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# Effectiveness of atosiban in women with previous single implantation failure undergoing frozen-thawed blastocyst transfer: study protocol for a randomised controlled trial

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## ABSTRACT

**Background** Uterine contractions may interfere with embryo implantation in assisted reproductive technology. To reduce these contractions and improve success rates, the oxytocin antagonist atosiban has been suggested for administration during embryo transfer. The aim of this study is to evaluate the effectiveness of atosiban in increasing live birth rates among women who have previously experienced a single implantation failure and are scheduled for single blastocyst transfer.

**Methods and analysis** We conduct a single-centre randomised controlled study comparing atosiban and placebo in women undergoing a single blastocyst transfer with a previous failed blastocyst transfer. Women with endocrine or systemic illnesses, recurrent miscarriages, uterine malformations or fibroids, untreated hydrosalpinx, endometriosis (stage III or IV) or uterine fibroids, as well as women undergoing preimplantation genetic testing, are ineligible. The primary outcome is live birth resulting from the frozen-thawed embryo transfer. Secondary outcomes include biochemical/clinical pregnancy, miscarriage, ectopic pregnancy, multiple pregnancies as well as maternal and perinatal outcomes. We plan to recruit 1100 women (550 women per group). This will allow us to demonstrate or refute an increase in live birth rate from 40% to 50%. Data analysis will follow the intention-to-treat principle. We will measure patterns of uterine peristalsis which will allow subgroup analysis for women with or without uterine peristalsis.

**Ethics and dissemination** This study has been approved by the Institutional Review Board of Northwest Women's and Children's Hospital (No. SZ2019001). Written informed consent will be obtained from each participant before randomisation. The results of the trial will be presented at scientific meetings and reported in publications.

**Trial registration number** ChiCTR1900022333.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a large, placebo controlled, randomised controlled trial that examines the live birth rates after atosiban and placebo.
⇒ Patterns of uterine peristalsis will be measured by ultrasound prior to freeze-thaw embryo transfer cycle, which will allow subgroup analysis for women with or without peristalsis.
⇒ Participants will be women with previous single blastocyst implantation failure. This may limit generalisability to the general in vitro fertilisation/intracytoplasmic sperm injection population.

## INTRODUCTION

Assisted reproductive technologies (ART) have witnessed significant changes in recent years, encompassing the usage of extended culture to the blastocyst stage, vitrification and other laboratory techniques. Nevertheless, the majority of transferred embryos do not ultimately result in successful pregnancies.[1] Thus, it is imperative to prioritise finding appropriate treatment for infertile patients who experience blastocyst-stage embryo implantation failure.

Several factors have previously been proposed as potential contributors to implantation failure.[2] The uterus in a non-pregnant state has dynamic characteristics as a result of the periodic contractions of the smooth muscles in the myometrium. The myometrium exhibits continuous contractility known as uterine peristalsis, contributing to the transportation of sperm and facilitating the successful implantation of the embryo.[3] It is suggested that decreased uterine peristalsis during the phase of implantation aids in the successful implantation of the embryo. However, in certain individuals undergoing in vitro fertilisation (IVF) treatment, it has been proposed that abnormal uterine peristalsis during embryo transfer may contribute to the failure of implantation.[4 5] The occurrence of uterine peristalsis during embryo transfer

(ET) has been found to be linked with reduced rates of clinical pregnancy in both fresh and frozen-thawed cycles of ET.[4]

Oxytocin is an endogenous hormone synthesised by the hypothalamus and subsequently released by the posterior pituitary gland. Its primary function is to induce uterine contractions through the activation of cell membrane receptors.[6] Previous studies have identified the presence of vasopressin type V1a and oxytocin receptors within the myometrium of a non-pregnant uterus.[7] Moreover, the presence of oxytocin receptors in the non-pregnant uterus exhibits variability during the menstrual cycle, with lower levels observed during the follicular phase and higher levels during the luteal phase. Additionally, the expression of these receptors is enhanced by supraphysiological amounts of estradiol.[8] The reduction of uterine contractility in non-pregnant patients can be efficiently achieved through the inhibition of oxytocin receptors.[9]

Atosiban, being widely recognised as an oxytocin antagonist, exerts its effects by inhibiting the activation of oxytocin receptors. Consequently, it has the potential to facilitate the process of embryo implantation by diminishing uterine peristalsis.[10] Moreover, the administration of atosiban has the potential to yield positive effects on the endometrial environment. It has been hypothesised that atosiban may improve endometrial blood flow and embryonic survival by preventing the uterus from producing prostaglandins.[11] Atosiban has emerged as a promising intervention for enhancing the chance of implantation and pregnancy subsequent to ET.

