Clinical trial results:
A long-term, multi-centre, randomised, controlled, double-blind, parallel-group trial, investigating the efficacy and safety of two doses of NN-220 in subjects with short stature born small for gestational age.

Summary

EudraCT number	2017-000914-47
Trial protocol	Outside EU/EEA
Global end of trial date	28 December 2009

Results information

Result version number	v1 (current)
This version publication date	08 February 2018
First version publication date	08 February 2018

Trial information

Trial identification

Sponsor protocol code	GHLIQUID-1517

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00184717
WHO universal trial number (UTN)	-
Other trial identifiers	Japanese trial Number: JapicCTI-050132

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allè, Bagsvaerd, Denmark, 2880
Public contact	Global Clinical Registry (GCR,1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com
Scientific contact	Global Clinical Registry (GCR,1452), Novo Nordisk A/S, clinicaltrials@novonordisk.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	31 May 2010
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 March 2006
Global end of trial reached?	Yes
Global end of trial date	28 December 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the long-term efficacy as assessed by change in height standard deviation score (SDS) for chronological age (CA) (delta height SDS for CA) after treatment in subjects with short stature born small for gestational age (SGA), comparing two doses of NN-220 (0.033 mg/kg/day and 0.067 mg/kg/day).

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki, MHW Ordinance on GCP(MHW Ordinance No. 28; 27 March 1997) and the applicable relevant regulations.

Background therapy: -

Evidence for comparator:

Not applicable

Actual start date of recruitment	17 August 2004
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	Japan: 98
Worldwide total number of subjects	98
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)	98
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:

The trial was conducted at 44 sites in Japan.

Pre-assignment

Screening details:

Subjects completed the main period (GHLiquid 1516) offered to continue in the extension period.(GHLIQUID 1517).

Period 1

Period 1 title	Main Period (GHLIQUID-1516)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Blinding implementation details:

Prior to randomisation and blinding , the trial products (NN220 5 mg/1.5mL and 10 mg/1.5mL) were confirmed to be visibly indistinguishable. The products (put in small and large boxes) were then assigned a randomisation number and blinded by the responsible person for randomisation. The trial products were injected using Nordipen 5 to maintain blinding.

Arms

Are arms mutually exclusive?	Yes
Arm title	0.033 mg/NN-220

Arm description:

In the 104-week main period, subjects received 0.033 mg/kg/day somatropin (NN-220) s.c. (under the skin) injected at bedtime followed by a 156-week extension period where subjects received 0.033 mg/kg/day somatropin (NN-220) s.c (under the skin) injected at bedtime.

Arm type	Experimental
Investigational medicinal product name	Somatropin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

The NN-220 was injected subcutaneously using Growth Hormone injection device (NordiPen®5) and PenNeedle®, or in combination with an injection supportive device (NordiPenMate®) in a daily regimen at bedtime. The stated dose/day of the trial products for each subject was determined based on the subject’s body weight at each visit.

Arm title	0.067 mg/NN-220

Arm description:

In the 104-week main period, subjects received 0.067 mg/kg/day somatropin (NN-220) s.c. (under the skin) injected at bedtime followed by a 156-week extension period where subjects received 0.067 mg/kg/day somatropin (NN-220) s.c. (under the skin) injected at bedtime.

Arm type	Experimental
Investigational medicinal product name	Somatropin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

The NN-220 was injected subcutaneously using Growth Hormone injection device (NordiPen®5) and PenNeedle®, or in combination with an injection supportive device (NordiPenMate®) in a daily regimen

at bedtime. The stated dose/day of the trial products for each subject was determined based on the subject's body weight at each visit.

Arm title	No treatment

Arm description:

No somatropin (NN-220) treatment was given in the 52-week main period. Subjects were re-randomized to receive two dosing regimens (0.033 mg/kg/day or 0.067 mg/kg/day) in the 208-week extension period.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	0.033 mg/NN-220	0.067 mg/NN-220	No treatment
Started	39	38	21
Exposed to trial drug	38	38	21
Completed	36	36	20
Not completed	3	2	1
Non completed	3	2	1

Period 2

Period 2 title	Extension Period (GHLIQUID -1517)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

The subjects in the no treatment arm were randomized to receive 0.033mg or 0.067mg in the extension period. Prior to randomisation and blinding, the trial products (NN- 220 5mg/1.5mL and 10 mg/ 1.5 mL) were confirmed to be visibly indistinguishable. The products (put in small and large boxes) were then assigned a randomisation number and blinded by the responsible person for randomisation. The trial products were injected using Nordipen 5 to maintain blinding.

Arms

Are arms mutually exclusive?	Yes
Arm title	0.033 mg/NN-220

Arm description:

In the 104-week main period, subjects received 0.033 mg/kg/day somatropin (NN-220) s.c. (under the skin) injected at bedtime followed by a 156-week extension period where subjects received 0.033 mg/kg/day somatropin (NN-220) s.c (under the skin) injected at bedtime.

Arm type	Experimental

Investigational medicinal product name	Somatropin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

The NN-220 was injected subcutaneously using Growth Hormone injection device (NordiPen®5) and PenNeedle®, or in combination with an injection supportive device (NordiPenMate®) in a daily regimen at bedtime. The stated dose/day of the trial products for each subject was determined based on the subject's body weight at each visit.

Arm title	0.067 mg/NN-220

Arm description:

In the 104-week main period, subjects received 0.067 mg/kg/day somatropin (NN-220) s.c. (under the skin) injected at bedtime followed by a 156-week extension period where subjects received 0.067 mg/kg/day somatropin (NN-220) s.c. (under the skin) injected at bedtime.

Arm type	Experimental
Investigational medicinal product name	Somatropin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

The NN-220 was injected subcutaneously using Growth Hormone injection device (NordiPen®5) and PenNeedle®, or in combination with an injection supportive device (NordiPenMate®) in a daily regimen at bedtime. The stated dose/day of the trial products for each subject was determined based on the subject's body weight at each visit.

Arm title	No treatment ->0.033 mg

Arm description:

In the 208- week extension period, subjects received 0.033 mg/kg/day somatropin (NN-220) s.c. (under the skin) injected at bedtime after having received no somatromin (NN-220) treatment in the 52-week main period.

