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Original article

# Clinical practice evaluation of atosiban in preterm labour management in six European countries

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**Objective** To evaluate the efficacy and safety of early administration compared with standard administration of atosiban, when predefined eligibility criteria were met.

**Design** A prospective, open-label, randomised clinical trial. Women were randomised to receive atosiban either immediately (early) or when specified criteria, in terms of duration/frequency of uterine contraction or status of cervical dilation/effacement, were fulfilled (standard).

**Setting** Carried out at 105 centres in six European countries.

**Population** Pregnant women admitted to hospital in threatened preterm labour between 24 and 34 weeks of gestation, comprising a subgroup of women enrolled in the Tractocile Efficacy Assessment Survey in Europe (TREASURE) clinical experience review.

**Main outcome measures** Efficacy was defined as the successful delay of delivery with no alternative tocolytic agent for 48 hours.

**Results** More women in the early group remained undelivered at 48 hours with no alternative tocolytic agent compared with those who received atosiban when specified criteria were fulfilled (88.9 versus 76.1%; $P = 0.03$). Safety was comparable between the groups. There were no statistical differences in maternal, fetal or neonatal adverse events between the early and standard atosiban arms.

**Conclusions** The use of atosiban was effective for the delay of preterm labour and presented no safety concerns irrespective of the time it was administered.

**Keywords** Atosiban, early administration, efficacy, preterm labour, safety

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## Introduction

### The definition and impact of preterm birth

Preterm birth, defined as birth at less than 37 completed weeks of gestation[1] occurs in 5–10% of all pregnancies, leading to an estimated 13 million preterm births worldwide.[2] Preterm birth contributes significantly to perinatal death and long-term handicap, which can require lifelong care at considerable expense. Infants delivered preterm are susceptible to life-threatening complications, such as respiratory distress syndrome, intracranial haemorrhage, necrotising enterocolitis, infection, jaundice, hypothermia and hypoglycaemia.[3]

### Treatment of preterm labour

The goals of managing spontaneous preterm labour are to minimise perinatal morbidity and mortality while preserving maternal health.[4] Tocolysis has not been convincingly shown to improve neonatal outcome or survival. Administration of a full course of corticosteroids to aid fetal pulmonary maturation and *in utero* transfer to a specialist unit where the neonate can receive optimal care, are associated with improved outcome.[5,6] The current main aim of tocolysis is to delay delivery long enough to achieve this, which means usually at least 48 hours.

A number of drugs have been used to treat spontaneous preterm labour, including beta-agonists. While these can

prolong pregnancy for 48 hours,[7] their nonspecific mode of action results in an unfavourable adverse-effect profile, particularly with respect to maternal cardiovascular events. A recent guideline published by the Royal College of Obstetricians and Gynaecologists has stated that the most commonly used beta-agonist, ritodrine, 'no longer seems to be the best choice', and has suggested the oxytocin receptor antagonist atosiban or calcium channel blockers (such as nifedipine) as alternatives, based on comparable efficacy and superior maternal and fetal adverse-effect profiles.[8]

Nifedipine, however, is unlicensed as a tocolytic and contraindicated in pregnancy. Although tested by randomised trials, most of the available data collated in meta-analyses and systematic reviews[9,10] comprise smaller and often poor quality trials, which may make their conclusions invalid.[11] There are no placebo-controlled trials of nifedipine and large follow-up studies on safety are lacking. A number of anecdotal reports have highlighted the occurrence of serious pulmonary and cardiovascular events following the use of nifedipine or other calcium channel blockers as tocolytics.[12–17]

In contrast, atosiban has been compared with placebo and beta-agonists in randomised controlled trials. Compared with placebo, significantly more women receiving atosiban remained undelivered after 48 hours without the need for additional tocolytic therapy. The levels of cardiovascular adverse events were similar between the two groups.[18] Atosiban has been compared with the beta-agonists ritodrine,[19] salbutamol[20] and terbutaline[21] in three separate double-blind studies. All three studies were of a similar design to allow the preplanned analysis of the pooled data for beta-agonists.[22] These trials showed the comparable efficacy and superior safety profiles of atosiban compared with beta-agonists.[19–22] In 2005, in a study of 80 women randomised to receive either atosiban or nifedipine,[23] the rate of delivery at 48 hours or 7 days was not significantly different between the two treatments. Atosiban was associated with significantly fewer maternal adverse events, particularly cardiovascular adverse events.

Our results from a large, randomised, multicentre European trial to evaluate the efficacy of atosiban compared with usual care in women admitted with threatened spontaneous preterm labour and eligible to receive atosiban have been presented previously.[24,25] Significantly, more women receiving atosiban remained undelivered at 48 hours with no alternative tocolytic compared with usual care (77.6 versus 56.6%; $P < 0.001$). The findings of this study clearly support the use of atosiban for delaying preterm birth and are consistent with previously conducted randomised controlled trials. Atosiban was associated with fewer maternal and fetal adverse events compared with other tocolytics and presented no safety concerns for either the mother or the unborn baby.[24]

While the indications for administration of atosiban in threatened spontaneous preterm labour can be extrapolated from clinical trials, they may not always be appropriate for guiding clinical management, since trials are designed to facilitate treatment comparison rather than to identify women who would benefit from a delay in delivery. Such difficulties reflect, at least in part, the problems in distinguishing progressive from threatened spontaneous preterm labour. In clinical practice, some women may receive atosiban, or could benefit from atosiban, prior to fulfilling the standard administration criteria. The aim of the current study was to evaluate early versus standard treatment with atosiban, i.e. according to the criteria specified in the summary of product characteristics in terms of duration/frequency of uterine contraction or status of cervical dilation/effacement. This article will present the results of this study and discuss them in light of the recent findings of the large atosiban versus usual care study.[24,25]

## Methods

### Design

This trial was a randomised, open-label, multicentre, prospective trial in pregnant women in threatened spontaneous preterm labour, performed in 105 centres in six countries (Austria, France, Germany, Italy, Spain and UK). Inclusion and exclusion criteria are given in Table 1.

### Randomisation and treatment

Two criteria determined patient assignment:

- regular uterine contractions lasting a minimum of 30 seconds at a rate of ≥4 per 30 minutes
- cervical dilatation of 1–3 cm for multiparous women or 0–3 cm for nulliparous women and effacement of ≥50%.

Women were randomised to receive atosiban immediately (early) when one of these criteria was met or to receive atosiban only when both criteria were met (standard), i.e. according to the criteria specified in the summary of product characteristics in terms of duration/frequency of uterine contraction or status of cervical dilation/effacement. The women were randomised and treated on the day of hospital admission. A follow-up visit took place 48 hours later followed by an end-of-study assessment at discharge; postdischarge data were also collected. Information recorded included details of concomitant medication, delivery details and maternal, fetal and neonatal safety information.

The protocol for atosiban administration was as follows; an initial bolus of 6.75 mg, followed by 300 microgram/minute for 3 hours, then 100 microgram/minute for up to 45 hours. Three further retreatments were permitted. The total dose given during a full course of atosiban therapy did not exceed 330 mg.

No restrictions were made on the use of concomitant medication, including tocolytics, prior to or during the study. However, other tocolytics were not permitted between randomisation and administration of atosiban.

**Table 1.** Summary of inclusion and exclusion criteria

| Inclusion criteria | Exclusion criteria |
|---|---|
| Women ≥18 years of age | Antepartum uterine haemorrhage |
| Gestational age between 24 and 33* completed weeks | Eclampsia or severe pre-eclampsia requiring delivery |
| Signed informed consent | Intrauterine fetal death |
| | Placenta praevia |
| | Any other condition of the mother or fetus in which continuation of the pregnancy was hazardous |
| | Known hypersensitivity to the active substance or any of the excipients |
| | Premature rupture of the membranes >30 weeks of gestation |
| | Intrauterine growth restriction and/or abnormal fetal heart rate |

*Defined as 24 weeks + 0 days to 32 weeks + 6 days.

