

Study code: TIP-15-01

**Efficacy and safety of Dexmedetomidine**  
**during analgesic and sedative drugs weaning**  
**in Pediatric Intensive Care Unit**

Multicenter, Randomized, Double-Blind, Placebo-Controlled, Spontaneous  
Clinical Trial

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## PROTOCOL SIGNATURE PAGE

**Study code: *TIP-15-01***

The study protocol was developed according to the Guidelines of Good Clinical Practice and in accordance with the Helsinki Declaration.

I state that I will conduct the Trial according to all the above requirements.

18/09/2016

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**ACRONYMS and ABBREVIATIONS**

AE	Adverse Event
AR	Adverse Reaction
CRF	Case Report Form
GCP	Good Clinical Practice
HR	Heart rate
MBP	Mean Blood Pressure
PICU	Pediatric Intensive Care Unit
PIM3	Paediatric Index of Mortality 3
PMA	Postmenstrual age
SBP/DBP	Systolic Blood Pressure/Diastolic Blood Pressure
SOS	Sophia Observational withdrawal Symptoms-scale
SPC	Summary of Product Characteristics
WAT-1	Withdrawal Assessment Tool-Version 1

## 1. Background

Children admitted to the Pediatric Intensive Care Unit (PICU) often need of analgosedation as an essential part of their treatment. However, exposure to analgosedation drugs can lead to undesirable effects like dependence, tolerance and withdrawal syndrome <sup>1,2</sup>.

The withdrawal syndrome may occur during the drug weaning process in patients that have developed dependence to both opioids and benzodiazepines. Withdrawal symptoms are due to central nervous system excitement, gastrointestinal disturbance, and sympathetic system activation. The resulting tremors, agitation, sleeplessness, inconsolable crying, sweating, yawning, sneezing, diarrhea, vomiting, that are among the most frequent signs, affect patients with intense suffering, increased morbidity and lengthen PICU stay <sup>3</sup>. Recently, two pediatric assessment tools have been validated to evaluate the degree of severity of the withdrawal: the withdrawal assessment tool version 1 (WAT-1) <sup>4</sup>, and the Sophia Observational withdrawal Symptoms-scale (SOS) <sup>5</sup>.

The cumulative dose and length of treatment are predictive risk factors for withdrawal as well as the overly rapid reduction or abrupt withholding of analgosedation drugs <sup>6</sup>.

Therefore, withdrawal syndrome prevention strategies are addressed both to the restriction of drug exposure (dose and length) and to the gradual tapering of infusion. However, these strategies have weak evidence of effectiveness, clinical signs of abstinence frequently occur requiring targeted treatment. To simplify weaning management, the drug switch is also proposed: the drug has changed with one of the same pharmacological class with a longer half-life, at an equipotent dose. Although at present no drug seems to have more advantage than another, methadone is the most commonly prescribed one <sup>7</sup>. Sometimes, in very critical children admitted to PICU, the most appropriate level of analgosedation is more challenging to achieve. Increase the dosage or replace the drug with a more potency one or even add adjuvants cannot always reach the goal while it may instead increase the risk of highest cumulative doses. From the literature data, the incidence of withdrawal syndrome in PICU is variable between 17 and 57%. In a multicenter study conducted at Italian PICUs, in the

process of being published, this incidence reaches 64.6% in patients undergoing five days or more of treatment.

In this study, we hypothesize that dexmedetomidine may be useful and effective during the weaning of analgesedation drugs in PICU, in preventing the withdrawal syndrome<sup>8,9</sup>. Dexmedetomidine is a selective  $\alpha_2$ -receptor agonist. The binding to the receptors at the locus ceruleus level, blocking the release of noradrenaline inducing the sedative and anxiolytic effects. The analgesic effects come from the inhibition of the release of the substance P at the dorsal horns level of the spinal cord<sup>10,11,12</sup>. The most common side effects are hypotension and bradycardia, due to sympatholytic action<sup>13</sup>. The dexmedetomidine used as adjuvant improves patient comfort and may contribute to containing the cumulative dose of sedative and analgesic drugs<sup>14</sup>.