Moraloglu *et al*[11] examined the impact of atosiban on women undergoing high-quality ETs. Their findings revealed a significant increase in implantation and pregnancy rates among participants who received atosiban compared with those who did not. A meta-analysis[2] of seven randomised controlled trials (RCTs) involving women who underwent IVF or intracytoplasmic sperm injection (ICSI) found that the use of atosiban resulted in an increased rate of clinical pregnancy when compared with the administration of a placebo (relative risk 1.49, 95% CI 1.18 to 1.88), but the effect on live birth was not certain. The study conducted by Ng *et al* failed to demonstrate any therapeutic advantages associated with the administration of atosiban in patients undergoing IVF, irrespective of history of IVF failure.[12] The latest RCT conducted by Buddhabunyakan *et al* did not show a statistically significant difference in uterine peristalsis and pregnancy rates between atosiban and placebo in the overall population.[13]

Excessive endometrial peristalsis in the frozen-thawed embryo transfer (FET) cycle was detected by a cohort study in women with recurrent implantation failure.[14] Given the potential effect on uterine relaxation, using atosiban for cryopreserved ET may be of greater benefit to those patients for whom IVF failed in the past without a known cause.[14 15]

In view of the inconclusive data mentioned above, we designed a large, randomised, placebo-controlled trial in women with previous single implantation failure. Our findings could provide evidence to recommend or disprove the clinical application of atosiban in fertility treatment and to explore the subgroup of women who may benefit more from this intervention.

## METHODS AND ANALYSIS

### Study design and governance

The study is a double-blinded, parallel-group (intervention vs placebo) single-centre RCT (1:1 ratio) conducted at Northwest Women's and Children's Hospital in China. The RCT will conform to the Consolidated Standards of Reporting Trials statement for reporting RCTs. The study has been prospectively registered at www.chictr.org.cn on 5 April 2019, and has been approved by the Institutional Review Board of Northwest Women's and Children's Hospital (No. SZ2019001). The study is overseen by an independent Data Safety Monitoring Committee (DSMC). Participant enrolment started in July 2019 and is expected to be completed in 2023. The study flow chart is shown in figure 1.

### Eligibility criteria

To be eligible, participants will need to fulfil the following inclusion criteria:

1. Infertile women undergoing IVF/ICSI treatment.
2. Women aged between 20 and 38 years old.
3. Body mass index <28 ($kg/m^2$).
4. One previous blastocyst implantation failure (fresh or frozen blastocysts).
5. Endometrial thickness >7 mm on trigger day in fresh cycle.
6. Planned single blastocyst transfer with hormone replacement therapy in FET cycles.

### Exclusion criteria

1. Severe endocrine diseases (eg, hyperthyroidism, hypothyroidism, hyperprolactinaemia) and other systematic diseases (eg, hypertension, diabetes).
2. Uterine malformations, uterine fibroids or untreated hydrosalpinx.
3. Recurrent spontaneous miscarriage.
4. Severe endometriosis (American Society for Reproductive Medicine staging (ASRM III and IV)).
5. Undergoing preimplantation genetic testing.
6. Known allergy to atosiban.
7. Involved in other clinical trials.

### Informed consent

Eligible women will be counselled by clinicians on the day before thawed-ET. Written informed consent for study participation will be obtained prior to randomisation.

### Withdrawal of individual participants

Participants have the right to withdraw from the trial at any time. The decision to withdraw will neither affect their clinical management nor their relationship with clinicians.

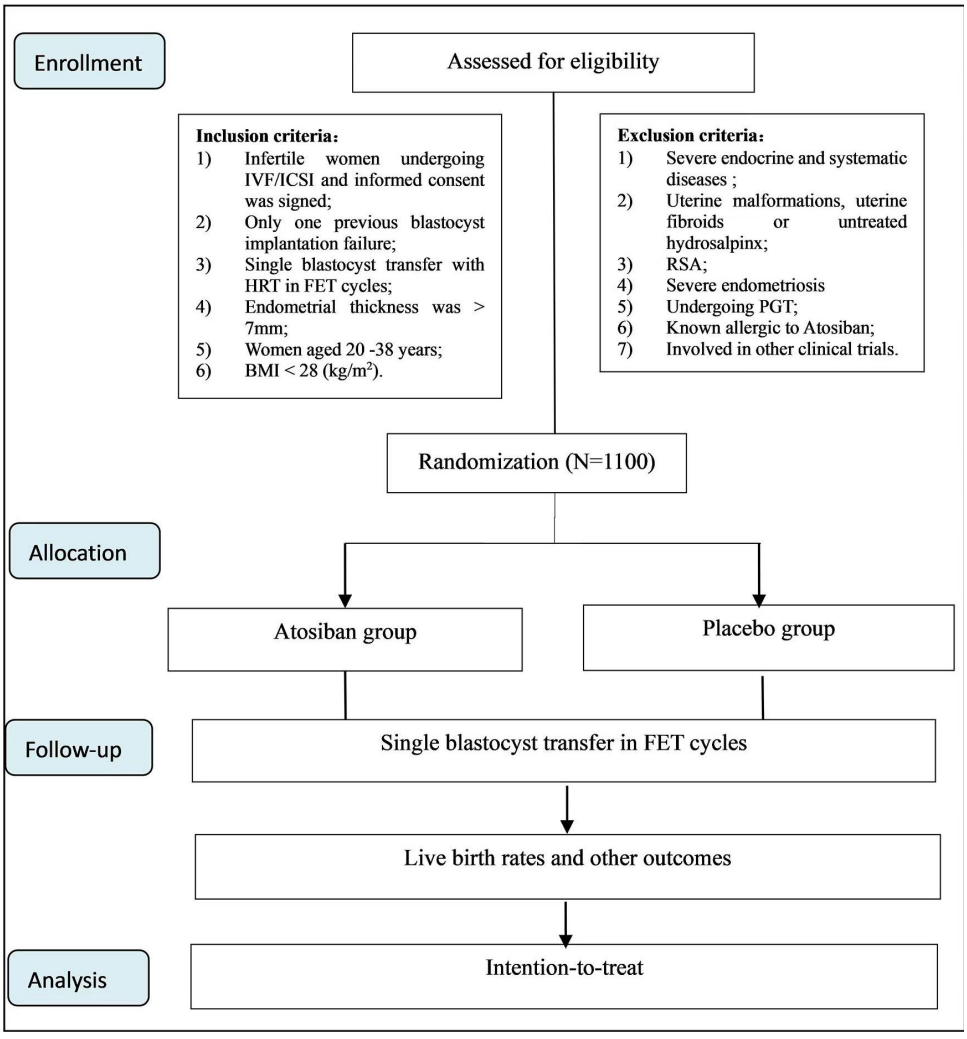


**Figure 1** Flow Chart. BMI, body mass index; FET, frozen-thawed embryo transfer; HRT, hormone replacement therapy; ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilisation; PGT, preimplantation genetic testing; RSA, recurrent spontaneous miscarriage.

### Randomisation, concealment of allocation and blinding

After informed consent, each study participant will be randomised on the day before ET to either atosiban or placebo in a 1:1 ratio according to a computer-generated randomisation list. Randomisation is centrally controlled by using web-based electronic data capture (ResMan). Randomisation will be done by research staff not directly involved in the present study.

To ensure blinding, atosiban or placebo will be administered with identical packaging and labelling of intravenous bags, which are prepared by nurses in our centre. Participants, clinicians (including transfer operators), embryologists, laboratory staff and the sponsor's study team will be blinded to the group assignment.

### Endometrial preparation and blastocyst transfer

Endometrial preparation will be initiated with oral estradiol valerate (Progynova; Bayer Schering Pharma AG, Berlin, Germany) at a daily dose of 6 mg from day 5 of the menstrual cycle. After 10–12 days of oestrogen therapy, endometrial thickness and pattern will be monitored by transvaginal ultrasound. Vaginal micronised progesterone (200 mg, three times a day) will be initiated and continued for 6 days when the endometrial thickness reaches 7 mm or more and serum progesterone <1.5 ng/mL. Participants will then receive luteal phase support according to the standard operation procedures of the centre.

### Interventions

Participants allocated to the atosiban group will be administered atosiban (37.5 mg/5 mL, Tractocile, Ferring Pharma, Geneva, Switzerland) as an intravenous bolus of 6.75 mg/0.9 mL in 1 min at 30 min prior to the ET procedure, followed by an intravenous infusion at a rate of 18 mg/hour for 1 hour. After 1 hour, the dose of atosiban will be reduced to 6 mg/hour, with a total dose of 37.5 mg. The dosage of atosiban used in the present study is being clinically applied to women experiencing preterm labour or with infertility undergoing ET[11 12 16] and is justified by its pharmacokinetics.[17] In the placebo group, participants will receive saline infusion that is administered with

identical packaging and labelling of intravenous bags to atosiban for the same duration.

### Measurement of uterine peristalsis

Initially, uterine peristalsis was not measured. A protocol change was approved by the Institutional Review Board on 27 September 2020. This alteration entailed the inclusion of a 4 min ultrasound examination of the uterus using transvaginal ultrasonography equipment (specifically, the Mindray DC-6 Expert with a 5–8 MHz transducer). The ultrasound scan was scheduled to take place approximately 1 hour prior to ET, specifically 30 min prior to the initiation of atosiban or placebo administration. The ultrasound examination was conducted by one of two examiners (He Cai or Lijuan Chen). Both examiners possess expertise in the field of gynaecology and have specialised in performing transvaginal ultrasound (TVUS) procedures. Both operators received identical training on how to assess uterine contractions.

The vaginal insertion of the probe will be performed with utmost care to minimise any potential stimulation of the cervix, allowing for the visualisation of uterine peristalsis along the sagittal plane of the uterus. The direction of uterine waves will be observed and documented for a minimum duration of 5 min. These waves will be categorised into five types: CF (representing waves moving from the cervix towards the fundus), FC (representing waves moving from the fundus towards the cervix), OP (indicating opposing waves that originate simultaneously at the cervix and fundus), R (representing random waves that initiate from various locations) or N (indicating no activity).[3 18]

### Embryo transfer and luteal phase support

Frozen blastocysts are warmed and transferred on day 6 of progesterone. All blastocyst transfers are performed using a catheter (Cook Ireland) under transabdominal ultrasound guidance by experienced operators at our institution with a minimum of 5 years of experience. Starting from the day of ET, a dosage of 600 mg of vaginal micronised progesterone, 30 mg of oral progesterone daily and 6 mg of estradiol valerate daily will be administered until the confirmation of biochemical pregnancy.

### Evaluation of pregnancy

A serum pregnancy test will be performed 12 days after blastocyst(s) transfer. If serum ß-hCG is positive, luteal phase support is continued, and a TVUS is carried out 5 weeks after ET.

### Outcome measurements

#### Primary outcomes

The primary outcome will be live birth per woman randomised, resulting from the first FET after randomisation. Live birth is defined as the delivery of a live fetus after 20 completed weeks of gestational age.

#### Secondary outcomes

1. Biochemical pregnancy: defined as serum β-hCG>50 IU/L.
2. Clinical pregnancy: defined as observed gestational sac or definitive clinical signs of pregnancy observed at ultrasonography (including clinically documented ectopic pregnancy).
3. Ongoing pregnancy: defined as the presence of a gestational sac and fetal heartbeat after 12 weeks of gestation.
4. Miscarriage: defined as a spontaneous loss of an intrauterine pregnancy prior to 20 completed weeks of gestational age.
5. Ectopic pregnancy: defined as a pregnancy outside the uterine cavity, diagnosed by ultrasound, surgical visualisation or histopathology.
6. Multiple pregnancy: defined as a pregnancy with two or more gestational sacs or positive heart beats at 7 weeks of gestation.
7. Obstetrical and perinatal outcomes: gestational diabetes mellitus; hypertensive disorders of pregnancy; preterm birth (<37 weeks); low and extremely low birth weight (<1500 g at birth), high birth weight (>4000 g at birth) and very high birth weight (>4500 g at birth); large for gestational age (defined as birth weight >90th centile for gestation, based on standardised ethnicity-based charts) and small for gestational age (defined as less than 10th centile for gestational age at delivery based on standardised ethnicity-based charts); perinatal mortality (fetal or neonatal death occurring during late pregnancy, childbirth or up to seven completed days after birth).
8. Congenital anomaly.

