

BMJ Open Opioid-free anaesthesia with dexmedetomidine and lidocaine versus remifentanyl-based anaesthesia in cardiac surgery: study protocol of a French randomised, multicentre and single-blinded OFACS trial

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ABSTRACT

Introduction Intraoperative opioids have been used for decades to reduce negative responses to nociception. However, opioids may have several, and sometimes serious, adverse effects. Cardiac surgery exposes patients to a high risk of postoperative complications, some of which are common to those caused by opioids: acute respiratory failure, postoperative cognitive dysfunction, postoperative ileus (POI) or death. An opioid-free anaesthesia (OFA) strategy, based on the use of dexmedetomidine and lidocaine, may limit these adverse effects, but no randomised trials on this issue have been published in cardiac surgery.

We hypothesised that OFA versus opioid-based anaesthesia (OBA) may reduce the incidence of major opioid-related complications after cardiac surgery.

Methods and analysis Multicentre, randomised, parallel and single-blinded clinical trial in four cardiac surgical centres in France, including 268 patients scheduled for coronary artery bypass grafting under cardiac bypass, with or without aortic valve replacement. Patients will be randomised to either a control OBA protocol using remifentanyl or an OFA protocol using dexmedetomidine/lidocaine. The primary composite endpoint is the occurrence of at least one of the following: (1) postoperative cognitive disorder evaluated by the Confusion Assessment Method for the Intensive Care Unit test, (2) POI, (3) acute respiratory distress or (4) death within the first 48 postoperative hours. Secondary endpoints are postoperative pain, morphine consumption, nausea–vomiting, shock, acute kidney injury, atrioventricular block, pneumonia and length of hospital stay.

Ethics and dissemination This trial has been approved by an independent ethics committee (*Comité de Protection des Personnes Ouest III–Angers* on 23 February 2021). Results will be submitted in international journals for peer reviewing.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The Opioid Free Anaesthesia for Cardiac Surgery (OFACS) trial is a multicentre, randomised, single-blinded study, guaranteeing robust results.
- ⇒ Exploration of major complications after cardiac surgery as the main endpoint aims to explore the clinical relevance of the strategy.
- ⇒ Both short-term and long-term outcomes will be explored.
- ⇒ The trial is not double blinded, which may induce a bias during data acquisition.
- ⇒ The trial will not explore the costs associated with both strategies.

Trial registration number NCT04940689, EudraCT 2020-002126-90.

INTRODUCTION

The use of opioid derivatives has been widespread in the perioperative setting for decades. Their administration allows the control of sympathetic response to nociceptive stimuli related to the surgical process, attenuating the intraoperative haemodynamic variations.^{1,2} Beyond this beneficial effect, opioids can present significant side effects: digestive disorders, from simple nausea and vomiting to postoperative ileus (POI)^{3,4}; respiratory depression through the central inhibition of breath control, with a risk of perioperative hypoxaemia⁵; postoperative cognitive dysfunction (POCD) and delirium^{6,7}; hyperalgesia^{8,9}; and possible suppressive effects on immunity and adrenal functions, which may favour postoperative infections.^{10,11} All of



these complications may hinder prognosis after surgery. Furthermore, in the context of the international ‘opioid crisis’, strategies limiting opioid administration during and after surgery may be of interest.^{12–13} Indeed, thousands of people die every year from opioid overdose, with approximately 25% of them having a medical prescription. More specifically, 2–9% of patients still use opioids several months after surgery, in many cases because of persistent pain, and this could therefore facilitate addiction.^{14–15} Limiting intraoperative opioids may therefore be part of a global perioperative opioid reduction programme, aimed at reducing secondary hyperalgesia and ultimately opioid addiction.

Cardiac surgery with cardiopulmonary bypass (CPB) is particularly vulnerable to the above-mentioned complications. Indeed, some of the side effects of this surgery overlap with the adverse effects of opioids. Postoperative pulmonary complications are observed in up to 50% of patients and POCD or delirium in 4–54% according to studies and definitions,^{16–18} whereas major gastrointestinal complications are estimated to occur in around 3% of patients, essentially acute pancreatitis and paralytic ileus.^{19–20} Nausea and vomiting have been observed in 10–15% of patients.²¹ All these data suggest a reasoned use of opioids which can present additive effects and their enhanced cardiac surgery-related side effects. Thus, the use of pharmacological alternatives may be considered in order to avoid their use as much as possible.

