

Clinical practice evaluation of  
atosiban  
**TREASURE**



TRactocile Efficacy Assessment SURvey in Europe

Professor Peter Husslein  
Vienna

**Presentation Details:**

**Slides:** 23

**Duration:** 00:10:46

<p><b>Slide 1</b> </p> <p><b>Clinical practice evaluation of atosiban</b>  <b>TREASURE</b>  <b>TRactocile Efficacy Assessment</b>  <b>SURvey in Europe</b></p> <p>Duration: 00:00:17  Advance mode: Auto</p>	<p>Clinical practice evaluation of atosiban</p> <p><b>TREASURE</b></p> <p><small>TRactocile Efficacy Assessment SURvey in Europe</small></p> <p>Professor Peter Husslein  Vienna</p>	<p><b>Notes:</b></p> <p>Today I am going to talk about an evaluation of Tractocile after it has been registered. The trial's name already says what we have been trying to do: TRactocile Efficacy Assessment SURvey in Europe.</p>
<p><b>Slide 2</b> </p> <p><b>Objectives</b></p> <p>Duration: 00:00:53  Advance mode: Auto</p>	<p><b>Objectives</b></p> <ul style="list-style-type: none"> <li>• To compare the efficacy of atosiban with usual care in the management of PTL</li> <li>• To evaluate the efficacy and safety of early versus standard administration of atosiban</li> </ul>	<p><b>Notes:</b></p> <p>We had two objectives and two parts of the trial. One objective was to compare the efficacy of Atosiban with the usual care, so with what the centre was normally doing in the treatment of pre-term labour. And the second part of the study was to have a look whether early treatment, when not all the prerequisites normally required for the use of Tractocile were already met, early treatment versus delayed treatment when all the criteria were met.</p> <p>So, it is a study in two portions. As I said, number one was to look at the efficacy of Atosiban versus the usual care, and the other one was early versus delayed treatment.</p>

### Slide 3

#### Study details

Duration: 00:01:01  
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#### Study details

- Prospective, open-label RCT divided into two parts
  - atosiban versus usual care
    - usual care includes  $\beta$ -agonists, alone or with magnesium, calcium channel blockers and bed rest
  - early versus standard atosiban
- Multi-centre trial in six European countries
- Women admitted to hospital with threatened PTL
  - between 24 and 34 weeks' gestation
- Primary efficacy endpoint = proportion of women remaining undelivered **AND** not requiring an alternative tocolytic at 48 hours

#### Notes:

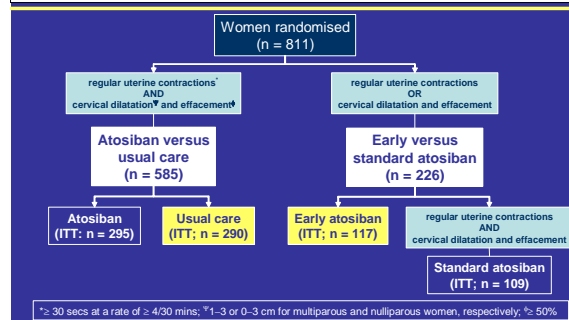
It was an open labour, randomized clinical trial, and the usual care was either beta agonists alone, or with magnesium, calcium channel blockers or bed rest, diverse control group but that is the way pre-term labour is being handled in the various countries in Europe. It was a multi-centre trial in six European countries and we looked at those women treated between 24 and 34 weeks of gestation. We defined the primary efficacy endpoint up front, and it was, since we were comparing it with a tocolytic treatment, it was defined as the proportion of women remaining undelivered at 48-hours and not requiring an alternative tocolytic treatment.

### Slide 4

#### Study profile







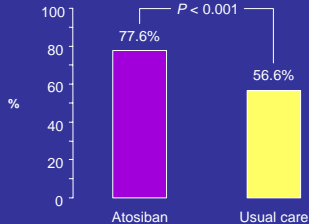
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#### Study profile



#### Notes:

It was a relatively large trial, 811 women in both arms, or in both trial aspects. Five hundred and eighty-one, so the larger portion, was the first trial. Looking at Atosiban, 295 patients versus usual care 290. Two hundred and twenty-six patients were randomized to use Atosiban as soon as they were admitted, or to wait until regular uterine contractions and cervical effacement or dilatation was present. This group consisted of a 109 patients.

<p><b>Slide 5</b> 🎧</p> <p><b>Participating countries</b></p> <p>Duration: 00:00:14 Advance mode: Auto</p>	<p style="text-align: center;"><b>Participating countries</b></p>    <p style="text-align: center;">91 centres 811 women</p>   	<p><b>Notes:</b></p> <p>Six countries were involved with 91 centres so it was a relatively large, complicated and time and money consuming trial.</p>						
<p><b>Slide 6</b> 🎧</p> <p><b>Efficacy assessments</b></p> <p>Duration: 00:00:04 Advance mode: Auto</p>	<p style="text-align: center;"><b>Efficacy assessments</b></p> <p style="text-align: center;">Atosiban versus usual care</p>	<p><b>Notes:</b></p> <p>So lets have a look at the efficacy assessment.</p>						
<p><b>Slide 7</b> 🎧</p> <p><b>Atosiban versus usual care</b></p> <p>Duration: 00:00:20 Advance mode: Auto</p>	<p style="text-align: center;"><b>Atosiban versus usual care</b></p> <p style="text-align: center;">Women remaining undelivered AND not requiring an alternative tocolytic within 48 hours</p>  <table border="1"> <thead> <tr> <th>Group</th> <th>Percentage</th> </tr> </thead> <tbody> <tr> <td>Atosiban</td> <td>77.6%</td> </tr> <tr> <td>Usual care</td> <td>56.6%</td> </tr> </tbody> </table>	Group	Percentage	Atosiban	77.6%	Usual care	56.6%	<p><b>Notes:</b></p> <p>There were more women undelivered and not requiring alternative tocolytic treatment within 48 hours in the Atosiban group compared to the usual care. Seventy-seven point six percent versus 56.6 percent, and that was highly statistically significant.</p>
Group	Percentage							
Atosiban	77.6%							
Usual care	56.6%							

## Slide 8

### Efficacy in patient subgroups

Duration: 00:00:52

Advance mode: Auto

### Efficacy in patient subgroups

	Atosiban (n = 295)	Usual care (n = 290)	P value
<b>Pregnancy type</b>			
Single	186/231 (80.5%)	130/228 (57.0%)	< 0.001
Multiple	43/64 (67.2%)	34/62 (54.8%)	0.30
<b>Gestational age</b>			
≤ 28 wks + 6 days	77/97 (79.4%)	44/95 (46.3%)	< 0.001
≥ 29 wks + 0 days	152/198 (76.8%)	120/195 (61.5%)	< 0.001
<b>PROM</b>			
Yes	5/11 (45.5%)	4/11 (36.4%)	< 0.001
No	224/284 (78.9%)	160/278 (57.6%)	< 0.001

### Notes:

If we look at the subgroups of this analysis it seems as if the single pregnancy Atosiban was more effective; 80 percent undelivered at 48 hours and not requiring an alternative tocolytic agent, versus 57 percent. In multiple gestations was a slightly less pronounced difference, whereas, when you subdivided before and after 29 weeks, it seemed to be no difference. We had some women with premature rupture of the membranes included in the study, but the numbers were so small that we were not able to draw any conclusion.

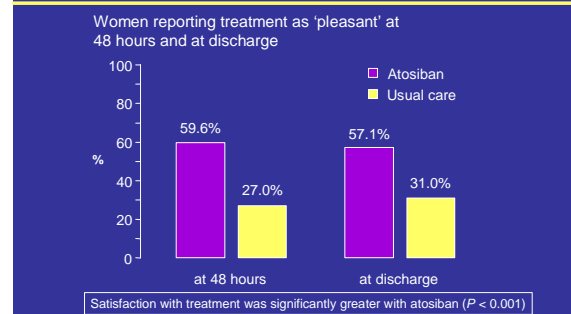
## Slide 9

### Atosiban versus usual care: overall satisfaction

Duration: 00:00:51

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### Atosiban versus usual care: overall satisfaction



### Notes:

Now we also asked the patient whether she was satisfied with the type of treatment she received from her subjective point of view, whether she felt the treatment was reasonably pleasant or unpleasant, and clearly Atosiban was superior to the usual care. At 48 hours, roughly 60 percent said that they were satisfied and that their treatment was considered subjectively to be pleasant, versus only 27 percent of the usual care group said that they felt the treatment was pleasant. Approximately the same numbers were picked up at discharge. So clearly, Atosiban is more, and easily, and better tolerated by patients.

## Slide 10

### Efficacy assessments

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## Efficacy assessments

Early versus standard atosiban

### Notes:

Now, if we look at the second part of the study, early versus standard Atosiban treatment.

## Slide 11

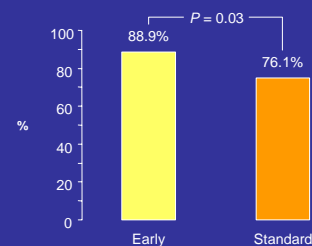
### Early versus standard atosiban

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## Early versus standard atosiban

Women remaining undelivered AND not requiring an alternative tocolytic within 48 hours



### Notes:

There was a slightly better result when Atosiban was used immediately when the patient presented. Almost 90 percent delivered only after 48 hours, and did not require an alternative tocolytic agent, compared to 76 percent when you waited until the full criteria were met. So there is a small indication that we might be waiting too long with our Atosiban treatment when we stick to the general guidelines.

## Slide 12

### Efficacy in patient subgroups

Duration: 00:00:31

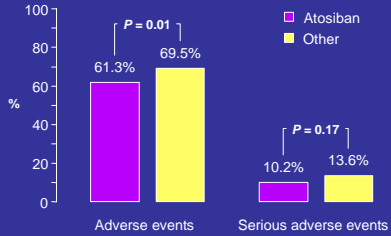
Advance mode: Auto

## Efficacy in patient subgroups

	Early (n = 117)	Standard (n = 109)	P value
<b>Pregnancy type</b>			
Single	83/94 (88.3%)	70/88 (79.5%)	0.16
Multiple	21/23 (91.3%)	13/21 (61.9%)	0.04
<b>Gestational age</b>			
≤ 28 wks + 6 days	41/48 (85.4%)	36/49 (73.5%)	0.27
≥ 29 wks + 0 days	63/69 (91.3%)	47/60 (78.3%)	0.04
<b>PROM</b>			
Yes	5/5 (100%)	1/3 (33.3%)	
No	99/112 (88.4%)	82/106 (77.4%)	0.08

### Notes:

Here again, if we look at the subgroups it is a little more difficult because the groups within themselves are small. So I think one should not over interpret this result. There seems to be an indication at least to do follow up trials comparing early versus standard treatment because there seems to be a benefit if you start with Atosiban early.

<p><b>Slide 13</b> 🎧  <b>Safety assessments</b>  Duration: 00:00:13  Advance mode: Auto</p>	<p style="text-align: center;"><b>Safety assessments</b></p> <p style="text-align: center;">Atosiban versus usual care</p>	<p><b>Notes:</b>  Now safety is an important issue and it has always been discussed whether Atosiban compared to others is safe, or safer.</p>												
<p><b>Slide 14</b> 🎧  <b>Adverse events reporting</b>  Duration: 00:00:29  Advance mode: Auto</p>	<p style="text-align: center;"><b>Adverse events reporting</b></p> <ul style="list-style-type: none"> <li>• Analysed by actual initial treatment and actual treatment regimen <ul style="list-style-type: none"> <li>▪ rather than randomisation group</li> </ul> </li> <li>• Treatment-emergent adverse events <ul style="list-style-type: none"> <li>▪ occurred between the start of treatment and the final visit</li> </ul> </li> <li>• Safety data were available for 754 women <ul style="list-style-type: none"> <li>▪ 577 in the atosiban versus usual care study</li> <li>▪ 177 in the early versus standard atosiban study</li> </ul> </li> </ul>	<p><b>Notes:</b>  Here we analyzed, not by the randomization method, but by the drug that was given. We included everything that happened during the start of treatment and the final visit, therefore we were able to collect events in a very large number of women.</p>												
<p><b>Slide 15</b> 🎧  <b>Maternal safety</b>  Duration: 00:00:27  Advance mode: Auto</p>	<p style="text-align: center;"><b>Maternal safety</b></p> <p style="text-align: center;">Women reporting treatment-emergent adverse events and serious adverse events by actual INITIAL treatment</p>  <table border="1"> <thead> <tr> <th>Event Type</th> <th>Atosiban (%)</th> <th>Other (%)</th> <th>P-value</th> </tr> </thead> <tbody> <tr> <td>Adverse events</td> <td>61.3%</td> <td>69.5%</td> <td>0.01</td> </tr> <tr> <td>Serious adverse events</td> <td>10.2%</td> <td>13.6%</td> <td>0.17</td> </tr> </tbody> </table>	Event Type	Atosiban (%)	Other (%)	P-value	Adverse events	61.3%	69.5%	0.01	Serious adverse events	10.2%	13.6%	0.17	<p><b>Notes:</b>  And as we included everything that happened it was a large number. But still within this large number we were able to show that with Atosiban, compared to any other drug that was used for tocolysis, there were fewer adverse effects in the Atosiban groups, and fewer serious adverse effects, however that not being significantly different.</p>
Event Type	Atosiban (%)	Other (%)	P-value											
Adverse events	61.3%	69.5%	0.01											
Serious adverse events	10.2%	13.6%	0.17											

## Slide 16

### Maternal safety

Duration: 00:00:28  
Advance mode: Auto

### Maternal safety

- Significantly fewer women had maternal treatment-emergent adverse events after initial treatment with atosiban
- Most frequently reported treatment-emergent adverse events were
  - cardiac
    - atosiban 5.9%
    - other 35.3%
  - gastrointestinal

### Notes:

The main problem with the other drugs, because most of them were using Betamimetics, were cardiac problems as we already know from the existing literature. Thirty-five point three percent of the other drug users were showing some sort of cardiac side effects.

## Slide 17

### Fetal and neonatal safety – treatment-emergent adverse events

Duration: 00:00:39  
Advance mode: Auto

### Fetal and neonatal safety – treatment-emergent adverse events

	Atosiban (n = 305)	Other (n = 272)	P value
<b>Fetal</b>			
Adverse events	26 (8.5%)	37 (13.6%)	0.03
Serious adverse events	12 (3.9%)	17 (6.3%)	0.18
<b>Neonatal</b>			
Adverse events	81 (26.6%)	73 (26.8%)	0.75
Serious adverse events	77 (25.2%)	68 (25.0%)	0.82

- None of 3 fetal deaths or 12 neonatal deaths was considered due to the study medication

### Notes:

Now, looking at the fetal and neonatal safety, to make a complicated slide simple, there were fewer adverse events, and the most important ones, the fetal death and neonatal death, there was no relation to the drug used. Almost all neonatal deaths were in the group with a short pregnancy duration, and to the best of our analysis none of the fetal deaths or neonatal deaths were considered to be due to the study medication.

## Slide 18

### Conclusions



Duration: 00:00:51  
Advance mode: Auto




### Conclusions

- Atosiban delayed delivery and reduced the need for an alternative tocolytic
- Atosiban was associated with fewer maternal and fetal adverse events
- Atosiban presents no safety concerns irrespective of the time it is administered
- This study confirms the efficacy and safety of atosiban previously demonstrated in registration trials

### Notes:

In conclusion, our post-marketing study was able to confirm the data already available in the literature: that Atosiban does delay delivery and reduces the need for alternative tocolytic drugs. That Atosiban is associated with fewer maternal and fetal adverse effects and that Atosiban presents no safety concerns, irrespective of the time of its administration. So, whether you start it early, or a little later, there is no safety concern. In final summary, the study confirmed efficacy and safety of Atosiban as previously demonstrated in the registration trials.

		Thank you for your attention.
<p><b>Slide 19</b> </p> <p><b>Q&amp;A</b></p> <p>Duration: 00:00:05 Advance mode: Auto</p>	<p style="text-align: center;"><b>Q&amp;A</b></p> <hr/> <p>Question:</p> <p>Can you tell us the fetal safety data by the groups as randomised?</p>	<p><b>Notes:</b></p> <p>Question: Can you tell us the fetal safety data by the groups as randomized?</p>
<p><b>Slide 20</b> </p> <p><b>Q&amp;A</b></p> <p>Duration: 00:00:29 Advance mode: Auto</p>	<p style="text-align: center;"><b>Q&amp;A</b></p> <hr/> <p>Response:</p> <p>Can you tell us the fetal safety data by the groups as randomised?</p>	<p><b>Notes:</b></p> <p>Response: There was one fetal death in the atosiban group and two fetal deaths in the control group. Three neonatal deaths in the atosiban group and nine neonatal deaths in the comparative group and almost all of them were in the group below 28 weeks and of the two that were in the group after 28 weeks group were in the non-atosiban group.</p>

<p><b>Slide 21</b> </p> <p><b>Q&amp;A</b></p> <p>Duration: 00:00:13 Advance mode: Auto</p>	<p style="text-align: center;"><b>Q&amp;A</b></p> <hr/> <p>Question:</p> <p>Did you do any doppler studies; did you see any effect of the drug on the fetal vessels?</p>	<p><b>Notes:</b></p> <p>Question: Did you do any Doppler studies during the trial and did you see any effect of the drug on the fetal vessels because there is some extent of vasopressin in these drugs.</p>
<p><b>Slide 22</b> </p> <p><b>Q&amp;A</b></p> <p>Duration: 00:00:17 Advance mode: Auto</p>	<p style="text-align: center;"><b>Q&amp;A</b></p> <hr/> <p>Response:</p> <p>Did you do any doppler studies; did you see any effect of the drug on the fetal vessels?</p>	<p><b>Notes:</b></p> <p>Response: We didn't do any Doppler studies in this trial and the amount of vasopressin is very, very low and based on all the data available there doesn't seem to be any negative effect on the blood circulation of the fetus.</p>
<p><b>Slide 23</b></p> <p><b>Next presentation</b></p> <p>Duration: 00:00:05 Advance mode: By user</p> <p> Flash movie: text-husslein.swf Display : In Articulate player</p>	<p style="text-align: center;"><b>Next presentation</b></p> <hr/> <p>Click here for: How to assess the quality of evidence from tocolytic studies Professor James G Thornton</p>	<p><b>Notes:</b></p>