



Clinical trial results:

PHASE IIIB, INTERNATIONAL, SINGLE GROUP, OPEN STUDY TO DEFINE AN OPTIMAL MONITORING OF IGF-I IN CHILDREN TREATED WITH NUTROPINAQ USING A NOVEL CAPILLARY BLOOD COLLECTION METHOD (OPTIMA)

Summary

EudraCT number	2004-000356-17
Trial protocol	ES IT DK AT SE FI Outside EU/EEA
Global end of trial date	22 July 2008

Results information

Result version number	v1
This version publication date	23 March 2016
First version publication date	23 March 2016

Trial information

Trial identification

Sponsor protocol code	2-79-58035700
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00234533
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Beaufour Ipsen Pharma
Sponsor organisation address	24, rue Erlanger, Paris Cedex 16, France, 75781
Public contact	Medical Director, Pediatric Endocrinology , Ipsen, clinical.trials@ipsen.com
Scientific contact	Medical Director, Pediatric Endocrinology, Ipsen, clinical.trials@ipsen.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 July 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 July 2008
Global end of trial reached?	Yes
Global end of trial date	22 July 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To establish an optimal monitoring regimen for IGF-I in NutropinAq treated children, using a newly developed capillary blood spot IGF-I measurements technology.

Protection of trial subjects:

This clinical study was designed and implemented and reported in accordance with the International Conference on Harmonisation (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 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	Belgium: 8
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Czech Republic: 8
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	Finland: 1
Country: Number of subjects enrolled	France: 86
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Greece: 6
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Romania: 16
Country: Number of subjects enrolled	Russian Federation: 52
Country: Number of subjects enrolled	Slovakia: 4
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Ukraine: 30
Worldwide total number of subjects	251
EEA total number of subjects	169

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)	3
Children (2-11 years)	145
Adolescents (12-17 years)	103
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment period: 12 months.

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	251
Number of subjects completed	248

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 1
Reason: Number of subjects	Patient's height did not meet screening criteria: 1
Reason: Number of subjects	Not included based on the Investigator's decision: 1

Period 1

Period 1 title	Patients receiving study medication
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	NutropinAq 10 mg/2 ml (30 IU)
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Arm description:

NutropinAq 10 mg/2 ml (30 IU) subcutaneous injection

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

Dosage and administration details:

NutropinAq 10 mg/2 ml (30 IU) injection subcutaneously

Number of subjects in period 1	NutropinAq 10 mg/2 ml (30 IU)
Started	248
Completed	244
Not completed	4
Withdrawn due to AE	1
Withdrawal of consent and other	3

Period 2

Period 2 title	NutropinAq 10 mg/2 ml (30 IU)
Is this the baseline period?	Yes ^[1]
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	NutropinAq 10 mg/2 ml (30 IU)
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Arm description:

NutropinAq 10 mg/2 ml (30 IU) subcutaneous injection

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

Dosage and administration details:

NutropinAq 10 mg/2 ml (30 IU) injection subcutaneously

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 is Patients receiving study medication (all patients who received at least one injection of treatment) and period 2 is ITT population [the ITT population was all treated patients (enrolled patients who received at least one injection of treatment) and who provided any follow-up data].

As the ITT population is considered for demographic representation in the study, period 2 is the choice of group.

Number of subjects in period 2^[2]	NutropinAq 10 mg/2 ml (30 IU)
Started	244
Completed	240
Not completed	4
Withdrawn due to AE	1
Withdrawal of consent	3

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Screened population is 251, the three screen failure subjects were excluded from the study and patients receiving study medication is 248.

Baseline characteristics

Reporting groups

Reporting group title	NutropinAq 10 mg/2 ml (30 IU)
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Reporting group description:

NutropinAq 10 mg/2 ml (30 IU) subcutaneous injection.