Opioid-free anaesthesia (OFA) strategies have emerged to avoid intraoperative opioid use. They are based on a drug combination that blocks the deleterious pathophysiological reactions related to nociception independently of opioid pathways. Among the various eligible drugs, lidocaine and dexmedetomidine may be of interest for this objective. Intravenous administration of lidocaine at doses up to 2 mg/kg/hour allows analgesia through a systemic blockade of peripheral neurons and anti-inflammatory proprieties.^{22–23} Its use during non-cardiac major surgeries showed a reduction in postoperative pain, nausea–vomiting, ileus and length of stay.^{24–25} Dexmedetomidine is an α_2 agonist with analgesic and sedative proprieties. Several studies showed its ability to reduce postoperative pain, opioid consumption, nausea–vomiting and circulatory failure.^{26–27} Dexmedetomidine presented sympatholytic proprieties that may allow control of circulatory status during surgical nociceptive stimulation.²⁸ Moreover, dexmedetomidine showed beneficial effects in ischaemia–reperfusion experimental models, and several studies have shown significant clinical effects of dexmedetomidine after cardiac surgery, making this drug of high interest in this field.^{29–31} Other drugs such as esmolol or magnesium have been used as alternatives to opioids. Nevertheless, we think that their use during cardiac surgery may favour circulatory failure and may interfere with CPB management through interference with cardioplegia drugs, delayed weaning from CPB, etc, suggesting the combination of lidocaine/dexmedetomidine as our first choice.

Preliminary results from retrospective studies with small sample size suggested that an OFA-based strategy is safe in cardiac surgery.^{32–34} However, a large randomised trial is expected to explore the clinical benefits of OFA. Thus, we hypothesise that OFA may reduce opioid-related complications, and therefore the current trial was designed in order to compare the effects of OFA and opioid-based anaesthesia (OBA) on the incidence of major opioid-related complications after cardiac surgery.

OBJECTIVES OF THE STUDY

The primary goal is to assess the superiority of the OFA strategy compared with the OBA strategy with a reduction in major opioid-related complications within 48 hours after cardiac surgery.

The secondary goals are to compare the influence of the OFA and OBA strategies on the following postoperative complications: nausea–vomiting, pain, arrhythmia, shock, relative adrenal insufficiency, acute kidney injury, length of stay and mortality.

METHODS AND ANALYSIS

The present protocol was elaborated according to the 2013 Standard Protocol Items: Recommendations for Interventional Trials version 1.3, elaborated on 26 March 2020.

Trial characteristics

We designed a multicentre, randomised and single-blinded clinical trial focusing on elective cardiac surgeries with at least two coronary artery bypass grafts (CABGs). The patients will be randomly assigned to OFA or OBA strategies with an allocation ratio of 1:1. The trial will be conducted in four university and non-university cardiac surgery centres in France from 1 July 2021 until 1 July 2024 for a 36-month recruitment period, with the possibility of extending the inclusion period in the event of incomplete enrolment and on express request to the ethics committee.

Patient selection

Inclusion criteria

- ▶ Adult patients 18–75 years old.
- ▶ Scheduled for an elective cardiac surgery under CPB, with at least one CABG and implying at least one internal mammary artery as graft. This specific population has been chosen because of the extended dissection of the chest wall and a higher expected pain level compared with other cardiac surgeries. An association with aortic valve replacement is permitted.
- ▶ Having signed written consent to participate.
- ▶ Affiliated with a social security scheme.

Non-inclusion criteria

- ▶ Treatment with opioid-based drugs (including tramadol) within 15 days before surgery.
- ▶ Past or ongoing history of drug abuse.

