Public Assessment Report for paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended

Norditropin Nordilet (Somatropin)

DK/W/0013/pdWS/003

Marketing Authorisation Holder: Novo Nordisk A/S

Rapporteur:	DK
Finalisation procedure (day 90):	09-08-2016

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Norditropin Nordilet
INN (or common name) of the active substance(s):	Somatropin
MAH:	Novo Nordisk A/S
Currently approved Indication(s)	Children: Growth failure due to growth hormone deficiency (GHD) Growth failure in girls due to gonadal dysgenesis (Turner syndrome) Growth retardation in prepubertal children due to chronic renal disease Growth disturbance (current height SDS < -2.5 and parental adjusted height SDS < -1) in short children born small for gestational age (SGA), with a birth weight and/or length below -2 SD, who failed to show catch-up growth (HV SDS < 0 during the last year) by 4 years of age or later. Adults: Childhood onset growth hormone deficiency: Patients with childhood onset GHD should be re-evaluated for growth hormone secretory capacity after growth completion. Testing is not required for those with more than three pituitary hormone deficits, with severe GHD due to a defined genetic cause, due to structural hypothalamic pituitary abnormalities, due to central nervous system tumours or due to high-dose cranial irradiation, or with GHD secondary to a pituitary/hypothalamic disease or insult, if measurements of serum insulin-like growth factor (IGF-I) is < -2 SDS after at least four weeks off growth hormone treatment. In all other patients an IGF-I measurement and one growth hormone stimulation test is required. Adult onset growth hormone deficiency: Pronounced GHD in known hypothalamic-pituitary disease, cranial irradiation, and traumatic brain injury. GHD should be associated with one other deficient axis, other than prolactin. GHD should be demonstrated by one provocative test after institution of adequate replacement therapy for any other deficient axis. In adults, the insulin tolerance test is the

	provocative test of choice. When the insulin tolerance test is contraindicated, alternative provocative tests must be used. The combined arginine-growth hormone releasing hormone is recommended. An arginine or glucagon test may also be considered; however these tests have less established diagnostic value than the insulin tolerance test.
Pharmaco-therapeutic group (ATC Code):	H01AC01
Pharmaceutical form(s) and strength(s):	Solution for injection in prefilled syringe 10 mg/1.5 ml

I. EXECUTIVE SUMMARY

No SmPC and PL changes are proposed.

II. RECOMMENDATION

No further action required.

III. INTRODUCTION

On 6 July 2015 the MAH submitted a completed paediatric study for Norditropin, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use (an amended clinical trial report was submitted on 26 February 2016).

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric study does not influence the benefit risk for Norditropin and that there is no consequential regulatory action.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the study(ies)

Norditropin (somatropin) is a liquid preparation of human growth hormone (hGH) that has been developed by Novo Nordisk A/S. Norditropin (somatropin [genetical recombination]) is synthesised by genetic recombination technology. Norditropin® Nordilet® contains the identical sequence of 191 amino acids constituting the naturally occurring pituitary human growth hormone (hGH) with a molecular weight of about 22,000 Daltons. The product was originally developed for the use in children, and the majority of studies have been in children.

Norditropin is used in over 90 countries for the indications of “growth failure due to growth hormone deficiency (GHD)”, “growth failure in girls due to gonadal dysgenesis (Turner syndrome)”, “growth retardation in prepubertal children due to chronic renal disease (CRD)”, “growth disturbance in short children born small-for-gestational age (SGA)” and “growth hormone deficiency in adults”.

In most diagnostic classifications of short stature in childhood, three main groups are distinguished: primary growth disorders (conditions intrinsic to the growth plate), secondary growth disorders (conditions that change growth plate physiology), and a remaining group in which no recognisable cause is found. This last group is currently known as idiopathic short stature (ISS). ISS describes short children with normal Growth hormone (GH) secretion. ISS is a condition in which the height of the individual is more than 2 SD (standard deviation) below the corresponding mean height for a given age, sex and population, in whom no identifiable disorder is present.

Assessor's comment:
By definition, a proportion of children in any population will have a height more than 2 SD below the mean height of the population (as well as a proportion will have a height more than 2 SD above the mean height of the population). Consequently, it is not possible to assign this condition as a pathology/disease, and the concept of "ISS" is controversial. The approved SmPC for Norditropin does not include "ISS".

IV.2 Clinical aspects

1. Introduction

The MAH submitted a final report for:
*A 12-month, open-labelled, randomised, parallel-group, multi-centre, interventional trial to evaluate the efficacy and safety of recombinant human growth hormone (hGH) (Norditropin® Nordilet®) therapy on height velocity (Ht-V) in patients with idiopathic short stature in Korea (*Trial ID: *GH-3899)*

2. Clinical study

- **Description**

Clinical trial GH-3899 was conducted in 10 centres in Korea. Novo Nordisk was responsible for preparing the protocol, providing clinical trial supplies and monitoring the trial.

- **Methods**

  - Objective(s)

Primary objective:
To evaluate the efficacy of recombinant human growth hormone (hGH) (Norditropin) therapy compared with untreated group assessed by height velocity after 6 months of treatment in subjects with idiopathic short stature (ISS) in Korea

Assessor's comment:
6 months duration of growth hormone therapy for growth improvement is very short and insufficient to define clinical relevant long-term impact on Height-SDS or final height (the ultimately goal). The end-point height velocity is not regarded as the most appropriate since Height-SDS is the preferred target in growth studies in childhood.

Secondary objectives:
To evaluate height standard deviation scores (Ht-SDS) in treatment group compared with untreated group after 6 months of treatment

To evaluate concentrations of IGF-I (insulin-like growth factor-I) and IGFBP-3 (insulin-like growth factor binding protein-3) in treatment group compared with untreated group after 6 months of treatment

To evaluate the safety profile of treatment group as assessed by adverse events, physical examination, vital signs, clinical laboratory tests and bone age compared with untreated group after 6 months of treatment

To evaluate the safety profile of Group A (12 months of Norditropin) as assessed by adverse events, physical examination, vital signs, clinical laboratory tests and bone age during the trial

To evaluate the safety profile of group B (6 months of observation followed by 6 months of Norditropin) as assessed by adverse events, physical examination, vital signs, clinical laboratory tests and bone age during the last 6-month treatment period

To compare Ht-V of the first 6-month treatment period with the following 6-month treatment period in group A

- Study design

The study was a 12-month, open-labelled, randomised, parallel-group, multi-centre, interventional trial with to evaluate the efficacy and safety of hGH (Norditropin) in Korean children with ISS.
The trial period consisted of 12 months. The trial period of Group B was divided into two phases: first 6 months of untreated, followed by last 6 months of hGH treatment.
The main objective of the trial is to evaluate the efficacy and safety of recombinant hGH (Norditropin) therapy on Ht-V in subjects with ISS in Korea. Ht-V is useful in the evaluation of subjects with short stature children in a short-term trial, since it is difficult to get obvious difference for Ht-SDS in a short-term trial. This also represents the clear limitation of the study, since the preferred end-point in clinical trials of rhGH in children is change in Height-SDS (or optimally final height).
At Visit 2, the subject was randomised to either GH treatment group (Group A) or 6-month untreated followed by 6-month GH treatment group (Group B). The randomisation was carried out in a 2:1 manner (Group A : Group B). The randomisation was performed by an external CRO. Any stratification was not made.
This trial was open-labelled as all subjects received the treatment eventually. This was done because it was considered unethical to inject placebo to children during first 6 months. However, the subjects were randomised to the different treatment groups in order to obtain valid unbiased data.

- Study population /Sample size

A total of 54 Korean subjects with ISS were planned for enrolment and height velocity decided as the primary end-point.
From a meta-analysis for controlled trials for ISS, the mean difference of height velocity between GH treatments (0.19-0.40 mg/kg/week) and control groups was estimated as 2.86 cm/year after one year. From this result, mean change in the primary endpoint of 1.43 cm/6-month was set for this trial with dose of 0.469 mg/kg/week. Since standard error of the mean difference was 0.37 (n=229 in total, the exact number of subjects of each treatment was not known in the article), the standard deviation of the height velocity for one year was estimated as 2.8 assuming equal sample size of GH treatments and control groups, and hence the standard deviation of the height velocity for 6 months (primary endpoint) was estimated as 1.4.
Using these assumptions, 2:1 randomisation scheme, significance level of 5% and power of 80%, 24 and 12 completers for group A and group B were calculated. Assuming 30% of withdrawal, 36 and 18 subjects for group A and group B were randomised.