Reporting group values	NutropinAq 10 mg/2 ml (30 IU)	Total	
Number of subjects	244	244	
Age categorical			
Units: Subjects			
Number of subjects	244	244	
Age continuous			
Units: years			
arithmetic mean	9.9		
standard deviation	± 3.9	-	
Gender categorical			
Units: Subjects			
Female	138	138	
Male	106	106	
Birth height			
Units: cm			
arithmetic mean	48.49		
standard deviation	± 3.36	-	
Birth weight			
Units: kg			
arithmetic mean	2.94		
standard deviation	± 0.64	-	
Duration of gestation (weeks of amenorrhea)			
Units: weeks			
arithmetic mean	38.7		
standard deviation	± 2.6	-	
Genetic target height			
Units: cm			
arithmetic mean	166.26		
standard deviation	± 8.16	-	
Calculated genetic target height SDS			
Units: SD			
arithmetic mean	-0.33		
standard deviation	± 0.95	-	
Growth Hormone (GH)			
Units: years			
arithmetic mean	1.68		
standard deviation	± 1.56	-	
Auxological Parameter - Height			
Units: cm			
arithmetic mean	122.95		
standard deviation	± 20.24	-	

Auxological Parameter - Calculated height SDS Units: SD arithmetic mean standard deviation	-2.68 ± 1.33	-	
Auxological Parameter - Weight Units: kg arithmetic mean standard deviation	27.97 ± 11.91	-	
Auxological Parameter - Calculated weight SDS Units: SD arithmetic mean standard deviation	-1.85 ± 1.88	-	
Auxological Parameter - Annualised GV Units: cm/year arithmetic mean standard deviation	4.94 ± 2.56	-	
Auxological Parameter - Calculated annualised GV SDS Units: SD arithmetic mean standard deviation	-0.56 ± 2.67	-	

End points

End points reporting groups

Reporting group title	NutropinAq 10 mg/2 ml (30 IU)
Reporting group description: NutropinAq 10 mg/2 ml (30 IU) subcutaneous injection	
Reporting group title	NutropinAq 10 mg/2 ml (30 IU)
Reporting group description: NutropinAq 10 mg/2 ml (30 IU) subcutaneous injection	
Subject analysis set title	NutropinAq 10 mg/2 ml (30 IU) – Morning
Subject analysis set type	Intention-to-treat
Subject analysis set description: Intention-to-Treat (ITT) population: The ITT population was all treated patients (enrolled patients who received at least one injection of treatment) and who provided any follow-up data.	
Subject analysis set title	NutropinAq 10 mg/2 ml (30 IU) – Evening
Subject analysis set type	Intention-to-treat
Subject analysis set description: Intention-to-Treat (ITT) population: The ITT population was all treated patients (enrolled patients who received at least one injection of treatment) and who provided any follow-up data.	

Primary: Timed Capillary Blood Spot IGF-I Measurements

End point title	Timed Capillary Blood Spot IGF-I Measurements ^[1]
End point description: Intention-to-Treat (ITT) population: The ITT population was all treated patients (enrolled patients who received at least one injection of treatment) and who provided any follow-up data.	
The Intra Class Correlation (ICC) was calculated each of the 2 series (morning and evening) of IGF1 measurements (weeks 21, 22 & 23).	
End point type	Primary
End point timeframe: At week 21, 22 and 23	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: An one-way Analysis of Covariance (ANCOVA) was used to calculate between patient variation and within patient variation and then to calculate ICC and its confidence limits.

An ICC ≥ 0.8 was considered satisfactory and indicated that a single sample was representative of the overall IGF-I status.

For overall ITT Population Intra-class Correlation Coefficient [95% confidence intervals] in morning was 0.92 (0.90; 0.93) and in evening was 0.90 (0.88; 0.92).

End point values	NutropinAq 10 mg/2 ml (30 IU) – Morning	NutropinAq 10 mg/2 ml (30 IU) – Evening		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	244	244		
Units: ng/mL				
arithmetic mean (standard deviation)				
Week 21 (n=226, 230)	223.54 ($\pm$ 161.86)	212.97 ($\pm$ 153.61)		
Week 22 (n=223, 229)	238.02 ($\pm$ 177.89)	226.9 ($\pm$ 164.38)		
Week 23 (n=226, 225)	241.58 ($\pm$ 167.75)	235.47 ($\pm$ 168.48)		

Statistical analyses

No statistical analyses for this end point

Secondary: Factors Affecting the Variability of Timed Capillary Blood Spots: Influence of week and daily timing (evening and morning)

End point title	Factors Affecting the Variability of Timed Capillary Blood Spots: Influence of week and daily timing (evening and morning)
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End point description:

The influence of daily timing on IGF-I measurements was tested in three-way analyses of variance with patient, day and daily timing as factors after appropriate transformation to obtain normally distributed parameters.

