Clinical trial results:
A Four-Year Open-Label Multi-Center Randomized Two-Arm Study Of Genotropin In Idiopathic Short Stature Patients: Comparing An Individualized, Target-Driven Treatment Regimen To Standard Dosing Of Genotropin

Summary

EudraCT number	2014-004172-32
Trial protocol	Outside EU/EEA
Global end of trial date	30 August 2012

Results information

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	01 August 2015

Trial information

Trial identification

Sponsor protocol code	A6281280

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00396097
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer
Sponsor organisation address	235 E 42nd Street, New York, United States, 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 February 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 August 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that an individualized, formula-based Genotropin regimen for children with Idiopathic Short Stature (ISS) will lead to a targeted height gain (to reach the target of 10th percentile (%), or -1.3 Standard Deviation Score (SDS)) during 24 months of treatment.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and inco mpliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelin es. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 December 2006
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: 316
Worldwide total number of subjects	316
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)	292
Adolescents (12-17 years)	24
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a 4-year, open-label, randomized study conducted at 40 centers across United States of America (USA). The first 2-years of the study constituted core phase and the last 2 years constituted the maintenance phase.

Pre-assignment

Screening details:

The subjects were randomized in 2:1 manner to formula-based dosing arm and standard dosing arm for initial 2 years of treatment, following which the subjects in formula-based dosing arm were re-randomized in a 1:1 manner to one of two physiological doses, for next 2 years, to identify the minimum genotropin dosage to maintain the growth.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard Dose Arm

Arm description:

The subjects received subcutaneous genotropin throughout the four years.

Arm type	Active comparator
Investigational medicinal product name	Genotropin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection in cartridge
Routes of administration	Subcutaneous use

Dosage and administration details:

The subjects received subcutaneous genotropin daily, at maintained standard dose of 0.37 milligram per kilogram per week (mg/kg/week), throughout the four years.

Arm title	Individualized Dose Arm

Arm description:

The subjects received subcutaneous genotropin daily, at formula-calculated dose for the initial 2 years and then lowered to physiological doses for the remaining 2 years.

Arm type	Active comparator
Investigational medicinal product name	Genotropin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The subjects received subcutaneous genotropin daily, at formula-calculated dose (up to maximum dose of 0.7 mg/kg/week) for the initial 2 years and then lowered to one of two approximately physiological doses (0.18 mg/kg/week or 0.24 mg/kg/week) for the remaining 2 years.

Number of subjects in period 1	Standard Dose Arm	Individualized Dose Arm
Started	114	202
Completed	88	156
Not completed	26	46
Consent withdrawn by subject	17	17
Adverse event, non-fatal	1	5
Not specified	3	5
Insufficient Clinical Response	1	4
Lost to follow-up	4	9
Protocol deviation	-	6

Baseline characteristics

Reporting groups	
Reporting group title	Standard Dose Arm
Reporting group description:	
The subjects received subcutaneous genotropin throughout the four years.	
Reporting group title	Individualized Dose Arm
Reporting group description:	
The subjects received subcutaneous genotropin daily, at formula-calculated dose for the initial 2 years and then lowered to physiological doses for the remaining 2 years.	

Reporting group values	Standard Dose Arm	Individualized Dose Arm	Total
Number of subjects	114	202	316
Age, Customized Units: Participants			
<= 7 years	37	70	107
>=7 years	77	132	209
Age Continuous Units: years			
arithmetic mean	8.3	8.4	
standard deviation	± 2.1	± 2.3	-
Gender, Male/Female Units: Participants			
Female	31	58	89
Male	83	144	227

End points

End points reporting groups

Reporting group title	Standard Dose Arm

Reporting group description:

The subjects received subcutaneous genotropin throughout the four years.

Reporting group title	Individualized Dose Arm

Reporting group description:

The subjects received subcutaneous genotropin daily, at formula-calculated dose for the initial 2 years and then lowered to physiological doses for the remaining 2 years.

Subject analysis set title	Individualized Dose Arm Overall
Subject analysis set type	Full analysis

Subject analysis set description:

The subjects received subcutaneous genotropin daily, at formula-calculated dose (up to maximum dose of 0.7 mg/kg/week) for the initial 2 years and then lowered to one of two approximately physiological doses (0.18 mg/kg/week or 0.24 mg/kg/week) for the remaining 2 years.

Subject analysis set title	Individualized Dose Arm 0.18 mg/kg/Week
Subject analysis set type	Full analysis

Subject analysis set description:

The subjects received subcutaneous genotropin daily, at formula-calculated dose (up to maximum dose of 0.7 mg/kg/week) for the initial 2 years and then lowered to one of two approximately physiological doses 0.18 mg/kg/week for the remaining 2 years.

Subject analysis set title	Individualized Dose Arm 0.24 mg/kg/Week
Subject analysis set type	Full analysis

Subject analysis set description:

The subjects received subcutaneous genotropin daily, at formula-calculated dose (up to maximum dose of 0.7 mg/kg/week) for the initial 2 years and then lowered to one of two approximately physiological doses 0.24 mg/kg/week for the remaining 2 years.

Primary: Absolute on-target Difference (AOTD) at 24 Months

End point title	Absolute on-target Difference (AOTD) at 24 Months

End point description:

This was defined as an absolute difference between the 24-month height standard deviation score (SDS) and targeted 24-month height SDS (10th percentile (%),or –1.3 SDS). SDS indicates how similar the subjects was to the reference population. These were calculated using 2000 Center for the Disease Control (CDC) growth reference tables (by age and gender). The Full Analysis Set (FAS) included all randomized subjects who received at least 1 dose of study treatment and had at least 1 post-baseline height SDS value available. Last observation carried forward (LOCF) rule was applied to impute Month 24 missing height SDS data.

End point type	Primary

End point timeframe:

2 years

End point values	Standard Dose Arm	Individualized Dose Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	202		
Units: Standard Deviation Score (SDS)				
arithmetic mean (standard deviation)	0.603 (± 0.2948)	0.625 (± 0.3003)		

Statistical analyses

Statistical analysis title	Absolute On-target Difference (AOTD) at 24 Months
Comparison groups	Standard Dose Arm v Individualized Dose Arm
Number of subjects included in analysis	316
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5762
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.006
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	-0.071
Variability estimate	Standard error of the mean
Dispersion value	0.033

Secondary: Variability of Height SDS at 24 Months

End point title	Variability of Height SDS at 24 Months

End point description:

The continuous endpoint of variability of height SDS at 24 months was defined as the SD of the 24 month height SDS. FAS included all randomized subjects who received at least 1 dose of study treatment and had at least 1 post-baseline height SDS value available. LOCF rule was applied to impute Month 24 missing height SDS data.

End point type	Secondary

End point timeframe:

2 years

End point values	Standard Dose Arm	Individualized Dose Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	202		
Units: Standard Deviation Score (SDS)				
arithmetic mean (standard deviation)				
Change from baseline at 24 months (n=101,184)	1.12 (± 0.408)	1.11 (± 0.518)		

Change from baseline at 24 months LOCF (n=114,202)	1.03 (± 0.475)	1.04 (± 0.544)		

Statistical analyses

Statistical analysis title	Variability of Height SDS at 24 Months
Comparison groups	Standard Dose Arm v Individualized Dose Arm
Number of subjects included in analysis	316
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.627
Method	ANOVA (Levene's Test)

Secondary: Time Cost (Months Until greater than or equal to (>=) -2 SDS)

End point title	Time Cost (Months Until greater than or equal to (>=) -2 SDS)

End point description:

Time cost was defined as the number of months needed until height SDS was within the normal limit (ie, greater than or equal to (>=) -2 SDS). FAS included all randomized subjects who received at least 1 dose of study treatment and had at least 1 post-baseline height SDS value available.