Inclusion criteria

Subjects were required to satisfy all the following criteria at the screening visit (Visit 1):

1. Informed consent obtained from subject's parents or legally acceptable representative before any trial-related activities. (Trial-related activities are any procedure that would not have been performed during normal management of the subject.)
2. Pre-pubertal status (males aged from 4 to 11 [both inclusive], females aged from 4 to 9 [both inclusive]): an absence of breast development in females (Tanner 1 only) and testicular volume <4 mL in males
3. Height below 3 percentile (According to the 2007 Korean National growth chart)
4. Epiphyses confirmed as open in subjects ≥10 years of age
5. Normal thyroid function
6. Growth hormone level above 10 ng/mL following a stimulation test (test result within 6 months from screening can be used)
7. Normal karyotype (assessed only female subjects)
8. Bone age ≤12 years

Exclusion criteria

1. Known presence of one or more pituitary hormone deficiencies (adrenocorticotropic hormone [ACTH], antidiuretic hormone [ADH], follicle-stimulating hormone [FSH], luteinising hormone [LH], thyroid-stimulating hormone [TSH])
2. Known primary hypothyroidism, adrenal insufficiency or hypogonadism (treated or untreated)
3. Specific types of growth failure including, but not limited to, known chromosomal abnormalities associated with growth failure and altered sensitivity to growth hormone e.g., Turner Syndrome, Noonan Syndrome, Prader Willi Syndrome, Chromosomal trisomies, Chronic renal failure, Type 1 Diabetes mellitus, Osteo- and chondrodystrophies, Hypochondroplasia, Achondroplasia, Small Gestational Age, Chronic inflammatory states (e.g., inflammatory bowel disease, rheumatoid arthritis, systemic lupus, cystic fibrosis), mitochondrial myopathies, intrauterine growth retardation (defined as a birth height and weight both below the 5th percentile and not exhibiting catch up growth by age 3), and syndromes known to be associated with growth failure
4. Bone age is advanced over chronological age more than 3 years (inclusive)
5. Active malignancy, CNS (central nervous system) trauma, active chemotherapy or radiation therapy for neoplasia within 5 years prior to screening (Visit 1)
6. Treatment with any growth hormone at lease for 12 months prior to the screening visit (Visit 1)
7. Concurrent therapy with substances known or suspected to be associated with alterations in growth including:
    - Methylphenidate, Adderall, Dexedrine and other substances used for the treatment of Attention Deficit Disorder
    - Anti-inflammatory doses of glucocorticoids
    - Oxandrolone, testosterone, estrogens and Lupron
8. Prior history of intracranial hypertension
9. Significant abnormality in clinical screening laboratories as determined by the physician
10. Any other social or medical condition, which, in the opinion of the physician, would be detrimental to either the subject or the trial
11. Hypertrophic cardiomyopathy
12. Known or suspected any chronic disease or nutritional disease
13. Mental incapacity, psychiatric disorder, unwillingness or language barrier precluding

adequate understanding or cooperation
14. Known or suspected allergy to any of the trial products or related products
15. Participation in any other trial within 3 months prior to Visit 1.

Assessor's comment:
The exclusion criteria are relevant and acceptable since they take into account the known adverse safety profile of somatropin as well as well established exclusions for participation in clinical trials

Removal of subjects from therapy and assessment
The subjects were able to withdraw at will at any time.
The subject were withdrawn from the trial at the discretion of the Investigator if judged noncompliant with trial procedures or due to safety concerns.
1. Pregnancy or intention of becoming pregnant
2. Withdrawal of informed consent or assent
3. Detection of an active malignancy
4. Commencement of medications as described in exclusion criteria
5. Failure to take more than 80% of scheduled Norditropin® Nordilet® injections
6. Onset of synostosis
7. Pubertal status defined as, for girls, Tanner breast, pubes score ≥2 and presence of menses, and, for boys, testicular volume ≥ 4mL and Tanner pubes, penis score ≥2 for each tests
8. Subject with safety concern at the discretion of the Investigator

- Treatments

In the open trial, a weekly dosage of 0.469 mg of somatropin (Norditropin) per kg of body weight was injected subcutaneously in the evening in 7 days per week.

- Outcomes/endpoints

The following efficacy variables were to be assessed:
- Height Velocity
- Ht-SDS
- IGF-I
- IGFBP-3

every 3 months during 12 months

- Statistical Methods

The following analysis sets were defined in the protocol and/or statistical analysis plan, and in accordance with ICH E9 guidance:
- **Full analysis set (FAS)** – included all randomised subjects in Group A who received at least one dose of the trial product and all randomised subjects in Group B. In exceptional cases subjects from the FAS could be eliminated. In such cases, the elimination was to be justified and documented. The statistical evaluation of the FAS was to follow the intention-to-treat (ITT) principle, and subjects was to contribute to the evaluation "as randomised."
- **Per protocol (PP) analysis set** – includes subjects from the FAS who completed the 6 months and did not have any major protocol violations that could affect the primary endpoint.

- **Safety analysis set** – includes all subjects in Group A receiving at least one dose of the trial product and all subjects in Group B who had any available data after Visit 2. Subjects in the safety analysis set contributed to the evaluation "as treated."

The primary endpoint was height velocity after 6 months of treatment. Primary endpoint was converted per 365 days for completers and applied LOCF for withdrawals.
Let D be a mean group difference of the primary endpoint. Null hypothesis H0: D = 0 vs. alternative H1: D ≠ 0 was statistically tested based on ANOVA model with group and sex as fixed effects and age as a covariate. P-value and confidence interval was presented together with the estimated mean effect (LS Means) for each group and estimated mean group difference.
The same analysis was performed on PP Analysis Set as a supportive analysis.

➢ Results

- Recruitment/ Number analysed

A total of 54 subjects were recruited to the study and randomised. In Group B, 3 patients withdrew as soon as they learned they were placed in the group with delayed start of active therapy, leaving 15 patients in group B.

14.1.1 Subject Disposition - Summary

	Group A N (%)	Group B N (%)	Total N (%)
Screened			70
Screening Failures			16
Withdrawn before Randomisation			0
Randomised	36 (100.0)	18 (100.0)	54 (100.0)
Exposed	36 (100.0)	15 (83.3)	51 (94.4)
Withdrawn after Randomisation			
Withdrawal criteria†		3 (16.7)	3 (5.6)
Completed	36 (100.0)	15 (83.3)	51 (94.4)
Full Analysis Set	36 (100.0)	15 (83.3)	51 (94.4)
PP Analysis Set	32 (88.9)	15 (83.3)	47 (87.0)
Safety Analysis Set	36 (100.0)	15 (83.3)	51 (94.4)

N: Number of subjects
%: Proportion of randomized subjects
† Three subjects in Group B were allocated but withdrawn of informed consent before trial product administration.

- Baseline data

Patients had a mean age of 6 years in both groups with 55% boys and 45% girls. The mean Height SDS at baseline was – 2.3, which is within the normal distribution in the population.

14.1.3 Demographics and Baseline Characteristics – Summary – Full Analysis Set

	Group A N (%)	Group B N (%)	Total N (%)
Number of Subjects	36	15	51
Sex			
N	36	15	51
Male	19 (52.8)	9 (60.0)	28 (54.9)
Female	17 (47.2)	6 (40.0)	23 (45.1)
Race			
N	36	15	51
Korean	36 (100.0)	15 (100.0)	51 (100.0)

N = Number of Subjects
%: Percentages are based on N

14.1.4 Baseline Characteristics – Descriptive Statistics - Full Analysis Set

	Group A	Group B	Total
Number of Subjects	36	5	51
Age (years)			
N	36	5	51
Mean (SD)	6.3 (1.5)	5.9 (1.2)	6.2 (1.5)
Median	6	6	6
Min ; Max	4 ; 11	4 ; 8	4 ; 11
Height (cm)			
N	32	5	47
Mean (SD)	107.7 (8.7)	05.8 (7.5)	107.1 (8.3)
Median	107.7	05.0	107.4
Min ; Max	92.6 ; 129.9	95.9 ; 119.8	92.6 ; 129.9
Weight (kg)			
N	32	5	47
Mean (SD)	17.8 (3.1)	6.3 (2.8)	17.4 (3.0)
Median	17.9	6.0	17.3
Min ; Max	12.3 ; 25	12.6 ; 24.5	12.3 ; 25

Assessor's comment:
Apparently, the figure has an error in the data for Group B, since it is probable that mean height was 105.8 cm, median height was 105.0 cm, mean weight was 16.3 kg and median weight was 16.0 kg.

- Efficacy results

It is a physiological action of somatropin to increase the levels of IFG-1, and results from Group A clearly demonstrates a change in IGF-1 concentrations, whereas concentrations in Group B did not change after 6 months. This supports good adherence to the treatment in Group A.

14.2.14 IGF-I and IGFBP-3 after 6 months of Treatment - Statistical Analysis - Full Analysis Set

	FAS	N	Estimate	SE	P-value
IGF-I					
LSMeans					
Group A	36	36	321.18	14.00	
Group B	15	15	156.61	21.81	
Change from Baseline					
LSMeans					
Group A	36	36	192.58	14.00	
Group B	15	15	28.03	21.81	
Group-Contrast					
Group A - Group B			164.56		<.0001

The primary end-point of the trial was changes in Height-velocity after 6 months, and it was observed that a difference between Group A (active therapy) and Group B (observation only) occurred. The mean difference was 5.4 cm.

14.2.4 Confirmatory Statistical Analyses - Full Analysis Set

Endpoint	LSMeans	95% CI	P-value	Conclusion
PRIMARY				
Ht-V after 6 months of treatment				
Group-Contrast				
Group A - Group B	5.40	[4.50;6.30]	<.0001	Superiority of Group A
CONFIRMATORY SECONDARY				
Ht-SDS after 6 months of treatment				
Group-Contrast				
Group A - Group B	0.60	[0.49;0.72]	<.0001	Superiority of Group A

The Ht-V after 6 months of treatment is analyzed using an ANOVA method with group and sex as fixed effects, and age as a covariate.
The Ht-SDS after 6 months of treatment is analyzed using an ANOVA method with group and sex as fixed effects, and age and baseline Ht-SDS as covariates.

Assessor's comment:
A more detailed analysis of height velocity at 3 months interval in both groups, however, revealed an initial strong efficacy which waned over the study period. Height velocity was 12.8 cm for the first 3 months, which had decreased to 10.4 at the 12 month visit. It is unknown if activity extends beyond 1 year of therapy. Also, it is surprising that the impact on height velocity in Group B was much weaker following 6 months of active treatment (height velocity change from 7.7 cm at visit 3 [3 months] to 9.5 cm at visit 6 [12 months]). The MAH does not comment why the efficacy apparently was different in the two groups.

14.2.8 Ht-V by Treatment Visit from Baseline – Descriptive Statistics - Full Analysis Set

	Group A	Group B	Total
Number of Subjects	36	15	51
Ht-V			
Visit 3 (Month 3)			
N	32	15	47
Mean(SD)	12.6 (2.7)	7.5 (2.3)	11 (3.5)
Median	12.8	7.7	10.8
Min ; Max	6.9 ; 18.4	2.8 ; 10.8	2.8 ; 18.4
Visit 4 (Month 6)			
N	32	15	47
Mean(SD)	12.2 (1.5)	6.9 (1.4)	10.5 (2.9)
Median	12.0	6.6	11.4
Min ; Max	9.4 ; 16.6	4.8 ; 9.8	4.8 ; 16.6
Visit 5 (Month 9)			
N	32	15	47
Mean(SD)	11.4 (1.6)	8.8 (0.6)	10.5 (1.8)
Median	11.1	8.6	10.3
Min ; Max	8.7 ; 14.8	7.9 ; 10.1	7.9 ; 14.8
Visit 6 (Month 12)			
N	32	15	47
Mean(SD)	10.6 (1.5)	9.2 (0.8)	10.1 (1.5)
Median	10.4	9.5	9.8
Min ; Max	8.4 ; 14.2	7.7 ; 10.0	7.7 ; 14.2

N = Number of Subjects, SD = Standard Deviation

A more appropriate end-point would be Height-SDS, and results showed improvement in Height-SDS from -2.3 at baseline to -1.2 after 12 months of active therapy in Group A. The change was primarily obtained during the first 6 months of treatment (difference 0.7) where the change from month 6 to month 12 only was a difference of 0.4 SDS.

14.2.11 Ht-SDS by Treatment Visit- Descriptive Statistics - Full Analysis Set

	Group A			Group B			Total		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
Number of Subjects	36			15			51		
Visit 1 (Screening)	36	-2.3	0.3	15	-2.2	0.3	51	-2.3	0.3
Visit 2 (Month 0)	32	-2.4	0.4	15	-2.2	0.3	47	-2.3	0.3
Visit 3 (Month 3)	32	-1.9	0.3	13	-2.1	0.3	45	-2	0.3
Visit 4 (Month 6)	36	-1.6	0.3	15	-2	0.4	51	-1.7	0.4
Visit 5 (Month 9)	33	-1.3	0.3	15	-1.6	0.4	48	-1.4	0.4
Visit 6 (Month 12)	36	-1.2	0.4	15	-1.4	0.3	51	-1.2	0.4

N = Number of Subjects, SD = Standard Deviation

By statistical analysis, a statistical significant difference after 6 months between Group A and Group B was demonstrated.

14.2.12 Ht-SDS after 6 months of Treatment - Statistical Analysis - Full Analysis Set

	FAS	N	Estimate	SE	P-value
Ht-SDS					
LSMeans					
Group A	36	32	-1.53	0.03	
Group B	15	15	-2.13	0.04	
Change from Baseline					
LSMeans					
Group A	36	32	0.79	0.03	
Group B	15	15	0.18	0.04	
Group-Contrast					
Group A - Group B			0.60		<.0001

N= Number of subjects contributing to analysis,
SE= Standandard Error of the Mean
The Ht-SDS and change from baseline after 6 month of treatment is analysed using an ANOVA method with treatment group and sex as fixed effects and age and Baseline Ht-SDS as covariates.

- Safety results

Norditropin has been administered to thousands of children over many years and the safety profile is well established. It is unlikely that exposure to 51 children in the study will change the safety profile of Norditropin. The adverse events (AEs) in the trials follow the well known pattern, mostly related to mild disorders common to childhood. The AEs were mostly mild.

There were no deaths in the trial.

A total of 6 serious adverse events (SAEs) were observed. All of these were considered not related to study drug by the investigators (Table 14.3.1.6). All subjects who underwent SAEs recovered at the end of the trial.

14.3.1.1 Adverse Events - Treatment Emergent – Summary – Safety Analysis Set

	Group A			Group B			Total		
	N	(%)	E	N	(%)	E	N	(%)	E
Number of Subjects	36			15			51		
Events	25	(69.4)	70	11	(73.3)	25	36	(70.6)	95
Serious									
Yes	4	(11.1)	4	2	(13.3)	2	6	(11.8)	6
No	24	(66.7)	66	10	(66.7)	23	34	(66.7)	89
MESI									
No	25	(69.4)	70	11	(73.3)	25	36	(70.6)	95
Severity									
Mild	22	(61.1)	59	8	(53.3)	18	30	(58.8)	77
Moderate	6	(16.7)	11	4	(26.7)	7	10	(19.6)	18

14.3.1.2 Serious Adverse Events – Treatment Emergent - Summary - Safety Analysis Set

	Group A			Group B			Total		
	N	(%)	E	N	(%)	E	N	(%)	E
Number of Subjects	36			15			51		
Events	4	(11.1)	4	2	(13.3)	2	6	(11.8)	6
MESI									
No	4	(11.1)	4	2	(13.3)	2	6	(11.8)	6
Severity									
Mild	3	(8.3)	3				3	(5.9)	3
Moderate	1	(2.8)	1	2	(13.3)	2	3	(5.9)	3
Outcome									
Recovered	4	(11.1)	4	2	(13.3)	2	6	(11.8)	6
Causality									
Unlikely	4	(11.1)	4	2	(13.3)	2	6	(11.8)	6

N = Number of Subjects
% = Percentage of Subjects
E = Number of Events

14.3.1.6 Serious Adverse Events by System Organ Class and Preferred Term - Summary - Safety Analysis Set

	Group A			Group B			Total		
	N	(%)	E	N	(%)	E	N	(%)	E
Number of Subjects	36			15			51		
Events	4	(11.1)	4	2	(13.3)	2	6	(11.8)	6
Congenital, familial and genetic disorders	1	(2.8)	1				1	(2.0)	1
Hydrocele	1	(2.8)	1				1	(2.0)	1
Infections and infestations	1	(2.8)	1	1	(6.7)	1	2	(3.9)	2
Pharyngotonsillitis	1	(2.8)	1				1	(2.0)	1
Pneumonia				1	(6.7)	1	1	(2.0)	1
Respiratory, thoracic and mediastinal disorders	1	(2.8)	1	1	(6.7)	1	2	(3.9)	2
Tonsillar hypertrophy	1	(2.8)	1	1	(6.7)	1	2	(3.9)	2
Vascular disorders	1	(2.8)	1				1	(2.0)	1
Kawasaki's disease	1	(2.8)	1				1	(2.0)	1

N = Number of Subjects
% = Percentage of Subjects
E = Number of Events

Side effects of special interest for somatropin are diabetes and bone maturation, since the physiology of growth hormone may influence these functions. The safety for both parameters was good and no unwanted effects were observed.

Fasting Glucose, Insulin and HbA1c by Treatment visit – Change from Baseline -Descriptive Statistics - Safety Analysis Set

	Group A	Group B	Total
Number of subjects	36	15	51
HbA1c			
Visit 4 (Month 6)			
N	36	15	51
Mean(SD)	0.2 (0.2)	0 (0.2)	0.1 (0.2)
Median	0.2	0	0.2
Min ; Max	-0.3 ; 0.6	-0.5 ; 0.4	-0.5 ; 0.6
Visit 6 (Month 12)			
N	36	15	51
Mean(SD)	0.1 (0.2)	0.1 (0.2)	0.1 (0.2)
Median	0.1	0	0.1
Min ; Max	-0.2 ; 0.5	-0.2 ; 0.6	-0.2 ; 0.6

N = Number of Subjects, SD = Standard Deviation

14.3.6.8 Bone Age by Treatment visit– Descriptive Statistics– Safety Analysis Set

	Group A	Group B	Total
Number of Subjects	36	15	51
Bone Age (years)			
Visit 1 (Screening)			
N	36	15	51
Mean(SD)	6.2 (1.9)	5.3 (1.9)	6.0 (1.9)
Median	5.9	4.7	5.7
Min ; Max	3.5 ; 10.4	3.0 ; 9.6	3.0 ; 10.4
Visit 4 (Month 6)			
N	36	15	51
Mean(SD)	6.7 (1.9)	5.8 (1.9)	6.4 (1.9)
Median	6.3	5.0	6.2
Min ; Max	3.8 ; 10.7	3.5 ; 9.9	3.5 ; 10.7
Visit 6 (Month 12)			
N	36	15	51
Mean(SD)	7.3 (1.8)	6.3 (1.8)	7.0 (1.8)
Median	7.0	5.4	6.7
Min ; Max	4.3 ; 10.9	4.0 ; 10.1	4.0 ; 10.9

3. Discussion on clinical aspects

The study included patients with ISS, which is not approved in the EU and the MAH does not apply for a change in label. Due to design of the study with a very short period of treatment it is not feasible to conclude on efficacy, since Height-SDS is the preferred end-point after prolonged exposure. However, initial increase in height velocity was demonstrated and adherence to active treatment apparently was high based on changes in IGF-1 levels. Safety in exposed patients was in agreement with previous data on Norditropin® in children, and no new adverse profile was observed. The adverse events documented were disorders common to childhood and they were in line with information provided in the approved SmPC.
There is no indication for a change in the SmPC based on this trial.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

The indication ISS is not approved in the EU and the trial is not sufficient to conclude on efficacy. The safety results from the limited number of patients in the trial are in agreement with previous studies and in agreement with information in the SmPC.

- **Recommendation**

No further action required.