- ▶ High-degree intracardiac conduction disorders.
- ▶ Bradycardia <50 bpm.
- ▶ Severe heart failure with left ventricle ejection fraction <40%.
- ▶ Myocardial injury within five preoperative days.
- ▶ Shock.
- ▶ Oxygen therapy.
- ▶ Chronic therapy with non-invasive ventilation.
- ▶ Contraindication to one of the trial drugs (dexmedetomidine, lidocaine, dexamethasone, ketamine, remifentanyl, morphine, non-steroidal anti-inflammatory drugs).
- ▶ Body mass index ≥ 35 kg/m².
- ▶ Chronic adrenal insufficiency or treatment with corticosteroids (≥ 20 mg of hydrocortisone or equivalents).
- ▶ Combined cardiac surgeries (other than aortic valve replacement).
- ▶ Acute cerebral disease.
- ▶ Liver failure (factor V <50%).
- ▶ Cognitive disorders.
- ▶ Inability to perform the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) test.
- ▶ Pregnant or breastfeeding women.
- ▶ Inability to give consent.
- ▶ Person deprived of liberty by an administrative or judicial decision or person placed under judicial protection/under guardianship.
- ▶ Participation in another experimental trial within the month before inclusion.

Endpoints

The primary endpoint is the occurrence of at least one of the following events within 48 postoperative hours (composite endpoint):

- ▶ POI defined as the absence of gas or solid transit or actual bowel occlusion.
- ▶ Acute respiratory failure defined as need for oxygen therapy ≥ 6 L/min and/or need for respiratory support (high-flow nasal cannula, curative non-invasive ventilation, invasive ventilation with a new tracheal intubation) and/or acute respiratory distress and/or inability to wean from invasive ventilation because of hypoxaemia.
- ▶ POCD defined as a positive CAM-ICU score or delirium.
- ▶ Death.

The secondary endpoints are defined as follows:

- ▶ Intraoperative safety concerns
 - Bradycardia requiring atropine administration (atropine will be used if heart rate <35 bpm for at least 120 s, or heart rate <40 bpm with circulatory failure).
 - Arterial hypotension or hypertension, defined as the necessity of any pharmacological treatments (antihypertensive drugs or vasopressors).
- ▶ Within 48 postoperative hours
 - Nausea–vomiting.

- Pain evaluated by a visual analogue scale (VAS) (maximal pain and number of episodes with VAS $\geq 3/10$) and total morphine consumption.
- De novo atrial or ventricular rhythm disorders.
- Shock.
- High-degree cardiac conduction disorders.
- Maximal troponin plasma level.
- Acute kidney injury defined by a Kidney Disease Improving Global Outcomes (KDIGO) score ≥ 1 (increase in creatinine over at least 26.5 μ mol/L).³⁵
- Relative adrenal insufficiency at 24 hours (increase in cortisol <250 nmol/L 1 hour after 250 μ g tetra-cosactide intravenous injection).
- ▶ Within hospital stay
 - Suspected or confirmed postoperative pneumonia.
 - Duration of invasive mechanical ventilation/intensive care unit (ICU) stay/hospital stay.
- ▶ Mortality within 2 months.
- ▶ Pain at 3 months, evaluated by VAS and 4-points Neuropathic Pain (DN-4) scales.

Design

Standard anaesthesia and postoperative care in both groups

Anxiolysis may be administered according to the practices of each centre. Preoperative chronic medication use will be managed as recommended by the French Society of Anesthesiology and Critical Care, and notably β blockers will be maintained on the day of the surgery, whereas calcium channel blockers and ACE inhibitors or equivalent will be stopped at least 24 hours before surgery.

Patients will be monitored according to the current guidelines for cardiac surgery³⁶: electrocardiography, pulse oximetry, capnography, invasive arterial catheter for blood pressure measurement, jugular or subclavicular central catheter with continuous central venous pressure, rectal or vesical temperature and bispectral index.

After preoxygenation with a 100 FiO₂ to achieve an end-expired oxygen fraction over 90%, general anaesthesia will be induced in both groups by using propofol (target concentration infusion (TCI)—site effect 1–5 μ g/mL) or etomidate (0.2–0.5 mg/kg) in association with a neuromuscular blocker (cisatracurium 0.2 mg/kg or atracurium 0.5 mg/kg). Anaesthesia will be maintained using TCI of propofol or volatile anaesthesia to target a bispectral index between 40 and 60, and intermittent or continuous administration of neuromuscular blockers to obtain a train of 4 at 0. In the absence of specific guidelines or recommendations on this topic, the choice of hypnotic and paralyzing drugs will be left at the discretion of the anaesthetist according to patient characteristics and local protocols. Patients will receive dexamethasone (0.1 mg/kg) and ketamine (0.2 mg/kg) at the beginning of anaesthesia, followed by a continuous infusion of ketamine (0.2 mg/kg/hour, stopped 45 min before the end of surgery), as recommended by the French guidelines.³⁷

