Efficacy of levosimendan pretreatment before coronary artery bypass graft (CABG) with the use of cardiopulmonary bypass in patients with left ventricular ejection fraction ≤40%: a multicenter, randomized, double-blind, placebo-controlled trial.

LICORN: Levosimendan In Coronary Revascularization

P110138 - IDRCB 2012-A00232-25
Version 4-0 dated 08/01/2015

Coordinating investigator: Professor Bernard Cholley
Service d’Anesthésie Réanimation
Tel: 33 1 56 09 25 15
Fax: 33 1 56 09 30 60
E-mail: bernard.cholley@egp.aphp.fr
Hôpital Européen Georges Pompidou
20 rue Leblanc – 75908 Paris cedex 15

Promoter: Assistance Publique – Hôpitaux de Paris
Direction de la Recherche Clinique et du Développement
Cécile Hoffart-Jourdain
Carré historique de l’hôpital Saint-Louis
1, avenue Claude Vellefaux - 75010 PARIS
E-mail: cecile.hoffart-jourdain@sls.aphp.fr
Tel: 33 1 44 84 17 32

Study coordinator: Unité de Recherche Clinique de l’HEGP
Delphine Hourton
Hôpital Européen Georges Pompidou
20 rue Leblanc – 75908 Paris cedex 15
E-mail: delphine.hourton@egp.aphp.fr
Tel: 33 1 56 09 58 22
Biomedical research study: P110138 - IDRCB 2012-A00232-25
Title: LICoRN: Efficacy of levosimendan pretreatment before coronary artery bypass graft (CABG) under cardiopulmonary bypass in high-risk patients (left ventricular ejection fraction below 40%): a multicenter, randomized, double-blind, placebo-controlled trial.

Version 4-0, dated 08/01/2015

Coordinating investigator:
Professor Bernard Cholley
Service d’anesthésie-réanimation
Hôpital Européen Georges Pompidou
20 rue Leblanc - 75015 PARIS

Promoter:
Assistance Publique – Hôpitaux de Paris
Département de la Recherche Clinique et du Développement
Hôpital Saint Louis
1 avenue Claude Vellefaux - 75010 PARIS

NB: This version corresponds to the text of the protocol and appendices sent to the ethics committee for evaluation and to the competent authority for approval, and to other parties involved in the study (e.g. hospital directors). If modifications lead to the writing of a new version, the new version must be signed by the relevant parties (those signing above) to ensure that the protocol in use is always the most recent version.
9 STATISTICS ........................................................................................................................................ 29

9.1 Number of subjects required ........................................................................................................ 29

9.2 Statistical analysis .......................................................................................................................... 29

9.2.1 General information .................................................................................................................. 29

9.2.2 Primary outcome measure ....................................................................................................... 29

9.2.3 Secondary outcome measures ................................................................................................ 29

10 EVALUATION OF SAFETY ........................................................................................................ 30

10.1 Description of the parameters for the safety evaluation ............................................................ 30

10.1.1 Adverse events ..................................................................................................................... 30

10.1.2 Adverse effects of an experimental drug .............................................................................. 30

10.1.3 Serious adverse events or effects .......................................................................................... 31

10.1.4 Unexpected adverse effects of an experimental drug ............................................................ 31

10.1.5 New findings ......................................................................................................................... 31

10.2 Description of the expected adverse effects of the study drug .................................................. 31

10.3 Methods for measuring, recording and analysing the safety evaluation parameters .................. 32

10.3.1 Co-ordinating centre ............................................................................................................. 32

10.3.2 Independent monitoring committee (IMC) for the trial .......................................................... 33

10.4 Procedures for the recording and notification of adverse events ............................................. 33

10.4.1 Adverse events (AEs) ............................................................................................................ 33

10.4.2 Serious adverse events (SAEs) ............................................................................................. 33

11 RIGHT OF ACCESS TO THE DATA AND DOCUMENTS ............................................................ 36

12 DATA MANAGEMENT AND STATISTICS ............................................................................ 36

12.1 Observation notebook ................................................................................................................. 36

12.2 Monitoring .................................................................................................................................. 37

12.3 Responsibility for the analysis, the analysis site and the software used .................................... 37

12.3.1 Observation notebook .......................................................................................................... 37

12.3.2 Monitoring ............................................................................................................................. 37

13 ETHICAL AND LEGAL CONSIDERATIONS ............................................................................ 38

13.1 Request for ANSM authorisation ............................................................................................... 38

13.2 Request for an expert opinion from the ethics committee ......................................................... 38

13.3 Modification of the protocol ..................................................................................................... 38

13.4 Declaration to the CNIL ............................................................................................................. 38

13.5 Information notice and informed consent ............................................................................... 38

13.6 Final study report ....................................................................................................................... 38

14 DATA PROCESSING AND THE STORAGE OF DOCUMENTS AND DATA RELATING TO THE STUDY .......................................................................................................................... 40

15 INSURANCE AND SCIENTIFIC COMMITMENT ................................................................ 40

15.1 Insurance .................................................................................................................................. 40

15.2 Scientific commitment ............................................................................................................... 40

16 PUBLICATION RULES ........................................................................................................... 41

16.1 Classification grid for AEs and SAEs ......................................................................................... 41

16.2 Declaration form for SAEs .......................................................................................................... 44

Protocol dated 08/01/2015
146 List of abbreviations
147
148 ASA: American Society of Anesthesiologists
149 BCPIA: intra-aortic balloon pump
150 CABG: coronary artery bypass grafting
151 COPD: chronic obstructive pulmonary disease
152 CPB: cardiopulmonary Bypass
153 CRU: clinical research unit
154 DRCD: Département de la recherche clinique et du développement (Clinical Research and Development Department)
156 ECLS: extracorporeal life support
157 ECMO: extracorporeal membrane oxygenation
158 LCOS: low cardiac output syndrome
159 LV: left ventricle
160 LVEF: left ventricular ejection fraction
161 NYHA: New York Heart Association
162 OR: odds ratio
163 POAF: postoperative atrial fibrillation
164 PR: prothrombin ratio
165 RR: relative risk
166 RRT: renal replacement therapy
167 SMB: Safety monitoring board
168 SPC: Summary product characteristics
169
1 SUMMARY

Scientific justification of the study

In France, almost 17,790 patients underwent coronary artery bypass grafting (CABG) surgery with the use of cardiopulmonary bypass (CPB) in 2009 (PMSI 2009 data from the ATIH). About 9% of these patients develop a postoperative low cardiac output syndrome (LCOS), a complication associated with a poor prognosis. Despite the use of inotropes and mechanical circulatory support, postoperative mortality remains close to 20% for patients with LCOS. By contrast, for patients without LCOS, postoperative mortality is below 1%.\(^1\)

The main risk factor for LCOS after CABG is a left ventricular ejection fraction (LVEF) ≤40% before surgery\(^1\),\(^2\). The prevalence of this risk factor is about 20%, corresponding to about 3560 patients/year among candidates for CABG.

Levosimendan is a new ino-vasodilator that sensitizes myofilaments to calcium, thereby increasing myocardial contractility. Three randomized trials have suggested that levosimendan pretreatment is potentially useful in patients with a LVEF ≤40% undergoing CABG, with or without valve surgery\(^3\),\(^4\),\(^5\). This treatment reduced:

- The duration of intubation,
- The need for inotropes,
- The need for mechanical support,
- The hospital and intensive care unit length of stay.

These data are encouraging, but not very robust, because they were obtained in single-blind single-center studies on very small numbers of patients. Levosimendan has not yet been scientifically validated for use as a pretreatment before CABG with the use of CPB. We propose to carry out a large-scale study that will validate or invalidate the use of levosimendan before surgery in patients with a LVEF ≤ 40%, who are considered at “high risk” of postoperative LCOS.

Objectives

**Primary:** To evaluate the efficacy of levosimendan treatment started at the time of anesthetic induction in order to decrease the incidence of LCOS in patients with a LVEF ≤ 40% undergoing CABG (isolated or combined with a valve surgery) with the use of CPB.

**Secondary:** To evaluate mortality and economic impact through a cost-efficacy analysis.

Selection criteria

**Inclusion criteria:** Age ≥ 18 years, patient with a preoperative LVEF ≤ 40% undergoing isolated or combined CABG with the use of CPB.

---


### Exclusion criteria:
Isolated valve surgery, pregnancy or breastfeeding, known allergy to levosimendan, surgery of the thoracic aorta, severe renal insufficiency, hemodialysis, severe hepatic insufficiency, dynamic obstruction of the left ventricular outflow tract, history of torsade de pointe, refusal to consent, lack of affiliation with social security, enrollment in another study.

### Ethics

Patients with particularly marked hemodynamic instability treated with inotropes or with an intra-aortic balloon pump before surgery may be included in the study, as treatment with levosimendan or placebo is additional to existing treatment.

### Methodology

Prospective, multicenter, randomized (two arms), double-blind, placebo-controlled study.

### Randomization

The randomization procedure will take into account the center, the type of surgery performed (isolated CABG or coronary surgery combined with valve surgery), LVEF (<30%, or between 30 and 40%), history of previous interventions, preoperative treatment with an inotrope or an intra-aortic balloon pump (IABP), and the preoperative use of beta-blockers. Treatments will be attributed by minimization (dynamic deterministic attribution) in order to balance the distribution of these prognostic factors between the two groups and within each center. We will introduce a random component to decrease the predictability of allocation. The randomization algorithm will be established by an independent statistician and installed on a website with secure access.

For reasons of feasibility, we will not impose the use of standardized anesthesia or cardioplegia techniques. Stratification by center will balance the distribution of these factors in each group.

### Outcome measures

**Primary outcome measure:** Composite criterion reflecting LCOS and combining (1) use of a positive inotrope more than 24 hours after the end of the study treatment infusion; or (2) use of mechanical circulatory support techniques (IABP or other) or the continuation of these techniques beyond 96 hours if already in use before surgery; or (3) use of a renal replacement therapy (RRT) (conventional intermittent hemodialysis or continuous blood filtration).

We deliberately chose to use this easy-to-determine criterion based on the hypothesis that levosimendan should decrease its occurrence if it is to be considered an effective treatment for preventing LCOS.

**Secondary outcome measures:** (1) mortality at day 28 (D28) and D180; (2) the individual items making up the composite criterion and (3) the number of days “out of intensive care”, “off the ventilator” and “out of hospital” at D28.

### Description of the treatments

Levosimendan and placebo will be administered as a continuous infusion over a 24-hour period. The dose will be 0.1µg/kg/min, with no bolus administration. The infusion will begin just after anesthetic induction.

The anesthesiologists and surgeons will be kept unaware of treatment group because the placebo will have the same pale yellow color as the levosimendan, once reconstituted.
Number of subjects required

Based on the following assumptions:

(1) Incidence of the composite criterion of 65% in the control group (estimated from the data stored in our departmental database for three consecutive years)

(2) Incidence of the composite criterion of 50% in the levosimendan group, according to the results of Levin et al.\(^6\).

(3) An \(\alpha\) risk of 5% and a \(\beta\) risk of 20%.

We calculate that we will need to include 170 patients per study arm, corresponding to a total of 340 patients.

Utility of this study

In France, about 3560 patients/year with a LVEF \(\leq 40\%\) undergo CABG on ECC. According to the database of the anesthesia and reanimation department of the HEGP, 65% of these patients present elements of our principal outcome measure after surgery. A 15% decrease in this incidence would mean that it might be possible to prevent LCOS in 534 patients if the entire target population in France were to be treated.

Such a decrease in the incidence of LCOS would also have an economic impact, by making it possible to decrease care consumption (mechanical circulatory support and hemodialysis sessions) and the number of days spent in hospital (in and out of intensive care).

Feasibility of the study

\begin{itemize}
  \item **Study duration**: 30 months
  \item **Duration of the inclusion period**: 24 months
  \item **Duration of individual participation for individual patients**: 6 months
  \item **Number of participating centers**: About 15 centers will participate in this study.
  \item **Feasibility**: All these centers perform almost 8000 CABGs with CPB/year. The proportion of patients with a LVEF \(\leq 40\%\) before surgery is about 20%, corresponding to about 1600 patients/year. These patients will constitute the study population. If each center includes a mean of one patient every two weeks, it will take about one year to recruit the number of patients required. The outcome criterion used was deliberately chosen so as to be simple and robust, to demonstrate a clear benefit of the study treatment and to facilitate its recording by clinical study technicians. The investigators will be responsible for including patients (selection and collection of informed consent) and administering the study product. Each center will be free to apply its routine anesthesia and cardioplegia techniques, to ensure adherence to the protocol and to maximize feasibility. The clinical study technicians will be recruited locally; their funding will be proportional to the number of inclusions.
  \item **Study products**: The Orion Corporation has agreed, in writing, to supply the study drug and the placebo free of charge.
\end{itemize}
2 SCIENTIFIC JUSTIFICATION OF THE STUDY AND PUBLISHED DATA

2.1 Definition of low cardiac output syndrome (LCOS)

In 5 to 10% of patients undergoing cardiac surgery on ECC, it is difficult to re-establish satisfactory hemodynamic competence after surgery. These patients may display postoperative low cardiac output syndrome (LCOS), a state of hypoperfusion due to hypocontractility and leading to organ dysfunction or even multiple organ failure \(^2,3\).

LCOS is defined on the basis of hemodynamic criteria: a cardiac index < 2.2 \(\text{L/min/m}^2\) and an occlusive pulmonary artery pressure >15 or 18 mm Hg, depending on the study considered \(^2,4-6\). Alternatively, postoperative LCOS is often defined as a need for catecholamine infusion to restore contractility, or a need for a mechanical circulatory assist device (intra-aortic balloon pump, Impella, or ECMO), after the exclusion of valve dysfunction, tamponade and cardiac ischemia.

The occurrence of postoperative LCOS is associated with longer stays in hospital and in intensive care, and greater use of healthcare in the form of a larger number of drugs and medical devices/procedures (inotropes, circulatory support, RRT) \(^3,7-9\).

2.2 Epidemiology of LCOS

The prevalence of LCOS after coronary artery bypass graft (CABG) on ECC is about 10% for the total population. Mortality after CABG is much higher in patients with LCOS than in patients without postoperative LCOS (17% versus 0.9%) \(^2\).

The principal predictive factor for LCOS is a low LVEF before surgery: the odds ratio is 5.1 for a LVEF <30% and 2.4 for a LVEF between 20 and 40%. \(^2,10\).

2.3 The search for an alternative treatment: levosimendan

The treatment of postoperative LCOS is based on the use of inotropic drugs or mechanical circulatory support devices, if drug treatment fails, and systems for replacing the functions of failing organs (kidneys, lungs).

Levosimendan is a positive inotrope and vasodilator developed in the 1990s and authorized for market release in 12 European countries (including Norway, Sweden, Finland, Austria, Germany, Italy and Spain). It has nominative expanded access status in France. In these countries, the official indication is the treatment of acute episodes of decompensation in patients with heart failure. According to the recommendations of the European Cardiology Society, levosimendan is indicated for the management of this disease with a level of proof of IIb and a level of evidence of B, meaning that it is “of utility and/or efficacy less well established by evidence and/or opinion” and for which the data were “obtained in a single controlled study or in non-controlled studies” \(^11\).

In 2010, a group of European anesthesiologists issued recommendations concerning the perioperative management of cardiac insufficiency in patients undergoing cardiac surgery. The authors of these recommendations drew attention to the utility of levosimendan in this clinical situation \(^12\).
2.3.1 Pharmacology and pharmacokinetics of levosimendan

Levosimendan has two pharmacological actions. It facilitates contact between actin and myosin and prolongs the time of contact between these two molecules, without modifying intracellular calcium concentration or myocardial oxygen consumption. This results in a **positive inotropic** effect. Through its agonistic effect on K⁺-ATP-dependent channels, levosimendan has a **vasodilator** effect (particularly on the coronary arteries) and a **cardio protective anti-ischemic** effect.

Unlike other positive inotropes, levosimendan does not modify intracellular calcium concentration (which can cause arrhythmia and cell death) or myocardial diastolic relaxation. It increases the contractile force of the myocardium without modifying its O₂ consumption, and is therefore a very useful active agent for the treatment of postoperative LCOS following CABG with CPB.

The pharmacokinetic characteristics of levosimendan are: a biological half-life of 60 minutes, a plasma clearance of 300 mL/min and a plasma protein binding rate of 97%. Equilibrium is reached four to eight hours after injection. Following its intravenous injection, levosimendan is rapidly metabolized by the liver to generate an active metabolite called OR-1986, which has pharmacological properties identical to those of levosimendan, but with a half-life of about three days.

The mechanisms of action of levosimendan are thus different from and complementary to those of dobutamine.

2.3.2 Levosimendan and LCOS prophylaxis in cardiac surgery

Table 1 summarizes the clinical data available for levosimendan pretreatment in cardiac surgery with ECC. The data presented in this table were obtained in controlled clinical trials (we have excluded “clinical case reports”). Levosimendan pretreatment consists of an injection of this drug between the induction of anesthesia and release of the aortic cross-clamp. In all cases, the injection is administered before the onset of LCOS. This use of levosimendan can be justified on the basis of:

1. The predictability of postoperative LCOS on the basis of preoperative risk factors (preoperative LVEF, history of cardiac surgery etc.),
2. The metabolism of levosimendan to generate an active metabolite with a long half-life (3 days), and
3. The good tolerance profile of levosimendan.

Six of the seven studies presented in this table were randomized, and four of these six studies were also carried out in double-blind conditions. In four studies, levosimendan was compared with placebo, whereas the comparator molecule was milrinone in the other three studies.

In total, five of the seven studies reported a greater clinical benefit for the patients treated with levosimendan: shorter duration of intubation (four studies), shorter stay in intensive care (two studies), shorter duration of IABP use (two studies) and shorter duration of positive inotrope use in intensive care (three studies). The two studies in which no clinical benefit was observed aimed to assess hemodynamic parameters and included only very small numbers of patients (24 per study).
Five studies reported a clinical benefit of pretreatment with levosimendan: two placebo-controlled studies and three studies in which milrinone was the comparator. These studies can be summarized as follows:

- Eriksson et al. \(^{20}\) studied patients undergoing isolated CABG, with a moderately altered LVEF before surgery (40 to 50%). The comparator was placebo and the primary outcome measure was successful weaning from CPB at the first attempt. This criterion was defined as the obtaining of a cardiac index $\geq 2.2$ L/m$^2$/min, an $\text{SvO}_2 \geq 70\%$ and a pulmonary capillary pressure $\leq 16$ mmHg, 10 minutes after the cessation of CPB, without the addition of another positive inotropic treatment. In this study, 73% of the patients in the levosimendan group and 33% of those in the placebo group were successfully weaned off CPB at the first attempt ($p=0.002$). There were 30 patients per group in this study.

- Tritapepe et al. \(^{25}\) studied patients undergoing isolated CABG, with a moderately altered LVEF before surgery (40 to 50%). The comparator was placebo and the primary outcome measure was the duration of the patient’s stay in intensive care. Patients left the intensive care unit when their cardiac and renal functions were considered satisfactory, without the need for an inotrope or vasoconstrictive agent. The patients in the levosimendan group spent significantly less time in intensive care: 24 hours versus 32 hours ($p=0.002$). This study included a total of 106 patients.

- In the study by De Hert et al. \(^{22}\), most of the patients included underwent CABG, with or without associated valve surgery, and all the patients included had a severely altered LVEF ($\leq 30\%$). The comparator was milrinone. From the start of CPB, all patients received dobutamine, together with either levosimendan or milrinone, injected at the time of aortic cross-clamp release. The primary outcome measure was hemodynamic and the secondary outcome measures were clinical (e.g. duration of intubation, duration of IABP use, length of hospital stay). Levosimendan treatment significantly decreased the duration of positive inotrope use (19 hours versus 171 hours; $p=0.005$) and the duration of tracheal intubation (11 hours versus 20 hours; $p=0.008$). This study included a total of 30 patients.

- Most of the patients included in the study by Brezina et al. \(^{24}\) underwent CABG, with or without associated valve surgery, and all had a severely altered LVEF before surgery ($\leq 30\%$). The patients were treated with levosimendan before the induction of anesthesia or with an inotropic agent administered at the end of CPB. The primary outcome measure was cardiac output, and the secondary outcome measures were clinical (e.g. time spent in intensive care, use of hemodialysis). The patients treated with levosimendan had significantly shorter hospital stays (10 days versus 26 days; $p=0.04$) and a lower mortality at D30 (0% versus 41.7%; $p=0.01$). This study included only 22 patients.