The possible cellular mechanisms of dexmedetomidine withdrawal-preventing effect may be, at least partly, related to the interaction among G protein-coupled receptors (GPCRs); both the adrenergic receptors and the opioid receptors, belong to this large family, as well as dopaminergic, serotonergic, and others again<sup>1</sup>. Up to now the off-label drug condition of the dexmedetomidine in pediatrics has limited the clinical research to retrospective observational studies or case series. Additional studies have been advocated to better define the role of dexmedetomidine in PICU, particularly in the management of weaning from analgesic and sedative drugs.

## **2. Trial Objectives**

### **Primary objective:**

To evaluate the efficacy of dexmedetomidine in reducing the occurrence of the withdrawal syndrome during the weaning of analgesic and sedative drugs.

### **Secondary objectives:**

1. To evaluate the safety of dexmedetomidine during the weaning of analgesic and sedative drugs.

2. To evaluate the efficacy of dexmedetomidine in reducing the duration (days) of the weaning of analgesic and sedative drugs.
3. To evaluate the efficacy of dexmedetomidine in reducing the duration (days) of mechanical ventilation.
4. To evaluate the efficacy of dexmedetomidine in reducing the PICU length of stay (days).
5. To compare the efficacy of dexmedetomidine among pediatric age groups, gender, race, Pediatric Index of Mortality (PIM3) score, and length of the analgosedation treatment.
6. To evaluate the effective dose range of dexmedetomidine in reducing the occurrence of the withdrawal syndrome.

### **3. Study plan**

An outline of the trial plan is given in the protocol flow chart.

#### **3.1. Study design**

Multicenter, randomized, double blind, placebo-controlled, spontaneous clinical trial.

#### **3.2. Study population**

The study population will include patients admitted to the PICU that meets the inclusion criteria:

##### **Inclusion Criteria**

- Continuous analgesic and sedative endovenous treatment for at least five days
- Invasive or non-invasive mechanical ventilation
- Clinical conditions that allow by clinical judgment the start of analgosedation weaning
- Age between 0 to 18 years
- Post-natal age  $\geq 7$  days and PMA beyond the 37 weeks

*Count of the PMA = gestational age at birth + age in number of weeks since birth*



- Written informed consent obtained

*For the childbearing girls (at least one menstrual cycle) the beta HCG test is scheduled and enrollment is subject to the negative result of the test*

**Exclusion Criteria**

- Hemodynamic instability
- Inotropic or antihypertensive treatments ( $\beta$ -blockers, calcium antagonists, ACE inhibitors, digoxin, nicardipine, nitroglycerin)
- Cardiac bundle-branch block of 2 or 3 degree
- Hypersensitivity to the alpha-agonists
- Persistent fever of unknown origin or sensitivity to malignant hyperthermia
- Use of alpha-agonist (clonidine or dexmedetomidine) in the last 30 days

**3.3. Assignment to treatment**

An identification code will individually assigned to each enrolled patient. The code cannot longer be re-used even if the patient for any reason interrupts the study.

Each patient will be randomly assigned to one of the two treatment groups:

- Treatment A: dexmedetomidine
- Treatment B: placebo (physiological saline solution)

The Investigational Drug Service (IDS) of the Coordinating Center generated a single randomization list for all the centers. This confidential document will be only available to the not blinded staff involved. The concealment of the randomization list implies that the allocation sequence is unknown by the blinded researchers, included the promoter of the study. The non-blind staff of each center one will carry out the preparation of the experimental drug.

### 3.4. Treatments

Twenty-four hours before the start of the weaning from analgosedation treatment, intravenous infusion of dexmedetomidine/placebo will start according to the below schedule.

The start dose is 0.4 mcg/kg/h, without a loading dose. The dose will increase, if well tolerated, of 0.2 mcg/kg per hour, until it reaches 0.8 mcg/kg/h. Given the pharmacological differences<sup>15</sup>, the start dose in newborn is 0.2mcg / kg / h without the loading dose, the hourly increase is 0.1mcg / Kg / h up to 0.4mcg / Kg / h.

After 24 hours of dexmedetomidine infusion, the weaning regimen will begin following the subsequent indications:

- 10% reduction of the dose every 12 hours

The Protocol allows the switch of opioids and/or benzodiazepines to an equipotent dose of drugs of the same pharmacological class with a longer half-life. The scheme of conversion refers to the National recommendations for analgosedation in PICU (<http://www.sarnepi.it/wp-content/uploads/2012/05/linee-guida-ANALG-SED-baroncini-2012-.pdf>). The optional switch to enteral drugs (methadone, morphine, lorazepam) may facilitate patient's management even without venous access. Enteral drugs, in the same way as iv drugs, are subsequently reduced by 10% every 12 hours.

