilation (D1-D28)</th>
<th>Extubation or cessation of invasive ventilation in tracheotomized patients</th>
<th>End of stay in intensive care or D28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood ionogram, glycemia, plasma creatinine and urea determinations</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Calcemia, BF, PR, hepatocellular evaluation</td>
<td>X</td>
<td>Every 5 days or as a function of clinical condition</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Uricemia, TSH</td>
<td>X</td>
<td>If symptoms suggestive of gout, kidney stones or dysthyroidism</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Treatment tolerance</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
8.3 Procedures implemented for the recording and notification of adverse events

8.3.1 Non-serious adverse events

All adverse events that are not considered serious according to the definition given above and are observed during the study and the period following the study should be reported in the observation, in the appropriate section:

- A single event should be reported per item. This event may be a symptom, a diagnosis or the result of an additional examination considered significant. All the clinical or paraclinical elements best describing the event concerned should be reported.

- The expected non-serious events (according to the SPC) are:
  o Asymptomatic hyperuricemia.
  o Asymptomatic hypokalemia.
  o Calcium metabolism problems.
  o Biological dysthyroidism (hyper- or hypothyroidism).
  o Hepatic disturbances (moderate, asymptomatic cytolysis or cholestasis).
  o Gastrointestinal problems (nausea, vomiting, abdominal pain).
  o Dysesthesia correctable by the addition of a potassium salt.
  o A decrease in platelet counts and PR without bleeding.
  o Hypersensitivity reactions, essentially in the form of skin rashes and fever.

- Potentially serious events not linked to the experimental drug but related to the natural and usual progression of the disease: all complications, including death, linked to the cause of COPD decompensation; all complications, including death, linked to the invasive mechanical ventilation of COPD patients (collapse and states of shock after intubation, pneumothorax, serious arrhythmia not linked to hypokalemia, nosocomial pneumonia, stress-linked digestive system hemorrhage, thromboembolic disease, intestinal ileus).

- Potentially serious adverse effects that are well known, frequent and well controlled, the declaration of which would not increase patient safety. Examples include:

  - Adverse events linked to intensive care procedures: all complications linked to invasive mechanical ventilation (collapse and states of shock after intubation, pneumothorax, serious arrhythmia not linked to hypokalemia, nosocomial pneumonia, stress-linked digestive system hemorrhage, thromboembolic disease, intestinal ileus) or complications linked to
8.3.2 Serious adverse events (SAE)

The form for declaring serious adverse events, validated for the study, is included in the protocol (Appendix 6). The grid for classifying serious and non-serious adverse events is also provided (Appendix 7). This grid was developed to assist investigators in their management of adverse events (i.e. to help them to differentiate between events of different degrees of gravity). This grid was developed and validated by key players in this study (the Head of the Clinical Research Unit, the PI for this study, the Project Leader for this study, the Medical Coordinator of the Clinical Research and Development Department and the Head of Pharmacovigilance of the Clinical Research and Development Department). Improvements to this grid may be made, during the study, depending on the declarations received by the promoter.

The investigators must immediately notify the promoter, AP-HP, of all serious adverse events as defined above.

The investigator must complete the serious adverse event declaration form (in the study observation notebook, Appendix 6) and send it to the Clinical Research and Development Department by fax (01 44 84 17 99), within 48 hours of the occurrence of the event (and having first called 01 44 84 17 23 immediately after the event in cases of death or a life-threatening event).

For each adverse event, the investigator should provide his or her opinion concerning the causality of the link between the event and each experimental drug or other possible treatment.

It is possible that information relating to the description and evaluation of an adverse event is not available during the time limits for the initial declaration.

The expected serious adverse effects (according to the SPC) are:

- Hyperuricemia with acute gout.
- Symptomatic hypokalemia (arrhythmia).
- Hematological incidents (thrombocytopenic purpura, agranulocytosis, medullary aplasia), probably due to sensitization to sulfamides.
- Anaphylactic shock.

Serious adverse effects (anaphylactic shock, arterial hypotension or arrhythmia refractory to usual treatment during perfusion of the test product, hyperuricemia with acute
gout, and symptomatic hypokalemia with arrhythmia) and their imputability to the treatment will be noted during follow-up.

Anaphylactic shock is defined as the sudden appearance, during the minutes following the injection of the study treatment, of cardiovascular signs (severe arterial hypotension, tachycardia or bradycardia, cardiac arrest), cutaneous/mucosal signs (erythema or enanthema) or respiratory signs (bronchospasm), these signs being potentially of various degrees of severity.

Refractory hypotension is considered to correspond to a mean arterial blood pressure below 70 mm Hg despite vascular filling with two boluses of 250 mL of saline and the injection of at least one vasoconstrictor or inotrope. Arrhythmia is considered refractory if it persists despite the administration of at least one anti-arrhythmia drug and the performance of defibrillation.

It is possible that information relating to the description and evaluation of an adverse event is not available within the time limits defined for the initial declaration.

Clinical progression and the results of possible clinical, diagnostic and/or laboratory analyses, or any other information contributing to appropriate analysis of causality will also be reported:

- On the initial declaration of the SAE, if immediately available,
- Or later, but as soon as possible, by faxing a new completed SAE declaration (specifying that the form sent corresponds to the follow-up of a SAE already declared, and giving the follow-up number).

All declarations made by investigators should identify the subject participating in the study by means of the unique code number attributed to the patient concerned.

In cases of the notification of the death of a subject participating in the study, the investigator will send the promoter all the additional information requested (hospital reports, autopsy results etc.).

All new findings arising during the study or in the context of the study, from published data or from studies underway, should be reported to the promoter.

- Declaration of serious adverse events to the health authorities

This declaration will be made by the Pharmacovigilance Unit of the Department of Clinical Research and Development, after evaluation of the gravity of the adverse event, the causal link with the experimental drug and any other treatments administered and the unexpectedness of the SAE observed.
All suspected unexpected SAEs will be declared to the competent authorities by the promoter, within the legal time limit.

