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Trials

STUDY PROTOCOL

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TREOCAPA: prophylactic treatment of the ductus arteriosus in preterm infants by acetaminophen—statistical analysis plan for the randomized phase III group sequential trial

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Abstract

Background Persistent patency of the ductus arteriosus (PDA) has challenged neonatologists for more than 40 years. Controversies persist about the management of PDA in extremely preterm infants. PDA is associated with morbidities, but no therapeutic strategy has resulted in an improved neonatal outcome. Acetaminophen appears to be a promising alternative with possibly fewer adverse effects. The primary objective is to determine whether a prophylactic pharmacological intervention with acetaminophen may increase the survival without severe morbidity at postmenstrual age of 36 weeks.

Methods and analysis TREOCAPA phase III is a randomized, multicenter, double-blind, stratified, placebo-controlled superiority trial, two arms in a 1:1 ratio performed in 43 NICUs of 14 European countries, evaluating whether the intervention increases the survival without severe morbidity by 10%, from 50% in control arm to 60% in treatment arm, until the age of 36 postmenstrual weeks. To detect this difference, 794 patients were required using a group sequential design. Recruitment has been closed, with 803 patients enrolled. Patients eligible for inclusion are preterm infants with a gestational age between 23 and 28 weeks. In the acetaminophen group, 20 mg/kg loading dose within 12 h after birth, followed by 7.5 mg/kg quarter in die (QID) for 5 days, will be administered to the 27–28 weeks gestational age group, and 25 mg/kg loading dose then 10 mg/kg QID will be administered to the 23–26 weeks gestational age group. The severe morbidities include severe bronchopulmonary dysplasia (BPD grade 3) according to NIH consensus, necrotizing enterocolitis (NEC) of Bell's stage II or III, intraventricular hemorrhage (IVH) grade III–IV according to Papile classification, or cystic leukomalacia.

Discussion Whatever the results, the conclusions of this study should be informative for the neonatal scientific community. The results will either confirm the benefit of treatment in increasing survival without severe morbidity, or indicate a worsening of outcomes with prophylactic acetaminophen treatment, or show no difference in the primary outcome. In the latter case, ultrasonographic assessments of ductus arteriosus status on day 7 may help explain the absence of a difference. This could indicate that acetaminophen is ineffective in promoting ductal closure

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or that early closure of the ductus arteriosus is inconsequential if, despite more frequent closures, there is no associated improvement in outcomes.

Ethics and dissemination Ethical approval of the trial has been performed in each of the 14 countries after approval, at the European level, by the Voluntary Harmonization Procedure committee on 04/07/2020. Results will be disseminated through articles in peer-reviewed journals.

Trial registration European Clinical Trials Database: EudraCT Number: 2019–004297-26.

ClinicalTrials.gov: NCT04459117, registered on July 7, 2020.

Introduction

This paper describes the statistical analysis plan (SAP) version 2 for the main paper reporting results of ongoing TREOCAPA phase III trial on infants born between 23 and 28 weeks of gestation, according to guidelines for the content of SAP in clinical trials [1]. TREOCAPA (prophylactic TREatment Of the duCtus Arteriosus in Preterm infants by Acetaminophen) trial is a phase II/III European multicenter double-blind trial. It has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No. 777389. TREOCAPA trial is one of the three academic proof of viability studies of the conect4children project (https://conect4children.org/studies/), a pan-European clinical trial network itself funded by the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No. 777389. The phase II was a dose finding trial, and it aimed to assess the minimum effective dose regimen of acetaminophen for the closure of PDA for preterm born before 27 weeks of gestational age. The results have been published [2], and this dosage regimen is given in the present phase III trial to infants born between weeks 23 and 26.

This paper details the analysis principles according to Version 10 of the protocol (05/09/2023), definitions of outcomes, methods for primary analysis, definitions of population, pre-specified subgroup analysis, secondary analysis, sensitivity analysis, and safety analysis. Any deviations from this plan will be described and justified in the final report of the trial.

Background

Premature birth is a serious cause of infant and child morbidity and mortality [3–5]. Despite technological advances and efforts during the last 20 years, extremely premature infants are associated to a 15–30% mortality risk and, in survivors, at least 20–30% are at risk of morbidity. The World Health Organization acknowledges the urgency of improving preterm neonates' outcomes but it remains a challenging task [6]. A relatively uncomplicated course in the neonatal intensive care unit (NICU), for an extremely premature infant, results in a discharge date close to the prenatal estimated due date with a better prognosis [7]. For that, priority conditions requiring study in newborns have been declined and studies must be performed using innovative trial designs to select doses and assess efficacy most efficiently [8]. Early prophylactic treatment of the ductus arteriosus by acetaminophen could reduce mortality and morbidity [9]. It may reduce pulmonary overflow and avoid the reduction of cerebral and mesenteric flow, according to left to right shunt through the ductus, without exposing preterm newborns to drugs associated to severe secondary effects.