We will follow the core-outcome for infertility studies as published by Duffy *et al*.[19]

### Sample size

The live birth rate in the placebo group is predicted to be ~40% based on the published studies.[20] A minimal increase of 10% in the live birth rate is considered clinically relevant. In order to detect a 10% increase, with a power of 90% at a significance level of 0.05, we need 519 cases in each group to detect or refute a difference of 10% difference. Taking into account a possible dropout rate and protocol violation rate of 7%, 550 cases will be recruited in each group (1100 participants in total). The sample size calculation was performed with StudySize V.2.0 software (CreoStat HB, Frolunda, Sweden).

### Statistical analysis

Baseline characteristics will be described by descriptive analysis, and the balance between the two arms will be assessed visually. For continuous variables, the normality test will be initially estimated using frequency histograms and the Shapiro test. If the parameters are non-normally distributed, their medians and IQRs will be reported. For categorical variables, we will present the proportions of the two arms. In addition, we will also report the numbers

of recruitment, participants lost to follow-up, protocol violations and other relevant descriptive data.

We will include all randomised women in the primary comparison between the two arms. The primary analysis will follow the intention-to-treat principle. Per-protocol analysis will be conducted as a secondary analysis.

The primary outcome, live birth, will be compared between the two arms using Pearson's $\chi^2$ test or Fisher's exact test for unadjusted analysis. We will also compute the unadjusted risk ratio (RR) and its 95% CI. We will perform multivariable Poisson regression or log-binomial modelling to compute the adjusted RR and its 95% CI in the event of a prominent imbalance of potential confounders between the two arms.

The analysis will exclude any missing observations for the primary outcome of live birth. In the event of missing data for the secondary endpoints of beta-hCG, clinical pregnancy and continued pregnancy, an attempt will be made to impute the missing observations using the results obtained from a subsequent pregnancy assessment. For instance, in cases where the result of beta-hCG is not available but clinical pregnancy is confirmed, the value of beta-hCG will be estimated as 'positive'. In the context of adverse events, any missing values will be regarded as missing, with the exception of causation, intensity and seriousness of adverse occurrences. In these specific cases, a worst-case approach will be employed. The specificities of the analysis will be outlined in a distinct statistical analysis plan, which will be established throughout the course of the study and completed prior to the finalisation of data collection.

### Subgroup-analysis

We plan to conduct subgroup analyses for peristaltic wave frequencies, embryo quality and ET difficulty.

1. We will perform a subgroup-analysis for participants with and without abnormal peristaltic waves as measured prior to randomisation. Abnormal peristaltic wave is defined as either a high-frequency (>4 times/min) peristaltic CF, OP or R wave or FC wave (negative wave) of any frequency before transplantation. In this study, the cut-off for high-frequency peristaltic waves was based on the findings of a previous study.[21] In addition, as a data-driven approach, we will use the quartiles of peristaltic waves to divide the population into four equal groups and analyse the outcome in each subgroup.
2. The second subgroup analysis will be performed for the quality of the embryo transferred (high quality and fair quality). Blastocysts cultured in vitro up to day 5 or 6 will be graded according to the Gardner grading system.[22] According to the grade of the inner cell mass and trophectoderm, blastocysts will be divided into high quality (≥BB) and fair quality (BC, CB and CC).
3. In the third subgroup analysis, women will be divided into two groups, based on the complexity of the ET (easy and difficult ET). A difficult ET means at least one of the following problems occurred: greater resistance is met, the procedure is time-consuming (>30 s), a more rigid catheter is needed, cervical dilatation is carried out or there is blood in any part of the catheter.[23]

### Interim analysis

An independent DSMC will evaluate the data after the recruitment of the first 500 participants. The DSMC will be asked to assess the endpoint of ongoing pregnancy from the first ET of the started treatment cycle, as data on live birth will not be available. Also, the DSMC will monitor serious adverse event (SAE's) that have occurred.

### Safety reporting

The investigator will inform subjects and the reviewing accredited medical research ethics committee if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than were foreseen in the research proposal. The investigator will ensure that subjects will be informed.

### Adverse event monitoring and reporting

All observed or volunteered adverse events, regardless of treatment group or suspected causal relationship to intervention, will be recorded. Adverse events are defined as any undesirable experience occurring to a subject during the trial, whether or not considered related to the intervention. The common side effects of atosiban are digestive system symptoms, including nausea and vomiting. Other reported treatment-adverse events are tachycardia, headaches, dizziness, hot flushing and injection site reactions.[24] This potential adverse event of atosiban will be discussed to all participants, and their informed consent will be obtained before randomisation. All adverse events reported spontaneously by the subject or observed by the investigator or their staff will be recorded.

An SAE is any untoward medical occurrence or effect, at any dose, that results in death; is life-threatening (at the time of the event); requires hospitalisation or prolongation of existing inpatients' hospitalisation; results in persistent or significant disability or incapacity; is a congenital anomaly or birth defect; or is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction.

### Patient and public involvement

There is no patient or public involvement in this study.

## DISCUSSION

Oxytocin/vasopressin V1A receptors have not been considered a therapeutic target for the treatment of infertility. Atosiban, however, may increase endometrial blood flow and receptivity,[16] interfering with prostaglandin F2a (PGF2a)/oxytocin systems and perhaps boosting uterine, receptivity. It is thought that ET itself increases the local release of prostaglandins and oxytocin. Any further manipulation of the cervix or vagina, like using a tenaculum,

stimulates the release of oxytocin and prostaglandin, which leads to an increase in uterine contractions.[25]

To mitigate uterine contractions during ART cycles, administering oxytocin antagonists just before ET may be useful.[14 15] Contrary to normal conception, ultrasonography examination of uterine contractions revealed an increased frequency of uterine peristalsis during ET.[26] The complex orientation (more transverse and longitudinal waves) at the time of ET in ART treatment was also linked to implantation failure or ectopic pregnancy in addition to the excessive waves of contraction.[27] Observational studies have showed that pregnancy outcomes might be better following the use of atosiban around the time of ET.[14 28] However, a recent Cochrane review found that it is still debatable if atosiban improves pregnancy outcomes for women using ART.[29] While some studies have chosen to study women with recurrent implantation failure,[30] usually defined as implantation failure of three high-quality ETs, our trial focuses on women who had one failed blastocyst ET to study the effectiveness of atosiban in an early phase of treatment. Data from a recent small sample RCT revealed that the live birth rate was 7% higher in the atosiban group than in the placebo group (42.3% vs 35.1%) despite the lack of a statistically significant difference.[30] The live birth rate in the general IVF population did not increase when atosiban was administered around ET, according to a previous multicentre randomised double blind research.[12] The authors did not, however, assess uterine contractions. We will measure the frequency and direction of uterine contractions at baseline to investigate if the benefits of atosiban would only exist in patients who have a high frequency of uterine contractions or fundo-cervical contractions.

Atosiban is currently approved for the treatment of preterm labour. With high specificity for the uterus, atosiban could reduce uterine contractility in both pregnant and non-pregnant women.[31] The safety of atosiban has been confirmed in human sperm or rabbit embryos in a preclinical study.[32] The first case of using atosiban in IVF treatment was reported in 2007,[33] followed by numerous studies on using atosiban in women with ART treatment.[14 23] No serious side effects and no increased risk of congenital anomalies have been reported for atosiban and other selective Oxytocin receptor (OTR) antagonists (eg, nolasiban).[23 34]

Our study will report on the live birth rate, adverse clinical outcomes and measurement of uterine peristalsis to provide evidence on the use of atosiban in supporting implantation following FET.

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**Contributors** JS conceived and designed the study. HC drafted the first version of the manuscript. CY, LC and JX recruited patients. SL, BWM and WL contributed to the design, revised the manuscript and edited language. All authors approved the final version of the manuscript.

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