Arm type	Experimental
Investigational medicinal product name	Somatropin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

The NN-220 was injected subcutaneously using GH injection device (NordiPen®5) and PenNeedle®, or in combination with an injection supportive device (NordiPenMate®) in a daily regimen at bedtime. The stated dose/day of the trial products for each subject was determined based on the subject's body weight at each visit.

Arm title	No treatment ->0.067 mg

Arm description:

In the 208-week extension period, subjects received 0.067 mg/kg/day somatropin (NN-220) s.c. (under the skin) injected at bedtime after having received no somatromin (NN-220) treatment in the 52-week main period.

Arm type	Experimental
Investigational medicinal product name	Somatropin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

The NN-220 was injected subcutaneously using Growth Hormone injection device (NordiPen®5) and

PenNeedle®, or in combination with an injection supportive device (NordiPenMate®) in a daily regimen at bedtime. The stated dose/day of the trial products for each subject was determined based on the subject's body weight at each visit.

Number of subjects in period 2[1]	0.033 mg/NN-220	0.067 mg/NN-220	No treatment - >0.033 mg
Started	33	33	10
Completed	23	27	7
Not completed	10	6	3
Non completers	10	6	3

Number of subjects in period 2[1]	No treatment - >0.067 mg
Started	10
Completed	5
Not completed	5
Non completers	5

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: A total of 92 subjects completed GHLiquid 1516. Of these subjects, all in the NN-220 treatment group of GHLiquid 1516, 6 subjects did not participate in GHLiquid 1517.

Baseline characteristics

Reporting groups	
Reporting group title	0.033 mg/NN-220
Reporting group description:	
In the 104-week main period, subjects received 0.033 mg/kg/day somatropin (NN-220) s.c. (under the skin) injected at bedtime followed by a 156-week extension period where subjects received 0.033 mg/kg/day somatropin (NN-220) s.c (under the skin) injected at bedtime.	
Reporting group title	0.067 mg/NN-220
Reporting group description:	
In the 104-week main period, subjects received 0.067 mg/kg/day somatropin (NN-220) s.c. (under the skin) injected at bedtime followed by a 156-week extension period where subjects received 0.067 mg/kg/day somatropin (NN-220) s.c. (under the skin) injected at bedtime.	
Reporting group title	No treatment
Reporting group description:	
No somatropin (NN-220) treatment was given in the 52-week main period. Subjects were re-randomized to receive two dosing regimens (0.033 mg/kg/day or 0.067 mg/kg/day) in the 208-week extension period.	

Reporting group values	0.033 mg/NN-220	0.067 mg/NN-220	No treatment
Number of subjects	39	38	21
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)	33	34	15
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Unknown	6	4	6
Age Continuous Units: years			
arithmetic mean	5.38	5.15	5.09
standard deviation	± 1.36	± 1.2	± 1.37
Gender Categorical Units: Subjects			
Female	11	14	8
Male	22	20	7
Unknown	6	4	6
Ethnicity Units: Subjects			
Not Hispanic or Latino	33	34	15
Unknown	6	4	6
Race Units: Subjects			
Asian	33	34	15

Unknown	6	4	6
Region of enrolment Units: Subjects			
Japan	33	34	15
Unknown	6	4	6
Height Units: cm			
arithmetic mean	95.68	94.57	94.42
standard deviation	± 8.46	± 7.28	± 8.48
Body weight Units: Kg			
arithmetic mean	13.24	12.62	12.47
standard deviation	± 2.61	± 1.81	± 2.93

Reporting group values	Total		
Number of subjects	98		
Age Categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	82		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Unknown	16		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender Categorical Units: Subjects			
Female	33		
Male	49		
Unknown	16		
Ethnicity Units: Subjects			
Not Hispanic or Latino	82		
Unknown	16		
Race Units: Subjects			
Asian	82		
Unknown	16		
Region of enrolment Units: Subjects			
Japan	82		
Unknown	16		

Height Units: cm arithmetic mean standard deviation	-		
Body weight Units: Kg arithmetic mean standard deviation	-		

End points

End points reporting groups

Reporting group title	0.033 mg/NN-220
Reporting group description:	
In the 104-week main period, subjects received 0.033 mg/kg/day somatropin (NN-220) s.c. (under the skin) injected at bedtime followed by a 156-week extension period where subjects received 0.033 mg/kg/day somatropin (NN-220) s.c (under the skin) injected at bedtime.	
Reporting group title	0.067 mg/NN-220
Reporting group description:	
In the 104-week main period, subjects received 0.067 mg/kg/day somatropin (NN-220) s.c. (under the skin) injected at bedtime followed by a 156-week extension period where subjects received 0.067 mg/kg/day somatropin (NN-220) s.c. (under the skin) injected at bedtime.	
Reporting group title	No treatment
Reporting group description:	
No somatropin (NN-220) treatment was given in the 52-week main period. Subjects were re-randomized to receive two dosing regimens (0.033 mg/kg/day or 0.067 mg/kg/day) in the 208-week extension period.	
Reporting group title	0.033 mg/NN-220
Reporting group description:	
In the 104-week main period, subjects received 0.033 mg/kg/day somatropin (NN-220) s.c. (under the skin) injected at bedtime followed by a 156-week extension period where subjects received 0.033 mg/kg/day somatropin (NN-220) s.c (under the skin) injected at bedtime.	
Reporting group title	0.067 mg/NN-220
Reporting group description:	
In the 104-week main period, subjects received 0.067 mg/kg/day somatropin (NN-220) s.c. (under the skin) injected at bedtime followed by a 156-week extension period where subjects received 0.067 mg/kg/day somatropin (NN-220) s.c. (under the skin) injected at bedtime.	
Reporting group title	No treatment ->0.033 mg
Reporting group description:	
In the 208- week extension period, subjects received 0.033 mg/kg/day somatropin (NN-220) s.c. (under the skin) injected at bedtime after having received no somatromin (NN-220) treatment in the 52-week main period.	
Reporting group title	No treatment ->0.067 mg
Reporting group description:	
In the 208-week extension period, subjects received 0.067 mg/kg/day somatropin (NN-220) s.c. (under the skin) injected at bedtime after having received no somatromin (NN-220) treatment in the 52-week main period.	