The promoter will transmit all safety data and new findings liable to modify the evaluation of the benefit/risk ratio for an experimental drug or for the study significantly, or that might lead to changes in the administration of the drug or the way in which the study is carried to the competent authorities, the ethics committee and the study investigators. For example:

a) Any clinically significant increase in the frequency of an expected serious adverse effect;

b) Suspected unexpected serious adverse effects in participants that have completed the trial, of which the promoter was notified by the investigator, and any follow-up reports;

c) Any new findings concerning the way in which the clinical trial is carried out or the development of the drug, if likely to affect the safety of the participants. For example:

- A serious adverse event likely to be linked to the investigations and diagnostic procedures of the study that might lead to changes in the way in which the study is carried out,

- A significant risk to the study population, such as a lack of efficacy of the drug used to treat the patient, placing the patient’s life at risk,

- Significant safety results from a recently completed study on animals (such as studies of carcinogenicity),

- Early ending or interruption of a study with the same drug in another country, for safety reasons,

d) Any unexpected serious adverse effect reported to the promoter by another promoter of a clinical trial of the same drug carried out in another country.

8.4 Mode and duration of follow-up for the individuals concerned following the occurrence of adverse events

All patients presenting an adverse event should be followed up until the resolution or stabilization of the event concerned.

- If the event is not serious, its progression will be reported on the corresponding page of the observation notebook, in the appropriate section.

- If the event is serious, a SAE follow-up form will be sent to the Department of Clinical Research and Development.
8.5. Unblinding procedure

An unblinding procedure will be implemented in cases of serious adverse events (anaphylactic shock, arterial hypotension or arrhythmia refractory to usual treatments during perfusion of the test product, hyperuricemia with acute gout, symptomatic hypokalemia with arrhythmia).

The investigator from the center at which the serious adverse effects are observed must imperatively follow the procedure for declaring serious adverse events to the promoter. Unblinding will be carried out by the Department of Clinical Research and Development (DRC), during office hours: Maud Jacubert (Project Leader) 01.40.27.57.27 / fax 01.44.84.17.01.

All requests for unblinding must be justified and a completed request for unblinding, signed by the investigator, must be sent by fax. Investigators are also asked to contact the structure to which the fax is sent.

There is no procedure for emergency unblinding at Fernand Widal Hospital, because the only justification for emergency unblinding is apparent anaphylactic shock occurring after injection of the product (if the placebo was administered, there is no real anaphylactic shock, but if the test product was administered, reinjection of the product must be prevented). If a decision must be taken as to whether or not the patient should have another injection, then unblinding should be requested, but this would not be an emergency procedure (the interval between two consecutive injections being at least 12 hours, it should be possible to carry out the unblinding during office hours).

9 COMMITTEES SPECIFIC TO THIS STUDY

Steering Committee

This committee will consist of the clinicians responsible for launching this project, the biostatistician for this project and representatives of the promoter and the Clinical Research Unit assigned to this project:

- Dr Christophe Faisy (HEGP), Coordinating Investigator
- Prof. Alexandre Duguet (Pitié-Salpétrière), Principal Investigator of center no. 4 (Pitié, Pneumo Med).
- Delphine Hourton, Clinical Study Coordinator of the Clinical Research Unit of HEGP; the Clinical Research Assistant assigned to this study.
- Dr Gilles Chatellier or Florence Gillaizeau, statisticians of the Clinical Research Unit of HEGP
- Saliha Djané, DRCD Project Leader, and Catherine Chastang, Assistant Project Leader

This committee will define the general organization of this study and the way in which it will be run and will coordinate information.

It will first determine the methodology to be used, and subsequently will decide, during the study, what action should be taken in cases of unexpected incidents. It will monitor the study, particularly as concerns adverse events.

**Independent Monitoring Committee**

The protocol does not make provision for the constitution of an independent monitoring committee, for the following reasons:

- The prescription of acetazolamide (indication, range of doses prescribed) in the study respects the currently authorized use of this drug for patients with COPD.
- Acetazolamide has been prescribed to COPD patients with metabolic alkalosis for decades and the adverse effects of acetazolamide are largely known and avoidable, provided that the absolute and temporary contraindications to the use of this drug are respected.
- The experimental plan for this protocol includes daily checking for contraindications to the use of acetazolamide. This should ensure the absence of serious adverse events other than undiagnosed allergy with severe clinical signs (anaphylactic shock), which is neither predictable nor avoidable.
- The patients in the placebo group have no major risk of adverse events linked to the administration of the placebo. The administration of the placebo (saline) is not associated with any particular risk and does not modify the management currently recommended for COPD patients on invasive respiratory assistance in intensive care.
10 STATISTICS

10.1 Description of the statistical methods to be used, including a timetable for the scheduled intermediate analyses

The principal objective of this study is to evaluate the effect of acetazolamide on the total duration of invasive mechanical ventilation.

The principal analysis will be an intention-to-treat analysis for the entire randomized population. Time interval data (duration of invasive mechanical ventilation as defined in §4.2.2, duration of weaning) will be subjected to survival analysis. Log-rank tests will be used to compare the two arms. If, despite the randomization, an imbalance is found between the two groups for prognostic variables (initial gravity and prior degree of change in respiratory function, for example), we will use appropriate post-randomization adjustment methods (Glen Heller. An adjustment for a post-randomization variable in the comparison of two treatments for survival. Statistics in Medicine. 2001, vol. 20, no22, pp. 3475-3485. Xun Chen, Minzhi Liu, Ji Zhang. A note on post-randomization adjustment of covariates. Drug Information Journal. 2005, vol. 39, no4, pp. 373-383). Data for patients dying before weaning off of mechanical ventilation will be censored on the date of death, for analysis of the duration of invasive mechanical ventilation (principal judgment criterion) and these cases will be excluded from the analysis of the duration of weaning.

The secondary judgment criteria will be assessed for the entire study population and for the per-protocol population, through Student’s $t$ tests (or non-parametric tests for non-normally distributed variables) to compare quantitative variables between groups, or $\chi^2$ (or Fisher’s exact tests if necessary) and Kruskal-Wallis tests for qualitative variables. The mortality analysis will compare survival, based on Kaplan-Meier curves and log-rank tests, possibly adjusted for initial severity and the prior degree of change to respiratory function.

10.2 Number of participants to be included in the study and planned degree of statistical significance

The sample size was calculated on the basis of the principal judgment criterion, the duration of invasive mechanical ventilation until extubation or its complete cessation in tracheotomized patients. No study has been published concerning the influence of acetazolamide on the total duration of invasive mechanical ventilation in intubated COPD patients in intensive care. However, our first preliminary study on the effect of acetazolamide
administered at low dose solely during the weaning of COPD patients developing metabolic alkalosis [38] indicated that the mean total duration of invasive ventilation in these patients was 12 ± 5 days.

We plan to include 190 subjects in each arm, resulting in a total of 380 patients included. This sample size should provide a power of 80% according to the following hypotheses:

- Median duration of the period without extubation or without the cessation of invasive ventilation in tracheotomized patients or without the restoration of usual ventilation in tracheotomized patients ventilated at home of 12 days for the placebo arm.
- Median duration of the period without extubation or without the cessation of invasive ventilation in tracheotomized patients or without the restoration of usual ventilation in tracheotomized patients ventilated at home of 10 days for the acetazolamide arm.
- A recruitment period of three years and individual patient follow-up for 28 days.
- An $\alpha$-risk of 5%.


11 RIGHT OF ACCESS TO DATA AND SOURCE DOCUMENTS

Individuals with direct access, in accordance with the legal and regulatory dispositions currently in force, including articles L.1121-3 and R.5121-13 of the Public Health Code, in particular (e.g. investigators, quality control agents, monitors, clinical research assistants, auditors and anyone asked to collaborate in the trial), will take all the necessary precautions to ensure the confidentiality of information relating to the experimental drugs, the trial, the people taking part in the study (particularly as concerns their identity) and the results obtained. The data collected by these individuals during quality control and audits will be rendered anonymous.
12 QUALITY CONTROL AND ASSURANCE

The study will be carried out in the framework of the standard operating procedures of the promoter. The research will be carried out and subjects will be managed, at the participating centers, in accordance with the Helsinki Declaration and good clinical practice.

12.1 Monitoring procedures

Evaluated risk level of the study: C

The clinical research assistants representing the promoter will visit the investigating centers at times determined by the scheduled follow-up of patients in the protocol, inclusions at the various centers and the risk level of C attributed to this study.

- Opening visit for each center (investigator and pharmacist): before inclusion, for establishment of the protocol and to meet the various people involved in the biomedical research study.

- During subsequent visits, the observation notebooks will be examined by the clinical research assistant, with the progression of the research. The PI at each center and the other investigators including or following up the patients participating in the study agree to regular visits from the clinical research assistant.

During these site visits, the following elements will be reviewed, in accordance with good clinical practice:

- Respect of the protocol and the procedures defined for the study.
- Informed consent from the patients.
- The source documents, comparing them with the data reported in the observation notebook, to verify their exactness and to check for missing data, and data consistency, in accordance with the procedures laid down by DRCD rules.

- Closing visit: recovery of the observation notebooks, the pharmacy evaluation and biomedical research documents, archiving.

12.2 Transcription of data in the observation notebook

All the information required by the protocol must be provided in the observation notebook and the investigator must provide an explanation for any missing data.
The data should be transferred to the observation notebooks as they are obtained, whether they are clinical or paraclinical in nature. The data should be copied into these notebooks clearly and legibly, in black ink (to facilitate duplication and computer entry).

Any erroneous data identified in the observation notebooks will be clearly crossed out and the new data will be copied into the notebook, with the date of the change and the initials of the member of the investigating team making the correction.

The anonymity of the subjects in study documentation will be ensured by the use of a code number and the initials of the person taking part in the study marked on all the documents required for the study, with appropriate means used to erase nominative data from copies of the source documents.

Computerized data will be included in a file, which will be declared to the CNIL according to the appropriate procedure.

13 LEGAL AND ETHICAL CONSIDERATIONS

The promoter is defined according to law 2004-806 from August 9 2004. In this study, AP-HP is the promoter and the Department of Clinical Research and Development (DRCR) is responsible for regulatory affairs.

Before the start of the study, each investigator will provide the promoter’s representative with a dated and signed personal curriculum vitae bearing his or her registration number with the French Medical College.

13.1 Request for authorization from AFSSAPS

AP-HP, as the promoter of this study, must submit a request for the authorization of this study to the competent authority, AFSSAPS. The competent authority, as defined in article L. 1123-12, will issue its opinion concerning the safety of the people taking part in the biomedical research study, taking into account, in particular, the safety and quality of the products used in the study in accordance, as appropriate, with current guidelines, their conditions of use and the safety of the participants with respect to the acts practiced and the methods used, together with the planned mode of follow-up of the participants.
13.2 Request for authorization from the ethics committee

In accordance with article L.1123-6 of the French Public Health Code, the promoter must submit the research protocol to the appropriate ethics committee (Comité de Protection des Personnes). The competent authority is informed of the decision of this committee by the promoter, before the start of the study.

13.3 Modifications

The DRCD must be informed, by the Coordinating Investigator, of all planned changes to the protocol.

The modifications must be classified as substantial or not substantial.

A substantial modification is any change likely, in any way, to modify the guarantees provided to the participants in the research study (changes to the inclusion criteria, prolongation of the inclusion period, participation of new centers, etc.).

Once the study has begun, any substantial modification at the promoter’s initiative must, before its implementation, be approved by the ethics committee and authorized by the competent authority. In this case, if necessary, the committee will ensure that informed consent is collected again from the participants in the study.

Any extension of the study (profound modification of the treatment plan or of the populations included, prolongation of treatments and/or therapeutic acts not initially included in the protocol) should be considered as a new study.

All substantial modifications should be the object of a request for authorization from AFSSAPS and/or a request for ethics committee approval submitted by the promoter.

13.4 CNIL declaration

The law requires a declaration of the computerized file of personal data collected for the study before the study begins.

A reference methodology specific to the treatment of personal data in the framework of biomedical research, defined by law 2004-806 of August 9 2004 applies under articles L.1121-1 and according to the French Public Health Code. This methodology was established by the CNIL in January 2006.
This methodology allows a **simplified declaration procedure** when the nature of the data collected in the study is compatible with the list provided by the CNIL in its reference document.