The interaction day*time was tested and kept in the model only if p-value <0.1.

The values listed are parameter estimate.

Method used for estimation was ANOVA. p-value for weeks was 0.1678 and p value for morning/evening was 0.3035.

End point type	Secondary
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End point timeframe:

At week 21, 22 and 23

End point values	NutropinAq 10 mg/2 ml (30 IU)			
Subject group type	Reporting group			
Number of subjects analysed	244			
Units: ng/ml				
least squares mean (confidence interval 95%)				
Week 21	218.3 (203 to 233.5)			
Week 22	232.4 (217.1 to 247.8)			
Week 23	238.5 (223.2 to 253.9)			
Timing: Evening	225.1 (212.6 to 237.6)			
Timing: Morning	234.4 (221.8 to 246.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Factors Affecting the Variability of Timed Capillary Blood Spots: Influence of sex, age and prepubertal status

End point title	Factors Affecting the Variability of Timed Capillary Blood Spots: Influence of sex, age and prepubertal status
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End point description:

Analysis of covariance model taking into account the week, time of the day as well as age, sex and pubertal status of the patients.

The values listed are parameter estimate.

Method used for estimation was ANCOVA. p-value for Age was <0.001, Sex was <0.001 and Pubertal stage was <0.001.

End point type	Secondary
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End point timeframe:

At week 21, 22, and 23

End point values	NutropinAq 10 mg/2 ml (30 IU)			
Subject group type	Reporting group			
Number of subjects analysed	244			
Units: ng/ml				
least squares mean (confidence interval 95%)				
Female	234.4 (224.7 to 244.4)			
Male	172.1 (162.7 to 181.9)			
Pubertal	238.9 (224.8 to 253.5)			
Prepubertal	168.4 (160.7 to 176.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Factors Affecting the Variability of Timed Capillary Blood Spots: Influence of individual factors/Multivariate linear regression analysis.

End point title	Factors Affecting the Variability of Timed Capillary Blood Spots: Influence of individual factors/Multivariate linear regression analysis.
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End point description:

The within-patient coefficient of variation was computed from the series of 6 measurements(Week 21,Week 22,Week 23).

The multivariate linear regression analyses was used to derive an explanatory model of WCV: age,sex,diseasecondition,dose expressed in mg/kg/d at V1,pubertal stage (genital development for boys/ breast development for girls and pubic hair),height and weight SDS at baseline, compliance(evaluated from the patient's diary),time of the year(all patients were not tested at the same time of the year),sample taken on a week day or a weekend day and country(country clusters were:1 France;2 Spain, Greece, Romania and Italy;3 UK, Belgium, Czech Republic, Denmark, Germany, Slovakia, Austria and Finland;4 Russia;5 Ukraine).

These variables were tested using a stepwise forward-backward elimination (with a significance level of $p=0.15$ for adding and keeping a term in the final model).

Values listed are p-values and method is Regression, linear

End point type	Secondary
End point timeframe:	
Up to week 24	

End point values	NutropinAq 10 mg/2 ml (30 IU)			
Subject group type	Reporting group			
Number of subjects analysed	244			
Units: NA				
number (not applicable)				
Disease condition	0.0012			
Country cluster	0.0701			

Statistical analyses

No statistical analyses for this end point

Secondary: Factors Affecting the Variability of Timed Capillary Blood Spots: Influence of time of year and calculated age at enrolment and Disease condition.

End point title	Factors Affecting the Variability of Timed Capillary Blood Spots: Influence of time of year and calculated age at enrolment and Disease condition.
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End point description:

PP Population: The per protocol (PP) population was all patients in the ITT population for whom no major protocol violations/deviations occurred.

Analysis of covariance model taking into account the time of year, calculated age at enrolment and disease condition.

Values listed are p-values and method is ANCOVA.

End point type	Secondary
End point timeframe:	
Up to week 24	

End point values	NutropinAq 10 mg/2 ml (30 IU)			
Subject group type	Reporting group			
Number of subjects analysed	244			
Units: NA				
number (not applicable)				
Time of the year	0.0139			
Calculated age at enrolment	0.0073			
Disease condition	0.0511			

Statistical analyses

No statistical analyses for this end point

Secondary: Precision Profile of Capillary Blood Random Spot versus Serum IGF-I

End point title	Precision Profile of Capillary Blood Random Spot versus Serum IGF-I
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End point description:

This is the correlation between capillary blood random spot IGF-I measurements and serum IGF-I assay.

The reported value is r (correlation coefficient)

End point type	Secondary
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End point timeframe:

Up to week 24

End point values	NutropinAq 10 mg/2 ml (30 IU)			
Subject group type	Reporting group			
Number of subjects analysed	244			
Units: NA				
number (not applicable)	0.73			

Statistical analyses

No statistical analyses for this end point

Secondary: IGFBP3 Measurements

End point title	IGFBP3 Measurements
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End point description:

End point type	Secondary
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End point timeframe:

At Visit 1 (Day 0), Visit 2 (Month 3) and Visit 3 (Month 6)

End point values	NutropinAq 10 mg/2 ml (30 IU)			
Subject group type	Reporting group			
Number of subjects analysed	244			
Units: ng/mL				
arithmetic mean (standard deviation)				
Visit 1 (n=241)	4786.8 ($\pm$ 1777.5)			
Change from baseline at visit 2 (n=235)	1112.4 ($\pm$ 1321.4)			
Change from baseline at visit 3 (n=230)	1285.2 ($\pm$ 1350.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Auxological Parameter - Height

End point title	Auxological Parameter - Height
End point description:	
End point type	Secondary
End point timeframe:	
At visit 3 (month 6)	

End point values	NutropinAq 10 mg/2 ml (30 IU)			
Subject group type	Reporting group			
Number of subjects analysed	244			
Units: cm				
arithmetic mean (standard deviation)				
Height: Change from baseline at Visit 3	4.73 ($\pm$ 1.69)			

Statistical analyses

No statistical analyses for this end point

Secondary: Auxological Parameter - Weight

End point title	Auxological Parameter - Weight
End point description:	
End point type	Secondary
End point timeframe:	
At visit 3 (month 6)	

End point values	NutropinAq 10 mg/2 ml (30 IU)			
Subject group type	Reporting group			
Number of subjects analysed	244			
Units: kg				
arithmetic mean (standard deviation)				
Weight: Change from baseline at Visit 3	2.01 ($\pm$ 1.87)			

Statistical analyses

No statistical analyses for this end point

Secondary: Auxological Parameter - Annualised GV

End point title	Auxological Parameter - Annualised GV
End point description:	
End point type	Secondary
End point timeframe:	
At visit 3 (month 6)	

End point values	NutropinAq 10 mg/2 ml (30 IU)			
Subject group type	Reporting group			
Number of subjects analysed	244			
Units: cm/year				
arithmetic mean (standard deviation)				
Annualised GV: Change from baseline at Visit 3	5.2 ($\pm$ 4.72)			

Statistical analyses

No statistical analyses for this end point

Secondary: Acceptability and Tolerance of NutropinAq and its Administration Device: NutropinAq Pen

End point title	Acceptability and Tolerance of NutropinAq and its Administration Device: NutropinAq Pen
End point description:	
This details is for Overall handling of pen	
End point type	Secondary

End point timeframe:

Up to week 22

End point values	NutropinAq 10 mg/2 ml (30 IU)			
Subject group type	Reporting group			
Number of subjects analysed	244			
Units: Percentage of subjects				
number (not applicable)				
Overall handling of pen - Very Easy	39.8			
Overall handling of pen - Easy	52.5			
Overall handling of pen - Moderately difficult	3.3			
Overall handling of pen - Difficult	0			
Overall handling of pen - Very difficult	0.4			
Overall handling of pen - Missing	4.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Evaluation - Posology

End point title	Safety Evaluation - Posology
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End point description:

The posology adopted at the first visit is summarized.