Primary: Change in height standard deviation scores (SDS) for chronological age (CA) at week 260-subjects received NN220 treatment for 5 years

End point title	Change in height standard deviation scores (SDS) for chronological age (CA) at week 260-subjects received NN220 treatment for 5 years[1]
End point description:	
Height SDS for chronological age were derived as follow; {Height – mean (age, sex)}/ SD (age, sex), where mean (age, sex) and SD (age, sex) were mean and SD of height for corresponding chronological age and sex (data of those in 2000). Height SDS was calculated using mean of three height observations at corresponding visit. The FAS consisted of all subjects who were randomised in each group and have any available efficacy data after receiving NN-220 in GHLiquid-1516 or GHLiquid-1517, except subjects with GCP nonconformity.	
End point type	Primary
End point timeframe:	
week 0, week 260	

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: The data is presented only for the treatment arms with NN-220 in GHLiquid-1516. The baseline period had an arm with no treatment for 52 weeks; hence no data is presented for this arm.

End point values	0.033 mg/NN-220	0.067 mg/NN-220		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	29		
Units: Standard deviations score				
arithmetic mean (standard deviation)				
week 0	-2.9988 (± 0.6336)	-2.8304 (± 0.6244)		
Change from baseline to week 260	1.2233 (± 0.5183)	2.0113 (± 0.6432)		

Statistical analyses

Statistical analysis title	Change in Height SDS for CA at 260 weeks

Statistical analysis description:

The analysis was based on an analysis of variance (ANOVA) model including dose group as a fixed effect and baseline height SDS for CA and age at start of treatment as covariates. Point estimate was derived as 0.067 mg/NN-220 minus 0.033 mg/NN-220.

Comparison groups	0.033 mg/NN-220 v 0.067 mg/NN-220
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	other
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	0.8208
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5093
upper limit	1.1322

Primary: Change in height Standard Deviation Score (SDS) for chronological age (CA) at week 208-subjects received NN220 treatment for 4 years

End point title	Change in height Standard Deviation Score (SDS) for chronological age (CA) at week 208-subjects received NN220 treatment for 4 years

End point description:

Height SDS for chronological age were derived as follow; {Height – mean (age, sex)}/ SD (age, sex), where mean (age, sex) and SD (age, sex) were mean and SD of height for corresponding chronological age and sex (data of those in 2000). Height SDS was calculated using mean of three height observations at corresponding visit. The FAS consisted of all subjects who were randomised in each group and have any available efficacy data after receiving NN-220 in GHLiquid-1516 or GHLiquid-1517, except subjects with GCP nonconformity.

End point type	Primary

End point timeframe:

week 0, week 208

End point values	No treatment ->0.033 mg	No treatment ->0.067 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	8		
Units: Standard Deviation Score				
arithmetic mean (standard deviation)				
Week 0	-2.9603 (± 0.6689)	-2.7481 (± 0.3524)		
Change from baseline to Week 208	1.0117 (± 0.4678)	1.9921 (± 0.6670)		

Statistical analyses

Statistical analysis title	Change in Height SDS for CA at 208 weeks

Statistical analysis description:

The analysis was based on an ANOVA model including dose group as a fixed effect and baseline height SDS for CA and age at start of treatment as covariates. Point estimate was derived as 0.067 mg/NN-220 minus 0.033 mg/NN-220.

Comparison groups	No treatment ->0.033 mg v No treatment ->0.067 mg
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	other
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	0.8154
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.0341
upper limit	1.5966

Secondary: Yearly Height velocity SDS for chronological age-subjects received NN220 treatment for 5 years

End point title	Yearly Height velocity SDS for chronological age-subjects received NN220 treatment for 5 years[2]

End point description:

Yearly Height velocity SDS for chronological age were summarised and graphically presented. The FAS consisted of all subjects who were randomised in each group and have any available efficacy data after receiving NN-220 in GHLiquid-1516 or GHLiquid-1517, except subjects with GCP nonconformity.

End point type	Secondary

End point timeframe:

weeks 0-260

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: The data is presented only for the treatment arms with NN-220 in GHLiquid-1516. The baseline period had an arm with no treatment for 52 weeks; hence no data is presented for this arm.

End point values	0.033 mg/NN-220	0.067 mg/NN-220		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	34		
Units: Standard Deviation Score				
arithmetic mean (standard deviation)				
Baseline, N= 31, 34	-1.6299 (± 0.9738)	-2.0303 (± 1.4527)		
Week 52, N=29, 34	2.4717 (± 1.9848)	4.7875 (± 1.9365)		
Week 104, N=29, 32	1.1344 (± 1.2782)	2.8877 (± 1.1272)		
Week 156, N=25, 29	0.8015 (± 1.0583)	2.1641 (± 1.5929)		
Week 208, N=25, 28	0.3991 (± 1.3006)	1.4724 (± 1.8696)		
Week 260, N=23, 27	0.4612 (± 2.1558)	0.7973 (± 2.1822)		

Statistical analyses

No statistical analyses for this end point

Secondary: Yearly Height velocity SDS for chronological age-subjects received NN220 treatment for 4 years

End point title	Yearly Height velocity SDS for chronological age-subjects received NN220 treatment for 4 years

End point description:

Yearly Height velocity SDS for chronological age were summarised and graphically presented. The FAS consisted of all subjects who were randomised in each group and have any available efficacy data after receiving NN-220 in GHLiquid-1516 or GHLiquid-1517, except subjects with GCP nonconformity.

End point type	Secondary

End point timeframe:

Week 0-280

End point values	No treatment ->0.033 mg	No treatment ->0.067 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	8		
Units: Standard Deviation Score				
arithmetic mean (standard deviation)				
Baseline, N=7, 8	0.073 (± 1.5681)	-1.356 (± 0.708)		
Week 52, N=7, 8	2.1677 (± 0.61)	5.9303 (± 1.2096)		

Week 104, N=6, 7	1.5268 (± 1.1715)	3.3979 (± 1.0542)		
Week 156, N=6, 7	1.7617 (± 2.0956)	2.3539 (± 1.3149)		
Week 208, N=6, 6	0.5475 (± 1.6055)	2.199 (± 1.5973)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in bone age (left hand X-Ray) at Week 260 - subjects received NN220 treatment for 5 years

End point title	Change in bone age (left hand X-Ray) at Week 260 - subjects received NN220 treatment for 5 years[3]

End point description:

Bone age is measured as years and months (displayed as xx.x years). The FAS consisted of all subjects who were randomised in each group and have any available efficacy data after receiving NN-220 in GHLiquid-1516 or GHLiquid-1517, except subjects with GCP nonconformity.

End point type	Secondary

End point timeframe:

Week 0, week 260

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: The data is presented only for the treatment arms with NN-220 in GHLiquid-1516. The baseline period had an arm with no treatment for 52 weeks; hence no data is presented for this arm.

End point values	0.033 mg/NN-220	0.067 mg/NN-220		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	26		
Units: Years				
arithmetic mean (standard deviation)	5.79 (± 1.05)	7.15 (± 1.05)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in bone age (left hand X-Ray) at Week 208 - subjects received NN220 treatment for 4 years

End point title	Change in bone age (left hand X-Ray) at Week 208 - subjects received NN220 treatment for 4 years

End point description:

Bone age is measured as years and months (displayed as xx.x years). The FAS consisted of all subjects who were randomised in each group and have any available efficacy data after receiving NN-220 in GHLiquid-1516 or GHLiquid-1517, except subjects with GCP nonconformity.

End point type	Secondary

End point timeframe:

Week 0, week 208

End point values	No treatment - >0.033 mg	No treatment - >0.067 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	6		
Units: Years				
arithmetic mean (standard deviation)	6.54 (± 1.26)	5.6 (± 1.68)		

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse events - subjects received NN220 treatment for 5 years

End point title	Adverse events - subjects received NN220 treatment for 5 years[4]

End point description:

Occurrence of Adverse Events (AEs) during treatment period (TEAEs), occurrence of possibly/probably related AEs during the treatment period, and occurrence of Serious Adverse Events (SAEs) during the treatment period. An AE is any undesirable medical event occurring to a subject in a clinical trial, whether or not related to the trial product(s). An SAE is an experience that at any dose is fatal, life-threatening, disabling or which results in the patient being hospitalised or, if already in hospital, that hospitalisation is prolonged, or ocurrence of congenital anomaly. The safety analysis set consisted of all subjects who received at least one dose of NN-220 in GHLiquid-1516 or GHLiquid-1517, except subjects with GCP nonconformity

End point type	Secondary

End point timeframe:

Week 0-260

Notes:

[4] - 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: The data is presented only for the treatment arms with NN-220 in GHLiquid-1516. The baseline period had an arm with no treatment for 52 weeks; hence no data is presented for this arm.

End point values	0.033 mg/NN-220	0.067 mg/NN-220		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	34		
Units: Subjects				
AEs	31	34		
AEs possibly/probably related	9	16		
SAEs	12	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse events - subjects received N220 treatment for 4 years

End point title	Adverse events - subjects received N220 treatment for 4 years

End point description:

Occurrence of Adverse Events during treatment period, occurrence of possibly/probably related AEs during the treatment period, and occurrence of Serious Adverse Events (SAEs) during the treatment period. An AE is any undesirable medical event occurring to a subject in a clinical trial, whether or not related to the trial product(s). An SAE is an experience that at any dose is fatal, life-threatening, disabling or which results in the patient being hospitalised or, if already in hospital, that hospitalisation is prolonged, or occurrence of congenital anomaly. The safety analysis set consisted of all subjects who received at least one dose of NN-220 in GHLiquid-1516 or GHLiquid-1517, except subjects with GCP nonconformity

End point type	Secondary

End point timeframe:

Weeks 0-208

End point values	No treatment - >0.033 mg	No treatment - >0.067 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	8		
Units: Subjects				
AEs	7	8		
AEs possibly /probably related	1	3		
SAEs	1	2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The adverse events were collected from Aug 2004 to Dec 2009.

Adverse event reporting additional description:

The safety analysis set consisted of all subjects who received at least one dose of NN-220 in GHLIQUID-1516 or GHLIQUID-1517, except subjects with GCP nonconformity.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20

Reporting groups

Reporting group title	0.033 mg / NN-220

Reporting group description:

In the 104-week main period, subjects received 0.033 mg/kg/day somatropin (NN-220) s.c. (under the skin) injected at bedtime followed by a 156-week extension period where subjects received 0.033 mg/kg/day somatropin (NN-220) s.c (under the skin) injected at bedtime.

Reporting group title	0.067 mg / NN-220

Reporting group description:

In the 104-week main period, subjects received 0.067 mg/kg/day somatropin (NN-220) s.c. (under the skin) injected at bedtime followed by a 156-week extension period where subjects received 0.067 mg/kg/day somatropin (NN-220) s.c. (under the skin) injected at bedtime.

Reporting group title	0.033 mg / No treatment

Reporting group description:

In the 208- week extension period, subjects received 0.033 mg/kg/day somatropin (NN-220) s.c. (under the skin) injected at bedtime after having received no somatromin (NN-220) treatment in the 52-week main period

Reporting group title	0.067 mg / No treatment

Reporting group description:

In the 208-week extension period, subjects received 0.067 mg/kg/day somatropin (NN-220) s.c. (under the skin) injected at bedtime after having received no somatromin (NN-220) treatment in the 52-week main period.

Serious adverse events	0.033 mg / NN-220	0.067 mg / NN-220	0.033 mg / No treatment
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 31 (38.71%)	11 / 34 (32.35%)	1 / 7 (14.29%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	0 / 31 (0.00%)	1 / 34 (2.94%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			

subjects affected / exposed	1 / 31 (3.23%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 34 (2.94%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Sebaceous naevus			
subjects affected / exposed	0 / 31 (0.00%)	1 / 34 (2.94%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Convulsion			
subjects affected / exposed	2 / 31 (6.45%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile convulsion			
subjects affected / exposed	2 / 31 (6.45%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Strabismus			
subjects affected / exposed	2 / 31 (6.45%)	1 / 34 (2.94%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	0 / 31 (0.00%)	1 / 34 (2.94%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			

subjects affected / exposed	1 / 31 (3.23%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Testicular retraction			
subjects affected / exposed	1 / 31 (3.23%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Adenoidal hypertrophy			
subjects affected / exposed	1 / 31 (3.23%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	1 / 31 (3.23%)	1 / 34 (2.94%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sleep apnoea syndrome			
subjects affected / exposed	1 / 31 (3.23%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillar disorder			
subjects affected / exposed	1 / 31 (3.23%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillar hypertrophy			
subjects affected / exposed	2 / 31 (6.45%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis atopic			

subjects affected / exposed	1 / 31 (3.23%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			
subjects affected / exposed	0 / 31 (0.00%)	1 / 34 (2.94%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitiligo			
subjects affected / exposed	0 / 31 (0.00%)	1 / 34 (2.94%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
IgA nephropathy			
subjects affected / exposed	1 / 31 (3.23%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Torticollis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Campylobacter gastroenteritis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 34 (2.94%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Epstein-Barr virus infection			
subjects affected / exposed	1 / 31 (3.23%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis rotavirus			
subjects affected / exposed	1 / 31 (3.23%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 31 (0.00%)	0 / 34 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impetigo			
subjects affected / exposed	0 / 31 (0.00%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 31 (3.23%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngitis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 34 (2.94%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis aseptic			
subjects affected / exposed	0 / 31 (0.00%)	2 / 34 (5.88%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mumps			
subjects affected / exposed	0 / 31 (0.00%)	1 / 34 (2.94%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media			

subjects affected / exposed	0 / 31 (0.00%)	1 / 34 (2.94%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 31 (6.45%)	1 / 34 (2.94%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia mycoplasmal			
subjects affected / exposed	1 / 31 (3.23%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	1 / 31 (3.23%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal infection			
subjects affected / exposed	0 / 31 (0.00%)	1 / 34 (2.94%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheobronchitis mycoplasmal			
subjects affected / exposed	1 / 31 (3.23%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	0.067 mg / No treatment		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 8 (25.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Joint dislocation			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Sebaceous naevus			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Febrile convulsion			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Strabismus			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia			

subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Testicular retraction			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Adenoidal hypertrophy			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Asthma			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sleep apnoea syndrome			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tonsillar disorder			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tonsillar hypertrophy			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Dermatitis atopic			

subjects affected / exposed	0 / 8 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urticaria				
subjects affected / exposed	0 / 8 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vitiligo				
subjects affected / exposed	0 / 8 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
IgA nephropathy				
subjects affected / exposed	0 / 8 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Torticollis				
subjects affected / exposed	0 / 8 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Bronchitis				
subjects affected / exposed	0 / 8 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchopneumonia				
subjects affected / exposed	0 / 8 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Campylobacter gastroenteritis				
subjects affected / exposed	0 / 8 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Epstein-Barr virus infection			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis rotavirus			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis viral			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Impetigo			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Laryngitis			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Meningitis aseptic			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Mumps			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Otitis media			

subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia mycoplasmal			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Postoperative wound infection			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Streptococcal infection			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tracheobronchitis mycoplasmal			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	0.033 mg / NN-220	0.067 mg / NN-220	0.033 mg / No treatment
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 31 (100.00%)	34 / 34 (100.00%)	7 / 7 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Fibromatosis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Skin papilloma			

subjects affected / exposed	4 / 31 (12.90%)	3 / 34 (8.82%)	0 / 7 (0.00%)
occurrences (all)	4	4	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 31 (0.00%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	10 / 31 (32.26%)	10 / 34 (29.41%)	0 / 7 (0.00%)
occurrences (all)	17	23	0
Immune system disorders			
Food allergy			
subjects affected / exposed	0 / 31 (0.00%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Seasonal allergy			
subjects affected / exposed	1 / 31 (3.23%)	1 / 34 (2.94%)	1 / 7 (14.29%)
occurrences (all)	1	1	3
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	7 / 31 (22.58%)	5 / 34 (14.71%)	1 / 7 (14.29%)
occurrences (all)	11	26	1
Cough			
subjects affected / exposed	2 / 31 (6.45%)	4 / 34 (11.76%)	1 / 7 (14.29%)
occurrences (all)	2	7	1
Epistaxis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 34 (2.94%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal pain			
subjects affected / exposed	2 / 31 (6.45%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Rhinitis allergic			
subjects affected / exposed	8 / 31 (25.81%)	8 / 34 (23.53%)	1 / 7 (14.29%)
occurrences (all)	10	21	1
Rhinitis seasonal			
subjects affected / exposed	0 / 31 (0.00%)	1 / 34 (2.94%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Rhinorrhoea			

subjects affected / exposed	4 / 31 (12.90%)	3 / 34 (8.82%)	0 / 7 (0.00%)
occurrences (all)	5	4	0
Tonsillar disorder			
subjects affected / exposed	0 / 31 (0.00%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Tonsillar hypertrophy			
subjects affected / exposed	0 / 31 (0.00%)	1 / 34 (2.94%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract inflammation			
subjects affected / exposed	22 / 31 (70.97%)	22 / 34 (64.71%)	5 / 7 (71.43%)
occurrences (all)	147	94	14
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 31 (3.23%)	1 / 34 (2.94%)	1 / 7 (14.29%)
occurrences (all)	1	1	2
Antibody test positive			
subjects affected / exposed	0 / 31 (0.00%)	2 / 34 (5.88%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 31 (0.00%)	0 / 34 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	2
Blood urine present			
subjects affected / exposed	0 / 31 (0.00%)	2 / 34 (5.88%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Neutrophil count decreased			
subjects affected / exposed	0 / 31 (0.00%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
White blood cell count decreased			
subjects affected / exposed	0 / 31 (0.00%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
White blood cell count increased			
subjects affected / exposed	1 / 31 (3.23%)	2 / 34 (5.88%)	0 / 7 (0.00%)
occurrences (all)	3	2	0
Injury, poisoning and procedural complications			

Arthropod sting			
subjects affected / exposed	1 / 31 (3.23%)	2 / 34 (5.88%)	2 / 7 (28.57%)
occurrences (all)	2	2	2
Chillblains			
subjects affected / exposed	1 / 31 (3.23%)	2 / 34 (5.88%)	1 / 7 (14.29%)
occurrences (all)	1	2	2
Contusion			
subjects affected / exposed	1 / 31 (3.23%)	6 / 34 (17.65%)	0 / 7 (0.00%)
occurrences (all)	1	7	0
Excoriation			
subjects affected / exposed	2 / 31 (6.45%)	3 / 34 (8.82%)	0 / 7 (0.00%)
occurrences (all)	2	4	0
Hand fracture			
subjects affected / exposed	0 / 31 (0.00%)	2 / 34 (5.88%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Joint sprain			
subjects affected / exposed	0 / 31 (0.00%)	3 / 34 (8.82%)	1 / 7 (14.29%)
occurrences (all)	0	3	1
Thermal burn			
subjects affected / exposed	0 / 31 (0.00%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Wound			
subjects affected / exposed	0 / 31 (0.00%)	2 / 34 (5.88%)	1 / 7 (14.29%)
occurrences (all)	0	2	1
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	0 / 31 (0.00%)	2 / 34 (5.88%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Nervous system disorders			
Convulsion			
subjects affected / exposed	2 / 31 (6.45%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences (all)	4	0	0
Febrile convulsion			
subjects affected / exposed	2 / 31 (6.45%)	2 / 34 (5.88%)	0 / 7 (0.00%)
occurrences (all)	3	3	0
Headache			

subjects affected / exposed	4 / 31 (12.90%)	4 / 34 (11.76%)	1 / 7 (14.29%)
occurrences (all)	4	10	1
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	2 / 31 (6.45%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Lymphadenitis			
subjects affected / exposed	1 / 31 (3.23%)	5 / 34 (14.71%)	0 / 7 (0.00%)
occurrences (all)	1	5	0
Lymphadenopathy			
subjects affected / exposed	0 / 31 (0.00%)	2 / 34 (5.88%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 31 (0.00%)	3 / 34 (8.82%)	0 / 7 (0.00%)
occurrences (all)	0	4	0
Motion sickness			
subjects affected / exposed	1 / 31 (3.23%)	2 / 34 (5.88%)	0 / 7 (0.00%)
occurrences (all)	5	2	0
Eye disorders			
Astigmatism			
subjects affected / exposed	0 / 31 (0.00%)	1 / 34 (2.94%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Conjunctival hyperaemia			
subjects affected / exposed	2 / 31 (6.45%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Conjunctivitis			
subjects affected / exposed	4 / 31 (12.90%)	7 / 34 (20.59%)	0 / 7 (0.00%)
occurrences (all)	4	13	0
Conjunctivitis allergic			
subjects affected / exposed	3 / 31 (9.68%)	5 / 34 (14.71%)	0 / 7 (0.00%)
occurrences (all)	5	7	0
Eye pain			
subjects affected / exposed	0 / 31 (0.00%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Eyelid oedema			

subjects affected / exposed	2 / 31 (6.45%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Myopia			
subjects affected / exposed	1 / 31 (3.23%)	2 / 34 (5.88%)	1 / 7 (14.29%)
occurrences (all)	1	2	1
Strabismus			
subjects affected / exposed	1 / 31 (3.23%)	0 / 34 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 31 (12.90%)	2 / 34 (5.88%)	0 / 7 (0.00%)
occurrences (all)	4	3	0
Constipation			
subjects affected / exposed	6 / 31 (19.35%)	5 / 34 (14.71%)	0 / 7 (0.00%)
occurrences (all)	8	7	0
Dental caries			
subjects affected / exposed	2 / 31 (6.45%)	6 / 34 (17.65%)	0 / 7 (0.00%)
occurrences (all)	2	7	0
Diarrhoea			
subjects affected / exposed	2 / 31 (6.45%)	4 / 34 (11.76%)	0 / 7 (0.00%)
occurrences (all)	3	5	0
Dyspepsia			
subjects affected / exposed	1 / 31 (3.23%)	2 / 34 (5.88%)	0 / 7 (0.00%)
occurrences (all)	1	4	0
Enterocolitis			
subjects affected / exposed	2 / 31 (6.45%)	1 / 34 (2.94%)	0 / 7 (0.00%)
occurrences (all)	8	1	0
Stomatitis			
subjects affected / exposed	1 / 31 (3.23%)	3 / 34 (8.82%)	0 / 7 (0.00%)
occurrences (all)	1	4	0
Toothache			
subjects affected / exposed	0 / 31 (0.00%)	2 / 34 (5.88%)	1 / 7 (14.29%)
occurrences (all)	0	2	1
Vomiting			
subjects affected / exposed	7 / 31 (22.58%)	4 / 34 (11.76%)	0 / 7 (0.00%)
occurrences (all)	7	6	0

Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	1 / 31 (3.23%)	2 / 34 (5.88%)	0 / 7 (0.00%)
occurrences (all)	2	2	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 31 (0.00%)	3 / 34 (8.82%)	0 / 7 (0.00%)
occurrences (all)	0	4	0
Dermatitis			
subjects affected / exposed	0 / 31 (0.00%)	2 / 34 (5.88%)	0 / 7 (0.00%)
occurrences (all)	0	4	0
Dermatitis atopic			
subjects affected / exposed	3 / 31 (9.68%)	4 / 34 (11.76%)	0 / 7 (0.00%)
occurrences (all)	3	4	0
Dermatitis contact			
subjects affected / exposed	1 / 31 (3.23%)	2 / 34 (5.88%)	1 / 7 (14.29%)
occurrences (all)	1	2	1
Dry skin			
subjects affected / exposed	2 / 31 (6.45%)	2 / 34 (5.88%)	0 / 7 (0.00%)
occurrences (all)	2	2	0
Eczema			
subjects affected / exposed	9 / 31 (29.03%)	10 / 34 (29.41%)	2 / 7 (28.57%)
occurrences (all)	14	24	2
Eczema asteatotic			
subjects affected / exposed	2 / 31 (6.45%)	3 / 34 (8.82%)	0 / 7 (0.00%)
occurrences (all)	2	5	0
Ingrowing nail			
subjects affected / exposed	1 / 31 (3.23%)	0 / 34 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Pruritus			
subjects affected / exposed	0 / 31 (0.00%)	2 / 34 (5.88%)	0 / 7 (0.00%)
occurrences (all)	0	3	0
Rash			
subjects affected / exposed	0 / 31 (0.00%)	2 / 34 (5.88%)	1 / 7 (14.29%)
occurrences (all)	0	2	1
Urticaria			

subjects affected / exposed	4 / 31 (12.90%)	3 / 34 (8.82%)	1 / 7 (14.29%)
occurrences (all)	5	3	1
Xeroderma			
subjects affected / exposed	0 / 31 (0.00%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Enuresis			
subjects affected / exposed	2 / 31 (6.45%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 31 (3.23%)	6 / 34 (17.65%)	1 / 7 (14.29%)
occurrences (all)	3	10	1
Dactylitis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	3 / 31 (9.68%)	3 / 34 (8.82%)	1 / 7 (14.29%)
occurrences (all)	3	7	1
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	1 / 31 (3.23%)	2 / 34 (5.88%)	0 / 7 (0.00%)
occurrences (all)	1	8	0
Acute tonsillitis			
subjects affected / exposed	2 / 31 (6.45%)	4 / 34 (11.76%)	0 / 7 (0.00%)
occurrences (all)	2	11	0
Adenoviral conjunctivitis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Adenovirus infection			
subjects affected / exposed	0 / 31 (0.00%)	1 / 34 (2.94%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Beta haemolytic streptococcal infection			
subjects affected / exposed	4 / 31 (12.90%)	4 / 34 (11.76%)	0 / 7 (0.00%)
occurrences (all)	5	5	0
Bronchitis			

subjects affected / exposed	14 / 31 (45.16%)	15 / 34 (44.12%)	0 / 7 (0.00%)
occurrences (all)	66	66	0
Chronic sinusitis			
subjects affected / exposed	0 / 31 (0.00%)	2 / 34 (5.88%)	0 / 7 (0.00%)
occurrences (all)	0	3	0
Enteritis infectious			
subjects affected / exposed	1 / 31 (3.23%)	2 / 34 (5.88%)	0 / 7 (0.00%)
occurrences (all)	1	2	0
Enterobiasis			
subjects affected / exposed	4 / 31 (12.90%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences (all)	5	0	0
Enterocolitis viral			
subjects affected / exposed	0 / 31 (0.00%)	3 / 34 (8.82%)	0 / 7 (0.00%)
occurrences (all)	0	3	0
Folliculitis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Furuncle			
subjects affected / exposed	2 / 31 (6.45%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Gastroenteritis			
subjects affected / exposed	10 / 31 (32.26%)	14 / 34 (41.18%)	0 / 7 (0.00%)
occurrences (all)	18	25	0
Gastroenteritis viral			
subjects affected / exposed	11 / 31 (35.48%)	9 / 34 (26.47%)	0 / 7 (0.00%)
occurrences (all)	20	14	0
Herpes simplex			
subjects affected / exposed	1 / 31 (3.23%)	2 / 34 (5.88%)	0 / 7 (0.00%)
occurrences (all)	1	3	0
Herpes zoster			
subjects affected / exposed	0 / 31 (0.00%)	2 / 34 (5.88%)	0 / 7 (0.00%)
occurrences (all)	0	3	0
Hordeolum			
subjects affected / exposed	2 / 31 (6.45%)	1 / 34 (2.94%)	0 / 7 (0.00%)
occurrences (all)	2	1	0
Impetigo			

subjects affected / exposed	6 / 31 (19.35%)	9 / 34 (26.47%)	2 / 7 (28.57%)
occurrences (all)	9	9	5
Infection			
subjects affected / exposed	0 / 31 (0.00%)	0 / 34 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	16 / 31 (51.61%)	25 / 34 (73.53%)	6 / 7 (85.71%)
occurrences (all)	30	39	7
Lymphadenitis bacterial			
subjects affected / exposed	0 / 31 (0.00%)	0 / 34 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Molluscum contagiosum			
subjects affected / exposed	2 / 31 (6.45%)	4 / 34 (11.76%)	0 / 7 (0.00%)
occurrences (all)	2	4	0
Mumps			
subjects affected / exposed	5 / 31 (16.13%)	6 / 34 (17.65%)	1 / 7 (14.29%)
occurrences (all)	5	6	1
Nasopharyngitis			
subjects affected / exposed	19 / 31 (61.29%)	27 / 34 (79.41%)	6 / 7 (85.71%)
occurrences (all)	66	212	38
Otitis externa			
subjects affected / exposed	2 / 31 (6.45%)	2 / 34 (5.88%)	1 / 7 (14.29%)
occurrences (all)	2	2	1
Otitis media			
subjects affected / exposed	7 / 31 (22.58%)	12 / 34 (35.29%)	1 / 7 (14.29%)
occurrences (all)	11	17	11
Otitis media acute			
subjects affected / exposed	4 / 31 (12.90%)	4 / 34 (11.76%)	1 / 7 (14.29%)
occurrences (all)	13	6	1
Parotitis			
subjects affected / exposed	1 / 31 (3.23%)	1 / 34 (2.94%)	1 / 7 (14.29%)
occurrences (all)	1	1	3
Pharyngitis			
subjects affected / exposed	8 / 31 (25.81%)	14 / 34 (41.18%)	2 / 7 (28.57%)
occurrences (all)	46	74	8
Pneumonia mycoplasmal			

subjects affected / exposed	2 / 31 (6.45%)	1 / 34 (2.94%)	0 / 7 (0.00%)
occurrences (all)	2	1	0
Rhinitis			
subjects affected / exposed	5 / 31 (16.13%)	6 / 34 (17.65%)	0 / 7 (0.00%)
occurrences (all)	9	9	0
Sinusitis			
subjects affected / exposed	1 / 31 (3.23%)	5 / 34 (14.71%)	1 / 7 (14.29%)
occurrences (all)	1	9	1
Tonsillitis			
subjects affected / exposed	1 / 31 (3.23%)	7 / 34 (20.59%)	1 / 7 (14.29%)
occurrences (all)	1	19	1
Varicella			
subjects affected / exposed	6 / 31 (19.35%)	4 / 34 (11.76%)	0 / 7 (0.00%)
occurrences (all)	6	4	0
Metabolism and nutrition disorders			
Hyperinsulinaemia			
subjects affected / exposed	0 / 31 (0.00%)	2 / 34 (5.88%)	1 / 7 (14.29%)
occurrences (all)	0	2	1

Non-serious adverse events	0.067 mg / No treatment		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Fibromatosis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Skin papilloma			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	5		
Pyrexia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		

Immune system disorders			
Food allergy			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Seasonal allergy			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Cough			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	4		
Oropharyngeal pain			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Rhinitis allergic			
subjects affected / exposed	5 / 8 (62.50%)		
occurrences (all)	6		
Rhinitis seasonal			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	6		
Rhinorrhoea			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	4		
Tonsillar disorder			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Tonsillar hypertrophy			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Upper respiratory tract inflammation			

subjects affected / exposed	6 / 8 (75.00%)		
occurrences (all)	32		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Antibody test positive			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Blood urine present			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Neutrophil count decreased			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
White blood cell count decreased			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
White blood cell count increased			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Arthropod sting			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Chillblains			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Contusion			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Excoriation			

subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Hand fracture			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Joint sprain			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Thermal burn			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Wound			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Febrile convulsion			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Lymphadenitis			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Lymphadenopathy			

subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all) Motion sickness subjects affected / exposed occurrences (all)	 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0		
Eye disorders Astigmatism subjects affected / exposed occurrences (all) Conjunctival hyperaemia subjects affected / exposed occurrences (all) Conjunctivitis subjects affected / exposed occurrences (all) Conjunctivitis allergic subjects affected / exposed occurrences (all) Eye pain subjects affected / exposed occurrences (all) Eyelid oedema subjects affected / exposed occurrences (all) Myopia subjects affected / exposed occurrences (all) Strabismus subjects affected / exposed occurrences (all)	 1 / 8 (12.50%) 1 0 / 8 (0.00%) 0 3 / 8 (37.50%) 4 2 / 8 (25.00%) 3 1 / 8 (12.50%) 1 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0		
Gastrointestinal disorders			

Abdominal pain subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Constipation subjects affected / exposed occurrences (all)	2 / 8 (25.00%) 3		
Dental caries subjects affected / exposed occurrences (all)	2 / 8 (25.00%) 2		
Diarrhoea subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Dyspepsia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Enterocolitis subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Stomatitis subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Toothache subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 2		
Vomiting subjects affected / exposed occurrences (all)	2 / 8 (25.00%) 2		
Hepatobiliary disorders Hepatic function abnormal subjects affected / exposed occurrences (all)	2 / 8 (25.00%) 4		
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Dermatitis			

subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	2		
Dermatitis atopic			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Dermatitis contact			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Eczema			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Eczema asteatotic			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Ingrowing nail			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Urticaria			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Xeroderma			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Renal and urinary disorders			
Enuresis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Dactylitis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	2		
Acute tonsillitis			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Adenoviral conjunctivitis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Adenovirus infection			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Beta haemolytic streptococcal infection			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	2		
Bronchitis			
subjects affected / exposed	6 / 8 (75.00%)		
occurrences (all)	19		
Chronic sinusitis			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Enteritis infectious			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Enterobiasis			

subjects affected / exposed	0 / 8 (0.00%)			
occurrences (all)	0			
Enterocolitis viral				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences (all)	2			
Folliculitis				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences (all)	1			
Furuncle				
subjects affected / exposed	0 / 8 (0.00%)			
occurrences (all)	0			
Gastroenteritis				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences (all)	2			
Gastroenteritis viral				
subjects affected / exposed	4 / 8 (50.00%)			
occurrences (all)	8			
Herpes simplex				
subjects affected / exposed	0 / 8 (0.00%)			
occurrences (all)	0			
Herpes zoster				
subjects affected / exposed	0 / 8 (0.00%)			
occurrences (all)	0			
Hordeolum				
subjects affected / exposed	0 / 8 (0.00%)			
occurrences (all)	0			
Impetigo				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences (all)	2			
Infection				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences (all)	1			
Influenza				
subjects affected / exposed	4 / 8 (50.00%)			
occurrences (all)	7			
Lymphadenitis bacterial				

subjects affected / exposed	0 / 8 (0.00%)			
occurrences (all)	0			
Molluscum contagiosum				
subjects affected / exposed	0 / 8 (0.00%)			
occurrences (all)	0			
Mumps				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences (all)	1			
Nasopharyngitis				
subjects affected / exposed	5 / 8 (62.50%)			
occurrences (all)	20			
Otitis externa				
subjects affected / exposed	2 / 8 (25.00%)			
occurrences (all)	2			
Otitis media				
subjects affected / exposed	3 / 8 (37.50%)			
occurrences (all)	12			
Otitis media acute				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences (all)	2			
Parotitis				
subjects affected / exposed	0 / 8 (0.00%)			
occurrences (all)	0			
Pharyngitis				
subjects affected / exposed	3 / 8 (37.50%)			
occurrences (all)	9			
Pneumonia mycoplasmal				
subjects affected / exposed	0 / 8 (0.00%)			
occurrences (all)	0			
Rhinitis				
subjects affected / exposed	0 / 8 (0.00%)			
occurrences (all)	0			
Sinusitis				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences (all)	9			
Tonsillitis				

subjects affected / exposed occurrences (all) Varicella subjects affected / exposed occurrences (all)	2 / 8 (25.00%) 4 1 / 8 (12.50%) 1		
Metabolism and nutrition disorders Hyperinsulinaemia subjects affected / exposed occurrences (all)	 0 / 8 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 April 2004	Some inadequate descriptions were corrected throughout the protocol.
29 June 2004	The main purposes of this amendment were: 1.To add one withdrawal criterion 'Epiphyseal fusion' based on a trial site's IRB comment. 2. To add 'GHLiquid-1517 will be changed to a post marketing clinical trial when the indication for short stature born small for gestational age (SGA) is approved before the completion of this trial.' 3. To amend subject information/informed consent form according to above protocol changes.
01 June 2005	1.The description of GCP guidelines was corrected. 2. Obsolete GCP operational guidelines had been referenced in the protocol. As these types of GCP related notifications/amendments or corrections were expected to be released further, the description was amended to read 'The trial must be conducted in accordance with the Helsinki Declaration, MHW Ordinance on GCP (MHW Ordinance No. 28; 27 March 1997) and the applicable relevant regulations.'
22 November 2005	1.PenNeedle® 31G, one of auxiliary supplies, was replaced by PenNeedle® due to the discontinuation of selling the product.
17 October 2007	The main purposes of this amendment were: 1.To include an interim analysis to be performed at a period 1 year shorter than the planned treatment period. 2.To extend the treatment period until NN-220 is approved for SGA indication. In line with the extension of the trial, the second part of the amendment No.2 (the possibility of switching this trial to a post marketing clinical trial) was deleted.
29 June 2009	The main purpose of this amendment was: 1.To explain that GHLiquid-1517 is switched to a post-marketing clinical trial after NN-220 is approved for SGA indication (from the date of approval and lasting until the final visit) and the post-marketing clinical trial is conducted in conformity to the protocol.

Notes:

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.

All the serious and non-serious AEs were coded using the MedDRA terminology, version 12.1. The coding has been changed to a more current version (at least version 20) in order for the EudraCT system to accept the data for this trial.

Notes: