Clinical trial results:
A randomised, placebo-controlled, double-blind, parallel groups, multinational, multicentre trial assessing the effect of barusiban administered subcutaneously on the day of transfer on implantation and pregnancy rates in IVF/ICSI patients.

Summary

EudraCT number	2012-001622-10
Trial protocol	BE CZ ES PL
Global end of trial date	28 April 2015

Results information

Result version number	v1 (current)
This version publication date	30 August 2018
First version publication date	05 August 2016

Trial information

Trial identification

Sponsor protocol code	000048

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01723982
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ferring Pharmaceuticals A/S
Sponsor organisation address	Kay Fiskers Plads 11, Copenhagen S, Denmark, 2300
Public contact	Clinical Development Support, Ferring Pharmaceuticals, DK0-Disclosure@ferring.com
Scientific contact	Clinical Development Support, Ferring Pharmaceuticals, DK0-Disclosure@ferring.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 July 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 October 2014
Global end of trial reached?	Yes
Global end of trial date	28 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of barusiban compared to placebo on implantation rate in in-vitro fertilisation (IVF)/intracytoplasmic sperm injection (ICSI) patients.

Protection of trial subjects:

The trial was performed in accordance with the Declaration of Helsinki and its amendments in force at the initiation of the trial.

Background therapy:

Vaginal progesterone tablets (LUTINUS/ENDOMETRIN, Ferring Pharmaceuticals) 100 mg twice daily were provided for luteal phase support from the day after oocyte retrieval and until the day of the clinical pregnancy visit. On the day of transfer, subjects inserted the progesterone tablets at least 3 hours before transfer and at least 3 hours after transfer. Progesterone support could be terminated earlier than the clinical pregnancy visit in case of a negative beta unit of human chorionic gonadotropin (βhCG) test or menses.

Evidence for comparator:

This was a randomised controlled trial with placebo as the comparator to adequately document the efficacy and safety of barusiban. A placebo group was justified for this trial as there is no therapy available for this indication.

Actual start date of recruitment	14 November 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 8
Country: Number of subjects enrolled	Canada: 12
Country: Number of subjects enrolled	Poland: 33
Country: Number of subjects enrolled	Spain: 85
Country: Number of subjects enrolled	Belgium: 60
Country: Number of subjects enrolled	Czech Republic: 57
Worldwide total number of subjects	255
EEA total number of subjects	235

Notes:

Subjects enrolled per age group

In utero	0

Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	255
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The participating subjects were recruited among the patients attending the clinics. A total of 12 sites randomised subjects into the trial : 1 in Australia, 2 in Belgium, 1 in Canada, 1 in Czech Republic, 1 in Poland and 6 in Spain.

Pre-assignment

Screening details:

A total of 363 subjects were screened in the trial, of whom 255 subjects were randomised: 130 to barusiban and 125 to placebo.

Period 1

Period 1 title	Randomisation to End-of-Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Barusiban

Arm description:

Subjects randomised to barusiban IMP were included in this group.

Arm type	Experimental
Investigational medicinal product name	Barusiban
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The barusiban IMP was a 20 mg/mL isotonic solution in acetate buffer. The 1st IMP administration of barusiban 40 mg subcutaneously (SC) was 45 min prior to transfer and 2nd administration of barusiban 10 mg SC was 60 min after the 1st administration.

Arm title	Placebo

Arm description:

Subjects randomised to placebo IMP were included in this group.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The placebo IMP was an isotonic acetate buffer solution. The 1st administration of isotonic acetate buffer SC was 45 min prior to transfer and 2nd administration of isotonic acetate buffer SC was 60 min after the 1st administration.

Number of subjects in period 1	Barusiban	Placebo
Started	130	125
Completed	123	118
Not completed	7	7
Protocol deviation	7	7

Baseline characteristics

Reporting groups	
Reporting group title	Barusiban
Reporting group description:	
Subjects randomised to barusiban IMP were included in this group.	
Reporting group title	Placebo
Reporting group description:	
Subjects randomised to placebo IMP were included in this group.	