### Efficacy and safety assessment

The primary efficacy endpoint was defined as the proportion of women remaining undelivered and not requiring an alternative tocolytic within 48 hours of randomisation. Alternative tocolytic was defined as the second pharmacological agent given. Retreatment with atosiban was not considered as an alternative tocolytic.

The secondary efficacy endpoints were proportion of women remaining undelivered 48 hours after randomisation; proportion of women who did not receive an alternative tocolytic within 48 hours; proportion of women retreated with atosiban; number of retreatments with atosiban; number of atosiban retreatments in women undelivered and not requiring an alternative tocolytic within 48 hours; proportion of women receiving a full course of steroids; description of treatment administration patterns; time to delivery or first use of an alternative tocolytic; time to delivery; delivery characteristics; and satisfaction of women at discharge (pleasant, indifferent, unpleasant).

Safety was evaluated by recording the occurrence of adverse events and serious adverse events in the mother, fetus and neonate. Each adverse event was graded (mild, moderate, severe), and its relationship to the administered medication was assessed (unrelated, unlikely, possible, probable). Serious adverse events were defined as any untoward medical occurrence that resulted in death; was life threatening; required continued hospitalisation; resulted in persistent or significant disability or incapacity; was a congenital anomaly or birth defect; was an important medical event. Serious adverse events included pulmonary oedema, haemorrhage and deep vein thrombosis (maternal), bradycardia, heart rate decelerations and tachycardia (fetal) and meconium ileus, bradycardia and anaemia (neonatal). Women were analysed according to the treatment received. Adverse events were regarded as 'pre-treatment' if they occurred between randomisation and the start of study treatment and 'treatment emergent' if they occurred in the time interval between the start of study treatment and the final visit.

The trial protocol was approved by the ethics committees of the participating centres, and was conducted in accordance with the principles outlined in the Declaration of Helsinki[25] and Good Clinical Practice. Signed informed consent was obtained from each participant at enrolment.

### Statistical analyses

The Cochran Mantel–Haenszel chi-square test, adjusted by country, was used to analyse the primary and secondary efficacy endpoints. Odds ratios and 95% CI were used to assess treatment effect. Logistic regression analysis of the primary endpoint was performed and adjusted for randomisation stratification factors (i.e. gestational age, pregnancy type, gravidity and prelabour rupture of the membranes). Analyses were performed on an intention-to-treat basis.

## Results

Ninety-one centres from six European countries recruited a total of 226 women who were assigned early versus standard atosiban. Three women (2.6%) in the early atosiban arm and three (2.8%) in the standard atosiban arm withdrew consent, and one woman in each group only attended the admission visit. In both the groups, baseline demographics were not significantly different (Table 2). There were no notable differences in the general physical examination characteristics at baseline or in the obstetric histories of the women within the two groups.

### Efficacy assessments

*Primary efficacy endpoint*

A significantly higher success rate was observed with respect to the primary efficacy endpoint in the early atosiban arm (88.9%; $n$ = 104/117) compared with the standard atosiban

**Table 2.** Summary of baseline demographics (randomised population; $n = 226$)

| | Early versus standard atosiban | |
|---|---|---|
| | **Early ($n = 117$)** | **Standard ($n = 109$)** |
| Age of mother (years) | | |
| Mean | 29.44 | 29.48 |
| Median | 30 | 28 |
| Range | 18–40 | 18–43 |
| Gestational age (weeks) | | |
| Mean | 28.87 | 28.81 |
| SD | 2.71 | 2.68 |
| Median | 29 | 29 |
| Range | 22–33 | 23–33 |
| In classes, *n* (%) | | |
| ≤28 weeks + 6 days | 48 (41.0) | 49 (45.0) |
| ≥29 weeks + 0 days | 69 (59.0) | 60 (55.0) |
| Pregnancy order | | |
| Single, *n* (%) | 94 (80.3) | 88 (80.7) |
| Multiple*, *n* (%) | 23 (19.7) | 21 (19.3) |
| Twins | 20 | 17 |
| Triplets | 3 | 4 |
| PROM**, *n* (%) | | |
| Present | 5 (4.3) | 3 (2.8) |
| Not present | 112 (95.7) | 106 (97.2) |