When the protocol is subject to data quality control by a clinical research assistant representing the promoter and falls into the field of application of the simplified procedure of the CNIL, the DRCD, as the promoter, will ask the person responsible for the computer file to provide a written commitment to respect the MR001 simplified reference methodology.

### 13.5 Information and informed consent forms

Individuals admitted to intensive care for respiratory insufficiency, including postoperative respiratory insufficiency, will be included in this biomedical research study. The patients will not initially be able to give consent themselves. Consent will therefore be requested from family members or close friends, if present, in accordance with article L. 1122-1-2 of the French Public Health Code.

The patient will be informed as soon as possible and, after a suitable period of reflection, will be asked for his or her consent to continue participation in the study. The patient may, at any time, oppose the use of his or her data in the framework of this study.

This study will not include individuals covered by articles L. 1121-5 to L. 1121-8 of the French Public Health Code: pregnant women, prisoners and institutionalized subjects, and adults subject to legal protection.

### 13.6 Final report

The final study report will be jointly written by the Coordinator and the Biostatistician for this study. This report will be submitted to each of the investigators for approval. Once a consensus has been reached, the final version will be endorsed by the signature of each of the investigators and sent to the promoter, as soon as possible after the effective end of the study. A report written according to the reference plan of the competent authority must be sent to this authority and to the ethics committee within one year of the end of the study, defined as the last follow-up visit of the last subject included. This time limit will be decreased to 90 days if the study ends early.

- First author: Principal Investigator, Dr Christophe Faisy
- Second author: Intensive care doctor
- Third author: representative of the Clinical Research Unit of HEGP
- Fourth, fifth and sixth authors: Intensive care doctors
- Penultimate author: Intensive care doctor
- Last author: Scientific Director, Prof. Jean-Yves Fagon

The ranking of the authors will be determined by the number of inclusions at each center.

14 DATA PROCESSING AND STORAGE OF DATA AND DOCUMENTS RELATING TO THIS STUDY

After monitoring, the data will be entered into an MS-Access database developed by the Clinical Research Unit of HEGP. A data-management plan consistent with the monitoring plan and developed jointly by the data manager, the clinical research assistant assigned to the study, the PI and the statistician will be produced. After the correction of any errors revealed by this plan, the database will be fixed for statistical analysis. Prof. Gilles Chatellier will be responsible for the processing of all the data generated by this study.

The study documents covered by the law on biomedical research will be archived by all the parties for a period of 15 years after the end of the study.

*(See GCP, chapter 8: Essential documents)*

The indexed archive will include:

- Copies of the letters of authorization from AFSSAPS and the ethics committee
- The successive versions of the protocol (identified by version number and date),
- All written correspondence with the promoter,
- The signed informed consent forms of the subjects, in sealed envelopes, with the corresponding inclusion list or register,
- The completed and validated observation notebook for each subject included,
- All the appendices specific to the study,
- The final report for the study, including the statistical analysis and quality control findings (a copy of which must be sent to the promoter).
- The certificates corresponding to any audits carried out during the study.

The database used for the statistical analysis must also be archived by the person responsible for the analysis (either on paper or a computerized version).
15 INSURANCE AND SCIENTIFIC COMMITMENT

15.1 Insurance

Assistance Publique-Hôpitaux de Paris is the promoter of this study. In accordance with biomedical research law, AP-HP has taken out an insurance policy with HDO GERLING for the entire duration of this study, covering its own civil responsibilities and those of anyone involved in the study (doctors and staff members carrying out the study; law no. 2004-806, Art L.1121-10 of the French Public Health Code).

Assistance Publique-Hôpitaux de Paris reserves the right to stop the study at any moment, for medical or administrative reasons. Should this occur, the investigator will be notified.

15.2 Scientific commitment

Each investigator will agree to respect legal obligations and to carry out the study in accordance with GCP and the terms of the Helsinki Declaration in force. A copy of the scientific commitment (DRCD-type document), dated and signed by each investigator at each of the participating centers will be supplied to representative of the promoter to ensure this.

16 PUBLICATION RULES

AP-HP owns the data, which must not be used or transmitted to a third party without the prior agreement of the AP-HP.

The first authors on publications will be the individuals who really participated in the development and running of the protocol, and in the generation and writing of results.

Assistance Publique-Hôpitaux de Paris must be cited as the promoter of the research and as the source of funding, as appropriate. The terms “Assistance Publique-Hôpitaux de Paris” must appear in the addresses of the authors.
17 REFERENCES


3- Seneff MG, Wagener DP, Wagener RP: Hospital and 1 year survival of patients admitted to intensive care units with acute exacerbations of chronic obstructive lung disease. JAMA 1995;274:1852-1857


6- Knaus WA. Prognosis with mechanical ventilation: the influence of disease, severity of disease, age and chronic status on survival from an acute illness. Am Rev Resp Dis 1989;140:S8-S13


12- Chevrolet JC. Perturbations de l’équilibre acide-base. Encyclopédie Médico-chirurgicale Pneumo, 6-000-A-75


14- Khanna A, Kurtzman A. Metabolic alkalosis. Respir Care 2001;46:354-365
18- Berthelsen P. Cardiovascular performance and oxyhemoglobin dissociation after acetazolamide in metabolic alkalosis. Intensive Care Med 1982;8:269-274
38- Faisy C, Mokline A, Sanchez O, Tadié JM, Fagon JY. Effectiveness of acetazolamide for reversal of metabolic alkalosis in weaning COPD patients from mechanical ventilation. Intensive Care Med 2010; 36:859-863
18 LIST OF APPENDICES

Appendix 1: SPC for DIAMOX
Appendix 2: Pharmacodynamic study in intensive care
Appendix 3: SOFA
Appendix 4: SAPS II
Appendix 5: List of the variables to be recorded in the observation notebook
Appendix 6: SAE declaration form
Appendix 7: Adverse events grid
Appendix 1: SPC for DIAMOX (AFSSAPS)

SUMMARY OF PRODUCT CHARACTERISTICS

1. MEDICINE NAME

DIAMOX 500 mg, powder and solvent for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Acetazolamide ................................................................................................................................. 500 mg

as acetazolamide sodium

For a vial of powder.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for injection

4. CLINICAL DATA

4.1. Therapeutic indications

• Attack treatment of high ocular hypertonia.
• Treatment of certain metabolic alkalosis, especially during decompensation chronic respiratory failure requiring the use of mechanical ventilation.