Uncertainty and controversy about management of patent ductus

In 2018, the management of the preterm patent ductus arteriosus (PDA) remained a conundrum [10]. There is still uncertainty and controversy about the significance, evaluation, and management of PDA in preterm infants [11] resulting in substantial heterogeneity in clinical practice in USA [12] and Europe [13, 14]. PDA could serve as risk factors or initiators of life-threatening diseases, such as cardiac failure, bronchopulmonary dysplasia (BPD), hypoxic-ischemic brain injuries, and necrotizing enterocolitis (NEC), all adversely affecting long-term outcomes. Moreover, hemodynamic assessment of the ductus combined with bedside neuromonitoring techniques improved our understanding of the role of the PDA in neurological injury [15]. Long-standing suboptimal cerebral oxygenation due to a patent ductus arteriosus is a risk factor for adverse neurodevelopmental outcomes [16]. Recently prolonged exposure to PDA might be associated with BPD and increased risk of pulmonary vascular disease in extremely preterm infants [17]. Moreover, in a national population-based cohort, early screening of PDA was associated with increase in survival without moderate to severe neurodevelopmental disabilities at 5 years [18]. Thus, it seems difficult to recommend an expectant management for PDA, even though it has recently been shown that such an approach is not inferior to early treatment by ibuprofen [19]. Actually no PDA management strategy has shown an increase of survival without morbidity in randomized trials [20].

Prophylactic or early targeted indomethacin or ibuprofen not recommended

Prophylactic treatment using indomethacin or ibuprofen may close the patent ductus before it becomes symptomatic is not recommended. Early cardio-echography targeted treatment reduced pulmonary hemorrhage but did not decrease other severe morbidities or mortality [21, 22]. Early treatment (≤72 h after birth) with ibuprofen for a large PDA did not modify the risk of death or moderate or severe bronchopulmonary dysplasia at 36 weeks of postmenstrual age in Baby-Oscar trial [23]. The BENEDUCTUS trial has shown that expectant management for PDA in extremely premature infants was non-inferior to early ibuprofen treatment with respect to necrotizing enterocolitis, bronchopulmonary dysplasia, or death at 36 weeks' postmenstrual age [19].

Acetaminophen to close the ductus arteriosus

A Cochrane meta-analysis including 24 studies evaluating more than 2000 infants [24] indicated that the success rate for acetaminophen to close a PDA was higher than that of placebo, and it was not significantly different from the corresponding effect of ibuprofen and indomethacin. Acetaminophen appears to have fewer adverse effects on the kidney, liver, and pulmonary vascular system. However, none of these studies addressed the potential effect of this intervention on survival or survival without associated morbidity.

Actually, in the ClinicalTrials.gov database, 27 studies about the effect of acetaminophen on PDA in very preterm infants are registered, including 12 studies that are recruiting or not yet recruiting. All of them are small, with a number of enrolled infants between 40 and 120, and the primary outcome has been the closure of the ductus. In six studies, acetaminophen is at least in some cases given within the first week of life. According to pharmacokinetic studies in term and preterm infants, acetaminophen appears safe, and it has been administered to small preterm infants shortly after birth [25]. There is little evidence of adverse consequences. However, the doses suggested in extreme preterm neonates to induce closure of the PDA are mostly higher than the doses used to treat pain, and theses doses have not yet been sufficiently evaluated regarding safety [26].

Hypotheses of the present study

The primary hypothesis is that a prophylactic pharmacological intervention with acetaminophen, a drug with allegedly few adverse effects and efficacious for closure of ductus arteriosus, may increase the survival without severe morbidity at postmenstrual age of 36 weeks in extremely preterm newborns. As secondary hypothesis, this trial aims at studying whether early administration of acetaminophen (i) increases the rate of closure of PDA at day 7, (ii) reduces the rate of back-up treatment of PDA (medical/surgical closure), and (iii) reduces the requirements of catecholamine, analgesic drugs, and parenteral nutrition during the first week of life.

Trial design

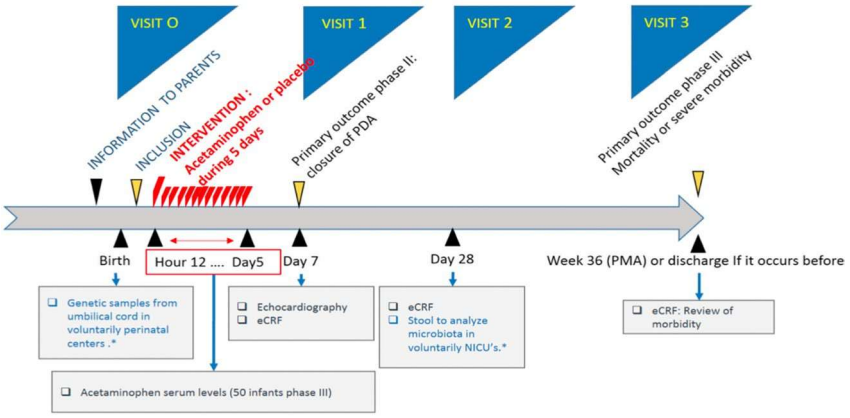
Design

Phase III is a randomized, multicenter, double-blind, stratified, placebo-controlled superiority trial, two arms in a 1:1 ratio, evaluating a difference of 10% of the percentage of survival without severe morbidity at 36 weeks of post menstrual age (from 50% in control arm to 60% in treatment arm) (Fig. 1). In the intervention arm, 20 mg/kg followed by 7.5 mg/kg quarter in die (QID) for 5 days is administered to the 27–28 weeks gestational age group. This dosage has been confirmed through PK/PD data analysis from the previous Finnish study [27]. As this study pointed out a lower effect of acetaminophen on extremely preterm neonates (below 27 weeks), a dose-finding study focusing specifically on extremely preterm neonates with treatment efficacy and toxicity was performed in phase II [2]. The minimum effective dose to close the ductus observed in phase II was 25 mg/kg loading dose then 10 mg/kg/6 h for 5 days in the 23–26 weeks gestational age group.

The TREOCAPA trial is registered with the European Clinical Trials Database (EudraCT Number: 2019–004297-26) and the registry sponsored by the United States National Library of Medicine Clinicaltrials.gov (NCT04459117, first posted on 07/07/2020).

Patient and public involvement

Patient and public representatives have been extensively involved in trial planning, grant/protocol writing, and preparing study materials. This trial has been developed in partnership with European representatives of parents of premature infants, European Foundation for the Care of Newborn Infants (EFCNI). This partnership began right at the start of the project, with the letter of intent submitted in response to the call to academic trials organized by conect4children. One central aspect of EFCNI's advocacy work is to advocate for all aspects important to patients and families. To ensure that they are well informed, considered, and supported throughout the whole trial, EFCNI coordinates and manages a Parent Advisory Board consisting of parent representatives who give input into the project based on their personal and professional expertise with preterm birth. EFCNI will be involved in dissemination of findings.



	STUDY PERIOD					
	Enrolment	**Allocation**	**Post-allocation**			**Close-out**
TIMEPOINT	***During the first 12 hours after birth***	**Before 13 hours after birth**	***H12-Day 5 after birth***	***day 7***	***Day 28 after birth***	***Post conceptional age of 36 weeks or Discharge if it occurs before***
	Visit 0	***Visit 0***		***Visit 1***	***Visit 2***	***Visit 3***
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Randomization		X				
Allocation		X				
INTERVENTIONS:						
Administration of IMP (20 doses)			X			
ASSESSMENTS:						
• *Baseline variables*	X	X				
• *Blood collected for AST/ALT analysis and Acetaminophen dosage for 50 preterm infants.*			X			
• *Clinical and treatment information*				From Day0 to Day7		
• *Cardiac echography*				Around Day 7 (Day 6-Day9)		
• *Optional Stool sample*					between Day 21 and Day28	
• *Mortality/ Morbidity (Primary outome)*					X	X

Fig. 1 SPIRIT figure of TREOCAPA trial phase III

Study setting

Patients are recruited from 43 neonatal intensive care units (NICUs) of 14 European countries: France, Switzerland, Finland, Estonia, Greece, Portugal, Denmark, Belgium, Sweden, Norway, Spain, Ireland, Italy, and Austria (Fig. 2).

Study participants

Inclusion criteria

Patients are eligible for inclusion if the following criteria are met: a gestational age between 23 and 28 weeks, a post-natal age of 12 h or less, and a writing of Parental or Legal Authority Consent. Furthermore, in some countries, parents are required to have a social security or health insurance.

Exclusion criteria

Exclusion criteria are as follows: presence of birth defect or congenital anomaly, detrimental twin-to-twin transfusion syndrome, suspicion of pulmonary hypoplasia, suspicion of hepatic impairment, i.e., hemorrhagic syndrome and/or severe hypoglycemia, clinical instability and high risk of acute death, failure to start treatment before 12 h of life, parents placed under judicial protection, participation in other clinical trial using acetaminophen during the first 5 days of life, indomethacin or ibuprofen during the first 3 days of life.

Randomization and data management

After checking of the inclusion and exclusion criteria entered by the investigator, a treatment number is assigned to the patient, respecting the blinding, the 1:1 randomization ratio, and stratification criteria previously defined (site, gestational age groups: 23–26 weeks and 27–28 weeks). Randomization within each stratum was performed using block randomization. Multiple birth infants are randomized independently. Data management is implemented according to Good Clinical Practice guidelines. Patient data are entered via an electronic case record form in a central web-based platform, the UPCET platform (Unité de Pharmacologie Clinique et Essais Thérapeutiques, www.upcet.fr) set up by Lyon 1 University, France. This platform has been certified by the European Clinical Research Infrastructure Network (https://ecrin.org) on September 2016.

Pharmacological intervention and blinding

Investigational medicinal product (IMP)

The active product is a 10-ml polyethylene ampoule of acetaminophen containing 100 mg of acetaminophen, solution for infusion, B BRAUN. The placebo product is a polyethylene ampoule of 10 ml of NaCl 0.9%, B BRAUN. Polyethylene ampoule of active and placebo products are with the same appearance, in accordance with Good Manufacturing Practices Drugs for Clinical Trials. The medicine supplier is Theradis Pharma, Cagnes sur mer, France, in charge of purchasing the products and of removing existing label as well as applying a new label and packaging the vials. Theradis Pharma has the certificate of Good Manufacturing Practice (GMP) compliance of a manufacturer and certificate of Good Distribution Practice compliance of a wholesale distributor. The labelling and the packaging are done in accordance with all applicable regulatory requirements and GMP Guidelines. The vials are secondary packed. Each kit contains 20 ampoules containing either acetaminophen

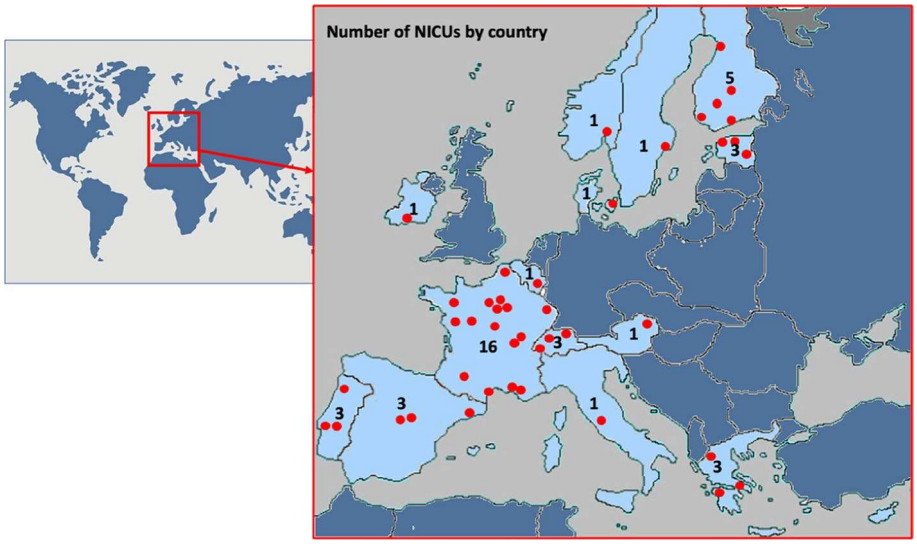


Fig. 2 TREOCAPA recruitment is performed in 43 neonatal intensive care units (red circle) of 14 European countries

or placebo. Each kit has a unique number according to the sealed randomization list for each of the two gestational age (24–26 weeks and 27–28 weeks) groups strata. After certification and batches' release, Theradis Pharma is in charge of the storage, distribution, and resupply to all IMP for TREOCAPA trial. So, trial participants, care providers, outcome assessors, and data analysts are blinded. If needed, Theradis Pharma is responsible of the batch recall and the destruction of the IMP.

IMP administration

The site should dispense the ampoule of IMP that corresponds to the number assigned at randomization. In the 27–28 weeks gestational age group, the dosage is 20 mg/kg loading dose within 12 h after birth followed by 7.5 mg/kg/6 h (± 15 min) during 5 days (total = 20 doses). In the 23–26 weeks gestational age group, the dosage is 25 mg/kg loading dose then 10 mg/kg/6 h for 5 days corresponding to the minimum effective dose of acetaminophen to close the ductus arteriosus before or at day 7, defined in the phase II trial [1]. In all cases, the IMP is administered by infusion during 15 min, preferably via a dedicated line. To minimize the risk of excess sodium intake, we recommend using the minimum sodium content solution for dilution of IMP and washout of the iv. catheters with as low volume as possible (i.e., dextrose 5%, hypotonic sodium solution 0.45%). If a dose is missed or not delivered, the following dose is administered, with a minimum interval of 5 h 45 min between 2 doses. Use of acetaminophen (paracetamol) is prohibited during the first 5 days of life to treat pain and/or fever and during all the hospitalization as rescue treatment of ductus arteriosus.

The TREOCAPA trial is a pragmatic trial. The study drug has to be stopped if a rescue treatment is given or if investigator considers that it is necessary based on medical judgement or in case of suspicion of acetaminophen toxicity. It may be necessary to unblind the allocation for a clinical reason in an emergency if it is the best interest of the participant; an unblinding procedure is available 24/7.

Timing of outcome assessments

In the phase III trial, three visits are planned after inclusion and randomization at day 0. During visit 1 at day 7 after birth, data describing baby care are recorded day by day from day 0 to day 7. At day 7, cardiac echography is performed. During visit 2 at day 28, a review of infant care between day 8 and day 28 is recorded. During visit 3 at 36 weeks of postmenstrual age or at first discharge home, whatever comes first, a review of morbidity—BPD, cerebral lesions, necrotizing enterocolitis, and retinopathy—is performed.

Primary outcome

The primary endpoint of phase III is the survival without severe morbidity at 36 weeks of post menstrual age or at first discharge home, whichever comes first. The severe morbidities include severe bronchopulmonary dysplasia (BPD grade 3) according to NIH consensus [28], necrotizing enterocolitis (NEC) of Bell's stage II or III [29], intraventricular hemorrhage (IVH) grade III–IV according to the Papile classification [30], or cystic leukomalacia observed at any time up to 36 weeks of post menstrual age. At 36 weeks of post menstrual age or at first discharge home, a review of morbidity (BPD, cerebral lesions, retinopathy, necrotizing enterocolitis) is performed at visit 3. BPD grade 3 is defined at a PMA of 36 weeks as invasive positive pressure ventilation or the need for nasal continuous positive airway pressure, noninvasive positive pressure ventilation, or nasal cannula ≥ 3 L/min with $FiO_2 \geq 30\%$ to maintain oxygen saturation (SpO_2) in the 90–95% range.

Secondary outcomes

Difference in secondary outcome between acetaminophen and placebo groups secondary outcomes will be explored. The secondary outcomes are as follows: number of infants with early pulmonary hemorrhage, analgesia/sedation drugs consumption during first week after birth, number of days during the first week the infants received sedation/analgesia treatment, number of days during the first week the infants received catecholamines in perfusion, volume of enteral nutrition during the first week, systemic arterial diastolic pressure during the first week, number of patients with a closed ductus arteriosus or a ductus flow with closing pattern assessed by echocardiography around day 7 after birth, number of the patients receiving back-up treatment of PDA, number of infants with retinopathy of stage 2 or more. The weight and head circumference gain was measured by change in z score between birth and 36 weeks of PMA (or discharge/death if sooner).

Sample size calculation

The trial employs a group sequential design featuring a total of three analyses, including two interim analyses and one final analysis, guided by O'Brien-Fleming boundaries to control the type I error rate. To achieve a power of 0.8 and maintain a type I error rate of 0.05 in a two-sided superiority test, 794 patients are required to detect a difference of 10% in the percentages of survival without severe morbidity at 36 weeks of post menstrual age in the two arms (the survival rate without severe morbidity, from 50% in control arm to 60% in treatment arm). The chosen difference of 10% between the two groups is justified by three published studies [14, 31,

32]. Overall mortality rate was 20.5%, while among the survivors, bronchopulmonary rate was 24%, and severe cerebral lesions rate was 8.5%. Consequently, the mortality rate was approximately 20%, accompanied by a morbidity rate of around 30% among the survivors. Furthermore, between the infants exposed to early screening of PDA and with no early PDA screening, a difference in mortality rate of 6.4% was evident in infants born at 24–26 weeks of gestation, and the rate was 2.7% in infants born at 27–28 weeks of gestation [14]. Therefore, we can expect an overall mortality rate difference of 4.55% [(6.4 + 2.7)/2]. Since acetaminophen has fewer adverse effects than indomethacin/ibuprofen, we assumed that both the mortality and the morbidity are reduced at similar rates. Thus, we predicted the mortality and morbidity rate would decrease by 11% [4.55 + (30/20) × 4.55]. Although a smaller difference could be clinically relevant, we chose a 10% difference to balance clinical significance with the feasibility of the study.

The strategy to reach this target of 794 inclusions is to maintain the attention of all investigators by mobilizing this pan-European network of pediatric clinical trials (our funder), organizing web conferences and regularly distributing newsletters (24 editions to date).

Interim analysis and stopping rules

In the present phase III trial, two interim analyses for the primary endpoint are planned when patient accrual reaches 397 and 595, respectively. At each analysis, the Z statistics (for a difference of binary endpoints) is computed, and it is compared to the O'Brien-Fleming thresholds, or to their approximation, using the Lan and DeMets alpha spending, in case of design modification: if its value exceeds the specific upper threshold or falls below the lower threshold at an interim analysis, the trial may be halted for demonstrated efficacy or futility, following consultation with the Data Safety Monitoring Board (DSMB). Otherwise, the trial will continue. For interpretability, the plots and the results are displayed on the maximum likelihood estimation scale. At the end, the adjusted p-value in case of early stopping will be computed.

A Bayesian sequential analysis is planned for safety endpoints when 198, 397, and 595 patients are recruited. It is an adaptation of the analysis proposed by Aupiais et al. [33] where an elicitation was conducted prior to the first interim analysis to model the accepted safety margin for each endpoint and establish the prior distributions. To achieve a weakly informative prior distribution, the elicitation results were used to specify a beta distribution with an effective sample size of 2 [34]. The safety analyses are done separately for each state group (23–26/27–28 week GA). The safety endpoints selected are the following: death; bronchopulmonary dysplasia at 36 weeks; necrotizing enterocolitis (Bell stage > 1) or focal intestinal perforation; intracranial abnormality (hemorrhage or focal white matter damage) on cranial ultrasound; pulmonary hemorrhage, retinopathy of prematurity.

Safety reporting

In our study, adverse events are defined as any unexpected medical occurrence in a patient or clinical trial participant including occurrences that are not necessarily caused by or related to that product. However, given the features and extreme fragility of the study population and to avoid drowning a possible signal in the midst of non-significant events, we did not consider as adverse event (AE) all usual signs or symptoms (including variation in laboratory parameters) reflecting the pre-existing condition of prematurity which are:

- Not associated with a seriousness criteria
- Not associated with an unusual nature, frequency or severity
- Not possibly related to the study treatment or study procedures

In addition, considering that disease-related events were already collected in the eCRF for primary and secondary endpoints analysis, the events listed below did not require an immediate reporting in a SAE form to the sponsor unless they were possibly related to IMP, resulted in death, or presented an atypical pattern:

- Sepsis (unless it is a bacille gram negative severe or sepsis following unusual germ)
- Chronic lung disease defined as long-term breathing problems or oxygen need after baby reaches an adjusted age of 36 weeks of gestation)
- Intracranial abnormality (hemorrhage or focal white matter damage) on cranial ultrasound scan or other imaging
- Pulmonary hemorrhage
- Patent ductus arteriosus
- Retinopathy requiring or not a treatment or surgery

On the other hand, some events, called "Notable event" and defined according to known toxicities of acetaminophen or safety signals, were closely monitored and required expedited reporting within 24 h of awareness to the sponsor. It includes:

- Severe liver failure, defined as elevated liver enzymes (ALT/glutamate-pyruvate transaminase and aspar-

tate aminotransferase/GOT) > 2 times the upper boundary of the normal range
- Hemorrhagic syndrome, which is when infant has bleeding to at least two organs (pulmonary, cerebral, digestive…) or has bleeding to one organ and at the puncture site
- Necrotizing enterocolitis which involves a variable extent of necrotic or perforated bowel, usually with extensive peritoneal contamination
- Focal intestinal perforation which involves a small, focal perforation with otherwise normal appearing intestine

At each formal interim analysis, the DSMB intends to employ the results of Bayesian analysis to assess the possibility of an earlier termination point for the trial, specifically for safety considerations.

Adherence and protocol deviations

During monitoring, 4 types of deviations are tracked in the monitoring tracker, concerning the following: patient safety, patient's rights, IMP management, and protocol non-compliance. Only non-corrected protocol deviations will be listed: no randomization, non-compliance with IMP administration schedules, use of acetaminophen as rescue treatment after unblinding procedure or not, echocardiography between day 5 and day 10 not performed, cerebral echography not performed before 36 weeks of post-menstrual age, no information about result of ophthalmological examination, AST and ALT post first IMP dose not collected.

Withdrawal from the trial

The number of withdrawals from the trial and the timing of each withdrawal will be reported. Data registered up to the date of withdrawal will be exploited, except for infants whose parents refuse the use of registered data.

Statistical analysis plan

Overall principles

Analyses will start once all data to discharge of the last included patient have been obtained (expected date July–August 2024); the database will be checked and locked after monitoring of all eCRF of all 43 NICUs in all 14 countries (expected date December 2024). The analyses will be performed by MU, CA, and JCR, using SAS version 9.4 or later and R version 4.1 or later.

Patient flow

The flow of participants through each stage of the trial will be summarized according CONSORT recommendations [35]. In this figure, will be indicated the number of preterm infants assessed for eligibility, the number of recruited infants, number of randomized infants, number of allocated to placebo or to acetaminophen groups, number of infant who did not receive allocated treatment with reasons and the number of infants with withdraw, and finally the number of infants included in the modified intention to treat analysis (Fig. 3).

Population definition

Intention to treat population

The intention to treat population will be all infants randomized, excluding infants whose parents requested withdrawal from the study before the 36-week PMA or hospital discharge or death, whichever comes first, or with a request not to use the data collected.

Per-protocol population

Per protocol population consists of all infants treated in accordance with the protocol, even those who did not receive the 20 doses of IMP, due to the administration of a rescue treatment in accordance with the protocol, with the exception of those whose rescue treatment was based on acetaminophen, not authorized by the protocol. As TREOCAPA trial is a pragmatic trial, the per-protocol population included preterm infants with a difference between previous and observed schedule of IMP administration was less than 2 h, because the previous PK analysis showed that the acetaminophen blood concentrations remain at an acceptable level even 8 h after the last injection.

Safety population

All infants randomized who received at least one dose of the IMP. Preterm infants will be analyzed according to the treatment they actually received.

Loss to follow-up

Minimal loss to follow-up is expected for the primary and secondary outcomes since these outcomes are recorded while the baby is in hospital.

Statistical analyses

Baseline characteristics

Baseline patient and clinical characteristics at randomization will be collected and presented in a table:

- Mother's baseline characteristics:
  - Country of birth
  - Age (years)
  - Socio-economic and educational characteristics
  - Number of previous births
  - Paracetamol consumption during pregnancy
  - Medical conditions of pregnancy

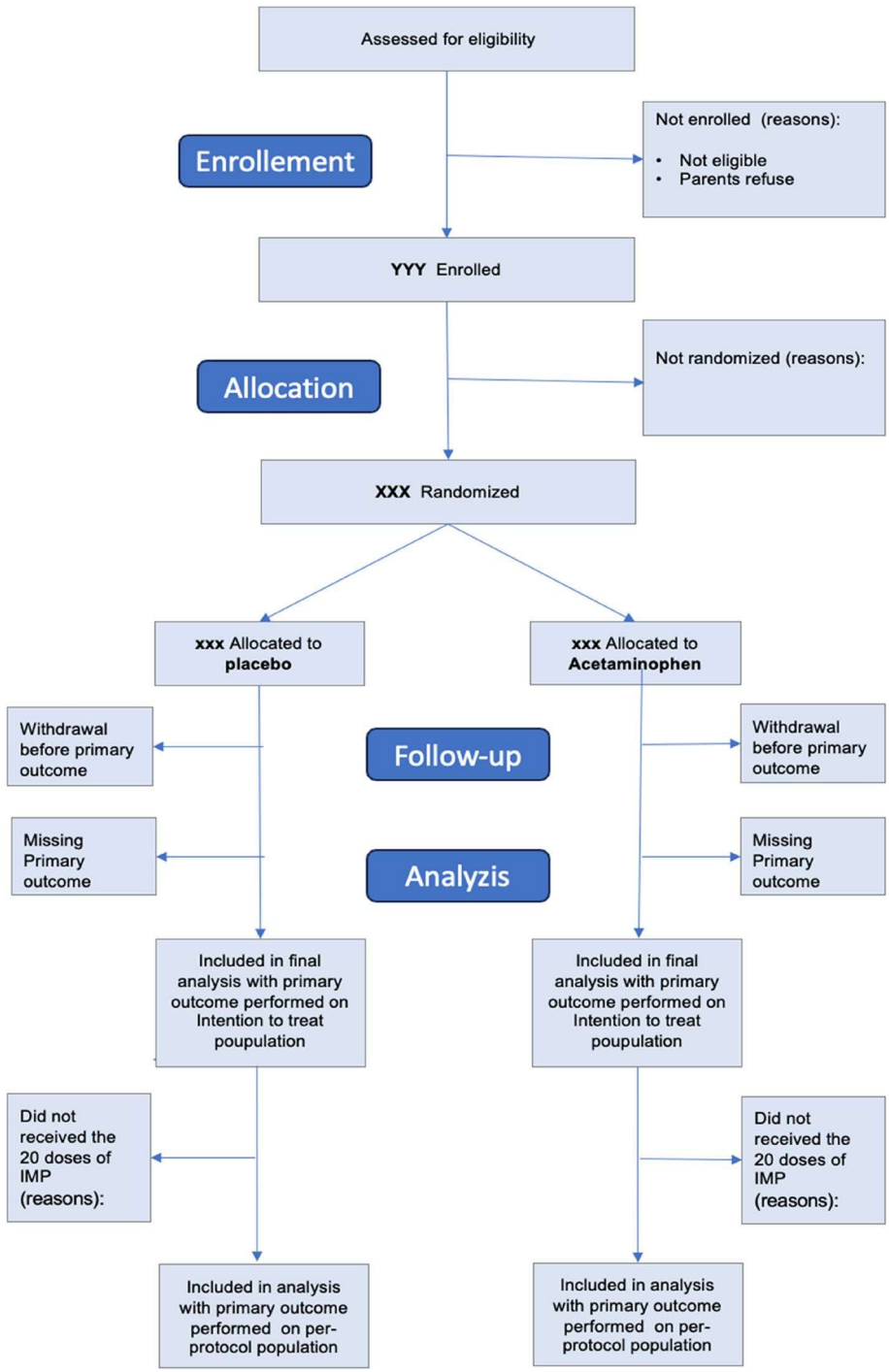


Fig. 3 Flow chart according to CONSORT

- Transfer of the mother
- Antenatal steroid use
- Antenatal magnesium sulfate use
- Type of prematurity (spontaneous/consented)
- Mode of onset of labor
- Mode of delivery
- Indication of cesarean if cesarean

- Infant's characteristics at trial entry

- Gestational age at birth (weeks)
- Birth weight (g) and Birth weight *z* score according to Olsen curves [36]
- Gender
- APGAR score 1 and 5 min
- Umbilical cord gases
- Mode of resuscitation
- Surfactant and mode of administration
- Ventilation and FiO_2
- Minimal base excess during the first 12 h
- Born in enrolling center
- Modality of transfer
- Echocardiography before inclusion
- Postnatal age at randomization (hours)
- Head circumference (cm) and head circumference *z* score according to Olsen curves

Continuous variables will be presented as mean and standard deviation if normally distributed and as medians and interquartile range if not normally distributed. Categorical variables will be presented as frequencies and percentage. A difference with a $p < 0.05$ is set as statistically significant.

Primary outcome analyses

The absolute risk difference of the primary outcome between the acetaminophen group and the placebo group will be calculated. The main analysis will be performed on ITT population, according to the group sequential analysis, and adjusted 95% confidence interval will be provided. Due to randomization, differences in baseline characteristics are unlikely. In case of an unexpected imbalance in baseline characteristics, corrections will be considered and reported as sensitivity analyses. For clarity and interpretability, the risk ratio will also be reported alongside the confidence interval.

Secondary outcome analyses

Secondary outcomes will be presented in tables with counts, percentages, and absolute risk differences with 95% confidence intervals for categorical outcome between treatment group or with means, standard deviations, and the estimated difference means between the two treatment groups with 95% confidence intervals. No formal adjustments or multiple comparisons will be made. In case of an unexpected imbalance in baseline characteristics, correction will be considered. SAP of the secondary outcome analyses, if necessary, includes similar adjustments described for the primary outcome analyses.

Subgroup analyses of primary outcome

We will perform pre-specified exploratory subgroup analyses for the primary outcome, using the following five approaches, each examining one subgroup: gestational age groups 23–26 weeks, 27–28 weeks, male gender, female gender, and among French recruitment corresponding to more than 50% of the recruitment. Moreover, we will present analyses for the primary outcome for infants born 23–24 weeks of gestation and then for each subsequent week. Finally, we will present analyses for the primary outcome for infants according to antenatal acetaminophen exposure.

Sensitivity analyses

Per-protocol analyses concerning primary and secondary outcomes will be performed. Moreover, an intention to treat analysis will be performed using a modified primary outcome: surviving without moderate or severe BPD grade 2 or grade 3 according to NIH consensus, NEC of Bell's stage II or III, IVH grade III–IV according to the Papile classification or cystic leukomalacia observed at any time up to 36 weeks of post menstrual age, and retinopathy of grade 2 or more. For BPD grade 2, a test of stop oxygen and non-invasive support is proposed, according to Walsh [37], if the preterm infant received less than 30% of oxygen and he can support the challenge. If the arterial saturation in oxygen during the challenge is < 90% or the infant is considered as not supporting the challenge, the infants is classed as BPD grade 2.

Moreover, the primary analyses will be repeated and correlation between siblings among multiple births will be accounted for using the generalized estimating equations as well as the influence of gender and gestational age [38]. We will perform survival analyses for relevant outcomes separately, when feasible.

Missing data

Missing data as a result of babies being lost to follow-up is expected to be minimal for short-term outcomes. Nevertheless, if necessary, we will carry out analyses with imputations.

Safety data analysis

All serious adverse events (SAEs) reported from the time of randomization until 30 days after the last visit, all notable events from the time of randomization until 30 days after the last visit, and all disease-related events (DREs) from the time of randomization until the last visit of the participant will be reported. These analyses will be performed on the intention-to-treat population.

For example, the following serious adverse events (SAEs), not included in the primary and secondary outcome, will be listed by treatment group allocation in a table.

- Thrombocytopenia, *n* (%)
- Pulmonary hemorrhage at any age, *n* (%)
- Pulmonary hypertension requiring treatment with pulmonary vasodilator, *n* (%)
- Renal failure, *n* (%)
- Isolated gastrointestinal perforation, *n* (%)
- Late-onset sepsis, *n* (%)
- Severe sepsis, *n* (%)
- Hypotension treated with inotropes, *n* (%)
- Multiple organ failure
- Anemia requiring transfusion
- AST/ALT level after dose 1 of acetaminophen more than 2 times the normal value
- *n* increase by 2 times of AST/ALT between the first AST/ALT level, measured after first dose of acetaminophen, and the second AST/ALT level, measured after the dose 10 of acetaminophen
- Hepatic impairment is suspected in case of hemorrhage syndrome
- In case of jaundice, a level of the ratio conjugated bilirubin/total bilirubin, higher than 20%, is predictive of cholestasis

In addition, a general table with safety data will be provided describing the number of events by maximum severity grade and the number and percentage of patients who experienced at least one event of a specific grade.

Each SAE, notable events, and DRE will be summarized with the number and percentage of patients with at least one of these events and the total number of events. The events will be presented by treatment arm.

Deviation from the analysis described in the protocol

Initially, 2 interim analyses for efficacity were planned, at 50% (397 infants) and 75% (595 infants) of expected final number of inclusions. The first analysis has been performed and presented to DSMB. But the TREOCAPA TEAM decided not to carry out this second interim analysis for efficacity, as it could only be performed in January 2024, after the 595th child having been included in August 2023 with a last visit in November 2023 and a monitoring in December 2023. However, by January 2024, 729 children had been included, leaving just 65 to be included over 3 months. This also saved study power.

Further sub-studies

One study will compare microbiota at day 28 between the 2 treatment allocation groups. Our hypothesis is that the reduction of left to right shunt by ductus in the acetaminophen exposed group will contribute to an easier implementation of enteral nutrition and to the implementation of a "more mature" microbiota. Microbiota during week 4 should be a biomarker of an effect of acetaminophen on the digestive tract. This biomarker was closely associated 2 year-outcome in previous study [39].

The second concerns the interaction between variation of practices and PDA. Large variation of practices between the 43 NICUs of 14 countries is attended, as observed at the national level [39] and European level [40]. We will analyze the interaction between practices and the intervention (paracetamol or placebo on primary and secondary outcomes).

The third will aim to define the minimum values of mean and diastolic arterial blood pressure associated with survival without severe morbidity at a PMA of 36 weeks. In this perspective, the values recorded daily in the two groups from day 0 to day 7 will be classified according to the primary outcome, allowing to develop linear regressions of means and 95% confidence intervals in this population during the first postnatal week.

Finally, the ancillary study on genetic polymorphisms will not be able to take place for lack of a sufficient number of cord blood samples.

Ethics

The study will be conducted according to the principles of the Declaration of Helsinki in respect of the legislation of the 14 European participating countries. The TREOCAPA trial protocol has been approved first on 04/07/2020 at the European level by the Voluntary Harmonization Procedure committee and then after by the competent authorities and ethical committee of each participating country in accordance with each national legislation. These two approvements, ethic committee and competent authorities, were obtained in France by April 17, 2020, Ireland by June 5, 2020, Estonia by July 9, 2020, Portugal by July 28, 2020, Finland by September 2, 2020, Denmark by September 8, 2020, Switzerland by September 17, 2020, Belgium by September 30, 2020, Sweden by October 12, 2020, Spain by December 17, 2020, Norway by December 21, 2020, Italy by March 2, 2021, Greece by November 18, 2021, and Austria by March 14, 2022. Important approved modifications are communicated by written communication to the investigators by the sponsor to inform them about the important changes in the trials. The processing of personal data of participants suitable for this research is for the sole purpose of

carrying out the research. All data related to the study are captured and saved in a computerized database under the supervision of the sponsor: data collection is done via Internet on an eCRF developed specifically for the study using a specific clinical trial management. The data are collected in a centralized database, managed by a professional specialized in database management, General Data Protection Regulation (GDPR) compliance, physical and logical security measures, flow diagram, backups, and archiving. A personal and confidential identifier allows access to the eCRF. The investigator is aware that all study documents and data related to the research could be subject to audit and inspection carried out with respect for professional secrecy, medical confidentiality may not be invoked to prohibit access to these documents. The investigator is aware that study results are the property of INSERM, the study sponsor. Access to data relating to participants is strictly confidential and not accessible in accordance with the GDPR in force in the European Union. The sponsor has taken out an insurance contract of civil responsibility which provides for a certain amount per participant to compensate them if necessary. None of the investigators has financial or other competing interests.

Trial design

An independent Data Safety Monitoring Committee (DSMB), including experienced neonatologists, a pharmacologist, and a statistician, help the Trial sponsor and investigators to make decisions during the trial for which independent judgment is desirable (additional amendment to the protocol or statistical analysis plan, opinion on premature stoppage of the trial), monitor the phase II and phase III on safety aspects, and will provide recommendations regarding continuing or stopping the trial after interim analysis. If the DSMB recommends modification or cessation of the study protocol, this will be discussed with the trial steering committee, who will make the decision. Each DSMB member have signed a confidentiality and conflict of interest agreement. The trial steering committee includes European experienced neonatologists who supervise the progress of the trial. Each month, information about the evolution of the trial is reported to the Network Infrastructure Office of conect4children.

Moreover, the sponsor has contracted an external auditor to audit the studies promoted by the sponsor at the sponsor's request.

Trial status

The first participant of phase III was recruited up in October 2020. Last patient last visit was initially planned for May 2023. But, due to the delay at the start of the project, in the context of the covid crisis, an extension of the inclusion period to April 2024 was accepted as part of the final amendment. The last patient last visit was performed on June 7, 2024. The end of final monitoring is planned for the end of December 2024. Recruitment status can be accessed at https://treocapa.inserm.fr/.

Trial reporting

The trial will be reported according to the principles of the CONSORT statement [35]. Analysis of the primary and secondary outcomes will be conducted after follow-up to discharge has been completed for the last baby to be discharged. The study results will be submitted for publication in a peer-reviewed journal and presented at international conferences. The participation of professional editors is not envisaged. A plan to disseminate the results to the parents who took part in the trial and to the general public is being drawn up in partnership with EFCNI.

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Declarations

Competing interests
The authors declare no competing interests.

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