*Information on number of fetuses not available for one woman with a multiple pregnancy.
**Data unavailable for one woman in the usual care arm.

arm (76.1%; $n = 83/109$) ($P = 0.03$). The differences remained significant for subgroup analyses of multiple pregnancies and later gestational ages (Table 3). Of the 109 women randomised to receive atosiban at the standard time, only 42 received active treatment with atosiban, suggesting that many of the women were not in true preterm labour at the time of randomisation.

*Secondary efficacy endpoints*

There was no significant difference between early and standard atosiban in either the proportion of women who remained undelivered or in the proportion of women who received an alternative tocolytic within 48 hours of randomisation.

In women who received atosiban, the mean total dose and duration of atosiban administered to women was similar in the early and standard atosiban arms, as was the mean duration of alternative tocolytic administration and the mean total duration of treatment. The majority of women who received atosiban either received no further treatment or were retreated with atosiban (70.8%; $n = 111/156$). Of those women retreated, the majority received one or two retreatments with atosiban. In women who received atosiban, the most frequently used second-line tocolytics were beta-agonists, which were given to 14.0% ($n = 16/114$) and 14.2% ($n = 6/42$) of women in the early and standard arms, respectively.

There was no significant difference in the number of women who received a full course of steroids, in the time to delivery, time to first use of an alternative tocolytic, duration of labour, gestational age at delivery or mode of delivery. Women who received early atosiban were more satisfied with treatment at 48 hours ($P < 0.002$) compared with those in the standard atosiban arm, although there was no significant difference at the time of discharge.

## Safety assessments

Safety analysis was performed in 177 women who were randomised, who had received active treatment and for whom the presence or confirmed absence of adverse events was available. A summary of treatment-emergent adverse events and serious adverse events is presented in Table 4. Treatment-emergent adverse events were events occurring between the start of treatment and the final visit. Adverse events were analysed according to treatment received rather than randomisation group.

**Table 3.** Proportion of women who remained undelivered and who did not receive an alternative tocolytic within 48 hours of randomisation (ITT population)

| | **Early atosiban ($n = 117$), *n* (%)** | **Standard atosiban ($n = 109$), *n* (%)** | **Odds ratio (95% CI)** | ***P* value** |
|---|---|---|---|---|
| Primary endpoint | 104/117 (88.9) | 83/109 (76.1) | 2.27 (1.09, 4.72) | 0.03 |
| Pregnancy type | | | | |
| Single | 83/94 (88.3) | 70/88 (79.5) | 1.75 (0.78, 3.92) | 0.16 |
| Multiple | 21/23 (91.3) | 13/21 (61.9) | 5.96 (1.05, 33.9) | 0.04 |
| Gestational age | | | | |
| ≤28 weeks + 6 days | 41/48 (85.4) | 36/49 (73.5) | 1.83 (0.63, 5.29) | 0.27 |
| ≥29 weeks + 0 days | 63/69 (91.3) | 47/60 (78.3) | 3.06 (1.03, 9.05) | 0.04 |
| PROM | | | | |
| Yes | 5/5 (100) | 1/3 (33.3) | Numbers too small to calculate | |
| No | 99/112 (88.4) | 82/106 (77.4) | 1.96 (0.93, 4.15) | 0.08 |

ITT, intention to treat. Mantel–Haenszel chi-square test (including country adjustment).

**Table 4.** Summary of treatment-emergent adverse events and serious adverse events by actual initial treatment; *n* (%), E*

| | Early (*n* = 115) | Standard (*n* = 43) | Standard (other**; *n* = 19) |
|---|---|---|---|
| Maternal | | | |
| Adverse Events | 70 (60.9), 145 | 28 (65.1), 66 | — |
| Serious Adverse Events | 21 (18.3), 29 | 13 (30.2), 17 | — |
| Fetal | | | |
| Adverse Events | 16 (13.9), 22 | 6 (14.0), 7 | — |
| Serious Adverse Events | 6 (5.2), 9 | 3 (7.0), 3 | — |
| Neonatal | | | |
| Adverse Events | 43 (37.4), 203 | 17 (39.5), 101 | 9 (47.4), 75 |
| Serious Adverse Events | 29 (25.2), 102 | 12 (27.9), 44 | 6 (31.6), 33 |

**n*, number of women; E, number of events.
**Other women were women not treated with atosiban as the initial treatment.

*Maternal safety*

The incidence of maternal treatment-emergent adverse events was comparable in women receiving early (60.9%) and standard (65.1%) atosiban. No maternal deaths were reported.

*Fetal safety*

Too few fetal treatment-emergent serious adverse events were reported for conclusions to be drawn. There were two intrauterine deaths, one in each arm of the study. The deaths were reported to be due to asphyxia caused by a cord accident and abruption. These were considered unrelated to the study medication.

*Neonatal safety*

No difference in the overall incidence of adverse events or in the incidence of individual adverse events was observed between women receiving early or standard atosiban. The three neonatal deaths in this study occurred in two women randomised to the early atosiban arm. All three neonates (one triplet and two twins) were admitted to neonatal intensive care unit, but died a few days later. None of the deaths was considered by the investigators to be related to the study medication, and all were at low gestational ages (24 weeks + 6 days [triplet] and 25 weeks + 6 days [twins]).

## Discussion

We have previously presented the findings of a large randomised trial that showed the benefits of atosiban over usual care in delaying preterm birth—significantly more women receiving atosiban remained undelivered at 48 hours, with no alternative tocolytic compared with usual care (77.6 versus 56.6%; $P < 0.001$).[24,25] These findings, which are consistent with previously conducted randomised controlled trials of atosiban, support its use for delaying preterm birth. Atosiban was associated with fewer maternal and fetal adverse events compared with other tocolytics and presented no safety concerns for either the mother or the unborn baby.[24,25]

In clinical practice, the subjective nature of the diagnosis of spontaneous preterm labour[26] results in the treatment of some women who are not in true spontaneous preterm labour. The principal objective of the current trial was to evaluate the efficacy and safety of atosiban in women who were randomised to receive atosiban either immediately or when fulfilling all specified eligibility criteria. The study was kept as flexible as possible to minimise interference with routine clinical practice. Evaluation was kept simple, focusing on global outcomes and safety assessments and avoiding the extra burden of protocol-induced evaluation and laboratory or explanatory medical procedures.

The composite or dual primary efficacy endpoint of women remaining undelivered and not requiring an alternative tocolytic 48 hours after randomisation reflects both the efficacy and tolerability of the treatment.[22] Compared with administration of atosiban at the standard time, early administration resulted in a significantly greater proportion of women remaining undelivered without the need for an alternative tocolytic. This may not be surprising, since the women assigned to early atosiban were, by definition, less well advanced in labour.

Less than one-half of the women randomised to the standard administration of atosiban received any study medication. This could indicate that these women were not in true spontaneous preterm labour and highlights the need for the use of accurate diagnostic techniques to avoid unnecessary treatment. Very few women underwent tests for fetal fibronectin, which has been shown to be a useful predictor of women who will go on to deliver preterm.[27] This may be due to the fact that the availability of such test was not widespread when women were recruited to this trial. The absence of statistical differences in maternal, fetal or neonatal adverse events between the early and standard atosiban arms suggests that the time of administration of atosiban has little impact on tolerability. The overall tolerability of atosiban is in agreement with previous randomised controlled trials.[22]

## Conclusions

Atosiban is effective for the delay of spontaneous preterm labour and presents no safety concerns irrespective of the time it is administered.

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