These studies demonstrated clinical benefits that increased with the degree of LVEF alteration before surgery (greatest for a LVEF of 40% or below) and were greater for earlier injections (during the induction of anesthesia or at the time of aortic cross-clamp release).
Finally, it should be noted that in four of these seven studies evaluating the clinical benefits of levosimendan for the prevention of LCOS post CPB, levosimendan was administered solely as a continuous infusion (no bolus).
Table 1: Clinical and hemodynamic evaluations of levosimendan for the prevention of LCOS in cardiac surgery

<table>
<thead>
<tr>
<th>Author</th>
<th>Study treatments (timing of injection and dose)</th>
<th>Study methodology</th>
<th>Number of patients</th>
<th>Preoperative LVEF</th>
<th>Type of surgery</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tritapepe 19</td>
<td>LVS versus placebo Preoperative injection of LVS: bolus of 24 µg/kg</td>
<td>Prospective, single-center, randomized, double-blind</td>
<td>$N = 24$ (12 per group)</td>
<td>&lt;40% X</td>
<td>CABG</td>
<td>Non-significant differences* in the durations of ventilation and hospitalization</td>
</tr>
</tbody>
</table>
| Tritapepe 25 | LVS versus placebo Injection of LVS at induction of anesthesia: bolus of 24 µg/kg | Prospective, single-center, randomized, double-blind | $N = 106$ (53 per group) | X | CABG | Significant differences* in:  
- Duration of intubation: shorter in the LVS group (11.3 h versus 13.6 h)  
- Use of inotropes 12 hours after the intervention: less frequent in the LVS group (4% versus 18%)  
- Time spent in intensive care: shorter in the LVS group (25 h versus 33h)  
Non-significant differences* in:  
- Mortality at D30: 0 patients / group  
- Total hospital stay: 11 days in the LVS group versus 12 days in the placebo group. |
<p>| Eriksson 20  | LVS versus placebo Injection of LVS at the induction of anesthesia: bolus followed by the infusion of 0.05 to 0.2 µg/kg/min for 24 h | Prospective, single-center, randomized, double-blind | $N = 60$ (30 per group) | X | CABG | Significant difference* in the rate of successful weaning of CPB: 73% of patients in the LVS group versus 33% of patients in the placebo group. |
| Järvelä 21  | LVS versus placebo Preoperative injection of LVS: infusion of 0.2 µg/kg/min for 24 h | Prospective, single-center, randomized, double-blind | $N = 24$ | X | Valve = 14 Combined = 10 | Non-significant difference* in the length of hospital stay |</p>
<table>
<thead>
<tr>
<th>Author</th>
<th>Study treatments (timing of injection and dose)</th>
<th>Study methodology</th>
<th>Number of patients</th>
<th>Preoperative LVEF</th>
<th>Type of surgery</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Hert</td>
<td><strong>LVS plus DOBU</strong>&lt;br&gt;versus&lt;br&gt;<strong>MRN plus DOBU</strong>&lt;br&gt;Injection of MRN or LVS at the time of aortic cross-clamp release&lt;br&gt;Infusion of LVS at 0.1 µg/kg/min&lt;br&gt;DOBU at 5 µg/kg/min&lt;br&gt;MRN at 0.5 mg/kg/min</td>
<td>Prospective, single-center, randomized, single-blind</td>
<td>N = 30 X</td>
<td></td>
<td>CABG=9&lt;br&gt;Valve=6&lt;br&gt;Combined=15</td>
<td>Significant differences* in&lt;br&gt;- <strong>The duration of intubation</strong>: shorter in the LVS group (11 h versus 20 h)&lt;br&gt;- <strong>Use of inotropes</strong>: shorter duration of use in the LVS group (duration of dobutamine use shortened by 19 h and duration of noradrenaline use shortened by 13 h)&lt;br&gt;- <strong>Duration of IABP use</strong>: shorter in the LVS group (41 h versus 171 h)&lt;br&gt;Non-significant differences* in:&lt;br&gt;- Hospital stay (10 days for the LVS group versus 12 days for the DOBU group),&lt;br&gt;- Mortality (0% in the LVS group versus 20% in the DOBU group).</td>
</tr>
</tbody>
</table>
LVS at induction of anesthesia plus DOBU (group 1)

versus

LVS at the time of aortic cross-clamp release plus DOBU (group 2)

versus

MRN at the time of aortic cross-clamp release plus DOBU (group 3)

Infusion of LVS at 0.1 µg/kg/min

DOBU at 5 µg/kg/min

MRN at 0.5 mg/kg/min

Prospective, single-center, randomized, single-blind

N = 60

20 patients per group

CABG=16

Valve=7

Combined=37

Significant differences* in the durations of:
- Intubation: 50 h shorter in groups 1 and 2
- Inotrope use: 16 h shorter in groups 1 and 2
- IABP use: 8 h shorter for group 1, 12 h shorter for group 2 and 42 h for group 3
- Hospitalization in intensive care: 42 h shorter for group 1, 58 h shorter for group 2 and 121 h shorter for group 3
- Hospital stay: 15 days shorter for group 1, 17 days shorter for group 2 and 22 days shorter for group 3

All these durations were shorter in the two groups treated with LVS than in those treated with MRN.

No significant difference* in mortality: 0% of the patients in group 1, 5% of the patients in group 2 and 20% of the patients in group 3
<table>
<thead>
<tr>
<th>Author</th>
<th>Study treatments (timing of injection and dose)</th>
<th>Study methodology</th>
<th>Number of patients</th>
<th>Preoperative LVEF</th>
<th>Type of surgery</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brezina</td>
<td><strong>LVS versus MRN plus DOBU</strong>&lt;br&gt;Injected at the <em>induction of anesthesia</em>&lt;br&gt;LVS: bolus of 24 μg/kg over 10 min, followed by the infusion of 0.1 μg/kg/min for 24 hours&lt;br&gt;MRN: bolus of 30 μg/kg followed by the infusion of 0.3 to 0.4 μg/kg/min&lt;br&gt;DOBU: infusion of 5 μg/kg/min</td>
<td>Retrospective, single-center, observational</td>
<td>(N = 22) (10 in the LVS group)</td>
<td>(\text{&lt;40}%) 40 to 50% &gt;50%</td>
<td>**</td>
<td>Significant differences* in:&lt;br&gt;- Mortality at D30: 0% in the LVS group versus 41.7% in the MRN plus DOBU group (5/12 patients)&lt;br&gt;- Total hospital stay: 10 days in the LVS group versus 26 days in the DOBU + MRN group&lt;br&gt;Non-significant differences* in:&lt;br&gt;- The duration of hospitalization in intensive care (mean of 5 days in each group)</td>
</tr>
</tbody>
</table>

310CABG: coronary artery bypass grafting; valve: valve surgery; combined: procedure combining CABG and valve surgery; CPB: cardiopulmonary bypass; LVS: levosimendan; DOBU: dobutamine; MRN: milrinone; "*: α risk of 5%.
2.3.3 Levosimendan tolerance

Table 2 presents the studies for which tolerance data were reported. We present here data from controlled studies only (clinical case reports have been excluded). Tolerance data were reported in two studies analyzing the effects of levosimendan for the treatment of LCOS\(^{26, 27}\) and in four studies dealing with levosimendan pretreatment as described above\(^{19, 22, 23, 25}\). The adverse effects observed were closely associated with the pharmacological properties of levosimendan as a positive inotrope and vasodilator.

In studies of treatment of LCOS, tolerance to levosimendan was compared with tolerance to dobutamine. The frequency of atrial fibrillation did not differ significantly between the two groups in either of these two studies\(^{26, 27}\). In addition, Levin et al.\(^{27}\) found that the prevalence of vasoplegia and ventricular arrhythmia were significantly lower in the levosimendan group.

In studies of the prevention of LCOS in patients undergoing cardiac surgery with CPB, levosimendan was not associated with a higher frequency of episodes of postoperative atrial fibrillation or of myocardial infarction than placebo. In these two studies, the patients included displayed moderate alterations of LVEF (≈ 40 to 50%) and received only a bolus dose of levosimendan \(^{19, 25}\). In the two studies comparing the levosimendan-dobutamine combination with the milrinone-dobutamine combination, no case of ventricular fibrillation or myocardial ischemia was observed, regardless of the treatment received \(^{22, 23}\). These studies show that the frequency of postoperative atrial fibrillation varies significantly with the timing of levosimendan injection. This frequency was lower if levosimendan was injected at the time of anesthetic induction. Indeed, this frequency was 5% for patients treated with levosimendan during the induction of anesthesia and 35% for patients receiving levosimendan injections at the time of aortic cross-clamp release.

These data suggest that the incidence of arrhythmia in patients treated with levosimendan is systematically lower than that in patients from the control group. In addition, levosimendan seemed to be tolerated even better if administered during the induction of anesthesia solely as a continuous infusion (no bolus injection).

In the SURVIVE study, which included 1327 patients and compared the injection of levosimendan with that of dobutamine for the management of cardiac insufficiency with acute decompensation, the incidence of the following adverse events was significantly higher in the levosimendan group than in the dobutamine group: hypokalemia (9.4% versus 5.9%), postoperative atrial fibrillation (9.1% versus 6.1%), migraine (8.3% versus 4.7%) and premature atrial contraction (6.1% versus 3.6%). This study was a multicenter, randomized, double-blind study. Levosimendan and dobutamine were injected according to the following regimen: a bolus of 12 \(\mu\)g/kg over 10 minutes followed by an infusion of 0.1\(\mu\)g/kg/ min for 50 minutes and then of 0.2\(\mu\)g/kg/min for 23 hours for levosimendan (the EA dose), and for dobutamine, an infusion of 5 \(\mu\)g/kg/min, which could be increased to 40 \(\mu\)g/kg/min for at least 24 hours\(^{28}\).

Finally, no drug interaction requiring specific management was described in studies of levosimendan use in combination with other positive inotropes\(^{14}\).
Table 2: Reported **tolerance** data for the injection of levosimendan during surgery

<table>
<thead>
<tr>
<th>Author</th>
<th>Objective of the study</th>
<th>Study methodology</th>
<th>Number and characteristics of the patients</th>
<th>Tolerance data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alvarez 26</td>
<td><strong>LVS versus DOBU</strong>&lt;br&gt; LVS: bolus and then infusion of 0.2 µg/kg/min for 24 h&lt;br&gt; DOBU: infusion over 24 h</td>
<td>Single-center, randomized, open</td>
<td>$N = 41$</td>
<td>Non-significant difference* in the prevalence of postoperative atrial fibrillation: 9.5% in the LVS group versus 10% in the DOBU group</td>
</tr>
<tr>
<td>Levin 27</td>
<td><strong>LVS versus DOBU</strong>&lt;br&gt; LVS: bolus and then infusion of 0.05 to 0.2 µg/kg/min for 24 h&lt;br&gt; DOBU: 5 to 12.5 µg/kg/min</td>
<td>Multicenter, randomized, open</td>
<td>$N = 137$</td>
<td>Significant difference* in the prevalence of:&lt;br&gt;- Perioperative infarction: 1.4% in the LVS group versus 11.8% in the DOBU group&lt;br&gt;- Vasoplegia: 1.4% in the LVS group versus 13.2% in the DOBU group&lt;br&gt;- Acute renal insufficiency: 7.2% in the LVS group versus 30.9% in the DOBU group&lt;br&gt;- Ventricular arrhythmia: 4.3% in the LVS group versus 17.6% in the DOBU group&lt;br&gt;- Sepsis: 1.4% in the LVS group versus 13.2% in the DOBU group&lt;br&gt;No significant difference* in the prevalence of postoperative atrial fibrillation between the two groups: 21.7% in the LVS group versus 39.7% in the DOBU group</td>
</tr>
<tr>
<td>Tritapepe 19</td>
<td><strong>LVS versus placebo</strong>&lt;br&gt; Preoperative injection of LVS: bolus of 24 µg/kg</td>
<td>Prospective, single-center, randomized, double-blind</td>
<td>$N = 24$</td>
<td>No significant difference* in the prevalence of:&lt;br&gt;- Postoperative atrial fibrillation: 16.6% in the LVS group versus 25% in the placebo group&lt;br&gt;- Myocardial ischemia: 8.3% in the LVS group versus 16.6% in the placebo group</td>
</tr>
<tr>
<td>Author</td>
<td>Objective of the study</td>
<td>Study methodology</td>
<td>Number and characteristics of the patients</td>
<td>Tolerance data</td>
</tr>
<tr>
<td>-------------</td>
<td>------------------------</td>
<td>---------------------------------------------</td>
<td>---------------------------------------------</td>
<td>-----------------------------------------------------------------</td>
</tr>
<tr>
<td>Tritapepe 25</td>
<td>LVS versus placebo</td>
<td>Injection of LVS at the induction of anesthesia: bolus of 24 µg/kg</td>
<td>Prospective, single-center, randomized, double-blind</td>
<td>$N = 106$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LVEF: between 40 and 50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| De Hert 22 | LVS plus DOBU versus. MRN plus DOBU | Injection of MRN or LVS at the time of aortic cross-clamp release | Prospective, single-center, randomized, single-blind | $N = 30$                                                                 |
|            |                                      | Infusion of LVS at 0.1 µg/kg/min DOBU at 5 µg/kg/min MRN at 0.5 mg/kg/min |                                             | LVEF < 40% |
|            |                                      |                                             |                                             | No significant difference* in the prevalence of: |
|            |                                      |                                             |                                             | - Postoperative atrial fibrillation: 40% in the LVS group versus 46.6% in the MRN group. |
|            |                                      |                                             |                                             | - Ventricular fibrillation: 0% in both groups |
|            |                                      |                                             |                                             | - Myocardial infarction: 0% in both groups |

| De Hert 23 | LVS at induction of anesthesia plus DOBU (group 1) versus LVS at the time of aortic cross-clamp release plus DOBU (group 2) Versus MRN at the time of aortic cross-clamp release plus DOBU (group 3) | Infusion of LVS at 0.1 µg/kg/min DOBU at 5 µg/kg/min MRN at 0.5 mg/kg/min | Prospective, single-center, randomized, single-blind | $N = 60$ patients                                                                 |
|            |                                      |                                             |                                             | LVEF < 40% |
|            |                                      |                                             |                                             | 50% of the patients underwent combined CABG and valve surgery |
|            |                                      |                                             |                                             | Significant difference* in the prevalence of postoperative atrial fibrillation: |
|            |                                      |                                             |                                             | - group 1 LVS-DOBU: 5% of patients |
|            |                                      |                                             |                                             | - group 2 LVS-DOBU: 35% of patients |
|            |                                      |                                             |                                             | - group 3 MRN-DOBU: 50% of patients |
|            |                                      |                                             |                                             | No case of ventricular fibrillation or myocardial infarction was reported. |

*: $\alpha$ risk of 5%; LVS: levosimendan; DOBU: dobutamine; MRN: milrinone.
2.4 Scientific justification of the study

The data from studies of levosimendan pretreatment — administration of this drug prior to surgery, at the time of anesthetic induction — are encouraging. However, due to their methodological bias, proof of concept has not been firmly established for the preoperative injection of levosimendan. Nevertheless, many requests for the use of this drug in this specific situation are made to the ANSM each year, attesting for a need from the community of anesthesiologists working in cardiac surgical centers.

For this reason, we felt that it was important to carry out a prospective, multicenter, randomized, double-blind, placebo-controlled study of the preoperative administration of levosimendan in patients at high risk of LCOS after CABG with the use of CPB.

3 OBJECTIVES OF THE STUDY

3.1 Primary objective

The principal objective is to evaluate the efficacy of levosimendan administered at the time of anesthetic induction in patients with a LVEF ≤ 40% undergoing CABG (with or without associated valve surgery) with CPB to decrease the incidence and severity of postoperative LCOS.

3.2 Secondary objectives

The secondary objectives will be:

(1) To compare mortality at D28 and D180 between the two groups.
(2) To evaluate the economic impact of levosimendan injection in a cost-efﬁcacy assessment during hospital stay.

4 OUTCOME MEASURES

4.1 Primary outcome measure

The principal outcome measure is a composite criterion reflecting LCOS. This criterion combines the following:

(1) The use of a positive inotrope beyond H48 hours after the start of the study drug infusion; or
(2) The use of mechanical circulatory assistance techniques (IABP, ECLS) or failure to wean from IABP within 96 hours following study-drug initiation, if inserted prophylactically before surgery; or
(3) The use of a renal replacement technique (conventional intermittent hemodialysis or continuous hemofiltration) in intensive care.

We deliberately chose to use these simple-to-record items, based on the assumption that levosimendan must decrease the occurrence of the composite criterion to be considered an effective treatment for preventing LCOS. We will consider pretreatment to be effective if the prevalence of the primary outcome measure is 15% lower in the pretreatment group than in the control group.
4.2 Secondary outcome measures

Our secondary outcome measures evaluate mortality and economic impact.

- The following criteria will be used to evaluate mortality:
  1. In-hospital mortality
  2. Mortality at D28

- The following criteria will be used to study economic impact:
  1. Total number of days out of hospital at D28
  2. The numbers of days spent in intensive care and in a conventional ward
  3. The total number of days without mechanical ventilation during the patient’s hospital stay
  4. The duration of catecholamine infusion
  5. The number of days on mechanical circulatory assistance
  6. The number of hours of RRT and the numbers of RRT kits used.

4.3 Measures taken to prevent bias

Mortality was not chosen as the primary outcome measure because the prevalence of death in this context was lower than that of the three elements comprising the composite criterion. The use of mortality as the primary outcome measure would thus have necessitated the inclusion of a much larger number of patients to achieve acceptable power. The elements of the primary outcome measure are universally recognized as strong markers of LCOS associated with a poor prognosis. It is not possible to combine morbidity-related elements with mortality in a composite criterion, due to the difference in seriousness between these elements.

The lack of consensus concerning the use of positive inotropes in the postsurgical period, in patients undergoing cardiac surgery, leads to diverse prescription practices. By contrast, the maintenance of inotrope treatment for more than 48 hours after surgery generally reflects a true alteration in myocardial contractility.

The study treatment should have similar effects on each of the three elements of the composite criterion.
5 DESIGN OF THE STUDY

5.1 Hypothesis tested

We hypothesize that the administration of levosimendan, at the time of anesthetic induction, in patients with a LVEF $\leq 40\%$ undergoing CABG with or without associated valve surgery, should decrease the frequency and severity of postoperative LCOS.

According to Levin et al. $^{27}$, the postoperative administration of levosimendan in patients with LCOS decreases:

- The frequency of additional positive inotrope use by 28% relative to patients receiving dobutamine,
- The use of IABPs by 12% relative to patients receiving dobutamine.

Based on these findings, we hypothesize that levosimendan will make it possible to decrease the incidence of the primary outcome measure by 15% in the treated group relative to the control group.

5.2 Study methodology

This French, multicenter, randomized, double-blind study with two parallel groups will compare the effects of a 24-hour infusion of levosimendan with placebo. About 15 centers will participate in this study. These centers will be anesthesia departments involved in cardiovascular surgery.

This study will require a total of 340 subjects: 170 per group.

5.3 Inclusion criteria

The inclusion criteria are as follows:

- Patients aged 18 years or older
- Patient covered by social security
- Patient having signed the informed consent form after having received and understood information about the study
- Patient undergoing isolated or combined CABG, with the use of CPB
- Preoperative LVEF $\leq 40\%$ (as demonstrated by an examination performed during the six months preceding inclusion. If several LVEF measurements are available, the most recent must be taken into account)
- Patients with acute preoperative circulatory insufficiency requiring treatment with a positive inotrope or by mechanical means (IABP or ECLS) may be included in the study. The levosimendan treatment or placebo will be added to the patient’s existing treatment regimen. Prophylactic IABP prior to surgery is also acceptable. A minimization technique will be used to balance the distribution of these patients between the two groups.

5.4 Exclusion criteria

- Refusal to give consent
- Beating heart CABG
- Valve surgery without coronary revascularization
- Pregnancy or breast-feeding
- Participation of the patient in another clinical research protocol.
- Contraindications to levosimendan (as listed in the monograph):
  - Known allergy to levosimendan or one of its excipients
  - Severe preoperative renal insufficiency (creatinine clearance <30 mL/min)
  - Patient requiring hemodialysis sessions before surgery
  - Severe hepatic insufficiency (PR < 50% in the absence of anti-vitamin K treatment)
  - Severe hypotension and tachycardia
  - History of torsade de pointe
  - Dynamic obstruction of the LV.

5.5 Planned duration of individual participation

The study subjects will be followed throughout their hospital stay, until hospital discharge. They will be contacted by telephone 28 days after the surgical intervention if they have already left the hospital, and then 180 days after the surgical intervention.

Patients will be followed for six months (signing of consent form on D-1, operation on D0 and postoperative follow-up until discharge from hospital), with telephone follow-up at 28 days and then at 6 months (corresponding to 180 days).

5.6 Ethics

No preoperative treatment is currently systematically recommended for patients at high risk of LCOS following CABG with the use of CPB, with or without associated valve surgery.

For patients with particularly high levels of hemodynamic instability before surgery, inotrope treatment may be initiated or an IABP implanted before surgery. These patients may be included in the trial, with the study treatment (or placebo) simply added to the existing pretreatment regimen.

6 STUDY PLAN

6.1 Chronology of the research project

This research project will be carried out in seven steps, as summarized in Figure 1.

Step ☐: Anesthesia consultation on D-n
- Checking of the inclusion and exclusion criteria
- Description of the protocol to the patient.
- Proposal of inclusion

Step ☒: Hospital admission, the day before surgery, D-1
- Inclusion in the protocol can be proposed at this stage if not already done at the time of anesthesia consultation
- Signing of the consent form by the patient, inclusion of the patient and randomization
- Delivery of the study-drug to the anesthesiologist by the pharmacy, upon presentation of the prescription. The treatment must be stored at a
temperature of 2 to 8°C before use: the anesthesiologist will systematically be reminded of the need to keep the drug in a refrigerator prior to reconstitution.

**Step Ω: In the operating theatre, D0**

- Delivery of the study drug, by the pharmacy, to the anesthesiologist, if not already done at step Ψ. The treatment must be stored in a refrigerator, at 2 to 8°C until use.
- Reconstitution of the study treatment, in 500 ml of 5% dextrose solution (G5%; 1 or 2 ampoules of study treatment per pouch, depending on the weight of the patient, see section 7.1).

The dilution of 12.5 mg levosimendan or of placebo in 500 ml Dextrose (5%) will be performed by the anesthesiologist immediately prior to administration, due to the poor stability of diluted levosimendan.

- At T₀, infusion of the study-drug will be initiated by the anesthesiologist just after the induction of anesthesia, once the central catheter (at least four channels) is in place. The product will be administered as a continuous infusion over 24 hours, with a flow rate defined as a function of weight to achieve 0.1µg/kg/min. (see section 7.1)

- Anesthesia, CPB, the surgical procedure and postoperative care will be performed according to the local standards by the team concerned.

**Step Ω: During hospitalization (in intensive care unit and in a conventional ward)**

- The continuous infusion of the study product will be stopped at T₀ + 24 hours.
- Recording, by a clinical study technician, of the therapeutic means used to maintain satisfactory hemodynamic function:
  - For agents with positive inotropic action, the dose and duration of the infusion will be recorded.
  - For circulatory assistance techniques (IABP or ECLS) and RRT: the date and time at which the use of these techniques begins and ends will be recorded. In addition, the number of RRT kits used will be noted (dialysis circuits and catheters).
- Recording, by a clinical study technician, of the clinical status of the patient:
  - Alive or dead (if appropriate, the day of death relative to D0 should be noted, together with the cause of death)
  - Mechanical or spontaneous ventilation
  - Extubation Date and time.
  - Date of discharge from intensive care
  - Date of discharge from the conventional ward.

**Step Ψ: on D28**

- Recording, by a clinical study technician, of the clinical status of the patient:
Same as above
If the patient has already left hospital, he/she will be contacted by telephone, either directly, or via his or her family (e.g. wife, child). If the patient has died, the date of death relative to D0 (the day on which the surgery was performed) will be noted.

Step ©: on D180
- Recording, by a clinical study technician, of the clinical status of the patient: Same as above.

6.2 Medical acts, and samples and items to be recorded

Preoperative parameters:
- Age, weight, height, sex
- Town of birth
- Type of surgery (CABG alone or in combination with valve surgery)
- Scores: Euroscore II, ASA class, NYHA class.
- LVEF
- History of previous cardiac surgery
- Comorbid conditions (COPD, diabetes, HTA, history of myocardial infarction or stroke, plasma creatinine clearance, cancer, cirrhosis, etc.)
- Beta-blocker treatment: yes/no; statin treatment: yes/no; antiplatelet treatment: yes/no

Peroperative parameters:
- Duration of aortic cross-clamping, duration of CPB
- Surgical interventions performed: number of arteries bypassed, location of bypasses and type of graft, type of valve surgery
- Use of a mechanical assistance technique after CPB.

Postoperative parameters:
- Vital status (alive or dead) of the patient: during hospitalization and on D28 and D180
- Use of vasoactive or inotropic agents (e.g. dobutamine, dopamine, noradrenaline, adrenaline, milrinone) more than 48 hours after initiation of the study treatment: dose schedule and name of the active agent, date and time at which the infusion began and ended,
- Use of mechanical assistance (prolongation of CPB, use of IABP or ECLS): data and time of initiation and withdrawal for each type of assistance,
- RRT (hemofiltration or conventional dialysis): date and duration of the purification procedure, number of circuits and catheters used,
- Number of episodes of heart rate problems, such as postoperative atrial fibrillation and ventricular tachycardia, and the therapeutic means used to correct them
- SAPS2 score
- Number of days “off mechanical ventilation” at D28
- Number of days “out of intensive care unit” and “out of hospital” at D28
- Total length of hospital stay
- Date on which beta-blocker and/or statin treatment reinitiated.
<table>
<thead>
<tr>
<th>Step:</th>
<th>No. 1: Consultation</th>
<th>No. 2: D-1, Admission</th>
<th>No. 3: D0</th>
<th>No. 4: From D1 to discharge</th>
<th>No. 5: D28</th>
<th>No. 6: D180</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proposal of the protocol</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-anesthesia evaluation</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical history</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical history</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient characteristics</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion/exclusion criteria</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Signing of the informed consent form</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Randomization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Transmission of the prescription to the pharmacy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Administration of the treatment tested: LVS or placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Adverse events</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recording of efficacy parameters</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>
Figure 1: Chronology of the research project

Admission
- Signature of the consent form, inclusion and randomisation
- Transmission of the anaesthetist’s prescription to the pharmacy
- Preparation of the study treatment by the pharmacy (levosimendan or placebo)

Anaesthesia consultation:
Presentation of the protocol if LVEF ≤ 40%

(1) Use of a positive inotrope more than 24 hours after the end of levosimendan or placebo perfusion ($T_{0+48}$)
(2) Use of mechanical circulatory assistance techniques (IABP, ECLS etc.) or the continuation of their use if initiated before surgery
(3) Use of an extrarenal purification technique in intensive care

Protocol dated 08/01/2015
6.3 Examinations/medical acts specific to the study

<table>
<thead>
<tr>
<th>Acts</th>
<th>Description</th>
<th>Associated risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection of levosimendan on D0</td>
<td>Injection immediately after the induction of anesthesia (continuous infusion of 0.1µg/kg/min for 24 hours)</td>
<td>Described in section 10.2</td>
</tr>
<tr>
<td>Recording of clinical status on D28</td>
<td>Recording, by telephone interview, of the vital status of the patient, treatments taken, and need for hospital readmission</td>
<td>None</td>
</tr>
<tr>
<td>Recording of clinical status on D180</td>
<td>Recording, by telephone interview, of the vital status of the patient</td>
<td>None</td>
</tr>
</tbody>
</table>

6.4 Anticipated duration of the study

The participation of 15 centers should make it possible to recruit 340 patients in 24 months. The duration of participation for each individual included in the project will be 180 days (6 months; signing of informed consent form on D-1 + operation on D0 + postoperative follow-up until hospital discharge), with telephone follow-up at 28 days and at 180 days (6 months)). The total duration of the study will be 30 months (inclusion period of 24 months + follow-up at six months).

6.5 Management of adverse events

6.5.1 Hypotension

Hypotensive episodes have been reported at the start of treatment with levosimendan. We do not plan to decrease the flow rate of the levosimendan infusion if such events occur in this study. If mean arterial blood pressure falls (<60 mm Hg), the anesthesiologist should first attempt vascular filling with a 250 m/ bolus of the solute of his/her choice. This procedure may be repeated. If hypotension persists, the anesthesiologist is free to make use of a vasopressor or an inotrope, according to his/her assessment.

6.5.2 Arrhythmias

Postoperative atrial fibrillation (POAF) seems to occur less frequently in cases of preconditioning with levosimendan than following the postoperative injection of this drug for LCOS treatment. Nevertheless, the anesthesiologist may use usual anti-arrhythmic treatments, or even cardioversion in cases of poor tolerance, after checking that serum potassium is normal.
6.5.3 Rules for stopping the study or withdrawal from the study

6.5.4 Stopping the study

An independent monitoring committee will meet regularly during the trial, to evaluate the frequency of serious adverse events. Depending on the results, this committee may recommend that the promoter stops the trial (see section 10.3).

6.5.5 Stopping the study treatment in a patient

The treatment evaluated will be administered as a infusion of 0.1µg/kg/min for 24 hours, with no loading dose. The reasons for stopping the treatment during the 24 hours of administration include:

- Anaphylactic shock
- Arterial hypotension or arrhythmia refractory to usual treatment during the infusion of the study-drug. Refractory hypotension is defined as a mean arterial blood pressure <60 mmHg despite vascular filling with two 250 mL boluses and the injection of at least one vasoconstrictor or inotrope. Refractory arrhythmia is defined as the persistence of an arrhythmia despite the administration of at least one anti-arrhythmic agent and the performance of cardioversion.

An investigator observing these serious adverse events (SAE) must follow the procedure for SAE reporting to the promoter.

6.5.6 Rules for the withdrawal of a patient from the study

All patients are free to withdraw from the study at any time if they wish, without having to provide an explanation.
7 TREATMENT EVALUATED

7.1 Study treatment

- **Active agent:** levosimendan, solution to be diluted for infusion, 12.5 mg/5 mL, 5 mL flask.
  
  - **Excipients:** povidone, citric acid, absolute ethanol

- **Placebo:** a clear yellow solution of similar appearance to the active agent.

  **Qualitative composition:** Riboflavin (sodium phosphate, absolute ethanol, water for injectable preparations)

---

Before administration, these study drugs must be diluted in 500 mL of G5% (one 500 mL pocket for one or two 12.5 mg flasks)

The study treatment, levosimendan or placebo, is administered intravenously, as a infusion of 0.1µg/kg/min over a fixed duration of 24 hours. The infusion will begin after the induction of anesthesia.

The pharmacy of each center will be responsible for dispensing the treatment attributed by randomization.

The treatment will be reconstituted by the anesthesiologist.

- **For patients weighing less than 85 kg**, this operation will involve taking 5 mL of solution from the flask (corresponding to the totality of the nominal volume of the flask), injecting it into a pouch containing 500 mL of 5% glucose, and gently mixing the preparation.

  The solution obtained has a **theoretical concentration** of about 25 µg/mL (0.025 mg/mL) levosimendan (or placebo).

- **For patients weighing 85 kg or more**, two flasks of levosimendan solution (12.5 mg/ml) or placebo will be required. The total contents of these flasks should be injected into a single 500 mL pouch of 5% glucose solution.

  The solution obtained will have a **theoretical concentration** of about 50 µg/mL (0.050 mg/mL) levosimendan (or placebo).

  The flow rate should be adapted for this double concentration (see the table below).

  *In accordance with the SPC for the specialty, there is some uncertainty on the true volume of solution present in a pouch of G5% with a nominal volume of 500 mL.*

---
The reconstitution of 12.5 mg/levosimendan or placebo in 500 mL Dextrose (5%) will be performed in the operating room, as close as possible to the start of the infusion, due to the time-limited stability of levosimendan. Indeed, after dilution, the stability of the solution (as defined in the SPC) is 24 hours at 25°C, which corresponds exactly to the duration of the infusion. The flow rate of the infusion will be the same for levosimendan and placebo.

The flow rate (in mL/h) is defined in the table below, as a function of the patient’s body weight and the concentration of the solution, for a fixed duration of administration of 24 h.

Dose and flow rate of the infusion as a function of body weight

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Flasks (12.5 mg/5 mL)</th>
<th>Flow rate of the infusion (mL/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 40 to 44</td>
<td>Content of 1 flask in a 500 mL of G5%</td>
<td>10</td>
</tr>
<tr>
<td>45 to 54</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>55 to 64</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>65 to 74</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>75 to 84</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>85 to 94</td>
<td>Contents of 2 flasks in 500 mL of G5%</td>
<td>11</td>
</tr>
<tr>
<td>95 to 104</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>105 to 114</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>≥ 115</td>
<td>14</td>
<td></td>
</tr>
</tbody>
</table>

7.2 Authorized treatments

No treatment is prohibited during the study. The choice of positive inotropes for LCOS management will be left at the discretion of each clinician in charge. The use of mechanical circulatory assist devices and indications for RRT will also be decided by clinicians according to their local practice. The preoperative use of positive inotropes or mechanical circulatory assistance is allowed.

7.3 Pharmacy manual (study drugs management)

Levosimendan and placebo will be supplied free of charge by the Orion Corporation, in the form of unlabeled flasks containing the products. The products will be packaged and labelled by the Clinical Trials Department of the General Agency for Health Equipment and Products (DEC-AGEPS) of the Parisian public hospital network (AP-HP), as packs of one flask of levosimendan or placebo labelled and numbered according to the list of treatment numbers provided by the promoter.
The participating centers will be supplied with the study-drugs by the DEC-AGEPS.

A pharmacy manual specifying and detailing these various points will be supplied to the hospital pharmacies of the various centers during the initiation visits for the trial.

8 RANDOMISATION

The treatment will be attributed by minimization (deterministic dynamic attribution). The procedure will take into account the center, the type of surgery (isolated or combined CABG), LVEF (<30%, or between 30 and 40%), history of previous cardiac surgery, preoperative treatment with an inotrope or an IABP, and preoperative treatment with beta-blockers. This approach will make it possible to ensure that these prognostic factors are evenly distributed between the two groups at each center. We will also introduce a random component to decrease the predictability of allocation.

We will use minimization because stratified randomization is not effective for small trials. This is the case here, because the three factors for which we wish to control (type of surgery, LVEF and preoperative treatment) would generate eight strata at each of the 15 centers. Minimization is a valid alternative in such cases.

The randomization algorithm will be established by a statistician other than the statistician who will analyze the data for the study. This algorithm will be installed on an internet site with secure access.

At the time of inclusion, each patient will be identified by a center number (three digits) taken from a list of centers, an inclusion number (four digits) that will be attributed in chronological order at each center and the first letters of the patient’s surname and first name. During randomization, the investigator will log on to the internet site containing the algorithm and enter the characteristics of the patient. The randomization results will be sent to the pharmacy.

9 STATISTICS

9.1 Number of subjects required

The total number of subjects required for this study is 340: 170 patients per group. This number was determined on the basis of the following hypotheses:

(1) Incidence of 65% for the composite criterion in the control group (estimated from HEGP data)

(2) Incidence of 50% for the composite criterion in the levosimendan group (according to the results of Levin et al., who reported that the preoperative administration of levosimendan in patients suffering LCOS decreased the frequency of use of an additional inotrope by 28% and the use of IABP by 12%, relative to the dobutamine group)²⁷

(3) α risk of 5% and β risk of 20%. 
9.2 Statistical analysis

9.2.1 General information

The results will be presented according to CONSORT guidelines. The estimates for the primary and secondary outcome measures will be supplied with 95% confidence intervals.

9.2.2 Primary outcome measure

The principal analysis will be an intention-to-treat analysis on all the patients included in the study and randomized to one of the treatment arms. The non-adjusted incidence of the composite criterion will be compared between the two groups using chi-squared tests. Multiple logistic regression analysis will then be performed, to compare incidences adjusted for the prognostic factors for LCOS: type of surgery (isolated coronary surgery or combined coronary and valve surgery), LVEF (<30% or between 30 and 40%), history of previous surgery, preoperative treatment with an inotrope and/or IABP, and preoperative treatment with beta-blockers.

Three subgroup analyses should make it possible to determine whether the effect of levosimendan varies with:

1. The type of surgical procedure (isolated CABG or combined CABG and valve surgery),
2. LVEF (< 30%, or 30% ≤ LVEF ≤ 40%)
3. Preoperative inotrope treatment and/or mechanical assistance.

The heterogeneity of the treatment effect will be evaluated using an interaction test and may be represented on a forest plot.

9.2.3 Secondary outcome measures

Log-rank tests will be used to compare unadjusted mortality between the two groups. A Cox regression model will be used to compare mortality adjusted for factors associated with a poor prognosis. If the assumption of proportional risks is not confirmed, the Cox regression model will be stratified for the variable not satisfying this assumption.

Count variables (numbers of days, numbers of hours) will be analyzed with a Poisson regression model taking exposure time into account. If the distribution of the observations is not normal or if the assumption of a Poisson distribution is not reasonable, other models will be used (e.g. a negative binomial regression model).

10 SAFETY EVALUATION

10.1 Description of the parameters for the safety evaluation

10.1.1 Adverse events

Any noxious or undesirable sign occurring in a person taking part in a biomedical study, regardless of its possible link to the study or to the study drug.

10.1.2 Adverse effects of a study drug

Any noxious and undesirable reaction to a study drug, regardless of the dose administered.
10.1.3 Serious adverse events or effects

Any undesirable event or effect leading to the death of the person taking part in the study or placing the life of that person in danger, requiring hospitalization or the prolongation of hospitalization, causing a major or persistent incapacity or disability or resulting in a congenital abnormality or malformation, attributable to the drug, regardless of the dose administered.

10.1.4 Unexpected adverse effects of a study drug

Any undesirable effect, the nature, severity or progression of which is not consistent with the information provided in the summary of product characteristics for drugs authorized for market release.

10.1.5 New findings

Any new safety data that could potentially lead to a re-evaluation of the benefit-risk ratio of the study drug, or of sufficient importance to suggest changes in the administration mode of the study-drug during the study.

10.2 Descriptions of the expected adverse effects of the study drug

The nature, frequency and severity of adverse effects have been presented in different manners in the clinical studies in which levosimendan has been used. The SURVIVE study (Mebazaa et al. JAMA 2009) is the clinical trial including the largest number of patients treated with levosimendan (660 patients) reported to date. However, the patients included in this study are not comparable to those of the LICORN study because they presented advanced heart failure.

Based on the data from the SURVIVE study, the expected adverse effects of levosimendan injection are as follows:

Non-serious adverse effects:
- Hypotension: 15% of patients
- Headaches: 8% of patients
- Hypokalemia: 9% of patients
- Nausea: 7% of patients
- Premature ventricular contraction: 6% of patients
- Insomnia: 6% of patients
- Tachycardia: 5% of patients
- Chest pain: 2% of patients
- Diarrhea: 4% of patients
- Renal dysfunction: 4% of patients
- Vomiting: 3% of patients

Serious adverse effects:
- Postoperative atrial fibrillation: 9% of patients
- Ventricular tachycardia: 8% of patients
- Ventricular fibrillation: 2% of patients

In the SURVIVE study, there was no significant difference in severe adverse effects between the group of patients treated with levosimendan and the group of patients treated with dobutamine.
In the studies shown in Table 2 in which levosimendan was administered during surgery, the prevalence of postoperative atrial fibrillation was between 12% (Alvarez et al. Rev Esp Cardiol 2006) and 40% (De Hert et al. Anesth Analg 2007). These studies included between 12 and 69 patients treated with levosimendan.

According to the summary of product characteristics, the administration of levosimendan is contraindicated for patients with a history of hypersensitivity to this active agent. In practice, this adverse effect is very rare and its exact incidence is unknown.

The following adverse effects are described in the SPC:

- Hypokalemia
- Insomnia
- Headaches
- Dizziness
- Ventricular tachycardia
- Postoperative atrial fibrillation
- Tachycardia
- Premature ventricular contraction
- Heart failure
- Myocardial ischemia
- Premature contraction
- Hypotension
- Nausea
- Constipation
- Diarrhea
- Vomiting

This information is summarized in a table of adverse events provided in the appendix.

Appropriate clinical evaluations and laboratory tests will be used to determine the cause of the adverse effect and the results of these explorations will be reported, together with the evolution of the problem.

10.3 Methods for measuring, recording and evaluating the safety parameters

10.3.1 Coordinating center

Responsibilities

- Production of the documents required for the study.
- Centre management: setting up and initiation of the study, onsite monitoring, periodic transmission of information and documents, validation of the observation notebooks by research assistants, collecting data forms.
- Follow-up of inclusions.
- Systematic study follow-up: timetable.
- Financial management.
- Management of the documents to be submitted to the safety monitoring board.
- Transmission of information about serious adverse events to the promoter.
- Periodic information letter.

Composition

- Permanent members of the Clinical Research Unit of the HEGP
Responsibilities

- Follow-up of the study, including inclusion rate, patient’s characteristics and the incidence of adverse events.
- Provide approval regarding the validity of the number of subjects required, with the possibility of modifying the trial plan (premature stopping of the study, continuation of inclusion) according to the data supplied by the coordinating center, with the agreement of the study statistician.
- Monitoring serious adverse events, and optimizing patient safety.

Composition

- Prof. Pascal Guéret (Cardiology Department, Henri Mondor Hospital, APHP)
- Prof. François Stephan (Intensive Care Unit, Marie Lannelongue Surgical Centre, Le Plessis-Robinson) (President)
- Raphaël Porcher (DBIM, Hôtel-Dieu, APHP, INSERM 1153)

Operating Mode

The SMB will hold a conference call meeting after the inclusion of 40 patients, and then after the inclusion of every subsequent 80 patients. The practical mode of functioning of the board may be modified if necessary by the SMB itself.

10.4 Procedures for the recording and notification of adverse events

10.4.1 Adverse events (AEs)

Any adverse event considered non-serious according to the definition given above and observed during the study-period should be reported in the observation notebook. A single event should be reported per item. The event may be a symptom, a diagnosis or the result of an additional examination considered of importance. All clinical or biological elements required to provide the best possible description of the event should be reported.

10.4.2 Serious adverse events (SAEs)

- Declaration of serious adverse events to the promoter
  The investigators should notify the promoter, AP-HP, immediately of any serious adverse events, as described in section 10.
  The investigator will complete a form for the declaration of serious adverse events (see the appendix) and send it to the DRCD by fax (01 44 84 17 99), within 48 hours (if possible, this declaration should follow a telephone call made to +33 (0)1 44 84 17 23 immediately after the event in case of death or life-threatening conditions).
For each serious adverse event, the investigator should express an opinion regarding the possibility of a causal link between the event and each study drug or other treatment used.

Serious adverse events and their imputability to treatment will be noted until six months after the levosimendan infusion.

It may not be possible to obtain all the information required for the description and evaluation of an adverse event during the time limit specified for the initial declaration. Clinical progression and the results of additional clinical evaluations, diagnostic examinations and laboratory tests should therefore be reported, together with any other information required for a satisfactory analysis:

- either, on the initial declaration for the SAE if immediately available, or
- by sending a new completed SAE declaration by fax as soon as possible, indicating that the declaration corresponds to the follow-up of a SAE that has already been declared, together with its follow-up number.

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

For notifications of the death of a subject participating in the study, the investigator should transmit any additional information requested (hospitalization reports, post mortem results etc.) to the promoter.

The promoter should be notified of any new finding arising during the study or in the context of the study.

- Declaration of serious adverse events to the health authorities

The Pharmacovigilance Unit of the DRCD will be responsible for the declaration of serious adverse events to the health authorities, after an evaluation of the seriousness of the event, the imputability to the study drug or any other treatment, and the unexpected nature of the adverse event.

The promoter will declare any unexpected serious adverse effect to the competent authorities within the timeframe laid down in law.

All safety data and any new finding that might significantly modify the benefit-risk ratio for a study-drug, which might lead to changes in the drug administration will be transmitted by the promoter to the ethics committee and the investigators of the study. For example:

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

b) Suspicions of an unexpected serious adverse effect in participants who have already completed the study, notified to the promoter by the investigator, together with any follow-up reports;

c) Any new finding concerning the course of the clinical trial or the development of the drug, if this new finding has implications for participant safety. For example:

- A serious adverse event likely to be linked to the investigations and diagnostic procedures of the trial that might modify the running of the trial,

- A significant risk to the trial population, such as a lack of efficacy of the drug used to treat a life-threatening disease,

- Significant safety results from a recently completed animal study (e.g. a study of carcinogenicity),

Protocol dated 08/01/2015 34/52
- An early ending or temporary interruption of another study carried out with the same drug in another country, for safety reasons,

d) Any unexpected serious adverse effect communicated to the promoter by another promoter of a clinical trial on the same drug carried out in another country.
- **Mode and duration of subject follow-up after the occurrence of adverse events**

Any patient presenting an adverse event must be followed until the resolution or stabilization of the adverse event. If the event is not serious, its course will be noted on the corresponding page of the observation notebook, in the section reserved for this purpose. If the event is serious, a SAE follow-up form will be sent to the DRCD.

- **Unblinding procedure**

In case of adverse events other than hypotension potentially linked to the study product and requiring knowledge of the treatment arm to which the patient was assigned to facilitate correct management, an unblinding procedure will be used. The investigator from the center at which the serious adverse event was observed should imperatively follow the procedure for declaring serious adverse events to the promoter. Unblinding will be performed by the DRCD during working hours: DRCD: Cécile Jourdain (project manager, DRCD) 01.44.84.17.32 / fax 01.44.84.17.01.

All requests for unblinding must be justified, and a completed unblinding request form, signed by the investigator, should be sent by fax. In parallel, the investigator should contact the structure to which the fax is sent.

In case of anaphylactic shock, arterial hypotension, or heart rate problems refractory to usual treatment, the study-drug administration will be interrupted (see section 6.6.2. Stopping the study treatment in a patient). Knowledge of the product administered will not change management, which is essentially symptomatic (e.g. vasopressors for arterial hypotension).

Emergency unblinding will be performed after discussions with the coordinating investigator, by the DRCD (during working hours) or Fernand Widal Hospital.

11 **RIGHT OF ACCESS TO DATA AND DOCUMENTS**

All persons with direct access to the study data, in accordance with the laws and regulations in force, including articles L. 1121-3 and R. 5121-13 of the Public Health Code (for example, the investigators, those responsible for quality control, monitors, clinical research assistants, auditors, and anyone collaborating in the trials) will take all the necessary precautions to protect the confidentiality of information related to the study drugs, the trial, and the people taking part in the trial, particularly regarding their identity and the results obtained.

12 **DATA MANAGEMENT AND STATISTICS**

12.1 **Observation notebook**

All the information required by the protocol (for the study or relating to safety and/or the declaration and follow-up of adverse events) will be supplied in the observation notebook provided for this purpose. This information will be monitored and an explanation for all items of missing or erroneous data will be requested from the investigator.
Each subject taking part in this study will receive a code number associated with their initials. This code will be marked on all the documents required for the study.

**12.2 Monitoring**

Given the risks related to the type of participants, this study will be classified as a level D study. The data monitored will be those essential for the scientific quality of the protocol and those concerning patient consent. The study will be monitored by clinical research assistants (CRAs) representing the promoter. Visits to the investigating centers will be scheduled for the opening of the study, corresponding to inclusion of the first patient, and its closing. Other visits will be scheduled according to the inclusion rate.

**12.3 Responsibility for the analysis, the analysis site and the software used**

The data will be managed by the CRU of the HEGP:

- A list of the study variables will be produced in operational data model (ODM) format by the CRU, working with the study investigators.
- This list will make it possible for the CRU to develop a paper-based notebook for recording data and a database in PostgreSQL format, into which the data will be entered after quality control.
- A data management plan developed jointly by the data manager, the principal investigator and the statistician will be implemented.
- After correction of the errors that this plan will have identified, the database will be frozen for statistical analysis.
- The data will be analyzed with SAS software (SAS Institute Inc., Cary, NC).

Prof. Gilles Chatellier will be responsible for data processing for this study.

**13 LEGAL AND ETHICAL CONSIDERATIONS**

The promoter is defined according to the law 2004-806 dated August 9, 2004. In this study, AP-HP is the promoter and the Department of Clinical Research and Development (DRCD) will be responsible for its regulatory missions. Before the start of the study, each investigator will provide the representative of the study promoter with a dated and signed copy of his/her personal curriculum vitae, bearing his or her national medical council registration number and Adéli number.

**13.1 Request for ANSM authorization**

As promoter of the study, AP-HP must submit a request for authorization for this study to the competent authority, the ANSM. The competent authority, as defined in article L. 1123-12 of the Public Health Code, will issue an opinion concerning the safety of the persons participating in the biomedical study, considering, if appropriate, the references in force, their conditions of use and the safety of the participants in terms of the acts performed, the methods used and the modes of follow-up for the study subjects.
13.2 Request for an expert opinion from the ethics committee

In accordance with article L. 1123-6 of the Public Health Code, the promoter must submit the research protocol to the appropriate ethics committee. The expert opinion of this committee must then be communicated to the competent authority by the promoter, before the research can begin.

13.3 Modification of the protocol

The DRCD must be informed, by the coordinating investigator, of all intended modifications to the protocol. Each modification must be qualified as substantial or insubstantial. A substantial modification is defined as a modification likely, in one way or another, to modify the guarantees provided to the subjects taking part in the biomedical study (modification of an inclusion criterion, prolongation of the inclusion period, participation of new centers etc.).

Once the study has begun, any substantial modification at the initiative of the promoter must receive approval from the ethics committee and authorization from the competent authority before its implementation. If necessary, the ethics committee may check that a new consent form has been signed by the individuals participating in the study.

Any extension of the study (profound modification of the therapeutic scheme or of the populations included, implementation of therapeutic acts not initially planned in the protocol, etc.) should be considered as a new study. All substantial modifications should be submitted by the promoter to the ANSM for authorization and/or the ethics committee for approval, after payment of a tax.

13.4 Declaration to the CNIL

According to the laws in force, the file of computerized personal data collected for the study must be declared before the effective start of the study.

This protocol will benefit from quality control by a CRA representing the promoter, and conforms to the field of application of a specific reference methodology for the processing of personal data in the framework of biomedical research defined in law 2004-806 from August 9, 2004 (covered by article L. 1121-1 and subsequent articles of the Public Health Code) and established by the CNIL in January 2006. This methodology allows a simplified declaration procedure when the types of data collected in the study match the contents of a list drawn up by the CNIL in its reference document.

As the promoter’s representative, the DRCD will ask the person responsible for managing the computer file to agree, in writing, to respect the MR06001 simplified reference methodology and to make the necessary declaration to the CNIL.

13.5 Information notice and informed consent

Informed consent must be obtained from all individuals participating in the study, before any of the acts required for the biomedical research study are performed.

The study population in this case is a population of autonomous adults. The information notice and the consent form are separate documents that must be given...
to the patient before any of the medical acts required for the biomedical study are performed.
13.6 Final study report

The final report for this study will be written jointly by the coordinator and the biostatistician. This report will be submitted to each of the investigators for approval. Once a consensus has been obtained, the final version should be signed by 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 supplied by the competent authority should be sent to the competent authority and to the ethics committee within a year of the end of the study, defined as the last follow-up visit (here, a telephone call on D180) for the last subject included. The final report should be submitted within 90 days of the end of the study if the study is stopped early.

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

The documents of any study covered by the law on biomedical research should be archived by all parties for 15 years after the end of the study (see good clinical practice chapter 8: essential documents).

The following documents should be archived:

- Copies of the ANSM authorization and expert opinion of the ethics committee concerning the study,
- The successive versions of the protocol (identified by version number and date),
- All correspondence with the promoter,
- The signed consent forms of the subjects, in a stamped, sealed envelope, together with the corresponding inclusion list or register,
- The completed and validated observation notebook for each subject included,
- All additional documents specific to the study,
- The final report of the study, after statistical analysis and quality control (copy sent to the promoter),
- The certificates for any audits performed during the study.

The database used for the statistical analysis should also be archived by the person responsible for the analysis (on paper or in a computerized format).

15 INSURANCE AND SCIENTIFIC COMMITMENT

15.1 Insurance

AP-HP (Assistance Publique - Hôpitaux de Paris) is the promoter of this study. In accordance with the law on biomedical research, AP-HP will take out an insurance policy covering its own civil responsibility and that of all those involved in the trial (doctors and other staff involved in the performance of the study; law no. 2004-806, Art L.1121-10 du CSP). AP-HP reserves the right to stop the study at any time, for medical or administrative reasons; in this case, the investigator will be notified.

15.2 Scientific commitment

Each investigator will agree to respect the obligations of the law and to follow good clinical practice, in accordance with the terms of the Helsinki Declaration. Each investigator from each participating center will provide a dated and signed declaration.
of scientific commitment (standard form available from the DRCD), which will be transmitted to the promoter's representative.

16 PUBLICATION RULES

For publication in the journals of the International Committee of Medical Journal Editors (ICMJE), this controlled comparative clinical trial will be registered with http://www.clinicaltrials.gov/ before the inclusion of the first patient. This website is independent of AP-HP and is managed directly by the editors.

AP-HP is the owner of all the data for this study, and no use or transmission of the data to a third party is permitted without its prior agreement. AP-HP must be mentioned as the promoter of this biomedical research study and as providing financial support, as appropriate. The terms “Assistance Publique- Hôpitaux de Paris” must appear in the authors' addresses.

A writing committee consisting of the members of the management committee and the coordinator of the critical events committee and a representative of the centers including the largest numbers of patients in the trial will write an initial draft of the first article for the approval of the scientific committee. The authors of the article will be the members of the management committee, the members of the scientific committee, the coordinator of the critical events committee and a representative from each of the centers including the largest numbers of patients in the trial. The article will then be submitted to an international peer-reviewed journal, with the agreement of the study promoter. Dr. Thibaut Caruba is the scientific director of this project and Prof. Bernard Cholley will be the corresponding author on the first article.

The results of the trial can be communicated only with the agreement of the scientific committee. All investigators including at least 10 patients in the trial may submit other articles based on the study results to the scientific committee for approval for publication, after acceptance of the first article for publication.