End point type	Secondary

End point timeframe:

2 years

End point values	Standard Dose Arm	Individualized Dose Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	202		
Units: Months				
median (confidence interval 95%)	12 (8 to 12)	12 (8 to 12)		

Statistical analyses

Statistical analysis title	Time Cost (Months Until >= -2 SDS)
Comparison groups	Standard Dose Arm v Individualized Dose Arm
Number of subjects included in analysis	316
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8016
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.033

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.802
upper limit	1.33

Secondary: Computed Cost of Height Gain at 48 Months

End point title	Computed Cost of Height Gain at 48 Months[1]

End point description:

The computed cost of height gain was defined as the amount of drug used relative to the observed height-gain, in terms of milligram per centimeter (mg/cm) , this was calculated at Month 48.

End point type	Secondary

End point timeframe:

4 years

Notes:

[1] - 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: Data was not collected at the end of study visit for Individual Dose Arm as comparison between the groups was not planned.

End point values	Standard Dose Arm	Individualized Dose Arm Overall	Individualized Dose Arm 0.18 mg/kg/Week	Individualized Dose Arm 0.24 mg/kg/Week
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	114	202	91	88
Units: mg/cm				
arithmetic mean (standard deviation)	72.77 (± 17.914)	67.3 (± 24.382)	63.07 (± 21.656)	69.62 (± 21.903)

Statistical analyses

Statistical analysis title	Height Gain at 48 Months
Comparison groups	Standard Dose Arm v Individualized Dose Arm Overall
Number of subjects included in analysis	316
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0101
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	5.822
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.395
upper limit	10.249
Variability estimate	Standard error of the mean
Dispersion value	2.25

Statistical analysis title	Height Gain at 48 Months: 0.18 mg/kg/week
Comparison groups	Standard Dose Arm v Individualized Dose Arm 0.18 mg/kg/Week
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	9.281
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.417
upper limit	14.145
Variability estimate	Standard error of the mean
Dispersion value	2.471

Statistical analysis title	Height Gain at 48 Months: 0.24 mg/kg/week
Comparison groups	Standard Dose Arm v Individualized Dose Arm 0.24 mg/kg/Week
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	3.204
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.707
upper limit	8.114
Variability estimate	Standard error of the mean
Dispersion value	2.495

Secondary: Estimated Cost of Height Gain Estimated Until Full Adult Height (FAH) at 48 Months

End point title	Estimated Cost of Height Gain Estimated Until Full Adult Height (FAH) at 48 Months[2]

End point description:

The estimated cost of long-term height gain until FAH was calculated. FAS included all randomized subjects who received at least 1 dose of study treatment and had at least 1 post-baseline height SDS value available. LOCF rule was applied to impute Month 24 missing height SDS data.

End point type	Secondary

End point timeframe:

4 years

Notes:

[2] - 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: Data was not collected at the end of study visit for Individual Dose Arm as comparison between the groups was not planned.

End point values	Standard Dose Arm	Individualized Dose Arm Overall	Individualized Dose Arm 0.18 mg/kg/Week	Individualized Dose Arm 0.24 mg/kg/Week
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	112	192	90	88
Units: mg/cm				
arithmetic mean (standard deviation)	127.99 (± 29.708)	91.34 (± 31.854)	80.06 (± 21)	92.24 (± 25.213)

Statistical analyses

Statistical analysis title	Full Adult Height
Comparison groups	Standard Dose Arm v Individualized Dose Arm Overall
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	36.899
Confidence interval	
level	95 %
sides	2-sided
lower limit	30.181
upper limit	43.618
Variability estimate	Standard error of the mean
Dispersion value	3.414

Statistical analysis title	Full Adult Height: 0.18mg/kg/Week
Comparison groups	Standard Dose Arm v Individualized Dose Arm 0.18 mg/kg/Week
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	48.517

Confidence interval	
level	95 %
sides	2-sided
lower limit	42.054
upper limit	54.98
Variability estimate	Standard error of the mean
Dispersion value	3.284

Statistical analysis title	Full Adult Height: 0.24 mg/kg/Week
Comparison groups	Standard Dose Arm v Individualized Dose Arm 0.24 mg/kg/Week
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	34.443
Confidence interval	
level	95 %
sides	2-sided
lower limit	27.936
upper limit	40.951
Variability estimate	Standard error of the mean
Dispersion value	3.306

Secondary: Change From Baseline in Height SDS at 48 Months.

End point title	Change From Baseline in Height SDS at 48 Months.[3]

End point description:

Change in height SDS was measured at 48 months. FAS included all randomized subjects who received at least 1 dose of study treatment and had at least 1 post-baseline height SDS value available. LOCF rule was applied to impute Month 24 missing height SDS data.

End point type	Secondary

End point timeframe:

4 years

Notes:

[3] - 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: Data was not collected at the end of study visit for Individual Dose Arm as comparison between the groups was not planned.

End point values	Standard Dose Arm	Individualized Dose Arm Overall	Individualized Dose Arm 0.18 mg/kg/Week	Individualized Dose Arm 0.24 mg/kg/Week
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	114	202	91	88
Units: Standard Deviation Score (SDS)				
arithmetic mean (standard deviation)	1.33 (± 0.717)	1.24 (± 0.668)	1.33 (± 0.637)	1.34 (± 0.633)

Statistical analyses

Statistical analysis title	Change From Baseline in Height SDS
Comparison groups	Standard Dose Arm v Individualized Dose Arm Overall
Number of subjects included in analysis	316
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2618
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.091
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.068
upper limit	0.249
Variability estimate	Standard error of the mean
Dispersion value	0.081

Statistical analysis title	Change From Baseline in Height SDS: 0.18mg/kg/Week
Comparison groups	Standard Dose Arm v Individualized Dose Arm 0.18 mg/kg/Week
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8926
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.013
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.172
upper limit	0.198
Variability estimate	Standard error of the mean
Dispersion value	0.094

Statistical analysis title	Change From Baseline in Height SDS: 0.24mg/kg/Week
Comparison groups	Standard Dose Arm v Individualized Dose Arm 0.24 mg/kg/Week

Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9566
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.005
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.192
upper limit	0.181
Variability estimate	Standard error of the mean
Dispersion value	0.095

Adverse events

Adverse events information

Timeframe for reporting adverse events:

4 years

Adverse event reporting additional description:

The same event may appear as both an AE and a SAE. However, what is presented are distinct events. An event may be categorized as serious in one subject and as nonserious in another subject, or one subject may have experienced both a serious and nonserious event during the study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Standard Dose Arm

Reporting group description:

The subjects received subcutaneous genotropin daily, at a maintained standard dose of 0.37 mg/kg/week, throughout the four years.

Reporting group title	Individualized Dose Arm

Reporting group description:

The subjects received subcutaneous genotropin daily, at formula-calculated dose (up to maximum dose of 0.7 mg/kg/week) for the initial 2 years and then lowered to one of two approximately physiological doses (0.18 mg/kg/week or 0.24 mg/kg/week) for the remaining 2 years.

Serious adverse events	Standard Dose Arm	Individualized Dose Arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 118 (11.02%)	7 / 198 (3.54%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Accident			
subjects affected / exposed	1 / 118 (0.85%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	1 / 118 (0.85%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			

subjects affected / exposed	1 / 118 (0.85%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foreign Body			
subjects affected / exposed	0 / 118 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	0 / 118 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 118 (0.00%)	1 / 198 (0.51%)	
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			
Arnold-chiari malformation			
subjects affected / exposed	1 / 118 (0.85%)	0 / 198 (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			
Convulsion			
subjects affected / exposed	1 / 118 (0.85%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial pressure increased			
subjects affected / exposed	1 / 118 (0.85%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocephalus			
subjects affected / exposed	1 / 118 (0.85%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

General disorders and administration site conditions			
Device breakage			
subjects affected / exposed	0 / 118 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 118 (0.85%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 118 (0.85%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	2 / 118 (1.69%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	0 / 118 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Affective disorder			
subjects affected / exposed	1 / 118 (0.85%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Scoliosis			
subjects affected / exposed	1 / 118 (0.85%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Appendicitis			
subjects affected / exposed	1 / 118 (0.85%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 118 (1.69%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	1 / 118 (0.85%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Standard Dose Arm	Individualized Dose Arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	103 / 118 (87.29%)	165 / 198 (83.33%)	
Nervous system disorders			
Headache			
subjects affected / exposed	33 / 118 (27.97%)	59 / 198 (29.80%)	
occurrences (all)	71	147	
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	5 / 118 (4.24%)	13 / 198 (6.57%)	
occurrences (all)	8	19	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	13 / 118 (11.02%)	22 / 198 (11.11%)	
occurrences (all)	14	35	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	6 / 118 (5.08%)	6 / 198 (3.03%)	
occurrences (all)	12	9	
Gastrointestinal disorders			

Abdominal discomfort			
subjects affected / exposed	2 / 118 (1.69%)	10 / 198 (5.05%)	
occurrences (all)	2	15	
Abdominal pain			
subjects affected / exposed	6 / 118 (5.08%)	6 / 198 (3.03%)	
occurrences (all)	7	9	
Abdominal pain upper			
subjects affected / exposed	9 / 118 (7.63%)	17 / 198 (8.59%)	
occurrences (all)	11	19	
Diarrhoea			
subjects affected / exposed	7 / 118 (5.93%)	12 / 198 (6.06%)	
occurrences (all)	7	12	
Nausea			
subjects affected / exposed	5 / 118 (4.24%)	11 / 198 (5.56%)	
occurrences (all)	5	13	
Vomiting			
subjects affected / exposed	15 / 118 (12.71%)	21 / 198 (10.61%)	
occurrences (all)	20	30	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 118 (6.78%)	26 / 198 (13.13%)	
occurrences (all)	10	36	
Nasal congestion			
subjects affected / exposed	10 / 118 (8.47%)	17 / 198 (8.59%)	
occurrences (all)	14	26	
Oropharyngeal pain			
subjects affected / exposed	6 / 118 (5.08%)	19 / 198 (9.60%)	
occurrences (all)	11	26	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	15 / 118 (12.71%)	24 / 198 (12.12%)	
occurrences (all)	24	33	
Pain in extremity			
subjects affected / exposed	14 / 118 (11.86%)	17 / 198 (8.59%)	
occurrences (all)	19	42	
Scoliosis			

subjects affected / exposed	11 / 118 (9.32%)	19 / 198 (9.60%)	
occurrences (all)	11	20	
Infections and infestations			
Ear infection			
subjects affected / exposed	1 / 118 (0.85%)	11 / 198 (5.56%)	
occurrences (all)	1	17	
Gastroenteritis			
subjects affected / exposed	10 / 118 (8.47%)	11 / 198 (5.56%)	
occurrences (all)	13	18	
Gastroenteritis viral			
subjects affected / exposed	7 / 118 (5.93%)	15 / 198 (7.58%)	
occurrences (all)	7	17	
Influenza			
subjects affected / exposed	16 / 118 (13.56%)	22 / 198 (11.11%)	
occurrences (all)	18	30	
Nasopharyngitis			
subjects affected / exposed	8 / 118 (6.78%)	25 / 198 (12.63%)	
occurrences (all)	25	54	
Otitis externa			
subjects affected / exposed	2 / 118 (1.69%)	10 / 198 (5.05%)	
occurrences (all)	2	13	
Otitis media			
subjects affected / exposed	11 / 118 (9.32%)	23 / 198 (11.62%)	
occurrences (all)	12	29	
Pharyngitis streptococcal			
subjects affected / exposed	15 / 118 (12.71%)	30 / 198 (15.15%)	
occurrences (all)	23	47	
Sinusitis			
subjects affected / exposed	9 / 118 (7.63%)	23 / 198 (11.62%)	
occurrences (all)	20	47	
Upper respiratory tract infection			
subjects affected / exposed	28 / 118 (23.73%)	45 / 198 (22.73%)	
occurrences (all)	52	73	
Viral infection			
subjects affected / exposed	9 / 118 (7.63%)	11 / 198 (5.56%)	
occurrences (all)	11	13	

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