In cases of hypotension with a mean arterial pressure ≤ 65 mm Hg during the off-CPB period, circulatory intervention will be initiated with the use of vasopressors

(ephedrine or phenylephrine or norepinephrine) in combination with fluid administration if required. Because the recommended threshold for mean arterial pressure (MAP) during the CPB period is large (50–80 mm Hg according to European Association for Cardio-Thoracic Surgery (EATCS) guidelines³⁶), vaso-pressor use will be left at the discretion of the anaesthetist, with a lower value of 50 mm Hg, and after optimisation of pump flow. In cases of hypertension, antihypertensive drugs will be administered (nicardipine 1 mg or urapidil 10 mg every 2–5 min to obtain adequate blood pressure). The maximal upper blood pressure level permitted will be determined between the anaesthetic and surgical team, and according to pre-existing protocols if existing.

Antibioprophylaxis will consist of cefazolin 2 g (+1 g every 4 hours and 1 g for CPB priming) or vancomycin 30 mg/kg in case of a history of allergy.

CPB will be carried out according to the recent guidelines and the local practices of each centre.³⁶

At the end of surgery, patients will receive analgesia with paracetamol 1 g, nefopam 20 mg and a non-steroidal anti-inflammatory (ketoprofen or diclofenac at the discretion of the clinician).

After surgery, patients will be transferred under invasive mechanical ventilation to cardiac surgical ICU for postoperative care. Extubation will be performed in awakened patients with spontaneous ventilation under pressure support of no more than 10 cmH₂O and positive end-expiratory pressure (PEEP) of no more than 5 cmH₂O. In cases of ventilation for more than 48 hours, extubation will be performed after a successful spontaneous breathing trial (low-pressure ventilation with pressure support of 7–8 cmH₂O and zero PEEP, or T-tube trial; absence of polypnoea, hypoxaemia, agitation, tachycardia or hypertension within 30 min of the trial).³⁸ Then, oxygen will be administered if required to obtain SpO₂ between 92% and 96%.

Circulation management (fluid therapy and vasoactive drugs) will be conducted according to each centre practice, with an objective of a mean arterial pressure of at least 65 mm Hg.

Postoperative analgesia within the first 48 hours will be performed using paracetamol 1 g/6 hours (intravenous or oral), nefopam 80 mg/day by continuous infusion, ketoprofen or diclofenac every 8 hours (respectively 100 and 75 mg, or 50 and 50 mg if weight <70 kg) and patient-controlled analgesia based on morphine 1 mg and droperidol 0.05 mg/7 min.

The design of the trial and the specificities of each arm are described below and in online supplemental file 1.

Control group (OBA)

Patients will receive 50 mL of NaCl 0.9% as placebo within 10 min before induction of general anaesthesia.

Remifentanyl will be added to standard care using TCI at an effect site concentration of 4 ng/mL for anaesthesia induction, followed by a TCI of 1–10 ng/mL according to

the clinical situation. Infusion will be stopped at the end of surgery.

Morphine 0.15 mg/kg will be administered at the end of surgery along with other analgesics.

Experimental group (OFA)

Dexmedetomidine (0.5 µg/kg) and lidocaine (1.5 mg/kg) will be administered within 10 min before induction of general anaesthesia, followed by a continuous infusion of lidocaine (2 mg/kg/hour, stopped 45 min before the end of surgery) and dexmedetomidine (1 µg/kg/hour until sternotomy, reduced at 0.5 µg/kg/hour until CPB onset and then stopped). Dexmedetomidine infusion may be reduced in cases of bradycardia or hypertension/hypotension, and even stopped in cases of severe bradycardia (see the ‘Safety concerns’ section). It also may be increased in cases of tachycardia.

Sample size calculation, statistics and allocation

Sample size calculation

The primary endpoint of this study is a composite endpoint defined by the occurrence of at least one of the four major opioid-related complications within 48 hours after cardiac surgery. The sample size was calculated with respect to Pearson’s χ^2 test at a one-sided 0.05 level, to compare the occurrence of complication between the two groups. In a recent French national survey, 50% of patients presented at least one complication among POCD, ileus or respiratory distress (data not published). In order to obtain 80% power for the difference given by the respective composite endpoint probabilities of 35% and 50% in the OFA and OBA arms, respectively, with one-sided type I error of 5% (reduction in complications of at least 30%), 134 patients will have to be included in each group, hence 268 patients overall. The unilateral characteristic of the test is justified by a previous retrospective study from Guinot *et al*, where OFA showed a reduction in postoperative outcomes. These data have been recently confirmed by another cohort study from the same authors.^{32 33}

Statistics

The main analysis will be carried out on all randomised patients according to the treatment group drawn at random (intention-to-treat principle).

Patient characteristics will be described using standard parameters: mean, SD, median, IQR and extreme values for quantitative variables and frequencies and percentages for categorical variables.

The proportion of patients experiencing the main outcome and its 95% CI will be estimated in each group and compared by means of Pearson’s χ^2 test.

This analysis will be complemented by a comparison using the logistic regression model with the main outcome (patients meeting the primary endpoint within 48 hours after cardiac surgery) as the response and the treatment group (OFA or OBA) and potential factors associated with the response as explanatory variables such as age,

body mass index, Euroscore 2, type of surgery (CABG or combined surgery) and duration of CPB.

The same general approach as outlined above will be used to compare the secondary qualitative outcomes (nausea–vomiting, pain, arrhythmia, shock, relative adrenal insufficiency, acute kidney injury, mortality) and Student's t-test will be used to compare quantitative parameters (length of stay).

No interim analysis will be performed.

Since this is an intention-to-treat analysis, in cases of missing value for the primary endpoint, imputation will be used according to the maximal bias assumption for incomplete observations. Namely, patients will be considered to experience the main outcome in the OFA group, and conversely in the OBA group.

All statistical tests are two sided, with a two-sided 0.05 level required for statistical significance.

Allocation and blinding

Patients who give written informed consent to participate in the study will be randomly assigned to the control (OBA) and experimental (OFA) groups. Inclusion and randomisation will be performed using the Ennov Clinical trial online software (Ennov, France), and a unique and anonymous number will be attributed to each patient. Randomisation will be stratified by centre in a 1:1 ratio using balanced blocks. All data will be collected and anonymised in an electronic case report form on the Ennov Clinical trial platform by a dedicated clinical research technician. Data will be monitored by a clinical research assistant in the presence of the clinical research technician and the main investigator of the site. Data will be stored for 15 years after the end of the trial in a dedicated secure server by the Clinical Research Department of the Rouen University Hospital.

Patients will be blinded to the allocated group and a 50 mL vial of 0.9% NaCl will be administered before induction of anaesthesia in the OBA group to reinforce the blindness. The anaesthesia team will not be blinded to the allocation, but the postoperative care team in ICU will be blinded.

Safety concerns

In accordance with French regulations, every serious adverse event related to the investigational medicinal products or not, expected or unexpected, will be immediately reported to the sponsor (Clinical Research Department of the Rouen University Hospital) by the investigator, with the exception of those that are identified as not requiring immediate reporting in the protocol. A serious adverse event is defined as one that results in death, is life threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, causes significant disability or prolonged incapacity, is a congenital anomaly or birth defect or is a medical event. The investigator will have to complete a 'serious adverse event' form on which will be indicated the date of onset, criterion of seriousness,

intensity, treatment dates, causality relationship with the investigational medicinal products and the outcome. The period in which serious adverse events should be reported begins from the date of the authorisation of the study until 48 hours after the end of the anaesthetic of the patient included in the study or without a time limit if it is possibly related to the investigational medicinal product and/or to the clinical trial.

As mentioned in the protocol, the following events will not require immediate reporting: complications associated with cardiac surgery and unrelated to investigational medicinal products will not require immediate reporting but will be collected in the case report form.

Moreover, in order to avoid collection duplication in the case report form, the events POI, acute respiratory failure and POCD will be recorded as the primary endpoint in the case report form but not reported on the 'adverse event' page. In the same way, nausea and vomiting and bradycardia will be recorded as secondary endpoints in the case report form, with the exception of bradycardia meeting one of the following definitions, which will be reported on the adverse event page and subject to immediate reporting: (1) appearance of profound bradycardia in relation to investigational medicinal products (heart rate below 35 bpm lasting more than 120 s or below 40 bpm with haemodynamic repercussions) will be considered as a serious adverse event; (2) episodes of atropine-refractory bradycardia, defined as failure to normalise heart rate (heart rate greater than or equal to 50 bpm), despite at least two administrations of 1 mg atropine.

In the case of profound and severe bradycardia (heart rate below 40 bpm), if there is no response to two doses of 1 mg atropine, the treatment will be stopped prematurely, and an alternative anaesthetic technique used to ensure the surgical procedure.

In addition, serious adverse events will be submitted to the data and safety monitoring board (DSMB). The DSMB is independent of the trial investigators and will perform an ongoing review of safety parameters and overall study conduct.

This is justified in view of the study population at risk of mortality (independently of this trial), the off-label use of anaesthesia drugs in the OFA group and the high rate of complications associated with cardiac surgery. The DSMB will comprise three experts: an anaesthetist, a drug safety expert and a methodologist. The members will meet before the start of the trial, then on a regular basis (after 10% and half of the patients included, at the end of the study after the database lock), and if necessary, at any time at the sponsor's request in the case of a significant event. The DSMB will have to assess the benefit/risk ratio of the trial and to give recommendations on whether the study should be discontinued or not. All serious adverse events for which the investigator or the sponsor considers that a causal relationship with the investigational medicinal products can be reasonably considered will be considered as suspected serious adverse reactions (SARs). If they are unexpected, they are

qualified as being suspected unexpected SARs and will be notified in a report by the sponsor to EudraVigilance (European pharmacovigilance database) and to the local regulatory agency within the regulatory time periods for reporting: immediate reporting if seriousness criteria are death or life threatening, and reporting within 15 days for other seriousness criteria.

Patient and public involvement

None

ETHICS, DISSEMINATION AND DATA SHARING

The protocol has been approved by an ethics committee (*Comité de Protection des Personnes Ouest III—No 2020-002126-90* on 9 December 2020) and by the national agency for drugs and health product safety (9 March 2021). In case of substantial modification in the protocol and eligibility of patient outcomes, the protocol will be resubmitted to these institutions. After presentation of the protocol by an investigator, written consent is mandatory for inclusion in this trial, and patients will be able to withdraw their consent at any time by simple request. The information and consent form is presented in online supplemental file 2.

Data generated by this trial will not be publicly available but on reasonable request to the corresponding author (EB, emmanuel.besnier@chu-rouen.fr). In this case, data will be totally deidentified. Requesters should provide a structured and detailed protocol for the proposed study and the reasons for reusing data.

The preparation of manuscripts and presentations at congresses resulting from the Opioid Free Anaesthesia for Cardiac Surgery (OFACS) trial will be carried out by the coordinating investigator or under his authorisation and responsibility. The principal investigators of each site will be cited in the articles, in a position based on their participation in the inclusion process. Other investigators, as well as people who have actively participated in the trial, may be cited in the manuscript according to their actual participation, or in an annexed list of investigators. The methodologist/biostatistician will also be listed among the authors. All publications will follow the 2010 Consolidated Standards of Reporting Trials guidelines.³⁹

CONCLUSION AND PERSPECTIVES

To our knowledge, this is the first randomised, blinded trial designed to compare an OFA strategy versus an OBA strategy in cardiac surgery. The interest of OFAs for anaesthesiologists is rising. Nevertheless, the current level of evidence is low given the lack of randomised trials and regarding the recent publication of negative results of the Postoperative and Opioid Free Anaesthesia (POFA) study in non-cardiac surgery.⁴⁰ Given the particularity of cardiac surgery and the encouraging initial retrospective publications in this field, the results of this trial could thus

rigorously define the place of this strategy in the intraoperative management of cardiac surgery patients.

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Contributors EB contributed to the design of the trial, coordinated the project and wrote the draft. MDM, PS and OA-A are the principal investigators of the centre. CT is responsible for statistics and methodology, and contributed to the study design. FV is responsible for the coordination of the project. ND is responsible for drug distribution and contributed to the study design. SR is responsible for the safety concerns of the trial. EL and VS are coinvestigators of the centre.

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