The dose of 0.8 mcg/Kg/h (0.4 mcg/Kg/h for the neonate) of dexmedetomidine/placebo does not change unless the WAT-1 score detects symptoms of withdrawal (see 3.5.); in this case the dose will be increased. Every single increase equal to 0.2 mcg/Kg/h (0.1 mcg/Kg/h for the neonate) is kept unchanged until the next WAT-1 measurement (see details in WAT-1 score). The dose of dexmedetomidine/placebo, titrated to the needs, can be increased to a maximum of 1.4 mcg/Kg/h.

#### 'Acute Withdrawal Crisis'

If the patient shows clinically significant iatrogenic withdrawal:

- Clinician administers a rescue dose of the opioid and/or benzodiazepine in use, repeatable until resolution of the crisis (see diagram below)

<b>Drug</b>	<b>Rescue Dose (iv)</b>
Methadone	0,05 – 0,1 mg/Kg
Morphine	0,05 -0,1 mg/Kg
Fentanyl	0,5 – 2 mcg/kg
Midazolam	0,05 – 0,2 mg/Kg

- Clinician evaluates a temporary suspension of the weaning regimen (see details in WAT-1 score).

Once analgesics and sedatives weaning is complete, dexmedetomidine will discontinue. A gradual reduction of the dexmedetomidine dose is strongly recommended to prevent the documented risk of dexmedetomidine withdrawal<sup>16,17</sup>. Since dexmedetomidine weaning is not a specific analysis topic in this study no specific protocol need to be followed.

### **Treatment Interruption**

The study can be interrupted at any time in case of:

- drug sensitivity
- intolerance
- hemodynamic instability (see safety assessment)
- changes in therapeutic needs
- withdrawal of consent

### **Adherence to the Treatment**

Since study treatment consists of an intravenous drug administration in patients admitted to PICU, the clinician investigator assumes the responsibility of adherence to the treatment.

### **3.5. Evaluations and visits**

For each enrolled patient, continuous observation time varies from a minimum of 5 days to a maximum of 7 days.

The indicated daily dose reduction allows the completion of analgosedation weaning in 5 days. If, as hypothesized, dexmedetomidine is effective in reducing the occurrence of withdrawal its administration will allow the perfect adherence to this regime. In case of extended weaning, further 48-hour of observation (7 days) will allow to evaluate the clinical trend.

### **WAT-1 Assessment Tool**

The Withdrawal Assessment Tool Version 1 (WAT-1) was chosen for the following reasons:

- it is validated in the pediatric age
- it is reliable and has shown high sensitivity (0.87) and specificity (0.88)
- it is easy and quick to use

The Italian version of WAT-1 scale will be administered every 12 hours from the start of weaning.

The score ranges from 0 to 12. A WAT-1 score  $<3$  indicates no withdrawal symptoms. A score  $\geq 3$  indicates the presence of signs/symptoms of withdrawal. The severity of withdrawal is grading from mild to severe, proportionally to the value of the score.

### **WAT-1 score**

Patients with a score of WAT-1  $<3$  continue the weaning regimen.

Patients with a score  $\geq 3$  increase the dose of dexmedetomidine / placebo of 0.2 mcg / kg / h (neonates 0.1 mcg/Kg/h) until the subsequent WAT-1 score control and temporarily stop the planned 10% dose reduction.

If the next WAT-1 score decreased by at least 1 point from the previous score, the weaning program restarted (10% reduction) without further changes in the dose of dexmedetomidine / placebo until the subsequent score.

The 'acute withdrawal crisis' will be treated as previously indicated.

### **Follow-up Visit**

Five days after discharge from PICU, a follow-up visit will be performed.

The following data are collected during the visit:

- duration (days) of the analgosedation weaning when longer than 5 days
- WAT-1 scores until 72 hours after the stop of the analgesics and sedatives
- dexmedetomidine weaning (% of daily reduction)
- duration (hours) of dexmedetomidine weaning
- occurrence of dexmedetomidine withdrawal
- signs/symptoms of dexmedetomidine withdrawal
- WAT-1 scores until 72 hours after dexmedetomidine stop

### **3.6. Assessment of the Efficacy**

The assessment of the efficacy of dexmedetomidine in reducing the occurrence of the withdrawal syndrome results from the evaluation of the following variables:

- WAT-1 score  $<3$  is recorded more frequently in the dexmedetomidine group compared to the placebo group.
- in the case of a WAT-1 score  $\geq 3$ , after the increase of dexmedetomidine /placebo, a reduction of 1 or more points at the next score is recorded more frequently in the dexmedetomidine group compared to the placebo group.
- number of rescue doses is lower in the dexmedetomidine group compared to the placebo group.
- number of temporary stop of drug dose reduction is lower in the dexmedetomidine group compared to the placebo group.

### **3.7. Assessment of the Safety**

In the dexmedetomidine Summary of Product Characteristics (SPC) the most frequently reported Adverse Reactions are hypotension, hypertension, and bradycardia. Patients enrolled in the study are admitted to the Pediatric Intensive Care Unit, as part of routine care they are usually continuously monitored and vital parameters as cardiac frequency, blood pressure, oxygen saturation, respiration rate, body temperature and glycemia are regularly recorded.

For the purposes of the study changes in heart rate and blood pressure will be recorded when their value differs more than 20% by the patient's baseline values.

All Adverse Reactions listed in the SPC (hyperglycemia, hypoglycemia, metabolic acidosis, hypoalbuminemia, dyspnea, hypothermia, hyperthermia) will be carefully monitored and reported.

Adverse Reactions (AR) are all those adverse events for which there is reasonable suspicion that a causal relationship may exist with the investigational medicinal product in the opinion of the investigators or of the clinical trial promoter.

Safety will also be assessed through monitoring and recording in the appropriate CRF of Adverse Events, Serious Adverse Events and Suspected Unexpected Serious Adverse Reactions (SUSARs).

An Adverse Event (AE) is any sign, symptom, damaging reaction or undesirable clinical condition occurring after the start of the experimental treatment, during any phase of the study, AE does not entail a causal relationship with the study drug.

Investigators are responsible for the collection and notification of all adverse events and adverse reactions to the Promoter.

The Promoter will evaluate the severity of the event, the causal relationship between the experimental medicinal product and the event considered, and whether the event is expected or not expected with respect to the information contained in the SPC of the product.

### **Evaluation of severity**

An adverse event or an adverse reaction is **serious** when it meets one or more of the following criteria:

- it is fatal;
- it is life-threatening;
- it lengthens hospital stay;
- it entails important and persistent disability, although not necessarily permanent;

- it requires medical or surgical intervention.

**Evaluation of causality**

The assessment of causality aims to establish whether there is a reasonable possibility that the experimental product has caused or contributed to an event.

In particular, the Promoter will have to define whether the event is related to the investigational medicinal product:

- unrelated
- probably unrelated
- possibly related
- probably related.

**Suspected Unexpected Serious Adverse Reactions (SUSARs)**

It is defined as Suspected Unexpected Serious Adverse Reaction (SUSAR) an Adverse Reaction to the experimental drug when it is **serious** and **unexpected**.

All SUSARs that occurred during the clinical trial will be registered by the Promoter in the EudraVigilance Clinical Trial Module database and transmitted to the Ethics Committee as follows:

- within 7 days SUSAR fatal or life threatening
- within 15 days all the others.

**Reference Safety Information (RSI)**

Reference Safety Information (RSI) for the purpose of reporting SUSARs is contained in the SPC.

**Development Safety Update Report (DSUR)**

The annual review of the Reference Safety Information related to the investigational medicinal product, will be transmitted by the Promoter to the Italian Medicines Agency (AIFA) and to the Ethics Committees involved once a year.

### **3.8. Evaluation of Risk-Benefit Ratio**

The potential and known risks associated with study participation include:

- risks associated with the investigational medicinal product illustrated in the SPC of the dexmedetomidine
- risk of withdrawal syndrome during dexmedetomidine weaning

Diagnostic procedures do not constitute an additional risk, as they do not differ from the usual ones within the care path in the PICU.

There is no risk of worsening of the withdrawal syndrome because the use of the drug/placebo in the study does not replace the recommended treatment, but is added to it.

The potential benefits associated with participation in the study will depend on the demonstration of the study hypothesis and may include:

- prevention and/or control of the withdrawal syndrome
- reduction of duration of analgosedation weaning
- reduction of length of PICU stay
- improvement of neurocognitive outcomes.

## **4. Data Management and Statistical Analysis**

### **4.1. Data management plan**

The Investigators and blinded staff of the PICU collect and record data on paper case report forms (CRFs). Paper CRFs will be stored within a locked cabinet/office in accordance with local and national regulations. Paper CRFs will have an identifiable patient data page in order to allow follow-up of clinical outcomes and data possibly monitoring visits by national coordinators or regulatory committees. Investigators onto an electronic CRF using the identification code will transcribe these data. No patient identifiable data will be directly accessible from the electronic CRF.

The data recorded on the CRF will be entered in a dedicated database, checked and subsequently processed.



## 4.2 Statistical analysis

### **! Characteristics, treatments and comorbidities**

The data collected by all participating centers will be grouped and summarized in relation to the demographic and clinical variables considered and to the efficacy and safety assessments.

Descriptive data analysis will be performed using: means and standard or median deviations and range for continuous variables, frequencies, and percentages for categorical variables.

The population who completed the study without any major protocol violations will be the one used for the analysis of primary and secondary efficacy variables and safety variables.

Furthermore, analytical lists will be produced that show detailed information regarding:

- patients who discontinued the study and related reasons
- patients who discontinued the study due to adverse events or adverse reactions

A two-sided P-value of less than 0.05 indicates statistical difference.

### **! Efficacy evaluation: primary outcome assessment**

The main variable is the WAT-1 score recorded every 12 hours during the observation period. In particular patients with a WAT-1 score  $<3$  do not have withdrawal symptoms, patients with a score  $\geq 3$  show mild to severe withdrawal symptoms in proportion to the score value.

Patients with a score of  $\geq 3$  that decreased by at least 1 point at the next measurement can be considered with controlled or improving symptoms and can continue the weaning program.

Considering the WAT-1 score patients will be divided into two outcomes groups (yes / no efficacy).

The group "yes efficacy" will include both patients who maintain score  $<3$  by administering the treatment (dexmedetomidine/placebo) at initial dose without variation, and those patients who respond to the increase in treatment dosage (dexmedetomidine/placebo) with the decrease in WAT -1 score of at least 1 point.

For each treatment the % of efficacy cases will be calculated and association with outcome will be investigated through the Pearson's  $\chi^2$  test or the Fisher's Exact test.

The two outcomes groups will also be compared on the basis of the other variables collected, using Pearson's  $\chi^2$  test or Fisher's Exact test for categorical variables, the t-test for parametric variables with normal distribution, and the Wilcoxon test or Mann-Whitney nonparametric test for continuous variables.

Furthermore, a Univariate Logistic Regression model will be estimated to quantify the effect of treatment on outcome and a Multivariate model to see if the association between treatment and outcome remains while considering possible confounding factors.

### **! Efficacy evaluation: secondary outcomes**

Considering the treatment patients were divided into two treatment groups (dexmedetomidine/placebo) and compared evaluating the following variables:

- number of rescue doses for acute withdrawal symptoms
- number of temporary stops of the drugs weaning
- duration (days) of the drugs weaning
- duration (days) of the mechanical ventilation
- PICU length of stay (days)
- comparison of efficacy between age groups, sex, race, PIM3 score, length (hours) of analgesia and sedation
- effective dose range
- adverse events/reactions

For continuous variables, the central trends (mean or median) will be compared, using t-test in the event of normal distribution or non-parametric test of Wilcoxon Mann-Whitney otherwise. For categorical variables, the Pearson  $\chi^2$  test or the Fisher Exact test will be used.

In the presence of a significant difference between the two treatment groups, the association will be further investigated using regression models, as with the primary variable.

**! Safety Evaluation**

The safety evaluation will be established on the frequency of adverse events and reported adverse reactions.

Patients who have had adverse events/reactions and have discontinued the study will be listed; furthermore, information on severity, unpredictability and a causal relationship will be collected and listed.

In the two treatment groups, the frequencies of the adverse events/reaction will be compared.

Changes in heart rate and blood pressure will be recorded in the CRF when their value differs by more than 20% of the patient's baseline value.

**! Sample size**

The study was designed to demonstrate the effectiveness of dexmedetomidine during weaning from analgesic and sedative drugs in reducing the occurrence of withdrawal syndrome.

A recent multicenter national study reported an incidence of 64.6% of withdrawal syndrome in Italian PICUs.

Sample size was calculated considering this incidence and estimating that dexmedetomidine could reduce the withdrawal syndrome by 29%. Assuming a confidence interval of 95% and a potency of 95% a number equal to 77 patients was calculated for each of the 2 groups for a total population of the study of 154 patients. To ensure correct balancing of the randomization 160 patients will be enrolled.

**5. Administrative proceedings****Standards of Good Clinical Practice**

This study will be conducted in accordance with the principles of Good Clinical Practice, the Helsinki Declaration and national regulations on the conduct of clinical trials. By signing the protocol, the Promoter agrees to adhere to the procedures and instructions contained therein and to carry out the study according to GCP, the Helsinki Declaration and the national regulations governing clinical trials.

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**Amendments or any other modification to the protocol of the study**

Any changes to the study protocol will be made by amendment. During the study period, modifications to the protocol are not permitted. Any unexpected changes in the conduct of the study will be recorded in the "Clinical Study Report".

**Ethics committees and Informed Consent**

The Ethics Committee of each Center must approve the study protocol, any protocol amendment, informed consent, and any other information for patients.

The Investigator can immediately apply an amendment upon written communication to the Ethics Committee without waiting for the approval of the Ethics Committee if the patient's safety is at risk. Furthermore, if the Investigator believes that for safety it is necessary to immediately change the protocol, he must inform the Promoter and the Ethics Committee within 10 working days.

To participate in the study each patient must provide written informed consent.

**Archive of the study documents**

The Investigator is responsible for archiving and storing the essential documents of the study, before, during the conduction and after the completion or the interruption of the study, as defined by the current legislation and by the Good Clinical Practice.

The data collected on the CRF will be strictly anonymous and each patient enrolled will only be identified with a number and with the initials.

The Investigator must retain the patient's original data (demographic and medical information, laboratory data etc.) and a copy of the signed informed consent.

**Emergency procedures for the suspension of blindness**

During the study, two sealed copies of the list of randomization codes will be available for emergencies: a sealed list will be kept in the archive of the Investigational Drug Service of the Coordinating Center and the other at the archive of the Principal Investigator of participating centers.

The list of randomization codes clearly shows the treatment attributed to the patient. The Investigator must document the reason for opening the sealed copy of the list of randomization codes, the date/time and sign the code that was opened.

The Investigator must also immediately notify the Promoter of the study.

**Inspection**

Regulatory Authorities may conduct inspections during the study to ensure that it is conducted in accordance with the protocol and applicable regulatory provisions.

If a Regulatory Authority requires an inspection, the Investigator must immediately inform the Promoter of the study. By signing the protocol, the Investigator consents both to the verification by the Promoter of the study and to the Regulatory Authority.

**Investigational medicinal product management**

The investigational medical product will be provided as packaged on market. The solution that contains the drug will be prepared and managed by non-blinded staff.

The Investigator must ensure that the study drug is used in accordance with the protocol.

The storage conditions indicated on the packaging of the drug must be respected.

**Publication of results**

Any formal presentation or publication of data derived from this study should be understood as a joint publication by the Promoter of the study and by Investigators. For multicenter studies, it is mandatory that the first publication is based on data from all the centers, analyzed according to protocol. Experimenters who participate in multicenter studies agree not to submit data from a single center or a small group of centers unless there is a formal consent from the other Investigators and the Promoter.

The Promoter of the study must receive a copy of any communication in advance on the publication itself.

### **Confidentiality and Privacy**

The documents of the study must be kept in a safe place to ensure the maintenance of confidentiality and privacy, cannot be disclosed to others without written permission of the Promoter of the study except to the extent necessary to obtain the consent of the patient to participate in the study.

### **Investigators and co-Investigator**

Investigators and co-Investigator are listed in the List of Centers document.

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