



Clinical trial results:

Effect of Early Growth Hormone Treatment on Long-term Growth and Skeletal Maturation in Girls with Turner Syndrome ("Turner Tweens and Teens" Study)

Summary

EudraCT number	2016-001502-42
Trial protocol	Outside EU/EEA
Global end of trial date	09 September 2015

Results information

Result version number	v2 (current)
This version publication date	03 May 2017
First version publication date	29 July 2016
Version creation reason	<ul style="list-style-type: none">• Correction of full data set Correction needed for data.

Trial information

Trial identification

Sponsor protocol code	10088
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00266656
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number : 10088, Trial Alias: B9R-US-GDGH

Notes:

Sponsors

Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, IN, United States, 46285
Public contact	Available Mon - Fri 9 AM - 5 PM EST , Eli Lilly and Company, 1 877-CTLilly,
Scientific contact	Available Mon - Fri 9 AM - 5 PM EST , Eli Lilly and Company, 1 877-285-4559,

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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 September 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	09 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is an extension study that will gather long-term data on the effect of early growth hormone (GH) treatment on adult height and other aspects of health and development in girls with Turner syndrome. The main purpose is to determine whether girls who received 2 years of GH treatment before 6 years of age achieve taller adult height than girls who were untreated during this time. The study will also look at middle ear and hearing function, and cognitive and behavioral development. Protocol completion is defined as attainment of height velocity less than or equal to 1.0 cm/year, or bone age greater than or equal to 15 years.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 December 2005
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	United States: 69
Worldwide total number of subjects	69
EEA total number of subjects	0

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)	69
Adolescents (12-17 years)	0
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

To be included in this study, participants had to be females with karyotype-proven Turner syndrome who were previously randomized in Study B9R-US-GDFG (NCT00406926).

Pre-assignment

Screening details:

No Text Entered

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Early Treated

Arm description:

Humatrope administered according to investigator's clinical practice and guided by the approved package insert.

Humatrope administered in B9R-US-GDFG (NCT00406926).

Arm type	Experimental
Investigational medicinal product name	Humatrope
Investigational medicinal product code	
Other name	LY137998, Somatropin, Growth hormone
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

According to investigator's clinical practice and guided by the approved package insert.

Arm title	Early Untreated
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Arm description:

Humatrope administered according to investigator's clinical practice and guided by the approved package insert.

Control: Humatrope was not administered in B9R-US-GDFG (NCT00406926).

Arm type	Experimental
Investigational medicinal product name	Humatrope
Investigational medicinal product code	
Other name	LY137998, Somatropin, Growth hormone
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

No drug administration in B9R-US-GDFG (NCT00406926).

According to investigator's clinical practice and guided by the approved package insert.

Number of subjects in period 1	Early Treated	Early Untreated
Started	36	33
Completed	22	20
Not completed	14	13
Adverse event, serious fatal	1	-
Parent/Caregiver Decision	1	2
Consent withdrawn by subject	4	2
Did Not Reach Final Height	4	8
Lost to follow-up	4	1

Baseline characteristics

Reporting groups

Reporting group title	Early Treated
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Reporting group description:

Humatrope administered according to investigator's clinical practice and guided by the approved package insert.

Humatrope administered in B9R-US-GDFG (NCT00406926).

Reporting group title	Early Untreated
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Reporting group description:

Humatrope administered according to investigator's clinical practice and guided by the approved package insert.

Control: Humatrope was not administered in B9R-US-GDFG (NCT00406926).

Reporting group values	Early Treated	Early Untreated	Total
Number of subjects	36	33	69
Age categorical Units: Subjects			
Children (2-11 years)	36	33	69
Adolescents (12-17 years)	0	0	0
Age Continuous Units: years			
arithmetic mean	8.29	8.41	-
standard deviation	± 1.22	± 1.3	-
Gender, Male/Female Units: participants			
Female	36	33	69
Male	0	0	0
Height Units: centimeter (CM)			
arithmetic mean	124.34	121.06	-
standard deviation	± 10.08	± 9.76	-
Height Standard Deviation Score (SDS) Units: Standard Deviation Score			
arithmetic mean	-0.84	-1.48	-
standard deviation	± 1.22	± 1.23	-
Bone Age Units: years			
arithmetic mean	8.73	8.34	-
standard deviation	± 1.55	± 1.57	-

End points

End points reporting groups

Reporting group title	Early Treated
Reporting group description: Humatrope administered according to investigator's clinical practice and guided by the approved package insert. Humatrope administered in B9R-US-GDFG (NCT00406926).	
Reporting group title	Early Untreated
Reporting group description: Humatrope administered according to investigator's clinical practice and guided by the approved package insert. Control: Humatrope was not administered in B9R-US-GDFG (NCT00406926).	

Primary: Most Mature Height Standard Deviation Score (SDS)

End point title	Most Mature Height Standard Deviation Score (SDS)
End point description:	
SDS reports the number of standard deviations from the mean for age and sex for an individual measurement (normal range is -2 to +2 SDS). Height SDS is derived by subtracting the population mean from individual's height value and then dividing that difference by the population standard deviation. Greater height SDS values indicate greater height.	
Population Description: All participants who achieved Near Adult Height (NAH). NAH is defined as first height measured when height velocity is less than or equal to 2.0 centimeter per year over the preceding year (in the absence of growth-impairing process such as hypothyroidism or inflammatory bowel disease), or bone age greater than or equal to 14.5 years.	
End point type	Primary
End point timeframe:	
Baseline through End of Study (10 years)	

End point values	Early Treated	Early Untreated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	26		
Units: standard deviation score				
arithmetic mean (standard deviation)	-1.37 (± 1.09)	-1.6 (± 1.21)		

Statistical analyses

Statistical analysis title	Statistical Analysis for Primary Outcome
Comparison groups	Early Untreated v Early Treated

Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.59
Method	ANCOVA

Secondary: Height SDS at various ages

End point title	Height SDS at various ages
End point description:	
SDS reports the number of standard deviations from the mean for age and sex for an individual measurement (normal range is -2 to +2 SDS). Height SDS is derived by subtracting the population mean from individual's height value and then dividing that difference by the population standard deviation. Greater height SDS values indicate greater height.	
Population Description: All participants who had a baseline visit and at least one post-baseline visit.	
End point type	Secondary
End point timeframe:	
Age 10, Age 13, Age 16	

End point values	Early Treated	Early Untreated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	32		
Units: Standard deviation score				
arithmetic mean (standard deviation)				
Age 10 (n=32, 30)	-0.66 (± 1.16)	-1.28 (± 1.17)		
Age 13 (n=29, 29)	-1.29 (± 1.24)	-1.87 (± 1.16)		
Age 16 (n=18, 18)	-1.66 (± 1.11)	-1.69 (± 1.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Age at attainment of Tanner 2 breast development

End point title	Age at attainment of Tanner 2 breast development
End point description:	
The Tanner 2 breast development is the age at first evidence of breast development.	
Population Description: All participants who had a baseline visit and at least one post-baseline visit.	
End point type	Secondary
End point timeframe:	
Baseline through End of Study (10 years)	

End point values	Early Treated	Early Untreated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	32		
Units: years				
arithmetic mean (standard error)	11.8 (\pm 0.26)	12.14 (\pm 0.31)		

Statistical analyses

No statistical analyses for this end point

Secondary: Chronological age at first visit participant attained bone age of 14.5 years

End point title	Chronological age at first visit participant attained bone age of 14.5 years
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End point description:

Bone age was measured by standard radiograph, x-ray at baseline and annually for 10 years or until attainment of height velocity less than or equal to 1.0 centimeter per year (cm/year) and bone age greater or equal to 15 years.

Population Description: All participants who achieved Near Adult Height (NAH). NAH is defined as first height measured when height velocity is less than or equal to 2.0 centimeter per year over the preceding year (in the absence of growth-impairing process such as hypothyroidism or inflammatory bowel disease), or bone age greater than or equal to 14.5 years.

End point type	Secondary
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End point timeframe:

Baseline through End of Study (10 years)

End point values	Early Treated	Early Untreated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	26		
Units: years				
arithmetic mean (standard error)	14.64 (\pm 0.25)	15.26 (\pm 0.23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Reports of serious adverse events

End point title	Reports of serious adverse events
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End point description:

Number of serious adverse events (SAEs) reported. Any adverse event (AE) from this study that results in one of the following outcomes, or is significant for any other reason were reported as an SAE: death, initial or prolonged inpatient hospitalization, a life-threatening experience (that is, immediate risk of dying), persistent or significant disability/incapacity, congenital anomaly/birth defect in the offspring of a study subject, significant for any other reason (includes cancer, other than superficial, and basal cell or squamous cell carcinomas of the skin, that did not meet other serious adverse event criteria).

A summary of other nonserious AEs, and all SAE's, regardless of causality, is located in the Reported Adverse Events section.

Population Description: All participants who had a baseline visit, regardless of whether or not they received Humatrope at any time.

End point type	Secondary
End point timeframe:	
Baseline through End of Study (10 years)	

End point values	Early Treated	Early Untreated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	33		
Units: events				
number (not applicable)	8	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Occurrence of pre-specified clinically relevant events

End point title	Percentage of Participants with Occurrence of pre-specified clinically relevant events
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End point description:

Percentage of participants for whom certain non-serious, pre-specified adverse events (AEs; those that are commonly observed in Turner syndrome or are known to be related to GH treatment: impaired glucose tolerance, diabetes mellitus, hypothyroidism, benign intracranial hypertension, scoliosis, slipped capital femoral epiphysis, solid tumor/leukemia, pancreatitis, ear infections, and high blood pressure) are reported.

Population Description: All participants who had a baseline visit, regardless of whether or not they received Humatrope at any time.

End point type	Secondary
End point timeframe:	
Baseline through End of Study (10 years)	

End point values	Early Treated	Early Untreated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	33		
Units: percentage of participants				
number (not applicable)				
Baseline Ear infections	13.9	18.2		
Baseline High Blood Pressure	0	3		
Baseline Hypothyroidism	13.9	6.1		
Baseline Scoliosis	22.2	9.1		
Year 1 Ear infections	38.9	39.4		

Year 1 High Blood Pressure	0	3		
Year 1 Hypothyroidism	11.1	12.1		
Year 1 Scoliosis	16.7	21.2		
Year 2 Diabetes	2.8	0		
Year 2 Dilatation of the Aorta	0	3		
Year 2 Ear infections	33.3	27.3		
Year 2 High Blood Pressure	0	3		
Year 2 Hypothyroidism	11.1	12.1		
Year 2 Scoliosis	22.2	24.2		
Year 3 Diabetes	2.8	0		
Year 3 Dilatation of the Aorta	0	6.1		
Year 3 Ear infections	30.6	36.4		
Year 3 High Blood Pressure	0	3		
Year 3 Hypothyroidism	11.1	12.1		
Year 3 Scoliosis	25	27.3		
Year 4 Diabetes	2.8	0		
Year 4 Dilatation of the Aorta	0	6.1		
Year 4 Ear infections	16.7	30.3		
Year 4 High Blood Pressure	0	3		
Year 4 Hypothyroidism	11.1	12.1		
Year 4 Scoliosis	25	27.3		
Year 5 Diabetes	2.8	0		
Year 5 Dilatation of the Aorta	0	6.1		
Year 5 Ear infections	22.2	27.3		
Year 5 High Blood Pressure	0	3		
Year 5 Hypothyroidism	13.9	18.2		
Year 5 Scoliosis	25	27.3		
Year 6 Diabetes	2.8	0		
Year 6 Dilatation of the Aorta	0	9.1		
Year 6 Ear infections	19.4	24.2		
Year 6 High Blood Pressure	0	3		
Year 6 Hypothyroidism	13.9	18.2		
Year 6 Scoliosis	16.7	30.3		
Year 7 Diabetes	2.8	0		
Year 7 Dilatation of the Aorta	0	9.1		
Year 7 Ear infections	19.4	18.2		
Year 7 High Blood Pressure	0	3		
Year 7 Hypothyroidism	13.9	15.2		
Year 7 Scoliosis	13.9	30.3		
Year 8 Diabetes	2.8	0		
Year 8 Dilatation of the Aorta	2.8	9.1		
Year 8 Ear infections	13.9	18.2		
Year 8 High Blood Pressure	0	3		
Year 8 Hypothyroidism	5.6	12.1		
Year 8 Scoliosis	13.9	33.3		
Year 9 Dilatation of the Aorta	0	3		
Year 9 Ear infections	2.8	3		
Year 9 High Blood Pressure	0	3		
Year 9 Hypothyroidism	2.8	6.1		
Year 9 Scoliosis	5.6	9.1		
Year 10 Scoliosis	2.8	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with abnormal tympanometry results

End point title	Percentage of participants with abnormal tympanometry results
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End point description:

Percentage of participants with abnormal tympanometry [defined as middle ear dysfunction / middle ear effusion / patent pressure equalizer tube or possible tympanic membrane perforation] results at baseline, age 10 years, and age 16 years or endpoint.

Population Description: All participants who had a baseline visit, regardless of whether or not they received Humatrope at any time.

End point type	Secondary
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End point timeframe:

Baseline, Age 10, Age 16, End of Study (10 years)

End point values	Early Treated	Early Untreated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	33		
Units: percentage of participants				
number (not applicable)				
Baseline Right Ear	44.4	54.5		
Baseline Left Ear	47.2	45.5		
Age 10 Right Ear	27.8	15.2		
Age 10 Left Ear	27.8	15.2		
Age 16 Right Ear	2.8	9.1		
Age 16 Left Ear	2.8	3		
Endpoint Right Ear	8.3	12.1		
Endpoint Left Ear	11.1	9.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with prevalence of abnormal Audiometry results

End point title	Percentage of participants with prevalence of abnormal Audiometry results
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End point description:

Percentage of participants with abnormal Audiometry results at baseline, age 10 years, and age 16 years or endpoint. Prevalence was calculated as number of participants with abnormal hearing divided by number of participants with measurable pure tone audiometry results at that visit.

Population Description: All participants who had a baseline visit, regardless of whether or not they received Humatrope at any time.

End point type	Secondary
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End point timeframe:

Baseline, Age 10, Age 16, End of Study (10 years)

End point values	Early Treated	Early Untreated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	33		
Units: percentage of participants				
number (not applicable)				
Baseline Visit (n=36, 33)	52.8	48.5		
Age 10 (n=27, 24)	44.4	29.2		
Age 16 (n=7, 9)	85.7	66.7		
Endpoint (n=24, 22)	37.5	40.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with abnormal Audiometry results Based on Pure Tone Average (PTA)

End point title	Percentage of participants with abnormal Audiometry results Based on Pure Tone Average (PTA)
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End point description:

Percentage of participants with abnormal Audiometry results at baseline, age 10 years, and age 16 years or endpoint. PTA is defined as the average of pure tone hearing thresholds at 500, 1000 and 2000 Hz (Hertz), calculated separately for each ear and for each testing method (air or bone); normal PTA is defined as pure tone hearing threshold less than or equal to 20 dB HL (decibels Hearing Level), and abnormal PTA is defined as pure tone hearing threshold greater than 20 DB HL.

Population Description: All participants who had a baseline visit, regardless of whether or not they received Humatrope at any time.

End point type	Secondary
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End point timeframe:

Baseline, Age 10, Age 16, End of Study (10 years)

End point values	Early Treated	Early Untreated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	33		
Units: percentage of participants				
number (not applicable)				
Baseline Left Ear Air (n=36, 32)	30.6	31.3		
Baseline Left Ear Bone (n=36, 32)	2.8	0		
Baseline Right Ear Air (n=36, 32)	22.2	37.5		
Baseline Right Ear Bone (n=36, 32)	22.2	2.8		
Age 10 Left Ear Air (n=27, 21)	29.6	14.3		
Age 10 Left Ear Bone (n=27, 21)	0	0		
Age 10 Right Ear Air (n=27, 22)	14.8	18.2		
Age 10 Right Ear Bone (n=27, 22)	0	9.1		
Age 16 Left Ear Air (n=7, 9)	57.1	66.7		
Age 16 Left Ear Bone (n=7, 9)	0	0		
Age 16 Right Ear Air (n=7, 9)	28.6	33.3		
Age 16 Right Ear Bone (n=7, 9)	0	22.2		
Endpoint Left Ear Air (n=20, 20)	30	35		
Endpoint Left Ear Bone (n=20, 20)	5	20		
Endpoint Right Ear Air (n=20, 20)	20	35		
Endpoint Right Ear Bone (n=20, 20)	10	25		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Entire Study

Adverse event reporting additional description:

B9R-US-GDGH

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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Reporting groups

Reporting group title	Early Untreated
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Reporting group description: -

Reporting group title	Early Treated
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Reporting group description: -

Serious adverse events	Early Untreated	Early Treated	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 33 (15.15%)	6 / 36 (16.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
medulloblastoma			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 33 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
anomalous pulmonary venous connection			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 33 (3.03%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
atrial septal defect			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	0 / 33 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pterygium colli			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 33 (3.03%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
headache			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 33 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
gastrointestinal haemorrhage			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 33 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
mediastinal mass			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 33 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
scoliosis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 33 (0.00%)	2 / 36 (5.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

cellulitis alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 33 (3.03%) 0 / 1 0 / 0	0 / 36 (0.00%) 0 / 0 0 / 0	
gastroenteritis alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 33 (0.00%) 0 / 0 0 / 0	1 / 36 (2.78%) 0 / 1 0 / 0	
lobar pneumonia alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 33 (3.03%) 0 / 1 0 / 0	0 / 36 (0.00%) 0 / 0 0 / 0	
pneumonia alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 33 (3.03%) 0 / 1 0 / 0	0 / 36 (0.00%) 0 / 0 0 / 0	

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

Non-serious adverse events	Early Untreated	Early Treated	
Total subjects affected by non-serious adverse events subjects affected / exposed	32 / 33 (96.97%)	34 / 36 (94.44%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps) haemangioma alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	2 / 36 (5.56%) 2	
melanocytic naevus alternative dictionary used: MedDRA 18.0			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>9 / 33 (27.27%)</p> <p>9</p>	<p>11 / 36 (30.56%)</p> <p>11</p>	
<p>skin papilloma</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>4 / 33 (12.12%)</p> <p>4</p>	<p>6 / 36 (16.67%)</p> <p>7</p>	
<p>Vascular disorders</p> <p>aortic dilatation</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>3 / 33 (9.09%)</p> <p>3</p>	<p>0 / 36 (0.00%)</p> <p>0</p>	
<p>hypertension</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>2 / 33 (6.06%)</p> <p>2</p>	<p>1 / 36 (2.78%)</p> <p>1</p>	
<p>lymphoedema</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>1 / 33 (3.03%)</p> <p>1</p>	<p>3 / 36 (8.33%)</p> <p>3</p>	
<p>Surgical and medical procedures</p> <p>adenoidectomy</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>0 / 33 (0.00%)</p> <p>0</p>	<p>2 / 36 (5.56%)</p> <p>2</p>	
<p>ear tube insertion</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>5 / 33 (15.15%)</p> <p>7</p>	<p>4 / 36 (11.11%)</p> <p>5</p>	
<p>mole excision</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>2 / 33 (6.06%)</p> <p>2</p>	<p>6 / 36 (16.67%)</p> <p>6</p>	
<p>oral surgery</p> <p>alternative dictionary used: MedDRA 18.0</p>		

subjects affected / exposed	0 / 33 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
orthodontic procedure			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	7 / 33 (21.21%)	4 / 36 (11.11%)	
occurrences (all)	7	4	
palatal operation			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 33 (0.00%)	3 / 36 (8.33%)	
occurrences (all)	0	3	
tooth extraction			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	2 / 33 (6.06%)	2 / 36 (5.56%)	
occurrences (all)	2	2	
tympanoplasty			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	3 / 33 (9.09%)	5 / 36 (13.89%)	
occurrences (all)	3	5	
wisdom teeth removal			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 33 (3.03%)	2 / 36 (5.56%)	
occurrences (all)	1	2	
General disorders and administration site conditions			
pain			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 33 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
peripheral swelling			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 33 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
pyrexia			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed occurrences (all)	8 / 33 (24.24%) 8	11 / 36 (30.56%) 11	
Immune system disorders drug hypersensitivity alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all) multiple allergies alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all) seasonal allergy alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0 0 / 33 (0.00%) 0 2 / 33 (6.06%) 2	2 / 36 (5.56%) 2 2 / 36 (5.56%) 2 5 / 36 (13.89%) 5	
Social circumstances corrective lens user alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all) orthodontic appliance user alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)	8 / 33 (24.24%) 8 7 / 33 (21.21%) 7	3 / 36 (8.33%) 3 9 / 36 (25.00%) 9	
Reproductive system and breast disorders dysmenorrhoea alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	3 / 36 (8.33%) 3	
Respiratory, thoracic and mediastinal disorders cough alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all) nasal congestion	6 / 33 (18.18%) 6	8 / 36 (22.22%) 8	

<p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>3 / 33 (9.09%)</p> <p>3</p>	<p>1 / 36 (2.78%)</p> <p>1</p>	
<p>oropharyngeal pain</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>4 / 33 (12.12%)</p> <p>4</p>	<p>5 / 36 (13.89%)</p> <p>5</p>	
<p>respiratory disorder</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 33 (6.06%)</p> <p>2</p>	<p>1 / 36 (2.78%)</p> <p>1</p>	
<p>rhinorrhoea</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>3 / 33 (9.09%)</p> <p>3</p>	<p>2 / 36 (5.56%)</p> <p>2</p>	
<p>sinus congestion</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 33 (3.03%)</p> <p>1</p>	<p>2 / 36 (5.56%)</p> <p>2</p>	
<p>Psychiatric disorders</p> <p>anxiety</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>depression</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>insomnia</p> <p>alternative dictionary used: MedDRA 18.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>obsessive-compulsive disorder</p> <p>alternative dictionary used: MedDRA 18.0</p>	<p>6 / 33 (18.18%)</p> <p>6</p> <p>3 / 33 (9.09%)</p> <p>3</p> <p>1 / 33 (3.03%)</p> <p>1</p>	<p>7 / 36 (19.44%)</p> <p>7</p> <p>2 / 36 (5.56%)</p> <p>2</p> <p>2 / 36 (5.56%)</p> <p>2</p>	

subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	2 / 36 (5.56%) 2	
Investigations			
echocardiogram normal alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)	6 / 33 (18.18%) 6	2 / 36 (5.56%) 2	
electrocardiogram normal alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	1 / 36 (2.78%) 1	
ultrasound kidney normal alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	2 / 36 (5.56%) 2	
ultrasound scan normal alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	0 / 36 (0.00%) 0	
Injury, poisoning and procedural complications			
joint dislocation alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	2 / 36 (5.56%) 2	
ligament sprain alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	0 / 36 (0.00%) 0	
radius fracture alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	3 / 36 (8.33%) 3	
wrist fracture alternative dictionary used: MedDRA 18.0			

subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	0 / 36 (0.00%) 0	
Cardiac disorders palpitations alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	2 / 36 (5.56%) 2	
Nervous system disorders headache alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)	9 / 33 (27.27%) 10	11 / 36 (30.56%) 13	
Ear and labyrinth disorders conductive deafness alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all) ear pain alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all) hearing impaired alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all) tympanic membrane perforation alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1 3 / 33 (9.09%) 4 3 / 33 (9.09%) 3 2 / 33 (6.06%) 2	4 / 36 (11.11%) 4 6 / 36 (16.67%) 8 2 / 36 (5.56%) 2 7 / 36 (19.44%) 8	
Eye disorders myopia alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	2 / 36 (5.56%) 2	
Gastrointestinal disorders			

abdominal pain		
alternative dictionary used: MedDRA 18.0		
subjects affected / exposed	2 / 33 (6.06%)	4 / 36 (11.11%)
occurrences (all)	2	4
abdominal pain upper		
alternative dictionary used: MedDRA 18.0		
subjects affected / exposed	3 / 33 (9.09%)	1 / 36 (2.78%)
occurrences (all)	3	1
coeliac disease		
alternative dictionary used: MedDRA 18.0		
subjects affected / exposed	3 / 33 (9.09%)	1 / 36 (2.78%)
occurrences (all)	3	1
constipation		
alternative dictionary used: MedDRA 18.0		
subjects affected / exposed	2 / 33 (6.06%)	3 / 36 (8.33%)
occurrences (all)	2	3
diarrhoea		
alternative dictionary used: MedDRA 18.0		
subjects affected / exposed	5 / 33 (15.15%)	5 / 36 (13.89%)
occurrences (all)	5	5
gastrooesophageal reflux disease		
alternative dictionary used: MedDRA 18.0		
subjects affected / exposed	2 / 33 (6.06%)	2 / 36 (5.56%)
occurrences (all)	2	2
tooth malformation		
alternative dictionary used: MedDRA 18.0		
subjects affected / exposed	1 / 33 (3.03%)	2 / 36 (5.56%)
occurrences (all)	1	2
toothache		
alternative dictionary used: MedDRA 18.0		
subjects affected / exposed	0 / 33 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	2
vomiting		
alternative dictionary used: MedDRA 18.0		

subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 3	12 / 36 (33.33%) 12	
Skin and subcutaneous tissue disorders			
acne			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 33 (0.00%)	3 / 36 (8.33%)	
occurrences (all)	0	3	
eczema			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 33 (3.03%)	2 / 36 (5.56%)	
occurrences (all)	1	2	
keloid scar			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 33 (3.03%)	2 / 36 (5.56%)	
occurrences (all)	1	2	
rash			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	5 / 33 (15.15%)	0 / 36 (0.00%)	
occurrences (all)	5	0	
seborrhoea			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	3 / 33 (9.09%)	1 / 36 (2.78%)	
occurrences (all)	3	1	
seborrhoeic dermatitis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	3 / 33 (9.09%)	1 / 36 (2.78%)	
occurrences (all)	3	1	
Renal and urinary disorders			
dysuria			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 33 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
enuresis			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	1 / 36 (2.78%) 1	
Endocrine disorders autoimmune thyroiditis alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	0 / 36 (0.00%) 0	
goitre alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	2 / 36 (5.56%) 2	
hypothyroidism alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)	5 / 33 (15.15%) 5	4 / 36 (11.11%) 4	
Musculoskeletal and connective tissue disorders kyphosis alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 3	5 / 36 (13.89%) 5	
neck pain alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	2 / 36 (5.56%) 2	
scoliosis alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)	10 / 33 (30.30%) 10	7 / 36 (19.44%) 7	
Infections and infestations bronchitis alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)	4 / 33 (12.12%) 4	5 / 36 (13.89%) 5	
conjunctivitis alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	3 / 33 (9.09%)	4 / 36 (11.11%)
occurrences (all)	3	4
croup infectious		
alternative dictionary used: MedDRA 18.0		
subjects affected / exposed	0 / 33 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	2
ear infection		
alternative dictionary used: MedDRA 18.0		
subjects affected / exposed	2 / 33 (6.06%)	7 / 36 (19.44%)
occurrences (all)	2	7
eye infection		
alternative dictionary used: MedDRA 18.0		
subjects affected / exposed	0 / 33 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	2
gastroenteritis viral		
alternative dictionary used: MedDRA 18.0		
subjects affected / exposed	4 / 33 (12.12%)	7 / 36 (19.44%)
occurrences (all)	5	7
impetigo		
alternative dictionary used: MedDRA 18.0		
subjects affected / exposed	1 / 33 (3.03%)	2 / 36 (5.56%)
occurrences (all)	1	2
influenza		
alternative dictionary used: MedDRA 18.0		
subjects affected / exposed	3 / 33 (9.09%)	6 / 36 (16.67%)
occurrences (all)	3	6
kidney infection		
alternative dictionary used: MedDRA 18.0		
subjects affected / exposed	0 / 33 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	2
mononucleosis syndrome		
alternative dictionary used: MedDRA 18.0		
subjects affected / exposed	2 / 33 (6.06%)	0 / 36 (0.00%)
occurrences (all)	2	0

nasopharyngitis		
alternative dictionary used: MedDRA 18.0		
subjects affected / exposed	4 / 33 (12.12%)	8 / 36 (22.22%)
occurrences (all)	5	9
otitis externa		
alternative dictionary used: MedDRA 18.0		
subjects affected / exposed	5 / 33 (15.15%)	3 / 36 (8.33%)
occurrences (all)	6	4
otitis media		
alternative dictionary used: MedDRA 18.0		
subjects affected / exposed	12 / 33 (36.36%)	9 / 36 (25.00%)
occurrences (all)	14	11
pharyngitis streptococcal		
alternative dictionary used: MedDRA 18.0		
subjects affected / exposed	9 / 33 (27.27%)	4 / 36 (11.11%)
occurrences (all)	9	4
pneumonia		
alternative dictionary used: MedDRA 18.0		
subjects affected / exposed	2 / 33 (6.06%)	2 / 36 (5.56%)
occurrences (all)	2	2
sinusitis		
alternative dictionary used: MedDRA 18.0		
subjects affected / exposed	7 / 33 (21.21%)	7 / 36 (19.44%)
occurrences (all)	7	7
upper respiratory tract infection		
alternative dictionary used: MedDRA 18.0		
subjects affected / exposed	6 / 33 (18.18%)	1 / 36 (2.78%)
occurrences (all)	7	1
urinary tract infection		
alternative dictionary used: MedDRA 18.0		
subjects affected / exposed	0 / 33 (0.00%)	8 / 36 (22.22%)
occurrences (all)	0	9
vaginal infection		
alternative dictionary used: MedDRA 18.0		

subjects affected / exposed occurrences (all) viral infection alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0 0 / 33 (0.00%) 0	2 / 36 (5.56%) 2 4 / 36 (11.11%) 5	
Metabolism and nutrition disorders hyperlipidaemia alternative dictionary used: MedDRA 18.0 subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	3 / 36 (8.33%) 3	

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

None reported