Safety population

End point type	Secondary
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End point timeframe:

Up to week 24

End point values	NutropinAq 10 mg/2 ml (30 IU)			
Subject group type	Reporting group			
Number of subjects analysed	248			
Units: mg/kg/day				
arithmetic mean (standard deviation)				
Posology	0.0382 ($\pm$ 0.0092)			

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Evaluation - Extent of Exposure

End point title	Safety Evaluation - Extent of Exposure
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End point description:

The treatment exposure, defined as the number of daily injections recorded is summarized.

Safety population

End point type	Secondary
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End point timeframe:

Up to week 24

End point values	NutropinAq 10 mg/2 ml (30 IU)			
Subject group type	Reporting group			
Number of subjects analysed	248			
Units: days				
arithmetic mean (standard deviation)				
Study Exposure	159.7 ($\pm$ 35.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Auxological Parameter - Calculated Height SDS

End point title	Auxological Parameter - Calculated Height SDS
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End point description:

The French growth charts (according to Sempé) were used for the calculation of SDS parameters.

End point type	Secondary
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End point timeframe:

At visit 3 (month 6)

End point values	NutropinAq 10 mg/2 ml (30 IU)			
Subject group type	Reporting group			
Number of subjects analysed	244			
Units: SD				
arithmetic mean (standard deviation)				
Calculated height: Change from baseline at Visit 3	0.45 ($\pm$ 0.37)			

Statistical analyses

No statistical analyses for this end point

Secondary: Auxological Parameter - Calculated Weight SDS

End point title	Auxological Parameter - Calculated Weight SDS
End point description: The French growth charts (according to Sempé) were used for the calculation of SDS parameters.	
End point type	Secondary
End point timeframe: At visit 3 (month 6)	

End point values	NutropinAq 10 mg/2 ml (30 IU)			
Subject group type	Reporting group			
Number of subjects analysed	244			
Units: SD				
arithmetic mean (standard deviation)				
Calculated weight: Change from baseline at Visit	0.2 ($\pm$ 0.56)			

Statistical analyses

No statistical analyses for this end point

Secondary: Auxological Parameter - Calculated annualised GV SDS

End point title	Auxological Parameter - Calculated annualised GV SDS
End point description: The French growth charts (according to Sempé) were used for the calculation of SDS parameters.	
End point type	Secondary
End point timeframe: At visit 3 (month 6)	

End point values	NutropinAq 10 mg/2 ml (30 IU)			
Subject group type	Reporting group			
Number of subjects analysed	244			
Units: SD				
arithmetic mean (standard deviation)				
Calculated annualised GV: Month 6	5.1 ($\pm$ 4.8)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to week 24

Adverse event reporting additional description:

NutropinAq 10 mg/2 ml (30 IU) subcutaneous injection.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	9.1
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Reporting groups

Reporting group title	NutropinAq 10 mg/2 ml (30 IU)
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Reporting group description: -

Serious adverse events	NutropinAq 10 mg/2 ml (30 IU)		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 248 (2.42%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Retinitis pigmentosa			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Pain in extremity			

subjects affected / exposed	1 / 248 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	3 / 248 (1.21%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis acute			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	NutropinAq 10 mg/2 ml (30 IU)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	84 / 248 (33.87%)		
Vascular disorders			
Wound haemorrhage			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 248 (0.81%)		
occurrences (all)	3		
Face oedema			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences (all)	1		
Feeling cold			

subjects affected / exposed	1 / 248 (0.40%)		
occurrences (all)	1		
Hyperthermia			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences (all)	1		
Injection site bruising			
subjects affected / exposed	2 / 248 (0.81%)		
occurrences (all)	2		
Injection site oedema			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences (all)	1		
Injection site pain			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences (all)	1		
Malaise			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	9 / 248 (3.63%)		
occurrences (all)	10		
Respiratory, thoracic and mediastinal disorders			
Allergic bronchitis			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences (all)	1		
Pharyngolaryngeal Pain			