4.2. Posology and method of administration

Posology

• **Adults**: the usual dosage is 1 to 2 g per day, 2- 4 vials of 500 mg/day.

• **Children over 6 years**: 5 to 10 mg/kg/day.

Method of administration

• Slow intravenous injection or in the tubing of the infusion

• The intramuscular route may be optionally used.

RESERVED FOR ADULTS AND CHILDREN OVER 6 YEARS.
4.3. Contraindications

This medicine is contraindicated in the following situations:

- Hypersensitivity to acetazolamide,
- Liver, renal or suprarenal gland severe failures,
- Intolerance to sulfonamides,
- Renal colic history.

This medication is usually not recommended during pregnancy and lactation.

4.4. Special warnings and precautions for use

**Special warnings**

This specialty contains an active ingredient (acetazolamide) that could produce a positive analytic result in doping tests in sports.

**Special precautions for use**

In some subjects at risk (elderly, diabetics or state of metabolic acidosis), or if long-term use, it is recommended to monitor blood electrolytes, blood sugar, uric acid, and blood count.

4.5. Interaction with other medicinal products and other forms of interaction

**Combinations requiring precautions for use**

**+ Carbamazepine**

Increased plasma concentrations of carbamazepine with signs of overdose.
Clinical monitoring; control of plasma levels of carbamazepine and possible reduction in dosage.

**+ Quinidiniques (hydroquinidine, quinidine)**

Increased plasma concentrations of quinidine and risk of overdosage (decreased renal excretion of quinidine by alkalinization of urine).
Clinical monitoring, ECG and possibly control the blood concentration of quinidine; if necessary, dose adjustment during alkalinizing treatment and after discontinuation.

4.6. Pregnancy and lactation

**Pregnancy**

Studies in animals have shown teratogenic effects.
Clinically, the use of acetazolamide sodium in a limited number of pregnancies has not revealed any particular malformative or foetotoxicto date. However, additional studies are needed to assess the consequences of exposure during pregnancy.
Given the indication and the lack of alternative, acetazolamide may be used intravenously, if necessary, during pregnancy.

**Lactation**

Given the passage of acetalozamide in milk, breastfeeding is not recommended.
4.7. Effects on ability to drive and use machines

None.

4.8. Undesirable effects

- Disturbance of carbohydrate metabolism, diabetes
- Hyperuricaemia with acute gout attack.
- Hypokalemia with metabolic acidosis.
- Disorders of calcium metabolism, nephrolithiasis.
- Metabolic disruption ammonia, hepatic coma in patients with cirrhosis (see section 4.3).
- Transient myopia.
- Rare: thyroid dysfunction, fatigue, drowsiness, gastrointestinal disorders, dysesthesia can be corrected by adding a potassium salt.
- Exceptionally, hypersensitivity reactions mainly type of skin rash and fever, isolated cases of anaphylactic shock can be fatal, accidents hematologic (thrombocytopenia purpura, agranulocytosis, aplastic anemia), possibly by sensitization to sulphonamides.
- Intramuscular injection can be painful.

4.9. Overdose

In case of overdose, hospitalization is required for the purpose of monitoring and fluid and electrolyte control.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Carbonic anhydrase inhibitors.

ATC Code: S01EC01

Specific carbonic anhydrase inhibitor at different levels: renal tubule, ciliary body, choroid plexus, central nervous system and gastrointestinal mucosa.
In the renal tubule, acetazolamide is a diuretic causing by ion substitution: an increase in water diuresis, high elimination bicarbonates, less excretion of sodium and potassium, a urine alkalinization.
The renal response to a dose of 5 to 10 mg is 6 to 12 hours.
At the eye, acetazolamide, by prior ocular hypertension causes a rapid drop in pressure action on the ciliary body and accelerated phase bicarbonates and other electrolytes normally found in high concentrations in the intraocular fluids. This accelerated phase decreases the osmotic pressure of Fluid media of the eye and, thereby, lowers the intraocular pressure.
In the nervous system antiserectory effect on choroid plexus reducing the formation of cerebrospinal fluid.
Effect on hematology: decreased by hypercapnia and metabolic acidosis urinary excretion of bicarbonate.

5.2. Pharmacokinetic properties

The gastrointestinal absorption of acetazolamide is very fast.
At the plasma level, it is highly bound to plasma proteins (90-95 %).
The plasma half-life of 5 hours and urinary excretion is complete in 24 hours as unmetabolized form.

5.3. Preclinical safety data

Nothing of note to prescriber.

6. PHARMACEUTICAL PARTICULARS
6.1. List of excipients

**Solvent**: water for injections.

6.2. Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other drugs.

6.3. Shelf life

5 years.

After opening / reconstitution / dilution: the product must be used immediately.

6.4. Special precautions for storage

No special storage conditions.

6.5. Nature et contents of container

Powder in vial (glass) and 5 ml of solvent ampoule (glass). Pack of 1 vial and ampoule.

Powder in a vial (glass). Box of 25.

6.6. Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

SANOFI-AVENTIS FRANCE

1-13, boulevard Romain Rolland

75014 PARIS

8. MARKETING AUTHORISATION NUMBER

- 303 053-3: Powder bottle (glass) + 5 ml of solvent in ampoule (glass).

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[to be completed by the holder]

10. DATE OF REVISION OF THE TEXT

[to be completed by the holder]

11. DOSIMETRY

None.

12. INSTRUCTIONS FOR REPARATION OF RADIOPHARMACEUTICALS

None.
List I.
Appendix 2: Pharmacodynamic study in intensive care

Submission: SRLF congress 2011
Summary number: 004217 (FR)
Title: Modeling pharmacodynamics of acetazolamide during weaning from mechanical ventilation in COPD patients
Authors/addresses: N Heming (1); S Urien (2); JY Fagon (1); C Faisy (1).
(1) Service de Réanimation Médicale, CHU Hegp, Paris; (2) Unité 0991, Inserm, Paris.
Speaker: N Heming

Summary:
Introduction
Acetazolamide (ACET) has been proposed (250 to 500 mg per day) to reduce metabolic alkalosis in COPD patients with metabolic alkalosis in order to facilitate weaning from mechanical ventilation. A recent study [1] showed that ACET, administered at a dose of 500 mg / day in this situation decreases moderately bicarbonates and has no impact on the PaCO2 and respiratory parameters. This could be the consequence of a change in the effectiveness of ACET on this particular field. The purpose of this study was to investigate the factors influencing the pharmacodynamics of ACET in this situation.

Patients and Methods
506 records (10 years) of COPD patients intubated in our service because of acute respiratory failure were reviewed. Patients who received ACET to treat metabolic alkalosis (bicarbonates> 26 mmol / l) during weaning from mechanical ventilation were selected for analysis. From the data available in the records (doses administered, timing of administration, dosing schedules of bicarbonates), modeling the effect of ACET on concentration of bicarbonate was performed using the software MONOLIX. The bicarbonate levels can be described as: dBicar (t) / dt = kin - kout × Bicar (t) where kin (mmol / d) and kout (day-1) represent respectively the rates of formation and elimination (first order kinetics) of bicarbonates. At equilibrium, Bicar0 = kin / kout. We then studied the impact of the covariates of interest (demographic characteristics, pulmonary function, biological and co-prescriptions) on this pharmacodynamic model.

Results
68 COPD [age 74 (44-99) years, FEV / CV 51 (24-66)%, SAPS II at intake 47 (20-95)] having received 1-6 doses ACET during weaning were included in the analysis. The covariates have a significant impact on Bicar0 were SAPS II, serum chloride prior to administration of ACET and prescription of corticosteroids by the general route. Co-prescription of furosemide during weaning significantly decreased the elimination of bicarbonates (effect on kout). The final pharmacodynamic model describing the effect of ACET on bicarbonates was thus: Bicar0 = TV (Bicar0) × (SAPS II / 50) -0.11 × (serum chloride / 100) -1.17 × (1.1 if corticosteroids) and kout = TV (kout) × [1 - Dose of furosemide / (furosemide dose Fur50 +)] where TV is a typical value and Fur50 the daily dose of furosemide which causes 50% decrease of kout. For a SAPS II of 50 and a serum chloride of 100 mmol / l, the unit ACET dose required to produce 50% of the maximum effect on bicarbonates is 139 mg ±37 (5 times the unit dose is about necessary to obtain a maximum effect on bicarbonates).

Conclusion
This pharmacodynamic model allows to understand that in the presence of elevated serum chloride and / or co-prescriptions of corticosteroids or furosemide larger unit doses ACET are needed to effectively reduce the bicarbonates in COPD patients with a metabolic alkalosis during weaning from mechanical ventilation.

References:
Faisy C, Mokline A, Sanchez O, Tadié JM, Fagon JY, Effectiveness of acetazolamide for reversal metabolic alkalosis in weaning COPD patients from mechanical ventilation. Intensive Care Medicine 2010;36(5):859-63
Appendix 3: SOFA

**SOFA (Sequential Organ Failure Assessment) SCORE**

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<thead>
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<th>0</th>
<th>1</th>
<th>2</th>
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<tr>
<td><strong>Pulmonary</strong> PaO2/FiO2(mmHg)</td>
<td>&gt;400</td>
<td>&lt;= 400</td>
<td>&lt;= 300</td>
<td>&lt;= 200 et ventilation</td>
<td>&lt;= 100 et ventilation</td>
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<tr>
<td><strong>Hematologic</strong> Platelets (Giga/L)</td>
<td>&gt;150</td>
<td>&lt;= 150</td>
<td>&lt;= 100</td>
<td>&lt;= 50</td>
<td>&lt;= 20</td>
</tr>
<tr>
<td><strong>Hepatic</strong> Bilirubine (mg/dL) (umol/L)</td>
<td>&lt;1.2</td>
<td>1.2-1.9 20-32</td>
<td>2-5.9 33-101</td>
<td>6-11.9 102-204</td>
<td>&gt;12 &gt;204</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td>Mean arterial pressure &lt;70 mmHg</td>
<td>Dopa &lt;= 5 gamma Doba</td>
<td>Dopa &gt;= 5 adrenaline &lt;= 0.1 noradrenaline &lt;= 0.1 gamma/kg/mn</td>
<td>Dopa &gt;15 adrenaline &gt; 0.1 noradrenaline &gt; 0.1 gamma/kg/mn</td>
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<tr>
<td><strong>Neurologic Glasgow Coma Score</strong></td>
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<td>10-12</td>
<td>8-9</td>
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<td><strong>Renal</strong> Creatinine (umol/L) Urine Output</td>
<td>&lt;=110</td>
<td>110-170</td>
<td>171-299</td>
<td>300-440 or &lt;500ml/jour</td>
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## Appendix 4: SAPS II

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<tbody>
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<td>Age (year)</td>
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<td>70–74</td>
<td>75–79</td>
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<tr>
<td>Heart Rate (Beat/min)</td>
<td>60–99</td>
<td>100–119</td>
<td>120–159</td>
<td>≥160</td>
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<td>Syst Blood Pressure (mmHg)</td>
<td>&lt;70</td>
<td>70–99</td>
<td>100–199</td>
<td>≥200</td>
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<tr>
<td>Body Temperature (°C)</td>
<td>&lt;35°</td>
<td>35.0–37.9</td>
<td>≥38°</td>
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<td>PaO2/FIO2 (mmHg)</td>
<td>&lt;100</td>
<td>100–199</td>
<td>≥200</td>
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<td>Only II VENT or CPAP</td>
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<td>Urinary Output (L/day)</td>
<td>&lt;0.50</td>
<td>0.50–0.99</td>
<td>≥1.00</td>
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<tr>
<td>Blood Urea (mMol/L)</td>
<td>&lt;10.0</td>
<td>10.0–29.9</td>
<td>≥30.0</td>
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<td>WBC Count (10E9/ml)</td>
<td>&lt;1.0</td>
<td>1.0–19.9</td>
<td>≥20.0</td>
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<td>Serum K (mEq/L)</td>
<td>&lt;3.0</td>
<td>3.0–4.9</td>
<td>≥5.0</td>
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<td>Serum Na (mEq/L)</td>
<td>135</td>
<td>135–144</td>
<td>≥145</td>
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<td>Serum HCO3 (mEq/L)</td>
<td>18</td>
<td>18–19.9</td>
<td>≥20</td>
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<td>Bilirubin (umol/L)</td>
<td>&lt;68.4</td>
<td>68.4–102.5</td>
<td>≥102.6</td>
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<td>Glasgow Coma Score Points</td>
<td>≤8</td>
<td>9–10</td>
<td>11–13</td>
<td>≥14–15</td>
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<td>Chronic disease:</td>
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<td>Type of admission</td>
<td>Ext.</td>
<td>Med</td>
<td>S. Em.</td>
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### Sum of Points

<table>
<thead>
<tr>
<th>TOTAL SAPS II</th>
<th>Pts</th>
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</thead>
<tbody>
<tr>
<td>RISK OF HOSPITAL DEATH</td>
<td>%</td>
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</tbody>
</table>

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Appendix 5: List of variables to be recorded in the observation notebook

A case report form will be made by the URC of HEGP and will be available in each investigation center. The data (anonymized) of the patient will be:
- Birth date
- Inclusion date
- Gender
- Weight
- Size
- Respiratory function tests available (FEV, FEV / CV, RV / TLC, CV)
- Smoking status
- Taking corticosteroids, diuretics or β2-agonists long-term (at least 8 weeks before hospitalization in intensive care)
- Oxygen therapy and / or non-invasive ventilation at home
- Tracheotomy or ventilation tracheotomy at home
- Clinical and laboratory elements for the calculation of the SOFA score (see Appendix 3)
- Clinical and laboratory elements for the calculation of the SAPS II at baseline (see Appendix 4)
- Cause(s) of the decompensation of COPD
- Estimation of LVEF (alteration of LVEF is a recognized factor as may make it difficult weaning from ventilation) by transthoracic echocardiography at weaning from mechanical ventilation, under mechanical ventilation and specifying the use or not of positive inotrope drugs
- Start of invasive mechanical ventilation (specifying the schedule)
- Date of extubation (specifying the schedule) or complete cessation of invasive ventilation in tracheotomy patients or restoration of normal ventilation in tracheotomy and ventilated home patients
- Calculation of the number of days in metabolic alkalosis
- Calculation of the number of days that acetazolamide (or placebo) was administered
- Failure or success of weaning from invasive ventilation (in particular use of ICU tracheotomy for weaning)
- Causes(s) of failure of weaning from invasive ventilation
- Use of non-invasive ventilation and / or re-intubation after extubation
- Calculation of invasive mechanical ventilation time (in hours)
- Calculation of the duration of weaning from invasive mechanical ventilation (in hours)
- Administration of purveyors of metabolic alkalosis drugs in intensive care unit (type, number of days) : loop diuretics, β-agonists, corticosteroids
- Date of diagnosis of nosocomial infection
- Type of nosocomial infections and their number during invasive ventilation
- Calculation of the ICU length of stay (days)

Biochemistry data (Biochemistry Services):
- Arterial Blood Gas of mechanical ventilation
- Serum electrolytes, glucose, calcium, NFS, TP, hepatocellular balance sheet, creatinine, plasma urea, uric acid and TSH
- Number of days in metabolic alkalosis

Parameters related to mechanical ventilation:
- Ventilatory mode used daily
- Minute Ventilation, tidal volume, FR, FiO2 at achieving blood gas and under mechanical ventilation.
Appendix 6: Form for the declaration of SAEs

DECLARATION FORM OF SERIOUS ADVERSE EVENT (SAEs) OCCURRING DURING A BIOMEDICAL RESEARCH INVOLVING DRUG PRODUCT

This form must be returned duly completed (2 pages) to DRCD by fax: +33 (0)1 44 84 17 99
For the attention of Ms Maud Jacubert

Date of notification: ___/___/____

Research code: P081208
N° EudraCT: 2011-000492-14 Initial statement □ SAE monitoring □ N° of the following □

Biomedical Research title: « Randomized trial of the efficacy of acetazolamide in patients with COPD developing metabolic alkalosis during invasive mechanical ventilation » -- « DIABOLO »

1) Name and address of center:

Center n°: ___/___ Investigator (Quality - Name- Surname):

2) Patient identification:

Name: ___/___ Surname: ___
Patient n°: ___/___/___
Gender: Male □ Female □
Date of birth: ___/___/___

Age: ___/___ years
Weight: ___/___ kg
Size: ___/___ cm
Date of inclusion: ___/___/___
Date of randomisation: ___/___/___

3) Evénement indésirable grave:

Death □
Serving life-threatening □
Requires or prolongs hospitalization: From ___/___/___ to ___/___/___ □ In progress □
Incapacity or disability □
Congenital anomaly □
Other(s) test(s) medically significant(s) (specify):

4) Complete description of the adverse event (final diagnosis, anatomical location, criteria for considering the event as severe):

Intensity: Mild □ Moderate □ Severe □

History (allergy, renal insufficiency …): ____________________________________________
Date of occurrence: _______ _______ _______ _______  And time of occurrence: _______ _______  
jj  mm  aaaa  hh  min

Delay occurred after the last shot: __________________________________________________________

5) Experimental drug(s) given before the occurrence of the adverse event:

<table>
<thead>
<tr>
<th>Trade name (preferred) or International Nonproprietary Name</th>
<th>Route</th>
<th>Dose/24h</th>
<th>Start date</th>
<th>In progress</th>
<th>End date</th>
<th>Indication</th>
<th>Causality* (1,2,3 ou 4)</th>
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* 1 = Likely  2 = Possible  3 = Not related  4 = Unknown

6) Drug(s) concurrent(s) excluding those used to treat the adverse event:

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<tr>
<th>Trade name (preferred) or International Nonproprietary Name</th>
<th>Route</th>
<th>Dose/24h</th>
<th>Start date</th>
<th>In progress</th>
<th>End date</th>
<th>Indication</th>
<th>Causality* (1,2,3 ou 4)</th>
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* 1 = Likely  2 = Possible  3 = Not related  4 = Unknown

7) Evolution (specify whether symptomatic measures were taken): no □ yes □  If yes, specify:

8) Date of SAE stop: _______ _______ _______  And time of SAE stop: _______ _______
jj  mm  aaaa  hh  min

9) Other(s) cause(s) considered:  no □ yes □  If yes, specify:

10) Review(s) additional(s) made:  no □ oui □  If yes, specify date, nature and results:
11) Treatments of Biomedical Research:

Unblinding:       no ☐ yes ☐ not applicable ☐ date: __________

Result of the unblinding procedure: ____________________________________________

Re-administration of drug(s):       no ☐ yes ☐ not applicable ☐ date: __________

If yes, which one(s): __________________________________________________________

Recurrence after re-administration:  no ☐ yes ☐ not applicable ☐ date: __________

12) According to the investigator, the SAE seems rather related:

☐ to drug research : which one(s) : ________________________________ ☐ to intercurrent illness
☐ at concomitant(s) drug(s) : which one(s) : ________________________________ ☐ to disease progression
☐ to procedures of biomedical research ☐ other : __________________________

Date: __________ Stamp service: Investigator name: __________________ Signature:

Name and function of the notifier: ___________________________ Phone __________________ Signature:

PART RESERVED TO THE SPONSOR: DO NOT FILL

Event ID: EV __________

Date of receipt by the sponsor: __________

Date of this report: __________ initial ☐ following n° __________

According to the sponsor, the SAE seems rather related:

☐ to drug research : which one(s) : ________________________________ ☐ to intercurrent illness
☐ at concomitant(s) drug(s) : which one(s) : ________________________________ ☐ to disease progression ☐
☐ to procedures of biomedical research ☐ Other : __________________________

If according to the sponsor, the event seems rather drug-related:

☐ The serious adverse event is expected ☐ The serious adverse event is unexpected

Comments of the sponsor:

______________________________________________________________

Name and quality of the sponsor’s representative : __________________ Signature:
### Appendix 7: AE grid

**Risk of research:** C  
**Independent oversight committee:** Yes ☐ No ■

<table>
<thead>
<tr>
<th>Other events</th>
<th>Non serious Adverse Effects expected</th>
<th>Serious Adverse Effects expected</th>
<th>Serious Adverse Events unexpected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Known to be linked at drug(s) or procedures of research.</td>
<td>Known to be linked at drug(s) or procedures of research.</td>
<td>This column will fill up as the notifications by the investigators.</td>
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<tr>
<td></td>
<td>- Hyperuricemia.</td>
<td>- Hyperuricemia with acute gout attack.</td>
<td>Notify all events having a severity criteria * as noted below, with the exception of those identified in other columns</td>
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<tr>
<td></td>
<td>- Hypokalemia asymptomatic.</td>
<td>- Hypokalemia symptomatic (cardiac rhythm disorders).</td>
<td>* Severity criteria:</td>
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<td></td>
<td>- Trouble calcium metabolism.</td>
<td>- Accidents hematologic (thrombocytopenia purpura, agranulocytosis, aplastic anemia), probably by awareness sulfinamides.</td>
<td>1- Death</td>
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<td>- Thyroid dysfunction (hyper or hypothyroidism).</td>
<td>- Anaphylactic shock.</td>
<td>2- Serving life-threatening</td>
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<td>- Disruption of liver function tests (cytolysis and/or asymptomatic moderate cholestasis).</td>
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<td>3- Requires or prolongs hospitalization</td>
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<td></td>
<td>- Gastrointestinal disorders (nausea, vomiting, stomach pains).</td>
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<td>4- lasting sequelae</td>
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<td>- Dysesthesia can be corrected by adding a potassium salt.</td>
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<td>5- anomaly or birth defect</td>
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<td>- Decreased platelet and TP.</td>
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<td>6- event considered serious by the investigator (reason to be specified)</td>
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<tr>
<td></td>
<td>- Hypersensitivity reactions mainly type of skin rash and fever.</td>
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<td>WARNING: Any discovery of a PREGNANCY during the biomedical research must be immediately reported to the sponsor and will be followed up until delivery.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Description</th>
<th>Name, surname and signature of coordinating investigator</th>
<th>Name, surname and signature the head of the URC:</th>
<th>Name, surname and signature of the project manager:</th>
<th>Name, surname and signature of the official of pharmacovigilance:</th>
<th>Name, surname and signature of Medical Coordinator:</th>
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<tbody>
<tr>
<td>1. Events that may be serious but not related to experimental(s) drug(s) or research procedures:</td>
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<tr>
<td>Description:</td>
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<td>- Complications or deaths related to causes of decompensation of COPD.</td>
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<tr>
<td>- All the complications of invasive mechanical ventilation in COPD patients: collapse and shock states after intubation (up to 24 H), pneumothorax, severe rhythm disorders not related to hypokalemia, nosocomial pneumonia, gastrointestinal bleeding from stress, thromboembolic disease, intestinal ileus, deaths related to these complications.</td>
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<td>2. SERIOUS SIDE EFFECTS MAY BE KNOWN BUT VERY FREQUENT AND WELL CONTROLLED WHICH THE DECLARATION would bring nothing to A PATIENT SAFETY (eg bone marrow suppression during chemotherapy...)</td>
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<tr>
<td>Description:</td>
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<tr>
<td>Adverse Events related to intensive care procedures: collapse and shock states after intubation (up to 24 H), pneumothorax, severe rhythm disorders not related to hypokalemia, nosocomial pneumonia, gastrointestinal bleeding from stress, thromboembolic disease, intestinal ileus, central venous catheterization complications ( infections, pneumothorax, hemorrage)</td>
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