17 APPENDICES

17.1 Classification grid for AEs and SAEs
Classification grid for adverse events in a biomedical study on a drug (Art. R. 1123-54 of the Public Health Code)

**LICORN study**

Project codes: P110138– EUD2012-000232-25

Risk of the study: D

IMC / DSMB: Yes ☑ No ☐

Efficacy of levosimendan pretreatment before coronary artery bypass graft on extracorporeal circulation in high-risk patients (LVEF < 40%): multicenter, randomized, double-blind, placebo-controlled trial. LICORN: Levosimendan In Coronary Revascularization

### NOT TO BE NOTIFIED TO THE PROMOTER

Events identified in the protocol as not requiring notification, but which may be reported in the observation notebook (CRF)

### TO BE NOTIFIED TO THE PROMOTER IMMEDIATELY

SAE to be sent by fax to 01 44 84 17 99 and information to be noted in the CRF

- All events presenting one of the criteria of seriousness noted below, except those identified as not requiring notification.
- 1. Death
- 2. Life-threatening situation
- 3. Need for hospitalization or its prolongation
- 4. Long-term sequelae
- 5. Congenital abnormality or malformation
- 6. Event considered to be serious by the investigator

**NOTE:** any discovery of PREGNANCY during a biomedical research study should be immediately declared to the promoter and the pregnancy should be monitored until delivery.

<table>
<thead>
<tr>
<th>Events that may be serious but are not linked to the study</th>
<th>EXPECTED non-serious adverse effects</th>
<th>EXPECTED serious adverse effects</th>
<th>UNEXPECTED serious adverse effects (USAEs)</th>
</tr>
</thead>
</table>

Protocol dated 08/01/2015
Anything related to the natural and usual course of the disease:
- New hospitalization for disease follow-up

Any serious adverse effect likely to be linked to treatments prescribed for routine care during the follow-up period of the study

Any event likely to be exclusively due to cardiac surgery occurring during the postoperative period and requiring a prolongation of hospitalization (e.g. pleural effusion).

**Known adverse effects of levosimendan (SPC)**
- Hypotension (grades 1 and 2, <20% decrease in mean arterial pressure under anesthesia)
- Moderate tachycardia (HR <110bpm)
- Precocious ventricular contraction
- Postoperative atrial contraction
- Nausea
- Vomiting
- Diarrhea – Constipation – Dizziness
- Headache
- Insomnia
- Decrease in hemoglobin level
- Mild to moderate hypokalemia (3 to 3.5 mmol/l)

Adverse effects reported in the SURVIVE study
- Renal insufficiency
  Considered non-serious if simply an increase in creatinine concentration of <50% preoperative levels or <40 µmol/l; with no need for dialysis.

**Known adverse effects of levosimendan (SPC)**
- Postoperative atrial fibrillation
- Ventricular fibrillation
- Torsades de pointes
- Ventricular tachycardia
- Profound arterial hypotension (decrease in mean arterial pressure of at least 20% the value AFTER anesthesia induction) or refractory to usual treatment during the infusion
- Myocardial ischemia
- Cardiac insufficiency

Any effect listed in the "non-serious adverse effects" column meeting one of the criteria for seriousness should be notified as a "non-serious adverse effect". The expected or unexpected nature of the effect will be evaluated by the promoter.

In general, any adverse effect making it necessary to stop the infusion should be notified as a "serious" effect.
Form for the notification of a serious adverse event (SAE) occurring during the course of a biomedical study on a drug or similar product

As soon as the investigator becomes aware of the SAE, he or she should complete this form (2 pages), and sign and return it immediately to the Vigilance unit of the DRCD-Siège by fax: +33 (0)1 44 84 17 99

1. Study identification

<table>
<thead>
<tr>
<th>Acronym LICORN</th>
<th>Date of notification:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Study code: P 110138</td>
<td>Date on which the investigator became aware of the SAE:</td>
<td></td>
</tr>
</tbody>
</table>

Complete title of the biomedical research study:
Efficacy of levosimendan pretreatment before coronary artery bypass graft (CABG) under cardiopulmonary bypass in high-risk patients (left ventricular ejection fraction below 40%): a multicenter, randomized, double-blind, placebo-controlled trial. LICORN: Levosimendan In Coronary Revascularization

2. Investigating center

<table>
<thead>
<tr>
<th>Name of the establishment:</th>
<th>Investigator (surname/first name):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Town and postcode:</td>
<td>Tel: ____________________________</td>
</tr>
<tr>
<td>Department:</td>
<td>Fax: ____________________________</td>
</tr>
</tbody>
</table>

3. Identification and history of the person taking part in the study

<table>
<thead>
<tr>
<th>Code number:</th>
<th>Date of birth:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centre no.</td>
<td>dd  mm  yyyy</td>
</tr>
<tr>
<td>selection order no.</td>
<td>dd  mm  yyyy</td>
</tr>
<tr>
<td>surname</td>
<td>dd  mm  yyyy</td>
</tr>
<tr>
<td>first name initial</td>
<td>dd  mm  yyyy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical/surgical or family antecedents relevant for the evaluation of this case (attach an anonymized hospital report if appropriate):</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Sex:</th>
<th>M</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight:</td>
<td></td>
<td>kg</td>
</tr>
<tr>
<td>Height:</td>
<td></td>
<td>cm</td>
</tr>
<tr>
<td>Date on which consent form signed:</td>
<td></td>
<td>dd  mm  yyyy</td>
</tr>
<tr>
<td>Date of randomization:</td>
<td></td>
<td>dd  mm  yyyy</td>
</tr>
<tr>
<td>Treatment no. (1st flask):</td>
<td></td>
<td>dd  mm  yyyy</td>
</tr>
<tr>
<td>Treatment no. (2nd flask):</td>
<td></td>
<td>dd  mm  yyyy</td>
</tr>
</tbody>
</table>

4. Study drug(s) (SDs) or similar products [specify which before the occurrence of the SAE] (cross out the box if treatment not initiated):

<table>
<thead>
<tr>
<th>Brand name (by preference) or international non-proprietary name</th>
<th>Route</th>
<th>Dose / 24 h</th>
<th>Date and time at which infusion initiated (dd/mm/yyyy)</th>
<th>Underwater</th>
<th>Date and time at which infusion stopped (dd/mm/yyyy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levosimendan or placebo</td>
<td>IV</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>
7. Serious adverse event [SAE]

**Diagnosis:**
- [ ] Definitive
- [ ] Provisional

**Organ(s) concerned:**

**Symptoms:**
- [ ] Life-threatening condition
- [ ] Major or long-term incapacity or disability
- [ ] Congenital abnormality or malformation
- [ ] Other clinically significant criteria; please specify:

**Date of symptom onset:**

**Please specify**

**Date of SAE onset:**

**Time between the last administration of the SD/similar product or the date of the additional procedure/act for the study and the occurrence of the SAE:**

**Criteria for seriousness:**
- [x] Necessitating or prolonging hospitalization:
  - from [ ] [ ] [ ] [ ] to [ ] [ ] [ ] [ ] [ ] still underway
- [ ] Death
- [ ] Life-threatening condition
- [ ] Major or long-term incapacity or disability
- [ ] Congenital abnormality or malformation
- [ ] Other clinically significant criteria; please specify:

**Degree of severity:**
- [ ] Mild
- [ ] Moderate
- [x] Severe

**Course of the event**
- [ ] Death
  - [ ] unrelated to the SAE
  - [ ] related to the SAE
  - [ ] Subject not yet recovered; specify:
    - [ ] Stable
    - [ ] Aggravation
    - [ ] Improvement

- [ ] Resolution of the event
  - [ ] without sequelae
  - [ ] with sequelae; please specify:

**Symptomatic measures taken:**

**Part reserved for the promotor**

---

**5. Additional procedures and acts for the study**

**Acronym LICORN:**

**Subject code number:**

**Centre no.**

**Order of selection no.**

**Surname**

**Initial**

**First name**

**Initial**

**Date performed (dd/mm/yyyy):**

**PART RESERVED FOR THE PROMOTOR**

---

**6. Drugs taken concomitantly at the time of the SAE, excluding those used to treat the adverse effect**

- [ ] Yes
- [ ] No

**Appendix sent with this form:**

- [ ] Yes
- [ ] No

**It is necessary, the appendix relating to concomitant drugs**

**Brand name (by preference) or international non-proprietary name, together with the pharmaceutical form and dose**

**Route of administration:**
- PO=per os (oral)
- IM=intramuscular
- IV=intravenous
- SC=subcutaneous or other (to be specified)

**Ongoing at the time of the SAE:**

**SAE occurrence**

**1) Route of administration:**
- (dd/mm/yyyy)
- (dd/mm/yyyy)
- (dd/mm/yyyy)
- (dd/mm/yyyy)
- (dd/mm/yyyy)

**2) Ongoing at the time of SAE occurrence:**

---

**7. Serious adverse event [SAE]**

**Diagnosis:**
- [ ] Definitive
- [ ] Provisional

**Organ(s) concerned:**

**Symptoms:**
- [ ] Life-threatening condition
- [ ] Major or long-term incapacity or disability
- [ ] Congenital abnormality or malformation
- [ ] Other clinically significant criteria; please specify:

**Date of symptom onset:**

**Please specify**

**Date of SAE onset:**

**Time between the last administration of the SD/similar product or the date of the additional procedure/act for the study and the occurrence of the SAE:**

**Criteria for seriousness:**
- [ ] Necessitating or prolonging hospitalization:
  - from [ ] [ ] [ ] [ ] to [ ] [ ] [ ] [ ] [ ] still underway
- [ ] Death
- [ ] Life-threatening condition
- [ ] Major or long-term incapacity or disability
- [ ] Congenital abnormality or malformation
- [ ] Other clinically significant criteria; please specify:

**Degree of severity:**
- [ ] Mild
- [ ] Moderate
- [x] Severe

**Course of the event**
- [ ] Death
  - [ ] unrelated to the SAE
  - [ ] related to the SAE
  - [ ] Subject not yet recovered; specify:
    - [ ] Stable
    - [ ] Aggravation
    - [ ] Improvement

- [ ] Resolution of the event
  - [ ] without sequelae
  - [ ] with sequelae; please specify:

**Symptomatic measures taken:**

---

**Protocol dated 08/01/2015**

45/52
8. Other potential causes identified:

<table>
<thead>
<tr>
<th>No</th>
<th>Yes</th>
<th>If yes, please specify:</th>
</tr>
</thead>
</table>

---

9. Additional examinations performed:

<table>
<thead>
<tr>
<th>No</th>
<th>Yes</th>
<th>If yes, please specify the date and nature of the examinations and their results [attach anonymised results]:</th>
</tr>
</thead>
</table>

---

10. According to the investigator, the serious adverse event is (several answers possible):

### Linked to the biomedical study:

- **Yes:**
  - linked to the SD/similar product of the study: Which?
    - SD/product: ____________________________
      - Clear link
      - Plausible link
      - Dubious link
  - linked to the procedures/acts used in the biomedical study: Which, or NA?
    - Procedure/act: ____________________________
      - Clear link
      - Plausible link
      - Dubious link

- **No:**
  - linked to a progression of the disease studied: (please specify)
    - linked to one or several drugs administered concomitantly with the SD/similar product. If so, which?
    - linked to a comorbid condition, please specify:
    - other, please specify:

---

Person making the notification

<table>
<thead>
<tr>
<th>Name and post:</th>
<th>Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signature:</td>
<td>Signature:</td>
</tr>
</tbody>
</table>

---

Protocol dated 08/01/2015
References