subjects affected / exposed occurrences (all)	1 / 248 (0.40%) 1		
Investigations Insulin-like growth factor increased subjects affected / exposed occurrences (all)	13 / 248 (5.24%) 13		
Injury, poisoning and procedural complications Accidental overdose subjects affected / exposed occurrences (all) Arthropod bite subjects affected / exposed occurrences (all) Arthropod sting subjects affected / exposed occurrences (all) Femur fracture subjects affected / exposed occurrences (all) Foot fracture subjects affected / exposed occurrences (all) Hand fracture subjects affected / exposed occurrences (all) Wound complication subjects affected / exposed occurrences (all)	1 / 248 (0.40%) 1 1 / 248 (0.40%) 1 1 / 248 (0.40%) 1 1 / 248 (0.40%) 1 1 / 248 (0.40%) 1 2 / 248 (0.81%) 2 1 / 248 (0.40%) 1		
Congenital, familial and genetic disorders Retinitis pigmentosa subjects affected / exposed occurrences (all)	1 / 248 (0.40%) 1		
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	1 / 248 (0.40%) 1		

Nervous system disorders			
Headache			
subjects affected / exposed	14 / 248 (5.65%)		
occurrences (all)	27		
Migraine			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Auricular swelling			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences (all)	1		
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 248 (1.61%)		
occurrences (all)	4		
Abdominal pain upper			
subjects affected / exposed	4 / 248 (1.61%)		
occurrences (all)	5		
Aptyalism			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	3 / 248 (1.21%)		
occurrences (all)	4		
Gastritis			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences (all)	1		
Gastrooesophageal reflux disease			

subjects affected / exposed	1 / 248 (0.40%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	3 / 248 (1.21%)		
occurrences (all)	3		
Stomatitis			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	5 / 248 (2.02%)		
occurrences (all)	8		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences (all)	1		
Dermatitis allergic			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences (all)	1		
Eczema			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	2 / 248 (0.81%)		
occurrences (all)	2		
Swelling face			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences (all)	1		
Renal and urinary disorders			
Polyuria			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences (all)	1		
Endocrine disorders			

Hypothyroidism subjects affected / exposed occurrences (all)	2 / 248 (0.81%) 2		
Thyroiditis acute subjects affected / exposed occurrences (all)	1 / 248 (0.40%) 1		
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	3 / 248 (1.21%) 3		
Back pain subjects affected / exposed occurrences (all)	3 / 248 (1.21%) 3		
Pain in extremity subjects affected / exposed occurrences (all)	3 / 248 (1.21%) 4		
Pubic pain subjects affected / exposed occurrences (all)	1 / 248 (0.40%) 1		
Scoliosis subjects affected / exposed occurrences (all)	1 / 248 (0.40%) 1		
Infections and infestations			
Acute sinusitis subjects affected / exposed occurrences (all)	1 / 248 (0.40%) 1		
Bronchitis subjects affected / exposed occurrences (all)	1 / 248 (0.40%) 1		
Bronchitis Acute subjects affected / exposed occurrences (all)	3 / 248 (1.21%) 3		
Bronchopneumonia subjects affected / exposed occurrences (all)	2 / 248 (0.81%) 2		
Cellulitis			

subjects affected / exposed	1 / 248 (0.40%)		
occurrences (all)	1		
Ear infection			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences (all)	2		
Enterovirus infection			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	2 / 248 (0.81%)		
occurrences (all)	2		
Gastroenteritis viral			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	3 / 248 (1.21%)		
occurrences (all)	4		
Lower respiratory tract infection			
subjects affected / exposed	2 / 248 (0.81%)		
occurrences (all)	3		
Nasopharyngitis			
subjects affected / exposed	3 / 248 (1.21%)		
occurrences (all)	3		
Otitis media			
subjects affected / exposed	5 / 248 (2.02%)		
occurrences (all)	6		
Pyelonephritis acute			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	6 / 248 (2.42%)		
occurrences (all)	6		
Scarlet fever			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences (all)	1		
Tonsillitis			

subjects affected / exposed	2 / 248 (0.81%)		
occurrences (all)	2		
Tonsillitis bacterial			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences (all)	2		
Upper respiratory tract infection			
subjects affected / exposed	7 / 248 (2.82%)		
occurrences (all)	10		
Viral infection			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences (all)	1		
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences (all)	2		
Hyperglycaemia			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences (all)	1		
Polydipsia			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences (all)	1		

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