Reporting group values	Barusiban	Placebo	Total
Number of subjects	130	125	255
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	130	125	255
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	32.7	33.5	
standard deviation	± 3.42	± 3.31	-
Gender categorical Units: Subjects			
Female	130	125	255
Male	0	0	0

End points

End points reporting groups

Reporting group title	Barusiban
Reporting group description:	
Subjects randomised to barusiban IMP were included in this group.	
Reporting group title	Placebo
Reporting group description:	
Subjects randomised to placebo IMP were included in this group.	
Subject analysis set title	Intention-to-Treat (ITT) Analysis Set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT analysis set was defined as all randomised subjects.	
Subject analysis set title	Per-Protocol (PP) Analysis Set
Subject analysis set type	Per protocol
Subject analysis set description:	
The PP analysis set was defined as all randomised and exposed subjects except those excluded as a result of major protocol deviations.	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety analysis set was defined as all randomised and exposed subjects.	

Primary: Ongoing Implantation Rate

End point title	Ongoing Implantation Rate
End point description:	
Ongoing implantation rate was defined as the number of viable fetuses 10-11 weeks after transfer divided by the number of embryos/blastocysts transferred. Data are presented for the ITT analysis set.	
End point type	Primary
End point timeframe:	
10-11 weeks after transfer.	

End point values	Barusiban	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130[1]	125[2]		
Units: Adjusted response rate (%)				
number (not applicable)	25	23.1		

Notes:

[1] - Number of embryos/blastocysts = 225

[2] - Number of embryos/blastocysts = 215

Statistical analyses

Statistical analysis title	Adjusted Ongoing Implantation Rate
Statistical analysis description:	
Analysis of hypothesis of ‘equal effect’ against the alternative of ‘different effect’ between the probability that an embryo/blastocyst would implant in the barusiban and placebo groups.	
Comparison groups	Barusiban v Placebo

Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.663 [4]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.78

Notes:

[3] - Comparison between the groups was based on logistic regression model with treatment, trial site, primary reason for infertility, and embryo/blastocyst quality as factors.
[4] - p-value corresponds to a two-sided test of superiority.

Primary: Ongoing Implantation Rate - Transfer Day 3

End point title	Ongoing Implantation Rate - Transfer Day 3

End point description:

Ongoing implantation rate was analysed for subjects with transfer on day 3. Data are presented for the ITT analysis set.

End point type	Primary

End point timeframe:

10-11 weeks after transfer.

End point values	Barusiban	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[5]	62[6]		
Units: Adjusted response rate (%)				
number (not applicable)	11.8	17.6		

Notes:

[5] - Number of embryos transferred = 117

[6] - Number of embryos transferred = 111

Statistical analyses

Statistical analysis title	Adjusted Ongoing Implantation Rate-Transfer Day 3

Statistical analysis description:

Analysis of ongoing implantation rate in subjects with transfer on day 3.

Comparison groups	Barusiban v Placebo
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.227 [8]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.628

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	1.34

Notes:

[7] - Comparison between the groups was based on logistic regression model with treatment, number of embryos transferred, trial site, and primary reason for infertility as factors.
[8] - p-value corresponds to a two-sided test of superiority.

Primary: Ongoing Implantation Rate - Transfer Day 5

End point title	Ongoing Implantation Rate - Transfer Day 5

End point description:

Ongoing implantation rate was analysed for subjects with transfer on day 5. Data are presented for the ITT analysis set.

End point type	Primary

End point timeframe:

10-11 weeks after transfer.

End point values	Barusiban	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[9]	63[10]		
Units: Adjusted response rate (%)				
number (not applicable)	41.3	23.2		

Notes:

[9] - Number of blastocysts transferred = 108

[10] - Number of blastocysts transferred = 104

Statistical analyses

Statistical analysis title	Adjusted Ongoing Implantation Rate-Transfer Day 5

Statistical analysis description:

Analysis of ongoing implantation rate in subjects with transfer on day 5.

Comparison groups	Barusiban v Placebo
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.022 [12]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.337
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.13
upper limit	4.84

Notes:

[11] - Comparison between the groups was based on logistic regression model with treatment, number of blastocysts transferred, trial site, primary reason for infertility, and blastocyst quality parameters as factors.

[12] - p-value corresponds to a two-sided test of superiority.

Secondary: Ongoing Pregnancy Rate

End point title	Ongoing Pregnancy Rate

End point description:

Ongoing pregnancy was defined as at least one intrauterine viable fetus 10-11 weeks after transfer. Data are presented for the ITT analysis set.

End point type	Secondary

End point timeframe:

10-11 weeks after transfer.

End point values	Barusiban	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	125		
Units: Adjusted response rate (%)				
number (not applicable)	34.2	35.1		

Statistical analyses

Statistical analysis title	Adjusted Ongoing Pregnancy Rate

Statistical analysis description:

Analysis of ongoing pregnancy rate was intended to provide supportive evidence of treatment effect of barusiban.

Comparison groups	Barusiban v Placebo
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.897 [14]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.963
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.71

Notes:

[13] - Comparison between the groups was based on logistic regression model with treatment, trial site, primary reason for infertility, and embryo/blastocyst quality as factors.
[14] - p-value corresponds to a two-sided test of superiority.

Secondary: Ongoing Pregnancy Rate - Transfer Day 3

End point title	Ongoing Pregnancy Rate - Transfer Day 3

End point description:

Ongoing pregnancy was analysed for subjects with transfer on day 3. Data are presented for the ITT analysis set.

End point type	Secondary

End point timeframe:

10-11 weeks after transfer.

End point values	Barusiban	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	62		
Units: Adjusted response rate (%)				
number (not applicable)	19.2	29.9		

Statistical analyses

Statistical analysis title	Adjusted Ongoing Pregnancy Rate- Transfer Day 3

Statistical analysis description:

Analysis of ongoing pregnancy rate in subjects with transfer on day 3.

Comparison groups	Barusiban v Placebo
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.219 [16]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.557
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	1.42

Notes:

[15] - Comparison between the groups was based on logistic regression model with treatment, number of embryos transferred, trial site, and primary reason for infertility as factors.
[16] - p-value corresponds to a two-sided test of superiority.

Secondary: Ongoing Pregnancy Rate - Transfer Day 5

End point title	Ongoing Pregnancy Rate - Transfer Day 5

End point description:

Ongoing pregnancy was analysed for subjects with transfer on day 5. Data are presented for the ITT analysis set.

End point type	Secondary

End point timeframe:

10-11 weeks after transfer.

End point values	Barusiban	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	63		
Units: Adjusted response rate (%)				
number (not applicable)	49.7	33.4		

Statistical analyses

Statistical analysis title	Adjusted Ongoing Pregnancy Rate- Transfer Day 5

Statistical analysis description:

Analysis of ongoing pregnancy rate in subjects with transfer on day 5.

Comparison groups	Barusiban v Placebo
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	= 0.147 [18]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.967
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	4.9

Notes:

[17] - Comparison between the groups was based on logistic regression model with treatment, number of blastocysts transferred, trial site, primary reason for infertility, and blastocyst quality parameters as factors.

[18] - p-value corresponds to a two-sided test of superiority.

Secondary: Implantation Rate

End point title	Implantation Rate

End point description:

Implantation rate was defined as the number of intrauterine gestational sacs with fetal heart beat (5-6 weeks after transfer) divided by the number of embryos/blastocysts transferred. Data are presented for the ITT analysis set.

End point type	Secondary

End point timeframe:

5-6 weeks after transfer.

End point values	Barusiban	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130[19]	125[20]		
Units: Adjusted response rate (%)				
number (not applicable)	27.1	24.4		

Notes:

[19] - Number of embryos/blastocysts = 225

[20] - Number of embryos/blastocysts = 215

Statistical analyses

Statistical analysis title	Adjusted Implantation Rate

Statistical analysis description:

Analysis of implantation rate was intended to provide supportive evidence of treatment effect of barusiban.

Comparison groups	Barusiban v Placebo
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	= 0.546 [22]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.154
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.83

Notes:

[21] - Comparison between the groups was based on logistic regression model with treatment, trial site, primary reason for infertility, and embryo/blastocyst quality as factors.

[22] - p-value corresponds to a two-sided test of superiority.

Secondary: Implantation Rate - Transfer Day 3

End point title	Implantation Rate - Transfer Day 3

End point description:

Implantation rate was analysed for subjects with transfer on day 3. Data are presented for the ITT analysis set.

End point type	Secondary

End point timeframe:

5-6 weeks after transfer.

End point values	Barusiban	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[23]	62[24]		
Units: Adjusted response rate (%)				
number (not applicable)	13.7	19.6		

Notes:

[23] - Number of embryos transferred = 117

[24] - Number of embryos transferred = 111

Statistical analyses

Statistical analysis title	Adjusted Implantation Rate - Transfer Day 3

Statistical analysis description:

Analysis of implantation rate in subjects with transfer on day 3.

Comparison groups	Barusiban v Placebo
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority[25]
P-value	= 0.251 [26]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.31
upper limit	1.35

Notes:

[25] - Comparison between the groups was based on logistic regression model with treatment, number of embryos transferred, trial site, and primary reason for infertility as factors.
[26] - p-value corresponds to a two-sided test of superiority.

Secondary: Implantation Rate - Transfer Day 5

End point title	Implantation Rate - Transfer Day 5

End point description:

Implantation rate was analysed for subjects with transfer on day 5. Data are presented for the ITT analysis set.

End point type	Secondary

End point timeframe:

5-6 weeks after transfer.

End point values	Barusiban	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[27]	63[28]		
Units: Adjusted response rate (%)				
number (not applicable)	44.6	24.6		

Notes:

[27] - Number of blastocysts transferred = 108

[28] - Number of blastocysts transferred = 104

Statistical analyses

Statistical analysis title	Adjusted Implantation Rate - Transfer Day 5

Statistical analysis description:

Analysis of implantation rate in subjects with transfer on day 5.

Comparison groups	Barusiban v Placebo

Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	superiority[29]
P-value	= 0.013 [30]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.471
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.21
upper limit	5.06

Notes:

[29] - Comparison between the groups was based on logistic regression model with treatment, number of blastocysts transferred, trial site, primary reason for infertility, and blastocyst quality parameters as factors.

[30] - p-value corresponds to a two-sided test of superiority.

Secondary: Clinical Pregnancy with Fetal Heart Beat Rate

End point title	Clinical Pregnancy with Fetal Heart Beat Rate

End point description:

Clinical pregnancy with fetal heart beat was defined as at least one intrauterine gestational sac with fetal heart beat 5-6 weeks after transfer. Data are presented for the ITT analysis set.

End point type	Secondary

End point timeframe:

5-6 weeks after transfer.

End point values	Barusiban	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	125		
Units: Adjusted response rate (%)				
number (not applicable)	37.4	36.4		

Statistical analyses

Statistical analysis title	Adj. Clinical Pregnancy with Fetal Heart Beat Rate

Statistical analysis description:

Analysis of clinical pregnancy with fetal heart beat rate was intended to provide supportive evidence of treatment effect of barusiban.

Comparison groups	Barusiban v Placebo
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	superiority[31]
P-value	= 0.882 [32]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.044

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	1.83

Notes:

[31] - Comparison between the groups was based on logistic regression model with treatment, trial site, primary reason for infertility, and embryo/blastocyst quality as factors.
[32] - p-value corresponds to a two-sided test of superiority.

Secondary: Clinical Pregnancy with Fetal Heart Beat Rate - Transfer Day 3

End point title	Clinical Pregnancy with Fetal Heart Beat Rate - Transfer Day 3

End point description:

Clinical pregnancy with fetal heart beat rate was analysed for subjects with transfer on day 3. Data are presented for the ITT analysis set.

End point type	Secondary

End point timeframe:

5-6 weeks after transfer.

End point values	Barusiban	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	62		
Units: Adjusted response rate (%)				
number (not applicable)	22.3	32.7		

Statistical analyses

Statistical analysis title	Adj. Clin. Pregnancy with Fetal Heart Beat Rate

Statistical analysis description:

Analysis of clinical pregnancy with fetal heart beat rate in subjects with transfer on day 3.

Comparison groups	Barusiban v Placebo
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority[33]
P-value	= 0.254 [34]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.592
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.24
upper limit	1.46

Notes:

[33] - Comparison between the groups was based on logistic regression model with treatment, number of embryos transferred, trial site, and primary reason for infertility as factors.

[34] - p-value corresponds to a two-sided test of superiority.

Secondary: Clinical Pregnancy with Fetal Heart Beat Rate - Transfer Day 5

End point title	Clinical Pregnancy with Fetal Heart Beat Rate - Transfer Day 5

End point description:

Clinical pregnancy with fetal heart beat rate was analysed for subjects with transfer on day 5. Data are presented for the ITT analysis set.

End point type	Secondary

End point timeframe:

5-6 weeks after transfer.

End point values	Barusiban	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	63		
Units: Adjusted response rate (%)				
number (not applicable)	53.9	33.8		

Statistical analyses

Statistical analysis title	Adj. Clin. Pregnancy with Fetal Heart Beat Rate

Statistical analysis description:

Analysis of clinical pregnancy with fetal heat beat rate in subjects with transfer on day 5.

Comparison groups	Barusiban v Placebo
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	superiority[35]
P-value	= 0.074 [36]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	5.68

Notes:

[35] - Comparison between the groups was based on logistic regression model with treatment, number of blastocysts transferred, trial site, primary reason for infertility, and blastocyst quality parameters as factors.

[36] - p-value corresponds to a two-sided test of superiority.

Secondary: Positive βhCG Rate

End point title	Positive βhCG Rate

End point description:

Positive βhCG was confirmed by a blood test 13-15 days after transfer. Data are presented for the ITT analysis set.

End point type	Secondary

End point timeframe:

13-15 days after transfer.

End point values	Barusiban	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	125		
Units: Adjusted response rate (%)				
number (not applicable)	47.9	44.4		

Statistical analyses

Statistical analysis title	Adjusted Positive βhCG Rate

Statistical analysis description:

Analysis of positive βhCG rate was intended to provide supportive evidence of treatment effect of barusiban.

Comparison groups	Barusiban v Placebo
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	superiority[37]
P-value	= 0.612 [38]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.154
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	2

Notes:

[37] - Comparison between the groups was based on logistic regression model with treatment, trial site, primary reason for infertility, and embryo/blastocyst quality as factors.
[38] - p-value corresponds to a two-sided test of superiority.

Secondary: Positive βhCG Rate - Transfer Day 3

End point title	Positive βhCG Rate - Transfer Day 3

End point description:

Positive βhCG rate was analysed for subjects with transfer on day 3. Data are presented for the ITT analysis set.

End point type	Secondary

End point timeframe:

13-15 days after transfer.

End point values	Barusiban	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	62		
Units: Adjusted response rate (%)				
number (not applicable)	33.5	43.3		

Statistical analyses

Statistical analysis title	Adjusted Positive βhCG Rate - Transfer Day 3

Statistical analysis description:

Analysis of positive βhCG rate in subjects with transfer on day 3.

Comparison groups	Barusiban v Placebo
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority[39]
P-value	= 0.313 [40]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.658
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	1.48

Notes:

[39] - Comparison between the groups was based on logistic regression model with treatment, number of embryos transferred, trial site, and primary reason for infertility as factors.
[40] - p-value corresponds to a two-sided test of superiority.

Secondary: Positive βhCG Rate - Transfer Day 5

End point title	Positive βhCG Rate - Transfer Day 5

End point description:

Positive βhCG rate was analysed for subjects with transfer on day 5. Data are presented for the ITT analysis set.

End point type	Secondary

End point timeframe:

13-15 days after transfer.

End point values	Barusiban	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	63		
Units: Adjusted response rate (%)				
number (not applicable)	63.4	43		

Statistical analyses

Statistical analysis title	Adjusted Positive βhCG Rate - Transfer Day 5

Statistical analysis description:

Analysis of positive βhCG rate in subjects with transfer on day 5.

Comparison groups	Barusiban v Placebo
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	superiority[41]
P-value	= 0.077 [42]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	5.73

Notes:

[41] - Comparison between the groups was based on logistic regression model with treatment, number of blastocysts transferred, trial site, primary reason for infertility, and blastocyst quality parameters as factors.
[42] - p-value corresponds to a two-sided test of superiority.

Secondary: Barusiban Concentration

End point title	Barusiban Concentration[43]

End point description:

The plasma concentration of barusiban at the expected tmax was analysed. Data are presented for the ITT analysis set.

End point type	Secondary

End point timeframe:

30 minutes after the 2nd IMP administration.

Notes:

[43] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results for this endpoint is only reported for the barusiban group since barusiban was not administered in the placebo group.

End point values	Barusiban			
Subject group type	Reporting group			
Number of subjects analysed	130			
Units: ng/mL				
arithmetic mean (standard deviation)	2643 (± 565)			

Statistical analyses

No statistical analyses for this end point

Secondary: Injection Site Reactions

End point title	Injection Site Reactions

End point description:

Presence and intensity (none, mild, moderate or severe) of redness, pain, itching, swelling and bruising was assessed by the investigator directly or by asking the subject, as applicable. Data are presented for the safety analysis set.
The numbers presented refer to number of subjects with at least one mild/moderate/severe reaction (out of a total of 20 assessments per subject).

End point type	Secondary

End point timeframe:

Injection site reactions were assessed immediately and 30 min after each IMP administration (i.e. post-1st IMP and post-2nd IMP).

End point values	Barusiban	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	125		
Units: Number of subjects				
Mild	121	95		
Moderate	67	37		
Severe	7	9		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were recorded from signing of informed consent to the end-of-trial.	
Adverse event reporting additional description:	
Adverse events with onset after start of the first IMP administration were considered treatment-emergent and are presented for the safety analysis set.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups	
Reporting group title	Barusiban
Reporting group description:	
Subjects randomised to barusiban IMP were included in this group.	
Reporting group title	Placebo
Reporting group description:	
Subjects randomised to placebo IMP were included in this group.	

Serious adverse events	Barusiban	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 130 (2.31%)	4 / 125 (3.20%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Pregnancy, puerperium and perinatal conditions			
Haemorrhage in pregnancy			
subjects affected / exposed	3 / 130 (2.31%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ectopic pregnancy			
subjects affected / exposed	0 / 130 (0.00%)	2 / 125 (1.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion spontaneous			
subjects affected / exposed	0 / 130 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast			

disorders			
Pelvic pain			
subjects affected / exposed	0 / 130 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Barusiban	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	59 / 130 (45.38%)	46 / 125 (36.80%)	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 130 (3.85%)	8 / 125 (6.40%)	
occurrences (all)	5	10	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	15 / 130 (11.54%)	12 / 125 (9.60%)	
occurrences (all)	15	13	
Haemorrhage in pregnancy			
subjects affected / exposed	12 / 130 (9.23%)	2 / 125 (1.60%)	
occurrences (all)	13	2	
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	14 / 130 (10.77%)	2 / 125 (1.60%)	
occurrences (all)	26	2	
Injection site swelling			
subjects affected / exposed	10 / 130 (7.69%)	2 / 125 (1.60%)	
occurrences (all)	15	2	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	6 / 130 (4.62%)	9 / 125 (7.20%)	
occurrences (all)	7	10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None

Notes: